

HTA 10-146-01. Duration of intravenous antibiotic therapy for children with acute osteomyelitis or septic arthritis: a feasibility study

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Osteomyelitis, septic arthritis, antibiotic therapy, child, service evaluation, PCR, qualitative interviews, Delphi, consensus

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Conflict of interests:

S.N. Faust (SNF) acts as principal investigator for clinical trials and other studies conducted on behalf of University Hospital Southampton NHS Foundation Trust/University of Southampton that are sponsored by vaccine manufacturers and antimicrobial agents and has participated in advisory boards for vaccine manufacturers. SNF is currently UK Chief Investigator and UHS NHS Principal Investigator for a Cubist-sponsored clinical trial of daptomycin against standard of care antibiotic therapy in paediatric osteomyelitis. All grants and honoraria are paid into accounts within the NHS Trust or University, SNF received no personal payment of any kind.

A. Finn (AF): is employed by the University of Bristol and University Hospitals Bristol NHS Foundation Trust. Prior to October 2014, both institutions, but not AF, have received funding for research conducted by AF and for consultancy and lectures from Pfizer, GSK, SPMSD and Novartis, who manufacture licensed and developmental meningococcal vaccines

S. C. Clarke (SCC) acts as principal investigator for clinical trials and other studies conducted on behalf of University Hospital Southampton NHS Foundation Trust/University of Southampton that are sponsored by vaccine manufacturers but receive no personal payments from them. He has participated in advisory boards for vaccine manufacturers and has received financial assistance from vaccine manufacturers to attend conferences but receives no personal payments for this work. All grants and honoraria are paid into accounts within the respective NHS Trusts or Universities.

J. Herberg (JH): is employed by Imperial College London. JH is local principal investigator for a Cubist-sponsored clinical trial of daptomycin against standard of care antibiotic therapy in paediatric osteomyelitis. JH received no personal payments.

A. Riordan (AR) is employed by Alder Hey Children's NHS Foundation Trust. The Trust, but not AR, has received funding for research sponsored by vaccine manufacturers and antimicrobial agents. AR was lead editor for an ELearning package on Meningitis produced by the Royal College of Paediatric and Child Health, funded by an unrestricted grant from Novartis Vaccines.

M. Emonts (ME) acts as principal investigator for clinical trials and other studies conducted on behalf of the Newcastle upon Tyne Hospitals Foundation Trust/Newcastle University that are sponsored by manufacturers of antimicrobial agents. ME is currently Newcastle upon Tyne Hospitals Foundation Trust Principal Investigator for a Cubist-sponsored clinical trial of daptomycin against standard of care antibiotic therapy in paediatric osteomyelitis. All grants and honoraria are paid into accounts within the NHS Trust or University, ME received no personal payment of any kind.

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Abstract (496 words)

Background: There is little current consensus regarding the route or duration of antibiotic treatment for acute osteomyelitis (OM) and septic arthritis (SA) in children.

Objective: To assess the overall feasibility and inform the design of a future randomised controlled trial (RCT) to reduce the duration of intravenous antibiotic use in paediatric OM and SA.

Design: a): Prospective service evaluation (cohort study) to determine the current disease spectrum and UK clinical practice in paediatric OM/SA; b) prospective cohort sub-study to assess the use of targeted PCR in diagnosing paediatric OM/SA; c) a qualitative study explored families views and experiences of OM/SA; and d) development of a core outcome set via systematic review of literature, Delphi clinician survey and stakeholder consensus meeting.

Setting: 44 UK secondary and tertiary UK centres (service evaluation).

Participants: Children with OM/SA

Results: Data was obtained on 313 cases of OM/SA of which 218 (61.2%) were defined as simple disease and 95 (26.7%) complex. The epidemiology of paediatric OM/SA in this study was consistent with existing European data. Children who met oral switch criteria less than 7 days from starting intravenous antibiotics had less treatment failure (9.6%) than children who meet oral switch criteria after 7 days of intravenous therapy (16.1% where switch was between 1-2 weeks, 18.2% switch >2 weeks). In 24 of 32 simple cases (75%) and 8 of 12 complex cases (67%) in whom the targeted PCR was used a pathogen was detected.

The qualitative study demonstrated the importance to parents and children of consideration of short and long term outcomes meaningful to families themselves. The consensus meeting agreed on the following outcomes: re-hospitalisation or recurrence of symptoms while on oral antibiotics, recurrence of infection, disability at follow-up, symptom free at 1 year, limb shortening or deformity, chronic osteomyelitis or arthritis, amputation or fasciotomy, death, need for paediatric intensive care and line infection. Oral switch criteria were identified, including resolution of fever for 48 hours or more, tolerating oral food and medicines, and pain improvement.

Limitations: Data were collected in a 6 month period which might not have been representative and follow up data for long term complications are limited.

Conclusions: A future RCT would need to recruit from all tertiary and most secondary UK hospitals. Clinicians have implemented early oral switch for selected patients with simple disease without formal clinical trial evidence of safety. However, the current criteria by which decisions to make the oral switch are made are not clearly established or evidence based.

Future work: An RCT in simple OM and SA comparing shorter or longer course IV therapy is feasible in children randomised after oral switch criteria are met after 7 days of intravenous therapy, excluding children meeting oral switch criteria in the first week of intravenous therapy. This study design meets clinician preferences and addresses parental concerns not to randomise prior to oral switch criteria being met

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Contents

List of Tables	10
List of Figures	12
List of Abbreviations	12
Plain English Summary (236 words)	15
Scientific Summary (2055 words)	16
 Chapter 1: Introduction	 23
Osteomyelitis and Septic Arthritis in Children	23
Commissioning brief and objectives	32
Research Objectives	33
 Chapter 2: Service Evaluation	 34
Aims and objectives	34
Methods	34
Results	36
Discussion	102
 Chapter 3: Microbiology sub-study	 117
Background	117
Aims and Objectives	117
Methods	117
PCR Analysis	119
Results	122
Discussion	128
Conclusions	131
 Chapter 4: Qualitative Interviews with Families and children	 133
Background	133
Aims	133
Methods	134
Findings	144
Discussion	157
Limitations	159
Recommendations	160
 Chapter 5: Systematic literature review	 163
Aims and objectives	163
Methods	163
Results	164
Conclusion	167

Chapter 6: Delphi survey	169
Aims and objectives	169
Methods:.....	169
Results	171
Chapter 7: Consensus meeting.....	179
Aims and objectives	179
Methods	179
Results	181
Chapter 8: Summary discussion and conclusions for further research	193
Acknowledgements.....	202
Word count approximately excluding tables: 50,000	203
Contributions of authors	204
References	205
Appendix 1: Service evaluation documents.....	213
1.1 Service evaluation protocol.....	213
1.2 Poster Dinosaur study.....	237
1.3 Data collection sheet on the website	239
Appendix 2: Microbiology sub-study documents.....	270
2.1 Protocol: see Appendix 1	270
2.2 Laboratory Standard Operating Procedure.....	271
2.3 Patient information sheets and consent form	274
Appendix 3: Qualitative Study documents	288
3.1 Protocol Qualitative study.....	288
3.2 RCT process diagram and information	297
3.3 Qualitative Study Topic Guide and Tools for Interviews	300
3.4 Patient information sheets	312
3.5 Consent forms	317
Appendix 4: Core Outcome Literature Review	320
4.1 Search Strategy Used to Identify Trials Investigating Duration of Antibiotics in Paediatric Bone and Joint Infection	320
Appendix 5: Clinician Survey – Delphi Study documents	321
5.1 Protocol clinician survey protocol.....	321
5.2 Questionnaire Round 1 and 2	332
5.3 Consensus meeting agenda.....	337

5.4	Consensus meeting breakdown of individual	Error! Bookmark not defined.
Appendix 6: Tables of the consensus meeting.....		339
6.1	Criteria for switching	339
6.2	Outcomes.....	350
Appendix 7: Service evaluation statistical analysis plan, 18/12/2014		383
Appendix 8: Additional statistical analyses carried out surplus to SAP 1.5.....		422

List of Tables

Table 1: Tertiary centres	38
Table 2: Secondary centres	39
Table 3: Case types	40
Table 4: Sample demographics	41
Table 5: Completeness of follow-up	42
Table 6: History of orthopaedic surgery	43
Table 7: Co-morbidities indicating complex case	44
Table 8: Medical history	44
Table 9: Other medical conditions	45
Table 10: Other infection history	47
Table 11: Prepresentation variables that affect drug choice, dosage and duration	48
Table 12: Where patients presented and bones/joints affected	49
Table 13: Joints/limbs affected (by SA/OM)	50
Table 14: Presentation blood tests	52
Table 15: Summary of blood test results at presentation	53
Table 16: Summary of blood test results at presentation (by Sa/OM)	53
Table 17: The clinical time-line for diagnosis	54
Table 18: The clinical time-line for diagnosis (by SA/OM)	55
Table 19: Blood tests on the day of or day preceding initiation of IV antibiotics	57
Table 20: Summary of blood test results at initiation of IV	57
Table 21: Summary of blood test results at the day of or the day preceding initiation of IV antibiotics (by SA/OM)	58
Table 22: Surgical procedures post presentation carried out prior to initiation of IV antibiotics	61
Table 23: Surgical procedures post presentation carried out prior to initiation of IV antibiotics (by SA/OM)	61
Table 24: Imaging types routinely used to aid diagnosis	62
Table 25: Imaging types routinely used to aid diagnosis (by SA/OM)	63
Table 26: Bones/joints affected where a diagnostic MRI was carried out (by SA/OM)	63
Table 27: Summary of results of conventional microbiology tests	64
Table 28: Other micro-organisms detected from blood/joint/bone/periosteal pus	65
Table 29: Summary of results of PCR tests	67
Table 30: Conventional testing sample types	69
Table 31: Clinical time-line for antibiotic treatment	73
Table 32: Clinical time-line for antibiotic treatment (by SA/OM)	73
Table 33: Types of antibiotic regimes experienced	75
Table 34: Types of antibiotic regimes experienced (by SA/OM)	78
Table 35: IV and oral antibiotics prescribed prior to discharge (Simple cases)	83
Table 36: IV and oral antibiotics prescribed prior to discharge (Complex cases)	84
Table 37: Characteristics of children that were given no IV	85
Table 38: Blood tests carried out immediately prior to oral switch	87
Table 39: Summary of blood tests at switch (by SA/OM)	88
Table 40: Surgery occurring after the initiation of IV antibiotics (post diagnosis)	89
Table 41: Single procedures	89
Table 42: Imaging types routinely used post diagnosis	90
Table 43: Length of stay in hospital by agegroup and presenting centre type	91
Table 44: Length of stay by SA/OM	91
Table 45: Antibiotics at discharge by SA/OM	93
Table 46: Antibiotic regimes prescribed at discharge	93
Table 47: Discharge antibiotic regimes adhered to	94
Table 48: Other reasons for shortening or changing antibiotics	94
Table 49: Complication types by action taken	95
Table 50: Other complications as they appear in the database	96
Table 51: Other actions in response to complications as they appear in the database	96

Table 52: On-going symptoms at follow-up.....	97
Table 53: Treatment failure by SA/OM.....	100
Table 54: Treatment failure by switch timing.....	100
Table 55: Treatment failure by length of time on antibiotics	100
Table 56: Treatment failure and surgery prior to discharge.....	102
Table 57: Elements to each of the multiplexes	122
Table 58: Total number and Patients consented to the study according to geographical site....	122
Table 59: Number of organisms detected by PCR according to geographical site.....	124
Table 60: number of organisms detected by PCR according to sample type.....	124
Table 61: Number of organisms detected by PCR from usually sterile sites according to geographical site	125
Table 62: Patients in which multiple organisms were identified	125
Table 63: Number of organisms detected by PCR from usually sterile sites according to sample type	126
Table 64: Total number of positive samples according to sample type.....	126
Table 65: Number of patients with organisms detected by PCR according to geographical site	127
Table 66: Summary of the results of the PCR	127
Table 67: Number of organisms detected by PCR from a throat swab according to geographical site.....	128
Table 68: Implications of subtle realist approach for the conduct of this qualitative research..	136
Table 69: Summary of Results from selected papers.....	165
Table 70: Outcomes identified from the systematic review	167
Table 71: Response rate to clinical stakeholder survey	172
Table 72: Results rating of CRP as outcome for future study	174
Table 73: Percentage of participants that scored 7, 8 or 9 for Switch Criteria Round 2 by stakeholder group.....	175
Table 74: Percentage of participants that scored 7, 8 or 9 for Infection related outcomes	176
Table 75: Percentage of participants that scored 7, 8 or 9 for Infection related outcomes	177
Table 76: Percentage of participants that scored 7, 8 or 9 for Treatment/Line related outcomes	178
Table 77: Definition of consensus for switch criteria.....	180
Table 78: Definition of consensus for outcomes	180
Table 79: Meeting Attendees.....	182
Table 80: Stakeholder representation.....	183
Table 81: Summary of switch criteria voting	186
Table 82: Summary of outcomes discussed.....	188
Table 83: Breakdown of individual switch criteria discussions and scores.....	339
Table 84: CRP (non-specific blood test done at diagnosis and for monitoring) <20.....	340
Table 85: CRP less than one third of the presenting value	340
Table 86: CRP less than two thirds of the presenting value	342
Table 87: ESR <20.....	343
Table 88: Resolution of fever for 48h or more	344
Table 89: Weight bearing / return of function to limb	345
Table 90: Resolution of pain.....	346
Table 91: Tolerating oral input	347
Table 92: Parental opinion regarding improvement or worsening of condition	348
Table 93: Pain improvement.....	349
Table 94: Breakdown of individual outcome discussions and scores.....	350
Table 95: Need for non-diagnostic surgical procedure.....	351
Table 96: Re-hospitalisation or recurrence of symptoms while on oral antibiotics.....	352
Table 97: Treatment failure – recurrence of infection	353
Table 98: Pain while on antimicrobial treatment.....	354
Table 99: Ongoing pain at follow-up.....	355
Table 100: Disability at follow-up.....	356

Table 101: Symptom free at 1 year.....	357
Table 102: Limb shortening or deformity.....	358
Table 103: Duration to CRP <5	359
Table 104: Duration to resolution of fever	360
Table 105: Duration to resolution of pain.....	361
Table 106: Duration of hospital stay.....	362
Table 107: Fracture at or near site of infection.....	362
Table 108: Prolonged antibiotic therapy.....	364
Table 109: Quality of life.....	365
Table 110: Chronic osteomyelitis	366
Table 111: Chronic arthritis	367
Table 112: Chronic myositis.....	368
Table 113: Amputation or Fasciotomy	369
Table 114: Death.....	370
Table 115: PICU requirement.....	371
Table 116: Agranulocytosis / neutropaenia	372
Table 117: Deranged (abnormal) liver function tests	373
Table 118: Clostridium difficile infection	374
Table 119: Rash or allergic reaction	375
Table 120: Suspected drug-related fever	376
Table 121: Line infection.....	377
Table 122: Line occlusion.....	378
Table 123: Vomiting / diarrhoea.....	379
Table 124: IV antibiotic necessitated insertion of PICC or other central line	380
Table 125: Infiltration or extravasation event.....	381
Table 126: Any complication of vascular access.....	382

List of Figures

Figure 1: Kaplan-meier plot showing time-to-switch	77
Figure 2: Kaplan-Meier plot showing time-to-switch (by SA/OM)	77
Figure 3: Initial process diagram	139
Figure 4: Ammended process diagram	140
Figure 5: R1 scores for those responding and not responding in R2 by stakeholder speciality .	173
Figure 6: Change in scores between R1 and R2	173
Figure 7: Process for proposed trial	298

List of Abbreviations

A&E	Accident and emergency
AB	Antibiotic
BNF	British National Formulary
BNFC	British National Formulary for Children
CC	Complex case
CLRN	Comprehensive Local Research Network
CRN	Comprehensive Research Network
CRP	C-Reactive Protein
CT	Computed Tomography

CVL	Central venous line
ESR	Erythrocyte Sedimentation Rate
for	Forward primer
GAS	Group A streptococcus
GBS	Group B streptococcus
GP	General practitioner
H. inf	<i>Haemophilus influenzae</i>
Hb	Haemoglobin
HF	Higher Formulary
HTA	Health Technology Assessment
IQR	Interquartile range
IV	Intravenous
K.k	<i>Kingella kingae</i>
lytA	N-acetylmuramoyl-l-alanine amidase
MALDI-TOF	Matrix assisted laser desorption/ionisation time of flight
MCRN	Medicines for Children Research Network
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
N	Neutrophils (or if a statistic then Number)
NHF	Not Higher Formulary
NHS	National Health Service
OAI	Osteoarticular infection
OM	Acute Osteomyelitis
OPAT	Outpatient parenteral antibiotic therapy
PCR	Polymerase chain reaction
PICC	Peripherally-inserted central catheter
PICU	Paediatric intensive care unit
PID	Paediatric infectious disease
Plt	Platelets
ply	Pneumolysin
PVL	Panton-Valentine Leukocidin
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
rev	Reverse primer
RN	Research Nurse
RT-PCR	Reverse transcription polymerase chain reaction
St. epi.	<i>Staphylococcus epidermidis</i>
St.a.	<i>Staphylococcus aureus</i>
S.pn	<i>Streptococcus pneumoniae</i>
SA	Septic Arthritis
Sal. Spp.	Salmonella species
SC	Simple case
STGG	Skim milk, tryptone, glucose, and glycerin
UKCRC	UK Clinical Research Collaboration

UKNCC	United Kingdom National Culture Collection
URTI	Upper respiratory tract infection
UTI	Urinary Tract Infection
WBC	White blood cell count

Plain English Summary (333 words)

Children's bone and joint infections are treated with intravenous and then switched to oral antibiotics. Historically, long courses of intravenous antibiotics were thought to be needed which often involves a long hospital stay. At present there is no consensus regarding how long to treat these infections for overall, or for how long to use each of intravenous or oral antibiotics. This study used a combination of methods to assess whether a clinical trial to reduce intravenous antibiotics in children will be feasible in the UK.

Data was collected from 44 UK centres to find out the current bacterial causes and clinical practice of children's bone and joint infections. A qualitative study explored families views and experiences of having had a child treated for bone or joint infection. A consensus meeting was informed by information from the clinical data collection, web-based clinician survey and qualitative study to establish the final set of outcomes, oral switch criteria and overall future trial feasibility.

We found that clinicians have already implemented early oral switch for selected patients with simple disease without formal clinical trial evidence of safety. This has important implications both for current practice and for the feasibility of different potential trial designs. We also found that a future randomised controlled trial of shorter or longer courses of intravenous antibiotics would be feasible by including only children who need more than a minimum of 7 days intravenous antibiotic before switching to oral medicine.

Scientific Summary (2055 words)

Background and aims:

Acute bacterial osteomyelitis (OM) and septic arthritis (SA) in children cause significant morbidity and use of health care resources. Limited data on disease spectrum and case load are available, and there is currently little international or UK consensus regarding the route or duration of antibiotic treatment for acute OM/SA in children.

This study comprised 4 components to assess the feasibility and inform the potential design of a Randomised Controlled Trial (RCT) to determine the safety of early oral switch from IV to oral antibiotic therapy we aimed;

- a) to understand the current case load, disease spectrum & clinical practice in the diagnosis and treatment of OM/SA in secondary and tertiary UK care by conducting a service evaluation of OM/SA in children 1 month (the lower limit of the clindamycin licence) to 16 years.
- b) to assess whether a new molecular test is an appropriate tool to assess the molecular epidemiology of children's bone and joint infections by conducting a substudy at six of the service evaluation centres.
- c) to understand parents and children's views and experiences of bone and joint infection and gather their views and perceptions of both participating in a clinical trial and potential trial outcomes by conducting a qualitative study.
- d) to develop a core outcome set for use in a future RCT using a systematic literature review of previously used clinical trial outcomes in children's bone and joint infections, a web-based clinician survey and results of the qualitative study to inform a stakeholder consensus meeting.

Methods:

Service evaluation

Clinical data from all paediatric patients presenting at 44 UK centres with presumed OM/SA was collected via electronic web-based database for a 6 month period at each centre, with 3 month clinical follow-up. Briefly, simple cases were defined as first

presentation of OM/SA with no co-morbidities. Complex cases had resistant or virulent organism (retrospectively allocated) infection of implant, or co-morbidity.

Microbiology sub-study

In six of the participating centres children were recruited for a molecular microbiology sub-study. After informed consent, routinely collected blood and tissue samples were transported to the central laboratory (Southampton Public Health England South East Regional Laboratory) for PCR analysis after being processed locally. Results were compared with clinical data collected as part of the service evaluation.

Qualitative interviews with families and children

Semi-structured interviews were employed to explore the views and experiences of parents and children treated for bone and joint infections within the previous year. Topics included in the interviews covered: a) experiences of becoming ill and diagnosis, b) understandings and perceptions about aspects of antibiotic therapy, c) understandings and perceptions about aspects of antibiotic therapy and d) views about participation in a hypothetical future RCT. Thematic analysis was used.

Development of a core outcome set

A systematic literature review, two rounds of Delphi clinician survey and a consensus meeting informed by the qualitative interviews with families and children were used to develop a core outcome set to use in a future RCT of shortened duration of antibiotic therapy for paediatric bone and joint infections; to identify the oral switch criteria for use in a future randomised controlled trial; and to make an overall assessment of the feasibility of a future RCT.

Results

Service evaluation

Data from 356 children were recorded, of which 313 were confirmed as OM or SA, or both OM and SA. 54% (of 313) cases were male, median age was 3.4 years (IQR 1.4, 9). 218 (61.2%) were simple, 95 (26.7%) complex. The most likely joints/limbs affected in simple disease were the hip (21.1%); the knee (24.8%); and the ankle (13.3%). Complex

cases showed similar proportions of joints/bones affected (23.2%, 20% and 17.9% respectively) though often with multiple rather than single joint/bone infections.

At presentation, CRP was higher in complex disease than simple cases (simple cases median 32, IQR (11.8, 66.7), complex cases median 54, IQR (24,141)). Total white cell/neutrophil count and ESR were used less in confirming SA or OM. Overall, a radiological diagnosis was obtained for 51.8% of simple cases (at a median of 1 day post presentation (IQR 0, 3)), and 52.6% of complex cases (median of 1 day post presentation (IQR 0, 4)). Diagnostic surgery was more common in SA than OM prior to IV antibiotics (for SA, 39 of 107 (36.4%) of simple and 15 of 35 (42.9%) complex cases; for OM, 21 of 109 (19.3%) of simple and 14 of 56 (25%) complex cases). 144 out of 218 (66.1%) children with simple OM or SA, and 59 out of 95 (62.1%) with complex OM or SA, had at least one test from either blood culture or tissue diagnosis (bone, joint aspirate or periosteal pus)

Of 103 simple SA, median total length of antibiotic course (IV and oral) was 30 days (IQR 18.41) of which median 7 days (4, 13) were IV. Of 105 simple OM treated with antibiotics, the median total course length was 40 days (IQR 21,48) of which median 9 days (6,16) were IV. The most commonly used IV antibiotics were flucloxacillin and ceftriaxone. 27% of simple cases and 42% of complex cases were discharged home on IV antibiotics. Overall, 40.4% simple cases received a higher formulary initial dose of antibiotics, compared with 29.5% of complex cases. Only 30 (13.8%) of simple cases and 9 (9.5%) of complex cases received the higher formulary dose of antibiotic treatment throughout. Overall, simple OM and SA combined had a median length of hospital stay of 7 days (IQR 4, 12), with 50% of children staying for 6 days or longer but no longer than 12 days. Of 73 initially defined simple cases that had very early oral switch (<1 week IV antibiotic), 9.6% experienced a defined treatment failure, compared with 16.1% that had switch between 1 and 2 weeks and 18.2% where switch was >2 weeks.

Microbiology sub-study

A total of 151 samples were received from 50 patients. Of these 113 (of 151) were bone, fluid and blood culture samples which were collected from 44 (of 50) patients across six geographical sites. The remaining 38 (of 151) samples were from throat and wound

swabs. For 5 (of 50) patients only throat swab samples were obtained and for 1 (of 50) only a skin swab sample was obtained.

Overall, excluding any data from skin or throat swabs, 32/44 patients (72.7 %) were PCR positive for one or more of the target organisms included in the RT-PCR panel. In 24 of 32 simple cases (75%) and 8 of 12 complex cases (67%) in whom the test was used a pathogen was detected.

Using PCR *Staphylococcus aureus* is the commonest detected pathogen (16 cases). *K. kingae* (7 cases) and *Group A streptococcus* (4 cases) were also common causes of OM/SA.

Qualitative interviews with families and children

Twenty six families were recruited to the qualitative study and interviewed. One of the most striking issues to emerge during the course of interviews was the length of time reported to have elapsed between children first presenting with symptoms, and a diagnosis being given/treatment starting. Participants understood the need for the use of IV antibiotics, and identified the positive benefits of making them/their child better in the fastest, most effective way possible. Parents expressed enthusiasm about participation in a theoretical trial, although the concerns of those potentially unwilling or not sure reflected anxiety about reduced courses of treatment or that rigid trial protocols might put their own child at risk. Key, or ‘pinch’ points of anxiety for parents included: lead up to diagnosis (especially in case of delays); occasions during which child experienced distress (for example during insertion of cannula); fears about child receiving a general anaesthetic; and some follow up anxiety around potential for future impacts, or re-occurrence of infection.

Development of a core outcome set for use in clinical trials and potential oral switch criteria for use in a clinical trial.

A systematic review identified 10 relevant papers to inform potential clinical trial outcomes. The key outcomes were combined and summarised and discussed with a study clinical co-investigators, who also had the opportunity to review the papers and consensus was gained that all of the available outcomes had been extracted. In two rounds of Delphi process 37 general paediatricians, 38 paediatric orthopaedic specialists, 34 paediatric infection specialists, 4 paediatric microbiologists and 13 paediatric

radiologists took part. The results of the service evaluation and the Delphi process were presented in a consensus meeting. The oral switch criteria and outcomes reported are a product of clinician and researcher choices during the Delphi and consensus meeting, informed by the qualitative findings.

Outcomes reaching consensus included: re-hospitalisation or recurrence of symptoms while on oral antibiotics, treatment failure- recurrence of infection, disability at follow-up, being symptom free at 1 year, limb shortening or deformity, chronic osteomyelitis or chronic arthritis, amputation or fasciotomy, death, need for paediatric intensive care and line infection.

Oral switch criteria considered important by consensus following the meeting voting were: resolution of fever for 48 hours or more, tolerating oral input (medicines and food/drink) and pain improvement (rather than resolution). While there was much variability in the Delphi survey and consensus meeting regarding what the CRP criteria should be, there was agreement that CRP is an important parameter in around 60% of respondents in both round 1 and round 2 of the Delphi survey, and by approximately 70% of those at the consensus meeting.

Discussion:

A core outcome set for future clinical trials in paediatric bone and joint infections was established by Delphi survey and consensus meeting. The same process established agreement on the criteria needing to be met for oral switch from intravenous therapy in any clinical trial.

A service evaluation, qualitative study and consensus meeting discussion provided information to inform the feasibility of a RCT, and of potential RCT designs.

1. An RCT of very early oral switch to intravenous antibiotics would be supported by the service evaluation data and was supported by the clinicians at the consensus meeting. However, the qualitative study suggested that parents might have considerable concerns regarding participation if asked to consent to early oral switch before what would currently be considered standard of care. In addition, the strict oral switch criteria identified, together with low numbers of cases of simple OM and SA likely to meet switch criteria in the first week of intravenous treatment, means such a study would not be likely to be feasible in a single country (UK) trial.

2. An RCT of reduced total length therapy after clinician directed oral switch (based on the criteria determined in this study) would be feasible but was not the first choice study of the consensus meeting participants. It would be possible to explain the study to parents and children, and feasible to recruit in terms of numbers of cases and clinician willingness. It is unlikely that such a study design would make an enormous impact on the overall cost to the NHS of treating bone and joint infections in children or on the overall antibiotic burden of children in the community.

3. An RCT in simple OM and SA comparing shorter or longer course IV therapy, with no reduction in total (intravenous and oral course combined) antibiotic therapy, would be feasible where children are included and randomised only if oral switch criteria are met after 7 days of intravenous therapy. Children would be excluded from the trial if they met the criteria for oral switch in the first week of intravenous therapy as the service evaluation suggests this group have less treatment failure than those having later oral switch. This study design meets clinician preference and addresses parental concerns not to randomise prior to currently-used oral switch criteria. It would also provide important information on whether intravenous therapy can be reduced without increasing treatment failure compared to longer course intravenous therapy, or whether outcomes are worse in those treated with more intravenous antibiotics due to treatment failures being caused by the treatment modality itself.

Regardless of RCT design, the qualitative study has demonstrated remaining gaps in understanding of parental and family decisions to participate in clinical trials that could be explored prospectively alongside any future trial.

Conclusion:

The epidemiology of paediatric OM/SA in this study was consistent with existing European data. Species-specific PCR provides important additional information compared to using culture-based microbiology methods alone. Clinicians have implemented early oral switch for selected patients with simple disease without formal clinical trial evidence of safety. However, the criteria by which decisions to make the oral switch are made are not clearly established or evidence based.

This study established a potentially feasible design for reduction of intravenous antibiotic course in a group of children with simple OM or SA. Agreement was reached

regarding a core outcome set for use in a future RCT and for oral switch criteria for use in a clinical trial.

Chapter 1: Introduction

“The text that follows “until operative procedures required as well as formal assessment of growth and function” on page 23. was written for the HTA application but was published separately as <http://adc.bmj.com/content/97/6/545>. INSERT STATEMENT RE PERMISSIONS IF NEEDED”

Osteomyelitis and Septic Arthritis in Children

Osteomyelitis (OM) is inflammation of the bone accompanied by bone destruction,¹ usually due to bacterial infection. It is an acute process but if not treated effectively, the inflammation can become chronic, leading to the development of sequestrae and fistulae.² Osteomyelitis and septic arthritis can both be divided into three types according to the source of the infection: haematogenous, secondary to contiguous infection and secondary to direct inoculation. Haematogenous OM can present acutely or as a more indolent, progressive process subacutely, with symptoms present for more than 2 weeks.³ In children osteomyelitis most often affects long bones (femur 36%, tibia 33%, humerus 10%, pelvis 2.8%).⁴ Single site infection is most common, but 5-20% of children have multifocal osteomyelitis.⁵ Septic arthritis (SA) is acute infection of synovial joints,^{6,7} usually secondary to bacteraemia. The infection affects the synovial membrane and the joint space. In younger children, the capsule of the joint often extends to the metaphysis, which when the cortex is damaged can lead to septic arthritis secondary to osteomyelitis and vice versa. The epiphyseal growth plate can also be affected, causing growth discrepancies and long term disability or permanent joint destruction if the acute infection is not treated promptly.²

The estimated incidence for both OM and SA arthritis in Western populations is between 5 to 12 cases per 100,000 children per year.² Half of the children with acute haematogenous osteomyelitis are under the age of 5.^{2,7} Boys are 1.2-3.7 times more likely to be affected by osteoarticular infection (OAI) than girls.² The incidence in Southampton from 1979-1997 was between 1.4 to 10.5 cases per 100,000 per year⁸ and in Newcastle from 1991 to 1999 was 7 per 100, 000 for SA and 11 per 100, 000 for OM (unpublished data). Recent unpublished national data from England shows the admission rate for osteomyelitis in children 0-18 year of age has varied between 4.8 and 7.0 per 100,000 child years (M. Sharland, personal communication). Subacute OM appears to be increasing over recent years,⁹ reported to be found in 5 per 100, 000 children in Norway.¹⁰ Neonatal infection can occur in preterm or term babies and is associated with a wider range of causative organisms (Table 1)¹¹ and potential complications. Neonatal

vascular anatomy allows infection within bone to reach the growth plate or joint in 76%.

12

The pathogens implicated in paediatric bone and joint infections:

commonly include methicillin-sensitive *Staphylococcus aureus* (MSSA) (44-80%) ^{7, 13, 14} and *Kingella kingae* (14-50% (increased <36 months)). ^{7, 14-18;}

rarely include methicillin-resistant *S. aureus* (MRSA) (40-50% in USA, rare in UK), ^{19, 20} Panton-Valentine Leukocidin (PVL) MSSA, ^{21, 22} Group A streptococci (GAS), Group B streptococci (GBS) (neonates), ^{11, 23} Non-typeable *Haemophilus* spp. (incidence unknown), *Haemophilus influenzae* type b (non-immunised or immunodeficient), *Escherichia coli* (neonates), ^{11, 23} *Streptococcus pneumoniae*, ²⁴ Coagulase negative staphylococcus (subacute);

and **very rarely (most in immunocompromised individuals) include** *Pseudomonas aeruginosa* (usually inoculation injuries therefore > 1 year old), *Neisseria gonorrhoeae*, *Neisseria meningitidis* (neonate, adolescent), *Mycobacterium tuberculosis* (older children as OAI develops 2 years from primary infection), *Salmonella* spp. (sickle cell disease), ²⁵ *Bartonella henselae*, *Neisseria gonorrhoeae*, *Non tuberculous mycobacteria* (associated with defects of the interferon gamma (IFNg/IL12) pathway), *Klebsiella* spp, *Bartonella henselae*, *Fusobacterium* (often multifocal), *Aspergillus* and *Candida albicans* (neonate, damaged bone).

The pathogens most frequently seen according to age are:

Neonate:	GBS, MSSA, <i>Escherichia coli</i> and other gram negatives, <i>Candida albicans</i>
< 2 years:	MSSA, <i>Kingella kingae</i> , <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> type b, Non-typeable <i>Haemophilus</i> spp., <i>E. coli</i> , MSSA PVL
2-5 years	MSSA, <i>Kingella kingae</i> , GAS, <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> type b, Non-typeable <i>Haemophilus</i> spp., <i>Pseudomonas</i> spp., Coagulase negative staphylococcus (subacute), MSSA PVL
> 5 years	MSSA, MSSA PVL

Clinical features

The clinical features of OM and SA are dependent on age, site of infection and type of disease. The diagnosis and management of osteoarticular infection in children should ideally be multidisciplinary, including paediatricians and orthopaedic surgeons with radiologists and microbiologists. The diagnosis of OM or SA is made on the basis of the clinical presentation, laboratory tests, imaging and where available microbiology results.

26

White Blood Cell Count, CRP and ESR

The white blood cell count (WBC) is an unreliable indicator of an osteoarticular infection (OAI) as in many cases it remains normal throughout the infection.²⁷ The inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are more reliable, although normal values also do not exclude osteomyelitis.²⁸ CRP levels are most sensitive (elevated in up to 98% of cases)^{6,7} but not specific for bone or joint infection. Two studies have shown that CRP increased and also decreased faster than ESR, predicting recovery with more sensitivity than the ESR or the white cell count.^{28,29} Differences in the causative organism may also cause differences in the acute phase markers. Patients with osteomyelitis caused by PVL-expressing *Staphylococcus aureus* isolates had significantly higher mean values for ESR at admission, and higher maximum CRP, ESR and absolute neutrophil counts at presentation compared with patients whose isolates were PVL negative.²² Other markers remain unproven. In a small study, procalcitonin has not shown benefit over CRP.³⁰

Imaging

Imaging is of great importance in the diagnosis of acute osteomyelitis.

Where available, Magnetic Resonance Imaging (MRI) with enhancement show the best results regarding sensitivity and specificity of diagnosis of both OM and SA (sensitivity 97% and specificity 92%,^{31,32} sensitivity 97-100% in OM).⁶ However, as young children often require an anaesthetic to undergo an MRI scan, and MRI is not immediately available in all UK centres, MRI is not widely used in the UK in the initial diagnosis.

Technetium radionuclide bone scan (^{99m}Tc) also has high sensitivity and specificity in the diagnosis of OM,³³ but due to the radiation burden is now used less often except in

difficult cases and is not useful in discitis. In SA, bone scan may be used to exclude underlying OM following aspiration and commencement of empirical therapy. Bone scan is especially useful where there is a suspicion of multifocal disease, but may give false negative results in infancy, and sensitivity is reduced for the first 48 hours. New nuclear medicine technologies are available in some centres to combine computed tomography (CT) with low dose radioactive substance, SPECT CT, which may be useful in increasing the resolution of nuclear medical images.³⁴

Plain radiographs are less helpful compared with other imaging techniques as osteolytic changes or periosteal elevation occur most often 10 to 21 days after the onset of symptoms.^{1, 7, 35} However, once apparent, the extent of bony change provides a good correlate to the severity of the disease. Plain radiographs also provide a baseline for comparison of subsequent change. Radiographic changes are frequently seen in subacute OM, but can be confused with malignancies such as Ewings sarcoma or osteiod osteoma.¹² In SA, plain radiographs are of limited use. In discitis, lateral radiographs of the spine 2-3 weeks into the illness often will reveal disc space narrowing with erosion of the vertebral end plates of the contiguous vertebrae. In vertebral OM, radiographs initially show localised rarefaction of a single vertebral body then anterior bone destruction.

Ultrasound is useful in SA for identifying the presence of deep effusions and in OM for subperiosteal collections, but cannot differentiate between purulent and non-purulent material.^{6, 36} Ultrasound may also be used to distinguish infection from other causes of similar symptoms or to direct fine needle aspiration.³⁷

Computed tomography (CT) is most valuable for guided procedures, such as aspiration or drainage of the infected bone or joint.³⁸ It effectively demonstrates air, sequestra and cortical destruction in chronic OM,³⁶ but gives non-specific results in discitis.

Microbiological investigation

Identification of the pathogenic organism by culture should be attempted with samples preferably taken prior to starting antibiotic therapy, as where positive it allows targeted antibiotic therapy. Blood cultures, joint fluid (from aspiration), periosteal pus or bone biopsy can all be used. Samples from the infected bone or joint require an invasive procedure but are more likely to be positive (40-50% positive) than blood cultures (9-

22% positive).^{14, 27} Yield is generally not high for identification of a bacteria in children with OM,²⁷ as unless therapeutic operative intervention is required, bone biopsy is infrequently necessary for diagnostic reasons alone.

New molecular techniques including polymerase chain reaction (PCR) and broad-range 16s rDNA PCR^{39, 40} have established the basis for more rapid and sensitive microbiological diagnosis,¹⁷ although these methods currently do not provide information on specific organism antibiotic resistance profiles.

Blood cultures (minimum 4 ml aerobic culture sample in older children, 2 ml in specific neonatal aerobic bottle)⁴¹ should therefore be taken, and where available samples from infected bone or joint placed in a sterile universal container and sent for culture and sensitivity testing. Older reports suggesting an increase in *K. kingae* recovery is gained from inoculating synovial fluid or bony exudates directly into blood-culture bottles have not been replicated in UK practice.¹⁶ *K. kingae* is detectable using new PCR techniques from cultures where conventional direct plating of specimens on solid media has been used.^{17, 18}

Surgical management

There is little current high quality evidence on which to base current surgical practice.

Osteomyelitis

Surgical drainage in acute OM is indicated if the patient is not responding to antibiotics after 48-72 hours (although this may be due to resistance) or if there is radiological evidence of a substantial pus collection.⁶ Best practice is to immobilise any surgically treated limb or focus of infection. Occasionally, where a soft tissue or sub-periosteal collection is clearly demonstrated by ultrasound or MRI, needle aspiration can be performed prior to starting intravenous antibiotics. When performed, the procedure should be carried out under sterile conditions. If there is bony destruction or pus aspirated, surgical debridement is usually required. With only early radiographic signs conservative intravenous antibiotic therapy may suffice.

Historically, the role of surgery is poorly defined. Cole⁴² identified three groups of patients: in the group of patients older than one year but who presented within 48 hours, antibiotic therapy alone was sufficient. In a group aged more than one year, five days after the onset of illness, patients usually required surgery and possibly multiple

procedures. In infants less than one year, in whom the exact diagnosis was difficult to make, a single operation and antibiotic therapy usually sufficed. In current practice, the relative roles of bacterial virulence and host age and immunity are unclear. More invasive surgery appears more common when bacteria have specific virulence genes, for example PVL.²¹ While most children recover rapidly with simple medical management, others require repeated debridement.

Septic Arthritis

In SA, prompt drainage and washout of the affected joint (either arthroscopic or open) is advocated by some for both diagnostic and therapeutic purposes as the articular cartilage is damaged early.⁶ The role of surgery in the treatment of septic arthritis is in fact poorly defined except in relation to the hip, where prompt surgical drainage is absolutely necessary. Open capsulotomy to allow continuing drainage of septic material is advocated, and if the arthrotomy does not provide turbid material drilling the femoral neck may decompress a proximal femoral osteomyelitis. The anterior approach is preferred as this also allows open reduction of any displacement of the femoral head.

The indications for surgical drainage of septic joints other than the hip remain controversial. Where there is a large effusion, drainage is usually advocated although in some joints arthroscopic irrigation may be appropriate, such as the knee or ankle. However, with arthroscopic treatment joint visualisation is less complete. Overall, for joints other than the hip, aspiration, irrigation and intravenous (IV) antibiotic therapy is the preferred first line of treatment. If the patient fails to respond then the joint should be surgically drained, usually by formal open arthrotomy rather than arthroscopic drainage.

Medical Management and Antibiotics

Current evidence for how to initiate treatment

Intravenous antibiotics are started empirically as soon as the clinical diagnosis of acute OM or SA is made, as delaying therapy until the bacterium is identified increases the risk of complications. In septic arthritis, where urgent surgery is indicated, a widespread pragmatic approach has been to start antibiotics following surgery unless it will take longer than 4 hours to get to theatre. As soon as organisms are isolated, antimicrobial treatment should be adjusted and optimised. In subacute OM with no systemic reaction, oral antibiotics can be used from the start.

Although there has not been a definitive randomised controlled trial, a number of observational and retrospective studies in the literature show several different antibiotic regimes have been effective in treating acute haematogenous osteomyelitis in children, including the use of beta-lactam and macrolide antibiotics.⁸

The initial antibiotics should always include potent cover against MSSA and GAS, and in younger children against *Kingella kingae*, although the choice will vary according to the age of the child, route of infection and local resistance patterns.⁷ Recent data from the US suggests increases in resistant *S. aureus* (MRSA) but these data have not been replicated in UK cohorts.⁴³ Activity against *H. influenzae* type b is essential in children who have not been fully immunised against it.

Switch to oral antibiotics and total duration of treatment

Currently there is no international and little UK consensus regarding the route or duration for antibiotic treatment of acute OAI in children.

a) Oral switch

Sequential intravenous and oral therapy has become usual as it is less inconvenient and painful for the patient, has fewer complications and is cheaper than longer courses of intravenous therapy alone.^{2, 6, 7} There is no current evidence to aid the clinical decision of when to switch from intravenous to oral therapy, which is widely accepted and usually occurs when the patient has shown a marked clinical improvement.⁸ A Canadian systematic review of short (≤ 7 days) versus long course (> 7 days) parenteral antibiotic treatment for acute haematogenous OM in children due primarily to *Staphylococcus aureus* showed no difference in the overall cure rate after 6 months between short course and long course parenteral antibiotic therapy.⁴⁴ A recent retrospective cohort study of 1969 children in the USA found that early switch to oral therapy (median 4 days) was as effective as prolonged intravenous treatment,⁴⁵ a finding also suggested in a smaller retrospective study of 186 children with septic arthritis.⁴⁶ The laboratory or clinical parameters that would determine the decision to switch to oral therapy remain undefined.

Most clinicians continue intravenous antibiotics until the child shows clinical improvement, is afebrile and oral fluids and medication could be established. Additionally, observing a decrease in inflammatory markers such as WBC, CRP and

ESR is thought to be of value.² Studies have shown that serum CRP level decreased more rapidly than ESR in children recovering from acute osteomyelitis, and that children with a raised CRP level were more likely to have symptoms or extensive radiographic abnormalities.^{28, 47, 48} A recent Finnish clinical trial showed apparently good long term results and apparently no failure rates using CRP as the biological marker of infection.^{47, 49}

Failure to improve necessitates repeat blood culture, additional imaging for metastatic infection, assessment for deep vein thrombosis, and consideration of unusual pathogens such as PVL *Staphylococcus aureus* or fusobacterium.

No UK consensus currently exists to guide the criteria for oral switch for use in clinical practice or a clinical trial, which will be determined as part of this feasibility study.

b) Total duration of antibiotic therapy

The suggested duration for parenteral antibiotic treatment ranges from 3 days up to 6 weeks, resulting from several, mainly observational studies with relatively poor level of evidence.^{8, 50} In the past, the overall duration of antibiotic treatment has been considered an important factor to improve outcome and reduce relapse. Several paediatric textbooks recommend at least 4 to 6 weeks of treatment.^{2, 51}

Although there are encouraging data from a recent clinical trial in Finland^{47, 49} and from other review papers and case series, no recent formal randomized controlled trial has been conducted to show good evidence for shorter courses of parenteral antibiotic treatment. There are a number of reasons why the recent Finnish data may not be directly applicable to practice in the United Kingdom or other countries.⁵² Some historical observational studies showed an association between short duration of antibiotic therapy and 15-19% poor outcome or relapse with courses of 3 weeks or less.

53-55

Currently there is no consensus about the route or duration for antibiotic treatment of acute osteomyelitis in children.

c) Oral antibiotic choice and dose

Many different regimens are used as oral therapy following switch from oral antibiotics, including co-amoxiclav, flucloxacillin and clindamycin. Although flucloxacillin and

clindamycin have good oral bioavailability and excellent tissue penetration, both drugs have to be given orally 4 times per day and both have poor taste and therefore poor drug adherence of the suspension in small children.⁵⁶ Although clindamycin rarely leads to *Clostridium difficile* disease in children, there is no current evidence or consensus regarding oral antibiotic choice that will be acceptable to children and parents both in terms of palatability and dose frequency.

d) Continuation of intravenous antibiotics for more than 2 weeks

Complex disease requiring continuing intravenous therapy poses problems of vascular access, hospitalisation and schooling. Most children will require central or peripherally-inserted central venous long line (Central venous line (CVL) or peripherally-inserted central catheter (PICC)) insertion for long term antibiotic treatment. Delivery of subsequent care is either in hospital, or at home dependent on local services and the ability to provide outpatient parenteral antibiotic therapy (OPAT), although OPAT services for children are not yet well developed in the UK. Central venous lines or peripherally-inserted central catheters and OPAT has attendant risks, with 3-11% CVL associated infection noted in the USA.^{57, 58}

e) Additional or 2nd line antibiotics for complex disease or where resistant pathogens are identified

Where cases are complex, additional antibiotics may be advised by local microbiologists, clinical infectious diseases specialists or national guidelines, for example PVL positive *S. aureus* infection.⁵⁹

Complications

Deep venous thrombosis and thromboembolism have been seen in up to 30% children with OM and is associated with a higher risk of disseminated infection.⁶⁰ In addition, joint stiffness, limb shortening, dislocation (acutely neonates) and avascular necrosis of affected epiphysis may occur.

Routine follow-up allows most children with simple disease to be discharged without the need for long term care or further assessment of growth or function.

In the context of clinical audit or clinical trials, outcome measures may include length of stay in hospital, total length of therapy, operative procedures required as well as formal assessment of growth and function.

Currently accepted clinical equipoise

At this time, all clinical co-investigators have agreed in writing that they agree there “is no international & little UK consensus regarding the route or duration for antibiotic treatment of acute bone and joint infections in children, and that there is also no clear evidence to aid the clinical decision of when to switch from intravenous to oral therapy”.

Commissioning brief and objectives

HTA provided background to commissioning brief:

“Usually treatment with an IV antibiotic is started as soon as possible. This may be continued for several weeks, with comorbidity caused by the need for prolonged IV access.

Empirically 3 – 6 weeks has been the usual regimen but there is little hard data upon which to base this opinion. Evidence is lacking for shorter duration IV antibiotics, but this could avoid the adverse events associated with protracted intravenous therapy, and still be an effective strategy to adopt in children.

In children with acute osteomyelitis or septic arthritis, can antibiotics be switched to the oral route after a short IV course to reduce the need for prolonged IV access”

The Health Technology Assessment (HTA) brief was to assess the feasibility of performing a hospital based trial of short duration (3-5 days) intravenous antibiotic therapy followed by oral therapy for the usually recommended duration compared to a minimum of 14 days intravenous therapy prior to oral switch in children who have a clinical diagnosis of acute osteomyelitis or septic arthritis (these two diagnostic groups should be considered separately) after any primary diagnostic or therapeutic surgical procedure. The feasibility study was required to identify appropriate non-inferiority margin and microbiological outcomes through surveys of different communities, and to assess if data will allow for sub group analysis by culture status. The expectation was not

for children to be actively recruited at this stage but for researchers to identify willingness of clinicians and families to participate.

Research Objectives

In order to assess the feasibility and inform the potential design of a Randomised Controlled Trial (RCT) to determine the safety of early oral switch from IV to oral antibiotic therapy we aimed to :

- a) to understand the current case load, disease spectrum & clinical practice in the diagnosis & treatment of OM/SA in secondary & tertiary UK care by conducting a service evaluation of OM/SA in children 1 month (the lower limit of the clindamycin licence) to 16 years.
- b) to assess whether a new molecular test is an appropriate tool to assess the molecular epidemiology of children's bone and joint infections by conducting a substudy at six of the service evaluation centres.
- c) to understand parents and children's views and experiences of bone and joint infection and gather their views and perceptions of both participating in a clinical trial and potential trial outcomes by conducting a qualitative study.
- d) to develop a core outcome set for use in a future RCT using a systematic literature review of previously used clinical trial outcomes in children's bone and joint infections, a web-based clinician survey and results of the qualitative study to inform a stakeholder consensus meeting.

Patient and Public Involvement in this project.

PPI involvement was integrated into the design of this project via NIHR Medicines for Children Network PPI representation in the study initiation (via involvement in the NIHR MCRN Allergy, Immunology and Infectious Diseases Clinical Studies Group). The PPI representative reviewed the study protocols and all patient and parent facing materials, and reviewed the qualitative study protocol and study guide in detail. In addition, there was PPI representation on the study steering committee, and consumer involvement at the study consensus meeting (PPI representative and member of NIHR CRN: Paediatric Theme London Young Persons Advisory Group).

Chapter 2: Service Evaluation

Aims and objectives

We aimed to conduct a service evaluation captured via electronic web-based database to record **every case of paediatric bone and joint infection** in a 6 month period in participating centres, with 3 month clinical follow-up. The research objective was to define the current case load, disease spectrum & clinical practice in the diagnosis & treatment of OM/SA in secondary & tertiary UK care.

Methods

a) Service evaluation case record forms.

A co-investigator meeting in November 2012 discussed the key items to include and exclude in the service evaluation, which were then further refined and discussed by the study team and investigators. These included demographic details and details of hospitalisation(s) including transfers between hospitals; type and site of disease; routine haematology, biochemistry and microbiology; radiological procedures; surgical procedures; length of IV therapy; antimicrobials used, route and duration; reason/criteria; used for oral switch (if any); and clinical outcomes at 3 months. As per our application we did not identify 3+ month adverse outcomes eg physical injury which will be evaluated in a later RCT. The case record forms and service evaluation protocol are included in *Appendix 1*.

b) Ethics approval was not required.

We confirmed with the NHS research ethics committee that formal Research Ethics Committee (REC) approval was not required for the service evaluation data collection, in line with the House of Lords Select Committee report on 'Fighting infection', ⁶¹ which recommended making infection surveillance a clear evidence based priority, establishment of collaboration between scientists (microbiologists), clinicians and epidemiologists, and encouragement of the use of electronic capture, and dissemination of information about infection.

c) Electronic records

A bespoke web based data entry system was developed by the Medicines for Children Clinical Trials Unit (MC CTU), a division of the Clinical Trials Research Centre, a UK Clinical Research Collaboration (UKCRC) fully registered CTU. The system, which

stored and managed the data was used as part of a national service evaluation. Data was collected using a custom web based data entry system written in c# .Net, using JQuery. The data collection system allowed data to be validated on input, providing help/additional information as required for questions and allow for the hiding of questions that did not need to be answered by the clinician..

d) Study sites

We recruited NHS Tertiary and Secondary care centres to participate in the service evaluation. Sites nominated a local principle investigator (paediatric infectious diseases, general paediatrics or paediatric orthopaedics) and achieved the support of local leads for all clinical stakeholders (paediatric medicine, orthopaedics, microbiology and radiology). All had the support of NIHR-funded research nurses (NIHR MCRN local research networks, paediatric clinical research facility or nurses funded by the local NIHR Comprehensive Local Research Network (CLRN) from April 2014 the NIHR Comprehensive Research Network, CRN).

d) Statistical analysis

A formal descriptive statistical analysis plan (SAP v1.6, November 2014, see *Appendix 7*) was developed and used to analyse the data. There were some major additions: notably that statistics have been generated for complex cases; that many statistics have been further split by diagnosis category (SA or OM); and some additional analyses have also been carried out (see *Appendix 8*).

e) Important definitions appearing in service evaluation tables

OM	Acute Osteomyelitis
SA	Septic Arthritis
IV	Intra-venous
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
Hb	Haemoglobin
Plt	Platelets
WBC	White blood-cell count
N	Neutrophils (or if a statistic then Number)

PICC	Peripherally inserted central catheter
SC	Simple case
CC	Complex case

Simple cases (SC)

Children presenting with SA or OM for the first time, and with no chronic comorbidities. Specifically:

- No orthopaedic surgery 6 months prior to presentation on same limb/joint
- No chronic co-morbidities (sickle cell disease, known immunocompromise, indwelling central venous catheter or PICC, cystic fibrosis, or cerebral palsy).

Complex cases (CC)

Children presenting with SA or OM who:

- (1) Have had any orthopaedic surgery in 6 months prior to presentation on same limb/joint; OR
- (2) Have chronic comorbidities: Sickle cell disease, known immunocompromise, indwelling central venous catheter or PICC, cystic fibrosis, or cerebral palsy); OR
- (3) Are presenting because of an infected implant from previous orthopaedic surgery.

Misdiagnosed

Some children captured by the database were treated for SA/OM but were later found to have a different diagnosis.

Other

Some children had discitis. This is a form of SA but is treated differently, and so is not of interest to this study.

Results

Sample descriptives

Participating centres

51 centres (49 hospital trusts) took part in the study. 18 of these were classed as Tertiary centres, and 33 as Secondary centres.

Together centres provided data for 356 children. In addition to these, 3 children were withdrawn as consent was withdrawn; and 5 excluded from analysis on the basis of a major lack of data. One tertiary centre (Chelsea and Westminster) and six secondary centres did not record any cases. For one of the secondary centres this was because the centre withdrew from the study.

Tertiary centres contributed 68% of the 356 cases (66% of all 218 simple cases). There was wide variation in the proportion of cases presenting with symptoms of OM/SA that were complex. In tertiary centres this varied from 0% up to 75% (*Table 1*), and in secondary centres from 0% to 66.7% (*table 2*).

Recruitment

The study opened to recruitment in June 2013, and closed one year later. During this time-frame sites recorded all children presenting with SA/OM. Sites did not all open for recruitment at the same time but most achieved a minimum of 6 months (with the exception of one tertiary centre and six secondary centres). The median (interquartile range (IQR)) recruitment time was 8.8 (6, 9.4) months for tertiary centres compared with 8.5 (6.3, 9.3) months for secondary care. (See *Table 1* and *table 2*)

Accrual rates for Simple and Complex Cases

The monthly rates of case accrual are given in *Table 1* and *table 2*. The median recruitment rate in tertiary centres was 0.7 (IQR 0.2, 1.7) cases per month for simple cases, and 0.4 (IQR 0.2, 0.7) for complex cases. For secondary centres the median recruitment rate was 0.2 (IQR 0.1, 0.5) for simple cases per month and 0 (IQR 0, 0.1) for complex cases.

TABLE 1: TERTIARY CENTRES

Site Name	Total		By Case type					
	n	Recruitment period (months)	Simple cases		Complex cases		Misdiagnosed / Discitis	
			n (%)	Monthly Rate	n (%)	Monthly Rate	n (%)	Monthly Rate
Alder Hey Childrens NHS Foundation Trust	33	9.6	29 (87.9%)	3	2 (6.1%)	0.2	2 (6.1%)	0.2
Barts Health NHS Trust (Newham and Royal London Hospitals)	7	9.1	5 (71.4%)	0.5	2 (28.6%)	0.2	0 (0%)	0
Cardiff and Vale University Health Board	13	9.6	6 (46.2%)	0.6	7 (53.8%)	0.7	0 (0%)	0
Central Manchester University Hospitals NHS FT (Royal Manchester)	15	6.8	14 (93.3%)	2.1	1 (6.7%)	0.1	0 (0%)	0
Chelsea and Westminster Hospital NHS Foundation Trust	0	9.1	0	0	0	0	0	0
Derriford Hospital, Plymouth	2	4.4	1 (50%)	0.2	1 (50%)	0.2	0 (0%)	0
Evelina Children's Hospital	4	6.8	0 (0%)	0	3 (75%)	0.4	1 (25%)	0.1
Great Ormond Street Hospital for Children NHS FT	4	9.1	1 (25%)	0.1	3 (75%)	0.3	0 (0%)	0
Leeds Teaching Hospital	21	9.3	16 (76.2%)	1.7	3 (14.3%)	0.3	2 (9.5%)	0.2
Leicester Royal Infirmary	4	8.5	2 (50%)	0.2	1 (25%)	0.1	1 (25%)	0.1
Newcastle Upon Tyne Hospitals	24	9.6	11 (45.8%)	1.1	8 (33.3%)	0.8	5 (20.8%)	0.5
Oxford University Hospitals NHS Trust	16	6	11 (68.8%)	1.8	3 (18.8%)	0.5	2 (12.5%)	0.3
Royal Alexandra (Brighton & Sussex Trust)	8	8.9	4 (50%)	0.4	4 (50%)	0.4	0 (0%)	0
Sheffield Children's Hospital NHS FT	17	8.6	6 (35.3%)	0.7	11 (64.7%)	1.3	0 (0%)	0
St Georges Healthcare NHS Trust	6	6	6 (100%)	1	0 (0%)	0	0 (0%)	0
St Mary's, Imperial College	8	6	3 (37.5%)	0.5	3 (37.5%)	0.5	2 (25%)	0.3
University Hospital Southampton NHS Foundation Trust	42	9.6	20 (47.6%)	2.1	13 (31%)	1.4	9 (21.4%)	0.9
University Hospitals Bristol NHS Foundation Trust	18	6	9 (50%)	1.5	6 (33.3%)	1	3 (16.7%)	0.5
Total	242		144 (59.5%)		71 (29.3%)		27 (11.2%)	
Median (IQR)		8.8 (6,9.4)		0.7 (0.2,1.7)		0.4 (0.2,0.7)		0.1 (0,0.3)

TABLE 2: SECONDARY CENTRES

Site Name	Total		By Case type					
	n	Recruitment period (months)	Simple cases		Complex cases		Misdiagnosed/Discitis	
			n (%)	Monthly Rate	n (%)	Monthly Rate	n (%)	Monthly Rate
Ashford & St Peters Hospitals NHS FT	3	6.8	0 (0%)	0	2 (66.7%)	0.3	1 (33.3%)	0.1
Birmingham Heartlands Hospital	2	6.0	2 (100%)	0.3	0 (0%)	0	0 (0%)	0
Bradford Teaching Hospitals NHS FT	3	9.4	2 (66.7%)	0.2	1 (33.3%)	0.1	0 (0%)	0
Burton Hospitals NHS FT (Queens Hospital)	7	9.6	4 (57.1%)	0.4	1 (14.3%)	0.1	2 (28.6%)	0.2
County Durham and Darlington NHS Foundation Trust	0	6.0	0	0	0	0	0	0
Dorset County Hospital	0	5.8	0	0	0	0	0	0
Furness General Hospital	0	5.1	0	0	0	0	0	0
Hampshire Hospitals NHS FT (Basingstoke)	1	8.5	0 (0%)	0	0 (0%)	0	1 (100%)	0.1
Kingston Hospital NHS Trust	2	6.6	1 (50%)	0.2	0 (0%)	0	1 (50%)	0.2
Leighton Hospital (Mid Cheshire Hospitals NHS FT)	2	9.6	2 (100%)	0.2	0 (0%)	0	0 (0%)	0
Luton and Dunstable NHS FT	1	6.6	1 (100%)	0.2	0 (0%)	0	0 (0%)	0
Mid Yorkshire NHS Trust (Pinderfields)	4	9.6	3 (75%)	0.3	1 (25%)	0.1	0 (0%)	0
Norfolk & Norwich University Hospitals NHS FT	4	8.9	2 (50%)	0.2	2 (50%)	0.2	0 (0%)	0
Manchester General Hospital	0	6.8	0	0	0	0	0	0
North West London Hospital NHS Trust	9	9.3	6 (66.7%)	0.6	1 (11.1%)	0.1	2 (22.2%)	0.2
Penine Acute Trust (Royal Oldham Hospital)	7	6.6	4 (57.1%)	0.6	2 (28.6%)	0.3	1 (14.3%)	0.2
Portsmouth Hospitals NHS Trust	1	7.5	1 (100%)	0.1	0 (0%)	0	0 (0%)	0
Princess Alexandra Hospital NHS Trust	5	8.7	4 (80%)	0.5	1 (20%)	0.1	0 (0%)	0
Royal Berkshire Hospital	4	9.4	3 (75%)	0.3	0 (0%)	0	1 (25%)	0.1
Royal Blackburn Hospital	12	9.1	2 (16.7%)	0.2	7 (58.3%)	0.8	3 (25%)	0.3
Royal Devon and Exeter NHS FT	6	9.6	5 (83.3%)	0.5	1 (16.7%)	0.1	0 (0%)	0
Royal Lancaster Infirmary	0	5.1	0	0	0	0	0	0
Royal Shrewsbury Hospital	7	8.9	5 (71.4%)	0.6	1 (14.3%)	0.1	1 (14.3%)	0.1
Royal Wolverhampton Hospitals NHS Trust (New Cross Hospital)	7	5.6	6 (85.7%)	1.1	1 (14.3%)	0.2	0 (0%)	0
Sandwell & West Birmingham NHS Trust	2	7.5	2 (100%)	0.3	0 (0%)	0	0 (0%)	0
Southend Hospital Trust	4	7.5	3 (75%)	0.4	1 (25%)	0.1	0 (0%)	0
Stockport NHS Foundation Trust	1	8.7	1 (100%)	0.1	0 (0%)	0	0 (0%)	0
Stafford General	2	9.2	1 (50%)	0.1	1 (50%)	0.1	0 (0%)	0
University Hospital of North Staffordshire	10	9.3	6 (60%)	0.6	1 (10%)	0.1	3 (30%)	0.3
University Hospitals Coventry and Warwickshire NHS Trust	6	8.9	6 (100%)	0.7	0 (0%)	0	0 (0%)	0
Westmoreland General Hospital	0	5.1	0	0	0	0	0	0
Wye Valley Hospitals NHS Trust	1	5.6	1 (100%)	0.2	0 (0%)	0	0 (0%)	0
Yeovil District Hospital NHS FT	1	9.6	1 (100%)	0.1	0 (0%)	0	0 (0%)	0
Total	114		74 (64.9%)		24 (21.1%)		16 (14%)	
Median (IQR)		8.5 (6.3,9.3)		0.2 (0.1,0.5)		0 (0,0.1)		0 (0,0.1)

Initial categorisation of types of cases and sample characteristics

356 children were recorded in the database as presenting with symptoms of SA or OM. 218 (61.2%) children were classified as simple cases of OM or SA, 95 (26.7%) were classified as complex cases, 5 (1.4%) had discitis and 38 (10.7%) presented with the symptoms of OM or SA but were found to have a different diagnosis. Discitis is a special case of SA, but is treated in a different way, so not of interest to this study.

table 3 gives the breakdown of how many children had OM or SA in each case type group, and the types of diagnosis of misdiagnosed children. Note that for 6 children there was either evidence of both SA and OM, or the diagnosis was ambiguous in the database, meaning that it could have been either SA or OM or both. **These children are not included in analyses split by diagnosis group.**

53.9% were male, their median age was 3.4 years and most were of North, East or Mid-European origin (73.3%). *table 4* gives demographics by gender, age-group, and ethnicity for all 356 children, and also for the 313 children that were diagnosed with SA or OM. When misdiagnosed children and children with discitis are excluded, the demography of the sample remains very similar.

TABLE 3: CASE TYPES

Case Type	n (%) full sample (n=356)
Simple cases ^(a)	218 (61.2)
OM	109 (50)
SA	107 (49.1)
OM/SA or both ^(b)	2 (0.9)
Complex cases ^(c)	95 (26.7)
OM	56 (58.9)
SA	35 (36.8)
OM/SA or both ^(b)	4 (4.2)
Misdiagnosed / Discitis	43 (12.1)
Misdiagnosed:	38 (88.4)
Cellulitis	7 (16.3)
Reactive arthritis	3 (7)
Joint effusion ^(d)	2 (4.7)
Soft tissue abscess	2 (4.7)
Other	22 (51.2)
Unknown/Undecided	2 (4.7)
Discitis	5 (11.6)

^(a) Acute SA/OM with no comorbidities; ^(b) Option label available in database for ambiguous cases; ^(c) 'Chronic SA/OM' or 'Acute SA/OM with comorbidities'; ^(d) No infection reported.

TABLE 4: SAMPLE DEMOGRAPHICS

Demographics	All	43 misdiagnoses / discitis excluded
Total number of children in database with data available for analysis ^(a)	356	313
Age (years) at presentation, Median (IQR)	3.4 (1.4, 9)	3.3 (1.4, 8.7)
< 1 year	46 (12.9%)	40 (12.8%)
1-6 years	182 (51.1%)	161 (51.4%)
6-16 years	128 (36%)	112 (35.8%)
Male	192 (53.9%)	173 (55.3%)
Ethnicity		
European North/East/Mid	261 (73.3%)	228 (72.8%)
European South (Mediterranean)	2 (0.6%)	2 (0.6%)
European Roma	1 (0.3%)	1 (0.3%)
African/Caribbean North African	2 (0.6%)	2 (0.6%)
African/Caribbean Sub Saharan	8 (2.2%)	7 (2.2%)
African/Caribbean Afro-caribbean	3 (0.8%)	2 (0.6%)
Asian Indian Subcontinent	30 (8.4%)	26 (8.3%)
Asian SE (Vietnam, Thailand, Indonesia, Malaysia, Phillipines)	3 (0.8%)	3 (1%)
Asian East Asia (China, Japan, Korea)	2 (0.6%)	2 (0.6%)
Asian West Asia (Afghanistan, Iranian)	1 (0.3%)	0
Middle Eastern Turkish	0	0
Middle Eastern Arab peninsula	1 (0.3%)	0
Other/Mixed	37 (10.4%)	35 (11.2%)
Missing	5 (1.4%)	5 (1.6%)

^(a)Database contained 361 cases. 4 children excluded because all but demographic data were missing; 1 child excluded as diagnostic data missing.

Completeness of follow-up

Children were followed-up approximately 3 months post discharge. 72% of simple cases and 80% of complex cases were contactable and followed up. In most cases where children were not followed up this was because children were not contactable (see *table 5*). 2.8% and 2.1% of simple and complex cases respectively had missing follow-up data for reasons unknown.

TABLE 5: COMPLETENESS OF FOLLOW-UP

Case Type	Total	Diagnosis ^(a)	
		SA	OM
Simple cases	(n=218)	(n=107)	(n=109)
Followed-up	157 (72%)	78 (72.9%)	79 (72.5%)
Not contactable	55 (25.2%)	26 (24.3%)	28 (25.7%)
Unknown/missing	6 (2.8%)	3 (2.8%)	2 (1.8%)
Complex cases	(n=95)	(n=35)	(n=56)
Followed-up	76 (80%)	27 (77.1%)	45 (80.4%)
Not contactable	17 (17.9%)	7 (20%)	10 (17.9%)
Unknown/missing	2 (2.1%)	1 (2.9%)	1 (1.8%)
Misdiagnosed / Discitis	(n=43)		
Followed-up	30 (69.8%)	-	-
Not contactable	10 (23.2%)	-	-
Unknown/missing	3 (7.0%)	-	-

^(a) 2 SC and 4 CC could not be categorised as uniquely SA or OM

Presentation and Diagnosis

For the rest of this report, data are presented for the 313 children that were either simple or complex cases. **The 43 misdiagnosed/ discitis children are excluded from further analyses.**

Medical history

Simple Cases

6 simple cases had a history of orthopaedic surgery more than 6 months prior to presentation (see *table 6* for details of bones/joints affected). Other medical history of interest was that 31 (14.2%) had at least one pre-existing medical condition not listed in *TABLE 7*; 43 (19.7%) had at least one history of a severe infection in the 12 months preceding presentation, and 29 (13.3%) had a history of trauma in the month preceding presentation (see *table 8*,

TABLE 9, *table 10*). 18.8% of simple cases had had at least one antibiotic in the month prior to presentation (see *TABLE 11* for further statistics by route type and for specific antibiotics).

Complex Cases

11 complex cases had a history of orthopaedic surgery – 6 of these within 6 months of presentation (see *TABLE 6* for details of bones/joints affected). 31 (33.7%) had an indwelling central venous catheter or PICC, 4 presented with an infected implant, 5 children had sickle cell disease, 1 had cystic fibrosis, 1 had cerebral palsy and 2 had known immunocompromise (see *TABLE 7*).

Other medical history of interest was that 25 (26.3%) had other pre-existing medical conditions not listed in *TABLE 7*; 26 (27.4%) had a history of infection in the 12 months preceding presentation, and 15 (15.8%) had a history of trauma in the month preceding presentation (see *TABLE 8*,

TABLE 9, *TABLE 10*).

TABLE 6: HISTORY OF ORTHOPAEDIC SURGERY

	Number of children with orthopaedic surgery Within 6 months prior to presentation ^(a)	Any time prior to presentation	
		Simple cases (n=218)	Complex cases (n=95)
Cases	6	6 (3.2%)	11 (16.8%)
Bone/joint types affected ^(b) :			
Knee	-	-	-
Clavicle	-	-	1
Radius	1	-	1
Ulna	-	-	-
Humerus	-	3	-
Tibia	1	1	2
Femur	-	1	1
Ankle	-	1	-
Hip	3	-	4

Spine	-	-	1
Toe	-	-	1
Elbow	-	-	1
Skull	1	-	1
Side:			
Right	-	4	2
Left	2	2	4
Both	3	-	3
N/a	1	-	2

(^a) Complex by definition; (^b) No. of patients with at least one prior orthopaedic surgery by bone/joint type (NB One complex case had history of surgery on three separate bones/joints, and one had surgery on the femur/tibia so both joints have been counted. All others' history pertained to a single bone/joint type.)

TABLE 7: CO-MORBIDITIES INDICATING COMPLEX CASE

Co-morbidities indicating complex case	Yes	No
Sickle cell disease*	5	210
Presentation due to infected implant	4	309
Known immunocompromise	2	311
Indwelling central venous catheter or PICC	31	282
Cystic Fibrosis	1	306
Cerebral Palsy	1	312

* 98 patients were not tested for Sickle cell disease

TABLE 8: MEDICAL HISTORY

Medical History	Simple cases (n=218)	Complex cases (n=95)
Other medical conditions:		
At least one	31 (14.2%)	25 (26.3%)
Congenital cardiac disease	1 (0.5%)	2 (2.1%)
Diabetes Mellitus	-	1 (1.1%)
Purpura Fulminans	-	-
Malnutrition	-	-
Other(^a)	30 (13.8%)	23 (24.2%)
Immune modulating treatment in last 6 calendar months?		
Steroid	-	1 (1.1%)
Radiotherapy	-	-
Chemotherapy	-	-
Azathioprine	-	-
Cyclosporin	-	-
Cyclophosphamide	-	-
Rituximab	-	-
Leflunomide	-	-
Tacrolimus	-	-
Sirolimus	-	-
Other	-	1 (1.1%)
Infection History in the last 12 calendar months?		
At least one	43 (19.7%)	26 (27.4%)
Pneumonia	1 (0.5%)	-
Septicaemia	-	2 (2.1%)
Pyelonephritis	-	-

Cellulitis / soft tissue infection	5 (2.3%)	1 (1.1%)
Meningitis	1 (0.5%)	-
Osteoarticular infection	-	6 (6.3%)
Abdominal sepsis	-	-
Varicella	4 (1.8%)	3 (3.2%)
Other ^(b)	32 (14.7%)	18 (18.9%)
History of Trauma in the last month?	29 (13.3%)	15 (15.8%)
Other Surgery in previous 12 months?	2 (0.9%)	4 (4.2%)

(a) See

TABLE 9; (b) See TABLE 10.

TABLE 9: OTHER MEDICAL CONDITIONS (AS INPUT IN THE DATABASE)

Simple cases (n=30)	Complex cases (n=23)
• Asthma (n=7) • Asthma, treated for one week with antibiotics for a 3 week dental abscess • Atopic eczema • Baker's Cyst Summer 2013 • Bilateral Talipes Valgus/Internal Tibial torsion • Capillary haemangioma currently undergoing laser treatment • Chronic ITP • Cleft Lip/Palate • Coeliac disease • Congenital dislocation of hips • Duplication of chromosome 8p11-21 and severe learning difficulties* • Eczema (n=3) • Haemophiliac • Hydronephrosis left kidney • Jaundice, edema, lymphadenopathy • Klipper-Trenaunay Weber Syndrome • Leucocyte adhesion deficiency type1**	• Abscess over the site of osteomyelitis in her humerus drained July 2012. • ADHD, Asthma, Growth deficiency, Insomnia • Asthma • Asthma, epilepsy, bilaterally death • Bilateral AVN, acute chest syndrome • Club foot • Congenital hip dislocation • Eczema (n=3) • Fish Odour Syndrome, microcephaly, postural scoliosis, clawing of toe • G6PD Deficiency • Gastro-oesophageal Reflux • Leucocyte adhesion deficiency type1 • Mild Asthma • MRSA abscess Left neck • Normocytic Normochromic Anaemia (secondary to infection?) • Osteosarcoma

• MRSA+ • Osteogenesis Imperfecta Type 1* • Patient born with neonatal thrombocytopenia, now resolved • Psychotic depression • Under weather for 4 weeks prior with ear and chest infections	• Patient has a small PDA. Born at 32 weeks. Pt was in NICU and treated with Fluconazole due to ? fungal infection (Patient born in August 2013). Patient home one week before starting symptoms. • Patient is being investigated for autism • Right MCA, gastrostomy, sigmoid colostomy • Spina bifida • Vitamin D Deficiency
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*Medical condition queried, and child still classified as simple; **Medical condition later found to denote 'known immunocompromise' implying this case should be reclassified as complex.

TABLE 10: OTHER INFECTION HISTORY (AS INPUT IN THE DATABASE)

Simple Cases (n=32)	Complex Cases (n=18)
• 2 x dental abscess, viral infection starting 19/08/2013 • Bronchiolitis (n=2) • Diarrhoea • Ear and chest infections • Ear infection and tonsillitis • Ear infection, cold • Hand, Foot and Mouth disease • MRSA • MRSA septicaemia and RSV positive • Nonspecific viral illness week before • Probable Viral Upper Respiratory Tract infection (URTI) • Recurrent bouts of tonsillitis • Recurrent Ear Infections • Scarlet Fever (n=2) • Severe eczema exacerbation • Sinusitis • Sore throat • Tick bite, Lyme serology negative • Tonsillitis (n=3) • URTI • URTI - coryzal, sore throat, decreased appetite and temp 38.3 • Urinary Tract Infection (UTI) • Viral diarrhoea • Viral illness (n=2) • Viral illness ? migraine • Viral infection • Vomiting and diarrhoea illness	• Chest Infection • Ear infection • Ear/throat • Fungal sepsis, patient grew <i>candida albicans</i> sensitive to fluconazole, premature neonate. • Left leg swelling/patient went to theatre for necrotising fascitis. Endocarditis. All initially presented to Royal Berkshire Hospital • Multiple bacterial URTI • Osteomyelitis/brodies abscess • Patient initially presented on the 30th june with server pain in the right distal tibia. Patient was placed in a back slab, and had 2 weeks of antibiotics... • Pleural effusion • Possible impetigo (nose) • Recurrent tonsillitis requiring tonsillectomy • Sinusitis and left frontoparietal subdural empyema. • Tonsillitis • Tonsillitis & inflamed ear • Urinary tract infection • Viral tonsillitis/URTI • Chronic infected Tibia • Vomiting illness

TABLE 11: PREPRESENTATION VARIABLES THAT AFFECT DRUG CHOICE, DOSAGE AND DURATION (SIMPLE CASES)

Antibiotic medical history prior to presentation	All simple cases (n=218)	Route		Duration > 1 week
		IV	Oral	
Penicillin allergy	7 (3.2)	-	-	-
One month pre-presentation				
At least one type antibiotic taken*	41 (18.8%)	18 (8.3%)	26 (11.9%)	14 (6.4%)
Types of antibiotics taken				
Flucloxacillin	18 (8.3%)	9	9	4
Clindamycin	5 (2.3%)	2	3	2
Cefuroxime	3 (1.4%)	3	0	0
Ceftriaxone	10 (4.6%)	9	1	5
Amoxicillin	9 (4.1%)	0	9	3
Co-Amoxiclav	8 (3.7%)	0	8	4
Rifampicin	2 (0.9%)	0	2	1
Vancomycin	2 (0.9%)	1	1	1
Fusidic Acid	1 (0.5%)	0	1	1
Teicoplanin	3 (1.4%)	2	1	1
Other	1 (0.5%)	1	0	1

*Patients may have received multiple antibiotics in the month pre presentation.

Presentation

Where children presented

Most children presented at emergency departments (65% of SC, 70% of CC). The next most likely was with a general practitioner (GP) (28% of SC, 14.7% of CC). Outpatient clinics, inpatient clinics, and walk-in centres were much less likely places for children to present. (See

Table 12).

Joints and Limbs affected

The most likely joints/limbs affected were the hip (21.7%); the knee (23.3%); and the ankle (14.7%). There are similarities between joints affected in simple and complex cases, though many joints/limbs were more affected in complex cases. (See

Table 12).

SA was more likely in hips and knees than OM (both simple and complex cases), whereas OM affected a much larger range of joints/limbs (See Table 13).

TABLE 12: WHERE PATIENTS PRESENTED AND BONES/JOINTS AFFECTED

Presentation	All (n=313 (%))	Simple cases (n=218 (%))	Complex cases (n=95 (%))
Presenting to:			
Outpatient Clinic	13 (4.2)	8 (3.7)	5 (5.3)
Inpatient	9 (2.9)	5 (2.3)	4 (4.2)
GP	75 (24)	61 (28)	14 (14.7)
Emergency Department	207 (66.1)	141 (64.7)	66 (69.5)
Walk-in Centre	9 (2.9)	3 (1.4)	6 (6.3)
Bones/Joints affected*:			
Hip	68 (21.7)	46 (21.1)	22 (23.2)
Shoulder	23 (7.3)	16 (7.3)	7 (7.4)
Knee	73 (23.3)	54 (24.8)	19 (20)
Ankle	46 (14.7)	29 (13.3)	17 (17.9)
Wrist	9 (2.9)	8 (3.7)	1 (1.1)
Skull	5 (1.6)	2 (0.9)	3 (3.2)
Mandible	0	0	0
Humerus	14 (4.5)	5 (2.3)	9 (9.5)
Clavicle	1 (0.3)	0	1 (1.1)
Radius	6 (1.9)	3 (1.4)	3 (3.2)
Ulna	4 (1.3)	2 (0.9)	2 (2.1)
Pelvis	11 (3.5)	4 (1.8)	7 (7.4)
Rib	0	0	0
Femur	26 (8.3)	16 (7.3)	10 (10.5)
Tibia	14 (4.5)	6 (2.8)	8 (8.4)
Fibula	9 (2.9)	4 (1.8)	5 (5.3)
Sternum	3 (1)	0	3 (3.2)
Elbow	29 (9.3)	15 (6.9)	14 (14.7)
Foot	11 (3.5)	4 (1.8)	7 (7.4)
Calcaneum	6 (1.9)	5 (2.3)	1 (1.1)
Lumbar vertebrae	4 (1.3)	2 (0.9)	2 (2.1)
Cervical vertebrae	0	0	0
Thoracic vertebrae	0	0	0
Sacrum vertebrae	4 (1.3)	1 (0.5)	3 (3.2)
Other	2 (0.6)	2 (0.9)	0 (0)

*Categories not mutually exclusive, so more than one bone/joint can be recorded per patient.

TABLE 13: JOINTS/LIMBS AFFECTED (BY SA/OM)

Presentation	Simple cases		Complex cases	
	SA	OM	SA	OM
Limbs/Joints affected*	(n=107(%))	(n=109(%))	(n=35(%))	(n=56(%))
Hip	31 (29)	15 (13.8)	11 (31.4)	9 (16.1)
Shoulder	7 (6.5)	8 (7.3)	3 (8.6)	4 (7.1)
Knee	41 (38.3)	13 (11.9)	9 (25.7)	10 (17.9)
Ankle	14 (13.1)	14 (12.8)	6 (17.1)	10 (17.9)
Wrist	4 (3.7)	4 (3.7)	1 (2.9)	0
Skull	0	2 (1.8)	0	3 (5.4)
Humerus	1 (0.9)	4 (3.7)	4 (11.4)	5 (8.9)
Clavicle	0	0	0	1 (1.8)
Radius	0	3 (2.8)	2 (5.7)	1 (1.8)
Ulna	0	2 (1.8)	1 (2.9)	1 (1.8)
Pelvis	0	4 (3.7)	1 (2.9)	5 (8.9)
Femur	0	10 (9.2)	3 (8.6)	12 (21.4)
Tibia	0	6 (5.5)	1 (2.9)	5 (8.9)
Fibula	0	4 (3.7)	1 (2.9)	4 (7.1)
Sternum	0	0	1 (2.9)	2 (3.6)
Elbow	7 (6.5)	8 (7.3)	9 (25.7)	5 (8.9)
Foot	0	4 (3.7)	2 (5.7)	4 (7.1)
Calcaneus	0	5 (4.6)	0	0
Lumbar vertebrae	1 (0.9)	1 (0.9)	0	2 (3.6)
Sacrum vertebrae	0	1 (0.9)	1 (2.9)	2 (3.6)
Other	1 (0.9)	1 (0.9)	0	0

*Categories not mutually exclusive, so more than one bone/joint can be recorded per patient.

Blood tests at presentation

Simple Cases

105 (48.2%) of children had blood tests taken at presentation. Of those tested, Hb, WBC, N, Plt and CRP were routinely measured in over 84% of cases. ESR was less tested (53.3%). 53 (50.5%) had both CRP and ESR tested. Of the 99 children with a CRP test result, 65 (65.7%) had their highest result at presentation. See *Table 14* for more details.

The prevalence of types of tests carried out were similar in tertiary and secondary centres. See *Table 14* for more details.

Table 15 presents median and inter-quartile ranges for blood test results at presentation. *Table 16* splits these results by diagnosis of SA or OM. Blood tests results were similar in these two groups.

Complex Cases

32 (33.7%) of children had blood tests taken at presentation. Of those tested, Hb, WBC, N, Plt and CRP were routinely measured in over 71% of cases. All but one had a CRP measurement (96.9%). ESR was less tested (34.4%). 11 (34.4%) had both CRP and ESR tested. Of the 31 children with a CRP test result, 15 (48.4%) had their highest result at presentation. See *Table 14* for more details.

The prevalence of types of tests carried out were similar in tertiary and secondary centres, though ESR was over three times as likely in a secondary centre. See *Table 14* for more details.

Table 15 presents median and inter-quartile ranges for blood test results at presentation. Table 16 splits these results by diagnosis of SA or OM. Blood tests results were similar in these two groups.

TABLE 14: PRESENTATION BLOOD TESTS

Blood test at presentation	Presentation centre type		
	All	Tertiary	Secondary
Simple cases	(n=218)	(n=106)	(n=112)
At least one blood test carried out at presentation:			
Yes	105 (48.2%)	51 (48.1%)	54 (48.2%)
No	113 (51.8%)	55 (51.9%)	58 (51.8%)
n (%) of children that had a test with:			
Hb	89 (84.8%)	43 (84.3%)	46 (85.2%)
WBC	96 (91.4%)	44 (86.3%)	52 (96.3%)
N	91 (86.7%)	44 (86.3%)	47 (87%)
Plt	89 (84.8%)	42 (82.4%)	47 (87%)
CRP	99 (94.3%)	47 (92.2%)	52 (96.3%)
ESR	56 (53.3%)	25 (49%)	31 (57.4%)
CRP & ESR	53 (50.5%)	23 (45.1%)	30 (55.6%)
CRP & <i>not</i> ESR	46 (43.8%)	24 (47.1%)	22 (40.7%)
CRP _{max} at presentation	65 (65.7%)*	33 (70.2%)*	32 (61.5%)*
Complex cases	(n=95)	(n=51)	(n=44)
At least one blood test carried out at presentation:			
Yes	32 (33.7%)	18 (35.3%)	14 (31.8%)
No	63 (66.3%)	33 (64.7%)	30 (68.2%)
n (%) of children that had a test with:			
Hb	26 (81.3%)	15 (83.3%)	11 (78.6%)
WBC	28 (87.5%)	16 (88.9%)	12 (85.7%)
N	25 (78.1%)	14 (77.8%)	11 (78.6%)
Plt	23 (71.9%)	14 (77.8%)	9 (64.3%)
CRP	31 (96.9%)	17 (94.4%)	14 (100%)
ESR	11 (34.4%)	3 (16.7%)	8 (57.1%)
CRP & ESR	11 (34.4%)	3 (16.7%)	8 (57.1%)
CRP & <i>not</i> ESR	20 (62.5%)	14 (77.8%)	6 (42.9%)
CRP _{max} at presentation	15 (48.4%)*	6 (35.3%)*	9 (64.3%)*

* Denominator is those who had CRP measured at presentation.

TABLE 15: SUMMARY OF BLOOD TEST RESULTS AT PRESENTATION

Blood test at presentation	Simple Cases		Complex Cases	
	n	Median (IQR)	n	Median (IQR)
Hb (g/dL)	89	117 (109, 126)	26	124 (112, 134)
WBC (10 ⁹ /L)	96	12.14 (9.6, 15.8)	28	12.68 (11, 14.5)
N (10 ⁹ /L)	91	7.3 (4.7, 10.7)	25	7.1 (5.47, 8.71)
Plt (10 ⁹ /L)	89	342 (256, 441)	23	333 (280, 419)
CRP (mg/L)	99	32 (11.8, 66.7)	31	54 (24, 141)
ESR (mm/hr)	56	32 (20.5, 70)	9*	28 (15, 55)

*2 ESR measurements missing

TABLE 16: SUMMARY OF BLOOD TEST RESULTS AT PRESENTATION (BY SA/OM)

Blood tests at presentation	SA		OM	
	n	Median (IQR)	n	Median (IQR)
Simple cases				
Hb (g/dL)	47	116 (108, 128)	42	120 (111, 124)
WBC (10 ⁹ /L)	48	12.66 (9.8, 16.5)	48	11.62 (9.5, 15.2)
N (10 ⁹ /L)	48	7.89 (5.4, 11.0)	43	6.2 (4.68, 10.7)
Plt (10 ⁹ /L)	45	341 (256, 431)	44	349.5 (258.5, 482.5)
CRP (mg/L)	49	32 (16.2, 65)	50	32.7 (10, 68)
ESR (mm/hr)	28	29 (14, 70.5)	28	35.5 (26, 68.5)
Complex cases*				
Hb (g/dL)	12	119.5 (109.5, 127)	13	127 (114, 137)
WBC (10 ⁹ /L)	13	12.9 (11.2, 14.2)	14	11.96 (10.65, 14.8)
N (10 ⁹ /L)	13	7 (5.55, 9.01)	11	7.1 (4.3, 8.4)
Plt (10 ⁹ /L)	12	331.5 (305.5, 351.5)	10	413 (269, 523)
CRP (mg/L)	15	53 (24, 156)	15	54 (16, 141)
ESR (mm/hr)	4	57.5 (41.5, 91)	4	15.5 (9.5, 33.5)

*1 complex case could not be classified as only SA or only OM and is excluded here.

Clinical time-line

All children in the study spent time in hospital. On average, children went straight to hospital (median time from presentation to hospital referral was 0 days), most children presented at A&E (see

Table 12).

Not all children received IV antibiotics (see

Table 31, paragraph describing treatment results). 15 (6.9%) simple cases and 2 (2.1%) complex cases either had no IV treatment, or the data are missing. Of those that did get IV antibiotics we can use the date of initiation of IV as a proxy for date of diagnosis.

The clinical time-line for first diagnostic x-ray, radiological diagnosis, first diagnostic surgery and the initiation of IV antibiotics are given in *for further* details.

Table 17. 61% of SC and 59% of CC had at least one x-ray post presentation and prior to initiation of IV antibiotics (i.e. had a diagnostic x-ray). These were usually on the day of or day after presentation (see *for further* details.

Table 17 for further details).

Diagnostic surgery was carried out in 28% of simple cases at a median of 1 day post presentation (25% carried out at 4 or more days post presentation). For complex cases, the surgery was slightly more likely (30.5%) at median of 1 day post presentation (25% carried out at 5 or more days post presentation).

A radiological diagnosis (an abnormal result via any imaging method: x-ray, ultrasound, MRI, bone-scan or CT-scan post presentation and prior to initiation of IV antibiotics) was obtained for 51.8% of simple cases (at a median of 1 day post presentation), and 52.6% of complex cases (at a median of 1 day post presentation).

Differences in clinical time-line between SA and OM

Hospital referral times were more varied for OM (75% referred in 4 days for SC and 6 days for CC) compared with SA (75% referred in 2 days for SC and 3 days for CC). The proportion of children with diagnostic x-rays was similar between SA and OM, as was the times at which these occurred. Radiological diagnosis was more likely in SA and at an earlier time compared with OM. Diagnostic surgery was more likely in SA and at an earlier time compared with OM. See

Table 18 for further details.

TABLE 17: THE CLINICAL TIME-LINE FOR DIAGNOSIS

Diagnostic and hospital stay time-line (days)	n (%)	Median (IQR)	Min, Max
Simple cases (n=218)			
From first presentation to:			
Hospital Referral	218 (100%)	0 (0,3)	0, 957
1 st X-ray ^(a)	133 (61%)	0 (0,1)	0, 957
Radiological diagnosis ^(b)	113 (51.8%)	1 (0,3)	0, 957
1 st Surgery ^(c)	61 (28%)	1 (1,4)	0, 56
Initiation of IV antibiotics	203 (93.1%)	1 (1,4)	0, 961

CRP _{max}	202 (92.7%)	0 (0,6)	0, 84
Complex cases (n=95)			
From first presentation to:			
Hospital Referral	95 (100%)	1 (0,4)	0, 1867
1 st X-ray ^(a)	56 (58.9%)	0 (0,1)	0, 2345
Radiological diagnosis ^(b)	50 (52.6%)	1 (0,4)	0, 2345
1 st Surgery ^(c)	29 (30.5%)	2 (1,5)	0, 223
Initiation of IV antibiotics	91 (95.8%)	2 (0,5)	0, 2345
CRP _{max}	86 (90.5%)	4 (1,8)	9, 2345

^(a) First X-ray post presentation and prior to initiation of IV antibiotics; ^(b) First abnormal result from any imaging method post presentation and prior to initiation of IV antibiotics; ^(c) First surgery post presentation and prior to initiation of IV antibiotics.

TABLE 18: THE CLINICAL TIME-LINE FOR DIAGNOSIS (BY SA/OM)

Diagnostic and hospital stay time-line (days)	SA		OM	
	n (%)	Median (IQR)	n (%)	Median (IQR)
Simple cases (n=218)	(n=107)		(n=109)	
From first presentation to:				
Hospital Referral	107 (100%)	0 (0,2)	109 (100%)	0 (0,4)
1 st X-ray ^(a)	66 (61.7%)	0 (0,1)	66 (60.6%)	0 (0,1)
Radiological diagnosis ^(b)	58 (54.2%)	1 (0,3)	54 (49.5%)	1 (0,5)
1 st Surgery ^(c)	39 (36.4%)	1 (1,2)	21 (19.3%)	2 (1,10)
Initiation of IV antibiotics	104 (97.2%)	1 (0,3)	97 (89%)	2 (1,5)
CRP _{max}	101 (46.3%)	2 (0,5)	99 (90.8%)	3 (0,7)
Complex cases (n=95)	(n=35)		(n=56)	
From first presentation to:				
Hospital Referral	35 (100%)	0 (0,3)	56 (100%)	1 (0,6)
1 st X-ray ^(a)	21 (60%)	0 (0,2)	33 (58.9%)	0 (0,1)
Radiological diagnosis ^(b)	16 (45.7%)	1 (0,2)	32 (57.1%)	1 (0,4)
1 st Surgery ^(c)	15 (42.9%)	2 (1,5)	14 (25%)	3 (1,8)
Initiation of IV antibiotics	33 (94.3%)	2 (0,4)	54 (96.4%)	2 (0,6)
CRP _{max}	33 (94.3%)	3 (1,6)	49 (87.5%)	4 (1,14)

^(a) First X-ray post presentation and prior to initiation of IV antibiotics; ^(b) First abnormal result from any imaging method post presentation and prior to initiation of IV antibiotics; ^(c) First surgery post presentation and prior to initiation of IV antibiotics.

Diagnosis

Day of diagnosis was defined as the day when IV antibiotics were initiated as the standard of care has always been for intravenous antibiotics to be started as soon as possible in paediatric OM/SA. This can be pinpointed for 203 (93.1%) of simple cases and 91 (94.6%) of complex cases. (See

Table 31 for more information on children that did not receive IV antibiotics).

Blood tests at diagnosis

Simple Cases

148 (72.9%) of children that had IV antibiotics had blood tests taken on either the day before or the day of diagnosis. Of these, over 85% had Hb, WBC, N, Platelets and CRP measured. ESR was less tested (57.4%). 80 (54.1%) had both CRP and ESR tested. Of the 137 children with a CRP test result, 89 (65%) had their highest result at diagnosis. See Table 19 for more details.

The prevalence of types of tests carried out were similar in tertiary and secondary centres. See Table 19 for more details.

Table 20 presents median and inter-quartile ranges for blood test results at diagnosis.

Complex Cases

54 (59.3%) of children that had IV had blood tests taken either on the day before or on the day of diagnosis. Of those tested, Hb, WBC, N, Plt and CRP were routinely measured in over 77% of cases. Most had a CRP measurement (88.7%). ESR was less tested (33.3%). 17 (31.5%) had both CRP and ESR tested. Of the 48 children with a CRP test result, 29 (60.4%) had their highest result at diagnosis. See Table 19 for more details.

The prevalence of types of tests carried out were similar in tertiary and secondary centres, though ESR was more likely in a secondary centre. See Table 19 for more details.

Table 20 presents median and inter-quartile ranges for blood test results at diagnosis.

Differences between SA and OM

The proportion of children receiving blood tests was similar between SA and OM. Blood cell parameters were similar between the groups but median CRP and ESR were higher in the SA group of the complex cases compared to the OM group (107 mg/L and 60 mm/hr vs. 46 mg/L and 31.5 mm/hr resp.). Within the simple cases this difference could not be found. See

Table 21 for further details.

TABLE 19: BLOOD TESTS ON THE DAY OF OR DAY PRECEDING INITIATION OF IV ANTIBIOTICS

Blood tests at diagnosis	Centre type where IV initiated		
	All	Tertiary	Secondary
Simple cases	(n=203)	(n=130)	(n=73)
At least one blood test carried out the day of or day preceding initiation of IV antibiotics:			
Yes	148 (72.9%)	82 (63.1%)	66 (90.4%)
No	55 (27.1%)	48 (36.9%)	7 (9.6%)
n (%) of children that had at least one test had:			
Hb	128 (86.5%)	72 (87.8%)	56 (84.8%)
WBC	133 (89.9%)	72 (87.8%)	61 (92.4%)
N	129 (87.2%)	72 (87.8%)	57 (86.4%)
Plt	127 (85.8%)	71 (86.6%)	56 (84.8%)
CRP	137 (92.6%)	75 (91.5%)	62 (93.9%)
ESR	84 (56.8%)	46 (56.1%)	38 (57.6%)
CRP & ESR	80 (54.1%)	43 (52.4%)	37 (56.1%)
CRP & <i>not</i> ESR	57 (38.5%)	32 (39%)	25 (37.9%)
CRP _{max} at diagnosis	89 (65%)*	52 (69.3%)*	37 (59.7%)*
Complex cases	(n=91)	(n=56)	(n=35)
At least one blood test carried out the day of or day preceding initiation of IV antibiotics:			
Yes	54 (59.3%)	34 (60.7%)	20 (57.1%)
No	37 (40.7%)	22 (39.3%)	15 (42.9%)
n (%) of children that had at least one test had:			
Hb	46 (85.2%)	28 (82.4%)	18 (90%)
WBC	50 (92.6%)	31 (91.2%)	19 (95%)
N	46 (85.2%)	28 (82.4%)	18 (90%)
Plt	42 (77.8%)	28 (82.4%)	14 (70%)
CRP	48 (88.9%)	29 (85.3%)	19 (95%)
ESR	18 (33.3%)	9 (26.5%)	9 (45%)
CRP & ESR	17 (31.5%)	7 (20.6%)	10 (50%)
CRP & <i>not</i> ESR	31 (57.4%)	22 (64.7%)	9 (45%)
CRP _{max} at diagnosis	29 (60.4%)*	18 (62.1%)*	11 (57.9%)*

*Denominator is those who had CRP measured at diagnosis.

TABLE 20: SUMMARY OF BLOOD TEST RESULTS AT INITIATION OF IV

Blood test at diagnosis	Simple cases		Complex cases	
	n	Median (IQR)	n	Median (IQR)
Hb (g/dL)	128	114 (106.5, 122)	46	115.5 (110, 125)
WBC (10 ⁹ /L)	133	12.18 (9.5, 16.4)	50	12.83 (10, 16.2)
N (10 ⁹ /L)	129	6.6 (4.7, 10.7)	46	7.365 (4.6, 11.3)
Plt (10 ⁹ /L)	127	361 (272, 471)	42	331.5 (269, 407)
CRP (mg/L)	137	38.3 (20, 74)	48	86.7 (29, 161)
ESR (mm/hr)	83*	46 (25, 78)	17*	40 (21, 60)

*1 ESR result missing for SC and 2 for CC.

TABLE 21: SUMMARY OF BLOOD TEST RESULTS AT THE DAY OF OR THE DAY PRECEDING INITIATION OF IV ANTIBIOTICS (BY SA/OM)

Blood tests at presentation	SA		OM	
	n	Median (IQR)	n	Median (IQR)
Simple Cases*				
Hb (g/dL)	66	115 (107, 123)	60	114 (106.5, 121.5)
WBC (10 ⁹ /L)	68	13.58 (9.95, 17.6)	64	11.2 (8.6, 15.2)
N (10 ⁹ /L)	65	7.52 (4.9, 11.1)	62	6.0 (4.5, 9.5)
Plt (10 ⁹ /L)	64	344 (257.5, 449)	61	368 (274, 485)
CRP (mg/L)	70	35.5 (21.2, 72)	66	39.5 (14, 81)
ESR (mm/hr)	41	46 (23, 81)	42	47 (26, 76)
Complex Cases*				
Hb (g/dL)	19	111 (103, 122)	25	119 (113, 130)
WBC (10 ⁹ /L)	22	12.4 (8.9, 17.2)	25	13.2 (10.7, 16.2)
N (10 ⁹ /L)	20	5.8 (3.6, 10)	23	8.23 (5.5, 12.1)
Plt (10 ⁹ /L)	19	312 (197, 354)	20	365 (298.5, 459.5)
CRP (mg/L)	22	107.0 (31, 168)	23	46 (13.9, 110)
ESR (mm/hr)	5	60 (40, 103)	10	31.5 (18, 48)

*2 SC and 4 CC complex cases could not be classified as uniquely SA or OM, and are excluded here.

Diagnostic surgery

The types of surgery carried out post presentation and prior to start of IV antibiotics are given in

Table 22. In simple cases, incision and drainage and aspiration were most likely types of surgery carried out (60.7% and 55.7% resp.), with arthroscopy third (9.8%). For complex cases, incision and drainage was most likely (62.1%), aspiration (24.1%) second and debridement (17.2%) third-most likely. (See

Table 22)

Some types of surgery were not carried out prior to IV treatment: amputation, compartment decompression, secondary closure, skin graft and other plastic surgery.

Differences between SA and OM

Surgery was carried out more often in children with OM compared to SA (63.6% vs 37.5% resp. in the simple cases and 25.9% and 15.5% in the complex cases). Incision and drainage was equally frequently performed in both groups, debridement was done more often in the OM group (See *Table 23*).

TABLE 22: SURGICAL PROCEDURES POST PRESENTATION CARRIED OUT PRIOR TO INITIATION OF IV ANTIBIOTICS

Surgery types	Simple cases n (%) ^{a)} (n=203)	Complex cases n (%) ^{a)} (n=91)
At least one	61 (30%)	29 (31.9%)
Aspiration	34 (55.7%)	7 (24.1%)
Incision and drainage	37 (60.7%)	18 (62.1%)
Drill decompression	2 (3.3%)	1 (3.4%)
Curettage/excision	1 (1.6%)	-
Arthrotomy	2 (3.3%)	3 (10.3%)
Arthroscopy	6 (9.8%)	1 (3.4%)
Amputation	-	-
Debridement	6 (9.8%)	5 (17.2%)
Fasciotomy	-	1 (3.4%)
Compartment decompression	-	-
Secondary closure	-	-
Skin graft	-	-
Other plastic surgery	-	-
Other	1 (1.6%)	4 (13.8%)

^(a)For each surgery type, frequencies are the number of children that had at least one diagnostic instance of that surgery; the denominator is the number of children that had a known date for initiation of IV.

TABLE 23: SURGICAL PROCEDURES POST PRESENTATION CARRIED OUT PRIOR TO INITIATION OF IV ANTIBIOTICS (BY SA/OM)

Surgery types	Simple cases, n (%) ^(a)		Complex cases, n (%) ^(a)	
	SA (n=104)	OM (n=97)	SA (n=33)	OM (n=54)
At least one	39 (37.5%)	21 (63.6%)	15 (15.5%)	14 (25.9%)
Aspiration	24 (23.1%)	10 (30.3%)	5 (5.2%)	2 (3.7%)
Incision and drainage	26 (25%)	11 (33.3%)	13 (13.4%)	5 (9.3%)
Drill decompression	-	2 (6.1%)	-	1 (1.9%)
Curettage/excision	1 (1%)	-	-	-
Arthrotomy	2 (1.9%)	-	3 (3.1%)	-
Arthroscopy	6 (5.8%)	-	1 (1%)	-
Debridement	1 (1%)	5 (15.2%)	1 (1%)	4 (7.4%)
Fasciotomy	-	-	1 (1%)	-
Other	-	1 (3%)	-	4 (7.4%)

^(a)For each surgery type, frequencies are the number of children that had at least one diagnostic instance of that surgery; the denominator is the number of children that had SA/OM and had a known date for initiation of IV.

Diagnostic imaging

X-rays were widely used as a diagnostic tool (64.5% of children that had IV antibiotics).

The proportion of these that were abnormal was 38% for simple cases, and 48% for complex cases.

The next most commonly used imaging method was ultrasound (41% of simple cases,

and 31% of complex cases). Of those imaged, 74.1% detected an abnormality.

MRI scans were used in 19% of simple cases with 89% detecting an abnormality; and 23% of complex cases were scanned with a detection rate of 95%. *Table 26* gives the numbers proportion of children presenting with each bone/joint that had a diagnostic MRI. CT scans and bone-scans were rarely used and only in OM cases. All four CT scans detected abnormalities (see *Table 24*).

Differences between SA and OM

X-ray and ultrasound were equally used for OM and SA cases; MRI was used more often in OM cases compared to SA cases (30% vs 9% resp.) (see *Table 25*). If an MRI was performed in OM the ankle and hip were most affected (16%), followed by the shoulder (11%) and humerus, pelvis and femur (9%). In SA the knee and the hip were most affected (46% and 23% resp.) (See *Table 26*). X-rays found similar percentages of abnormalities for simple cases, but found higher percentages in OM for complex cases. Ultrasound detected a higher percentage of abnormalities in SA than OM in both simple and complex cases. (See *Table 26*)

TABLE 24: IMAGING TYPES ROUTINELY USED TO AID DIAGNOSIS

Imaging Type	Simple cases		Complex cases	
	n ^(a) (%) (n=203) ^(b)	n (%) abnormal	n ^(a) (%) (n=91) ^(b)	n (%) abnormal
X-ray	133 (66%)	51 (38%)	56 (62%)	27 (48%)
CT scan	3 (1%)	3 (100%)	1 (1%)	1 (100%)
Ultrasound	84 (41%)	62 (74%)	28 (31%)	21 (75%)
MRI	38 (19%)	34 (89%)	21 (23%)	20 (95%)
Bone-scan	4 (2%)	3 (75%)	0	-

^(a)Number of children with at least one image post presentation, prior to start of IV treatment, by image type; ^(b)Denominator represents those where initiation date of IV known.

TABLE 25: IMAGING TYPES ROUTINELY USED TO AID DIAGNOSIS (BY SA/OM)

Imaging Type	SA n ^(a) (%)	n (%) abnormal	OM n ^(a) (%)	n (%) abnormal
Simple cases	(n=104) ^(b)		(n=97) ^(b)	
X-ray	66 (63%)	24 (36%)	66 (68%)	26 (39%)
CT scan	0	-	3 (3%)	3 (100%)
Ultrasound	53 (51%)	43 (81%)	31 (32%)	19 (61%)
MRI	9 (9%)	8 (89%)	29 (30%)	26 (90%)
Bone-scan	1 (1%)	1 (100%)	3 (3%)	2 (67%)
Complex cases	(n=33) ^(b)		(n=54) ^(b)	
X-ray	21 (64%)	8 (38%)	33 (61%)	18 (55%)
CT scan	0	-	1 (2%)	1 (100%)
Ultrasound	11 (33%)	9 (82%)	16 (30%)	11 (69%)
MRI	4 (12%)	3 (75%)	16 (30%)	16 (100%)
Bone-scan	0	-	0	-

^(a)Number of children with at least one image post presentation, prior to start of IV treatment, by image type; ^(b)Number of SA/OM where initiation date of IV known.

TABLE 26: BONES/JOINTS AFFECTED WHERE A DIAGNOSTIC MRI WAS CARRIED OUT (BY SA/OM)

Limbs/Joints affected ^(b)	n (%) ^(a) children with limbs/joints examined by diagnostic MRI			
	Simple cases		Complex cases	
	SA (n=9)	OM (n=29)	SA (n=4)	OM (n=16)
Hip	2 (22%)	4 (14%)	1 (25%)	3 (19%)
Shoulder	1 (11%)	4 (14%)	-	1 (6%)
Knee	4 (44%)	1 (3%)	2 (50%)	2 (13%)
Ankle	-	3 (10%)	2 (50%)	4 (25%)
Wrist	1 (11%)	1 (3%)	-	-
Skull	-	-	-	1 (6%)
Humerus	-	3 (10%)	-	1 (6%)
Clavicle	-	-	-	1 (6%)
Pelvis	-	2 (7%)	-	2 (13%)
Femur	-	3 (10%)	-	1 (6%)
Tibia	-	1 (3%)	-	2 (13%)
Fibula	-	-	1 (25%)	3 (19%)
Elbow	1 (11%)	2 (7%)	-	-
Calcaneum	-	2 (7%)	-	-
Lumbar vertebrae	-	1 (3%)	-	2 (13%)
Sacrum vertebrae	-	1 (3%)	-	1 (6%)
Other	-	1 (3%)	-	-

(a) Percentage of children with each joint/limb affected out of those that had a diagnostic MRI - by SA/OM. (b) See

Table 12 for total number of children presenting with each joint/limb listed.

Microbiology

Conventional tests: Micro-organisms

244 children (simple and complex combined) are known to have had conventional microbiology tests. Of these, 203 had at least one test from either bone; joint aspirate; blood or periosteal pus. Results for these 203 children are summarised in

Table 27. Of the simple cases, 38.2% tested positive for at least one micro-organism compared with 52.5% of complex cases. In OM cases 58% of the children had microbiology tests of which at least one microorganism was detected in 49%. In SA cases 73% was tested and in 36% a microorganism was found.

Of those tested, 20.1% of simple cases were found to have *Staphylococcus aureus*, compared with 32.2% of complex cases. This was the most prevalent micro-organism detected. Other microbes were rare. See also

Table 28 for further details on other microbes that were detected.

TABLE 27: SUMMARY OF RESULTS OF CONVENTIONAL MICROBIOLOGY TESTS

	Simple cases		Complex cases	
Tested	Total n	Tested ^(a) n (%)	Total n	Tested ^(a) n (%)
Children	218	144 (66.1%)	95	59 (62.1%)
SA	107	79 (73.8%)	35	24 (68.6%)
OM	109	64 (58.7%)	56	32 (57.1%)
Detected	Tested n	Yes n (%)	Tested n	Yes n (%)
At least one micro-organism detected?	144	55 (38.2%)	59	31 (52.5%)
SA	79	27 (34.2%)	24	10 (41.7%)
OM	64	28 (43.8%)	32	19 (59.4%)
Specification micro-organisms		n (%)		n (%)
<i>Staphylococcus aureus</i>		29 (20.1%)		19 (32.2%)
<i>PVL</i>		2 (6.9%)		1 (5.3%)
<i>MRSA</i>		1 (3.4%)		1 (5.3%)
<i>Erythromycin resistant</i>		0		1 (5.3%)
Not tested / missing		26 (89.7%)		16 (84.2%)
<i>Kingella kingae</i>		3 (2.1%)		1 (1.7%)
<i>Streptococcus pyogenes</i>		5 (3.5%)		5 (8.5%)
<i>Pseudomonas</i>		1 (0.7%)		0
<i>Group B Streptococcus</i>		2 (1.4%)		2 (3.4%)
<i>Salmonella</i>		-		-
<i>Candida</i>		-		-
<i>Tuberculosis</i>		-		-
Other ^(b)		17 (11.8%)		7 (11.9%)

^(a) Results of bone, joint aspirate, blood or periosteal pus samples only ^(b) See *Table 28*

TABLE 28: OTHER MICRO-ORGANISMS DETECTED FROM BLOOD/JOINT/BONE/PERIOSTEAL PUS (AS INPUT IN DATABASE)

Simple cases (n=17)	Complex cases (n=7)
• Diptheroids (n=2) • Gram +ve cocci • <i>Staphylococcus epidermis</i> • Unspecified (n=13)	• Unspecified (n=7)

PCR tests (sub-study): organisms

Presented fully in chapter 3, the summarised results of the microbiology sub-study are given in

Table 29. 50 children were tested out of 63 that consented to being part of the substudy. Of the 13 children that were not tested, 5 were at a centre that failed to carry out tests, 6 did not have a complete set of samples taken, one gave partial consent (but not for PCR) and one had no data in the database. Of those 50 children where tests were performed 6 had no final diagnosis of OM or SA and were excluded from further analyses. Results are therefore shown for 44 tested cases of OM or SA.

In 75% of the simple cases tested, at least one micro-organism was detected - this is a higher detection rate than conventional testing. Micro-organisms were detected in 67% of the complex cases tested – this was a similar detection rate to conventional tests. PCR detection rates were similar between SA and OM in complex cases, but in simple cases the detection rate for SA was higher than for OM (89% vs 57% respectively).

As in the conventional testing, the micro-organism most prevalent was *Staphylococcus aureus* (34.4% in SC and 41.7% in CC). However *Kingella kingae* was more prevalent according to PCR in simple cases (21.9%) compared with conventional testing (2.1%).

TABLE 29: SUMMARY OF RESULTS OF PCR TESTS

	Simple cases (n=218)		Complex cases (n=92)	
Consented to the microbiology sub-study	48 (22.3%)		15 (16.3%)	
Tested	Total	Tested n (%)	Total	Tested n (%)
Children	48	32 (67%)	15	12 ^(a) (53%)
SA		18		6
OM		14		5
Centre failed to test		4 (8.3%)		1 (6.7%)
Other reason not tested		4 (8.3%)		2 (13.3%)
Detected cases	Tested n	Yes n (%)	Tested n	Yes n (%)
At least one micro-organism detected	32	24 (75%)	12 ^(a)	8 (67%)
SA	18	16 (89%)	6	4 (67%)
OM	14	8 (57%)	5	3 (60%)
Specification micro-organisms				
<i>Staphylococcus aureus</i>		11 (34.4%)		5 (41.7%)
<i>Kingella kingae</i>		7 (21.9%)		0
Group A <i>Streptococcus</i>		2 (6.3%)		2 (16.7%)
<i>Streptococcus pneumoniae</i> lytA		1 (3.1%)		0
<i>Streptococcus pneumoniae</i> ply		0 (0%)		1 (8.3%)
<i>Staphylococcus epidermidis</i>		3 (9.4%)		0

Data from microbiology sub-study (See Chapter 3) ^(a) One case undecided OM or SA

Conventional tests: types of sample

Simple Cases

Blood samples were most commonly used for conventional microbiology tests (blood cultures, 62% of children tested). Joint aspirates were next most used (43.6%). There were few bone biopsies taken. There were some differences between the proportions of children with each type of sample taken – tertiary centres took more of all sample types except blood. The order of prevalence of types of sample was the same.

We have microbiology test results for 46 centres treating simple cases - 16 tertiary and 30 secondary. Blood samples were similarly very likely in both types of centre. Of the tertiary centres 14 took blood samples (87.5%) and the same number took joint aspirate samples. 56.3% took pus/wound swabs. Secondary centres were just as likely to take blood samples (83.3%) but not as likely to use joint aspirate (46.7%) or pus/wound swabs (30%). (See Table 30)

Complex Cases

Blood samples were most commonly used for conventional microbiology tests (54.3% of children tested). Pus/wound swabs were next most used (25.7%). There was a difference between the proportion of children with each type of sample taken between tertiary and secondary centres. As for simple cases, all sample types except blood were more likely for children in a tertiary centre. The order of prevalence of types was different.

We have microbiology test results for 32 centres treating complex cases - 16 tertiary and 16 secondary. Blood samples were equally likely in both types of centre. Of the tertiary centres, 10 (62.5%) took at least one blood sample. Other sample types were similarly likely to be taken. Secondary centres were less likely to use non-blood sample. (See *Table 30*)

TABLE 30: CONVENTIONAL TESTING SAMPLE TYPES

Sample types	n (%) of children with at least one sample of each type			n (%) of centres with at least one example of each type of sample		
	All (n=163)	Tertiary (n=98)	Secondary (n=67)	All (n=46)	Tertiary (n=16)	Secondary (n=30)
Simple cases						
Blood	101 (62%)	58 (59.2%)	43 (64.2%)	39 (84.8%)	14 (87.5%)	25 (83.3%)
Bone biopsy	6 (3.7%)	4 (4.1%)	2 (3%)	5 (10.9%)	3 (18.8%)	2 (6.7%)
Joint aspirate	71 (43.6%)	49 (50%)	23 (34.3%)	28 (60.9%)	14 (87.5%)	14 (46.7%)
Pus (periosteal)	25 (15.3%)	17 (17.3%)	8 (11.9%)	8 (17.4%)	6 (37.5%)	2 (6.7%)
Pus/Wound swab	15 (9.2%)	12 (12.2%)	3 (4.5%)	18 (39.1%)	9 (56.3%)	9 (30%)
Other	35 (21.5%)	26 (26.5%)	9 (13.4%)	14 (30.4%)	7 (43.8%)	7 (23.3%)
Missing / unknown	6 (3.7%)	1 (1%)	5 (7.5%)	5 (10.9%)	1 (6.3%)	4 (13.3%)
Complex cases	(n=70)	(n=48)	(n=23)	(n=32)	(n=16)	(n=16)
Blood	38 (54.3%)	27 (56.3%)	13 (56.5%)	20 (62.5%)	10 (62.5%)	10 (62.5%)
Bone biopsy	5 (7.1%)	5 (10.4%)	0	5 (15.6%)	5 (31.3%)	0
Joint aspirate	17 (24.3%)	12 (25%)	5 (21.7%)	12 (37.5%)	8 (50%)	4 (25%)
Pus (periosteal)	14 (20%)	13 (27.1%)	1 (4.3%)	9 (28.1%)	8 (50%)	1 (6.3%)
Pus/Wound swab	18 (25.7%)	14 (29.2%)	4 (17.4%)	10 (31.3%)	7 (43.8%)	3 (18.8%)
Other	16 (22.9%)	12 (25%)	4 (17.4%)	12 (37.5%)	8 (50%)	4 (25%)
Missing/ unknown / not applicable	4 (5.7%)	3 (6.3%)	1 (4.3%)	4 (12.5%)	3 (18.8%)	1 (6.3%)

Treatment

Antibiotic treatment

Clinical time-line

Almost all children received antibiotics both intravenously and orally..

Table 31 below gives time-lines for antibiotic use where data for start and end dates are available.

202 (93%) of simple cases received IV, compared with 91 (96%) of complex cases. However for one SC discharge antibiotic data were missing so no end-date was known, and for two CCs dates for antibiotics were missing. The average time on IV for SC was a median (IQR) of 8 (5, 15) days. For CC, time on IV antibiotics was on average longer: median of 17 (IQR 8, 34) days. See

Table 31 for more information on children that did not have IV.

Not all children that had IV switched to oral antibiotics. Some oral antibiotics were given concurrent to IV treatment. 81% of simple cases had some form of oral antibiotic for a median total of 28 days. 66.3% of complex cases had oral antibiotics, also for a median total of 28 days.

The total time from first antibiotic to last was a median of 34 days in simple cases and 39 days in complex cases. Note that a small number of children had breaks in treatment - this measure included these breaks in the total.

Differences between SA and OM

Duration of IV antibiotics used for SA is similar to OM, both in complex as in simple cases. The median of total antibiotic treatment is 40 days for OM versus 30 days for SA for simple cases. This difference is also present in the complex cases (42 days vs 28.5 days, respectively) (See *Table 32*).

TABLE 31: CLINICAL TIME-LINE FOR ANTIBIOTIC TREATMENT

Antibiotic Treatment Time-line (Days)	n (%)	Median (IQR)	Min, Max
Simple cases (n=218)			
Length of time on:			
IV ^(a)	202 ^(c) (92.7%)	8 (5, 15)	(0, 220) ^(d)
Oral ^(a)	176 (80.7%)	28 (16, 36.5)	(0, 197) ^(d)
Total ^(b)	210 (96.3%)	34 (20, 45)	(0, 220) ^(d)
Complex cases (n=95)			
Length of time on:			
IV ^(a)	91 ^(e) (95.8%)	17 (8, 38)	(0, 112) ^(d)
Oral ^(a)	63 (66.3)	28 (16, 42)	(1, 226)
Total ^(b)	92 (96.8%)	39 (23, 53)	(1, 236)

^(a)Number of days taking antibiotics; ^(b)Number of days from first to last antibiotic irrespective of route (includes breaks in treatment); ^(c)One additional simple case had IV but only the start date is known, so time on IV cannot be calculated; ^(d)Where a child's treatment was started and stopped on the same day, the length of time is calculated as 0 days; ^(e)Two additional complex cases had IV but start and end-dates are missing.

TABLE 32: CLINICAL TIME-LINE FOR ANTIBIOTIC TREATMENT (BY SA/OM)

Antibiotic Treatment Time-line (Days)	SA		OM	
	n (%)	Median (IQR)	n (%)	Median (IQR)
Simple cases (n=107)			(n=109)	
Length of time on:				
IV ^(a)	103 (96.3%)	7 (4, 13)	97 (89%)	9 (6, 16)
Oral ^(a)	85 (79.4%)	28 (14, 34)	90 (82.6%)	30.5 (21, 42)
Total ^(b)	103 (96.3%)	30 (18, 41)	105 (96.3%)	40 (21, 48)
Complex cases (n=35)			(n=56)	
Length of time on:				
IV ^(a)	33 (94.3%)	14 (7, 24)	54 (96.4%)	18.5 (8, 42)
Oral ^(a)	24 (68.6%)	25.5 (14, 35)	35 (62.5%)	28 (23, 42)
Total ^(b)	34 (97.1%)	28.5 (15, 46)	54 (96.4%)	42 (26, 57)

Antibiotic regimes: overall

At initiation of IV treatment, over half of children (both types of case combined) were given one antibiotic (57.7%).

Switch from IV to oral was different for simple cases to complex cases. In SC switch occurred at a median of 7 days from start of IV, whereas for CC this was at a median of 13.5 days. See

Table 33 for percentages of children with known switch dates that switched less than 1 week; 2 weeks; and more than 2 weeks post commencement of IV treatment. See also *Figure 1* below for a profile of time-to-switch in the form of a Kaplan-Meier plot. This clearly shows that in CCs the switch to oral antibiotics was later, and that half of the simple cases had switched or stopped IV by 9 days compared to 21 days for complex cases (time when curves drop to 0.5 on the vertical axis).

Of those where no switch date is known, the majority had no record of any oral antibiotics to be prescribed consecutive to their IV treatment.

In simple cases 63.8% had less than 6 weeks total antibiotic treatment compared with 51.6% of complex cases. *Figure 2*: Kaplan-Meier plot showing time-to-switch (by SA/OM) shows there is little difference in time to switch to oral antibiotics between OM and SA in the simple cases group. For complex cases, switch timing was similar for OM and SA when switch took place before 2 weeks, but after this OM cases were switched to oral antibiotics later than the SA cases.

For each antibiotic prescribed, a daily dose per kg weight of child was calculated. Each dose was classified as ‘Higher Formulary’ (HF) (recommended intensive dosing as recommended by the current bone and joint infection guidelines on the treatment of severe infections) or ‘Not Higher Formulary’ (NHF) (following standard British National Formulary for Children (BNFC) dosing guidelines for antibiotics). In simple cases 40.4% of children received a higher formulary initial dose of antibiotics, compared with 29.5% of complex cases. Most children received both HF doses and NHF doses during their treatment (57% for SC and 62% for CC). 13.8% of simple cases received higher formulary doses throughout their treatment compared with 9.5% of complex cases. See

Table 33 for further details.

The total number of antibiotics prescribed for each route was calculated for each child. So for example if a child had 2 records of oral flucloxacillin and one record of co-amoxiclav, then they would have had a total of 2 antibiotics orally. NB this calculation is limited to instances of the antibiotics: flucloxacillin, clindamycin, cefuroxime, ceftriaxone, amoxicillin, co-amoxiclav, rifampicin, vancomycin, fusidic acid, benzyl penicillin, teicoplanin, and ‘other’. All ‘other’ antibiotics were combined as one type for the sake of parsimony. In simple cases,

a single IV antibiotic and/or a single oral antibiotic was the most common treatment strategy employed, whereas for complex cases there were even likelihoods of 1, 2 or more than 2 IV antibiotics being used together with a single oral antibiotic type. See

Table 33 for further details.

TABLE 33: TYPES OF ANTIBIOTIC REGIMES EXPERIENCED

Antibiotic Regime	Simple cases (n=218)		Complex cases (n=95)	
	n (%)	Median (IQR) days	n (%)	Median (IQR) days
No. of different antibiotics given at initiation of IV treatment				
1	131 (60.1%)		53 (55.8%)	
2 or more	72 (33%)		38 (40%)	
No IV antibiotics given	12 (5.5%)		3 (3.2%)	
Unknown	3 (1.4%)		1 (1.1%)	
Timing of oral switch				
Switch date known	168 (77.1%)	7 (5, 13)	62 (65.3%)	13 (7, 24)
< 1 week	73 (43.5%)	4 (3, 5)	12 (19.4%)	3.5 (2.5, 5.5)
1-2 wks	62 (36.9%)	10 (8, 13)	21 (33.9%)	9 (8, 10.5)
> 2 wks	33 (19.6%)	21 (16, 30)	29 (46.8%)	26 (20, 41)
No switch date	50 (22.9%)		33 (34.7%)	
Child stayed on IV	35 (70%)	15 (7, 30)	29 (87.9%)	25 (11, 44)
No IV	15 (30%)		4 (12.1%)	
Total course of antibiotics				
< 6 weeks	139 (63.8%)		49 (51.6%)	
≥ 6 weeks)	71 (32.6%)		43 (45.3%)	
Had no antibiotics / unknown	8 (3.7%)		3 (3.2%)	
Dose				
First dose HF ^(a)	88 (40.4%)		28 (29.5%)	
HF ^(a) throughout	30 (13.8%)		9 (9.5%)	
No HF ^(a) doses given	53 (24.3%)		23 (24.2%)	
Combination	124 (56.9%)		59 (62.1%)	
Unknown / N/a	11 (5%)		4 (4.2%)	
Total number of antibiotics prescribed				
IV:				
0	15 (6.9%)		4 (4.2%)	
1	88 (40.4%)		26 (27.4%)	
2	81 (37.2%)		31 (32.6%)	
>2	34 (15.6%)		34 (35.8%)	
Oral:				
0	41 (18.8%)		28 (29.5%)	
1	129 (59.2%)		41 (43.2%)	
2	43 (19.7%)		20 (21.1%)	
>2	5 (2.3%)		6 (6.3%)	

^(a)HF: higher formulary dose treatments recommended for bone/joint infections.

FIGURE 1: KAPLAN-MEIER PLOT SHOWING TIME-TO-SWITCH

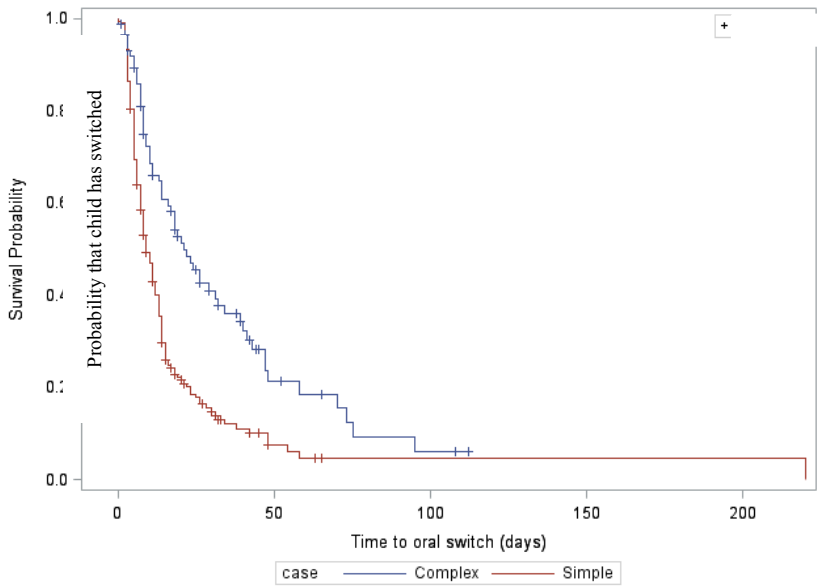


FIGURE 2: KAPLAN-MEIER PLOT SHOWING TIME-TO-SWITCH (BY SA/OM)

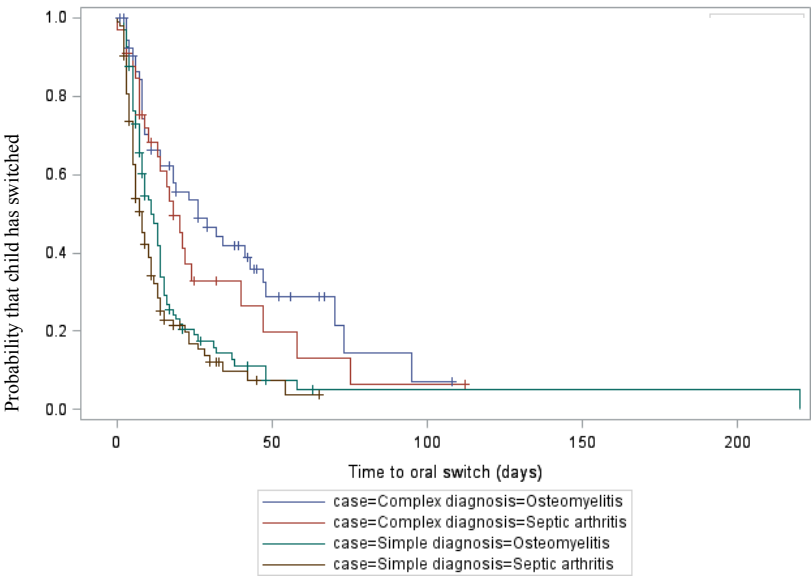


TABLE 34: TYPES OF ANTIBIOTIC REGIMES EXPERIENCED (BY SA/OM)

Antibiotic Regime	SA n (%)	Median (IQR) days	OM n (%)	Median (IQR) days
Simple cases	(n=107)		(n=109)	
Timing of oral switch				
Switch date known	85 (79.4%)	6 (4, 11)	82 (75.2%)	8.5 (5, 14)
< 1 week	47 (55.3%)	4 (3, 5)	26 (31.7%)	5 (3, 5)
1-2 wks	26 (30.6%)	10 (8, 12)	35 (42.7%)	9.5 (8, 13)
> 2 wks	12 (14.1%)	26 (18, 34)	21 (25.6%)	18.5 (15.5, 25.5)
No switch date	22 (20.6%)		27 (24.8%)	
Child stayed on IV	18 (81.8%)	14.5 (7, 30)	15 (55.6%)	17 (7, 27)
No IV	4 (18.2%)		12 (44.4%)	
Total course of antibiotics				
< 6 weeks	79 (73.8%)		58 (53.2%)	
≥ 6 weeks)	24 (22.4%)		47 (43.1%)	
Had no antibiotics / unknown	4 (3.7%)		4 (3.7%)	
Complex cases	(n=35)		(n=56)	
Timing of oral switch				
Switch date known	23 (65.7%)	13.5 (7, 21)	35 (62.5%)	10.5 (7.5, 26)
< 1 week	5 (21.7%)	2 (2, 5)	7 (20%)	4 (3, 6)
1-2 wks	7 (30.4%)	9 (7, 13)	12 (34.3%)	8.5 (8, 10.5)
> 2 wks	11 (47.8%)	21.5 (18, 47)	16 (45.7%)	29 (23, 41)
No switch date	12 (34.3%)		21 (37.5%)	
Child stayed on IV	10 (83.3%)	38 (11, 52)	19 (90.5%)	14.5 (8, 25)
No IV	2 (16.7%)		2 (9.5%)	
Total course of antibiotics				
< 6 weeks	22 (62.9%)		26 (46.4%)	
≥ 6 weeks)	12 (34.3%)		28 (50%)	
Had no antibiotics/ unknown	1 (2.9%)		2 (3.6%)	

Antibiotic regimes in hospital

Table 33 and

Table 34 summarise which antibiotics were prescribed during hospital stay.

Simple Cases

Of the 199 children that had IV antibiotics during their hospital stay flucloxacillin (47.2%), ceftriaxone (36.7%) and cefuroxime (33.2%) were the most likely antibiotics to be prescribed. These three were also most likely as part of the initial treatment (see

Table 33).

78 (35.8%) of simple cases had at least one oral antibiotic prescribed. Of these, flucloxacillin was most likely (43.6%). Oral antibiotics were rarely used in conjunction with the initial IV treatment (see

Table 33).

Average doses in mg/kg-weight of child, statistics on frequency of dosing and proportion of doses prescribed for more than a week are given in

Table 33.

Complex Cases

Of the 91 children that had IV during their hospital stay flucloxacillin (52.7%), ceftriaxone (40.7%), clindamycin (27.5%) and cefuroxime (24.2%) were the most likely antibiotics to be prescribed. Flucloxacillin was most likely as part of the initial treatment (see

Table 36).

36 (37.9%) of complex cases had at least one oral antibiotic prescribed. Of these, clindamycin was most likely (33.3%). Oral antibiotics were not frequently used in conjunction with the initial IV treatment (see

Table 36).

Average doses in mg/kg-weight of child, statistics on frequency of dosing and proportion of doses prescribed for more than a week are given in

Table 36.

TABLE 35: IV AND ORAL ANTIBIOTICS PRESCRIBED PRIOR TO DISCHARGE (SIMPLE CASES)

Antibiotic	n (%) ^(a) of children		Median daily dose per kg weight of child (IQR) ^(b)	No. of prescriptions ^(b) given:					N(%) ^(c) of prescriptions of duration > 1 week ^(b)
	At least once	As part of initial ^(d) treatment		6 hourly	8 hourly	12 hourly	Once daily	Other or NK	
Simple cases									
IV	199 ^(e)								
Flucloxacillin	94 (47.2%)	85 (42.7%)	188.1 (100.8, 200)	106	4	0	2	3	32 (26.7%)
Clindamycin	22 (11.1%)	13 (6.5%)	39.9 (18.5, 40.6)	23	0	0	0	1	7 (28%)
Cefuroxime	66 (33.2%)	60 (30.2%)	141.5 (83.7, 150.6)	14	52	4	4	4	7 (8.4%)
Ceftriaxone	73 (36.7%)	51 (25.6%)	50.3 (50, 79.3)	1	1	1	82	1	38 (43.2%)
Benzyl Penicillin	20 (10.1%)	16 (8%)	160 (100.3, 191.2)	17	4	1	1	0	5 (20.8%)
Co-amoxiclav	16 (8%)	13 (6.5%)	89.5 (87.2, 89.95)	0	16	0	0	1	2 (11.8%)
Other	44 (22.1%)	24 (12.1%)	36.8 (11.25, 77.7)	11	28	10	11	2	16 (24.2%)
Oral	78								
Flucloxacillin	34 (43.6%)	2 (2.6%)	52.6 (38.5, 73.5)	37	0	0	0	0	11 (28.9%)
Clindamycin	17 (21.8%)	3 (3.8%)	22.7 (20.6, 37.3)	15	2	0	0	0	8 (44.4%)
Amoxicillin	4 (5.1%)	1 (1.3%)	96.4 (40.5, 167.1)	0	3	0	0	0	1 (25%)
Co-amoxiclav	18 (23.1%)	0	89.5 (87.2, 90.0)	0	14	3	0	2	6 (31.6%)
Rifampicin	10 (12.8%)	3 (3.8%)	20 (14.7, 20.3)	0	0	8	2	0	5 (45.5%)
Other	18 (23.1%)	3 (3.8%)	35 (21.6, 56.5)	5	8	3	4	1	8 (40%)

^(a) Denominators are the number of children that had IV/oral antibiotics during hospital stay; ^(b) More than one prescription of an antibiotic possible for an individual child; ^(c) Denominator is total number of antibiotic type prescribed where a duration is known. This is not always the same as the total number of frequencies of doses, as some frequencies were unknown – data not displayed; ^(d) Initial treatment defined as first course of IV; ^(e) 4 children that had IV did not start till the day of discharge from hospital.

TABLE 36: IV AND ORAL ANTIBIOTICS PRESCRIBED PRIOR TO DISCHARGE (COMPLEX CASES)

Antibiotic	n (%) ^(a) of children		Median daily dose per kg weight of child (IQR) ^(b)	No. of prescriptions ^(b) given:					n(%) ^(c) of prescriptions of duration > 1 week ^(b)
	At least once	As part of initial treatment ^(d)		6 hourly	8 hourly	12 hourly	Once daily	Other or NK	
Complex cases									
IV	91 ^(e)								
Flucloxacillin	48 (52.7%)	38 (41.8%)	142.6 (98, 198.5)	46	2	1	0	4	20 (35.1%)
Clindamycin	25 (27.5%)	10 (11%)	33.3 (24.1, 39.2)	21	0	0	0	4	9 (30%)
Cefuroxime	22 (24.2%)	17 (18.7%)	128 (83.3, 150)	7	13	2	0	3	4 (14.3%)
Ceftriaxone	37 (40.7%)	19 (20.9%)	77.7 (49, 80)	0	0	0	43	0	13 (28.9%)
Benzyl Penicillin	16 (17.6%)	10 (11%)	100 (87.3, 173.2)	11	1	0	1	3	7 (41.2%)
Co-amoxiclav	10 (11%)	10 (11%)	90 (74.2, 91.5)	0	11	0	0	0	3 (25%)
Other	30 (33%)	19 (20.9%)	30.6 (17.1, 142.9)	17	28	15	15	7	33 (35.5%)
Oral	36								
Flucloxacillin	6 (16.7%)	0	65.2 (42.9, 88.2)	6	0	0	0	0	3 (42.9%)
Clindamycin	12 (33.3%)	1 (2.8%)	23.8 (12, 24.4)	10	1	0	0	2	6 (46.2%)
Amoxicillin	5 (13.9%)	0	33.1 (3.1, 52.1)	0	3	0	0	1	1 (20%)
Co-amoxiclav	9 (25%)	1 (2.8%)	43 (31.8, 49.7)	0	8	1	0	1	3 (33.3%)
Rifampicin	4 (11.1%)	0	18.6 (17.8, 20)	0	0	6	0	0	13 (28.9%)
Other	13 (36.1%)	4 (11.1%)	30.2 (18.5, 46.9)	0	12	5	4	0	9 (39.1%)

^(a) Denominators are the number of children that had IV/oral antibiotics during hospital stay; ^(b) More than one prescription of an antibiotic possible for an individual child; ^(c) Denominator is total number of antibiotic type prescribed where a duration is known. This is not always the same as the total number of frequencies of doses, as some frequencies were unknown – data not displayed; ^(d) Initial treatment defined as first course of IV; ^(e) 2 children that had IV have missing dates, so can't ascertain whether this was prior to discharge.

Children that did not have IV antibiotics

15 simple cases did not receive any IV antibiotics. 13 were given oral antibiotics, and 2 had no record of receiving any antibiotic treatment neither in hospital nor at discharge.

4 complex cases had no IV antibiotics. Two of these have missing antibiotic data, and two had no record of receiving any antibiotic treatment neither in hospital nor at discharge.

Table 37 gives information about the characteristics of these 19 children.

TABLE 37: CHARACTERISTICS OF CHILDREN THAT WERE GIVEN NO IV

Presentation	Simple cases (n=15)	Complex cases (n=4)
Age		
< 1 year	0	2
1-6 yrs	9	0
6-16 yrs	6	2
Presenting to:		
GP	6	3
Emergency Department	9	1
Limbs/Joints affected:		
Hip	3	1
Shoulder	-	1
Knee	3	-
Ankle	2	1
Humerus	-	1
Femur	-	1
Foot	1	-
Tibia	1	-
Fibula	1	-
Elbow	1	-
Calcaneum	2	-
Not specified	1	-
Diagnosis:		
OM	11	2
SA	4	2
Given oral antibiotics:		
Yes	13	0
No	2	2
Missing antibiotics data	0	2

Use of blood tests to determine switch

This section investigates which blood test were carried out at switch from IV to oral antibiotics. *Table 38* provides statistics for blood tests on the day of switch or the day before, for children where a switch date could be ascertained. Where blood tests were available for both days, the tests on the day of switch were used.

Of the children where a switch date is known, 37.9% of simple cases had a blood test at switch; 22.8% of complex cases. Most of these had the full range of measurements, with the exception of ESR. Where blood tests were taken, CRP was measured in 91.8% of simple cases and 84.6% of complex cases.

Median and inter-quartile ranges for blood tests are given in *Table 39*. 42 simple cases and 9 complex cases had blood tests both at presentation and switch. For each of these children switch results were expressed as a percentage of diagnosis results. These percentages are summarised in the table. Median percentages close to 100 indicate no change on average from diagnosis. For most children's measurements of Hb stayed the same; WBC, N and CRP dropped to greater or lesser degrees; ESR varied – halving for some and doubling for others; and Platelets rose. CRP was the measurement that had the lowest median percentage of the concentration at diagnosis. CRP as a proportion of its maximal value prior to switch was a median of 25% in both simple and complex cases, though the inter-quartile ranges show that children varied considerably in this.

TABLE 38: BLOOD TESTS CARRIED OUT IMMEDIATELY PRIOR TO ORAL SWITCH

Blood tests ^(a) at switch ^(b)	n (%) of cases with test results at switch ^(b)			Median (IQR) test results	Median (IQR) percentage of diagnosis results	Median (IQR) percentage of CRP _{max}
	All	Tertiary	Secondary			
Simple cases	(n=161)^(c)				(n=42)^(d)	(n=56)^(e)
At least one test	61 (37.9%)	44	17	-		
Hb	48 (78.7%)	32 (72.7%)	16 (94.1%)	111 (106, 120)	99.55 (92.75, 105.1)	-
WBC	47 (77%)	32 (72.7%)	15 (88.2%)	8.9 (7.47, 11.3)	70.6 (61.7, 85)	-
N	48 (78.7%)	32 (72.7%)	16 (94.1%)	3.345 (2.5, 4.635)	48.95 (29.7, 74.5)	-
Plt	46 (75.4%)	31 (70.5%)	15 (88.2%)	470.5 (397, 576)	126.5 (106.05, 152.05)	-
CRP	56 (91.8%)	40 (90.9%)	16 (94.1%)	9.15 (4.55, 21.5)	32.6 (12.5, 74.1)	25 (10.2, 63.4)
ESR	19 (31.1%)	10 (22.7%)	9 (52.9%)	23 (13, 43)	107.2 (46.2, 200)	-
CRP & ESR	17 (27.9%)	9 (20.5%)	8 (47.1%)	-	-	-
CRP & not ESR	39 (63.9%)	31 (70.5%)	8 (47.1%)	-	-	-
Complex cases	(n=57)^(c)				(n=9)^(d)	(n=11)^(e)
At least one test	13 (22.8%)	10	3	-	-	-
Hb	9 (69.2%)	7 (70%)	2 (66.7%)	108 (96, 111)	100 (88.1, 100)	-
WBC	9 (69.2%)	7 (70%)	2 (66.7%)	8.7 (7.9, 10.1)	92.9 (46.9, 100)	-
N	8 (61.5%)	6 (60%)	2 (66.7%)	2.25 (1.715, 3.2)	51.3 (23.3, 80)	-
Plt	11 (84.6%)	9 (90%)	2 (66.7%)	383 (311, 569)	108.05 (102.4, 177.7)	-
CRP	11 (84.6%)	8 (80%)	3 (100%)	13 (4, 26)	28.8 (14.5, 100)	25 (9.1, 100)
ESR	4 (30.8%)	3 (30%)	1 (33.3%)	35 (15.5, 63)	94.6 (57.5, 131.7)	-
CRP & ESR	3 (23.1%)	2 (20%)	1 (33.3%)	-	-	-
CRP & not ESR	8 (61.5%)	6 (60%)	2 (66.7%)	-	-	-

^(a) See Table 39 for units of measurements; ^(b) On same day or day before switch; ^(c) Total number of children that had a switch; ^(d) Total number of children that had at least one blood test both at diagnosis and immediately prior to switch; ^(e) Total number of children that had at least one measurement of CRP at switch

TABLE 39: SUMMARY OF BLOOD TESTS AT SWITCH (BY SA/OM)

Blood tests at switch	SA		OM	
	n	Median (IQR)	n	Median (IQR)
Simple cases				
Hb (g/dL)	29	111 (107, 123)	19	109 (101, 117)
WBC (10 ⁹ /L)	28	8.85 (7.035, 11.065)	19	9.1 (7.98, 12.2)
N (10 ⁹ /L)	29	3.12 (2.5, 3.91)	19	3.5 (2.5, 5.1)
Plt (10 ⁹ /L)	28	495 (390.5, 583.5)	18	466 (426, 563)
CRP (mg/L)	33	12.4 (6, 22)	23	7 (4, 16)
ESR (mm/hr)	12	30.5 (18.5, 48)	7	13 (12, 37)
Complex cases				
Hb (g/dL)	3	100 (89, 111)	5	111 (108, 111)
WBC (10 ⁹ /L)	3	4.9 (4.24, 7.9)	5	10.1 (9, 10.36)
N (10 ⁹ /L)	3	1.7 (1.44, 3.4)	4	2.75 (2.25, 4.645)
Plt (10 ⁹ /L)	3	312 (202, 375)	6	492.5 (311, 569)
CRP (mg/L)	4	24.3 (7.8, 76)	6	15.35 (4, 25)
ESR (mm/hr)	0	-	2	15.5 (8, 23)

*2 SC and 4 CC complex cases could not be classified as uniquely SA or OM and are excluded here.

Post diagnosis surgery

21.6% of simple cases went on to have surgery after the start of IV, compared with 41.1% of complex cases. In both groups OM and SA cases were equally represented.

The most common procedure among the simple cases was aspiration (7.3%), for complex cases it was incision and drainage (16.8%) and this was often a wash-out in conjunction with another procedure. 11.6% of complex cases had at least one debridement (See *Table 40*).

When there was only one post diagnosis procedure carried out, this was most likely to be incision and drainage (52.6% and 43.8%) of single procedures for SC and CC respectively (see *Table 41*).

TABLE 40: SURGERY OCCURRING AFTER THE INITIATION OF IV ANTIBIOTICS (POST DIAGNOSIS)

Surgery post initiation of IV	n (%) of Simple cases (n=218)	n (%) of Complex cases (n=95)
At least one procedure	47 (21.6%)	39 (41.1%)
SA	24	17
OM	23	20
Number of procedures:		
1	19 (8.7%)	16 (16.8%)
2	21 (9.6%)	11 (11.6%)
>2	7 (3.2%)	12 (12.6%)
Type of procedure – n (%) of children with at least one:		
Aspiration	16 (7.3%)	8 (8.4%)
Incision and drainage	14 (6.4%)	16 (16.8%)
Drill decompression	2 (0.9%)	0
Curettage/excision	2 (0.9%)	2 (2.1%)
Arthrotomy	3 (1.4%)	1 (1.1%)
Arthroscopy	3 (1.4%)	5 (5.3%)
Amputation	0	1 (1.1%)
Debridement	5 (2.3%)	11 (11.6%)
Fasciotomy	0	0
Compartment decompression		
Secondary closure	2 (0.9%)	1 (1.1%)
Skin graft	0	1 (1.1%)
Other plastic surgery	7 (3.2%)	2 (2.1%)
Other	2 (0.9%)	0

TABLE 41: SINGLE PROCEDURES

Surgery post initiation of IV	Simple cases n (%) (n=19)	Complex cases n (%) (n=16)
Type of procedure where child had just one post IV surgery:		
Aspiration	4 (21.1%)	3 (18.8%)
Incision and drainage	10 (52.6%)	7 (43.8%)
Drill decompression	1 (5.3%)	-
Curettage/excision	1 (5.3%)	1 (6.3%)
Arthrotomy	-	1 (6.3%)
Arthroscopy	-	1 (6.3%)
Amputation	-	-
Debridement	2 (10.5%)	2 (12.5%)
Secondary closure	-	1 (6.3%)
Other	1 (5.3%)	-

Post diagnosis imaging

Imaging was carried out post diagnosis, both during hospital stay and after discharge. MRIs were the most used imaging technique in hospital, followed by x-rays and ultrasounds. This was the case in both simple and complex cases.

Of those scanned with MRI, a high proportion had abnormalities detected both prior to and post discharge. See *Table 42* for further detail.

TABLE 42: IMAGING TYPES ROUTINELY USED POST DIAGNOSIS

Imaging Type	n (%) of cases imaged at least once post-diagnosis		Of those imaged: n (%) with at least one abnormal result	
	Prior to discharge	Post discharge	Prior to discharge	Post discharge
Simple cases (n=215)				
X-ray	28 (12.8%)	45 (20.6%)	14 (50%)	18 (40%)
CT scan	3 (1.4%)	0	2 (66.7%)	-
Ultrasound	16 (7.3%)	6 (2.8%)	11 (68.8%)	5 (83.3%)
MRI	49 (22.5%)	14 (6.4%)	42 (85.7%)	13 (92.9%)
Bone-scan	5 (2.3%)	1 (0.5%)	3 (60%)	1 (100%)
Complex cases (n=92)				
X-ray	24 (25.3%)	28 (29.5%)	15 (62.5%)	14 (50%)
CT scan	3 (3.2%)	1 (1.1%)	3 (100%)	0
Ultrasound	21 (22.1%)	2 (2.1%)	18 (85.7%)	1 (50%)
MRI	36 (37.9%)	10 (10.5%)	35 (97.2%)	9 (90%)
Bone-scan	2 (2.1%)	0	2 (100%)	-

Length of hospital stay

Simple cases

The median length of stay in hospital was 7 days, with 50% of children staying for 6 days or longer but no longer than 12 days. Where children presented at a Tertiary centre, the length of stay was on average 3 days shorter than if presenting to a Secondary centre. Older children (> 6 years) had longer stays in hospital than younger children with a median stay of 10 days. (See *Table 43*)

Complex cases

The median length of stay in hospital was 9 days, with 50% of children staying for 6 days or longer but no longer than 18 days. Where children presented at a Tertiary centre, the length of stay was on average one day longer than if presenting to a Secondary centre.

The children that had the longest stays were under one year of age, staying on average for more than 2 weeks.

Differences between OM and SA

Patients with a simple SA tend to have a shorter hospital stay than the simple OM group (medians 6 days versus 9 days resp.) In the complex group this difference is less clear

(medians 8 days versus 9 days, resp.). See Table 44.

TABLE 43: LENGTH OF STAY IN HOSPITAL BY AGE GROUP AND PRESENTING CENTRE TYPE

Presenting Centre Type	n	Median (IQR) days			
		Age group			
		All	< 1 year	1-6 years	6-16 years
Simple cases			n=27	n=116^(a)	n=74
All	217 ^(a)	7 (4, 12)	7 (5, 12)	6 (3.5, 10.5)	10 (6, 15)
Tertiary	115	7 (4, 11)	7 (5, 10)	6 (3, 9)	8.5 (5, 13)
Secondary	102	9 (4, 14)	9.5 (5, 19.5)	7 (4, 12.5)	10.5 (7, 17)
Complex cases			n=13	n=44	n=38
All	95	9 (6, 18)	16 (9, 27)	8 (5, 14)	10 (6, 16)
Tertiary	54	9 (7, 19)	16 (9, 29)	8 (6, 19)	12 (7, 16)
Secondary	41	8 (6, 14)	18 (8, 27)	6 (3, 12)	8.5 (6, 15.5)

^(a)One child has missing discharge date and is excluded from this table. NB total numbers of children by case-type and age-group given in bold.

TABLE 44: LENGTH OF STAY BY SA/OM

Length of stay (days)	All	Diagnosis ^(b)	
		SA	OM
Simple cases	(n=217^(a))	(n=106)	(n=109)
Median (IQR)	7 (4, 12)	6 (4, 11)	9 (5, 13)
Complex cases	(n=95)	(n=35)	(n=56)
Median (IQR)	9 (6, 18)	8 (6, 15)	9 (6, 18.5)

^(a)One child has missing discharge date and is excluded from this table; ^(b) 2 SCs and 4 CCs could not be categorised as uniquely SA/OM.

Discharge antibiotics

A large proportion of children were known to have gone home on IV antibiotics (27.1% of SC and 42.1% of CC). No difference in proportion of children on IV treatment at discharge was seen between SA and OM patients (see

Table 45). For these children, the most likely IV antibiotic was ceftriaxone (69.5% for SC and 77.5% for CC). See *Table 46* for further details, including a summary of the dose in mg/kg-weight of child and a median prescribed duration for each antibiotic.

Oral antibiotics were quite varied. The key antibiotics for both case types were co-amoxiclav, flucloxacillin, clindamycin and cefalexin. See *Table 46* for further details, including a summary of the dose in mg/kg-weight of child and a median prescribed duration for each antibiotic.

TABLE 45: ANTIBIOTICS AT DISCHARGE BY SA/OM

Antibiotics at discharge	Diagnosis		
	All	SA	OM
Simple cases	(n=218)	(n=107)	(n=109)
Went home on:			
IV ^(a)	59 (27.1%)	30 (28%)	28 (25.7%)
Oral alone	130 (59.6%)	64 (59.8%)	65 (59.6%)
None/Unknown	29 (13.3%)	13 (12.1%)	16 (14.7%)
Complex cases	(n=95)	(n=35)	(n=56)
Went home on:			
IV ^(a)	40 (42.1%)	16 (45.7%)	23 (41.1%)
Oral alone	42 (44.2%)	15 (42.9%)	24 (42.9%)
None/Unknown	13 (13.7%)	4 (11.4%)	9 (16.1%)

(a) Children recorded as having a PICC line or peripheral cannula in situ at discharge and/or had IV antibiotics prescribed at discharge.

TABLE 46: ANTIBIOTIC REGIMES PRESCRIBED AT DISCHARGE

Antibiotic	n (%)	Median (IQR) daily dose per kg weight of child	Median (IQR) days planned duration
Simple cases (n=218)			
IV (n=59)			
Ceftriaxone	41 (69.5%)	50.7 (49.3, 79.4)	7 (3, 14)
Flucloxacillin	4 (6.8%)	98.05 (43.5, 155.7)	28 (14, 42)
Clindamycin	2 (3.4%)	21.6 (5.3, 37.9)	21 (14, 28)
Cefuroxime	1 (1.7%)	46.7 (46.7, 46.7)	14 (14, 14)
Other	9 (15.3%)	9.7 (9.7, 46.7)	17 (8, 42)
Oral (n=156) ^(a)			
Co-amoxiclav	58 (36.5%)	30.4 (13.8, 41.8)	28 (21, 31)
Flucloxacillin	46 (28.9%)	37.45 (14.15, 82.3)	28 (14, 38.5)
Clindamycin	17 (10.7%)	18.1 (6.1, 23.6)	34 (25, 42)
Cefalexin	20 (12.6%)	35 (24.5, 91.1)	26.5 (16.5, 35)
Other	62 (39%)	20.55 (9.3, 40.5)	28 (14, 42)
Complex cases (n=95)			
IV (n=40)			
Ceftriaxone	31 (77.5%)	65.35 (49, 80.3)	14 (10, 33)
Flucloxacillin	2 (5%)	35.8 (0.2, 71.4)	31.5 (14, 49)
Clindamycin	3 (7.5%)	4 (0.2, 8)	28 (13, 42)
Cefuroxime	0	-	-
Other	5 (12.5%)	12 (10.2, 55.3)	42 (42, 42)
Oral (n=58) ^(a)			
Co-amoxiclav	17 (28.8%)	23.1 (12.1, 47.6)	28 (14, 39)
Flucloxacillin	15 (25.4%)	41.7 (36.4, 54.1)	28 (21, 42)
Clindamycin	17 (28.8%)	15.1 (6, 23.8)	28 (14, 38.5)
Cefalexin	2 (3.4%)	62 (28.8, 95.2)	14 (7, 21)
Other	23 (39%)	18.7 (6.9, 28.7)	24.5 (14, 42)

(a) All children that had at least one dose of an oral antibiotic prescribed at discharge.

Follow-up

Adherence to discharge antibiotics

Almost three-quarters of children were followed up (71.6% of SC and 80.4% of CC, no difference between SA and OM). Of these, almost all reported that antibiotics were completed as planned (92.4% of SC and 92.1% of CC). See *Table 47* and *Table 48* for further details of the reasons for non-adherence in the 9 children where this did not happen.

TABLE 47: DISCHARGE ANTIBIOTIC REGIMES ADHERED TO

Adherence to prescribed antibiotic regimes	Simple cases (n=218)	Complex cases (n=95)
Number of children contacted for follow-up	157 (72%)	76 (80%)
SA	78 (72.9%)	27 (77.1%)
OM	79 (72.5%)	45 (80.4%)
Antibiotics completed as planned		
Yes	145 (92.4%)	70 (92.1%)
No	8 ^(a) (5.1%)	3 ^(a) (3.9%)
Stopped early	2	1
Changed	5	3
Unknown	2	0
Stopped early by:		
Parent	1	0
Hospital	0	1
GP	1	0
Changed by:		
Hospital	5	3
GP	0	0
Reason for shortening / change of regime:		
Unpalatable antibiotic	1	0
Diarrhoea	0	1
Rash	1	0
Resolution of symptoms	1	0
Recurrence of infection	2	1
Other ^(b)	2	2

^(a) One SC and one CC recorded antibiotics as having been both stopped early and changed; ^(b) See *Table 48*

TABLE 48: OTHER REASONS FOR SHORTENING OR CHANGING ANTIBIOTICS (AS RECORDED IN DATABASE)

Simple cases (n=2)	Complex cases (n=2)
• Patient refused to take medication	• Parent refusal for ongoing intravenous treatment
• PICC line stopped working so swapped to oral	• Hickman Line Infection

Complications

8.3% of simple cases and 16.8% of complex cases experienced at least one complication.

Table 49 lists the numbers of types of complication by action taken. The types listed were options given for data entry – as the table shows, many were not experienced (dislocation, subluxation, pathological complication, fracture and sinus). The category ‘Other’ was most selected – text entered to give more detail about these complications is given in Table 50 and Table 51.

TABLE 49: COMPLICATION TYPES BY ACTION TAKEN

Complication	n (%)	Action taken				
		None	Surgery	Change of antibiotic regime	Re-admission to hospital	Other action ^(b)
Simple cases (n=218)						
At least one complications	18 (8.3%)					
SA	8 / 107					
OM	9 / 109					
Complication type:						
Fever	1	-	-	-	1	-
Recurrence of infection	3	-	1	1	2	1
Dislocation	0	-	-	-	-	-
Subluxation	0	-	-	-	-	-
Pathological	0	-	-	-	-	-
Fracture	0	-	-	-	-	-
Sinus	0	-	-	-	-	-
Other (n=16) ^(a)	16	3	2	4	1	7
Complex cases (n=95)						
At least one complications	16 (16.8%)					
SA	8 / 35					
OM	7 / 56					
Complication type:						
Fever	0	-	-	-	-	-
Recurrence of Infection	4	-	3	2	1	1
Dislocation	0	-	-	-	-	-
Subluxation	0	-	-	-	-	-
Pathological	0	-	-	-	-	-
Fracture	0	-	-	-	-	-
Sinus	0	-	-	-	-	-
Other (n=13) ^(a)	19	0	1	4	2	12

^(a)See Table 50, ^(b)See Table 51.

TABLE 50: OTHER COMPLICATIONS AS THEY APPEAR IN THE DATABASE

Simple cases (n=16) *	Complex cases (n=13) *
• Possible infectious endocarditis • Allergic reaction - rash • Post traumatic arthritis ankle • Possible development of Brodies abscess • Coccydynia pain around scar • Diagnosis inconclusive. Patient underwent drilling and washout of right femur • Diarrhoea • Femoral vein thrombus • Increased swelling of knee • Patient experiencing increased pain of the left knee • Phlebitis • Reaction to Teicoplanin • Self limiting pain episodes • Stiffness • Urticarial rash on lower abdomen, upper back, left side of back, behind both knees, right wrist and antecubital fossa and right leg around patella region • Worsening pain in sacrum	• Acute Kidney Injury • Blocked PICC line, replaced under general anaesthesia • Cardiac Tamponade • Conjunctivitis & dermatitis • Fever Abdominal pain and diarrhoea • Forearm rotation reduced • Hickman line sepsis • Long line blocked • Long line leaking • Major haemorrhage post Renal Biopsy • Needs insoles to stop foot going into varus position due to removal of navicular • Numbness to toes • Pain, night sweats • Pneumococcal meningitis • Post-op complications – Staph. aureus septicaemia/osteomyelitis • Respiratory distress • RSV bronchiolitis • Skin rash • Tracheostomy

*n is number of children

TABLE 51: OTHER ACTIONS IN RESPONSE TO COMPLICATIONS AS THEY APPEAR IN THE DATABASE

Simple cases (n=8) *	Complex cases (n=13) *
• Blood cultures, Electrocardiogram • Blood tests and ultrasound scan • Cold press • Enoxaparin on Haematology advice • Follow up, ankle fusion required in medium term • Hand therapist mobilisation • Bloods and MRI, referral to tertiary hospital	• 48 hours high frequency oscillation ventilation then conventional ventilation. • Embolisation of left kidney • Long line removed • On Haemofiltration • Pericardial drain in situ • Physiotherapy • Podiatry - insoles • PICC line removed and replaced under general anaesthesia • Repeat MRI scan • Not specified (n=4)

*n is number of children

On-going symptoms

Of the children that were followed up, 27 (17.2%) of simple cases had at least one on-going symptom. 18 of these were still in pain. Other symptoms were less common. 18 (24%) of complex cases had at least one on-going symptom. Types of symptoms were more diverse in this group: 8 of were still in pain, 8 had joint stiffness and 5 had a deformity. (See *Table 52*)

TABLE 52: ON-GOING SYMPTOMS AT FOLLOW-UP

Symptom	Simple cases (n=157)	Complex cases (n=76)
At least one on-going symptom at follow-up	27 (17.2%)	18 (23.7%)
SA	9 / 78	6 / 27
OM	18 / 79	10 / 45
Types of symptom:		
Pain	18 (11.5%)	8 (10.5%)
Fever > 38C	3 (1.9%)	2 (2.6%)
Joint Stiffness	6 (3.8%)	8 (10.5%)
Immobility	4 (2.5%)	3 (3.9%)
Fracture	0	0
Sinus	2 (1.3%)	0
Deformity	2 (1.3%)	5 (6.6%)

Treatment failure

Treatment failure is defined as any of the following complications or on-going symptoms at follow-up:

- Fever
- Recurrence of infection
- Dislocation
- Subluxation
- Pathological fracture
- Development of a draining sinus
- Other: pain, stiffness, mobility problems, swelling, numbness, increase in CRP compared to discharge

And/or any of the following actions arising from a complication:

- Re-admission to hospital
- Surgery

- Change of antibiotics

Under this definition, 32 simple cases (14.7%) experienced a treatment failure, compared with 24 (25%) of the complex cases. *Table 53* till

Table 56 investigate associations between treatment failure and diagnosis, switch timing, length of time on antibiotics, and surgery during hospital stay. Note that observed associations do not necessarily imply causal links that explain likelihood of treatment failure.

Diagnosis group

In simple cases treatment failure was half as likely in SA compared with OM (9.3% vs 19.3% resp.), whereas for complex cases treatment failure was more likely in SA than OM (28.6% vs 21.4% resp.). (See *Table 53*)

Switch timing

In simple cases treatment failure was less likely, the earlier switch occurred. Of the 73 simple cases that had a very early oral switch (less than a week), 9.6% experienced a treatment failure, compared with 16.1% that had an early switch (between one and 2 weeks), and 18.2% where switch was standard (after 2 weeks of IV). These comparisons are also represented by odds ratios, showing that the chance of failure for very early switch is half that for switch after 2 weeks. For complex cases, switches after 2 weeks had the highest chance of complication (37.9%), compared with 25% of very early switches and 19% of switches at between 1 and 2 weeks. (See *Table 54*)

Length of time on antibiotics

In simple cases, treatment failure was equally likely for children that had antibiotics for less than 6 weeks as for those that had courses for more than 6 weeks. For complex cases however, children given antibiotics for less than 6 weeks were much less likely to have a treatment failure than those given more than 6 weeks (14.3% vs 37% resp.). (See *Table 55*)

Surgery during hospital stay

Table 56 gives the numbers of children that had treatment failures according to and whether any surgery was carried out during their hospital stay. There was no indication of an association between treatment failure and surgery in either case type.

TABLE 53: TREATMENT FAILURE BY SA/OM

Treatment Failure	All n (%)	Diagnosis	
		SA	OM
Simple cases	(n=218)	(n=107)	(n=109)
Treatment failed	32 (14.7%)	10 (9.3%)	21 (19.3%)
Other	186 (85.3%)	97 (90.7%)	88 (80.7%)
Odds ratio ^(a)	-	0.43	1.00
Complex cases	(n=95)	(n=35)	(n=56)
Treatment failed	24 (25.3%)	10 (28.6%)	12 (21.4%)
Other	71 (74.7%)	25 (71.4%)	44 (78.6%)
Odds ratio ^(a)	-	1.47	1.00

^(a) Odds of treatment failure (SA compared with OM)

TABLE 54: TREATMENT FAILURE BY SWITCH TIMING

Treatment Failure	All n (%)	Switch			
		< 1 wk	1-2 wks	> 2 wks	No switch / unknown
Simple cases	(n=218)				
Treatment failed	32 (14.7%)	7 (9.6%)	10 (16.1%)	6 (18.2%)	9 (18%)
Other	186 (85.3%)	66 (90.4%)	52 (83.9%)	27 (81.8%)	41 (82%)
Odds ratio ^(a)	-	0.48	0.87	1.00	-
Complex cases	(n=95)				
Treatment failed	24 (25.3%)	3 (25%)	4 (19%)	11 (37.9%)	6 (18.2%)
Other	71 (74.7%)	9 (75%)	17 (81%)	18 (62.1%)	27 (81.8%)
Odds ratio ^(a)	-	0.55	0.39	1.00	-

^(a) Odds of treatment failure (switch timings compared with > 2wks switch time)

TABLE 55: TREATMENT FAILURE BY LENGTH OF TIME ON ANTIBIOTICS

Treatment Failure	All n (%)	Total course of antibiotics		
		< 6 wks	≥ 6 wks	Unknown
Simple cases	(n=218)			
Treatment failed	32 (14.7%)	20 (14.4%)	10 (14.1%)	2 (25%)
Other	186 (85.3%)	119 (85.6%)	61 (85.9%)	6 (75%)
Odds ratio ^(a)	-	1.03	1.00	-
Complex cases	(n=95)			
Treatment failed	24 (25.3%)	7 (14.3%)	16 (37.2%)	1 (33.3%)
Other	71 (74.7%)	42 (85.7%)	27 (62.8%)	2 (66.7%)
Odds ratio ^(a)	-	0.28	1.00	-

^(a) Odds of treatment failure (compared with ≥ 6 wks on antibiotics)

TABLE 56: TREATMENT FAILURE AND SURGERY PRIOR TO DISCHARGE

Treatment Failure	All n (%)	Had any surgery prior to discharge?		
		Yes	No	Unknown
Simple cases	(n=218)			
Treatment failed	32 (14.7%)	15 (15.6%)	17 (14.5%)	0
Other	186 (85.3%)	81 (84.4%)	100 (85.5%)	5 (100%)
Odds ratio ^(a)	-	1.09	1.00	-
Complex cases	(n=95)			
Treatment failed	24 (25.3%)	16 (28.1%)	8 (22.2%)	0 (0%)
Other	71 (74.7%)	41 (71.9%)	28 (77.8%)	2 (100%)
Odds ratio ^(a)	-	1.37	1.00	-

^(a)Odds of treatment failure (compared with no surgery)

Discussion

This multicentre national UK service evaluation has defined the current case load, disease spectrum and clinical practice in the diagnosis & treatment of OM/SA in secondary & tertiary UK care to provide information regarding the feasibility of a future RCT design.

Number of cases who may be offered participation in a future RCT

Any future RCT will need to enrol cases defined as simple disease where there is no underlying chronic disease, no orthopaedic implants and no recent (within 6 months) orthopaedic surgery. Overall, 313 cases had simple or complex disease, of which 109 had simple OM, 107 simple SA and 2 were defined as having simple disease but both or undifferentiated OM or SA. The monthly accrual was 0 to 3 simple cases per month in tertiary centre, 0-0.7 per month in secondary centres. The overall sample characteristics were as expected from previous literature. Of the 313 cases, 55.3% were male, 12.8% were under 1 year, 51.4% between the 1st and 6th birthday and 35.8% aged 6-16 years. The most likely joints/limbs affected in simple disease were the hip (21.1%); the knee (24.8%); and the ankle (13.3%). Complex cases showed similar proportions of joints/bones affected (23.2%, 20% and 17.9% respectively) though often with multiple rather than single joint/bone infections. SA was more likely in hips and knees than OM in both simple and complex cases, whereas OM affected a much larger range of joints/limbs.

In considering the healthcare environment to which children first presented, most attended emergency departments (65% of simple cases, 70% complex). Only a third presented to primary care (28% simple, 14.7% complex) and very few to hospital outpatient clinics (3.7% of simple, 5.3% of complex cases).

Although not likely to impact on RCT choices, it was interesting to note that of simple cases, nearly 20% were described as having had a severe infection in the 12 months preceding the presentation, 13.3% a history of trauma and 18.8% at least one antibiotic in the month before presentation.

The diagnosis of OM and SA in children

As described in chapter 1, making a diagnosis of bone or joint infection in children involves history, clinical examination and non-specific and specific investigations. Our data suggested inconsistency between treating UK centres that appears unrelated to whether the patients presented to, or were treated by, secondary or tertiary centres.

Blood tests

In order to inform diagnostic decisions, we organised our data collection to record the details of blood tests both at presentation and on the day of or the day preceding the diagnosis. It was perhaps surprising that in our cohort, only 105 (48.2%) of the children with simple disease were recorded as having blood tests taken at presentation (*Table 14*). The fact that these data also show only 33.7% of complex case children to have had a blood test at presentation is surprising as this figure might have been expected to be higher than for simple cases. At first glance this suggests that our database question may not have been worded with enough clarity for the research staff to extract the correct information from the clinical records, or that not all blood tests carried out were recorded. However, we also collected information on the blood tests performed on the day of or the day immediately preceding the initiation of intravenous antibiotics (*Table 19*), the time-point at which for most cases there is an assumption that the diagnosis was made. It is also likely that clinicians performed blood tests at any point from presentation (with or without definitive symptoms suggestive of the diagnosis) or at any point up to when the diagnosis was actually made. As clinicians try to limit repeat blood tests in children unless there is clinical change or clinical uncertainty, it is probable that the blood test data are valid but that for some cases the blood tests at presentation are available; for others only the blood tests just prior to the initiation of antibiotics (ie just before diagnosis) are available; and for some both time-points are recorded.

We analysed whether white cell/neutrophil counts, CRP and ESR were performed at presentation/before diagnosis as well as the values of these parameters to inform decisions regarding potential entry to a clinical trial ie the usefulness in making the diagnosis of bone

and/or joint infection. We also tried to establish at which point the CRP reached maximum (CRP_{MAX}) recorded value to inform both diagnostic and subsequent monitoring decisions. These data need to be interpreted in the light of the fact that the CRP_{MAX} recorded may have occurred before or after the initiation of antibiotics.

Of currently available and routinely requested non-specific blood test biomarkers, CRP alone was used most often of routinely measured parameters in making the diagnosis of OM or SA (although a low CRP does not exclude OM or SA). At presentation, CRP was higher in complex disease than simple (simple cases median 32 (IQR 11.8, 66.7), complex cases median 54 (IQR 24, 141)), which was not true for ESR (simple cases median 32 (IQR 20.5, 70)), complex cases median 28 (IQR 15, 55)) (*Table 15*). At this time point, neither CRP nor ESR were able to distinguish between SA or OM (CRP for SA median 32 (IQR 16.2, 65), for OM median 32.7 (IQR 10, 68); ESR for SA median 29 (IQR 14, 70.5), for OM median 35.5 (IQR 26, 68.5)) (*Table 16*). As expected, around half the number of ESR results were available for analysis compared to CRP (56 of 218 simple cases and 9 of 95 complex cases had ESR available compared to 99 of 218 and 31 of 95 for CRO in simple and complex cases respectively (*Table 15*). This was probably due both to the perceived lack of need (many paediatric clinicians are less likely to request ESR in current practice) and to the related fact that ESR is a technically harder test to perform than CRP due to the blood volume required and laboratory processes. A similar analysis is available for the blood tests performed on the day of or preceding the day of diagnosis. At this time point, CRP was also higher in complex disease than simple (simple cases median 38.3 (IQR 20, 74), complex cases median 86.7 (IQR 29, 161)), which was again not true for ESR (simple cases median 46 (IQR 25, 78), complex cases median 40 (IQR 21, 60)) (*Table 20*). Neither CRP or ESR were able to distinguish between SA or OM (CRP for SA median 35.5 (IQR 21.2, 72), for OM median 39.5 (IQR 14, 81); ESR for SA median 46 (IQR 23, 81), for OM median 47 (IQR 26, 76)) (*Table 21*). Again, around half the number of ESR results were available for analysis compared to CRP (83 of 218 simple cases and 17 of 95 complex cases had ESR available compared to 137 of 218 and 48 of 95 for CRP in simple and complex cases respectively (*Table 20*).

Overall, the CRP reached its highest recorded value at the start of the illness for simple disease and a few days after presentation for complex disease (CRP_{MAX} highest median day 0 (IQR 0, 6) for simple disease and median day 4 (IQR 1, 8) for complex disease (*Table 17*).

The total white cell or specific neutrophil counts at both presentation or just prior to initiation antibiotics were not shown to be of clinical use in determining whether to suspect or confirm SA or OM. Although for total WCC and neutrophil counts the normal ranges vary at different ages, there was overlap for both parameters between the normal range and WCC/neutrophil values recorded for children with simple or complex OM and SA (*Tables 15, 16, 20, 21*). As for many other serious infections in children, if the WCC and/or neutrophil count are raised this can inform making a diagnosis of bacterial infection, but normal results do not preclude the diagnosis and must not be used to rule out OM or SA.

Imaging

The use of imaging performed prior to intravenous antibiotics (prior to diagnosis of bone or joint infection) was determined. Overall, a radiological diagnosis was obtained for 51.8% of simple cases (at a median of 1 day post presentation (IQR 0, 3)), and 52.6% of complex cases (median of 1 day post presentation (IQR 0, 4)) (*Table 17*) although, as can be seen from the detailed discussion below, these data may be skewed by soft tissue abnormalities reported in formal X-ray reports. Regardless of the caution needed in interpreting this result overall, MRI has been shown to offer very high pick up rates of abnormalities compared to X-ray or ultrasound, and has almost completely replaced technicium bone scanning in current UK practice (*Tables 24, 25*). In detail, X-rays were commonly used (66% of simple cases of OM or SA combined, 62% complex cases); ultrasound was used in 41% of simple cases and 31% of complex cases; and MRI in 19% of simple and 21% of complex cases respectively. CT and technicium bone scan were rarely used (1% had CT for both simple and complex disease, 2% simple disease (and no complex cases) had a bone scan) (*Table 24*).

In simple disease, X-ray and ultrasound were equally used for OM and SA cases (*Table 25*). Around two thirds of simple and complex SA and OM had an X-ray prior to the initiation of intravenous antibiotics (*Table 18*). For simple SA 66 (63%) had X-ray of which 24 (36%) were abnormal. For simple OM, 66 (68%) had X-ray of which 26 (39%) were reported as abnormal. For complex SA, 8 (38%) of 21 X-rays reported abnormalities compared to 18 (55%) of the 33 complex OM who had X-rays taken prior to antibiotics. Due to the nature of the data collection in the study, these data must be interpreted with caution as it is likely that abnormalities recorded in the databased included soft tissue changes visible (and reported by radiologists) and not just bony abnormalities that would not be expected to be present early in the OM disease process. Ultrasound was used in 53 (51%) of simple SA cases and reported abnormal

in 43 (81%) where used. In complex SA there were 11 scans (33% cases) of which 9 were reported as abnormal (82%). In complex OM there were 16 scans (30% cases) of which 11 (69%) were reported as abnormal.

MRI was used more often in OM cases compared to SA cases and there was a high pick up rate of abnormalities where used (*Table 25*). 29 (30%) of simple OM had MRI of which 26 (90%) were reported as abnormal, and 16 (30%) of complex OM had MRI of which 16 (100%) were reported abnormal. For SA, MRI also had a high rate of diagnostic pickup. 9 (9%) of simple SA had MRI of which 8 (89%) were reported as abnormal, and 4 (12%) of complex SA had MRI of which 3 (75%) were reported abnormal.

For both simple and complex OM, MRI showed abnormalities in many different bones whereas for SA abnormalities were only seen in large joints (*Table 26*). The ability of MRI to detect widespread abnormalities explains the infrequency of technicium bone scanning over the course of the evaluation period. No bone scans were performed in complex SA or OM, only 1 in simple SA (which was abnormal) and only 3 (3% of cases) in simple OM of which 2 (67%) showed abnormality. No CT imaging was used in SA, 3 (3%) were used in simple OM (100% abnormal) and 1 (2%) in complex OM which was also abnormal (*Table 25*).

Surgery

Surgery is carried out before starting intravenous antibiotics in SA or OM in clinically severe disease, either to prevent destructive outcomes or in order to try to achieve microbiological diagnosis from surgical specimens; or where there is diagnostic dilemma.

Diagnostic surgery was carried out in more cases of SA than cases of OM prior to intravenous antibiotic therapy (for SA, 39 of 107 (36.4%) of simple and 15 of 35 (42.9%) complex cases; for OM, 21 of 109 (19.3%) of simple and 14 of 56 (25%) complex cases). Overall (SA and OM combined) surgery occurred earlier for SA than OM. For SA, the first surgery occurred at a median of 1 day from presentation, with 75% first surgical procedures by day 2 in simple cases and a median of 1 day from presentation, with 75% first surgical procedures by day 5 in complex cases. For OM, the first surgery occurred at a median of 1 day from presentation, with 75% first surgical procedures by day 10 in simple cases and at a median of 3 days from presentation, with 75% first surgical procedures by day 8 in complex cases. (*Table 18*).

In simple cases (OM and SA), “incision and drainage” (in 60.7%) and “aspiration” (in 55.7%) were the most likely types of surgery carried out before intravenous antibiotics were started,

with arthroscopy 3rd (9.8%). For complex cases, incision and drainage was most likely (62.1%), aspiration (24.1%) 2nd and debridement (17.2%) 3rd-most likely (*Table 22*).

Surgery was carried out more often in children with OM compared to SA (63.6% vs 37.5% resp. in the simple cases and 25.9% and 15.5% in the complex cases). From discussion at the investigator meeting (see *Chapter 5*), there remains the possibility that although the database has been populated directly from terms used in the clinical records, there may be overlap between different the technical terms used by orthopaedic surgeons for “incision and drainage” and “aspiration”. At database design we had intended “aspiration” to record needle aspiration, expected to be mainly of infected joints in suspected SA; and “incision and drainage” to represent a more formal open surgical procedure, expected to be of either OM or SA. In these data, incision and drainage was equally frequently performed in both groups (simple case SA 25%, OM 33%; complex case SA 13.4%, OM 9.3%) but there were also no reported differences in aspiration rates between SA and OM (simple case SA 23.1%, OM 30.3%; complex case SA 5.2%, OM 3.7%).

Surgical treatment after the initiation of antibiotics

21.6% of simple cases went on to have surgery after the start of IV, compared with 41.1% of complex cases. In both groups OM and SA cases were equally represented (*Table 40*).

The most common procedure among the simple cases was aspiration (7.3%), for complex cases it was incision and drainage (16.8%) and this was often a wash-out in conjunction with another procedure. 11.6% of complex cases had at least one debridement (*Table 40*).

Conventional microbiological tests

As for any invasive infections in children or adults, clinical best practice in OM and SA is to take samples for microbiological diagnosis prior to starting empirical antibiotics. The aim of tests is to make a microbiological diagnosis in order to determine further more specific antibiotic therapy and, for some specific pathogens such as PVL positive *Staphylococci*, to consider more complex or prolonged treatment regimens. Routinely available NHS microbiological tests are reported here, with a summary of the molecular data from a new targeted PCR test reported in *Chapter 3*.

Only 144 out of 218 (66.1%) children with simple OM or SA, and 59 out of 95 (62.1%) with complex OM or SA, had at least one test from either blood culture or tissue diagnosis (bone, joint aspirate or periosteal pus) (*Table 27*). Only 62% of simple cases and 54.3% of complex

cases had a blood culture. There was no difference in blood culture reporting rate between secondary and tertiary centres (*Table 30*).

Of the simple cases, in 38.2% the blood, tissue or synovial fluid sample tested positive for at least one micro-organism compared with 52.5% of complex cases. In OM cases 58% of the children had microbiology tests of which at least one microorganism was detected in 49%. In SA cases 73% was tested and in 36% a microorganism was found. (*Table 27*)

Of the blood, tissue or synovial fluid samples tested, *Staphylococcus aureus* was found in 20.1% of simple cases and 32.2% of complex. Other pathogens were far less common by routinely available tests (*Table 27*). The rates of PVL positive and MRSA positive *S. aureus* detected by all sample types were similar in simple and complex cases (PVL 2 of 29 (6.9%) *S. aureus* positive samples in simple cases, 1 of 19 (5.3%) *S. aureus* positive samples in complex cases; MRSA 1 of 29 (3.4%) *S. aureus* positive samples in simple cases, 1 of 19 (5.3%) *S. aureus* positive samples in complex cases). Only 1 case (complex) reported *S. aureus* erythromycin resistance (*Table 27*). Group A *Streptococcus*, *Kingella kingae*, Group B *Streptococcus* were not commonly detected by conventional microbiology (*Table 27*).

Medical treatment – intravenous course length and time before oral switch

All children in the study spent time in hospital. Most children with SA or OM went straight to hospital (median time from presentation to hospital referral 0 days (IQR 0,3) in simple cases, 1 day (IQR 0, 4) in complex) (*Tables 17, 18*).

Not all children received IV antibiotics. Overall, 15 (6.9%) simple cases and 4 (4.2%) complex cases either had no IV treatment, or the data are missing (SA simple 104 of 107 (97.2%) received IV antibiotic, complex 33 of 95 (94.3%); OM simple 97 of 109 (97%), complex 54 of 56 (96.4%)) (*Tables 17, 18*). Where started, antibiotics were initiated a little earlier in SA than OM (simple SA simple median 1 day (IQR 0, 3), complex median 2 days (0,4); OM simple median 2 days (1,5), complex 2 days (1,5)) (*Table 18*).

Although there was no difference in overall course length between simple or complex SA or between simple or complex OM, for both SA and OM complex cases spent more time on intravenous therapy (*Table 32*):

- For the 103 cases of simple SA treated with antibiotics, the median total course length was 30 days (IQR 18, 41) of which median 7 days (4, 13) were IV.

- For the 34 cases of complex SA treated with antibiotics, the median total course length was 28.5 days (IQR 15, 46) of which median 14 days (7, 24) were IV.
- For the 105 cases of simple OM treated with antibiotics, the median total course length was 40 days (IQR 21, 48) of which median 9 days (6, 16) were IV.
- For the 54 cases of complex OM treated with antibiotics, the median total course length was 42 days (IQR 26, 57) of which median 18.5 days (8, 42) were IV.

For a potential clinical trial of antibiotics in simple OM or SA, these data suggest that while the total course length may need to differ between OM and SA, it may be possible to plan for a similar length of initial IV therapy for both conditions.

The switch from IV to oral antibiotics was related to disease complexity, and not whether cases were SA or OM. Cases of simple SA/OM received less days of IV antibiotics than complex cases (*Figures 1, 2 and Tables 32, 33*). Of the children where a switch date is known, only 37.9% of simple cases and 22.8% of complex cases had a blood test at the switch (*Table 38*).

Where the switch date was recorded in the database:

- For the 85 of 107 (79.4%) cases of simple SA the median switch was after 6 days of IV (IQR 4, 11) and for 82 of 109 (75.2%) cases of simple OM the median switch was after 8.5 days of IV (IQR 5, 14).
- For the 23 of 35 (65.7%) cases of complex SA the median switch was after 13.5 days of IV (IQR 7, 21) and for 35 of 56 (62.5%) cases of complex OM the median switch was after 10.5 days of IV (IQR 7.5, 26).

As described above, the Kaplan-Meier plot showing time to switch (by SA/OM) shows there is little difference in time to switch to oral antibiotics between OM and SA in the simple cases group. For complex cases, switch timing was similar for OM and SA when switch took place before 2 weeks, but after this OM cases were switched to oral antibiotics later than the SA cases.

Overall, 63.8% simple cases (OM/SA) had less than 6 weeks total antibiotic treatment compared with 51.6% of complex cases (*Table 33*). Simple OM and SA were most commonly treated with a single IV antibiotic and/or a single oral antibiotic, whereas for complex SA/OM more than 2 IV antibiotics were used most often together with a single oral antibiotic type (*Table 33*).

Medical treatment – initial empirical antibiotic

In order to design a randomised clinical trial, consensus needs to be reached regarding the initial empirical antibiotic to be started intravenously, and also regarding the post-switch oral antibiotic(s) to be used both for the cases where there is or is not a formal microbiology diagnosis. Although not investigated in this study, data from Finland suggests children with culture-negative signs and symptoms of SA or OM can be treated in similar fashion to children where the organism is identified in respect of type and duration of antimicrobial therapy⁶². The aim of the microbiology component of this study aimed to establish the most appropriate initial empirical therapies.

Beta lactam antibiotics, either “simpler” penicillins or second or third generation cephalosporins are used widely in UK practice for the treatment of SA and OM. For the initial intravenous treatment of simple SA or OM in the 199 children that had IV antibiotics at any point during their hospital stay, 85 (42.7%) received flucloxacillin, 13 (6.5%) clindamycin, 60 (30.2%) cefuroxime, 51 (25.6%) ceftriaxone, 16 (8%) benzyl penicillin and 13 (6.5%) co-amoxiclav (with 24 (12.1%) receiving other antibiotics) (*Table 35*). For the initial intravenous treatment of complex SA or OM in the 91 children that had IV antibiotics at any point during their hospital stay, 38 (41.8%) received flucloxacillin, 10 (11%) clindamycin, 17 (18.7%) cefuroxime, 19 (20.9%) ceftriaxone, 10 (11%) benzyl penicillin and 10 (11%) co-amoxiclav (with 19 (20.9%) receiving other antibiotics) as part of initial treatment (*Table 36*).

Oral antibiotics were uncommon as part of initial therapy. 78 (35.8%) of simple cases had at least one oral antibiotic prescribed. Flucloxacillin (34 cases, 43.6%) clindamycin (17, 21.8%), co-amoxiclav (18, 23.1%) were all prescribed prior to discharge while in hospital (*Table 35*). 36 (37.9%) of complex cases had at least one oral antibiotic prescribed while in hospital, with a similar range of antimicrobials as for simple disease although more children had “other” antibiotics used for complex compared to simple disease (*Tables 35, 36*).

Medical treatment – antibiotic at hospital discharge

Children with OM or SA were discharged on either intravenous or oral antibiotics. At discharge, 30 (28%) of 107 cases of simple SA, and 28 (25.7%) of 109 cases of simple OM remained on intravenous antibiotics. Around 60% (64, 59.8% SA; 65, 59.6% OM) were taking only an oral antibiotic, and similar numbers of simple SA and OM were either on no antibiotic or the data is missing (13, 12.1% SA; 16, 14.7% OM). Children with complex disease were more likely to remain on intravenous medication at discharge (overall 40 of 95 (42.1%)

complex SA/OM were intravenous antibiotics, 42 (44.2%) oral and 13 (13.7%) none/unknown/missing) (*Table 45*).

As expected due to the formulations available for outpatient or home based therapy, a narrower range of drugs were prescribed compared to in-hospital therapy. For simple cases, most post-discharge intravenous therapy used ceftriaxone (41 of 59 (69.5%)), although a few children remained on flucloxacillin (4, 6.8%), clindamycin (2, 3.4%), cefuroxime (1, 1.7%) or other drugs (9, 15.3%). Complex cases were also mostly treated after discharge with ceftriaxone (31 of 40 (77.5%)), but a few were treated with flucloxacillin (2, 5%), clindamycin (3, 7.5%) or other drugs (5, 12.5%) (*Table 46*).

For oral discharge drugs, co-amoxiclav was used in approximately one third of cases (58 of 156 (36.5%) simple cases, 17 of 58 (28.8%) complex) and flucloxacillin in about one quarter (46 of 156 (28.9%) simple cases, 15 of 58 (25.4%) complex). Clindamycin was used more frequently orally in complex than simple cases (17 of 156 (10.7%) simple cases, 17 of 58 (28.8%) complex). Cefalexin was used in simple SA/OM but infrequently in complex disease (20 of 156 (12.6%) simple cases, 2 of 58 (3.4%) complex) (*Table 46*).

Medical treatment – dose of intravenous and oral antibiotics prescribed

Adequate dosing is a major concern of modern antimicrobial stewardship to ensure clinical cure with minimal risk of inpatient and in-hospital inter-patient antimicrobial resistance⁶³. Recent legislative changes to clinical trial legislation ensure newly available drugs are properly tested in children to establish dosing regimens and efficacy. However, almost all the widely used paediatric doses of antibiotics have been included in paediatric formularies having been established by opinion and practice rather than formal clinical trial. With much variation in international practice, the UK British National Formulary for Children (<https://www.evidence.nhs.uk/formulary/bnfc/current/>) as recently began to revise the recommended doses of commonly used antibiotics, for example in 2014 doubling the recommended age-band doses of oral amoxicillin compared to previous values. In addition, the UK BNFC is set out so that minimum and maximum doses for weight or age are specified. Many specialists in paediatric infection and paediatric microbiology, and NICE guidelines where they exist⁶⁴⁻⁶⁶ consider the high quoted doses to be the correct doses for serious (in-hospital) infections and that the low quoted doses are suboptimal. In order to inform the dose strategy for future a clinical trial it was important to assess the antibiotic doses used in current practice in the context of overall reported clinical outcomes.

Overall, only 40.4% simple cases received a higher formulary initial dose of antibiotics, compared with 29.5% of complex cases. Only 30 (13.8%) of simple cases and 9 (9.5%) of complex cases received the higher formulary dose of antibiotic treatment throughout (*Table 33*).

Specifically for the most commonly prescribed intravenous empirical antimicrobials in hospital:

For simple disease (*Table 35*), flucloxacillin (median 188.1 mg/Kg/24 hr (IQR 100.8, 200), formulary higher dose 200 mg/Kg/24 hr), clindamycin (median 39.9 mg/Kg/24 hr (IQR 18.5, 40.6), formulary higher dose 40 mg/Kg/24 hr) and cefuroxime (median 151.5 mg/Kg/24 hr (IQR 83.7, 150.6), formulary higher dose 150 mg/Kg/24 hr) were prescribed at or near to the recommended formulary higher doses. However, ceftriaxone (median 50.3 mg/Kg/24 hr (IQR 50, 79.3), formulary higher dose 80 mg/Kg/24 hr) was generally prescribed at the lower formulary dose.

For complex disease (*Table 36*) however, prescribing trends for complex disease suggest that inadequate dosing (less than higher formulary dose) was more common. While ceftriaxone (median 77.7 mg/Kg/24 hr (IQR 49, 80), UK formulary higher dose 80 mg/Kg/24 hr, EMEA approved maximum dose 100 mg/Kg/24 hr) was generally prescribed at the higher formulary dose where it was used (in 20.9% of initial treatment and 40.7% of complex cases overall), flucloxacillin (median 142.6 mg/Kg/24 hr (IQR 98, 198.5), formulary higher dose 200 mg/Kg/24 hr), clindamycin (median 33.3 mg/Kg/24 hr (IQR 24.1, 39.2), formulary higher dose 40 mg/Kg/24 hr) and cefuroxime (median 128 mg/Kg/24 hr (IQR 83.3, 150), formulary higher dose 150 mg/Kg/24 hr) were all prescribed at less than formulary higher doses.

Following discharge, doses of intravenous and oral antimicrobials were also less than higher formulary doses overall. Specifically for the most commonly prescribed intravenous empirical antimicrobials at discharge (for use out of hospital) (*Table 46*):

Due to the once daily regimen, ceftriaxone was the commonest intravenous agent prescribed for community based care in both simple (69.5% of cases receiving IV home based therapy) and complex (77.5% of cases receiving IV home based therapy) cases. At discharge, ceftriaxone (median 50.7 mg/Kg/24 hr (IQR 49.3, 79.4), formulary higher dose 80 mg/Kg/24 hr) was generally prescribed at the lower formulary dose in simple disease, although in complex disease the dose was slightly higher but not at higher formulary dose (median 65.4

mg/Kg/24 hr (IQR 49, 80.3). Where used out of hospital, intravenous flucloxacillin and clindamycin for both simple and complex disease were generally prescribed at under the lower formulary recommended doses (flucloxacillin simple disease median 98.1 mg/Kg/24 hr, complex disease median 35.8 mg/Kg/24 hr; clindamycin simple disease median 21.6 mg/Kg/24 hr, complex disease median 4 mg/Kg/24 hr) (*Table 46*).

For orally prescribed out of hospital antibiotic treatments, comparison with formulary doses is more complicated due to the age band variations in the current British National Formulary for Children (BNFC). For reference, Co-amoxiclav (expressed as mg/kg/24 hours of amoxicillin component) dose ranges quoted are 1 month – 6 years (18.75 mg/kg/24 hrs low dose – 37.5 mg/kg/24 hrs higher dose); 6-12 years (22.5 mg/kg/24 hrs low dose – 45 mg/kg/24 hrs higher dose); and 12-18 years (15 mg/kg/24 hrs low dose – 30 mg/kg/24 hrs higher dose). Flucloxacillin dose ranges are 1 month-2 years (31 mg/kg/24 hrs low dose – 62 mg/kg/24 hrs higher dose); 2-10 years (43.3 mg/kg/24 hrs low dose – 46.5 mg/kg/24 hrs higher dose); and 2-18 years (25 mg/kg/24 hrs low dose – 50 mg/kg/24 hrs higher dose). Clindamycin has oral dose range for all ages 12 mg/kg/24 hrs low dose – 24 mg/kg/24 hrs higher dose, and cephalexin oral dose range for all ages 25 mg/kg/24 hrs low dose – 50 mg/kg/24 hrs higher dose.

Most oral antibiotic dosing was nearer to lower range dose than higher range dose for the 4 most commonly prescribed antibiotics given for simple disease. Discharge oral co-amoxiclav median dose was 30.4 mg/Kg/24 hr (IQR 13.8, 41.8), flucloxacillin median 37.5 mg/Kg/24 hr (IQR 14.2, 82.3), clindamycin median 18.1 mg/Kg/24 hr (IQR 6.1, 23.6) and cephalexin median 35 mg/Kg/24 hr (IQR 24.5, 91.1) (*Table 46*).

Perhaps worryingly, children with complex disease appear to have received lower doses of co-amoxiclav and clindamycin (28.8% and 28.8% respectively of complex patients given oral antibiotics) than children with simple OM or SA. In complex disease, discharge oral co-amoxiclav median dose was 23.1 mg/Kg/24 hr (IQR 12.1, 47.6), flucloxacillin median 41.7 mg/Kg/24 hr (IQR 36.4, 54.1), and clindamycin median 15.1 mg/Kg/24 hr (IQR 6, 23.8) (*Table 46*).

Follow-up (three months): completion of antimicrobial courses as planned at discharge

One of the key concerns in any clinical trial of oral therapies, and of antibiotics in particular, is the course completion rate. Although not all children with OM or SA were reported to have been followed up (72.9% simple SA, 72.5% simple OM, 77.1% complex SA, 80.4% complex

OM were reported followed up), those that were reported had very high course completion rates (92.4% simple disease overall, 92.1% complex disease overall) (*Table 47*). The reported reasons for non-completion of therapy were reassuring for future trial planning where, to study clinical outcomes in relation to length of therapy, it will be important to know that prescribed medication is being given as planned. Only one child with simple disease reported stopping for each of: unpalatable antibiotic, rash, symptom resolution and refusal to take the medication.

Hospital Stay

Overall, simple OM and SA combined had a median length of hospital stay of 7 days (IQR 4, 12), with 50% of children staying for 6 days or longer but no longer than 12 days. In complex cases the median length of stay in hospital overall was 9 days (IQR 6, 18), with 50% of children staying for 6 days or longer but no longer than 18 days (*Table 43*).

Children with OM spent longer in hospital than those with SA, for both simple and complex disease (*Table 44*). The median length of stay for simple SA was 6 days (IQR 4, 11) compared to 9 days for simple OM (IQR 5, 13). The median length of stay for complex SA was 8 days (IQR 6, 15) compared to 9 days for complex OM (IQR 6, 18.5). For simple SA and OM the median length of hospital stay is similar to the time on intravenous therapy prior to oral switch (simple SA and OM oral switch after median 6 and 8.5 days respectively) but in complex SA or OM children were more likely to remain on intravenous at the time of hospital discharge (complex SA and OM oral switch after median 13.5 and 10.5 days respectively).

Younger (less than 1 year old) and older (6-16 years old) children were more likely to stay in hospital longer than the 1-6 year group, which is probably a reflection of the difficulties of imposing bed rest on the younger mobile children compared to babies and older children. For simple disease, the median length of stay if < 1 year was 7 days (IQR 5, 12), 6-16 years was 10 days (6, 15) but 1-6 years was 6 days (3.5, 10.5). For complex disease, the median length of stay if < 1 year was 16 days (IQR 9, 27), 6-16 years was 10 days (6, 16) but 1-6 years was 8 days (5, 14) (*Table 43*).

The slightly longer time in hospital prior to discharge for children treated in secondary care centres compared to tertiary centres (*Table 43*) is difficult to explain fully, but may be a reflection of the fact that some children are transferred back to their secondary care centre prior to final discharge from hospital and this may incur delays overall prior to discharge home.

Follow-up (three months): complications of the disease and therapies, and treatment failure.

The data collection included complications and ongoing symptoms as separate items in order to try to capture all post-treatment events and problems that may need to be included as future clinical trial outcomes.

8.3% of simple cases and 16.8% of complex cases experienced at least one complication (*Table 49*). Only 3 (of 218) simple cases and 4 (of 95) complex cases reported recurrence of infection requiring medical or surgical intervention. Other complications were reported only once per event, and were related to the disease (clinical outcomes such as stiffness or pain), antibiotic therapy (such as possible allergy or drug reaction) or mode of giving the drug (such as phlebitis) (*Table 50*). The complications of complex disease were generally more severe than those reported for simple disease, including acute kidney injury, Hickman line sepsis, pneumococcal meningitis and tracheostomy (*Table 50*).

27 (17.2%) of simple cases and 18 (24%) of complex cases had at least one on-going symptom. 18 of 157 (11.5%) simple SA or OM and 8 of 76 (10.5%) complex SA or OM followed up were still in pain. 6 (3.8%) simple disease and 8 (10.5%) reported joint stiffness and 4 (2.5%) simple and 3 (3.9%) complex immobility of some kind. Other symptoms were less common and there were no fractures reported (*Table 52*).

So as to capture all possible cases where the initial empirical antibiotic and/or surgical therapy had failed requiring further treatment, we used a broad definition of treatment failure including fever, recurrence of infection including increase in CRP or development of draining sinus, dislocation, subluxation, pathological fracture, pain, mobility problems, swelling, numbness, hospital readmission, surgery and change of antibiotics. Using these criteria, 32 of 218 (14.7%) simple cases experienced a treatment failure, compared with 24 of 95 (25%) complex cases (*Table 53*). In simple cases treatment failure was half as likely in SA (9.3%) compared with OM (19.3%), whereas for complex cases treatment failure was more likely in SA (28.6%) than OM (21.4%) (*Table 53*).

Very important for the design of an RCT of shortened intravenous and/or total length of antibiotic therapy, these data demonstrate less treatment failure in simple disease where there was an early oral switch, suggesting also that more complex disease is more likely to fail initial therapy or require additional interventions. Of the 73 simple cases that had a very early oral

switch (less than a week), 9.6% experienced a treatment failure, compared with 16.1% that had an early switch (between one and 2 weeks), and 18.2% where switch was after 2 weeks of intravenous antibiotic. For complex cases, switches after 2 weeks also had the highest chance of complication (37.9%), compared with 25% of very early switches and 19% of switches at between 1 and 2 weeks (*Table 54*).

Regarding the total length of therapy, treatment failure for simple SA and OM was equally likely for children that had antibiotics for less than 6 weeks as for those that had courses for more than 6 weeks. For complex cases, children given antibiotics for less than 6 weeks were much less likely to have a treatment failure than those given more than 6 weeks (14.3% compared to 37%) although this is likely to be a reflection of disease severity itself and not due to the treatments given (*Table 55*).

Chapter 8 presents a detailed discussion of how the service evaluation data impact, with other study components, on potential RCT design.

Chapter 3: Microbiology sub-study

Background

The current “gold standard” for detection of bacteria associated with OM/SA is bacterial culture, although in the UK the pathogen detection rate from culture in children’s bone and joint infections is low.²⁶ This means that the true spectrum of organisms causing bone and joint infections in the UK is not known, and treatment is usually empirical.

New molecular techniques can enhance diagnostic detection rates. The use of 16S real-time PCR has become available in some specialist centres however in the UK it is available at one centre with a turnaround time of days to weeks. 16S real-time PCR is expensive, and while capable of detecting many pathogenic and non-pathogenic organisms, it has low sensitivity because the load of bacteria in the primary sample needs to be sufficiently high to allow detection.

Species-specific reverse transcription polymerase chain reaction (RT-PCR) to identify bacteria associated with OM/SA has been used in specialist centres to enhance the detection of certain organisms, in particular *Kingella kingae* which is difficult to grow in routine culture. However although it is much cheaper than 16S PCR, species-specific PCR is not routinely available in most UK or EU laboratories.

Aims and Objectives

This study evaluated the potential for the species-specific RT-PCR to be used both to establish the baseline UK microbiology of paediatric bone and joint infections better than would have been obtained by culture alone, and to assess the use of the test in a larger RCT.

We also aimed to understand the pathophysiology of *K. kingae* by using PCR to test throat swabs (taken from patients who have provided consent) for *K. kingae* to determine how many had concurrent pharyngeal colonisation with this organism.

Methods

a) Clinical cases

Children presenting to participating centres with bone and joint infection at one of the 6 participating centres were approached by the Dinosaur study research team and recruited after informed consent. Clinical data was collected as part of the standard Dinosaur service evaluation.

Inclusion criteria

1. Children between the ages of 1 month and 16 years with a clinical diagnosis of osteomyelitis or septic arthritis.
2. Written informed consent of participant or parent/legal guardian, and assent where appropriate for
 - a) PCR to be done on routine samples taken for culture and microscopy;
 - b) Throat swab to be taken for PCR and culture and microscopy
 - c) Additional 5ml blood sample to be taken and stored for future analysis.

Exclusion criteria

Patients for whom informed consent is not obtained (parents/patients could decline consent for certain procedures, e.g. additional blood aliquot but still give consent for others e.g. PCR on routine samples).

*The culture and preparation of control organisms***b) Sample handling and preparation**

Samples from routinely collected blood and tissue cultures were taken in the local microbiology laboratory and processed according to the study SOP (see *Appendix 2*) before storage and transfer to the central laboratory (Southampton Public Health England South East Regional Laboratory) for PCR analysis.

All samples were taken for PCR after initial bacterial culture had been carried out. For blood cultures, an aliquot of sample was removed after at least 19 hours incubation (unless they had already been identified as positive), using a sterile needle and syringe, 1ml of blood culture sample was removed and placed into a sterile nuclease free skirted 2ml tube before being capped and labelled and placed into storage at -80°C until extraction and PCR was to be carried out. For liquid samples such as synovial fluid, pus and blood or joint washouts, 500µl was taken from the original sample (where limited sample volume remained, 200µl was used thus allowing for repeat culture or further analysis using another method). Solid samples were divided and where sample quantity allowed, a minimum of two aliquots of tissue or bone weighing around 10mg each were taken and placed in to a sterile nuclease free skirted

2ml tube and stored at -80°C. All samples were handled in a class one cabinet to prevent the risk of contamination.

For throat swabs, after swabbing, the cotton end was snipped off using sterile scissors into a flat bottom 2ml tube containing 1ml of skim milk, tryptone, glucose, and glycerin (STGG) media used to preserve bacteria whilst being frozen at -80°C.

PCR Analysis

Control bacteria used in this study were sourced from Pro-Lab Diagnostics and the United Kingdom National Culture Collection (UKNCC). Bacterial DNA was extracted by standard methods and multiplex PCR used for analysis.

Table 57 shows the multiplex panels used for all samples.

Table 57 shows the constituent elements to each of the multiplexes. Two separate targets were used to detect *S. pneumoniae* as *ply* is also common to other closely related streptococcal species including *S. mitis*, *S. oralis* and *S. pseudopneumoniae*. *lytA* was later chosen as it is common only for *S. pneumonia*.

TABLE 57: ELEMENTS TO EACH OF THE MULTIPLEXES

Multiplex 1	Multiplex 2	Multiplex 3
K.k. for	Sal. Spp. for	GBS for
K.k. rev	Sal. Spp. rev	GBS rev
GAS for	S. a. for	H. inf. for
GAS rev	S. a. rev	H. inf. rev
S. pn. ply for	S. epi. for	S. pn. lytA for
S. pn. ply rev	S. epi. rev	S. pn. lytA rev
K.k.	Sal. spp	GBS
GAS	S. a.	H. inf.
S. pn. ply	S. epi.	S. pn. lytA

K.k.: *Kingella kingae*, S.pn: *Streptococcus pneumoniae*, S.a.: *Staphylococcus aureus*, S. epi.: *Staphylococcus epidermidis*, Sal. Spp.: *Salmonella species*, GBS: *Group B streptococcus*, GAS: *Group A streptococci*, H. inf: *Haemophilus influenza*, ply: Pneumolysin, lytA: N-acetylmuramoyl-L-alanine amidase, for: Forward primer, rev: Reverse primer

Results

Of the seven sites that took part in the study, only samples from six of the sites were processed due to incorrect sampling, an error subsequently acknowledged by the local principal investigator. The total number of samples and patients consented to the study from each site can be seen in *Table 58*.

Table 58 shows the number of patients consented to the study from each site and the number of samples (both throat swabs and native bone and joint samples). Site number refers to tables below.

TABLE 58: TOTAL NUMBER AND PATIENTS CONSENTED TO THE STUDY ACCORDING TO GEOGRAPHICAL SITE

Geographical site	Number of throat swabs	Number of samples excluding throat swabs	Total number of samples	Total number of patients
Oxford (1)	9	25	34	11
Birmingham (2)	1	4	5	1
Imperial (3)	0	22	22	4
Bristol (4)	11	28	39	12
Liverpool (5)	9	18	27	10
Southampton (6)	8	16	24	12
Total	38	113	151	50

A total of 151 samples were received from 50 patients. Of these 113 were bone, fluid and blood culture samples which were collected from 44 patients across six geographical sites. The remaining 38 samples were from throat and wound swabs. For 5 only throat swab samples were obtained and 1 only skin swab sample were obtained.

Of the 113 native tissue samples collected 39 were blood cultures of which pathogenic bacteria were identified in 16 using the RT-PCR panel. 60 of the total native samples collected were joint fluids including pus of which 46 were positive using the RT-PCR panel. 11 tissue samples and 3 bone samples were collected of which 10 and one respectively were positive using the RT-PCR panel.

Of the 16 blood culture samples that were found to be positive, nine were identified as *S. aureus* while no *K. kingae* were detected in this sample type. Other notable results identified in blood cultures were three positives for *S. epidermidis*, two positive for Group A Streptococci, one positive for *H. influenza* and one for *S. pneumoniae* (ply).

Of the 46 positive joint fluid samples which included aspirates and pus, 19 were identified as positive for *S. aureus*. *K. kingae* was identified in ten and Group A Strep in 11 different samples. *S. epidermidis* and *S. pneumoniae* (lytA) were also identified in four and one sample respectively. In three samples which were *S. epidermidis* positive in this sample type, another more pathogenic organism was actually identified and in these cases *S. epidermidis* was assumed to be a contaminant.

Of the 11 tissue samples received as part of this study, ten were positive by RT-PCR of which eight were identified as *S. aureus* with one sample each positive for *K. kingae* and Group A strep. Three bone samples were also received of which one was positive for *S. aureus*.

Overall, excluding any data from skin or throat swabs, 32/44 patients (72.7 %) were PCR positive for one or more of the target organisms included in the RT-PCR panel. Detailed results are shown in Table 59 - Table 67.

Table 59 shows the number of positive samples detected for each target organism from all of the six sites for all sample types (including skin and throat swabs) expressed as a percentage of the total sample number from each location.

TABLE 59: NUMBER OF ORGANISMS DETECTED BY PCR ACCORDING TO GEOGRAPHICAL SITE

Site	<i>K.k.</i>	GAS	<i>S. pn.</i> (<i>ply</i>)	<i>S. pn.</i> (<i>lytA</i>)	<i>Sal.</i> <i>Spp.</i>	<i>St. a.</i>	<i>St. epi.</i>	GBS	<i>H. inf.</i>
1	6	0	9	1	0	14	8	1	4
n=34	(17.6%)	(0%)	(26.4%)	(2.9%)	(0%)	(41.1%)	(23.0%)	(2.9%)	(8.8%)
2	0	0	1	0	0	3	1	0	1
n=5	(0%)	(0%)	(20.0%)	(0%)	(0%)	(60.0%)	(20.0%)	(0%)	(20.0%)
3	0	11	0	0	0	8	1	0	0
n=22	(0%)	(50.0%)	(0.0%)	(0%)	(0%)	(36.3%)	(4.5%)	(0%)	(0%)
4	3	1	6	0	0	7	2	0	4
n=39	(10.3%)	(3.44%)	(20.6%)	(0%)	(0%)	(24.1%)	(6.8%)	(0%)	(13.7%)
5	1	4	8	0	0	8	5	0	2
n=27	(3.7%)	(14.1%)	(29.6%)	(0%)	(0%)	(29.6%)	(18.5%)	(0%)	(7.4%)
6	1	5	7	1	0	11	4	0	2
n=24	(4.1%)	(20.8%)	(29.1%)	(4.16%)	(0%)	(45.8%)	(16.6%)	(0%)	(8.3%)
TOTAL n=151	11 (7.2%)	21 (13.9%)	31 (20.5%)	2 (13.2%)	0 (0%)	51 (33.7%)	21 (13.9%)	1 (0.6%)	13 (8.6%)

Table 60 identifies the number of positives for each PCR target detected based on all sample types across all geographical sites.

TABLE 60: NUMBER OF ORGANISMS DETECTED BY PCR ACCORDING TO SAMPLE TYPE

Sample type	<i>K.k.</i>	GAS	<i>S. pn.</i> (<i>ply</i>)	<i>S. pn.</i> (<i>lytA</i>)	<i>Sal.</i> <i>Spp.</i>	<i>St. a.</i>	<i>St. epi.</i>	GBS	<i>H. inf.</i>
Throat swab	0	6	30	1	0	14	14	1	12
Blood culture	0	2	1	0	0	9	3	0	1
Joint fluid /aspirates/pus	10	11	0	1	0	19	4	0	0
Tissue	1	1	0	0	0	8	0	0	0
Bone	0	0	0	0	0	1	0	0	0
Swabs	0	1	0	0	0	0	0	0	0
Total N=151	11	21	31	2	0	51	21	1	13

Table 61 shows the number of positive organisms for samples of usually sterile sites (excluding skin and throat swabs) from each geographical site expressed as a percentage of the total number of fluid, tissue, bone and blood samples collected at each location.

TABLE 61: NUMBER OF ORGANISMS DETECTED BY PCR FROM USUALLY STERILE SITES ACCORDING TO GEOGRAPHICAL SITE

Site	<i>K.k.</i>	GAS	<i>S. pn.</i> (<i>ply</i>)	<i>S. pn.</i> (<i>lytA</i>)	<i>Sal.</i> <i>Spp.</i>	<i>St. a.</i>	<i>St. epi.</i>	GBS	<i>H. inf.</i>
1	6	0	1	0	0	9	3	0	1
n=25	(24.0%)	(0%)	(3.8%)	(0%)	(0%)	(36.0%)	(12.0%)	(0%)	(4.0%)
2	0	0	0	0	0	2	0	0	0
n=4	(0%)	(0%)	(0%)	(0%)	(0%)	(50.0%)	(0%)	(0%)	(0%)
3	0	11	0	0	0	8	1	0	0
n=22	(0%)	(50.0%)	(0%)	(0%)	(0%)	(36.3%)	(4.5%)	(0%)	(0%)
4	3	0	0	0	0	6	1	0	0
n=28	(10.7%)	(0%)	(0%)	(0%)	(0%)	(21.4%)	(3.5%)	(0%)	(0%)
5	1	1	0	0	0	4	1	0	0
n=18	(5.6%)	(5.6%)	(0%)	(0%)	(0%)	(22.2%)	(5.6%)	(0%)	(0%)
6	1	2	0	1	0	8	1	0	0
n=16	(6.2%)	(12.5%)	(0%)	(6.2%)	(0%)	(50.0%)	(6.2%)	(0%)	(0%)
TOTAL n=113	11 (9.7%)	14 (12.3%)	1 (0.8%)	1 (0.8%)	0 (0%)	37 (32.7%)	7 (6.1%)	0 (0%)	1 (0.8%)

Table 62 identifies a small number of tissue and fluid samples that were positive for more than one of the target organisms in the bone and joint PCR panel/

TABLE 62: PATIENTS IN WHICH MULTIPLE ORGANISMS WERE IDENTIFIED

Patient	Site	Specimen type	Organisms identified			
1	1	blood culture	<i>S. pn. (ply)</i>	<i>St. a.</i>	<i>St. epi.</i>	<i>H. inf.</i>
2	1	aspirate	<i>K.k</i>	<i>St. epi</i>		
3	4	tissue	<i>St. a</i>	<i>St. epi</i>		
4	5	synovial fluid	<i>K.k</i>	<i>St. a.</i>		
5	6	tissue	GAS	<i>St. a.</i>		
6	3	pus	GAS	<i>St. epi</i>		

Table 63 identifies the number of positives for each PCR target detected based on blood, tissue and fluid sample types only across all geographical sites.

TABLE 63: NUMBER OF ORGANISMS DETECTED BY PCR FROM USUALLY STERILE SITES ACCORDING TO SAMPLE TYPE

Sample type	<i>K.k.</i>	GAS	<i>S. pn.</i> (<i>ply</i>)	<i>S. pn.</i> (<i>lytA</i>)	<i>Sal.</i> <i>Spp.</i>	<i>St. a.</i>	<i>St. epi.</i>	GBS	<i>H. inf.</i>
Blood culture	0	2	1	0	0	9	3	0	1
Joint fluid /aspirates/pus	10	11	0	1	0	19	4	0	0
Tissue	1	1	0	0	0	8	0	0	0
Bone	0	0	0	0	0	1	0	0	0
Total	11	14	1	1	0	37	7	0	1

Table 64 identifies the total number of samples positive for any of the target organisms by sample type; these data excludes throat swabs and skin/wound swabs.

TABLE 64: TOTAL NUMBER OF POSITIVE SAMPLES ACCORDING TO SAMPLE TYPE

Sample type	Total number of each sample type	Total PCR positive for any target organism included in the PCR panel
Blood culture	39	16 (41%)
Joint fluid/aspirates/pus	60	46 (76%)
Tissue	11	10 (91%)
Bone	3	1 (33%)
Total	113	73 (64.6%)

Table 65 identifies the number of positives detected for each of the multiplex targets based on patient number rather than the actual number of samples from each geographical location (ie combining results from duplicate samples from individual patients). These data exclude throat and skin swabs.

TABLE 65: NUMBER OF PATIENTS WITH ORGANISMS DETECTED BY PCR ACCORDING TO GEOGRAPHICAL SITE

Site	<i>K.k.</i>	GAS	<i>S. pn.</i> (<i>ply</i>)	<i>S. pn.</i> (<i>lytA</i>)	<i>Sal.</i> <i>Spp.</i>	<i>St. a.</i>	<i>St. epi.</i>	GBS	<i>H. inf.</i>
1	3	0	1	0	0	4	1	0	0
2	0	0	0	0	0	1	0	0	0
3	0	1	0	0	0	1	0	0	0
4	2	0	0	0	0	4	1	0	0
5	1	1	0	0	0	2	1	0	0
6	1	2	0	1	0	4	0	0	0
Total n=32	7	4	1	1	0	16	3	0	0

TABLE 66: SUMMARY OF THE RESULTS OF THE PCR

Simple cases (n=218)					Complex cases (n=95)			
Tested n (%) 32 (14.7%)					Tested n (%) 12 (12.6%)			
Cases								
Detected	Tested n		Yes n (%)		Tested n		Yes n (%)	
	Samples	Cases	Samples	Cases	Samples	Cases	Samples	Cases
At least one micro- organism detected?		32		24 (75%)		12		8 (67%)
<i>Blood</i>	31	22	12 (39%)	8 (36%)	9	8	3 (33%)	3 (38%)
<i>Synovial fluid</i>	30	20	25 (83%)	18 (90%)	3	3	3 (100%)	3 (100%)
<i>Pus</i>	7	2	6 (86%)	2 (100%)	14	6	12 (86%)	4 (67%)
<i>Tissue</i>	5	5	5 (100%)	5 (100%)	5	4	5 (100%)	4 (100%)
<i>Bone</i>	1	1	1 (100%)	1 (100%)	0	0	0	0

Note: PCR was done on samples of 6 patients with no OM/SA (misdiagnosed) which are not shown in the table

Table 67 shows the number of positive throat swabs for each of the target organisms taken from the six geographical sites also expressed as a percentage of the total of throat swabs collected at each location.

TABLE 67: NUMBER OF ORGANISMS DETECTED BY PCR FROM A THROAT SWAB ACCORDING TO GEOGRAPHICAL SITE

Site	<i>K.k.</i>	<i>GAS</i>	<i>S. pn.</i> (<i>ply</i>)	<i>S. pn.</i> (<i>lytA</i>)	<i>Sal.</i> <i>Spp.</i>	<i>St. a.</i>	<i>St. epi.</i>	<i>GBS</i>	<i>H. inf.</i>
1	0	0	8	1	0	5	5	1	3
n=9	(0.0%)	(0%)	(88.8%)	(11.1%)	(0%)	(55.5%)	(55.5%)	(11.1%)	(33.3%)
2	0	0	1	0	0	1	1	0	1
n=1	(0%)	(0%)	(100%)	(0%)	(0%)	(100%)	(100%)	(0%)	(100%)
3	0	0	0	0	0	0	0	0	0
n=0	(0%)	(0%)	(0.0%)	(0%)	(0%)	(0.0%)	(0.0%)	(0%)	(0%)
4	0	0	5	0	0	1	1	0	4
n=11	(0%)	(0%)	(45.4%)	(0%)	(0%)	(9.0%)	(9.0%)	(0%)	(36.3%)
5	0	3	8	0	0	4	4	0	2
n=9	(0%)	(33.3%)	(88.8%)	(0%)	(0%)	(44.4%)	(44.4%)	(0%)	(22.2%)
6	0	3	8	0	0	3	3	0	2
n=8	(0%)	(37.5%)	(100%)	(0.0%)	(0%)	(37.5%)	(37.5%)	(0%)	(25.0%)
TOTAL n=38	0 (0.0%)	6 (15.7%)	30 (78.9%)	1 (2.63%)	0 (0.0%)	14 (36.8%)	14 (36.8%)	1 (2.6%)	12 (31.5%)

Discussion

The microbiology sub-study has demonstrated the diagnostic yield of the relatively cheap species-specific RT-PCR compared to routinely used microbiology culture based techniques in children's bone and joint infections, achieving a definitive bacterial diagnosis in 32 of 44 patients (75%, 24 of 32 simple cases and 67%, 8 of 12 complex cases) in whom the test was used (table 66). While the sub-study was not designed to estimate formal sensitivity and specificity, a positive diagnosis in around 65-70% overall is higher than the reported yields of 40-50% (where tissue samples are achieved at surgical intervention) or 9-22% (where only blood cultures are achieved).^{14, 27}

The study has also demonstrated the feasibility of the test being performed centrally or locally/regionally in a future randomised clinical trial. The protocol of the easy to perform species-specific PCR panel is such that routine NHS molecular microbiology laboratories could adopt the test, or it could be performed on a regional or national basis for UK practice. A future trial could use results from locally or nationally performed tests depending on availability, as long as results were obtained in NHS/PHE accredited laboratories performing routine molecular microbiological investigations.

The microbiology sub-study has also provided important data on the current UK molecular epidemiology of children's bone and joint infections. *Staphylococcus aureus* remains the commonest detected pathogen. While pilot data (and anecdotal use of the species-specific panel on an ongoing basis at the Southampton site in routine clinical practice) suggested that *Kingella kingae* is almost as common in young children as *S. aureus*, these data also suggest that overall during the period of this study, Group A streptococcus (4 cases detected by PCR) was as common cause of OM/SA as *K. kingae* (7 cases detected by PCR). In this study, GAS was identified by PCR in children aged between 2.3-12.4 years whereas *K. kingae* was only identified in children aged 0.8-2.3 years. GAS caused simple (2 cases) and complex (2 cases) disease while *K. kingae* caused only simple OM or SA. While numbers are not high, our data confirms previous reports that *K. kingae* bone and joint infection primarily affects very young children. As expected, other pathogens were found more uncommonly.

The *S. aureus* data correlates with the existing literature and clinical experience, as historically, *S. aureus* has been known to be the most common cause of infection in both native and prosthetic bone and joint infections.⁶⁷ 37 native tissue samples from 16 patients (11 simple disease, 5 complex disease, age range 2.5 years to 15.9 years, median 11.4 years) were positive for *S. aureus* using PCR including eight tissue samples, nine blood cultures, one bone sample, one wound swab and 19 fluid samples (this includes joint fluids, pus and aspirates). *S. aureus* is a known coloniser of the upper respiratory tract so to identify it in throat swabs is not uncommon. One patient (site 1) had significant levels of *S. aureus* in 8 out of 9 samples that had been taken including pus and blood culture samples. Another patient (site 4) had high levels *S. aureus* in both blood culture and pus whilst another (site 5) had *S. aureus* identified in 3 out of 6 samples received.

A total of 11 samples taken from 7 patients (all simple disease, age range 0.8 months to 2.3 years, median 1.15 years) were positive for *K. kingae*. These included ten joint fluids and aspirates and one other tissue sample. While one group in Israel have reported that culture of tissue in blood culture bottle systems can increase the culture yield of this fastidious organism,¹⁶ this study has demonstrated again that species-specific PCR on routine blood culture samples or directly on tissue samples can formally diagnose *K. kingae*.¹⁸

Four children (2 simple, 2 complex disease; age range 2.3 years to 12.4, median 6.7 years) had OM/SA caused by Group A streptococcus detected by PCR from a total of 14 native tissue samples. 11 samples were fluids including pus, two were blood cultures and one was a

tissue. While a higher frequency than previously reported,²⁶ this study was conducted during the time period of a reported outbreak of Group A streptococcal infections nationwide in the UK.⁶⁸

Two patients (ages 5.2 years and 0.8 months) were found to have OM/SA due to *S. pneumoniae*. One blood culture sample from one patient was positive for the *ply* gene of *S. pneumoniae*. One other joint sample from a different patient was positive for the more specific target for *lytA* gene. The species-specific panel uses two targets identify the presence of *S. pneumoniae* (the pneumolysin gene (*ply*) and the autolysin gene (*lytA*)). This is because the *ply* gene shows a degree of cross reactivity between *S. pneumoniae* and *Streptococcus mitis*, *Streptococcus oralis* and *Streptococcus pseudopneumoniae*. The *lytA* target was chosen⁶⁹ as it is common only for *S. pneumoniae*.

H influenzae was identified in one blood culture from one patient aged 5.2 years but not from any PCR test. As expected this was an unusual organism but potentially an important factor in the potential antibiotic choice in the 5 years and under age group²⁶ in a future randomised controlled trial.

No native tissue samples in this study were positive for group B streptococcus (GBS), included in the panel due to their frequency in neonatal OM/SA.²⁶ As no children under the age of 2 months were included in this microbiology sub-study, this finding is not unexpected as GBS infections are rare in older infants and children.

No samples were found to be positive for *Salmonella* spp, an organism included in the PCR panel due to the reported frequency in OM/SA in children with sickle cell anaemia.⁷⁰

S. epidermidis is generally considered a contaminant in skin and surface swabs, and in OM/SA infections overall in the absence of prosthetic material⁷¹. However, in the absence of other pathogens detected from usually sterile sites, and when *S. epidermidis* is detected in samples from those previously sterile sites, the role of this organism in bone and joint infections pathophysiology is under more detailed investigation. In this study there were three blood cultures, four fluid samples were positive for *S. epidermidis*. One patient positive for this organism was also positive for GAS in 12 different samples whilst another patient was positive for *S. aureus* but at low levels. Our data concurs with the overall concept that in children without prosthetic joints or artificial implants of any kind, *S. epidermidis* is an unlikely pathogenic cause of the SA/OM even when detected in sterile samples.

Our study also investigated *K. kingae* and other pathogens detected by PCR in throat (oropharyngeal) swabs ⁷² to further investigate the relationship between OM/SA and respiratory tract carriage reported by a French group during the conduct of this study. ⁷³ 38 throat swabs were received in total of which *K. kingae* was identified in none, 30 were positive for *S. pneumoniae* (*ply*) of which only one was positive for *lytA* indicating that in 27 throat swabs, the RT-PCR was detecting *S. mitis*, *S. oralis* or *S. pseudopneumoniae* due to the *ply* gene cross-reactivity. 14 swabs were positive for *S. aureus*, 14 positive for *S. epidermidis*, 12 positive for *H. influenza*, six were positive for Group A streptococcus and one was positive for GBS.

The advantage of having the ability to perform species specific RT-PCR in a local laboratory setting, can benefit both patient and healthcare system. By allowing targeted antibiotic therapy to a known organism, accurate treatment can be given which can facilitate the transfer from intravenous to oral therapy and can shorten the patient's hospital stay. While this study was not big enough to conduct a formal health economic analysis, it is intuitive that being able to use directed therapy will result in shorter hospital stays due to earlier oral switch as well as a reduction in treatment failure, lowering costs, time, the risk of unnecessary antibiotics being used, and minimising the risk of antimicrobial resistance and nosocomial infections (the acquisition of which is proportional to length of stay among other causes).

Rapid identification of a bacterial organism causing OAI is important for a number of reasons. The use of conventional culture and microscopy can take a minimum of 48 hours, 24 of which are to establish organism growth (providing it is a non-fastidious species) and a further 24 hours for identification and sensitivity profiling in order to correctly target antibiotic therapy. This process can be marginally speeded up by the use of matrix assisted laser desorption/ionisation time of flight (MALDI-TOF) which can identify bacteria to a species level providing that a pure culture can be grown initially. ⁷⁴ The use of species-specific RT-PCR on bone and joint samples can speed up the identification process to a matter of hours. ⁷⁵

Conclusions

This study evaluated the potential for the species-specific RT-PCR to be used both to establish the baseline UK microbiology of paediatric bone and joint infections better than would have been obtained by culture alone, and to assess the use of the test in a larger RCT.

We have established that the test identifies a pathogenic organism more frequently than by conventional culture methods alone. The multiplex assay used has provided additional information on the UK molecular epidemiology of OM/SA in children in addition to the conventional culture results collected as part of the service evaluation (chapter 2). The test is feasible to use in a larger RCT and would be cheap and useful to implement in local microbiology laboratories for routine clinical care in the UK.

Data gained in the service evaluation and PCR sub-study showed that the predominant pathogens in bone and joint infections in children in the UK are: antibiotic-sensitive *Staphylococcus aureus* in simple and complex disease in children of all ages outside the neonatal period; *Kingella kingae* in simple disease in young children (under the age of 4 years old in this study but under 6 years old if currently unpublished data collected outside the timeframe of the service evaluation and sub-study is included); and Group A *Streptococcus* in simple and complex disease in children of all ages.

Chapter 4: Qualitative Interviews with Families and children, treated for bone and joint infections

Background

There has been little previous qualitative research exploring the views of children or their parents about treatment for, or the impact of, acute bone and joint infections, on family life during and after admission to hospital with infection, in a previously healthy child. Patient and parent perceptions and understanding of risks of complications, disability or adverse effects of treatment have also been previously underexplored.

In exploring the feasibility of a future randomised controlled trial (RCT) to identify optimum point of switch from intravenous to oral antibiotics in the treatment of osteomyelitis (OM) or septic arthritis (SA), it is critical that the views of affected children and their parents are included in the data used to inform decision making. We were also interested in understanding what information might help children and parents to make an informed decision about participating in such a trial, and in understanding what both children and parents view as important and meaningful outcomes which indicate that treatment has been successful. These data could potentially help to optimise meaning, acceptability and recruitment within a future RCT.

Aims

The overall purpose of the interviews was to explore parents' and children's views, understanding and experiences of both bone and joint infections and treatment, and willingness to participate in a future RCT. Our aims were:

1. To explore the experiences of parents and children treated with intravenous and/or oral antibiotic therapy for bone and joint infection about their condition and understanding about treatment.
2. To identify which clinical outcomes are most important to parents and young people with bone and joint infections, in order to contribute to the wider stakeholder Delphi and stakeholder consultation process.
3. To explore the views of parents and children admitted to hospital with bone and joint infections about participating in a RCT, in particular focusing on:

- a. information required in order to provide informed consent;
- b. views about and acceptability of potential interventions;
- c. willingness to be randomised to either arm (i.e. treatment or control) and
- d. influences on the above factors.

Methods

Research approach

In line with the service evaluation and Delphi study included as part of the overall feasibility work, this qualitative study acknowledged the external reality of the experiences of both parents and child participants, drawing on a realist research tradition. However, in line with a critical or subtle realist research position ⁷⁶ we argue that in recounting these experiences, accounts will be mediated by subjective views and perspectives of those being interviewed. ⁷⁷ This subtle realist approach has a number of implications for the conduct of this qualitative research, which we have identified and addressed below (see

Table 68):

TABLE 68: IMPLICATIONS OF SUTBLE REALIST APPROACH FOR THE CONDUCT OF THIS QUALITATIVE RESEARCH

IMPLICATION	STRATEGY
Interview guides are not designed to uncover objective facts, but to explore subjective reflections of events.	Open questions are designed to orientate to the interviewees' agendas, allowing them space to explore and describe subjective impressions associated with experiences. Where possible, children were interviewed in addition to parents, acknowledging the potential for different perspectives.
The researcher's role in making sense of and interpreting interview accounts is acknowledged.	Field notes and a research diary were kept, to promote reflection by the researcher about how she made sense of the data. These reflections were further surfaced during supervision with the senior researcher. Interpretation is partial, acknowledging the potential for multiple readings.
The proposed quality criteria against which it is suggested that this research should be evaluated acknowledge the subjective and co-constructed nature of the findings (see 'Rigour' section).	The researcher kept reflective notes to highlight her own role in interpretation. Interviewees were offered the opportunity to revisit the synthesised findings and to comment if they felt their own views/experiences were insufficiently represented. The junior and senior qualitative researchers carried out independent analysis of a transcript to facilitate discussion about how meaning was created from the interviews.

Semi-structured interviews

Semi-structured interviews were employed to explore the views and experiences of parents and children treated for bone and joint infections within the previous year. Semi-structured interviews are characterised by:

- an interactional exchange
- a topic centred dialogue, but with a flexible structure
- an acknowledgement that within an interview context, meaning and knowledge is co-produced.⁷⁸

As recommended by Mason,⁷⁹ the interview guides for parents and children were developed with reference to existing literature (e.g. qualitative work in this field, factors impacting on participation in RCTs, qualitative research interviews with children), researchers with expertise in this subject area and in working with children, and in consultation with our patient and public involvement contributors.

Interviews took the form of a conversation in which respondents initially told the story of their child's (or their own) experience of bone and joint infection. Throughout the narrative, respondents were encouraged to describe both the events happening, and the feelings and responses associated with them. Interviews covered a number of topics, with prompt materials used at various points as described below:

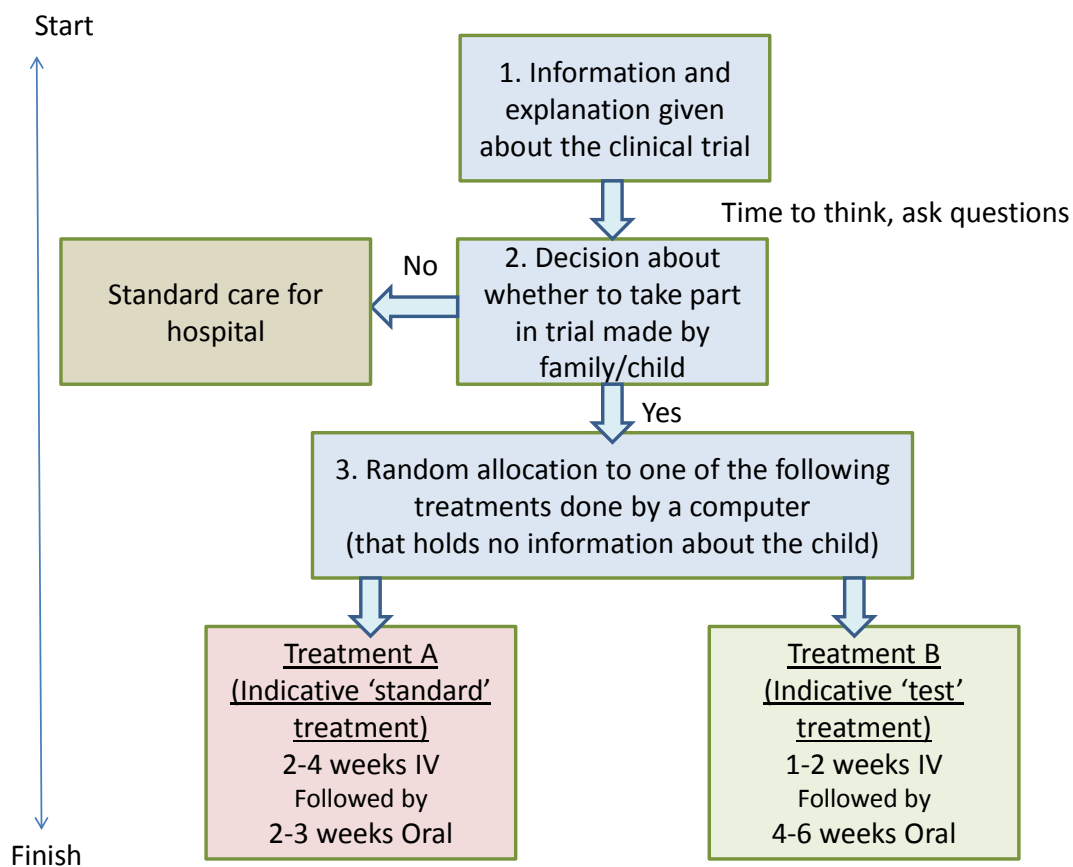
- ***Experiences of becoming ill and diagnosis***
 - Experiences of becoming ill with bone and joint infection, symptoms experienced
 - Experiences of seeking treatment and diagnosis
 - Treatments/interventions given, both in hospital and at home, including IV and oral antibiotic (antibiotic) therapy
 - Experience of both IV and Oral antibiotic
 - Emotional responses to events happening

A 'timeline' was used during the early section of the interview. The timeline consisted of three parallel, horizontal lines. The top horizontal line was labelled 'Becoming Ill', the second 'Hospital' and the lowest 'At home/Getting Better'. As respondents talked about their experiences, the researcher scribed key points/events on to the timeline in relevant places, with depiction of frequency, duration etc. Initially we had intended that respondents should scribe the timelines themselves as they spoke. However, during early pilot interviews it became apparent that this was distracting for respondents and interrupted the flow of their narratives. On the other hand, once the researcher began scribing, the timeline became a useful visual depiction of events. It also served as a reference point at later points during the interview.

- ***Participants' understandings and perceptions about aspects of antibiotic (antibiotic) therapy***
 - Perceptions about *clinical* reasons, advantages and disadvantages of both forms of antibiotic therapy (IV and Oral)

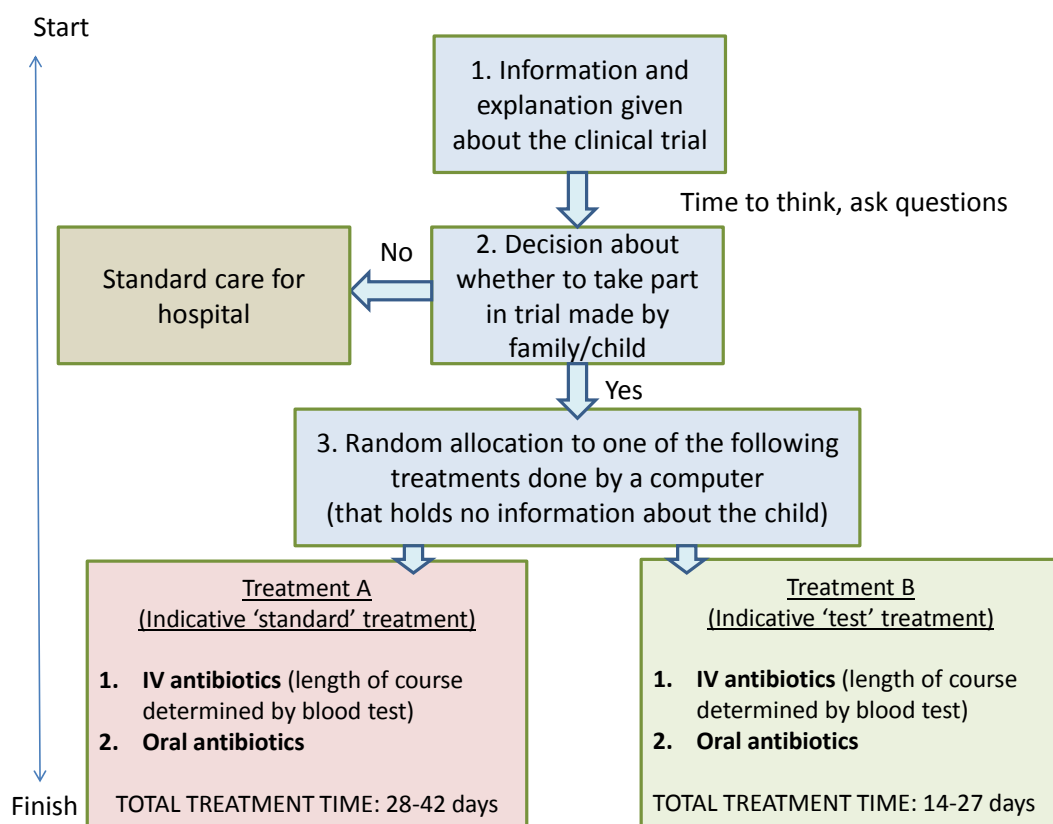
- o Perceptions about length of treatment arms (IV and oral) and about point of switch from IV to Oral
- ***Perspectives about the success of the treatment overall and important outcomes of recovery***
 - o Signs that indicated child was getting better
 - o Judgement of overall success of treatment and factors important when assessing level of success
- ***Views about participation in a hypothetical future RCT*** (Prompt Material: RCT process diagram and information – see *Appendix 3*).
 - o Initial reactions
 - o Information required (content and delivery) to assist decision making
 - o Feelings about being randomised
 - o Views on alternate treatment arms
 - o Level of willingness to participate – and why

The prompt material describing the trial was altered during the course of fieldwork to reflect the finding that most patients were now receiving shorter courses of IV than the traditional ‘standard’, and that the switch was being determined by a blood test. Initially, the adult prompt description of the trial showed the following process diagram, *Figure 3*.

FIGURE 3: INITIAL PROCESS DIAGRAM

This was replaced by

Figure 4 below, to show that the difference between trial arms would relate to length of overall antibiotic treatment and that the point of switch would be guided by blood tests.

FIGURE 4: AMMENDED PROCESS DIAGRAM

Because of the broad age span of children involved, three age appropriate versions of interview guides and prompt material were developed:

- **Young children up to the age of 7** – this interview guide (*Appendix 3*) consisted of simple questions about children's experiences and understandings, involving the use of a doctor glove puppet and a dinosaur toy. Because of the complex issues involved,

this interview guide did not include a section on the proposed RCT. As detailed in the findings section below, however, no children in this age group took part in interviews. This was primarily because parents did not wish to involve younger children in talking about an event that had often been upsetting and traumatic for them.

- **Children aged 8-12** – this interview guide (*Appendix 3*) involved simplified language, but did cover all topics identified above, including seeking views about proposed trial ('test').
- **Young people aged 13 + and adult:** the same guide (*Appendix 3*) was used for both young people and adults.

Participants

A purposive sample of children aged 0 to 16 years was identified from four of the seven centres in the South of England, who had participated in the main Dinosaur service evaluation and microbiology sub-study: Bristol Children's Hospital, Oxford Children's Hospital (University Hospitals Oxford NHS Trust), University Hospital Southampton NHS Foundation Trust and St George's Hospital London. The purposive sampling strategy addressed variation with regard to age, gender, and ethnicity.

The Inclusion criteria identified were:

- Parents and children from 3 months to sixteen-years-old, treated for osteomyelitis and/or septic arthritis;
- Children who had been treated for bone and joint infections at one of the seven sites participating in main service evaluation and microbiology sub-study;
- Parents/children who had taken part in the main Dinosaur study and also consented to take part in this qualitative study.

Procedure

At the point of initial consent for participation in the larger study, participants (i.e. children and their families) were asked if they would be willing to be contacted later, about possible participation in a smaller qualitative study. Only families who had already participated in the

larger study, and who had expressed willingness to be re-contacted, were invited to participate in the interviews.

Once ethics and site-specific approvals were received, the qualitative researcher made contact with each site to arrange the procedure to be followed to contact potential respondents. In one site, a member of nursing staff at the hospital telephoned pre-consented families to check that they were still happy to be contacted by the qualitative researcher. The qualitative researcher then contacted those agreeing, by telephone.

In the remaining three sites, the qualitative researcher made the initial contact with families by phone. During this initial phone call, the qualitative researcher described the interview process to families and asked if they would be interested in taking part. Provisional appointments were made, and a letter confirming arrangements was sent, with a participant information sheet, by email or post. Contact details of the researcher were included, in case families needed to change or cancel the appointment, or if they had any subsequent questions. The researcher also telephoned respondents on the day of (or the day before) the agreed appointment to check that it was still convenient for the family. If not, the appointment was re-scheduled, or on one occasion, cancelled. Signed consent was provided by families interviewed in person just prior to the interview, and those interviewed by telephone were asked to sign and return consent forms by post.

Ethics

Ethical approval for the qualitative interviews with parents and children was obtained from the National Research Ethics Committee – NRES Committee Yorkshire & The Humber - Leeds West, Ref: 14/YH/1166. All parents gave informed written consent to their participation and the use of quotation from their interviews for dissemination purposes. Assent was obtained from children. Because of the age of the children involved and the fact that families were being asked to talk about experiences that had been difficult and upsetting, the interview format, and appointment times, were kept flexible according to the needs and wishes of individual families and children. Parents of children who were under, or around, seven were in general not willing to involve their children directly in interviews revisiting experiences that they had found upsetting or traumatic. These parents therefore opted to take part in an interview whilst their child was at school. Very young children (babies or toddlers) were often present in the room, although too young to be directly involved with answering questions.

Older children were more likely to be involved and interview appointments were therefore arranged for times when they would be at home. Children chose whether they wished to be interviewed along with their parents, or separately from them. Eight children were interviewed along with (in seven cases) or separately from (one case) their parents, according to the preferences of the child and their family. Children could participate in interviews as they wished – for example, one child joined in answering questions early in the interview, but then drew her own (separate) timeline later, as she became tired. A range of family members contributed to interviews including mothers, fathers, child treated, siblings and (on one occasion) grandparents.

Analysis

Interviews mainly took place at respondents' homes between January and March 2015. Three interviews were conducted over the telephone due to issues of location and availability. The interviews were digitally recorded, with permission from the families and children. The recordings were transcribed by a professional transcribing agency and returned to the qualitative researcher for analysis.

Thematic analysis ⁸⁰ was employed in this study. Thematic analysis is a method for identifying, analysing and reporting patterns (themes) across a data set. The following stages were followed:

1. Familiarisation with the data
2. Generating initial codes
3. Searching for themes
4. Reviewing themes
5. Defining and naming themes
6. Producing the report

Data was stored and managed through the use of NVivo 10. Using this software package, transcripts were read in detail and coded, with codes being re-named, re-grouped, merged or disregarded, as issues emerged and re-emerged in subsequent transcripts. The coding frame was increasingly refined, discussed amongst members of the research team, and used as a basis for analysis and writing. Coding was both deductive (themes identified in interview guide/research questions were looked for within the text) and inductive (codes that have not been pre-conceived were allowed to 'emerge' from within the data).

Rigour

Based on guidelines for producing good quality qualitative research, we employed the following strategies:

- Reflexive notes were made during data collection by AL, in which she recorded contextual information and emerging ideas relating to analysis
- Data were sought from a diverse group of respondents in terms of factors thought to be pertinent to experiences of septic arthritis or osteomyelitis (e.g. age of child, infection, location of treatment, ethnicity, gender)
- CB and AL conducted some ‘double’ coding of transcripts initially. The broader research team (with variety of experience and expertise) were also involved in discussions about analysis and coding.
- Member checking – a summary of the study’s findings was circulated to all participants, who were contacted to seek their views about the study, to ask if findings ‘rang true’ and if there was anything they would like to add.
- We invited all interview participants to attend a stakeholder day at which findings from the qualitative study were presented to the wider clinical team involved in the service evaluation and Delphi study.

Findings

Demographic data

Twenty six families were recruited to the study. Families recruited represented children ranging in age from 0 to 16 at the time of treatment. 17 children were male and 9 female. The majority of families were white British, with two families being European, one Pakistani and one Chinese/Caucasian. In terms of specific condition treated, 11 were treated for Osteomyelitis (OM), 11 for Septic Arthritis (SA), 4 children had both SA and OM. Of these 4 OM/SA, for one the parent reported that the infection had been caused by Group A *Streptococcus* and for another the parent reported the cause as PVL positive *Staphylococcus aureus*. Children had been treated in Southampton (n=11), Bristol (n=4), Oxford (n=9) and London (n=2).

Themes

The key themes that emerged from the data are discussed below. After each theme a short discussion of its implications for the feasibility of a future trial, and more broadly, is presented.

Theme one: experiences of diagnosis and seeking treatment

One of the most striking issues to emerge during the course of interviews was the length of time reported to have elapsed between children first presenting with symptoms, and a diagnosis being given/treatment starting. Whilst this information was not explicitly sought as part of the interview guide, this point was repeatedly mentioned by interviewees. It also appears to have some relevance to parents' subsequent thinking about the design of the potential RCT, (discussed further under theme 4).

Respondents often described a process of to-ing and fro-ing between GPs and A&E (or equivalent departments) at local hospitals over a period of days or weeks before a diagnosis was made. In a number of cases, children were admitted to local hospitals for investigations during the pre-diagnosis period.

Children presenting at GP surgeries were often referred immediately to a local hospital, but once there symptoms could be attributed to a range of factors other than bone or joint infection, such as injury, irritable hip, synovitis or Erb's Palsy.) This period of delay in diagnosis, at a time when parents were convinced there was something more serious wrong with their child was described as frustrating and anxiety provoking.

"I took him to the GP the following day and he was just complaining of a pain in his knee. Basically for the next two weeks we kept going backwards and forwards to the GP. I was told to take him to hospital to get his knee x-rayed, which they did, and that all came back fine and I was told he had some soft tissue damage. I felt that there was something wrong with him. I was very worried, but then I suppose I was beginning to think am I just being neurotic because five different doctors have told me that he's fine, so are we just being neurotic?" Mother, Pt 365

A number of families also spoke of how much their child deteriorated during this period:

"We didn't go to his GP, we bypassed it to (local) Hospital...They said, 'Look, the best thing is come back in a day or so, come back and we'll put his leg in plaster. It may

improve in that period of time.' So we go, no painkillers, no anything. We then went for this other appointment and they turned around and said, 'Look, we've made an appointment with a bone specialist'. So we go to the bone specialist, this appointment, which was another week or so on again. In the process, he turned around and said, 'We can't really find any particular damage or crack or anything', this is what this bone specialist said. He said, 'Give it another week, then come back.' Within that last week he then was in dire straits with pain. He was in terrible pain...he's to the point he's literally got his head on my shoulder, he can't go on any longer. We're in the waiting room, he was literally slumped over me and I've got him in my arms." Grandfather, Pt 349

Issues including apparent lack of pain, absence of fever, referred pain and following alternative diagnoses were all highlighted as factors contributing to delay in diagnosis. Rarity of OM/SA was seen also seen as contributing to a slower diagnosis, as was the lack of experience of a number of health professionals, in particular within A&E departments where staff may be more junior.

Consultants with relevant expertise (or other professionals recognising symptoms, wherever they were located in the system) were praised for their expert knowledge. Contact with these experts after a period of delay in which parents felt untrusting of advice they were given, was experienced as very reassuring, and at times, even life-saving.

"If it hadn't have been for him I think we were in big trouble. I'll tell you that now. What his name was, who he was, I don't know but if I could shake his hand I would do because he was the one who got it underway. He knew there was something...wrong with (name of child), it was him who done it...Being fair with you, when we went for the x-ray, they didn't come up with the right answers so weeks and weeks were going past. That was the problem but he sussed it. He knew straightaway. He said, 'And what sort of pain?' and that was it, he'd already come to me, he said, 'I'm not happy with this at all', then it kicked off. Thank heavens it was for him... I don't know where we'd be today if they hadn't have got behind it and that fellow. If it had been left another few days I don't think we'd have had (name of child) back here, that's how bad it was." Grandfather, Pt 349

For these families, experience of treatment was often described as being in two halves – an unsatisfactory experience up to diagnosis, characterised by period of delay and frustration – followed by the treatment period with antibiotic and operation as necessary, often perceived by parents to be much more successful, in the hands of trusted experts.

A smaller number of families, however, did report positive experiences of diagnosis and swift commencement to treatment. In these cases, alignment of expert professionals occurred such that referral between different treatment locations went smoothly and symptoms were recognised without delay. Positive experiences at the start of the illness offered a number of benefits for families:

- Early experience of treatment/seeking diagnosis was less anxiety provoking and frustrating overall.
- Families felt that their concerns were being listened to and acted upon.
- Child's condition less likely to deteriorate due to early commencement of treatment.
- Overall experience less negatively impactful, with potential ramifications for thinking about potential clinical trial.

Respondents recognized that a number of factors about the condition itself could confound an early diagnosis (e.g. symptoms like that for an injury, absence of temperature or visible swelling/red patch on skin). However, it did often appear that the level of awareness and expertise of the professional with whom they came into contact directly affected how quickly symptoms were recognised to indicate bone or joint infections. This was evidenced by a number of instances in which children with unchanged symptoms were quickly diagnosed when a second opinion was sought from a practitioner with more experience in this field. Such experiences suggest that increased awareness amongst health professionals, in general, of the possibility of bone/joint infection may enhance trajectories of care:

"I understood all of that but I guess after two weeks when it wasn't better I just wonder whether there are better guidelines that GPs or A&E practitioners could have in terms of - there must be decision trees and it could have been irritable hip but it's not getting better as quickly as it should have done with irritable hip, so what other things could it be? Instead of being fixated on irritable hip and carrying on x-raying my daughter's hip and not her knee, what else could we look for and check for? She had a slightly hot knee and she had one knee slightly bigger than the other and I could see it and the

private consultant could see it but nobody in A&E or the GP could really see it.”

Mother, Pt 281

Theme two: experiences and understanding of antibiotic therapy

This theme reflects the experiences, knowledge and views of parents and children about both intravenous and oral antibiotic treatment. All participants understood the need for the use of IV antibiotics, and identified the positive benefits of making them/their child better in the fastest, most effective way possible.

“It seemed to be really, really important that the antibiotics were administered in that way and the explanation I was given seemed to make sense to me as somebody without any medical knowledge at all. I understood that it was really important that the antibiotics really got to where they needed to go as quickly as possible and that time was really important at this stage and that that was the best way of treating. So, I was totally in favour of having that treatment, if they'd said, 'Look, let's not bother with the cannula, let's just go to oral', having had that explanation before, I would've been really uneasy with that. I wanted him to have the IV treatment...I just felt that it would just get rid of the bug that was making him ill and get rid of it as quickly as possible and make him better and also to reduce the possibility of long-term complications and any damage to the joint.” Mother of Pt 204

Most commonly, participants understood IV antibiotics to be an intensive, strong form of treatment that, because injected straight into the blood stream, would reach the site of infection in the shortest possible time. As alluded to in the quote below, a smaller number of respondents also pointed out the benefit of the guaranteed delivery of antibiotic.

“Mother: I mean it was horrible just to get the cannula for the whole week, but also it was reassuring to know that he was getting all the antibiotic because you never know. Sometimes when he was in there with the oral one sometimes he spit a little bit so you were worried, you're not allowed to waste any of this because it might be really necessary for you.

Father: Yes, that's true. The most reassuring thing is that you know that everything that should go in, the treatment, is going in.

Mother: Everything was going through.” Parents of Pt 178

Notwithstanding the perceived need for IV antibiotic treatment, a number of negative experiences related to the IV delivery were reported. Of particular significance was pain associated with insertion of the cannula, which was often described as a difficult and stressful process. Parents used emotive language to convey the distress this caused their children, and therefore also to them, using descriptors such as ‘traumatic’, ‘grim’, ‘horrible’ and even ‘barbaric’:

“they could not cannulate him, it was just this horrific scenario of two or three doctors in the room with me trying to hold this baby who'd been through so, he was only 13 months at the time, he'd been through so much I felt. He was just being prodded and poked and he was, as you would, trying to wriggle away and I was trying to hold him down so they could do this and it just felt really, really wrong and horrible, because I was the person that he trusted and that I was helping this to happen and he didn't understand. I knew that it was being done for the right reasons, but it just, from his point of view, I could just feel this must be awful for him that the people he trusts are basically contributing to making this really, really traumatic situation. So, it still makes me emotional, as you can see, talking about it.” Mother, Pt 204

There was a suggestion by some parents that health professionals did not always show sufficient empathy of the level of distress children and parents were experiencing at this time. Other negative experiences reported were allergic reactions to antibiotics administered intravenously (resulting in rashes and abdominal pains), pain when drug was being administered and need to re-insert cannula (or replace with PICC line) if cannula was pulled out, or veins collapsed. A number of children also expressed their discomfort at the administration of IV antibiotics:

“it felt like something biting me with only one tooth” Pt 233

“Yes, which I didn't like it. It really hurt.” Pt 276

It is also important to note that not all patients experienced distress at the administration of IV antibiotics.

“He was amazing with it really. I don't know if it was his age, he just didn't let it bother him too much.” Mother, Pt 285

In particular, parents spoke highly of the skill of community nurses who came to administer IV in the child's home in putting children at ease and making delivery of antibiotics as easy as possible.

In contrast, parents often described oral antibiotics as a less intensive treatment, used to finish off the course, more as a backup or precaution than a first line treatment. Oral antibiotics were also perceived as a more convenient way of taking medicine that fitted better with the family's routine and enabled the child to be at home. Often parents reported that their child took the medicine with no problems. For others though, administering oral antibiotics to children who really disliked the taste was challenging and in a number of cases resulted in tummy upsets and sickness. In one case, a child completely refused oral antibiotic resulting in a longer course of IV. Two parents reported that their children's teeth had suffered brown staining from the use of oral antibiotics.

In the quote below, Pt 276 makes her distaste for the medicine clear!

“It was cream and (makes a disgusted sounding noise). Oh, I don't even know, it just smelt gross..and then when mum had to mix it up a few days later there was loads of bits in it, and I was like (makes a disgusted sounding noise), 'I'm not drinking that', but I had to...So I literally went (demonstrates swallowing fast).

Interviewer: Did you have to have some chocolate or something afterwards?

No, just water.” (Makes a disgusted sounding noise)

In line with this, a small number of parents (and children) expressed that they would prefer a longer course of IV treatment rather than a combined course including oral antibiotics.

Despite the reported challenges, parents and children persevered with the oral course of treatment, only coming off these medicines when the course was finished, or on specific medical advice.

Participants were specifically asked about their views about the point during treatment when children were 'switched' from IV to oral antibiotics. Respondents were in general happy about the timing of the switch, feeling that their child had made sufficient progress by this

time. Often this was perceived to have been guided by the results of blood tests and respondents were happy to follow doctors' lead as to the timing of the switch.

Respondents also indicated that they felt that the medical team had listened to their own particular concerns regarding a desire to leave hospital and try oral antibiotics.

“He wanted to come home, I mean we'd been in there that long but they were still... They were a bit, like, whether to let him home but as long as he took the antibiotics orally but if anything happened we were to go straight back. Well there was a specialist from East Surrey, a lady specialist...She said, 'That's where I am. If there's any indication you're not happy, either bring him or ring me and then we'll get things under way, we'll bring him back in.' She was just like, 'Ring our line straightaway and one of us will be here waiting for you.' They were brilliant, they were really good.”
Grandfather and mother, Pt 349.

In a small number of cases parents had experienced some anxiety that their children were being switched on to oral antibiotics too early.

“My only concern was that we'd been told that you normally treat the osteo, they do three weeks of IV antibiotics and I suppose I was probably over-thinking it. I was thinking that, although he's had three-and-a-half weeks, he had one week of an antibiotic that effectively didn't do anything because it wasn't for the right bacteria, so in terms of the right antibiotic he'd only had that for two weeks four days I think so I felt a little bit concerned about that and I asked about that and was just told that you don't know for sure what exactly is the right number of days. Is it two weeks or is it three weeks? I think based on his progress and bloods and x-rays they decided that that was all right, so I did feel slightly anxious about that.” Mother, Pt 365

In two cases, parents expressed concerns that their children hadn't been ready to leave hospital, resulting in them being re-admitted at a later stage.

Theme three: signs and outcomes of recovery

This theme reflects participants' views about factors such as activity levels which indicated to them personally that children were recovering from OM/SA, and also their longer term evaluation of treatment. Parents were asked how they first recognised that their children were

getting better. In order of frequency, comments were made in relation to resumption of movement/walking/weight bearing; being 'better in themselves' and improved appetite (with associated weight gain in some cases). In terms of speed of recovery, responses were varied, with a number of parents commented that their children seemed to 'bounce back' very quickly, but others reflecting that recovery was a slow and gradual process.

When asked which outcomes were important to them in judging the success of the treatment, the following were offered: no ill effects on bone/joint/growth; activity levels resumed; infection gone and no reoccurrence of infection. In the majority of cases parents reported that there were no long term impacts of the condition.

Yes, successful, because then we had a follow-up appointment at the end of February of that year where he had an x-ray and a consultation with the orthopaedic consultant and she was really happy with how it looked and then we had another follow-up in the August, so six months later where they said, 'This is totally fine, there's been absolutely no impact on the growth or anything. Please just forget about it. Don't worry about it.'

Pt 204

There were a small number of exceptions to this. Parents of one child who was newborn at the time of infection reported that the infection had affected her growth plate, but that the impacts of this were as yet unknown.

Mum: "They say it has definitely affected the growing.

Dad: And then it will just catch up or it won't catch up they said...They said that the top of her humerus isn't as visible as it should be.

Mum: Yes, so it was definite that the infection has affected it." Mother and father, Pt

343

In another instance, doctors had been unable to resolve the infection despite repeated courses of antibiotics and the child continued to experience painful symptoms, with ongoing visits to the hospital to try to resolve the situation. This appeared to be due to a longstanding infection present since an earlier abscess. The longevity of the condition was upsetting and wearing for the child and her family.

"One of the doctors, the surgeons, she said maybe she will need more surgery, because the infection hasn't gone yet, it's still there, because it went chronic. It was there for a

long time...they're not sure if it was something to do with the first operation when they took the abscess out and they left the wound open, just to heal from inside out. So they don't know if it was from there or not... She keeps on complaining. Every day she takes tablets for the pain. Every day. Yes, she has temperatures, she has night sweats every day. She can't sleep when she's in pain. She has to wake up six o'clock in the morning to go to school and she feels really tired and it's hard sometimes when she comes, 'Mummy, I'm so tired, can I stay at home?' "Mother, Pt 202

Two other children, although recovered from their bone or joint infections, had ongoing bone problems and therefore continued to experience discomfort and undergo further medical treatment and potentially further operations.

Despite physical recovery of their children a number of parents continued to experience a level of anxiety and heightened vigilance with regards to the possibility of a re-emergence of the condition. Parents often described the whole episode of their child being unwell as highly anxiety provoking and distressing:

"We have had one bit where we got a bit scared thinking perhaps was he getting it again, but it didn't. So I guess what I'm trying to say is we're very aware of it." Father of pt 250.

"He didn't have any significant cuts that had obviously been infected, so if it was through a cut it was one small one that I hadn't really noticed. I've now got a little thing of Dettol spray, so I drive him mad by every time he gets a little scratch I'm chasing him round spraying this stuff on him to clean him." Mother, Pt 365

Theme four: Views on proposed RCT

In response to the question 'Would you be willing for your child to take part in a (hypothetical) trial?' supported with the process diagram and additional description of trial (appended), parents were a little more likely to respond positively than negatively. Those who expressed positive views about the trial gave the following reasons for being supportive in principle: personal interest and belief in medical research; belief that enrolment in a trial would ensure good care and better provision of information about treatment; and being supportive of aim to reduce antibiotic therapy (and shorten treatment time), illustrated in the following excerpt:

“Although personally, I normally say yes to trials because it often means we get better care - or at least more follow-up and stuff. But yes, so I suppose that's just a thought that crossed my mind. I think it's a good idea to want to not over-treat, basically, isn't it, not give antibiotics longer than you have to. You need to have evidence about whether that's an effective thing to do, to cut down the length of antibiotics.” Mother, Pt 214.

Those who gave negative opinions about the trial presented two main concerns – fears about the risks of a potentially shorter course of treatment and that a ‘set’ or ‘scheduled’ trial treatment would not be sufficiently flexible to respond sufficiently to the individual needs of patients, putting them at unnecessary risk. There appeared to be some link (although not in every case) between families’ views about participation in a potential trial and how seriously ill their child had been, including the length of time taken for diagnosis– and thus how much deterioration (and fears of long term damage) had taken place during this time.

The two quotes below illustrate this – pt 349’s period of diagnosis was lengthy and the child had become seriously ill, whilst in a less severe case, pt 350’s delay in diagnosis led to parental fears about possibilities of long term damage.

“Reading through your reasons for proposing the study, which is to reduce the length of time and hopefully not reduce the risk, sorry not increase the risk. If the situation was different and we had a diagnosis on the first day, then my decision might have been different, but, no, I was glad it was of the length that it was and I wouldn't have questioned, as a precaution, if they wanted it to be longer still. I would have had concerns if it was shortened, but that was because of our situation that we were in, that the eight days, I think it was nine days from when we first noticed the symptoms to seeing him and actually having the first (signal breaks up)...so my concern was that the longer that the infection had a hold, the greater the risk that there might be a long-term problem, either (signal breaks up) eradicate the infection totally or having any deterioration in his joint in the long term.” Father, Pt 350 (expressing that a desire for a longer treatment period would make him unwilling for his son to join the trial).

“If it had been left another few days I don't think we'd have had (child) back here, that's how bad it was. I would recommend no set pieces. Let the doctors decide what they're going to do, let them have the say, no set guidelines on that one, that's crazy.

Let them do what they've got to. That's what they did with him, they didn't hesitate. There was no set pieces. They put this into motion. Whatever he needed, they gave him, that was it.” Grandfather, Pt 349

Such findings suggest that heightened concerns about the risks of harm to children may reduce potential willingness to participate in a trial. This was indicated in other ways by respondents. Families positively disposed to participation in such a trial nevertheless required reassurances about safety in information presented. Information required included: details of how child would be monitored to ensure infection was being treated successfully; trajectory of care in case of failure to recover on shorter course of antibiotics; data to support the safety of shorter arm and equipoise.

“I guess it would be in the way it's presented and the information that patients have, as in the outcomes maybe of those other areas where they have used a shorter course and they still had positive outcomes. I guess also would there be those caveats that, say you had been allocated the treatment B and at the end of day 25 or 26, that there was a noticeably, that wasn't working or there was still an issue, surely there'd be a duty of care or something to put in that you wouldn't just take them off anyway and see what happened? Or would there be? Do you know what I mean?” Mother, Pt 350

Some parents suggested that children with more severe or difficult to treat OM/SA would be less suited to enrolment in a trial:

“And I suppose it depends where it goes, where you get it as well. Because her feet are like, the blood supply is not very good and the chances are that they couldn't do it there because it wouldn't get through and it's so deep in the bottom of her foot. Whereas if you have it in your knee, the antibiotics might work within two days, mightn't they? That would depend how poorly your child is, wouldn't it? It depends how ill you were wouldn't it? It would depend how bad it is.” Mother, Pt 248

Other factors that may dissuade against participation would be a trial that required extra invasive interventions, or where families' routines would be significantly disrupted.

The way information is presented about the trial was recognised as critical by respondents – who delivered it appeared less important – other than it should be done by someone

knowledgeable and that consistent messages about the trial should be delivered by all those involved in a child's care. Above all, parents would be looking for reassurance that participation in the trial would not be putting their child at increased risk.

"I guess I'd have wanted to. I mean I work in a university where research is really important, so I would have wanted to. If I was given the right information and I thought that it was safe, then I would have done. If I was in any doubt that it might not have been safe, then I would have said no." Mother, Pt 247.

Theme five: timings, parental anxiety and capacity to absorb information

The final theme emerging from data analysis concerns the level of anxiety and distress experienced by parents at the time of their child's illness and treatment. Key, or 'pinch' points of anxiety for parents included: lead up to diagnosis (especially in case of delays); occasions during which child experienced distress (for example during insertion of cannula); fears about child receiving a general anaesthetic; and some follow up anxiety around potential for future impacts, or re-occurrence of infection.

Reflecting on these feelings, respondents reported that their capacity to think about, and remember, important information (about treatment as well as potentially about the trial) was reduced during this time – exacerbated by fear, heightened emotions, the strangeness/unexpected nature of the situation and input from many different professionals:

"Because it's quite an awkward time, when your child's poorly and you're not quite sure what's wrong with them and you're all a bit all over the place, your headspace is not really right and you don't really know what's going on and you're just being led by what doctors and nurses are telling you, you're quite terrified." Mother, Pt 174

"So I think there were three, and that was why it was a little bit confusing because obviously one doctor is trying to coordinate these other two deciding what antibiotics and how much and this and that and then the other person looking after her joint. Yes, it was very confusing, and a lot of the time I think you are just so tired you don't really take it all on and you are on your own, and then your husband comes along and says, 'Oh, what happened this morning?' I can't really remember all of it." Mother, Pt 267

Bearing these responses in mind, participants suggested that the timing of the invitation to participate in the trial, along with associated information and the manner in which it is delivered is likely to be key. Once antibiotic has started and parents feel reassured that their child is receiving treatment, capacity to consider trial information is likely to be enhanced.

“I personally think, yes, in order to make any sort of rational decisions about anything you have to know your child is safe. Particularly as, yes, I don't know if your research would - I don't think there'd be any reasons not to wait (until treatment had started), would there? Maybe there are, but I can see obviously if you're testing something in the emergency period, you have to approach people before the thing happens. But if you don't have to then I think you would be more likely to engage parents.” Mother, Pt 214

A need for sensitivity and awareness of parental vulnerability at this time (in inviting participation in a trial, but also throughout the care trajectory) was also stressed.

“just remembering that sensitivity, that the person that you're talking to, it's the first time they're in this situation and it's very stressful and emotional. It's just that giving a little bit of time I guess to process that information.” Mother, Pt 350

“If I'd been approached in a not very positive way it probably would have put me off to be honest.” Mother, Pt 174

Discussion

In this section, we discuss findings arising from the thematic analysis of the interview data, particularly with reference to a future randomised controlled trial. Some limitations of this qualitative study are also highlighted. We conclude with some brief recommendations for practice and for research.

Many families described the early stages of their child's illness and seeking/commencement of treatment as a highly distressing and anxiety provoking time. However, once a working diagnosis had been obtained, expert advice given and antibiotic treatment commenced, parents began to feel reassured and less anxious, especially when signs of improvement were noted in their children. In the main, despite its challenges, families were satisfied with treatment for OM/SA and the outcomes achieved, most importantly, those of 'no ill effects on bone/joint/growth'; 'activity levels resumed'; 'infection gone' and no 'reoccurrence of infection'.

One of the major issues highlighted by this empirical work was the delay experienced by many of the families in obtaining a diagnosis, and the consequent stress and anxiety experienced. Whilst not the direct focus of this qualitative study, the obvious concern experienced by families around the issue of diagnosis has led us to identify some recommendations both for future research and for practice. In terms of implications for participation in a future clinical trial, it is important to recognise that some children and families approached for recruitment may have experienced a long period of uncertainty and interaction with primary and secondary care prior to the definitive diagnosis. The child may have become seriously ill prior to a diagnosis being reached. These circumstances might increase family anxiety about long term harm to their child, and negatively impact on willingness to expose their child to any further uncertainty or 'risk'. It is therefore important that research staff recruiting for a trial understand what the child and family have experienced prior to admission/recruitment, and explore any continuing concerns.

Similarly, with regard to prior experiences of both IV and oral antibiotic therapy for OM/SA, whilst understanding the rationale for the different modes of delivery, parents and children in our study had both positive and negative experiences of both forms. It will therefore be important to provide an opportunity to discuss this, prior to inviting participation in the trial. Potential randomisation to either standard care or the intervention arm could therefore lead to anxiety about 'more of the same', and it may be important to provide reassurance in either eventuality.

Within interviews, both children and parents had clear views about both how they knew they/their children were recovering, and also on what they based their judgements about the success or otherwise of treatment for OM/SA. Some of these measures reflect clinical tools used both in every day practice and in research, but others are less well reflected in commonly used measures in this specialism. Our recommendations both the future RCT, for practice and for general research reflect children/parental perspectives about indications of recovery and outcomes.

Although we recognise that participants in our study are probably more enthusiastic about research participation than within a general sample of children with OM/SA and their parents (by virtue of having accepted the invitation to participate in this qualitative study), it was encouraging to note that more were positive about participation in a trial than not, at least in theory. The concerns of those who were potentially unwilling or not sure reflected anxiety

about reduced courses of treatment, and that rigid trial protocols might put their own child at risk. The previous section highlights a potential (albeit subjectively observed) correlation between length of time to diagnosis (and seriousness of child's condition) and willingness to participate in a trial, which might perhaps suggest either an inclusion criterion or at a minimum, the need to sensitively explore prior experiences, and provide tailored reassurance and data. Families positively disposed to participation in such a trial, would also require reassurances about safety in information presented. Information required included: details of how child would be monitored to ensure infection was being dealt with; trajectory of care in case of failure to recover on shorter course; data to suggest safety of shorter arm; and equivalence/equipoise about treatment in both arms.

As highlighted previously, levels of anxiety and distress experienced by parents at the time of their child's illness and treatment were at times high. Key, or 'pinch' points of anxiety appeared to be: during the lead up to diagnosis, periods of child distress, anxiety about general anaesthetic and some follow up anxiety around potential for future impacts, or re-occurrence of infection. Parents reported that they had diminished capacity during these times to attend to, absorb and reflect on information, relating to both treatment and potentially an invitation to participate in a trial. Awareness and empathy at these 'pinch points' plus avoidance of these where possible in presenting information would be helpful and useful.

Limitations

- Participants in this study had initially responded positively to an invitation to take part in the service evaluation phase of the study, and also to being approached with regard to inclusion in the qualitative interview phase. They are therefore unlikely to be representative of the general population of children/parents treated for OM/SA.
- Via purposive sampling, invitations to participate in this phase were extended to those treated within four centres in the South of England, and findings may not therefore represent those receiving different treatment regimens at different centres.
- Although most of our interviews were carried out in person, a few were conducted over the telephone. Although there didn't appear to be any difference in terms of the quality of data generated, it is possible that due to the difficulty in responding to non-verbal cues, these interviews were slightly less responsive to participants' emotions/agendas.

- For practical reasons of time/convenience, interviews with children were usually carried out in the presence of parents, reducing the opportunity to explore differences in perspective.

Recommendations

a) For a future randomised controlled trial

- There is an opportunity for parents and children to share their experiences with research staff prior to invitation to participate in trial, and reassurance that inclusion in the RCT will not further compromise the child's health.
- This is also an opportunity for child and family to discuss previous experiences (including negative) of both modes of antibiotic delivery, and reassurance about randomisation to either arm.
- Pre-trial information giving should provide:
 - clear information about the oral to IV switch criteria, and reassurance that the trial protocol wouldn't override the individual needs of the child in terms of when the switch from IV to oral antibiotics is made.
 - data to support the switch point in both standard care and the experimental intervention.
 - details of how child would be monitored to ensure infection was being dealt with.
 - trajectory of care in case of failure to recover in shorter treatment arm.
 - data to demonstrate safety of shorter arm.
 - information regarding the equivalence/equipoise about treatment in both arms.
- Consideration of short term outcomes which accord with children and parents' observations ie appetite and weight, temperature, pain, weight-bearing on affected limb, functional movement in activities of daily living, X-ray findings.
- Inclusion of longer outcome measures which reflect children's and parents' perspectives and priorities ie functional activity and mobility levels, pain, end of infection with no reoccurrence, impact on bone/joint/growth.
- Consideration about whether an exclusion criterion relating to seriousness of child's condition and/or previous trajectory leading to diagnosis should be included.

- If no exclusions are made based on severity, particular care and attention to explanations about treatment and risk in a trial will be needed for those with difficult prior experiences, attending to children and parents' specific concerns about risk.
- Where possible, researchers should avoid 'pinch points' of anxiety/distress when inviting trial participation. If such timing is unavoidable, parents and children will need to be offered clear, written information, supported by verbal explanation, with time to reflect, and several opportunities to revisit/ask questions.
- Discussion about perceptions of risks, precautions and safety within the context of a trial will be required, to check understanding

b) For practice

- Information about signs, symptoms and diagnosis of osteomyelitis and septic arthritis could be more readily available to frontline clinicians (eg GPs, junior doctors in A&E), with access to more experienced colleagues for a second opinion.
- Clinicians could provide more clarity around:
 - orientation to parents'/families' concern about child and trust in their judgement as a stimulus to further clinical tests, in the absence of any clinical diagnoses;
 - understanding and empathy with child/family during course of both IV and oral antibiotic treatment, recognising that previous experience might lead to anxiety;
 - discussion with parents about strategies for addressing problems with administration of oral antibiotics (eg objection to taste, teeth staining, upset stomach and vomiting);
 - exploration of potential of healthcare providers to safely administer IV antibiotics at home, in order to facilitate faster discharge;
 - sharing switch criteria (eg blood test results) and decision making from IV to oral antibiotics with child and parents;
 - reassurance and explanation about routes to infection in OM/SA;
 - discussion and explanation about how children and parent focused outcomes are reflected/used in clinical decision making; and
 - discussion about understandings of risks and outcomes in relation to OM/SA both during treatment, and at follow up appointments

- The provision of written resources to support information provision at particularly stressful times during the care trajectory may be useful, for example, about treatment, risk, and outcomes.
- Signposting to reliable and trustworthy information on a website might also prove reassuring and helpful.

c) For future research more generally

- It may be useful to
 - explore and evaluate strategies to improve the speed and accuracy of diagnosis amongst non-specialist primary and secondary care providers at initial point of contact
 - research improved delivery mechanism of oral antibiotics for children (eg taste, consistency)
 - develop and and test sensitive and robust Patient Reported Outcome Measures for children recovering from OM/SA, including Quality of Life measures
 - investigate possible correlation between prior negative OM/SA illness experiences (eg serious illness, long time to diagnosis) and willingness to participate in RCT, plus effectiveness of strategies to address specific concerns (eg child/parent focused information provision)
 - explore mitigating strategies as times of maximum stress during the child's illness trajectory (eg optimum level of information provision, whether critical information provided through more than one medium is more easily retained)

Chapter 5: Systematic literature review

Aims and objectives

The aim of this component of the study was to use a systematic review to inform development of a core outcome set to use in a future RCT of shortened duration of antibiotic therapy for paediatric bone and joint infections.

Methods

Types of study included in the review, types of intervention and types of participant:

The research group recognised that there is a lack of high quality data in this clinical area and that previous RCTs investigating the duration of antibiotic treatment have generally been small. As no large RCTs were expected to be found, the review aimed to include:

- Large or small RCTs, retrospective cohort studies and case series
- 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.
- 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. In addition, predominantly adult studies with small numbers of children were also excluded because the criteria for adult treatment are not the same as for paediatric cases and there are different outcome risks.

Search strategy

Embase and Medline databases were searched using the search strategy shown in *Appendix 4*. All publications from 1946-present were included in the search. The search was carried out in May 2012 and updated in July 2014.

Results

Eligibility of studies

Of 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 al found 12 prospective studies including one RCT comparing duration of antibiotics for acute haematogenous osteomyelitis.⁴⁴ 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 and Isaacs also published a systematic review of treatment of sub-acute and chronic pyogenic osteomyelitis in 2010.⁸¹ 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 would not be comparable to a group with only bone and joint infections. 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 the stakeholder survey 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 (SNF). These outcomes were then discussed with a study clinical co-investigators, 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 69* below.

TABLE 69: SUMMARY OF RESULTS FROM SELECTED PAPERS

Paper	Interventions	Study design and number	Outcome Measures
Paakkonen et al Scand J Inf Dis Sept 2012 ⁸² Shortened hospital stay for childhood bone and joint infections: analysis of 265 prospectively collected culture-positive cases in 1983-2005.	2-4 days IV + up to 20 or 30days oral for OM, up to 10 or 30 days for SA	RCT (culture positive only, culture negative excluded) 265	Time to normalisation of CRP and ESR Duration of hospital stay Sequelae at one year
Peltola et al PIDJ December 2010 ⁴⁹ Short- Versus Long-term Antimicrobial Treatment for Acute Hematogenous Osteomyelitis of Childhood Prospective, Randomized Trial on 131 Culture-positive cases	2-4 days IV 9-108 days oral	RCT (culture positive only, culture negative excluded) 131	As above Pain / deformity at 3 months and one year
Bachur et al Clin Paed Jan 2007 ⁸³ Success of short-course parenteral antibiotic therapy for acute osteomyelitis of childhood	7days or less intravenous vs more than 7 days intravenous Median 4 days intravenous	Retrospective cohort 29, all uncomplicated acute haematogenous osteomyelitis	Absence of symptoms 1 year after stopping antibiotics Number needing to be put back on IV antibiotics from oral
Zaoutis et al, Pediatrics Feb 2009 ⁵⁸ Prolonged Intravenous Therapy vs Early Transition to Oral Antimicrobial Therapy for acute osteomyelitis in children	Prolonged IV vs early oral switch,	Retrospective cohort 1969	Rehospitalisation with bone and joint infection within 6 months of discharge, Chronic osteomyelitis Surgical procedure after treatment with antibiotics

			Myositis / arthritis / complication of osteomyelitis Clostridium difficile Line related complication Adverse drug reaction associated with antibiotic, e.g. agranulocytosis, allergic reaction, neutropaenia
Messina et al, PIDJ Dec 2011 ⁸⁴ Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis	Oral septrin, median duration 31 days	Prospective cohort 20	Adverse event to antibiotic Resolution of symptoms at end of therapy
Tetzlaff et al Pediatrics 1978 ⁸⁵ Oral antibiotic therapy for skeletal infections of children. II. Therapy of osteomyelitis and suppurative arthritis.	7 days IV then up to 6 weeks oral. Blood antibiotic concentrations monitored and dose adjusted	Prospective cohort 35	Resolution of symptoms Chronic osteomyelitis
Ballock, R. T. et al Journal of Pediatric Orthopaedics Sep 2009 ⁴⁶ A comparison of early versus late conversion from intravenous to oral therapy in the treatment of septic arthritis,	Prolonged IV vs early oral switch, prolonged total duration (Median 7.4 days vs median 18.6 days) 2 different hospitals compared	Retrospective cohort 186	Duration to defervescence Duration to normalisation of ESR Number of complications (specifically avascular necrosis)
Kolyvas et al Pediatrics 1980 ⁸⁶	72h IV then total 4 weeks oral vs 4 weeks IV	Randomised controlled trial 15	Time to ESR <20 Resolution of symptoms Relapse
Jaberi et al Journal of Pediatric Orthopaedics 2002 ⁸⁷ Short-term Intravenous Antibiotic Treatment of Acute Hematogenous Bone and Joint Infection in Children: A Prospective Randomized Trial	All had surgical drainage prior to antibiotic treatment 7 days IV vs 14 days IV for septic arthritis 10days IV vs 21 days IV for osteomyelitis	Randomised controlled trial 33	Scoring system used twice a month for 6 months Scored on pain, gait, ability to walk and use of walking aids Radiological changes on plain x ray Sinus or discharge

Jagodzinski et al Journal of Pediatric Orthopaedics 2009 ⁸⁸	Assessed after 3 days IV ? for oral conversion	Prospective cohort 70	Followed up for 1 year Time to normalisation of fever Time to CRP <20 X ray changes Pain, disability, deformity at 1 year
Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children	86% converted to oral after 5 days		
	All had 3 weeks oral antibiotics		

Conclusion

The key outcomes were combined and summarised all of which are shown in *Table 70*. These were then discussed with the clinical co-investigator 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 (see *Chapter 7*).

TABLE 70: OUTCOMES IDENTIFIED FROM THE SYSTEMATIC REVIEW

	Specific Outcome
Infection-related	Number of days to CRP <5 Duration to resolution of fever Duration of hospital stay Duration to resolution of pain Need for one or more non-diagnostic surgical procedures Chronic osteomyelitis Chronic Arthritis Chronic Myositis Amputation or Fasciotomy Duration to CRP <20 Duration to CRP less than one third of highest value Duration to ESR<20
Line or antibiotic related complication	Vomiting / diarrhoea / gastrointestinal Agranulocytosis or neutropaenia <i>C. difficile</i> infection Rash / adverse drug reaction

Long term outcome	Line infection
	Need for line removal or replacement
	Pain at 3 months
	Pain at 12 months
	Limp/ Disability at 3 months
	Limp / Disability at 12 months
	Number of cases symptom free at 12 months
	Treatment failure / recurrence of infection within 18 months
	Growth plate involvement / damage
	Rehospitalisation within 6 months
	Limb shortening or deformity (timeframe hard to decide in future RCT as could be 3-5 year follow up)

Chapter 6: Delphi survey to identify oral switch criteria, develop core outcomes and assess the overall feasibility of a future RCT in children with bone and joint infections.

Aims and objectives

Through a Delphi process we aimed to:

- Identify the oral switch criteria for use in a future randomised controlled trial.
- Develop a core outcome set for use in clinical trials of children with bone and joint infections
- Assess overall feasibility of a future randomised clinical trial in children with bone and joint infections

Methods:

Delphi clinical stakeholder survey

Two rounds of Delphi process were performed. Programming for the online system was carried out by the Liverpool Medicines for Children Clinical Trials Unit (Director co-investigator PW).⁸⁹

Participants

Prior to the study the national societies of the clinical stakeholder groups agreed that the Delphi survey could be sent to members via the society email lists (those of the RCPCH Speciality Group for General Paediatrics, the British Paediatric Allergy, Immunology and Infection Group (BPAIIG), British Society for Children's Orthopaedic Surgery (BSCOS), the British Society of Paediatric Radiology (BSPR) and the British Society for Antimicrobial Chemotherapy (BSAC). In addition, due to the general rarity of the condition and the study requested participation criteria (see above) the study also made use of the wider Royal College of Paediatrics and Child Health (RCPCH) regional mailing lists to try to be able to invite a larger group of general paediatricians.

Clinical stakeholders were asked to participate if they had personally treated a child with septic arthritis or osteomyelitis in the last 12 months or had been part of a wider multidisciplinary team providing that clinical care. While some of the participants were also principle investigators for the service evaluation, the survey was not limited to sites

participating in the service evaluation in order to obtain as wide range as possible of clinical opinion and views. In the invitation email all participants were also reminded of the importance of completing both rounds of the Delphi process.

Delphi round 1

The survey was presented in an online format (*Appendix 5*) with participants allocated a unique identifier (via name and email address) so as to allow identification of individuals completing all rounds of the Delphi exercise. All participants were asked to record their grade and clinical role. At the beginning of the survey, participants were presented with selected information from the study service evaluation.

Questions that were asked:

- ‘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 were invited to score each of the outcomes listed using the Grading of Recommendations, Assessment, Development and Evaluations scale of 1 to 9, with 1 to 3 labelled ‘not important’, 4 to 6 labelled ‘important but not critical’ and 7 to 9 labelled ‘critical’. Participants were provided with an option to add additional outcomes that they think are relevant together with a score for each outcome added.

Outcomes were listed alphabetically to avoid potential weighting of outcomes caused by the order in which they were displayed. For each outcome, the number of participants who scored the outcome and the distribution of scores (percentages of who had scored each outcome) were summarised by stakeholder group. All outcomes were carried forward to round 2.

Predefined Delphi survey outcomes were: 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).

Following initial screening by 2 senior investigators (SNF and PW), the clinical co-investigators reviewed the additional outcomes added during round one and assessed whether these differed significantly from those already on the list. Additional outcomes were added prior to round 2 for additional scoring.

Delphi round 2

In the second round of the Delphi process each participant was 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. Due to the low numbers of paediatric microbiology respondents, the microbiology and clinical paediatric infection data were presented together.

Participants in round two were asked if they would be willing to participate in a future RCT.

Results

Participants

Due to the national society email distribution lists used to send out the invitation to as many clinical stakeholders as possible, it was not possible to accurately assess the denominator number of clinicians sent invitations for the general paediatrics and paediatric radiology clinical stakeholder groups. In addition the number of orthopaedic surgeons actually in clinical paediatric practice was not accurately represented by the mailing list of the national society

Engagement reflected both the expected uncommonness of the condition in general paediatric practice and that the most interested groups are paediatric orthopaedic specialists and paediatric infection specialists. Of note, only around 80 consultants are members of the RCPCH general paediatric special interest group. The “denominator” of the number of paediatricians sent the invitation email was impossible to establish with accuracy as the email was also attempted to be sent to all RCPCH active members, but this was not reflected in co-investigator RCPCH members receiving the email apparently “sent”. The responses of paediatric radiologists reflected the general literature opinion that treatment outcomes are clinical rather than radiological. Approximately one half of British Paediatric Infection

specialists participated, and approximately half of the known number of paediatric orthopaedic surgeons. Approximately 15 microbiologists were invited via the speciality's email list. Further accuracy of these data are unobtainable.

In round 1, 37 general paediatricians, 38 paediatric orthopaedic specialists, 34 paediatric infection specialists, 4 paediatric microbiologists and 13 paediatric radiologists took part. Of the 13 paediatric radiologists, 7 answered "unable to score" for every outcome.

The response rates in round 2 are shown in

Table 71

TABLE 71: RESPONSE RATE TO CLINICAL STAKEHOLDER SURVEY

Speciality	R2 Response rate (number/R1 response)	% of R1 response
General Paediatricians	31/36*	86.1%
Orthopaedic Surgeons	21/36*	58.3%
Radiologists	8/9**	88.9%
Microbiologists	4/4	100%
Paediatric Infectious Disease Specialists	33/33*	100%

* R2 Non response (known reasons) denominator reduced:

1 general paediatrician : ongoing issue meant that they couldn't complete R2

2 surgeons: 1 has moved abroad, 1 has retired

1 PIDS: Phone number couldn't be found to chase (appears to work abroad)

** Radiologists denominator reduced from 13 to 9 because R1 was not completed or participants were unable to score any outcomes in R1

Response bias was assessed between rounds 1 and 2 by comparing the average R1 score from those responding in both rounds to those responding in R1 only. There is no evidence of attrition bias.

FIGURE 5: R1 SCORES FOR THOSE RESPONDING AND NOT RESPONDING IN R2 BY STAKEHOLDER SPECIALITY

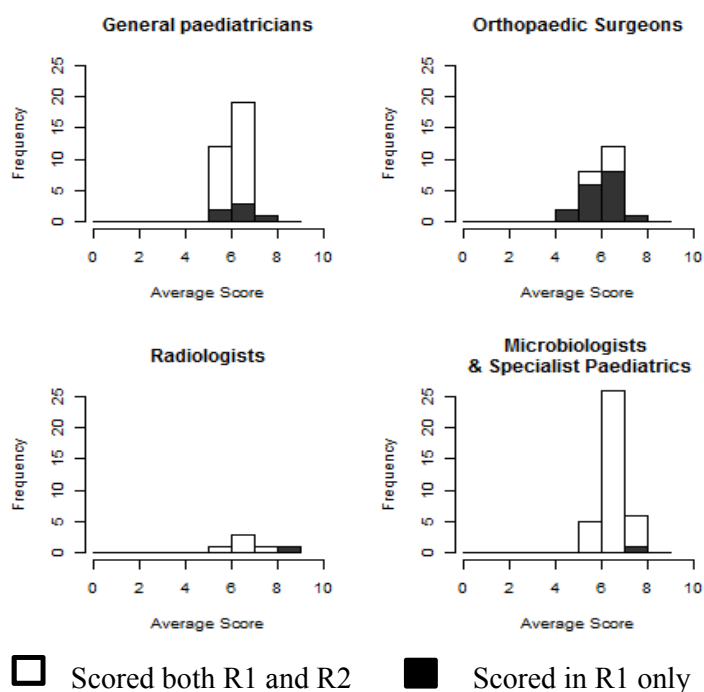


FIGURE 6: CHANGE IN SCORES BETWEEN R1 AND R2

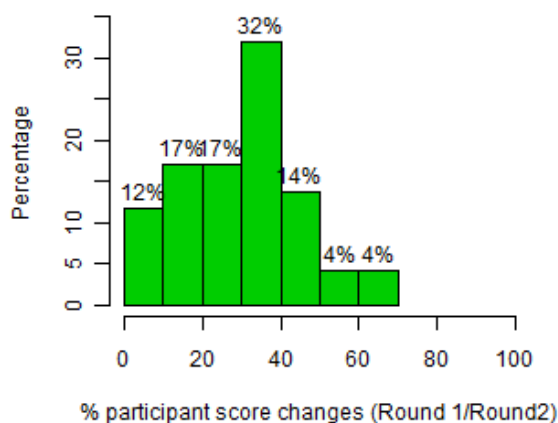


Figure 6 shows the participant distribution of percentage of outcomes with changed scores between R1 and R2 for the group as a whole. Three participants did not change their score for any outcome. These results suggest that including a second round in the Delphi was a useful exercise.

Summary of the answers from the Delphi process

A summary of the results are shown in *Table 72 - Table 76*. Detailed tables on voting results are included in *Appendix 5*.

TABLE 72: RESULTS RATING OF CRP AS OUTCOME FOR FUTURE STUDY

	Delphi Survey	Delphi Survey	Consensus meeting
	Round 1	Round 2	
Number of participants (n)	126	97	17
No. of respondents that gave a rating for at least one CRP outcome (N)	116	92	17
No. that scored at least one CRP outcome ≥ 7 (A)	72	55	12
Percentage (A/N)	62.1%	59.8%	70.6%

TABLE 73: PERCENTAGE OF PARTICIPANTS THAT SCORED 7, 8 OR 9 FOR SWITCH CRITERIA ROUND 2 BY STAKEHOLDER GROUP

Outcome- Health Professionals	Outcome- Parents and Young Person	General Paediatrics	Orthopaedic Surgeons	Radiologists	Microbiologists and PID Specialists
CRP<20	Blood test showing level of inflammation in body	39%	38%	0%	38%
CRP less than one third of the presenting value		10%	19%	67%	28%
CRP less than two thirds of the presenting value		13%	0%	33%	17%
ESR <20	Blood test showing level of inflammation in the body (not used as often in children as needs more blood for technical reasons)	3%	10%	0%	0%
Resolution of fever for 48h or more	Childs body temperature has been normal for past 48 hours	* 9%	* 95%	* 100%	* 86%
Weight bearing / return of function to limb	Child able to put weight on affected limb/ use affected body part as normal	55%	* 71%	67%	65%
Resolution of pain	Child no longer feels any pain	48%	52%	0%	43%
Tolerating oral input	Child able to drink and eat	* 83%	9%	0%	* 97%
Parental opinion regarding improvement or worsening of condition	Parents opinion about wellness of their child	16%	5%	* 75%	25%
Pain improvement (rather than resolution) as oral switch criteria	Less pain felt by child	13%	33%	* 100%	33%

* Consensus criteria were met: >70% scored 7, 8 or 9 and <15% scored 1, 2 or 3

TABLE 74: PERCENTAGE OF PARTICIPANTS THAT SCORED 7, 8 OR 9 FOR INFECTION RELATED OUTCOMES

Outcome- Health Professionals	Outcome- Parents and Young Person	General Paediatrics	Orthopaedic Surgeons	Radiologists	Microbiologists and PID Specialists
Need for non-diagnostic surgical procedure (e.g. decompression, debridement)	Child has had to have surgery in order to treat the infection	48%	38%	60%	61%
Re-hospitalisation or recurrence of symptoms whilst on oral antibiotics	Child has returned to the hospital or symptoms have returned whilst taking antibiotics by mouth	* 97%	* 95%	* 100%	* 97%
Treatment failure: recurrence of infection (either at original site or at new site)	Child has a new infection in the same area or a different area.	* 100%	* 100%	* 100%	* 100%
Pain while on antimicrobial treatment	Pain experienced by the child whilst being treated for the infection	0%	10%	0%	0%
Ongoing pain at follow-up	Pain still experienced at outpatient appointments	19%	38%	0%	16%
Disability at follow-up	Child has continuing movement problems at outpatient appointments	* 81%	67%	67%	* 78%
Symptom free at 1 year	Child has not experienced any symptoms after one year	61%	* 9%	* 83%	68%
Limb shortening or deformity	Childs limbs have become shorter or changed shape/ appearance	* 87%	* 8%	* 83%	* 76%
Duration to CRP<5	Time taken for inflammation level to return to normal in the body	0%	19%	25%	5%
Duration to resolution of fever	Time taken for child's temperature to return back to normal	16%	19%	0%	43%
Duration to resolution of pain	Time taken for pain to go away	16%	5%	60%	8%
Duration of hospital stay	Time child has had to stay in hospital	10%	5%	20%	27%
Fracture at or near site of infection	Bone broken in the same location as the infection or near to the infection	34%	40%	67%	44%
Prolonged antibiotic therapy	Antibiotics needed for longer than expected	27%	24%	50%	56%
Quality of life	Childs ability to enjoy normal activities.	* 71%	50%	33%	44%

* Consensus criteria were met: >70% scored 7, 8 or 9 and <15% scored 1, 2 or 3. These should be considered for primary and secondary outcomes in a future clinical trial

TABLE 75: PERCENTAGE OF PARTICIPANTS THAT SCORED 7, 8 OR 9 FOR INFECTION RELATED OUTCOMES

Outcome- Health Professionals	Outcome- Parents and Young Person	General Paediatrics	Orthopaedic Surgeons	Radiologists	Microbiologists and PID Specialists
Chronic osteomyelitis	Infection of the bone which does not get better with treatment.	* 94%	* 100%	* 100%	* 95%
Chronic arthritis	Joint inflammation that does not get better with treatment	* 84%	* 100%	* 83%	* 76%
Chronic myositis	Muscle inflammation that does not get better with treatment	68%	48%	* 100%	39%
Amputation or Fasciotomy	Removal of body part by surgery or skin and muscle have to be cut by a surgeon to relieve pressure between the skin and bone	* 97%	* 86%	* 100%	* 94%
Death	Death	* 97%	* 100%	* 100%	* 94%
PICU requirement (e.g. PICU-free days at day 30, if admitted)	Admission into a ward (Paediatric Intensive Care Unit) specialising in the care of critically ill children.	* 77%	52%	40%	* 81%

* Consensus criteria were met: >70% scored 7, 8 or 9 and <15% scored 1, 2 or 3. These are rarer events to consider which need to be captured in a clinical trial

TABLE 76: PERCENTAGE OF PARTICIPANTS THAT SCORED 7, 8 OR 9 FOR TREATMENT/LINE RELATED OUTCOMES

Outcome- Health Professionals	Outcome- Parents and Young Person	General Paediatrics	Orthopaedic Surgeons	Radiologists	Microbiologists and PID Specialists
Agranulocytosis / neutropaenia	Child more prone to infection due to low white cell count in body as a result of infection or treatments	32%	43%	* 75%	64%
Deranged liver function	Detection of inflammation/ damage to the liver	3%	14%	0%	47%
Clostridium difficile infection	An infection affecting the digestive system caused by antibiotics (very rare in children under 2 years old)	10%	33%	33%	28%
Rash or allergic reaction	Rash or allergic reaction	23%	10%	17%	67%
Suspected drug-related fever	Childs temperature increases in line with taking treatment	19%	5%	20%	44%
Line infection	Infection of the drip that is giving treatment to the patient	45%	33%	33%	* 83%
Line occlusion	Blockage of the drip that is giving treatment to the patient	6%	10%	33%	50%
Vomiting / diarrhoea	Sickness and diarrhoea	3%	5%	17%	17%
Insertion of PICC or other central line due to need for prolonged antibiotics at home or in hospital	The need to provide the child with a drip which can be used for a longer period	32%	24%	60%	* 75%
Infiltration or extravasation event	Medicine being given into the veins is accidentally delivered to the surrounding area due to the drip coming out of place	29%	10%	17%	50%
Any complication of vascular access	Any complication of the drip itself.	23%	24%	60%	58%

* Consensus criteria were met: >70% scored 7, 8 or 9 and <15% scored 1, 2 or 3. These are rarer events to consider whether there is a need to capture in a clinical trial

Chapter 7: Consensus meeting to assess the feasibility of a future randomised clinical trial in children with bone and joint infections

Aims and objectives

In the consensus meeting we aimed to:

- Identify the oral switch criteria for use in a future randomised controlled trial.
- Develop a core outcome set for use in clinical trials of children with bone and joint infections
- Assess overall feasibility of a future randomised clinical trial in children with bone and joint infections

Methods

A consensus meeting was held on the 27th April 2015 and an invitation to attend the meeting was sent to:

- Health professionals who had completed both rounds of the online Delphi survey and expressed an interest in attending future meetings.
- Principal Investigators who had taken part in the Service Evaluation component of the study (although individuals were advised that if they had not completed both rounds of the Delphi survey that they would be ineligible to formally vote but could be involved in discussions).
- Members of the CRN: Paediatrics London Young Persons Advisory Group (YPAG).
- All parents and children who had taken part in a qualitative interview (although none of the parents participating in the qualitative study were able to attend, the meeting was attended by the study PPI representative and a member of the YPAG).

A separate session was scheduled immediately before the main consensus meeting for 30 minutes to allow the qualitative investigators to meet with the parent and young person that attended the meeting. This meeting allowed any questions to be answered about the structure of the day, expectations and for additional information to be given with relation to the switch and core outcomes.

The meeting was chaired by Professor Adam Finn (AF, University of Bristol), co-investigator who had not been part of the core study management group and who was a non-voting participant, to avoid the possibility of Saul Faust (SF) introducing bias into discussion when voting, and Carrol Gamble (CG), who monitored from a statistics perspective to ensure an unbiased session. The meeting was structured according to the Dinosaur consensus meeting agenda version V1.0, 23.04.2015 (*Appendix 5*). Preliminary results from the service evaluation (*Chapter 2*) and qualitative study (*Chapter 4*) were used to inform the consensus meeting. The definition of consensus is shown in *Table 77 and 78*.

TABLE 77: DEFINITION OF CONSENSUS FOR SWITCH CRITERIA

Consensus Classification	Description	Definition
Consensus in	Consensus that criterion is important when deciding when or whether to switch from IV to oral AB	70% or more participants scoring as 7 to 9 AND <15% participants scoring as 1 to 3
Consensus out	Consensus that criterion is not important when deciding when or whether to switch from IV to oral AB	70% or more participants scoring as 1 to 3 AND <15% of participants scoring as 7 to 9
No consensus	Uncertainty about importance of criterion	Anything else

TABLE 78: DEFINITION OF CONSENSUS FOR OUTCOMES

Consensus Classification	Description	Definition
Consensus in	Consensus that outcome should be included in the core outcome set	70% or more participants scoring as 7 to 9 AND <15% participants scoring as 1 to 3
Consensus out	Consensus that outcome should not be included in the core outcome set	70% or more participants scoring as 1 to 3 AND <15% of participants scoring as 7 to 9
No consensus	Uncertainty about importance of outcome	Anything else

Results

Participants

Meeting attendees and their representation are shown in *Table 79* and

TABLE 80. In the items below, co-investigators are referred to by initials (see Table 79) but other meeting participants by stakeholder group.

TABLE 79: MEETING ATTENDEES

Attendee	Stakeholder group /role	Initials
Prof Saul Faust+	Chief Investigator, Paediatric Infectious Diseases	SF
Prof Adam Finn+	Meeting Facilitator, Paediatric Infectious Diseases	AF
Prof Nick Clarke+	Orthopaedic Surgeon	NC
Priya Sukhtanker	Clinical Research Fellow	PS
Eileen Baildam*	Paediatric Rheumatology Specialist	EB
Deborah Eastwood*	Orthopaedic Surgeon	DE
Marieke Emonts*	Paediatric Infectious Disease Specialist	ME
Katy Fidler*	Paediatric Infectious Disease Specialist	KF
Vana Gandhi*	General Paediatrician	VG
Adam Irwin*	Paediatric Infectious Disease Specialist	AI
Dominic Kelly*	Paediatric Infectious Disease Specialist	DK
Nick Makwana*	General Paediatrician	NM
Nuria Martinez-Alier*	Paediatric Infectious Disease Specialist	NMA
Piers Mitchell*	Orthopaedic Surgeon	PM
Fergal Monsell*	Orthopaedic Surgeon	FM
Karyn Moshal*	Paediatric Infectious Disease Specialist	KM
Ann Pallett*	Microbiologist with an interest in Paediatrics	AP
Colin Powell*+	General Paediatrician	CP
Fiona Shackley *	Paediatric Infectious Disease Specialist	FS
Stefania Vergnano*	Paediatric Infectious Disease Specialist	SV
Andy Wainwright*	Orthopaedic Surgeon	AW
Benjamin Jacobs**	General Paediatrician	BJ
Kadri Ayo**	General Paediatrician	KA
Kuldeep Stohr**	General Paediatrician	KS
Catherine Prichard**	Parent Representative	CaP
Esme Lynch**	Young Persons Advice Group Representative	EL
Prof Carrol Gamble+	Statistician	CG
Claire Ballinger+	Qualitative Researcher	CB
Amanda Lees	Qualitative Researcher	AL
Nicola Harman	Meeting Coordinator	NH
Cath Spowart	Meeting Coordinator	CS
Abigail Bennett	Meeting Coordinator	AB
Chloe Middleton	Meeting Coordinator	CM

+Co-investigator; *Eligible to vote via Turning Point software; **Paper based voter

TABLE 80: STAKEHOLDER REPRESENTATION

Stakeholder Group	Number of voting members attending the consensus meeting	Percentage representation at consensus meeting
General Paediatrician	3	18%
Microbiologist with an interest in Paediatrics	1	6%
Orthopaedic Surgeon	4	23%
Paediatric Infectious Disease Specialist	9	53%
Radiologist	0	0%
Participants in qualitative study*	0	0%

*Although no qualitative study participants were able to attend, the consensus meeting was attended by the study PPI representative and a member of the NIHR CRN: London Young Persons Advisory Group.

Formal voting was performed via Turning Point software (www.turningtechnologies.co.uk/). Only those attendees who had previously completed Round 1 & 2 of the Delphi Survey were eligible to vote but involvement in discussion of the switch criteria and outcome set was encouraged from all attendees. Two public contributors were present who voted separately using a paper based voting system (as they had not been involved in the qualitative interviews). One was the Patient and Public representative from the Study Steering Committee and had direct experience of a child suffering from the condition; the other was a “trials experienced” member of the Medicines for Children Young Persons Advice Group. Three clinicians attended the meeting who had not completed the online survey, votes again were collected using a paper based voting system (2 complete voting sets and 1 partial were produced). These votes have not been included in the results presented in this report.

Presentation of the service evaluation data

a) The definitions of Complex and Simple cases of Septic Arthritis (SA) or Osteomyelitis (OM) were discussed as well as the numbers of each case type. Forty nine cases of misdiagnosis were recorded and the meeting queried if the patients were treated appropriately in each of the cases. The data captured did not cover this information.

b) A query was raised as to whether some infection body sites were more common than others. Within the study population the most commonly affected joints were hip, knee and ankle for simple cases. Femur and elbow infections were more prevalent amongst complex cases (and that this reflects the historical literature).

c) The potential issue of whether data were missing was raised as 7% of simple cases and 3% of complex cases did not appear to have received IV antibiotic treatment. While concerning,

there are reports of oral therapy alone being used in recent European cohorts to treat bone and joint infections (oral data from Spain presented at European Society for Paediatric Infectious Diseases, Leipzig May 2015).

d) There seems to be a lack of detailed information about the date that child/parents first noticed symptoms. The date of first presentation at Health Care Service Provider is recorded but the meeting participants agreed that this is often days, if not weeks, after first symptoms appear.

e) The definition of diagnostic surgery was discussed as many of the surgeries listed as diagnostic would normally be seen as therapeutic. For the Service Evaluation diagnosis was defined as the start of IV antibiotic therapy and therefore any surgery completed before this was included in diagnostic category.

f) Surprise was expressed at the number of aspiration surgeries. Research Nurses reported these based on surgeons notes and/or cross-checking discussions with surgeons.

g) The participants discussed and felt that lavage should fall into arthrotomy and that they would expect the numbers of arthrotomy procedures to be much higher as this is standard practice for simple septic arthritis. The lower numbers of arthrotomy procedures is very likely due to their inclusion in the 'Incision and Drainage' category.

h) There were concerns over the low numbers of abnormal bone X-Ray images being performed, wondering if this suggests that a few centres lying outside of the norms of standard practice may be skewing the results. This discrepancy could be caused by department/specialist that child is first referred to, or junior doctors who lack experience.

i) The number of blood cultures taken prior to initiation of antibiotic therapy is not available in the existing dataset.

j) Preliminary results show that of the 75.8% of children that had microbiology tests, only 42.3% had at least one micro-organism detected, which may have been expected to be higher.

k) Results of the Service Evaluation suggest that standard practice in the UK is short course IV antibiotic therapy (*Chapter 2*). Data also implies that average timing of IV/oral switch is between 1 and 2 weeks. The dataset does not provide information about whether location of infection impacted timing of switch or length of overall antibiotic treatment.

- l) Concerns were shared regarding discrepancies in dosing of intravenous ceftriaxone. There was general agreement that in clinical practice a high (80mg/kg) dose should be used for bone and joint infections (the manufacturer (Roche) European SPC states up to 1000 mg/kg/day) but one participant noted that the BNF for children (BNFC) allows a lower dose of 50mg/kg.
- m) It was noted that only 40% had a blood test at the switch. It was queried whether the blood tests could have been done a few days before which would be standard practice but not captured in the database. All agreed this was an important question in relation to future discussions for the trial.
- n) The results found for length of stay in hospital were discussed; hospital stay could be influenced by i) as a result of patients being transferred to a District General Hospital (DGH) in case of tertiary centres ii) the age of the patient.
- o) The group noted that there are not as many complications as might be expected but that this could be due to the short length of follow up.
- p) Discussed was if pain at follow-up should be classified as a treatment failure.

Presentation of the qualitative study

- a) Interviews provided a reminder that both IV and oral antibiotic therapy can be traumatic for children; some may tolerate tablets/liquid well and find the IV insertion stressful but others may not be bothered by IV line but find tablets/liquid hard to take/keep down. *Parents need to feel that therapy for their child is tailored to their individual case and this may make recruiting to a randomised trial difficult as it removes the element of personalised care.*
- b) Parents expressed their concern that complex conditions might not be suited to a randomised trial and would remove any parental choice regarding the methods of treatment. The data indicated that the period before diagnosis causes a high level of anxiety and a longer safer standard treatment arm would be preferred.
- c) The qualitative researchers had thought carefully about how to explain a randomised controlled trial to a child in the interviews. From a young person's perspective it is important to get all the information (patient information leaflet/ consent and assent) tailored for their needs and that patient and public involvement is important at this stage. Parents may be more concerned with safety specifics but child/young person may be more focussed on what is

required of them, e.g. blood test. It is sometimes important to discuss the trial with the child separate to the parent/guardian and pointed out that there appeared to be a lack of child's opinions within the qualitative research presentation.

d) Timing of consent is important as parents are unlikely to consent to a trial whilst waiting for child to go in for surgery or come round from anaesthetic for example. It was suggested to wait to discuss the trial until treatment has started. Once the patient is settled, parents are more likely to be receptive to a trial.

e) It was also pointed out that bone and joint infection is perhaps not on a junior doctors' 'radar'. Parents felt the speed of diagnosis was often down to which medic they were treated by and therefore a case of luck. It was pointed out that a trial would increase awareness.

f) The group should consider any sub-groups of patients that clinicians would not be comfortable randomising.

Discussion and voting results

Oral to intravenous antibiotic switch criteria

Results from voting on oral to intravenous antibiotic switch criteria are presented in *Table 81*. Overall, resolution of fever for 48 hours or more, tolerating oral input (medicines and food/drink) and pain improvement (rather than resolution) were considered important criteria by consensus following the meeting voting.

While there was no clear consensus regarding the absolute or relative (to presentation) of the CRP, there was agreement that CRP is an important parameter in around 60% of respondents in both round 1 and round 2 of the Delphi survey, and by approximately 70% of those at the consensus meeting. In addition, the patient representative felt that CRP<20 was important but not critical.

TABLE 81: SUMMARY OF SWITCH CRITERIA VOTING

Switch criterion	Percentage of meeting participants scoring 7-9	Percentage of meeting participants scoring 1-3	Consensus
CRP <20	35.29%	11.76%	No consensus*
CRP less than one third of the presenting value	23.53%	17.65%	No consensus*

CRP less than two thirds of the presenting value	25.53%	29.41%	No consensus*
ESR <20	11.76%	47.06%	No consensus
Resolution of fever for 48h or more	100%	0%	Consensus in
Weight bearing/ return of function to the limb	64.71%	5.88%	No consensus
Resolution of pain	29.41%	11.76%	No consensus
Tolerating oral input	100%	0%	Consensus in
Parental opinion regarding improvement or worsening of condition	35.29%	0%	No consensus
Pain improvement (rather than resolution)	70.59%	0%	Consensus in

*while there was no clear consensus regarding the absolute or relative (to presentation) of the CRP, 86.35% of participants scored one of the 3 CRP criteria 7-9, showing consensus that the CRP is an important parameter but not providing clear evidence regarding which should be used.

Discussion about switching criteria:

- CRP levels are an important test for recognising improvement but picking an arbitrary absolute CRP level may not be appropriate
- A two-thirds reduction in CRP might not be sufficient reduction if the baseline CRP was very high
- A very high CRP level could also indicate a complex case as opposed to simple and should therefore not be ignored
- If CRP was used as switch criterion parents could find conflicting evidence online and not wish to consent and/or withdraw their child from the study.
- The overall trend should be more important than any particular figure as a fixed figure

Conclusion: monitoring CRP in terms of absolute value and trend would be important despite consensus not being reached.

Core Outcomes Voting

A summary of core outcome consensus is presented in

Table 82. Overall, the outcomes assessed as “consensus in” voting include: Re-hospitalisation or recurrence of symptoms while on oral antibiotics, treatment failure- recurrence of infection, disability at follow-up, being symptom free at 1 year, limb shortening or deformity, chronic osteomyelitis or chronic arthritis, amputation or fasciotomy, death, need for paediatric intensive care and line infection.

TABLE 82: SUMMARY OF OUTCOMES DISCUSSED

Outcome	Percentage of meeting participants scoring 7-9	Percentage of meeting participants scoring 1-3	Consensus
Need for non-diagnostic surgical procedure (e.g. decompression, debridement)	25%	25%	No consensus
Re-hospitalisation or recurrence of symptoms while on oral antibiotics	100%	0%	Consensus in
Treatment failure- recurrence of infection	100%	0%	Consensus in
Pain while on antimicrobial treatment	6.25%	37.5%	No consensus
Ongoing pain at follow-up	31.25%	6.25%	No consensus
Disability at follow-up	81.25%	0%	Consensus in
Symptom free at 1 year	100%	0%	Consensus in
Limb shortening or deformity	100%	0%	Consensus in
Duration to CRP <5	18.75%	43.75%	No consensus
Duration to resolution of fever	31.25%	18.75%	No consensus
Duration to resolution of pain	18.75%	6.25%	No consensus
Duration of hospital stay	18.75%	18.75%	No consensus
Fracture at or near site of infection	56.25%	0%	No consensus
Prolonged antibiotic therapy	50%	0%	No consensus
Quality of life	62.5%	0%	No consensus
Chronic osteomyelitis	100%	0%	Consensus in
Chronic arthritis	100%	0%	Consensus in
Chronic myositis	50%	6.25%	No consensus
Amputation or Fasciotomy	100%	0%	Consensus in
Death	100%	0%	Consensus in
Paediatric Intensive Care Unit (PICU) requirement (e.g. PICU-free days at day 30, if admitted)	75%	0%	Consensus in
Agranulocytosis / neutropaenia	56.25%	0%	No consensus
Deranged liver function	25%	6.25%	No consensus
<i>Clostridium difficile</i> infection	18.75%	12.5%	No consensus

Rash or allergic reaction	37.5%	0%	No consensus
Suspected drug-related fever	6.25%	25%	No consensus
Line infection	81.25%	0%	Consensus in
Line occlusion	50%	6.25%	No consensus
Vomiting / diarrhoea	6.25%	49.75%	No consensus
IV antibiotic necessitated insertion of PICC or other central line	31.25%	18.75%	No consensus
Infiltration or extravasation event	31.25%	6.25%	No consensus
Any complication of vascular access	50%	0%	No consensus

Discussion about core trial outcomes

- All would be uncomfortable taking part in a study where only outcomes that had been voted as critical were included.
- Critical outcomes would form a core outcome set and other important outcomes would be included
- 12 out of 16 participants felt that an outcome should be included for both parental and child stress/anxiety.
- It was agreed that a barrier to collecting quality of life data would be that often in these cases the negative impacts may not be seen for several decades after recruitment.

Overall feasibility of future trial

It was noted that the number of cases reported in the service evaluation was very promising in terms of a future trial.

Standard Care

Concerns about standard care in a future RCT:

- No uniform agreement for diagnosis, antibiotic dosing or defined standard care procedures as identified in Service Evaluation is a concern for a future RCT. A study aiming to standardised care is a different research question that might be hard to achieve funding for as there is no specific clinically-related research question. Part of the rationale for this Dinosaur study was to review the current UK practice and establish the parameters for current standard of care that can be tested against.

- Delay in diagnosing simple bone and joint infections overall in UK settings. The process of running a study itself could help to define the approach to these cases and improve diagnosis and treatment by raising awareness in participating centres. There is therefore a need to ensure that a study is accessible to all and does not just take place in tertiary centres.
- Is the service evaluation coherent with personal experience of clinicians? This is the largest prospective global study to date on childhood bone and joint infections and that part of the problem in this condition is that treatment has been based on personal experience and mostly retrospective small cohort studies.
- Should primary care trusts be included in the future study to ensure that standard care was consistent across the board? Running the future study would be the best way to increase awareness of these conditions and improve normal care.
- Is a 3 month follow-up, like it is used in Service Evaluation long enough to capture long term complications like growth problems? A relatively short follow-up is often standard practice (in routine clinical care of the simple cases being considered for an RCT) but that perhaps conducting this study could improve follow-up times for normal care.
- A future trial needs to consider the cost to the NHS within research costings

Adherence to potential trial treatments

Adherence to oral antibiotics regimens potentially can influence/disrupt results for trial treatments involving oral antibiotic therapy at home.

Items discussed:

- Parents are often better at complying with antibiotic regimens than doctors or nurses
- Parents in the qualitative research had reported high levels of adherence to antibiotic therapy as parents had strong understanding of the consequences of not completing the course. This finding could be influenced by a study effect and selection bias.
- Clinical experience shows concerns about adherence
- Older children and young adults are often given responsibility for their own treatment by parents and may report a higher level of compliance than is the case.
- Adult RCTs successfully used oral treatment strategy

Recruitment and inclusion criteria issues

- Parents often self-inform and have preferences for their child's treatment (length of IV therapy, PICC line, liquid/tablet form).
- Clinician preference for one type of therapy over another has made some paediatric clinical trials hard to recruit to than anticipated, for example the TORPEDO trial (<http://www.torpedo-cf.org.uk/>). Despite these issues the trial has proceeded and achieves a consent rate of approximately 40%.
- Service evaluation data suggest that short course IV therapy is now more common. Randomising patients to a longer than normal treatment arm may reduce participation.
- Parents are sometimes less willing to take part in randomised trials due to the lack of personalised care. The design and patient/parent information would have to clearly explain this issue and the appearance of shortened therapy lengths may be off-putting to parents. Parents interviewed in the qualitative research were generally happy with the timing of their child's switch from IV to oral antibiotic as they felt they were well enough to be switched.
- Children with bony (rather than soft tissue) abnormalities on X-ray imaging would need to be excluded from participation in a clinical trial of simple OM or SA. The final feasibility assessment needs to take into account cases from the service evaluation where no bony abnormalities were found.
- The study population will remain heterogeneous despite aiming for clear definitions because patients take different amounts of time to present at health care service providers, doctors take differing amounts of time to diagnose the infection and infections progress at differing rates.

Developing the research question

A future study is thought to be important to reduce the use of antibiotics, reduce length of hospital stay and to avoid complications of IV therapy.

Possible research questions:

1. How long should bone and joint infections be treated with antibiotics for overall
2. When should the switch from IV to oral therapy occur?
3. Early vs. late switch rather than type of antibiotic treatment.
4. Early switch point of 48 hours compared with longer such as 9 days, as this appeared to be the median time for switch in the data from the Service Evaluation.

Concerns:

- Assessing more than one research question in one study may impact on results, creating smaller groups of patients with more compounding factors and reducing the power of the study.
- The umbrella title of bone and joint infections covers two very different conditions; Acute OM is perceived to have lower risk than SA, despite shorter historical treatment course length of antibiotic therapy. Differences in standard care procedures need to be examined from the service evaluation to decide whether OM and SA need to be evaluated in different study groups.
- Setting an arbitrary switch date would not take different infecting organisms into account. Any defined switch timings should be within range that is comfortable for clinicians and parents.
- Many clinicians would be uncomfortable switching as early as 48 hours. This would only be possible in a mild subgroup, effecting the recruitment and power of the study.

Conclusion:

The meeting concluded that a future study looking switch timing should be prioritised over one reducing the overall length of antibiotic therapy.

Chapter 8: Summary discussion and conclusions for further research

Any future RCT will need to enrol cases defined as simple disease where there is no underlying chronic disease, no orthopaedic implants and no recent (within 6 months) orthopaedic surgery. This study set out to establish the feasibility of a study in pre-defined simple or less complex bone and joint infection in children, and the qualitative component of the study confirmed that parents would also be less likely to consent to their children participating in such a trial if there was concern regarding the seriousness of child's condition and/or previous trajectory leading to diagnosis.

Number of cases:

A future RCT would need to recruit from all tertiary and most secondary hospitals in the UK NIHR Comprehensive Research Network where there are resources for recruiting children to clinical trials. The number of cases seen in UK clinical practice is currently less than previously reported. There were 109 simple OM and 107 simple SA seen in 49 Trusts over the 6 month study period. Given the lower than expected monthly accrual (0 to 3 simple cases per month in tertiary centre, 0-0.7 per month in secondary centres), in tertiary centres there would be approximately 24-36 cases of eligible simple disease per year and 8-12 potential eligible cases in secondary care centres.

Logistics of a clinical trial including criteria for oral switch

From the service evaluation data, it appears that most cases present to the emergency department and not primary care. These data do not align directly with parental concerns expressed in the qualitative study regarding their reported experience of the length of time before a formal diagnosis was made. From the observations in the qualitative study, pre-trial information provided to and gathered from parents will need to specifically address this issue by acknowledging that parents might have perceived a delay prior to diagnosis and by researchers giving the parents a chance to express themselves. If parents have experienced a delay in diagnosis, the service evaluation data can also be used to explain to parents of potential participants that the clinical severity at presentation to hospital, rather than the length of non-specific symptoms prior to presentation at hospital, is the key determinant of whether an individual child should be considered for recruitment to a clinical trial.

Although in some centres home based antibiotic delivery is possible (paediatric outpatient antimicrobial therapy, p-OPAT), the overall length of hospital stay for children in our cohort

with simple SA and OM was very similar to the length of intravenous antibiotic course (median 6 days for simple SA, 9 days for simple OM).

The service evaluation suggested that the at home or in-hospital completion of antibiotic course will not be of any concern in an RCT. Parents of children with bone and joint infection understand the need to complete antibiotic courses and report that they do so as per clinicians' instructions. This is also reflected in the experience of many past and current paediatric trials where there are few reports of problems with adherence to trial medications where adequate in-trial support is provided.

From a trial operation and logistical perspective, the qualitative study has shown the importance of offering parents the opportunity to discuss their immediate experiences of the condition and its presentation with the research team prior to being considered for a study. Embedding a future RCT in the routine NHS care of children with OM or SA would be a way of achieving this, which would also provide reassurance that both potential arms of a study would not be expected in advance to negatively impact on an individual child's quality of care. Enrolment as part of routine care is also supported by a recent survey showing that NHS patients are more likely to participate in research if the topic is introduced by the potential research participants own doctor ⁹⁰.

The qualitative study also provided clear advice regarding the need to approach parents at times other than "pinch points" of anxiety/distress if at all possible, and regarding the need for clear explanation of potential risk and safety aspects.

Oral switch criteria for use in a clinical trial

In preparing the design and materials for a future trial, it will be important to clearly state that a research protocol would not override the individual need of the child in terms of when an oral switch was made. This is feasible as an RCT would not be testing the oral switch criteria which will be according to an agreed standard current practice. From the service evaluation current clinical practice clearly is to switch with no consistent evidence base used to make this decision. By ensuring a switch criteria was strict clinicians would be able to support following the trial protocol using predefined criteria such a modification of that previously proposed ²⁶. The Delphi survey and consensus meeting showed that resolution of fever for 48 hours or more, tolerating oral input (medicines and food/drink) and pain improvement (rather than resolution) were considered important criteria. While there was much variability in the Delphi survey and consensus meeting regarding what the CRP criteria should be, there was

agreement that CRP is an important parameter in around 60% of respondents in both round 1 and round 2 of the Delphi survey, and by approximately 70% of those at the consensus meeting. These criteria resonate with views parents expressed during interviews. Parents were confident in the switch point when they had perceived an improvement in their child's condition and felt that doctors were basing decisions on clinical indicators. Where this was not perceived to have been the case, parents expressed dissatisfaction and anxiety.

Recruitment following a child meeting specific clinical criteria in acute paediatric care has been used successfully in the recently published NIHR HTA funded clinical trial of the management in infants admitted with bronchiolitis, who were randomised following admission requiring oxygen therapy to maintain saturations⁹¹. Other information that will be important to include in the pre-trial information includes data to support the switch point in both standard care and the experimental intervention, details of how child would be monitored to ensure infection was being dealt with, trajectory of care in case of failure to recover in shorter treatment arm and data to demonstrate safety of shorter arm and regarding the equivalence/equipoise about treatment in both arms.

Defining the core outcomes of a future RCT in bone and joint infections in children.

The qualitative study demonstrated the importance to parents and children of consideration of short and long term outcomes meaningful to the families themselves. Short term examples which accord with children and parents' observations include appetite and weight, temperature, pain, weight-bearing on affected limb, and functional movement in activities of daily living. Longer term outcome examples reflecting children's and parents' perspectives and priorities include functional activity and mobility levels, pain, end of infection with no reoccurrence, and the impact on bone/joint/growth.

Overall, the outcomes assessed as "consensus in" from the Delphi and consensus meeting voting include: re-hospitalisation or recurrence of symptoms while on oral antibiotics, treatment failure- recurrence of infection, disability at follow-up, being symptom free at 1 year, limb shortening or deformity, chronic osteomyelitis or chronic arthritis, amputation or fasciotomy, death, need for paediatric intensive care and line infection.

Consideration of possible trial designs in relation to the current standard of care for length of intravenous and oral therapy courses in relation to treatment failure reported in the service evaluation cohort

The most striking aspect of our data is that for simple, non-complex disease, clinicians currently use an oral switch early, at a median of 7 days in simple SA and 9 days in simple OM. Very important for the design of an RCT of shortened intravenous and/or total length of antibiotic therapy, these data also demonstrate less treatment failure in simple disease where there was an early oral switch, suggesting also that “more severe simple” disease is more likely to fail initial therapy or require additional interventions. Of the 73 simple cases that had a very early oral switch (less than a week), 9.6% experienced a treatment failure, compared with 16.1% that had an early switch (between one and 2 weeks), and 18.2% where switch was after 2 weeks of intravenous antibiotic.

Although there was no difference in overall intravenous course length between simple SA or OM, SA is treated with overall course length around 10 days shorter than simple OM (median 30 days (IQR 18,41) compared to 40 days (IQR 21, 48)). These data suggest that while there has been a move to short course intravenous antibiotic therapy for simple disease in current NHS practice, overall course lengths have remained similar to “textbook” longer overall courses of treatment. Due to the length of treatment differences between SA and OM, the diseases would need to be enrolled in different groups in a future RCT.

To be able to conduct an RCT of even shorter courses of IV therapy (eg for example randomise children with simple OM or SA to very short course IV therapy of 3-4 days compared to 7 days), clinicians, parents and researchers would have to be convinced regarding the equipoise of potential treatment failure/safety, and agree on clear oral switch criteria.

The service evaluation showed that while 8.3% of simple cases experienced at least one complication, only 3 (of 218) simple cases reported recurrence of infection requiring medical or surgical intervention. However, in order to capture all possible cases where the initial empirical antibiotic and/or surgical therapy had failed requiring further treatment, we instead used a broad definition of treatment failure including fever, recurrence of infection including increase in CRP or development of draining sinus, dislocation, subluxation, pathological fracture, pain, mobility problems, swelling, numbness, hospital readmission, surgery and change of antibiotics. Using these criteria, 32 of 218 (14.7%) simple cases experienced a treatment failure and treatment failure was half as likely in SA (9.3%) compared with OM

(19.3%). In summary, treatment failure was a) less likely the earlier switch occurred (9.6% in switch at less than a week, 16.1% when between one and 2 weeks, 18.2% when after 2 weeks of IV therapy); b) treatment failure for simple SA and OM was equally likely for children that had antibiotics for less than 6 weeks as for those that had courses for more than 6 weeks; and c) differences between treatment failure in simple SA and OM suggest the OM and SA should be enrolled in separate groups in any future RCT.

Regarding the feasibility of an RCT to compare early compared to late oral switch, or of a trial to compare overall short compared to longer course therapy in simple OM or SA, a series of statements can be made on the basis of the service evaluation data:

1. Clinicians and researchers would only feel comfortable enrolling children to a trial of reduced total antibiotic length of course, and parents would only consent to their children taking part, if there is genuine equipoise regarding whether or not reduced intravenous course length, and/or reduced total length of therapy, would cause increased treatment failure.
2. Because of the current practice of early oral switch apparent in the service evaluation data, there appears to be a group of children with simple disease who get better rapidly even though they receive less intravenous antibiotic. It is a reasonable clinical assumption (though not proved by these data) that such children have less treatment failure because they have less severe disease than children who have a later oral switch. Together with data from this study and from other countries (data from Spain presented at ESPID 2015 Congress, Leipzig May 2015), and with strict oral switch criteria, an RCT could be considered for the very mild cases to be treated with very short course (1-3 days) intravenous antibiotic therapy prior to oral switch. However, the Delphi survey and consensus meeting showed that for oral switch, while CRP is considered important (with no consensus regarding level), consensus was achieved that criteria for oral switch include resolution of fever for 48 hours or more, tolerating oral input (medicines and food/drink) and pain improvement (rather than resolution). This finding, together with low numbers of children likely to meet oral switch criteria in the first week of treatment, probably means such a study will not be feasible as a single country (UK) trial.
3. An alternative strategy would be to consider a trial to randomise children where a clinician has decided on early oral switch to reduced overall length of antibiotic therapy compared to current standard of care. This trial design would avoid the potential problem of parental

anxiety regarding stopping IV therapy early described in the qualitative study, as children currently treated with intravenous antibiotics for less than a week have less complications than those where oral switch is later. From the service evaluation data, it would be possible to plan for a similar length of initial IV therapy prior to oral switch for both SA and OM, but to treat each for a different defined length of time following the switch in different study arms. For example treating for 20 days compared to 30 days for simple SA and 30 days compared to 40 days for simple OM. However, while this study design (reduced compared to standard length of oral antibiotic after oral switch) appears to make sense based on current practice data, the expressed preference of the consensus meeting was for prioritising investigation of early oral switch rather than overall length of therapy.

In addition, given the invasive nature of the initial diagnosis and the relatively cheap cost of home based antibiotic therapy given at times around school attendance, whether the cost-benefit to the NHS is great enough in such an uncommon disease to justify the large costs of a national multicentre clinical trial of reduced course oral antibiotics after oral switch is debatable. While a positive outcome of such a trial would indeed reduce overall antibiotic use and consumption, as the condition affects so few children the overall impact on antimicrobial resistance in the community or the individual children will be very small. The cost saving of such a home based reduction in oral therapy would also be small both in terms of actual costs of antibiotics saved and clinician time, as well as economically as children with disease mild enough to be randomised in this study would almost all be back at nursery or school during their period of oral therapy.

4. A third study design is to conduct a reduction of antibiotic trial in children who have simple disease but do not meet the criteria for oral switch in the first week of treatment, a group which appears to represent most children with simple OM and SA. The clinical course of these patients is less predictable, and it is not currently possible to predict clinically or from biomarkers which patients would potentially do well with less intravenous or shorter total course length of antibiotic therapy. In a RCT, the oral switch criteria defined in this study together with a strict CRP cut off could act as a key enrolment criterion, with oral therapy then randomised to be immediate or delayed after the oral switch criteria were met after 7 days of intravenous therapy. Although this study did not achieve consensus on what the CRP cut off should be (reflecting wide variation in currently unevidenced based clinical practice), recent experience in a commercial clinical trial suggests that a “cautious” level of

CRP change would be accepted by investigators in the context of an RCT. In the recent commercial study that has completed recruitment but not yet reported (clinicaltrials.gov NCT01922011), the CRP criteria was “CRP decreased by at least 30% from baseline (if available)”, but we would anticipate a UK study needing this to be reduced by at least 50% or perhaps two thirds from baseline to make sure there was wide participation. Children would be excluded from the trial if they met the criteria for oral switch in the first 7 days of intravenous therapy as the service evaluation suggests this group have less treatment failure than those having later oral switch. This study would compare shorter to longer IV therapy (for example 12-14 days total IV therapy compared to 21-28 days IV). It would therefore establish the safety and treatment-failure equivalence of shorter or longer course IV antibiotic therapy, keeping the total length of antibiotic (IV and oral combined) the same. In this design, that meets the preference of clinicians at the consensus meeting, there would be clear differences in intravenous therapy course length and a potential large impact on clinical and cost (length of stay) outcomes in the NHS.

5. While this study has established three potentially feasible RCT designs (very short course IV antibiotics in children with simple SA or OM compared to current standard practice; reduced overall length of therapy compared to current standard practice following clinician-determined oral switch; shorter or longer IV therapy course after defined oral switch are met with no difference in total intravenous or oral antibiotic combined total course), key questions remain. There are currently no biomarkers (currently used or research) that would provide certainty of potential study eligibility to a trial of very early IV to oral switch, or aid decision making in other trial designs. New biomarkers are required in order to better stratify the severity of children with simple OM or SA.

Do the microbiological conventional and molecular data provide information on which empirical antimicrobial agent(s) could be used in a randomised clinical trial?

The available conventional tests and results of the targeted PCR sub-study suggest that while *Staphylococcus aureus* remains the most common single identified pathogen in children of all ages, *Kingella kingae* occurs in a significant proportion of younger children (aged 0.8-2.3 years in the molecular data from this study but more common under 6 years in other series) and Group A Streptococcus (*Streptococcus pyogenes*) is an important pathogen in children of

all ages. Other pathogens are much rarer, but using data from both conventional and molecular tests included the pneumococcus (*Streptococcus pneumoniae*), Group B *Streptococcus*, one child with *Haemophilus influenzae*, and one child with *Pseudomonas spp.* Importantly, where *S. aureus* was the identified pathogen, only 2 cases (one simple, one complex) of resistant bacteria (MRSA) were identified. The incidence of the more virulent PVL-positive *S. aureus* disease was also very low (2 simple cases, 1 complex case) in our data.

Regarding dose, while it is impossible from the service evaluation data to determine whether any treatment failures are a result of non-maximum dose prescribing, for the major in-hospital intravenous antibiotics prescribed for simple disease (flucloxacillin, clindamycin and cefuroxime) clinicians mostly used the maximum (high-dose) BNFC dose recommendations. Where ceftriaxone was prescribed however, the lower dose band was prescribed more than the higher, severe infection dose. Dosing strategies for orally prescribed antibiotics were more variable and often much lower than the formulary maximum recommended for age or weight.

For a clinical trial, these data overall suggest a broad-spectrum intravenous antibiotic (such as cefuroxime 50 mg/kg/three times per day) should be used in younger children (possibly under the age of 6) to cover less common pathogens not completely sensitive to high dose flucloxacillin. A narrower spectrum antibiotic such as high dose flucloxacillin (50 mg/kg/four times per day) could be used in older children and teenagers where *S. aureus* and Group A *Streptococcus* predominate. To enable discharge from hospital while still on intravenous antibiotic therapy, once daily ceftriaxone at maximum dose (80 mg/kg/once per day to maximum 4 g daily) would provide empirical antibiotic cover for all common and less common organisms, as antimicrobial resistance is still very uncommon. For children with definite penicillin allergy, clindamycin is an acceptable in-hospital alternative (10 mg/kg/four times per day) but there is no clear out of hospital once/day alternative.

To complete the total course length after oral switch, in order to maximise the risk of treatment failure a RCT would need to carefully define doses of antibiotic to use at the higher BNFC dose recommendations that have both an acceptable palatability (taste) and achievable treatment regime. Although not shown in our data, it is established paediatric practice that parents and children are more likely to achieve 3 times a day dose regimes accurately (such as midnight, 0800 hours and 1600 hours) than four times a day regimes (such as midnight, 0600

hours, 1200 hours and 1800 hours) that mean both 2 night-time (usually when asleep) doses for children and a dose during school or nursery hours.

Summary

A core outcome set for future clinical trials in paediatric bone and joint infections was established by Delphi survey and consensus meeting.

A service evaluation, qualitative study and consensus meeting discussion provided information to inform the feasibility of a RCT, and of potential RCT designs.

1. An RCT of very early oral switch would be supported by the service evaluation data. However, the Delphi survey and consensus meeting showed that for oral switch, while CRP is considered important (with no consensus regarding level), consensus was achieved that criteria for oral switch include resolution of fever for 48 hours or more, tolerating oral input (medicines and food/drink) and pain improvement (rather than resolution). Such strict criteria, together with low numbers of cases of simple OM and SA likely to meet switch criteria in the first week of intravenous treatment, means such a study will likely not be feasible as a single country (UK) trial.
2. An RCT of reduced total length therapy after clinician directed oral switch based on the criteria determined in this study would be feasible even though it was not the first choice study of the consensus meeting participants. It would be possible to explain the study to parents and children, and feasible to recruit in terms of numbers of cases and clinician willingness. It is unlikely that such a study design will make enormous impact on the overall cost to the NHS of treating bone and joint infections in children or on the overall antibiotic burden of children in the community.
3. An RCT in simple OM and SA comparing shorter or longer course IV therapy, with no reduction in total (intravenous and oral course combined) antibiotic therapy, would be feasible with children randomised after the strict oral switch criteria had been met after 7 days of intravenous therapy. Children would be excluded from the trial if they met the criteria for oral switch in the first week of intravenous therapy as the service evaluation suggests this group have less treatment failure than those having later oral switch. This study design meets clinician preference and addresses parental concerns not to randomise prior to currently-used

oral switch criteria. It would also provide important information on whether intravenous therapy can be reduced without increasing treatment failure compared to longer course intravenous therapy, or whether outcomes are worse in those treated with more intravenous antibiotics due to treatment failures being caused by the treatment modality itself.

Regardless of RCT design, the qualitative study has demonstrated remaining gaps in understanding of parental and family decisions to participate in clinical trials. In order to explore prospectively the issues identified in the qualitative study (such as understanding of the condition, actual circumstances around making a choice to join a study etc), a longitudinal qualitative study could take place alongside any trial, including semi-structured interviews with parents and children, focus groups with staff and ethnographic observation.

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Contributions of authors

SF: Chief investigator, initiated study, oversaw set up and delivery of all study components. Involved in data collection, analyses and report writing.

NC: Lead orthopaedic surgeon, involved in initiation of study, development of protocols and study components, analyses and report writing.

HdG: Analyses of the service evaluation, microbiological data, and writing of the report.

PS: Setting up of the service evaluation and microbiology sub study protocol and NHS REC applications, literature review for Delphi survey and outcomes, input to design of qualitative study and NHS REC application, support to CTU in delivery of service evaluation.

NA: did the laboratory work and analyses of the microbiology substudy supervised by PM, SF overseen by AP and SCC.

Patient recruitment was done by: AF, AJP, ME, MS, PH, CP, AJ, KA, AR, JH, SH, DS and enrolling collaborators and their colleagues at the other NHS sites

Statistical planning and analyses was done by: BA with PW and CG

Coordination of Delphi process and consensus meeting: PW, AL, AB, CG

HH and C Spowart. CTU project manager

CB and AL designed the qualitative study with SF and PS, AL conducted the interviews and drafted the chapter, supervised and with input from CB.

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Appendices

Appendix 1: Service evaluation documents

1.1 Service evaluation protocol

DINOSAUR: Duration of Intravenous antibiotic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population.

Sponsor: University Hospital Southampton NHS Foundation Trust

Sponsor Code: RHM CHI 0639

NHS REC have advised that no formal approval is required for this service evaluation: committee comments are incorporated into study materials.

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Table of Contents

Duration of Intravenous antibiotic therapy for Septic Arthritis or acUte osteomyelitis in a paediatric population

1. Hypothesis and aims	199
2. Background	199
Osteomyelitis and Septic Arthritis in Children	199
Clinical features	201
Imaging	202
Microbiological investigation	203
Surgical management	203
Osteomyelitis	204
Septic Arthritis	204
Medical Management and Antibiotics	205
Current evidence for how to initiate treatment	205
Complications	208
3. Aims and objective	208
4. Study design	208
Participant selection	208
Participant identification and recruitment	209
Study sponsorship	209
Data Capture and Confidentiality	209
Electronic Records	209
Data analysis	210

	216
7. Research governance, monitoring and Ethics and R&D approval	210
8. Finance	210
9. Reporting and Dissemination	210
10. References	210

1. Hypothesis and aims

Currently there is little international or UK consensus regarding the route or duration of antibiotic treatment for acute osteomyelitis (OM)/septic arthritis (SA) in children. Data regarding paediatric bone and joint infections in the UK are scarce and outdated. This service evaluation will be used to:

1. Assess current case load, disease spectrum & clinical practice in the diagnosis & treatment of OM/SA in secondary & tertiary UK care
2. Determine whether a randomised controlled trial to investigate shorter duration of intravenous antibiotic therapy for bone and joint infections in children is feasible in the future.

This will be achieved in conjunction with a future component of the study obtaining qualitative & quantitative data on:

- a) willingness of clinicians to randomise to proposed protocol
- b) willingness of patients & parents to be randomized
- c) number of patients seen;
- d) clinical stakeholder & consumer perception of relevant outcomes

2. Background

The text that follows until operative procedures required as well as formal assessment of growth and function on pp 199 was written for the HTA application but was published separately as <http://adc.bmj.com/content/97/6/545>. INSERT STATEMENT RE PERMISSIONS IF NEEDED

Osteomyelitis and Septic Arthritis in Children

Osteomyelitis (OM) is inflammation of the bone accompanied by bone destruction (1), usually due to bacterial infection. It is an acute process but if not treated effectively, the inflammation can become chronic, leading to the development of sequestrae and fistulae (2). Osteomyelitis and septic arthritis can both be divided into three types according to the source of the infection: haematogenous, secondary to contiguous infection and secondary to direct

inoculation. Haematogenous OM can present acutely or as a more indolent, progressive process subacutely, with symptoms present for more than 2 weeks (3). In children osteomyelitis most often affects long bones (femur 36%, tibia 33%, humerus 10%, pelvis 2.8%) (4). Single site infection is most common, but 5-20% of children have multifocal osteomyelitis (5). Septic arthritis (SA) is acute infection of synovial joints (6, 7), usually secondary to bacteraemia. The infection affects the synovial membrane and the joint space. In younger children, the capsule of the joint often extends to the metaphysis, which when the cortex is damaged can lead to septic arthritis secondary to osteomyelitis and vice versa. The epiphyseal growth plate can also be affected, causing growth discrepancies and long term disability or permanent joint destruction if the acute infection is not treated promptly (2).

The estimated incidence for both OM and SA arthritis in Western populations is between 5 to 12 cases per 100,000 children per year (2). Half of the children with acute haematogenous osteomyelitis are under the age of 5 (2, 7). Boys are 1.2-3.7 times more likely to be affected by osteoarticular infection (OAI) than girls (2). The incidence in Southampton from 1979-1997 was between 1.4 to 10.5 cases per 100,000 per year (8) and in Newcastle from 1991 to 1999 was 7 per 100, 000 for SA and 11 per 100, 000 for OM (unpublished data). Recent unpublished national data from England shows the admission rate for osteomyelitis in children 0-18 year of age has varied between 0.048 and 0.070 per 1000 child years (M. Sharland, personal communication). Subacute OM appears to be increasing over recent years (9), reported to be found in 5 per 100, 000 children in Norway (10). Neonatal infection can occur in preterm or term babies and is associated with a wider range of causative organisms (table 1, (11)) and potential complications. Neonatal vascular anatomy allows infection within bone to reach the growth plate or joint in 76%(12).

From the current literature, the pathogens implicated in paediatric bone and joint infections:

- commonly include *Staphylococcus aureus* (MSSA) (44-80%) (7, 13, 14) and *Kingella kingae* (14-50% (increased <36 months)) (7, 14-18);
- rarely include Methicillin-resistant *S. aureus* (MRSA) (40-50% in USA, rare in UK (19, 20)), Pantón-Valentine Leukocidin (PVL) MSSA (21, 22), *Group A streptococci* (GAS) , *Group B streptococci* (GBS) (neonates) (11, 23), *Non-typeable Haemophilus spp.* (incidence unknown), *Haemophilus influenzae type b* (non-immunised or immunodeficient), *Escherichia coli* (neonates) (11, 23), *Streptococcus pneumoniae* (24), *Coagulase-negative staphylococcus* (subacute);

- very rarely (most in immunocompromised individuals) include *Pseudomonas aeruginosa* (usually inoculation injuries therefore > 1 year old), *Neisseria gonorrhoeae*, *Neisseria meningitidis* (neonate, adolescent), *Mycobacterium tuberculosis* (older children as OAI develops 2 years from primary infection), *Salmonella spp.* (sickle cell disease) (25), *Bartonella henselae*, *Neisseria gonorrhoeae*, *Non tuberculous mycobacteria* (associated with defects of IFN γ /IL12 pathway), *Klebsiella spp.*, *Bartonella henselae*, *Fusobacterium* (often multifocal), *Aspergillus* and *Candida albicans* (neonate, damaged bone).

The pathogens most frequently seen according to age are:

- Neonate: GBS, MSSA, *Escherichia coli* and other gram negatives, *Candida albicans*
- < 2 years: MSSA, *Kingella kingae*, *S. pneumoniae*, *Haemophilus influenzae type b*, *Non-typeable Haemophilus spp.*, *E. coli*, MSSA PVL
- 2-5 years MSSA, *Kingella kingae*, GAS, *S. Pneumoniae*, *Haemophilus influenzae type b*, *Non-typeable Haemophilus spp.*, *Pseudomonas spp.*, Coagulase-negative staphylococcus (subacute), MSSA PVL
- > 5 years MSSA, MSSA PVL

Clinical features

The clinical features of OM and SA are dependent on age, site of infection and type of disease. The diagnosis and management of osteoarticular infection in children should ideally be multidisciplinary, including paediatricians and orthopaedic surgeons with radiologists and microbiologists. The diagnosis of OM or SA is made on the basis of the clinical presentation, laboratory tests, imaging and where available microbiology results.

White Blood Cell Count, CRP and ESR

The white blood cell count (WBC) is an unreliable indicator of an OAI as in many cases it remains normal throughout the infection (26). The inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are more reliable, although normal values also do not exclude osteomyelitis (27). CRP levels are most sensitive (elevated in up to 98% of cases) (6, 7) but not specific for bone or joint infection. Two studies have shown that CRP increased and also decreased faster than ESR, predicting recovery with more sensitivity than the ESR or the white cell count (27, 28). Differences in the causative organism may also cause differences in the acute phase markers. Patients with osteomyelitis

caused by PVL-expressing *Staphylococcus aureus* isolates had significantly higher mean values for ESR at admission, and higher maximum CRP, ESR and absolute neutrophil counts at presentation compared with patients whose isolates were PVL-negative (22). Other markers remain unproven. In a small study, procalcitonin has not shown benefit over CRP (29).

Imaging

Imaging is of great importance in the diagnosis of acute osteomyelitis.

Where available, Magnetic Resonance (MR) Imaging with enhancement show the best results regarding sensitivity and specificity of diagnosis of both OM and SA (sensitivity 97% and specificity 92% (30, 31), sensitivity 97-100% in OM) (6)) However as young children often require a general anaesthetic to undergo an MR scan, and MR imaging is not immediately available in all UK centres, MR is not widely used in the UK in the initial diagnosis.

Technetium radionuclide bone scan (^{99m}Tc) also has high sensitivity and specificity in the diagnosis of OM (32), but due to the radiation burden is now used less often except in difficult cases and is not useful in discitis. In SA, bone scan may be used to exclude underlying OM following aspiration and commencement of empirical therapy. Bone scan is especially useful where there is a suspicion of multifocal disease, but may give false negative results in infancy, and sensitivity is reduced for the first 48 hours. New nuclear medicine technologies are available in some centres to combine bone scan with low dose CT (SPECT CT) which may be useful in increasing the resolution of nuclear medical images (33).

Plain radiographs are less helpful compared with other imaging techniques as osteolytic changes or periosteal elevation occur most often 10 to 21 days after the onset of symptoms (1, 7, 34). However, once apparent, the extent of bony change provides a good correlate to the severity of the disease. Plain radiographs also provide a baseline for comparison of subsequent change. Radiographic changes are frequently seen in subacute OM, but can be confused with malignancies such as Ewings sarcoma or osteiod osteoma (12). In SA, plain radiographs are of limited use. In discitis, lateral radiographs of the spine 2-3 weeks into the illness often will reveal disc space narrowing with erosion of the vertebral end plates of the contiguous vertebrae. In vertebral OM, radiographs initially show localised rarefaction of a single vertebral body then anterior bone destruction.

Ultrasound is useful in SA for identifying the presence of deep effusions and in OM for subperiosteal collections, but cannot differentiate between purulent and non-purulent material (6, 35). Ultrasound may also be used to distinguish infection from other causes of similar symptoms or to direct fine needle aspiration (36).

Computed tomography (CT) is most valuable for guided procedures, such as aspiration or drainage of the infected bone or joint (37). It effectively demonstrates air and sequestra and cortical destruction in chronic OM (35), but gives non-specific results in discitis.

Microbiological investigation

Identification of the pathogenic organism by culture should be attempted with samples preferably taken prior to starting antibiotic therapy, as where positive it allows targeted antibiotic therapy. Blood cultures, joint fluid (from aspiration), periosteal pus or bone biopsy can all be used. Samples from the infected bone or joint require an invasive procedure but are more likely to be positive (40- 50% positive) than blood cultures (9-22% positive) (14, 26). Yield is generally not high for identification of bacteria in children with OM (26), as unless therapeutic operative intervention is required, bone biopsy is infrequently necessary for diagnostic reasons alone.

New molecular techniques including PCR and broad-range 16s rDNA PCR (38, 39) have established the basis for more rapid and sensitive microbiological diagnosis (17), although these methods currently do not provide information on specific organism antibiotic resistance profiles.

Blood cultures (minimum 4 ml aerobic culture sample in older children, 2 ml in specific neonatal aerobic bottle (40)) should therefore be taken, and where available samples from infected bone or joint placed in a sterile universal container and sent for culture and sensitivity testing. Older reports suggesting an increase in *K. kingae* recovery is gained from inoculating synovial fluid or bony exudates directly into blood-culture bottles have not been replicated in UK practice (16). *K. kingae* is detectable using new PCR techniques from cultures where conventional direct plating of specimens on solid media has been used (17, 18).

Surgical management

There is little current high quality evidence on which to base current surgical practice.

Osteomyelitis

Surgical drainage in acute OM is indicated if the patient is not responding to antibiotics after 48-72 hours (although this may be due to resistance) or if there is radiological evidence of a substantial pus collection (6). Best practice is to immobilise any surgically treated limb or focus of infection. Occasionally, where a soft tissue or sub-periosteal collection is clearly demonstrated by ultrasound or MRI, needle aspiration can be performed prior to starting intravenous antibiotics. The procedure should be carried out under sterile conditions. If there is bony destruction or pus aspirated, surgical debridement is usually required. With only early radiographic signs, intravenous antibiotic therapy may suffice.

Historically, the role of surgery is poorly defined. Cole (41) identified three groups of patients: in the group of patients older than one year but who presented within 48 hours, antibiotic therapy alone was sufficient. In a group aged more than one year, five days after the onset of illness, patients usually required surgery and possibly multiple procedures. In infants less than one year in whom the exact diagnosis was difficult to make, a single operation and antibiotic therapy usually sufficed.

In current practice, the relative roles of bacterial virulence and host age and immunity are unclear. More invasive surgery appears more common when bacteria have specific virulence genes, for example PVL (21). While most children recover rapidly with simple medical management, a small proportion may require repeated debridement.

Septic Arthritis

In SA, prompt drainage and washout of the affected joint (either arthroscopic or open) is advocated by some for both diagnostic and therapeutic purposes as the articular cartilage is damaged early (6). The role of surgery in the treatment of septic arthritis is in fact poorly defined except in relation to the hip, where prompt surgical drainage is absolutely necessary. Open capsulotomy to allow continuing drainage of septic material is advocated, and if the arthrotomy does not provide turbid material drilling the femoral neck may decompress a proximal femoral osteomyelitis. The anterior approach is preferred as this also allows open reduction of any displacement of the femoral head.

The indications for surgical drainage of septic joints other than the hip remain controversial. Where there is a large effusion, drainage is usually advocated although in some joints arthroscopic irrigation may be appropriate, such as the knee or ankle. However, with

arthroscopic treatment joint visualisation is less complete. Overall, for joints other than the hip, aspiration, irrigation and IV antibiotic therapy is the preferred first line of treatment. If the patient fails to respond then the joint should be surgically drained, usually by formal open arthrotomy rather than arthroscopic drainage.

Medical Management and Antibiotics

Current evidence for how to initiate treatment:

Intravenous antibiotics are started empirically as soon as the clinical diagnosis of acute OM or SA is made, as delaying therapy until the bacterium is identified increases the risk of complications. In septic arthritis, where urgent surgery is indicated, a widespread pragmatic approach has been to start antibiotics following surgery unless it will take longer than 4 hours to get to theatre. As soon as organisms are isolated, antimicrobial treatment should be adjusted and optimised. In subacute OM with no systemic reaction, oral antibiotics can be used from the start.

Although there has not been a definitive randomised controlled trial, a number of observational and retrospective studies in the literature show several different antibiotic regimes have been effective in treating acute haematogenous osteomyelitis in children, including the use of beta-lactam and macrolide antibiotics (8). The initial antibiotics should always include potent cover against MSSA and GAS, and in younger children against *Kingella kingae*, although the choice will vary according to the age of the child, route of infection and local resistance patterns (7). Activity against *H. influenzae type b* is essential in children who have not been fully immunised against it.

Switch to oral antibiotics and total duration of treatment:

Currently there is no international and little UK consensus regarding the route or duration for antibiotic treatment of acute OAI in children.

a) Oral switch

Sequential intravenous and oral therapy has become usual as it is less inconvenient and painful for the patient, has fewer complications and is cheaper (2, 6, 7). There is no current evidence to aid the clinical decision of when to switch from intravenous to oral therapy, which is widely accepted and usually occurs when the patient has shown a marked clinical improvement (8). A Canadian systematic review of short (≤ 7 days) versus long course (> 7

days) parenteral antibiotic treatment for acute haematogenous OM in children due primarily to *Staphylococcus aureus* showed no difference in the overall cure rate after 6 months between short course and long course parenteral antibiotic therapy (42). A recent retrospective cohort study of 1969 children in the USA found that early switch to oral therapy (median 4 days) was as effective as prolonged intravenous treatment (43), a finding also suggested in a smaller retrospective study of 186 children with septic arthritis (44). The laboratory or clinical parameters that would determine the decision to switch to oral therapy remain undefined. Most clinicians continue intravenous antibiotics until the child shows clinical improvement, is afebrile and oral fluids and medication could be established.

Additionally, observing a decrease in inflammatory markers such as white blood count (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is thought to be of value (2). Studies have shown that serum CRP level decreased more rapidly than ESR in children recovering from acute osteomyelitis, and that children with a raised CRP level were more likely to have symptoms or extensive radiographic abnormalities (27, 45, 46). A recent Finnish clinical trial showed apparently good long term results and apparently no failure rates using CRP as the biological marker of infection (45, 47). Failure to improve necessitates repeat blood culture, additional imaging for metastatic infection, assessment for deep vein thrombosis, and consideration of unusual pathogens such as PVL *Staphylococcus aureus* or *Fusobacterium*.

No UK consensus currently exists to guide the criteria for oral switch for use in clinical practice or a clinical trial, which will be determined as part of this feasibility study. Currently there is no consensus about the route or duration for antibiotic treatment of acute osteomyelitis in children.

b) Total duration of antibiotic therapy

The suggested duration for parenteral antibiotic treatment ranges from 3 days up to 6 weeks, resulting from several, mainly observational studies with relatively poor level of evidence (8, 48). In the past, the overall duration of antibiotic treatment has been considered an important factor to improve outcome and reduce relapse. Several paediatric textbooks recommend at least 4 to 6 weeks of treatment (2, 49).

Although there are encouraging data from a recent clinical trial in Finland (45, 47) and from other review papers and case series, no recent formal randomized controlled trial has been

conducted to show good evidence for shorter courses of parenteral antibiotic treatment. There are a number of reasons why the recent Finnish data may not be directly applicable to practice in the United Kingdom or other countries in 2011 (50). Some historical observational studies showed an association between short duration of antibiotic therapy and 15-19% poor outcome or relapse with courses of 3 weeks or less (51-53).

c) Oral antibiotic choice and dose

Many different regimens are used as oral therapy following switch from oral antibiotics, including co-amoxiclav, flucloxacillin and clindamycin. Although flucloxacillin and clindamycin have good oral bioavailability and excellent tissue penetration, both drugs have to be given orally 4 times per day and both have poor taste and therefore poor drug adherence of the suspension in small children (54). Although clindamycin rarely leads to *Clostridium difficile* disease in children, there is no current evidence or consensus regarding oral antibiotic choice that will be acceptable to children and parents both in terms of palatability and dose frequency.

d) Continuation of intravenous antibiotics for more than 2 weeks

Complex disease requiring continuing intravenous therapy poses problems of vascular access, hospitalisation and schooling. Most children will require central or peripherally-inserted central venous long line (CVL/PIC) insertion for long term antibiotic treatment. Delivery of subsequent care is either in hospital, or at home dependent on local services and the ability to provide outpatient parenteral antibiotic therapy (OPAT), although OPAT services for children are not yet well developed in the UK. Central venous lines (CVL) or peripherally-inserted central catheters (PICC) and OPAT has attendant risks, with 3-11% CVL associated infection noted in the USA (55, 56).

e) Additional or 2nd line antibiotics for complex disease or where resistant pathogens are identified

Where cases are complex, additional antibiotics may be advised by local microbiologists, clinical infectious diseases specialists or national guidelines, for example PVL positive *S. aureus* infection (57). Organisms that cause complicated disease may be more readily identifiable using molecular techniques, which may allow antibiotic therapy to be adapted accordingly.

Complications

Deep venous thrombosis and thromboembolism have been seen in up to 30% of children with OM and is associated with a higher risk of disseminated infection (58). In addition, joint stiffness, limb shortening, dislocation (acutely neonates) and avascular necrosis of affected epiphysis may occur. Routine follow-up allows most children with simple disease to be discharged without the need for long-term care or further assessment of growth or function.

In the context of clinical audit or clinical trials, outcome measures may include length of stay in hospital, total length of therapy, operative procedures required as well as formal assessment of growth and function.

3. Aims and objective

We aim to assess the incidence of septic arthritis and osteomyelitis, and the severity and spectrum of disease within the UK. We also aim to assess whether there are significant differences in management between sites, and whether consensus may be gained in future.

This study will inform the future design of a possible randomised controlled trial (RCT) investigating short versus long courses of antibiotic therapy for paediatric bone and joint infections. The results will be used to achieve consensus regarding the antimicrobial agents to be used in different ages within the RCT.

4. Study design

As part of a national service evaluation, we will record demographic details and details of hospitalisation(s) including transfers between hospitals; type and site of disease; routine haematology, biochemistry and microbiology; radiological procedures; surgical procedures; length of IV therapy; antimicrobials used, route and duration; reason/criteria; used for oral switch (if any); and clinical outcomes at 3 months.

This data is to be collected from the patients' clinical notes. Training will be provided for these teams at participating centres. The study will use a password protected web based data collection form that can be accessed at all participating hospitals.

Participant selection

All eligible patients presenting to participating centres with a diagnosis of bone and joint infection will be enrolled with no maximum, and data will be entered into a web-based database. The following eligibility criteria will be applied:

Inclusion criteria

All children from birth to 16 years with a clinical diagnosis of osteomyelitis or septic arthritis admitted to participating hospitals from home, or referred from another centre.

Exclusion criteria

Patients whose parents have specifically requested for their child not to be included in the study.

Participant identification and recruitment

Posters displayed on admitting wards will notify parents and patients that the centre is participating in a national service evaluation of children's bone and joint infections. Parents will have the opportunity to inform a member of their child's care team if they do not want their child's information entered into the database.

Study sponsorship

The sponsor will be University Hospital Southampton NHS Foundation Trust

Data Capture and Confidentiality

Demographic and clinical data will be collected by appropriately trained delegated staff within participating centres and entered into a secure database via a web based system, as part of a national bone and joint infection database involving around 40 participating centres.

Records will be assigned a unique study number and centres will maintain a separate log locally for patient tracking purposes. No data that is identifiable outside of the research team will be kept and the database will be password protected.

Electronic Records

Managed as part of a national service evaluation, the data will be stored and managed by the MCRN Clinical Trials Unit, a division of the UKCRC fully registered Clinical Trials Research Centre based at the University of Liverpool.

Data will be collected using a custom web based data entry system written in c# .Net, using JQuery. These data collection pages will be designed and implemented in the same way as the data collection that was used for the NASH (National Audit of Seizure Management in Hospitals) study - <http://www.nashstudy.org.uk/>. The NASH study collected data from 130 hospitals, with each hospital entering data for between 20 and 30 participants. The data collection system will allow data to be validated on input, provide help/additional information as required for questions and allow for the hiding of questions that do not need to be answered by the clinician.

Data analysis

Descriptive statistical techniques will be used to analyse the data.

7. Research governance, monitoring and Ethics and R&D approval

The research will comply with the Research Governance Framework and International Conference on Harmonisation Good Clinical Practice (ICH GCP).

The study will be sponsored by University Hospital Southampton NHS Foundation Trust, subject to the relevant governance approvals. The Sponsor will delegate appropriate responsibilities to the Chief Investigator, and to the NIHR Medicines for Children Clinical Trials Unit (study co-applicants) who will co-ordinate the study.

8. Finance

This study is supported by the NIHR HTA project 10/146/01 - Duration of intravenous antibiotic therapy for children with acute osteomyelitis or septic arthritis: a feasibility study

9. Reporting and Dissemination

We will use the normal channels of journal publication and conference presentations. In addition, we are committed to ensuring that our research is available via open access and we will have a dissemination strategy that includes rapid web-based publishing of lay summaries once research articles have undergone peer-review and links to University and Trust press offices.

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THE DINOSAUR STUDY BONE AND JOINT INFECTION

SERIOUS ADVERSE EVENT REPORTING GUIDANCE

A Serious Adverse Event (SAE) form must be completed and reported to the MCRN CTU as soon as possible if an adverse event occurs in the DINOSAUR study that meets the following criteria:

- meets serious criteria
- is considered to be related to either the throat swab or additional 5mls of blood taken for the study
- occurs within 2 hours of the throat swab being carried out or within 2 hours of the additional 5mls of blood being taken

Please contact the DINOSAUR trial coordinator should the above occur on Tel: 0151 282 4707.

Serious Criteria:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Relatedness

An event is considered to be 'related' if it is judged to be **possibly, probably** or **almost certainly** related to the throat swab procedure or the taking of the additional 5mls of blood.

1.2 Poster Dinosaur study

To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY
(CHILDREN'S BONE AND JOINT INFECTION STUDY)
www.dinosaur-study.org.uk



We are trying to find out the best way to look after children with bone and joint infections by doing a study to look at the bugs causing the infection.

If you are admitted with a bone or joint infection we will be collecting information about your illness to help us treat children with bone and joint infections in the future.

If you do not want us to collect this information, please let your doctor or nurse know.

We would like to ask for the help of children admitted with a bone or joint infection. We will be giving you and your child or teenager an information sheet that explains what we would like to do and why.

If you have any questions, please contact
 ENTER LOCAL PI/NURSE TELEPHONE
Thank You.

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 10/146/01) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

	Duration of INtravenous ANtibiOTic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)		Form: 1 Page 1 of 4

PATIENT DETAILS

Study Identifier 	0-9	0-9	0-9		Participant Initials 	A-Z	A-Z
Enrolling Centre Number 							
Enrolling Centre Name 							
Enrolment Date 	D	D	M	M	Y	Y	Y

1.1 Date of Birth 

D	D	M	M	Y	Y	Y	Y	
---	---	---	---	---	---	---	---	---

1.2 Gender 

☒ Male	☒ Female
--	--

1.3 Ethnicity 

☒	European – North/East/Mid
☒	European – South (Mediterranean)
☒	European – Roma
☒	African/ Caribbean – North African
☒	African/ Caribbean – Sub Saharan
☒	African/ Caribbean – Afro-caribbean
☒	Asian – Indian Subcontinent
☒	Asian – South East (Vietnam, Thailand, Indonesia, Malaysia, Phillipines)
☒	Asian – East Asia (China, Japan, Korea)
☒	Asian – West Asia (Afghanistan, Iranian)
☒	Middle Eastern – Turkish
☒	Middle Eastern – Arab peninsula
☒	Other / Mixed

If Other/Mixed please specify:

--

1.4 Weight on admission 

		.		kg
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**Duration of INtravenous Antibiotic therapy
for Septic Arthritis or acUte osteomyelitis in a
paediatRic population (DINOSAUR)**

Form: 1

Page 2 of 4

PREVIOUS MEDICAL HISTORY

- 1.5 Penicillin allergy ☐ Yes ☐ No
- 1.6 Sickie cell disease ☐ Yes ☐ Not Tested ☐
- 1.7 Known immunocompromise ☐ Yes ☐ No If yes please complete Q1.9 else go to Q1.10

1.8 Please select one of:

Combined immunodeficiency
HIV
Bone marrow transplant
Chronic granulomatous disease

Specify if other immune deficiency

transplant date

1.9 Other medical conditions

☐	Congenital cardiac disease
☐	Indwelling central venous catheter or PICC

----> ☐ less than 7 days since insertion
☐ 7 days or more since insertion

☐	Cystic Fibrosis
☐	Diabetes Mellitus
☐	Cerebral Palsy
☐	Purpura Fulminans
☐	Malnutrition
☐	Other

Specify cause if known

Specify

1.10 Antibiotics in the last month 

☐

Yes

☐

No

If yes please complete
Q1.12 else go to Q1.13

1.11 Which antibiotic (select all that apply) 

Version 1.6 (23/01/2013)

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form: 1
		Page 3 of 4

Antibiotic	Route		Duration > 1 week			
☐ flucloxacillin	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ clindamycin	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ cefuroxime	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ ceftriaxone	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ amoxicillin	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ co-amoxiclav	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ rifampicin	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ vancomycin	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ fusidic acid	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ benzyl penicillin	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ teicoplanin	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
☐ other						

If Other

Name	Route		Duration > 1 week			
	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No
	☐ Oral	☐ IV	☐ Yes	☐ No	☐ No	☐ No

1.12 Immune modulating treatment in last 6 months  ☐ Yes ☐ No

Which treatment?

Steroid 2mg/kg for >=1 week or 1mg/kg for >=1 month

☐ Radiotherapy	
☐ Chemotherapy	
☐ Azathioprine	
☐ Cyclosporin	
☐ Cyclophosphamide	
☐ Rituximab	
☐ Leflunomide	
☐ Tacrolimus	
☐ Sirolimus	
☐ Other	Please specify

	Duration of INtravenous AntiBiOtic therapy for <u>S</u>eptic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form: 1 Page 4 of 4
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1.13 Infection History in the last 12 months

☒ None


- ☒ Pneumonia
- ☒ Septicaemia
- ☒ Pyelonephritis
- ☒ Cellulitis / soft tissue infection
- ☒ Meningitis
- ☒ Osteoarticular infection
- ☒ Abdominal sepsis
- ☒ Other

1.14 History of trauma in the last month

☒ Yes ☒ No

Date	Area affected	R/L	History	Surgery
D D M M Y Y Y Y		R L		Y N
	☒ Head		☒ Laceration	
	☒ Neck		☒ Sprain	
	☒ Forearm		☒ Fracture	
	☒ Arm		☒ Open fracture	
	☒ Abdomen		☒ Haematoma	
	☒ Back			
	☒ Buttock			
	☒ Thigh			
	☒ Knee			
	☒ Lower leg			
	☒ Ankle			
	☒ Foot			

1.15 History of orthopaedic surgery

☒ Yes ☒ No

Date	Bone	R/L	Procedure Details
D D M M Y Y Y Y		R L	
	☒ Radius		
	☒ Ulna		
	☒ Humerus		

1.16 History of other surgery

☒ Yes ☒ No

Date	Details
D D M M Y Y Y Y	

1.3.2 Form 2: Current OAI

	Duration of INtravenous AntibiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatric population (DINOSAUR)	Form: 2 Page 1 of 2
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CURRENT OAI									
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Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z	A-Z	
Enrolling Centre Number								
Enrolling Centre Name								

2.1. Date of first symptoms 

D	D	M	M	Y	Y	Y	Y	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---	---	---

2.2. Date of first presentation 

D	D	M	M	Y	Y	Y	Y	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---	---	---

to

GP	X
Emergency Department	X
Walk-in Centre	X
N/A	X

2.3. Hospital Admission 

Date	Hospital	Diagnosis	Reason for transfer
D D M M Y Y Y Y Y		Osteomyelitis <input style="width: 20px;" type="checkbox"/> X Septic arthritis <input style="width: 20px;" type="checkbox"/> X Septicaemia <input style="width: 20px;" type="checkbox"/> X Cellulitis <input style="width: 20px;" type="checkbox"/> X Other <input style="width: 20px;" type="checkbox"/> X specify	Surgical <input style="width: 20px;" type="checkbox"/> X Management <input style="width: 20px;" type="checkbox"/> X Medical <input style="width: 20px;" type="checkbox"/> X Other <input style="width: 20px;" type="checkbox"/> X specify No transfer <input style="width: 20px;" type="checkbox"/>

2.4. Date of discharge from hospital (to home) 

D	D	M	M	Y	Y	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

2.5. Date treatment completed 

D	D	M	M	Y	Y	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---

Version 1.6 (23/01/2013)



**Duration of INtravenous AntibiOtic therapy for Sep^tic Arth^ritis or acUte osteomyelitis in a
paediatRic population (DINOSAUR)**

Form: 2
Page 2 of 2

2.6. Bones or joints affected

- a) Hip
- b) Shoulder
- c) Knee
- d) Ankle
- e) Wrist
- f) Skull
- g) Mandible
- h) Humerus
- i) Clavicle
- j) Radius
- k) Ulna
- l) Pelvis
- m) Rib
- n) Femur
- o) Sternum
- p) Elbow
- q) Foot
- r) Calcaneum
- s) Tibia
- t) Fibula
- u) Lumbar vertebra
- v) Thoracic vertebra
- w) Sacrum
- x) Cervical vertebra

Infected implant: Yes / No

1.3.3 Form 3: Surgical procedures

	Duration of <u>I</u>Ntravenous <u>A</u>ntibi<u>O</u>tic therapy for <u>S</u>ep^tic <u>A</u>rthritis or ac<u>U</u>te osteomyelitis in a paediat<u>R</u>ic population (DINOSAUR)	Form: 3 Page 1 of 2
---	---	-------------------------------

SURGICAL PROCEDURES							
Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z	A-Z
Enrolling Centre Number							
Enrolling Centre Name							

3.1 Surgical Procedures Undertaken  ☐ Yes ☐ No

If "Yes" please complete this form for all surgical procedures undertaken for this participant.

	Hospital	Date	Time of Procedure	Description
				
				
				

Add New

Note:

- (1) The table displayed on this page will provide a summary of the data entered for this participant
- (2) Clicking on the  associated with a record will allow editing of that record.
- (3) Clicking on the "Add New" button will allow a new record to be entered.
- (4) Actions (2) and (3) will result in the form on the following page being displayed to the user.

	Duration of INtravenous Anti<u>b</u>i<u>O</u>tic therapy for <u>S</u>ep<u>t</u>ic <u>A</u>rth<u>r</u>itis or ac<u>U</u>te osteomyelitis in a paediat<u>R</u>ic population (DINOSAUR)	Form: 3 Page 2 of 2
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SURGICAL PROCEDURES

Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z	A-Z
Enrolling Centre Number							
Enrolling Centre Name							

Hospital 											
Date of Procedure 		D	D	M	M	Y	Y	Y	Y		
Time of procedure 	h	h	:	m	m						
Description 	☐	Aspiration									
	☐	Incision and drainage									
	☐	Drill decompression									
	☐	Curettage/excision									
	☐	Arthrotomy									
	☐	Arthroscopy									
	☐	Amputation									
	☐	Debridement									
	☐	Fasciotomy									
	☐	Compartment decompression									
	☐	Secondary closure									
	☐	Skin graft									
	☐	Other plastic surgery									
If "other plastic surgery" please specify:											
Additional Notes 											

1.3.4 Form 4: Immobilisation

	Duration of <u>I</u>Ntravenous <u>A</u>ntibi<u>O</u>tic therapy for <u>S</u>ep^tic Arthritis or ac<u>U</u>te osteomyelitis in a paediat<u>R</u>ic population (DINOSAUR)	Form: 4 Page 1 of 1
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IMMOBILISATION						
Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z A-Z
Enrolling Centre Number						
Enrolling Centre Name						

4.1 Participant Immobilised since
diagnosis 

☐ Yes

☐ No

1.3.5 Form 5: Antibiotics

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form: 5 Page 1 of 1
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ANTIBIOTICS

Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z	A-Z
Enrolling Centre Number							
Enrolling Centre Name							

5.1 Antibiotics prescribed  ☒ Yes ☐ No

Antibiotic	Hospital (Centre#)	mg/dose	Frequency	Route	Date Started (dd/mm/yyyy)	Date Stopped (dd/mm/yyyy)	Ongoing	Reason stopped						
flucloxacillin ☐	[Autopopulated from data entry person]			IV ☐	DD/MM/YYYY 	DD/MM/YYYY 	☐							
clindamycin ☐				Oral ☐										
cefuroxime ☐				IM ☐										
Ceftriaxone ☐				SC ☐										
amoxicillin ☐														
co-amoxiclav ☐														
rifampicin ☐														
vancomycin ☐														
fusidic acid ☐														
benzyl penicillin ☐														
teicoplanin ☐														
Other ☐														
Specify: _____														

1.3.6 Form 6: Microbiology

	Duration of INtravenous Antibiotic therapy for Septic Arthritis or acUte osteomyelitis in a paediatric population (DINOSAUR)	Form: 6 Page 1 of 1
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MICROBIOLOGY SAMPLES

Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z	A-Z
Enrolling Centre Number							
Enrolling Centre Name							

5.1 Antibiotics prescribed  ☒ Yes ☐ No

Antibiotic	Hospital (Centre#)	Date Started (dd/mm/yyyy)	mg/dose	Frequency	Route	Date Stopped (dd/mm/yyyy)	Ongoing	Reason stopped
flucloxacillin ☒	[Autopopulated from data entry person]	dd/mm/yyyy 			IV ☒	dd/mm/yyyy 	☐	
clindamycin ☒					Oral ☒			
cefuroxime ☒					IM ☒			
Ceftriaxone ☒					SC ☒			
amoxicillin ☒								
co-amoxiclav ☒								
rifampicin ☒								
vancomycin ☒								
fusidic acid ☒								
benzyl ☒								
penicillin ☒								
teicoplanin ☒								
Other ☒								
Specify: _____								

1.3.7 Form 7: Bloods

	Duration of INtravenous Antibiotic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form: 7 Page 1 of 1
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BLOOD RESULTS							
Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z	A-Z
Enrolling Centre Number							
Enrolling Centre Name							

5.1 Blood sample taken?  ☒ Yes ☒ No

Hospital (Centre#)	Date (dd/mm/yyyy)	Hb	WCC	Neutrophils	Platelets	CRP	ESR
[Autopopulated from data entry person]	DD/MM/YYYY 						

1.3.8 Form 8: Imaging

1.3.9 Guideline for radiologists reporting images

Guideline for Radiology Reports
DINOSAUR Study

Guideline for Radiologists Reporting Images for DINOSAUR Study

Dear Radiology team,

Thank you very much for your support with this study; it is greatly appreciated by the research team.

The DINOSAUR study is an NIHR HTA funded, multicentre service evaluation, looking at all children presenting to participating hospitals with osteoarticular infections. Currently there is little international or UK consensus regarding the route or duration of antibiotic treatment for acute osteomyelitis (OM)/septic arthritis (SA) in children. Data regarding paediatric bone and joint infections in the UK are scarce and outdated.

The aims of this study are to

1. Assess current case load, disease spectrum & clinical practice in the diagnosis & treatment of OM/SA in secondary & tertiary UK care
2. Determine whether a randomised controlled trial to investigate shorter duration of intravenous antibiotic therapy for bone and joint infections in children is feasible in the future.
3. This will be achieved in conjunction with a future component of the study obtaining qualitative & quantitative data on:
 - a) willingness of clinicians to randomise to proposed protocol
 - b) willingness of patients & parents to be randomized
 - c) clinical stakeholder & consumer perception of relevant outcomes

The imaging and radiological diagnosis are an important part of this service evaluation.

Information is being collected using a web based data collection form will usually be completed by a research nurse, using the radiology report. Please find enclosed the data collection form for imaging. It would be helpful if the report could be written to allow all of these sections to be filled in by the research nurse.

Thank you very much for your help and understanding. Please contact the research team if you have any queries or comments regarding the study:

Dr Priya Sukhtankar

Clinical Research Fellow, University Hospital Southampton

p.sukhtankar@soton.ac.uk

02380 794956

1.3.9.1 - Form for X-ray report

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 8a X-Ray Report
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PATIENT DETAILS						
Study Identifier	0-9	0-9	0-9		Participant Initials	A-Z A-Z
Enrolling Centre Name						

SUMMARY OF X-RAY RESULT

Number of views

Date of X-Ray

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

X-Ray result:

Normal ☐Abnormal ☐*Please complete below*

Abnormalities:

a) Soft tissue swelling?

Yes	No
☐	☐

b) Focal bone lytic change?

Yes	No
☐	☐

i) Focal

☐

ii) Diffuse

☐

c) Periosteal reaction

Yes	No
☐	☐

d) Cortical loss or destruction

Yes	No
☐	☐

e) Physeal widening

Yes	No
☐	☐

f) Fracture

Yes	No
☐	☐

g) Bony sequestrum

Yes	No
☐	☐

h) Epiphysis

Normal ☐Abnormal ☐

i. Lucency

Yes	No
☐	☐

ii. Sclerosis

Yes	No
☐	☐

iii. Epiphyseal separation

Yes	No
☐	☐

i) Radiological diagnosis (*select one option*)

i. Probable acute OM

☐

ii. Probable sub-acute OM

☐

iii. Chronic OM

☐

1.3.9.2 - Form for CT scan report

	Duration of INtravenous Antibiotic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 8b CT Report
---	---	------------------------------

PATIENT DETAILS						
Study Identifier	0-9	0-9	0-9		Participant Initials	A-Z A-Z
Enrolling Centre Name						

SUMMARY OF CT SCAN

Date of CT

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

CT result:

Normal ☐ Abnormal ☐ Please complete below

Abnormalities:

a) Soft tissue swelling?		Yes	No
b) Focal bone lytic change?			
i) Focal	☐		
ii) Diffuse	☐		
c) Periosteal reaction			
d) Cortical loss or destruction			
e) Physeal widening			
f) Fracture			
g) Bony sequestrum			
h) Epiphysis	Normal ☐ Abnormal ☐	Yes	No
i. Lucency			
ii. Sclerosis			
iii. Epiphyseal separation			
i) Radiological diagnosis (select one option)			
i. Probable acute OM	☐		
ii. Probable sub-acute OM	☐		
iii. Chronic OM	☐		

1.3.9.3 - Form for Ultrasound scan report

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 8c Ultrasound
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PATIENT DETAILS							
Study Identifier	0-9	0-9	0-9		Participant Initials	A-Z	A-Z
Enrolling Centre Name							

SUMMARY OF ULTRASOUND RESULT

Date of Ultrasound

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Ultrasound Result: Normal ☐ Abnormal ☐ Please complete below

Abnormalities:

- a) Periosteal reaction
- b) Cortical breach/destruction
- c) Sub-periosteal collection/abscess
- d) Muscle increased echogenicity
- e) Focal muscle/soft tissue abscess/abscesses
- f) Joint effusion?

Yes No

☐ ☐

☐ ☐

☐ ☐

☐ ☐

☐ ☐

↓ Yes No

Echogenic? ☐ ☐

1.3.9.4 - Form for MRI scan report

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 8d MRI Report
---	---	-------------------------------

PATIENT DETAILS						
Study Identifier	0-9	0-9	0-9		Participant Initials	A-Z A-Z
Enrolling Centre Name						

SUMMARY OF MRI RESULT

Date of MRI

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Technique: Gadolinium enhancement With ☐ Without ☐
If Gadolinium enhancement not used, go to Section 2

Fat suppression With ☐ Without ☐
 Diffusion Diffusion ☐ No Diffusion ☐

MRI result: Normal ☐ Abnormal ☐ *Please complete findings below*

Section 1		Yes	No	Not applicable
		☐	☐	☐
	a. Focal marrow enhancement after gadolinium	☐	☐	☐
	b. Muscle enhancement after gadolinium (myositis)	☐	☐	☐
	c. Focal abscess (defined as ring enhancement after gadolinium on T1 high signal on STIR/ T2FS)	☐	☐	☐
	i. Intra-osseous (bone marrow) abscess	☐	☐	
	ii. Sub-periosteal abscess	☐	☐	
	iii. Soft tissue abscess - <i>select from options below</i>	☐	☐	
	1) Deep parosteal	☐	☐	
	2) Muscle	☐	☐	
	3) Soft tissues/ fascial plains	☐	☐	
		Yes	No	Uncertain
	d. Physeal involvement - enhancement of the physis after gadolinium	☐	☐	☐

	Duration of INtravenous Anti<u>b</u>i<u>O</u>tic therapy for <u>S</u>ep<u>t</u>ic <u>A</u>rth<u>r</u>itis or ac<u>U</u>te osteomyelitis in a paediat<u>R</u>ic population (DINOSAUR)	Form 8d MRI Report		
Section 2	a. Abnormal marrow signal	Yes ☐	No ☐	
	i. Low signal on T1	☐	☐	
	ii. High on STIR/ T2FS	☐	☐	
	b. Abnormal muscle signal on T1 (low) and STIR/T2FS (High)	☐	☐	
	c. Joint involvement (septic arthritis)	☐	☐	
	i. Joint effusion	☐	☐	
	ii. Synovial enhancement	☐	☐	
		Yes	No	Uncertain
	d. Physeal involvement – Increased signal intensity or widening of the physis on STIR/T2FS	☐	☐	☐

1.3.9.5 - Form for bone scan report

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 8e Bone Scan
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PATIENT DETAILS							
-----------------	--	--	--	--	--	--	--

Study Identifier	0-9	0-9	0-9		Participant Initials	A-Z	A-Z
Enrolling Centre Name							

SUMMARY OF NUCLEAR MEDICINE (TECHNETIUM BONE SCAN) RESULT

Date of Bone Scan

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Bone Scan Result: Normal ☐ Abnormal ☐ *Please complete below*

Abnormalities:

- i) Solitary lesion with increased uptake
- ii) Multiple lesions with increased uptake

Yes	No
☐	☐
☐	☐

1.3.10 Form 9: Complications

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form: 9 Page 1
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COMPLICATIONS						
Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z A-Z
Enrolling Centre Number						
Enrolling Centre Name						

4 Any Complications ☐ Yes ☐ No

If Yes please give details

.....

	Duration of INtravenous Anti<u>b</u>i<u>O</u>tic therapy for <u>S</u>ep<u>t</u>ic <u>A</u>rth<u>r</u>itis or ac<u>U</u>te osteomyelitis in a paediat<u>R</u>ic population (DINOSAUR)	Form: 9
		Page 2

SURGICAL PROCEDURES

Study Identifier	0-9	0-9	0-9	(Auto Assigned)	Participant Initials	A-Z	A-Z
Enrolling Centre Number							
Enrolling Centre Name							

Hospital 											
Date of Procedure 		D	D	M	M	Y	Y	Y	Y		
Time of procedure 	h	h	:	m	m						
Description 	☐	Aspiration									
	☐	Incision and drainage									
	☐	Drill decompression									
	☐	Curettage/excision									
	☐	Arthrotomy									
	☐	Arthroscopy									
	☐	Amputation									
	☐	Debridement									
	☐	Fasciotomy									
	☐	Compartment decompression									
	☐	Secondary closure									
	☐	Skin graft									
	☐	Other plastic surgery									
If "other plastic surgery" please specify:											
Additional Notes 											

1.3.11 Form 2a: Discharge form

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 2A Discharge form
---	---	----------------------------------

PATIENT DETAILS

Study Identifier	0-9	0-9	0-9	Participant Initials	A-Z	A-Z
Enrolling Centre Name						

DISCHARGE SUMMARY

Date of discharge:

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Yes No

1) PIC line in situ at discharge?

☐ ☐

2) Peripheral cannula in situ at discharge?

☐ ☐

3) Planned Antibiotic therapy at discharge:

Antibiotic Name (if other please specify)	Daily dose (mg)	Route	Planned duration (days)
		IV ☐	
		Oral ☐	
		IV ☐	
		Oral ☐	
		IV ☐	
		Oral ☐	
		IV ☐	
		Oral ☐	
		IV ☐	
		Oral ☐	
1 Flucloxacillin 2 Clindamycin 3 Cefuroxime 4 Ceftriaxone 5 Amoxicillin 6 Co-amoxiclav 7 Rifampicin 8 Vamcomycin 9 Fusidic Acid 10 Benzyl penicillin 11 Teicoplanin 12 Fluconazole	13 Amphotericin b 14 Itraconazole 15 Caspofungin 16 Micafungin 17 Anidulafungin 88 Other antibiotic 89 Other antifungal		

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 2A Discharge form
---	---	----------------------------------

4) Follow-up planned

Yes No

Discharged from follow-up

☐ ☐

X rays

☐ ☐

MRI

☐ ☐

Growth monitoring

☐ ☐

Physiotherapy

☐ ☐

Orthotic e.g. brace

☐ ☐

General paediatric follow-up

☐ ☐

Orthopaedic follow-up

☐ ☐

Removal of line

☐ ☐

Other follow up (please specify if yes)

☐ ☐

1.3.12 Form 10: Three month follow up

	Duration of INtravenous AntiBiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population (DINOSAUR)	Form 10 3 Month Follow-up
---	---	--------------------------------------

PATIENT DETAILS

Study Identifier	0-9	0-9	0-9		Participant Initials	A-Z	A-Z
Enrolling Centre Name							

DETAILS OF 3 MONTH FOLLOW-UP



Date of follow-up

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Please tick here if unable to contact patient or patient did not attend

☐

Type of follow-up

Orthopaedic OP Appointment

☐

Paediatric OP Appointment

☐

Telephone call

☐

1) Readmission to hospital related to current SA/OM diagnosis?

Yes ☐No ☐

Reason for readmission 1:

[Date of readmission 1:](#)

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

[Approx date](#)
☐
[Actual date](#)
☐

Reason for readmission 2:

[Date of readmission 2:](#)

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

[Approx date](#)
☐
[Actual date](#)
☐

Reason for readmission 3:

[Date of readmission 3:](#)

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

[Approx date](#)
☐
[Actual date](#)
☐
[Please complete/update microbiology form if applicable \(hyperlink\)](#)

2) Ongoing symptoms

Yes No

Pain ☐ ☐Fever >38C ☐ ☐Joint stiffness ☐ ☐Immobility ☐ ☐

Yes No

Fracture ☐ ☐Sinus ☐ ☐Deformity ☐ ☐



**Duration of INtravenous AntiBiOtic therapy
for Septic Arthritis or acUte osteomyelitis in a
paediatRiC population (DINOSAUR)**

**Form 10
3 Month Follow-up**

FOLLOW-UP OF LINES INSERTED

Please tick here if this section is not applicable to the participant (no line in situ at time of discharge and no lines inserted after discharge). ☐

Type of line		Date line inserted	Current status of line	Date of removal (if applicable)	Line infection? *
1 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		
2 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		
3 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		
4 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		
5 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		
6 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		
7 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		
8 PIC Line	☐ If other line, specify:	Approx date ☐ In situ	Approx date ☐ Yes		
Other intravenous catheter	☐ specify:	Actual date ☐ Removed	Actual date ☐ No		

* any time between discharge and this follow-up

Please update microbiology form



**Duration of INtravenous AntiBiOtic therapy
for Septic Arthritis or acUte osteomyelitis in a
paediatRic population (DINOSAUR)**

**Form 10
3 Month Follow-up**

ANTIBIOTIC THERAPY

3) Course of antibiotic therapy completed as planned? (based on antibiotic regimen at discharge).

Yes ☐ No ☐

Please update Form 5 with end date for these antibiotics where possible. (hyperlink)

Reason antibiotics stopped early

	Yes	No
Unpalatable antibiotic	☐	☐
Diarrhoea	☐	☐
Rash	☐	☐
Resolution of symptoms	☐	☐
Other	☐	☐

Specify:

Decision to stop antibiotics:

	Yes	No
Parent decision	☐	☐
Hospital decision	☐	☐
GP medical decision	☐	☐

Details:

CHANGES TO PLANNED ANTIBIOTIC THERAPY (AS PER PLAN AT DISCHARGE)

4) Were oral antibiotics changed? Yes ☐ No ☐

Changed by:

	Yes	No
GP	☐	☐
Hospital	☐	☐

Reason for change

	Yes	No
Unpalatable antibiotic	☐	☐
Diarrhoea	☐	☐
Rash	☐	☐
Recurrence of infection	☐	☐
Other (e.g. resistant organism)	☐	☐

Details:



**Duration of INtravenous AntiBiOtic therapy
for Sep^tic Arth^ritis or acUte osteomyelitis in a
paediatRic population (DINOSAUR)**

**Form 10
3 Month Follow-up**

DETAILS OF FOLLOW-UP

5) Follow-up planned

	Yes	No
X rays	☐	☐
MRI	☐	☐
Growth monitoring	☐	☐
Physiotherapy	☐	☐
Orthotic e.g. brace	☐	☐
General paediatric follow-up	☐	☐
Orthopaedic follow-up	☐	☐
Discharged from follow-up	☐	☐
Other follow-up (please specify if yes)	☐	☐

6) Please select any follow-ups that have already taken place:

	Yes	No	Outcome	
X rays	☐	☐	Normal	☐ Details if abnormal:
			Abnormal	☐
MRI	☐	☐	Normal	☐ Details if abnormal:
			Abnormal	☐
Physiotherapy	☐	☐	Details:	
Orthotic e.g. brace	☐	☐		
General paediatric follow-up	☐	☐		
Orthopaedic follow up	☐	☐		

Appendix 2: Microbiology sub-study documents

2.1 Protocol: see Appendix 1

2.2 Laboratory Standard Operating Procedure

DINOSAUR microbiology laboratory SOP for taking, processing and storage of samples

The collection of paediatric bone and joint samples for real time polymerase chain reaction (RT-PCR): SOP for sample handling and processing in the routine microbiology laboratories of participating sites

The DINOSAUR (Duration of INtravenous antiBiOtic therapy for Septic Arthritis or acute osteomyelitis in a paediatric population) microbiology sub study is collecting samples pragmatically from the routinely collected samples sent to microbiology, as well as additional throat swabs for batched multiplex PCR analysis.

Please ensure that measures are taken to prevent contamination of the sample in the routine laboratory, this will include the wearing of gloves and the use of safety cabinets where available while handling the sample.

Once routine culture and microscopy have taken place, please carry out the following for samples to be processed by RT-PCR: **(PLEASE LABEL ALL STORED SAMPLES WITH PRE-PRINTED STUDY LABELS).**

a. Tissue and bone fragments

1. Using a clean petri dish and sterile scalpel and tweezers, remove the sample from the collection tube.
2. Place the sample on to the petri dish and remove between two and four 10mg sections of the sample using the scalpel and place them in a sterile, nuclease free 2 ml plastic tube (Sarstedt) and cap.
3. Place the Sarstedt in to a -80°C freezer for storage.
4. Replace the original sample back in to its collection tube and store according to the laboratory SOP.

b. Fluid samples

1. Vortex the sample in its original collection tube to homogenise.
2. Using a sterile pastette (or other plastic pipette), remove approx. 500 µl of sample and place in a sterile nuclease free Sarstedt and cap.
3. Place the Sarstedt at -80°C for storage.
4. The original sample can then be refrigerated according to the local SOP.

DINOSAUR microbiology laboratory SOP for taking, processing and storage of samples

c. Blood cultures in paediatric (or adult) blood culture bottles and joint washouts that have been placed in these bottles (if relevant for site, most sites place in universal containers as routine practice)

(Please collect both positive and negative samples that are from paediatric patients with OAI)

1. Place the blood culture bottle on to the processing machine.
2. The sample should then be removed after 19 hours incubation for sampling (unless the sample has already "flagged" positive). If this is not possible the aliquot should be taken when the sample flags positive, or when the sample is removed from the machine.
3. Clean the top of the bottle with an alcohol wipe.
4. Agitate the bottle to fully mix the contents and whilst wearing gloves, use a sterile needle and syringe to remove 1ml of the contents.
5. Replace the sample back on to the culture machine if further incubation is required.
6. Place this carefully in to a nuclease free sterile Sarstedt and freeze at -80°C.

d. Throat swabs

1. Remove the swab from its packaging and take the sample from the patient.
2. Remove the lid from the tube containing the STGG transport media and whilst wearing gloves and using a clean pair of scissors, cut the end of the swab off so that it falls in to the media.
3. Close the lid and agitate to mix.
4. Store at -80°C.

2.3 Patient information sheets and consent form

2.3.1 Patient information sheet and consent form Parents



To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY (CHILDREN'S BONE AND JOINT INFECTION STUDY)

Parent Information and Consent Form
Version 1.4 Dated 21/10/2013
(www.dinosaur-study.org.uk)

We would like to invite your child to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you and your child. One of our team will go through this information sheet with you and answer any questions you may have.

Why is this study needed?

Bone and joint infections are uncommon in children. It is not known exactly how many children are affected, but it is estimated at 5-10 per 100,000 children per year. Diagnosis and treatment of bone and joint infections varies in different countries, and within the UK.

Bone and joint infections in children are usually caused by bacteria (bugs) carried in the blood being deposited in bone or in the joint, and multiplying. The bacteria causing these infections vary and can be different depending on the age of the child. We would like to find out which bacteria are causing the infections and see if some children are more likely to suffer from infections than others. Your hospital is helping us to look at this.

Why has my child been chosen?

Your child has been asked to take part because they were admitted with a bone and/or joint infection.

What will happen to my child if we join the study?

When your child has routine blood samples taken, or if samples taken from the bone or joint, a small amount will be sent for an extra test called PCR to try and find out what is causing the infection. This does NOT involve taking any extra blood, and using a PCR test may make it easier to detect which bacteria causing the problem. In addition, while blood tests are being done, an extra 5ml (1 teaspoon) of blood may also be taken if possible at this point to be stored for future testing to see if some children are more likely to get bone infections than others. This will not require any extra needles and will be done during the taking of the clinical tests your child needs.

Recent research from the United States has suggested that a throat swab may be useful to detect the bacteria causing bone and joint infections in children, and we would like to take a simple throat swab from your child to identify whether the bacteria detected by PCR are also present in the throat. . The results will not be known until the treatment is complete, and so will not affect treatment.

Consent:

If you and your child are happy to take part, you will be asked to sign a consent form on behalf of your child before they take part. You will get a copy of the signed consent form and information sheet to keep. Your child will also be given information about the study in a format appropriate to their age group.

Are there any risks or benefits to my child if they join the study?

We cannot promise the study will help your child but the information we get might help treat children with bone and joint infections in the future. It will also help us to decide whether to carry out a study in the future comparing different lengths of courses of antibiotics for the treatment of bone and joint infections. There are no known risks to taking part.

Will anyone else know my child is taking part in this study?

Yes. Only people working on the study or working to ensure the study is run correctly will have access to the data. All information collected about your child during this study will be confidential and will be handled, stored and destroyed in accordance with the Data Protection Act 1998.

What will happen to the samples given by my child?

The PCR samples for the study will be analysed by the study team. The additional blood test will be the 5ml blood sample will be stored anonymously and used in future research into childrens' bone and joint infections and to compare with information from other serious infections.

What will happen to the results of the study?

We aim to publish the results of this study in medical literature. Your child's confidentiality will be maintained at all times and your child will not be identifiable in any publication. A short summary of the study will be provided on our website (www.dinosaur-study.org.uk).

What if there is a problem?

There are no risks to your child's health by participating in this study. If you or your child has any concerns about any aspect of this study, you should speak with the doctor and/or nurse who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Who is doing this study?

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 10/146/01) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA Programme, NIHR, NHS or the Department of Health.

It is being run in the hospital where your child is being treated, and is being organised by The University of Southampton, University Hospital Southampton NHS Foundation Trust and the University of Liverpool. This research has been approved by a research ethics committee, who are happy that the study is being conducted in an appropriate manner. This study is also supported by the Medicines for Children Research Network (www.mcrn.ac.uk).

Please ask us if there is anything that is not clear or if you would like more information.

Please Contact: < Insert Name and Title>
 <Telephone Number>
Or Contact: < Insert Name and Title>
 <Telephone Number>

**THANK YOU FOR READING THIS INFORMATION SHEET.
WE HOPE YOU HAVE FOUND THIS SHEET HELPFUL**



To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY
(CHILDREN'S BONE AND JOINT INFECTION STUDY)

Parent Consent Form Version 1.4 21/10/2013

www.dinosaur-study.org.uk

	Please initial box
1. I confirm that I have read and understand the information sheet dated 21/10/2013 (version 1.4) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that participation is voluntary and that I am free to withdraw my child at any time, without giving a reason, and without my child's care or legal rights being affected.	
3. I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals from the research team, regulatory authorities, sponsor or from the NHS Trust, where it is relevant to my child taking part in this study. I give permission for these individuals to have access to my child's records.	
4. I understand that my child's medical data will be collected for this study and may be used to develop new research and that data protection regulations will be observed.	
5. I agree for my consent form and my child's details, which will include my child's name, to be passed to the Medicines for Children Research Network Clinical Trials Unit for the administration of the study.	
6. a/ I give permission for my child's extra blood test to be taken and used for this study, and to be transferred to research institutes in the UK.	
b/ I give permission for my child's extra blood test to be used for future research related to this study.	
7. a/ I give permission for my child's throat swab to be taken and used for this study, and to be transferred to research institutes in the UK.	
b/ I give permission for my child's throat swab to be used for future research related to this study.	
8. I agree to medical personnel, responsible for my child's welfare, being informed of my child's participation in the study.	
9. I agree to take part in the above study.	
Optional: I agree that I may be contacted in the future in relation to this study.	Yes ☐ No ☐

 Name of Patient

 Name of Parent / Guardian

 Signature

 Date

 Researcher

 Signature

 Date

When completed, 1 (original) to be kept in medical notes, 1 for parent/guardian, 1 for researcher site file; 1 for the MCRN CTU, University of Liverpool

2.3.2 Patient information sheet Children under 5 years



To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY (CHILDREN'S BONE AND JOINT INFECTION STUDY)

Information for under 5yrs
Version 1.3 24/05/2013
(www.dinosaur-study.org.uk)

Would you and your mummy or daddy or the grown up who looks after you be able to help us?



We are trying to find out the best way to look after children like you with poorly bones and joints.

We would like to ask for your help.

We are asking lots of other children to help us too.

If you want to help us

Your doctor or nurse will ask if you are happy for us to do some extra tests on the blood samples we take. We would also like to do a test called a throat swab to help us look at the bugs making you poorly.



Your mummy or daddy or the grown up who looks after you will need to say that this is okay.

This might help us help other children who have poorly bones and joints just like you.

Thank You

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2.3.3 Patient information sheet Children 6-10 years



To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY (CHILDREN'S BONE AND JOINT INFECTION STUDY)

Children's Information and Assent Form

Version 1.3 Dated 24/05/2013

(www.dinosaur-study.org.uk)



What is a study? Why is this being done?

Research is what you do when you want to learn about something or find out something new.

This research looks at bone and joint infections and the best way to treat them.

We will be collecting samples from children at a number of different hospitals across the country.

Why have I been chosen?

You are being asked to take part in this study because you have a bone or joint infection.

Do I have to help?

Not if you and your mum or dad decide you do not want to.

What will happen to me if I say yes?

1. If you are able you will be asked to write your name on a form.

This is to say that you understand the study and what will happen. You will be given your own form to keep, as well as



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this leaflet. This is all you need to do. The doctors and nurses will take care of everything else.



2. We will do some extra tests on samples we take to check on your bone and joint infection. There are no extra blood tests but there is an extra test called a throat swab.

We will ask your mum and dad if we can do an extra test on your blood tests to use a new way to test the bugs that grow there. This would be done when you would have your normal tests anyway. We will also ask if we can take a throat swab and take some extra blood during your normal tests. There are NO extra needles in this study.

What good will happen if I take part?

We hope to find out how we can best treat children like you in the future, so you will be helping children with bone and joint infections in future to try to give them better treatments.

Will anything bad happen to me if I take part?

No, nothing bad will happen to you for choosing to help us.

What do I have to do now?

If you want to help, your mum and dad or the grown up looking after you will need to say it's okay.

What if I have questions?

If you have any questions, you can ask your mum or dad or the grown up looking after you to contact:

Please Contact: < Insert Name and Title >
< Telephone Number >

Or Contact: < Insert Name and Title >
< Telephone Number >



**Thank you for reading this information.
Please ask any questions if you need to.**

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To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY
(CHILDREN'S BONE AND JOINT INFECTION STUDY)
 Children's Information Sheet (Age 6-10 years) Assent Form
 Version 1.3 24/05/2013
www.dinosaur-study.org.uk

Child (or if unable, parent on their behalf) to circle all they agree with:

Has somebody explained this study to you?	Yes / No
Do you understand what this study is about?	Yes / No
Have you asked all the questions you want?	Yes / No
Have your questions been answered in a way you understand?	Yes / No
Do you understand it's OK to stop taking part at any time?	Yes / No
Are you happy to join in?	Yes / No

If any answers are 'no' or you **don't** want to join in, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your name _____ Date _____

Your parent or guardian must write their name here too if they are happy for you to do the study

 Print Name Signature Date

The researcher who explained this study to you needs to sign too:

 Researcher Signature Date

Thank you for your help.

When completed, 1 (original) to be kept in medical notes, 1 for parent/child, 1 for site file and 1 for MCRN CTU.

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2.3.4 Patient information sheet Children 11-15 years



To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY (CHILDREN'S BONE AND JOINT INFECTION STUDY)

Young Persons Information and Assent Form

Version 1.3 Dated 24/05/2013

(www.dinosaur-study.org.uk)

What is the purpose of the study?

Bone and joint infections in children are usually caused by bacteria (bugs) carried in the blood being deposited in bone or in the joint, and multiplying. The bugs causing these infections vary and can be different depending on the age of the child. We would like to find out which bacteria are causing the infections and see if some children are more likely to suffer from infections than others. Your hospital is one of a number of hospitals across the country helping us to look at this.

We are inviting you to take part in our research study. Before you join in, it's important to understand why the research is being done and what it will mean for you. So please read this leaflet carefully. Talk about it with your family, friends, doctor or nurse if you want to.

Why have I been chosen?

You have been asked to take part because you have a bone and/or joint infection.

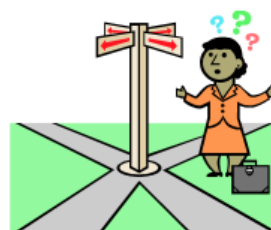
Do I have to take part?

No. You can stop taking part at any time if you want to, and this will not affect any of your medical treatment now or in the future.

What will happen if I take part?

1. You will write your name on a form.

If you agree to take part you will be asked to write your name on the form at the end of this leaflet. This is just to say that you understand the study and what will



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happen. You will be given a copy of the form to keep as well as this information leaflet.

Your mum or dad or guardian will need to sign a consent form to agree to you taking part. Your information will be kept confidential and in a safe place. Apart from this you will not need to do anything else. The doctors and nurses will do everything else.

2. We will do some extra tests on samples we take to check on your bone and joint infection. There are no extra blood tests but there is an extra test called a throat swab.

We will ask your mum and dad if we can do an extra test on your blood tests to use a new way to test the bugs that grow there. This would be done when you would have your normal tests anyway. We will also ask if we can take a throat swab and take some extra blood during your normal tests. There are NO extra needles in this study.



What will happen if I don't take part?

Nothing, you will still be looked after in the same way.

What are the benefits of taking part?

We cannot promise the study will help you but the information we get might help treat children with bone and joint infections in the future. It will also help us to decide whether to carry out a study in the future comparing different lengths of courses of antibiotics for the treatment of bone and joint infections.

What are the risks of taking part?

There are no known risks to taking part.

What if I have any questions?

If you have any questions, you can contact:

Please Contact: < Insert Name and Title >
< Telephone Number >

Or Contact: < Insert Name and Title >
< Telephone Number >



**THANK YOU FOR READING THIS INFORMATION SHEET.
WE HOPE YOU HAVE FOUND THIS SHEET HELPFUL**

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To be presented on local headed paper

Centre Name and Number:

THE DINOSAUR STUDY (CHILDREN'S BONE AND JOINT INFECTION STUDY)

Young Persons Information and Assent Form

Version 1.3 Dated 24/05/2013

(www.dinosaur-study.org.uk)

TO BE COMPLETED BY THE CHILD AND THEIR PARENT/GUARDIAN

Child (or if unable, parent on their behalf) to circle all they agree

Please circle

Have you read (or had read to you) information about this project.

YES / NO

Has somebody else explained this study to you?

YES / NO

Do you understand what this study is about?

YES / NO

Have you asked all the questions you want?

YES / NO

Have you had all your questions answered in a way you understand?

YES / NO

Do you understand it's ok to stop taking part at any time?

YES / NO

Are you happy to take part?

YES / NO

If any answers are 'no' or you don't want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your Name: _____ Date: _____

Your **parent or guardian** must write their name here too if they are happy for you to take part

Print Name

Sign

Date

The **doctor** who explained this project to you needs to sign too:

Researcher

Signature

Date

Thank you for your help

When completed, 3 copies need to be made, 1 for the participant, 1 for the investigator site file and the original must be kept in the medical notes.

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DINOSAUR Young Persons Information Sheet (Age 11-15 years) and Assent Form V1.3 Dated 24/05/2013 Page 3 of 3

Appendix 3: Qualitative Study documents

3.1 Protocol Qualitative study

Duration of Intravenous antibiotic therapy for Septic Arthritis or acute osteomyelitis in a paediatric population: QUALITATIVE SUB-STUDY

Sponsor: University Hospital Southampton NHS Foundation Trust

Sponsor Code: RHM CHI 0725

NHS REC No: 14/YH/1166

Protocol Version: 1.0 date 11 June 2014

Chief Investigator: Prof Saul Faust, Professor of Paediatric Immunology and Infectious Diseases

NIHR Wellcome Trust Clinical Research Facility

University Hospital Southampton

Qualitative study to explore the views of parents and paediatric patients, who have had bone and/or joint infection about participating in a hypothetical randomised controlled investigating shortened duration of intravenous antibiotic therapy for osteomyelitis and septic arthritis

1. INTRODUCTION AND BACKGROUND

Osteomyelitis (OM) and septic arthritis (SA) are relatively unusual infections in children, however, they confer considerable morbidity. At present there is limited evidence and no UK or global consensus on how to optimally treat these infections with antibiotics. The DINOSAUR study (Duration of Intravenous Antibiotic Therapy for Acute Osteomyelitis and

Septic Arthritis in a Paediatric Population) has 3 components to determine the feasibility of whether a trial of shortened courses of intravenous and oral antibiotics for the treatment of bone and joint infections in children will be feasible in the UK. (www.dinosaur-study.org.uk). The feasibility study comprises a service evaluation, Delphi survey and stakeholder meeting to establish consensus from the different clinical stakeholder groups, and a qualitative study to input young people and parent's views into the Delphi and stakeholder process.

Parents were consulted during the proposal application for the DINOSAUR study and agreed that a qualitative component engaging parents of children who had had bone and joint infections would be beneficial. This qualitative study incorporates parents' views and experiences into the question of whether a formal clinical trial will be feasible.

Historically patients with OM/SA have been treated with up to six weeks intravenous antibiotics as inpatients in hospital. It is now more common practice to treat paediatric OM/SA with intravenous antibiotics initially, and then switch to oral antibiotics once clinical improvement is seen, and the child is able to take and absorb oral antibiotics. An alternative has been the use of outpatient intravenous antibiotic therapy (OPAT) before the switch to oral medicines. The criteria for switching from intravenous to oral antibiotics, and the total duration of antibiotics varies between centres within the UK and internationally.

Diagnosis of OM/SA combines haematological and biochemical blood results, microbiological analysis of blood and tissue samples and imaging using plain x-rays, ultrasound and MRI scan. Treatment may include surgery, such as drainage of a joint, and drilling and decompression, although the mainstay of treatment is immediate, intravenous antibiotic therapy.

The advantages of switching from intravenous to oral antibiotics are that the duration of hospital stay may be shortened. Additionally the risks of line-site infection and bacteraemia when a venous catheter is in place for antibiotic administration for prolonged periods are reduced. Where used, these intravenous lines may need replacing if they become occluded or displaced necessitating hospital admission and often general anaesthetic for the procedure.

The advantage of prolonged intravenous therapy is guaranteed delivery of the antibiotic, not dependent on child or family-specific factors such as adherence or absorption. This allows more reliable treatment of invasive and potentially destructive infection.

Prolonged intravenous therapy may increase the risks of reaction to the antibiotic, and side effects such as bone marrow suppression. On the other hand, incompletely or inadequately treated bone or joint infection may rarely lead to chronic infection with destruction of cartilage, bone and growth plate, which can then cause permanent deformity and disability. However, whilst it may be desirable for many families to spend less time in hospital, with reduced duration of intravenous therapy, the perception of risks of complications secondary to potentially incomplete treatment may mean that a trial of shortened duration of antibiotics is not acceptable to parents and/or clinical stakeholders.

There has been little previous qualitative research exploring the views of paediatric patients or their parents about treatment for or the impact of acute bone and joint infections, or of the medical or surgical treatment family life during and after admission to hospital with infection in a previously healthy child. Additionally, evidence regarding patient and parent perception and understanding of risks of complications, disability or adverse effects of treatment remains anecdotal.

Importantly, the willingness of parents and patients to participate in a RCT, and what factors may influence this is not known, and will vary depending on proposed study design.

The importance of patient and family involvement (PPI) in NHS based research has become a priority at all stages of development of research projects. This qualitative study will involve patients and parents in assessing the feasibility of a future RCT, by determining their willingness to participate in a trial once specific potential study outcomes have been considered. Parents and patients may prioritise outcomes of a randomised controlled trial differently from clinicians, and this qualitative study will identify which outcomes are most important to parents and children, and where possible these can be incorporated as important outcomes to assess in a RCT.

DINOSAUR Qualitative Sub-study Team

Professor Saul Faust is the Chief Investigator of the DINOSAUR study as a whole and will oversee this study.

Dr Claire Ballinger is an experienced qualitative researcher and patient-public involvement lead, who will lead the qualitative methodology and supervise the qualitative researcher employed to interview young people and families.

Dr Amanda Lees, a trained qualitative researcher, who has previous experience interviewing families including children will be employed for six months to conduct the interviews and analyse the transcripts, supervised by Dr Ballinger. She may be assisted by another trained and experienced qualitative researcher.

Dr Priya Sukhtankar is the clinical research fellow based at the Southampton NIHR Wellcome Trust Clinical Research Facility coordinating clinical aspects of the DINOSAUR trial and liaising with individual sites.

Other investigators:

Prof Nick Clarke, Professor of Paediatric Orthopaedic Surgery, Southampton

Dr Stuart Clarke, Reader in Infectious Disease Epidemiology, Southampton

Prof Mike Sharland, Prof of Paediatric Infectious Diseases, St Georges London

Prof Andrew Pollard, Prof of Paediatric Infectious Diseases, Oxford

Prof Adam Finn, Prof of Paediatric Infectious Diseases, Bristol

Mr Philip Henman, Consultant in Paediatric Orthopaedics, Newcastle

Dr Colin Powell, Senior Lecturer in General Paediatrics, Cardiff

Dr Kate Armon, Consultant in General Paediatrics, Norwich

Dr Patricia Fenton, Consultant Paediatric Microbiologist, Sheffield

Dr Andrew Riorden, Consultant in Paediatric Infectious Diseases, Liverpool

Dr Jethro Herberg, Lecturer in Paediatric Infectious Diseases, Imperial College London

Dr Delane Shingadia, Consultant in Paediatric Infectious Diseases, Great Ormond Street London

Dr Scott Hackett, Consultant in Paediatric Immunology & Infectious Diseases, Birmingham Heartlands

Dr Carrol Gamble, Reader in Medical Statistics, Liverpool

Professor Paula Williamson, Professor of Medical Statistics and Director MCRN CTU, Liverpool

Ms Helen Hickey, Senior Trials Manager, MCRN CTU, Liverpool

Dr Annemarie Jeanes, Consultant in Paediatric Radiology, Leeds

2. AIMS OF STUDY

Qualitative research aims to understand: how social (including health) experiences are understood; uses methods which are sensitive to social context; and employs analytic strategies which involve an appreciation of complexity and context [1]. The research methodology employed within this study will draw on constructivist grounded theory [2]. This study aims to explore parents' and children's views, understanding and experiences of both bone and joint infections and treatment, and the parental willingness to participate in a future clinical trial.

Detailed aims:

1. To explore the experiences of parents and children treated with intravenous and/or oral antibiotic therapy for bone and joint infection about their condition and understanding about treatment
2. To identify which clinical outcomes are most important to parents and young people with bone and joint infections, in order to contribute to the wider clinical stakeholder Delphi and stakeholder consultation process.
3. To explore the views of parents and children admitted to hospital with bone and joint infections about participating in a RCT, in particular focusing on: information required in order to provide informed consent; views about and acceptability of potential interventions; willingness to be randomised to either arm (i.e. treatment or control); influences on these factors.

3. METHODS

Semi-structured interviews

Semi-structured interviews will be used within this study to explore the views and experiences of parents and children who have had bone and joint infections. Parents and children will be interviewed together. Semi-structured interviews are characterised by:

- an interactional exchange
- a topic centred dialogue, but with a flexible structure
- an acknowledgement that within an interview context, meaning and knowledge is co-produced [1]

The interview guides for parents and children will be developed with reference to existing literature (e.g. qualitative work in this field, factors impacting on participation in RCTs, qualitative research interviews with children); by experts in the field including our Research Fellow, Dr Amanda Lees, and in consultation with our patient and public involvement contributors. The interview guide will be piloted with between three and five children and their parents, (although as is usual practice in qualitative research, these data will be included in the final analysis).

The interviews will be digitally recorded, with permission from the families and children, all identifying features will be omitted, and the recordings will then be transcribed by a professional transcribing agency. The transcriptions will then be returned to the qualitative researcher for analysis.

Sample and Consent

A purposive sample of children aged 0 to 16 years who have had bone and joint infection within the previous year will be identified from seven centres who have participated in the main Dinosaur service evaluation. The purposive sample strategy will be developed to address variation with regard to age, gender, and ethnicity. Parents/carers, and, where appropriate and consent has been obtained, young people, will be interviewed together with their parents. We anticipate that a sample size of thirty families should be sufficient, but will continue sampling until data saturation is reached. [3] All families approached who agree to participate will be interviewed.

Inclusion criteria

- Parents and children from 3months to sixteen-years-old with osteomyelitis and septic arthritis
- who have been treated for bone and joint infections at seven sites identified below
- who have consented to take part in this qualitative study

Children and their parents at the following seven sites have participated in the main DINOSAUR study: Bristol Children's Hospital, Oxford Children's Hospital (University Hospitals Oxford NHS Trust), University Hospital Southampton NHS Foundation Trust, Imperial College Healthcare (St Mary's Hospital London), St George's Hospital London, Birmingham Children's Hospital and Liverpool Alder Hey Hospital. At the point of initial consent for participation in the larger study, participants (i.e. children and their families) were also asked if they would be willing to be contacted about possible participation in a smaller qualitative study. Once ethics and site specific approvals have been received, letters will be sent to those parents and children consenting to be contacted about the qualitative study, to include Participant Information Sheets. Potential participants will be invited to make contact with the research team if they are interested in hearing more. The qualitative researcher will make contact with interested parents and children to explain further about the study, answer any queries, and arrange to meet.

On meeting, any additional concerns/queries will be addressed, and if happy to continue, written consent will be received immediately prior to conduct of the interview.

4. TIME LINE

We anticipate contacting families early October 2014, with a view to organising interviews between October 2014 and January 2015.

5. DATA ANALYSES

As is usual in qualitative analysis, data collection and analysis will occur concurrently, in this instance using the constant comparative method. Analysis will move from the generation of initial 'in vivo' codes to more abstract, theoretical frameworks, which explain the vast majority of the data generated [2]. The qualitative research will also use memos to capture analytic thoughts and ideas which will inform the analysis, and will also provide evidence of an audit trail, one of the strategies which can demonstrate the credibility of the analysis [4]

6. RESEARCH GOVERNANCE, MONITORING, ETHICS AND R&D APPROVAL

The research will comply with the Research Governance Framework and International Conference on Harmonisation Good Clinical Practice (ICH GCP).

The study will be sponsored by University Hospital Southampton NHS Foundation Trust, subject to the relevant governance approvals. The Sponsor will delegate appropriate responsibilities to the Chief Investigator, and to Dr Ballinger (lead qualitative researcher) who will co-ordinate the study and will during pilot phase provide at least weekly supervision, and thereafter a minimum of two weekly supervision to Dr Amanda Lees.

There are some ethical considerations with this study that requires trained researchers not directly involved with the patients' medical care to have access to limited confidential information.

7. FINANCE

This study is supported by the NIHR HTA project 10/146/01 - Duration of intravenous antibiotic therapy for children with acute osteomyelitis or septic arthritis: a feasibility study

8. REPORTING AND DISSEMINATION

We will use the normal channels of journal publication and conference presentations. In addition, we are committed to ensuring that our research is available via open access and we will have a dissemination strategy that includes rapid web-based publishing of lay summaries once research articles have undergone peer-review and links to University and Trust press offices.

9. REFERENCES

1. Mason, J, Qualitative Research, Qualitative Researching, Second Edition, SAGE Publications 2002
2. Charmaz, K.C. Constructing Grounded Theory, SAGE Publications 2006
3. Baker, S.E. and Edwards R, How Many Qualitative Interviews is Enough?
<http://eprints.ncrm.ac.uk/2273/> National Centre for Research Methods Review Paper

4. Ballinger, C 'Writing up rigour: Representing and evaluating good scholarship in qualitative research' *British Journal of Occupational Therapy* 67 (12) 540-7. (2004)

3.2 RCT process diagram and information

Possible trial design

In the past, patients with bone and joint infections stayed in hospital for up to 6 weeks, and were treated with intravenous antibiotics. This is what we could call the ‘text book’ treatment.

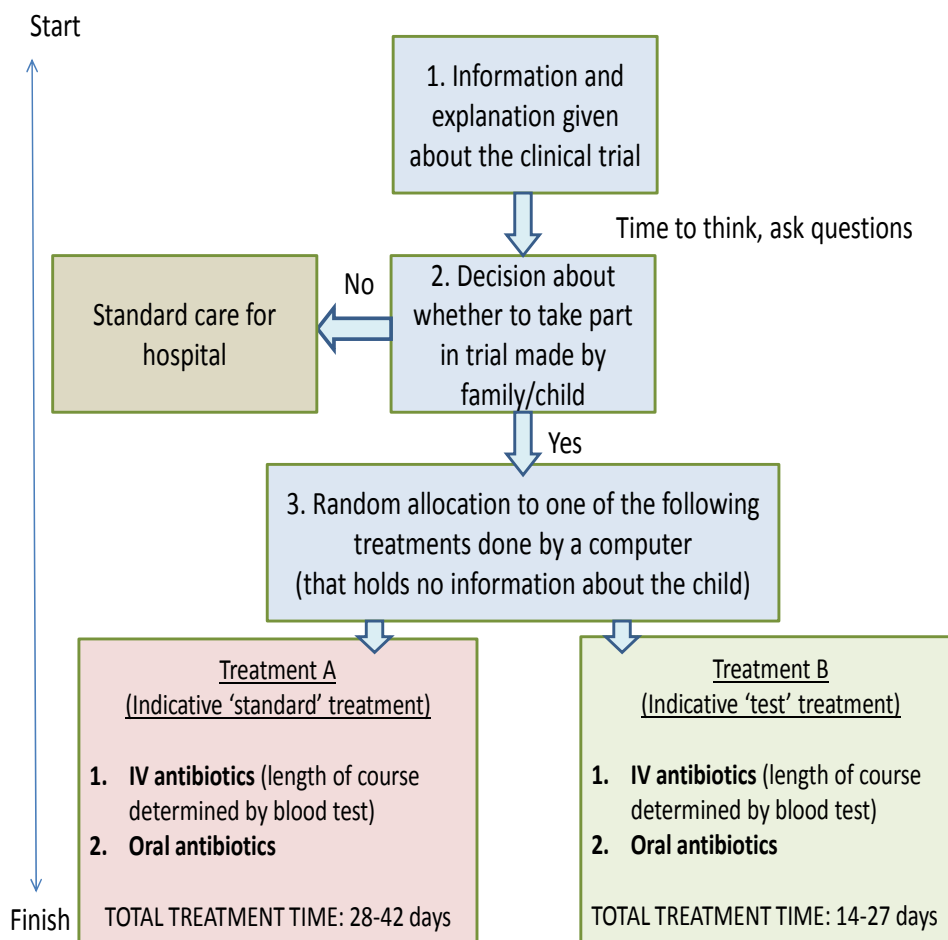
Nowadays, it is more common for patients to be given intravenous antibiotics at first, with a switch being made to oral antibiotics (tablets or medicine), when they start to get better. There has also been a move towards using less total antibiotic treatment, but the exact length of treatment varies within the UK and similar countries abroad.

At the moment, doctors do not have clear evidence about the best length of time for patients to stay on intravenous antibiotics, or on the signs of improvement that show a switch to oral antibiotics can be made.

Conducting a clinical trial would determine:

- The best length of the total antibiotic treatment and whether this could be shortened
- The best length of intravenous antibiotic treatment, and the signs of recovery needed before a switch to oral antibiotics can be made
- The best length of oral antibiotic treatment

The process for the trial is shown on the next page. This type of trial is called a randomised controlled trial. It compares two groups of people: one group who receive the new treatment and another group, who receive the standard treatment (this group is called the ‘control group’). The control group allows the researchers to see whether the treatment they are testing is any more or less effective than the usual or standard treatment. In a randomized controlled trial, the decision about which group a person joins is random (i.e. based on chance). A computer will decide rather than the researcher or the participant. Randomization ensures that the two groups are as similar as possible, except for the treatment they receive. This is important because it means that the researcher can be sure that any differences between the groups are only due to the treatment.

FIGURE 7: PROCESS FOR PROPOSED TRIAL

Some questions

- Who/where should study information come from?
- What information would you like?
- How long would you need to think/decide?
- Who would you talk to?
- How would you feel about being randomly allocated to a treatment arm?
- Thoughts about either treatment option?

Would you be willing for your child to take part in this trial?
Why?



3.3 Qualitative Study Topic Guide and Tools for Interviews

3.3.1 Risks and benefits prompt cards

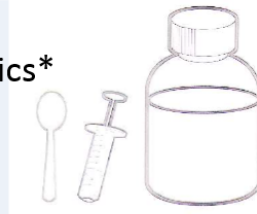
LATER switch to oral antibiotics*
(Longer IV treatment)



<u>Benefits</u>	<u>Risks</u>
• Guaranteed delivery of the antibiotic • Treatment not dependent on child being willing to take medicine (or on remembering doses) • No drug gut absorption problems that sometimes happens in very ill children • Reliable treatment of the infection	• More time in hospital or under community nurse team • Disruption of daily activities • Risk of infection at site of IV line • Risk of displaced or blocked lines • Increased risk of reaction to antibiotic • Increased risk of side effects such as bone marrow suppression

*Switch only made once pain, fever and infection (measured by a blood test) is reduced.

EARLY switch to ORAL antibiotics* (shorter period of IV)



Benefits

- Shortened stay in hospital (or daily visits by community nurse to give intravenous antibiotics)
- Reduced risk of infection at site of intravenous line (where drug is administered)
- Avoids problems with displaced or blocked lines
- Lower risk of reaction to antibiotic and side effects

Risks

- Reduced IV therapy may result in incompletely or inadequately treated bone or joint infection
- Incompletely or inadequately treated infection may rarely lead to chronic infection with destruction of cartilage, bone and growth plate, which can then cause permanent deformity and disability.

* Switch only made once pain, fever and infection (measured by a blood test) is reduced.

3.3.2 Risks and benefits prompt cards 8-12 years

Longer IV (like treatment A)



Advantages

- Drug goes straight into your blood and treatment is reliable
- Don't have to remember to take it, or take medicine that tastes horrible!

Disadvantages

- More time in hospital or visits from nurse at home.
- You can get infections from the tube
- The tube might get blocked or knocked out of place.

Shorter IV (like treatment B)



Benefits

- Less time in hospital, or having nurse visit at home
- Can't get infections, blocked or knocked out of place (like a tube can!)

Risks

- May forget, or not want to take it
- This means the illness might not get completely better -
- Which could mean long term problems or disability.

3.3.3 Topic guide Children 4-7 years

CHILDREN 4-7

(using one 'patient' teddy/toy and one 'doctor' teddy/toy).

First section

This first bit of the interview is all about YOU and OM/SA.

1. What it was like for you when you were poorly with OM/SA? How did it make you feel?
 - What was it like staying in hospital? PROMPT on whether mum/dad etc. could stay and how that was for them.

Second section

This part of the interview is to ask what YOU think about how the doctors found out your illness and explained it to you. I've brought a doctor friend of mine along to help with the questions (show teddy/toy doctor).

2. What did the doctor (*show toy*) do to find out was wrong with you? (like tests or anything?)
 - What was that like? PROMPT for feelings, experiences.
3. How did the doctors (*show toy*) explain the illness?
4. What treatments did the doctor talk about?
 - What did you feel about them?
 - What would have happened without the treatment?

Third section

In this part I would like to ask what it was like to have the different types of treatment for your illness.

5. Did you have to have any operations?
 - What were they for?
 - What was it like to have those/that operation? How did you feel before/after?

The type of medicine that you were given is called antibiotics and the doctors gave it to you in two different ways. First of all you were given the antibiotic medicine into your blood, through a tube which looks like this (show picture of cannula/PICC) and then you were given them to take as a medicine, like this (show picture of oral antibiotic):

6. This teddy (introduce patient teddy) has got the same illness that you had and has to have some antibiotics. Could you tell teddy what it is like to have this type of antibiotics (*put IV by 'patient' teddy*)?
 - What will he like about it and what won't he like? **PROMPT:** hospital stay? Nurse giving IV? Waking up at night?

7. And how about this type of antibiotic (give 'patient' teddy the antibiotic bottle)?
 - What was good and bad about this one? **PROMPT:** taste, remembering to take it.
8. Why did the doctors give you (and teddy!) this first (*show IV prop/picture*) and then this? (*show oral prop/picture*)
9. Which way treats the illness best?
 - **PROBE** which one/why? What makes you say that?
10. When they were helping you, what did the doctors and nurses do well?
11. What would you like done differently or better?
12. Do you feel completely better from OM/SA now? (Yes/No) Why?
13. Do mum and dad (relevant adult) think you are completely better now? Why?

3.3.4 Topic guide Children 8-12 years

CHILDREN 8-12

First section

This first bit of the interview is all about YOU and OM/SA.

1. What it was like for you when you were poorly with OM/SA? How did it make you feel?
 - What was it like staying in hospital? PROMPT on whether mum/dad etc. could stay and what that was like for them.

Second section

This part of the interview is to ask what YOU think about how the doctors found out your illness and explained it to you.

2. What did the doctors do to find out was wrong with you? (like tests or anything?)
What was that like? PROMPT for feelings, experiences.
3. How did the doctors explain the illness?
 - What was it like to learn you had this illness?
4. What treatments did the doctor talk about? (Did they talk to you as well as your mum and dad?)
 - What did you feel about them?
 - What would have happened without the treatment?

Third section

In this part I would like to ask you what it was like to have the different types of treatment for your illness.

5. Did you have to have any operations?
 - What were they for?
 - What was it like to have those/those operation? How did you feel before/after?

The type of medicine that you were given is called antibiotics and doctors gave it to you in two different ways. First of all you were given the antibiotic medicine straight into your bloodstream, through a tube which looks like this ([picture of cannula/PICC](#)), and then you were given them as a liquid like this ([show picture of oral antibiotic](#)):

6. What was it like having to have [this](#) type of antibiotic (show picture/prop of [IV antibiotic](#))
 - Can you say what was good about it and what wasn't good about it? **PROMPT:** hospital stay? Nurse giving IV? Waking at night?
7. And how about this type of antibiotic (show picture/prop of [oral antibiotic](#))?

- What was good and bad about this one? **PROMPT:** taste, remembering to take it, waking at night?
8. Why did the doctors give you this first (show IV picture) and then this? (show oral picture)
9. Which way do you think treats the illness best?
- PROBE which one/why? What makes you say that?
10. Do you feel completely better from OM/SA now? (Yes/No) Why?
11. Do mum and dad (relevant adult) think you are completely better now? Why?

Fourth section

In this final section, I would like to ask you what you think about an idea that doctors have to compare two different types of treatments for this kind of illness, in a kind of test. This test would help doctors to find out the very best treatment for children who have bone or joint infections. As you have had already had OM/SA your opinions would be very helpful to us.

Here is a picture which explains what would happen if a family and a child are asked if they want to take part in this kind of test. SHOW PROCESS DESIGN FOR RCT 8-12 YRS and talk through it.

First of all the test I is explained to the child and their family. Then they have time to think whether they want to take part or not. If they don't want to take part that is absolutely fine. If they do want to take part, then a computer (that doesn't have any information about the child) decides WHICH treatment the child would receive. The main difference in this test is to do with how long the child would stay on IV antibiotics, that is the antibiotics given through a tube. You can see the different options in the picture.

12. Do you have any questions or comments about the test?

Let's have a look at the questions on this sheet together and see if you can answer them. Allow child to read (or read out depending on age) the questions on the sheet Process Design for RCT 8-12 years. Go through each in turn, seeking responses.

- What information would you need about the test?
- Who should give you this information?
- Who would you talk to about it?
- How would you feel about a computer deciding which treatment?
- Which treatment is better?
- Would you like to take part in this test? Why

13. Just to finish, here is a card that shows the advantages and disadvantages of staying on IV antibiotics for a long time. SHOW CARD 8-12 years. Allow child to read, or read to them.
- Having seen those, would you like to take part in this test ? *Probe reasons for any changes in/maintenance of original decision. (Explain/reassure afterwards, as necessary, that this is only a theoretical question. Not actually requesting participation.)*

3.3.5 Topic guide Adults Version 7 15/01/2015

Adult (and 13+) Interview guide

1. I would like to understand what it was like for you when your child first got ill with SA/OM.
Could you tell me about the condition and how it affected them?
2. And please could you tell me how the condition was *diagnosed*?
3. What did you understand about:
 - a. longer term impacts of the condition?
 - b. possible complications of the condition?
 - c. the treatment options available?
 - d. and how did you feel about these?
4. Could you talk me through the different treatments that your child received (including any operations and antibiotics?) What was the order in which those treatments were given?
PROMPTS as relevant
 - a. Operation – number/ purpose?
 - b. Antibiotic – how was this administered to your child IV (drip, driver etc.)/Oral?
 - c. Location of treatment (hospital/home)

SCRIBE ON TIMELINE

"I would like to ask you in more detail about the different methods for giving antibiotics, that is intravenously (straight into the blood stream), and orally – shown on the timeline here."

5. Could you tell me what it was like for you and your child, when the IV antibiotics were being administered, for (time indicated on timeline) weeks? (*e.g. ease or discomfort of treatment, experience of being in hospital etc.*)
Then (if not covered above) –
 - a. What did you understand about the clinical reasons for, or the advantages of, the use of IV antibiotics?
 - b. What were the advantages for you and your child?
 - c. What did you understand about the clinical disadvantages of using IV antibiotics?
 - d. What were the disadvantages for you and your child?
6. And could you tell me now about your child's treatment with oral antibiotics? What was this part of the treatment like for you and your child? (*e.g. release from hospital, adherence etc*)
Then (if not covered above)
 - a. What did you understand about the clinical reasons for, or the advantages of, oral antibiotics?
 - b. What were the advantages for you and your child?

V7:15/10/14

Ease of use

1

- c. What did you understand about the clinical disadvantages of using oral antibiotics? What were the disadvantages for you and your child?
- 7. Thinking about the point when the switch was made from intravenous antibiotics to oral antibiotics – here (indicate on timeline). What was the reason for the switch being made for at that point?
 - a. How (and by whom?) was the decision about the switch made? Did you and your child contribute to that decision?
 - b. Were you happy with the decision to switch at that point? Why?
- 8. Looking at the timeline, what do you think about the length of the treatment period overall?
 - a. Could it be shortened and what risks/advantages might this carry?
- 9. We've spoken about how you knew your child was becoming unwell. Could you tell me about any other problems/symptoms that your child experienced during the course of their illness and treatment? WHEN they happened? What did you think was causing these symptoms?
- 10. Could you tell me now about signs that showed you your child was getting better? What did you think was bringing about these improvements?
- 11. We've spoken about how your child was feeling during the course of their illness. I'd like to ask you about your feelings – could you run me through how you were feeling from when you noticed your child was getting ill, through treatment and finally to recovery?
- 12. How successful do you feel your child's treatment has been overall and why? (*Prompt side effects/complications*)
 - a. What are the factors that are most important to you in judging whether treatment has been successful? (PROMPTS: recovery? Time in hospital? Pain? Ease of giving treatment?)

"In this final section, I would like to ask your views about a possible clinical trial to determine the best course, combination and duration of antibiotics, for this type of infection. For this type of trial, doctors would need to recruit children with a bone/joint infection to take part. Would you mind having a read through this brief background information, and then I will ask you a few questions about it."

SHOW PROMPT BACKGROUND TO TRIAL SHEET AND TRIAL PROCESS DIAGRAM (SEE SEPARATE ATTACHMENTS)

V7:15/10/14

Ease of use

2

13. Would you mind taking a few minutes to look at this diagram? In the middle it shows the basic process that families would follow from being invited to take part in a trial through to their decision to participate or not. I would like to hear your comments about the various aspects of this process.

Then (as necessary – also referring to questions shown on RCT process sheet)

- a. Is there anything that you don't understand?
- b. Initial reactions?

WORK THROUGH QUESTIONS ON SHEET TOGETHER

14. I'd like to ask you to think back to when your child had first been diagnosed with this condition. How would you would have felt if your doctor or nurse approached you at this point to discuss a research study?
- a. What factors would affect your decision making?
 - b. What advice would you give to a friend with a child in the same position?
15. We were talking earlier about the advantages and disadvantages of IV and oral antibiotics. Just to finish, this card shows the 'clinical' advantages and disadvantages of an early switch to oral antibiotics in the treatment of bone and joint infections. SHOW CARD.
- a. Which of these (if any) particularly strike you? Which ones would be important to you and your family?
 - b. Having been made aware of this information, would you be willing for your child to take part in this trial? *Probe reasons for any changes in/maintenance of original decision. (Explain/reassure afterwards, as necessary, that this is only a theoretical question. Not actually requesting participation.)*

V7:15/10/14

Ease of use

3

3.4 Patient information sheets

3.4.1 Patient information sheet Parents



THE DINOSAUR STUDY (CHILDREN'S BONE AND JOINT INFECTION STUDY)

Parent Information Sheet

Qualitative Sub-study

Version 1.1 Dated 27-08-2014

www.dinosaur-study.org.uk

Thank you very much for participating in the DINOSAUR microbiology sub-study.

We would now like to invite your child to take part in our qualitative research study. Before you decide we would like you to understand why the research is being done and what it would involve for you and your child. One of our team will go through this information sheet with you and answer any questions you may have.

Why is this study needed?

As you may know, the best duration of antibiotics for bone and joint infections is not known, and we would like to find out whether shortened courses of antibiotics are safe and effective. The DINOSAUR study will give us some information about this, as many hospitals are already giving shorter courses of intravenous antibiotics, and using oral antibiotics when there is improvement in the child's condition. This may have been the case with your child's treatment.

This part of the study is to find out about parents' and children's understanding of bone and joint infection. We would like to find out more about your personal experiences and about your understanding about the risks and benefits of different types of treatment. We would also like to know about your experience and understanding of research.

Why has our family been chosen?

You were approached because you participated in the DINOSAUR microbiology sub-study, providing small amounts from your child's existing samples for extra testing. At the time of consent you agreed to be approached for this qualitative study. If you do not want to participate, please let us know and we will not contact you again.

What will happen if we join the study?

A questionnaire has been prepared by a qualitative researcher. This will be used by the researcher to speak to you and your child about their experiences and understanding of bone and joint infections, and of research. The discussion between you and the researcher will take approximately

Contact: Dr Priya Sukhtankar, Mailpoint 218, Wellcome Trust, University of Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD
Email: dinosaur.study@liverpool.ac.uk

between 30 minutes and two hours (depending on how much you would like to discuss) and can be done at a time and place that is convenient to you and your child.

Consent:

If you and your child are happy to take part, you will be asked to sign a consent form on behalf of your child before they take part. You will get a copy of the signed consent form and information sheet to keep. Your child will also be given information about the study in a format appropriate to their age group.

Are there any risks or benefits to my child if they join the study?

It is unlikely that the study will help your child but the information we get might help treat children with bone and joint infections in the future.

Will anyone else know my child is taking part in this study?

Yes. Only people working on the study or working to ensure the study is run correctly will have access to the data. All information will be made anonymous before publication. All information collected about your child during this study will be confidential and will be handled, stored and destroyed in accordance with the Data Protection Act 1998.

What if there is a problem?

There are no risks to your child's health by participating in this study. If you or your child has any concerns about any aspect of this study, you should speak with the qualitative researcher, or contact the DINOSAUR study team via the DINOSAUR website (www.dinosaur-study.org.uk). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Who is doing this study?

The study is funded by the Department of Health (National Institute of Health Research Health Technology Assessment Programme). It is being run in the hospital where your child is being treated, and is being organised by The University of Southampton, University Hospital Southampton NHS Foundation Trust and the University of Liverpool. This research has been approved by a research ethics committee, who are happy that the study is being conducted in an appropriate manner. This study is also supported by the Medicines for Children Research Network (www.mcrn.ac.uk).

**THANK YOU FOR READING THIS INFORMATION SHEET.
WE HOPE YOU HAVE FOUND THIS SHEET HELPFUL**

Contact: Dr Priya Sukhtankar, Mailpoint 218, Wellcome Trust, University of Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD
Email: dinosaur.study@liverpool.ac.uk

3.4.2 Patient information sheet Child

Participant Information Sheet Children V1.1 27-08-2014 DINOSAUR Qualitative Sub Study



THE DINOSAUR STUDY (CHILDREN'S BONE AND JOINT INFECTION STUDY)

Child Information Sheet

Qualitative Sub-study

Version 1.1 Dated 27-08-2014

www.dinosaur-study.org.uk

Thank you very much for participating in the DINOSAUR microbiology sub-study.

What is a qualitative study? Why is this being done?

Research is what you do when you want to learn about something or find out something new. Qualitative research means that we ask people who have experience of being sick and then being treated about what it was like, and what they have learned from it so that we can learn from it too.

Why have I been chosen?

You are being asked to take part in this study because you had a bone or joint infection and were treated in hospital. You very kindly helped us by taking part in another study looking for germs in your blood and throat. We would like to know what all of this was like for you.

Do I have to help?

No, if you and your mum and dad don't want to do this then you don't have to.

What will happen to me if I say yes?

If you are able you will be asked to write your name on a form. This is to say that you understand the study and what will happen. You will be given your own form to keep, as well as this leaflet. This is all you need to do.

A person who knows all about qualitative research will come to see you and your mum and dad to talk about what happened when you



Participant Information Sheet Children V1.1 27-08-2014 DINOSAUR Qualitative Sub Study

were in hospital and what you understand about the treatment and the research. They will ask you some questions about this. It will take about half an hour, but maybe longer if you and your parents have more to say.

Will anything good happen to me if I take part?

No, we will be very grateful for your time, and what you tell us may help other children who have bone and joint infections in future.

Will anything bad happen to me if I take part?

No, this is not a test.

What do I have to do now?

If you have any questions you can ask the qualitative researcher, or ask your mum and dad to explain this leaflet to you. If you say yes then all you have to do is meet the qualitative researcher at a time and place that is easy for you, and spend half an hour talking to her/him.

3.5 Consent forms

3.5.1 Parent consent form



CONSENT FORM V1.1 10-09-2014 QUALITATIVE STUDY

THE DINOSAUR STUDY
(CHILDREN'S BONE AND JOINT INFECTION STUDY)

Qualitative Sub-study

Parent Consent Form Version 1.0 07-07-2014

www.dinosaur-study.org.uk

	Please initial box
1. I confirm that I have read and understand the information sheet dated 27-08-2014 (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my or my child's care or legal rights being affected.	
3. I understand that data collected during the study may be looked at by responsible individuals from the research team, regulatory authorities, sponsor or from the NHS Trust, where it is relevant to me and my child taking part in this study.	
4. I understand that qualitative data will be collected for this study and may be used to develop new research and that data protection regulations will be observed.	
5. I agree for my consent form and my child's details, which will include my child's name, to be passed to the Medicines for Children Research Network Clinical Trials Unit for the administration of the study.	
6. I give permission for a qualitative researcher to interview me and my child.	
7. I agree to medical personnel, responsible for my child's welfare, being informed of our participation in the study.	
8. I agree to take part in the above study.	

Name of Parent / Guardian

Signature

Date

Researcher

Signature

Date

When completed, 1 (original) to be kept in medical notes, 1 for parent/guardian, 1 for researcher site file; 1 for the MCRN CTU, University of Liverpool

3.5.2 Assent form

ASSENT FORM V1.1 10-09-2014 QUALITATIVE STUDY

THE DINOSAUR STUDY
(CHILDREN'S BONE AND JOINT INFECTION STUDY)
Qualitative Sub-study
Children's Assent Form Version 1.1 10-09-2014
www.dinosaur-study.org.uk

	Please initial box
1. I have read and understand the information sheet dated 28-08-2014 (version 1.1) for this study. I had time to think about it and to ask questions	
2. I understand that it is up to me whether or not I take part and that I can change my mind at any time.	
3. I understand that I will be interviewed, and a researcher will ask me questions about having a bone and joint infection.	
4. I understand that the information from my interview will be used to learn about bone and joint infections in children, and that other researchers will be able to see this information.	
5. I agree to take part in the DINOSAUR Qualitative study.	

Name of Child_____
Signature_____
Date_____
Researcher_____
Signature_____
Date

When completed, 1 (original) to be kept in medical notes, 1 for parent/guardian, 1 for researcher site file; 1 for the MCRN CTU, University of Liverpool

Appendix 4: Core Outcome Literature Review

4.1 Search Strategy Used to Identify Trials Investigating Duration of Antibiotics in Paediatric Bone and Joint Infection

Search was executed using Medline and Embase databases. All publications from 1946-present were included in the search.

	Search Term	Number of Hits
1	osteomyelitis.mp.	39394
2	bone infection.mp.	3979
3	osteitis.mp.	9113
4	septic arthritis.mp.	7340
5	bacterial arthritis.mp	6369
6	joint infection.mp	2450
7	Staphylococc*.mp.	322123
8	Streptococc*.mp.	230550
9	Skeletal infection.mp	109
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	565232
11	child\$.mp	2991039
12	paediatric or pediatric.mp.	432403
13	neonat\$.mp	367776
14	infan\$.mp.	1244482
15	(baby or babies).mp.	119622
16	11 or 12 or 13 or 14 or 15	4882434
17	10 and 16	98071
18	antibiotic.mp.	549340
19	treatment.mp.	6513851
20	18 or 19	6866563
21	duration.mp.	914091
22	course.mp.	1010339
23	length.mp	831145
24	shortened.mp.	56581
25	21 or 22 or 23 or 24	2641076
26	17 and 25	7342
27	remove duplicates from 26	1321

Appendix 5: Clinician Survey – Delphi Study documents

5.1 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 4

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 al 2002 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 4) 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 4).

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 of 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 be 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 sent 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 appendix).

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 1 to 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 included. 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.

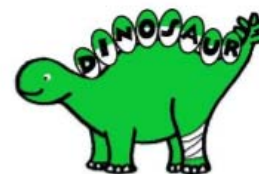
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5.2 Questionnaire Round 1 and 2

Last update: 20150408 CM
Version 1.0



DINOSAUR Consensus Meeting

27th April 2015

Delphi Questionnaire Scoring Sheet

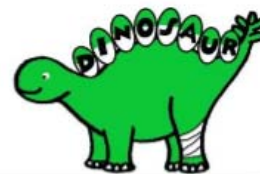
Please answer each question by using the scoring system provided. If you feel you do not have the clinical expertise to answer a particular question please select 'unable to score'.

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.

Last update: 20150408 CM
Version 1.0



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											

Last update: 20150408 CM
Version 1.0



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)											

Last update: 20150408 CM
Version 1.0



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											
<i>Clostridium difficile</i> 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											

Last update: 20150408 CM
Version 1.0



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):

5.3 Consensus meeting agenda



Duration of INtravenous antibiOtic therapy for Septic Arthritis or acUte osteomyelitis in a paediatRic population

Monday 27th April 2015 09:30 AM

VENUE: George Fox Room, 173-177 Euston Road, London, NW1 2BJ.

Contact for the day: Prof Saul Faust- 07889 541122, Abigail Bennett- 07931 106144

Agenda

09:30 Arrival and registration

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

10:30 How feasible is a future trial?

- o Results from service evaluation
- o Results from qualitative interviews
- o 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?

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

12:45 Lunch

13:15 What are the core outcomes?

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

14:45 Summary

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

16:00 Meeting close

Appendix 6: Tables of the consensus meeting

6.1 Criteria for switching

TABLE 83: BREAKDOWN OF INDIVIDUAL SWITCH CRITERIA DISCUSSIONS AND SCORES

Switch Criteria	Discussion	Number voting
	<i>What criteria are important to you when deciding when or whether to switch from intravenous to oral antibiotic therapy?</i>	17

TABLE 84: CRP <20

Switch Criterion	<u>CRP (non-specific blood test done at diagnosis and for monitoring) <20</u>																						
Number of participants scoring 1-9	13																						
Number of participants unable to score	4																						
Notes																							
Discussed and voted. The room felt that this is difficult to assess as CRP results would be more important in a patient with a very high baseline score than patients with a lower baseline score. However it was pointed out that it would be very unusual not to include CRP. Unanimous decision that CRP should be included but that the criteria needed clarification and re-wording. Agreement to re-word and re-circulate.																							
Results of scoring																							
<table border="1"> <caption>Data for Table 84 Results of scoring</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>6.7%</td> </tr> <tr> <td>2</td> <td>0.8%</td> </tr> <tr> <td>3</td> <td>6.7%</td> </tr> <tr> <td>4</td> <td>12.5%</td> </tr> <tr> <td>5</td> <td>12.5%</td> </tr> <tr> <td>6</td> <td>6.7%</td> </tr> <tr> <td>7</td> <td>24.1%</td> </tr> <tr> <td>8</td> <td>0.8%</td> </tr> <tr> <td>9. Very Important</td> <td>12.5%</td> </tr> <tr> <td>Unable to score</td> <td>24.1%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	6.7%	2	0.8%	3	6.7%	4	12.5%	5	12.5%	6	6.7%	7	24.1%	8	0.8%	9. Very Important	12.5%	Unable to score	24.1%
Score	Percentage Scoring																						
1. Not important	6.7%																						
2	0.8%																						
3	6.7%																						
4	12.5%																						
5	12.5%																						
6	6.7%																						
7	24.1%																						
8	0.8%																						
9. Very Important	12.5%																						
Unable to score	24.1%																						

TABLE 85: CRP LESS THAN ONE THIRD OF THE PRESENTING VALUE

Switch Criterion	<u>CRP less than one third of the presenting value</u>
Number of participants scoring 1-9	13
Number of participants unable to score	4
Notes	
No discussion, voting only.	
Results of scoring	

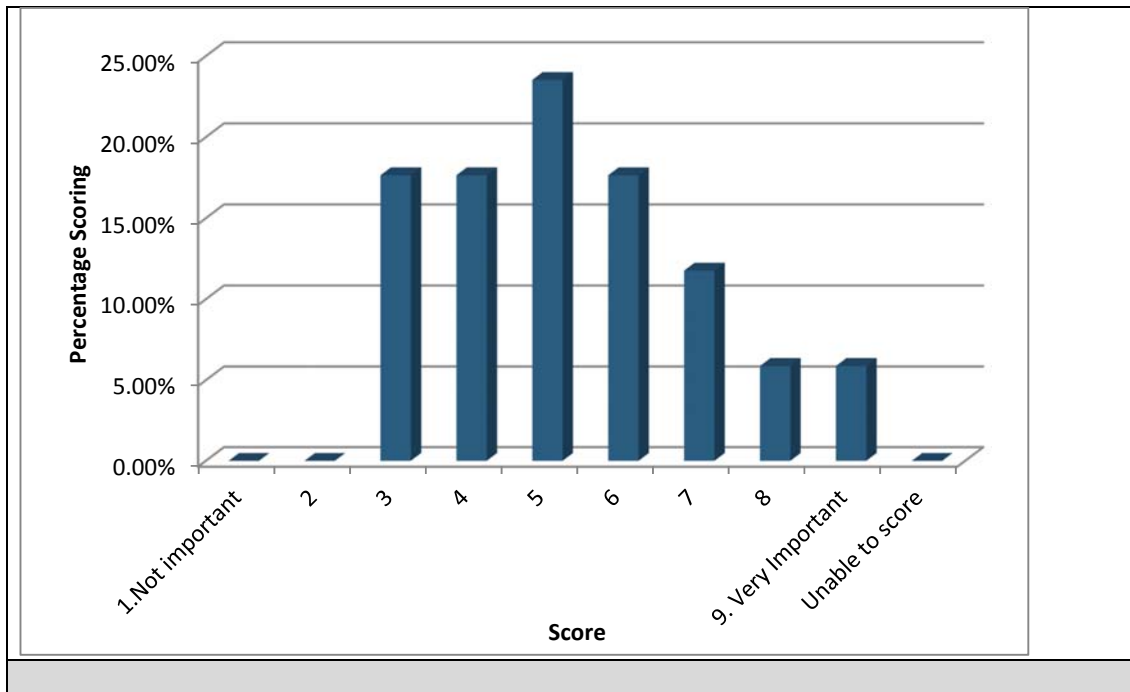


TABLE 86: CRP LESS THAN TWO THIRDS OF THE PRESENTING VALUE

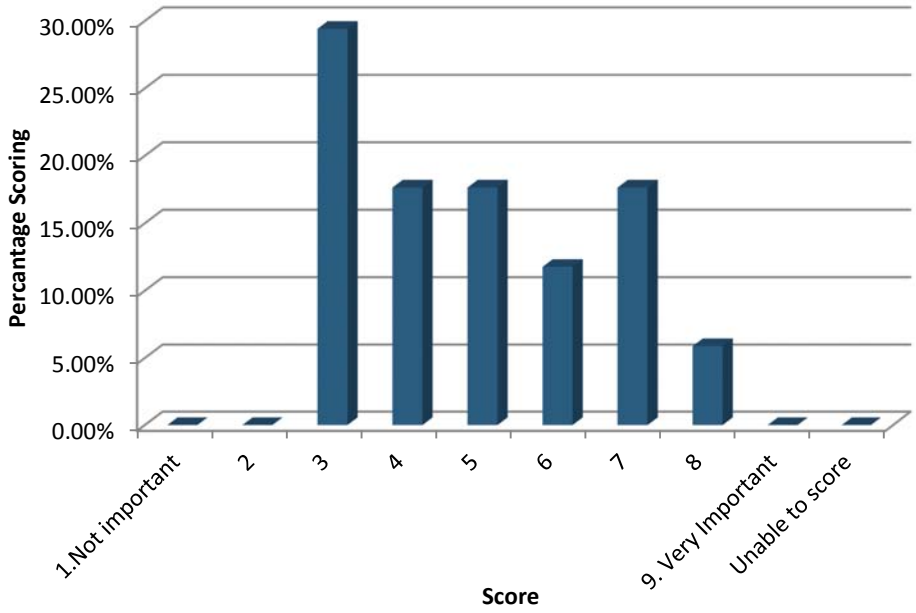
Switch Criterion	<u>CRP less than two thirds of the presenting value</u>																						
Number of participants scoring 1-9	17																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only.																							
Results of scoring																							
 <table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr><td>1. Not important</td><td>0.5%</td></tr> <tr><td>2</td><td>0.5%</td></tr> <tr><td>3</td><td>30.0%</td></tr> <tr><td>4</td><td>18.5%</td></tr> <tr><td>5</td><td>18.5%</td></tr> <tr><td>6</td><td>12.5%</td></tr> <tr><td>7</td><td>18.5%</td></tr> <tr><td>8</td><td>6.5%</td></tr> <tr><td>9. Very Important</td><td>0.5%</td></tr> <tr><td>Unable to score</td><td>0.5%</td></tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.5%	2	0.5%	3	30.0%	4	18.5%	5	18.5%	6	12.5%	7	18.5%	8	6.5%	9. Very Important	0.5%	Unable to score	0.5%
Score	Percentage Scoring																						
1. Not important	0.5%																						
2	0.5%																						
3	30.0%																						
4	18.5%																						
5	18.5%																						
6	12.5%																						
7	18.5%																						
8	6.5%																						
9. Very Important	0.5%																						
Unable to score	0.5%																						

TABLE 87: ESR <20

Switch Criterion	<u>ESR <20</u>																						
Number of participants scoring 1-9	17																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted.																							
There was a brief discussion regarding the relative merits of ESR over other tests.																							
Results of scoring																							
<table border="1"> <caption>Results of scoring data</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>24.0%</td> </tr> <tr> <td>2</td> <td>18.0%</td> </tr> <tr> <td>3</td> <td>6.0%</td> </tr> <tr> <td>4</td> <td>18.0%</td> </tr> <tr> <td>5</td> <td>6.0%</td> </tr> <tr> <td>6</td> <td>18.0%</td> </tr> <tr> <td>7</td> <td>0.5%</td> </tr> <tr> <td>8</td> <td>6.0%</td> </tr> <tr> <td>9. Very Important</td> <td>6.0%</td> </tr> <tr> <td>Unable to score</td> <td>0.5%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	24.0%	2	18.0%	3	6.0%	4	18.0%	5	6.0%	6	18.0%	7	0.5%	8	6.0%	9. Very Important	6.0%	Unable to score	0.5%
Score	Percentage Scoring																						
1. Not important	24.0%																						
2	18.0%																						
3	6.0%																						
4	18.0%																						
5	6.0%																						
6	18.0%																						
7	0.5%																						
8	6.0%																						
9. Very Important	6.0%																						
Unable to score	0.5%																						

TABLE 88: RESOLUTION OF FEVER FOR 48H OR MORE

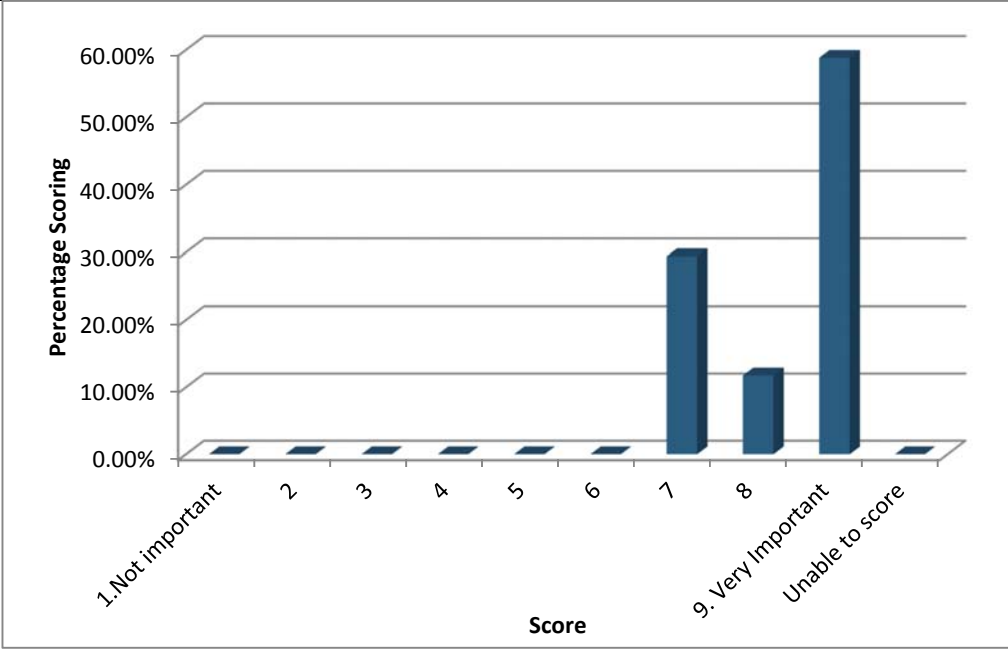
Switch Criterion	<u>Resolution of fever for 48h or more (body temperature normal)</u>																				
Number of participants scoring 1-9	17																				
Number of participants unable to score	0																				
Notes																					
No discussion, voting only.																					
Results of scoring																					
 <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr><td>1</td><td>31.00%</td></tr> <tr><td>2</td><td>0.00%</td></tr> <tr><td>3</td><td>0.00%</td></tr> <tr><td>4</td><td>0.00%</td></tr> <tr><td>5</td><td>0.00%</td></tr> <tr><td>6</td><td>0.00%</td></tr> <tr><td>7</td><td>0.00%</td></tr> <tr><td>8</td><td>13.00%</td></tr> <tr><td>9</td><td>60.00%</td></tr> </tbody> </table>		Score	Percentage Scoring	1	31.00%	2	0.00%	3	0.00%	4	0.00%	5	0.00%	6	0.00%	7	0.00%	8	13.00%	9	60.00%
Score	Percentage Scoring																				
1	31.00%																				
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5	0.00%																				
6	0.00%																				
7	0.00%																				
8	13.00%																				
9	60.00%																				

TABLE 89: WEIGHT BEARING / RETURN OF FUNCTION TO LIMB

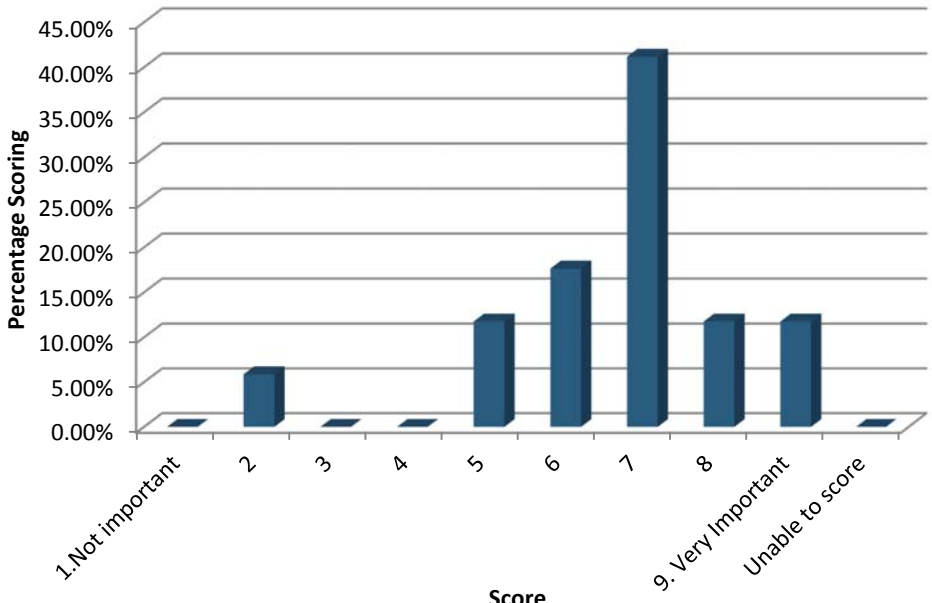
Switch Criterion	<u>Weight bearing / return of function to limb</u>																						
Number of participants scoring 1-9	17																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. There was some participant confusion over whether this referred to weight bearing before or after surgery. SF confirmed that this should be interpreted as being non-surgical cases. All were asked to score based on a child who has not had surgery and should not be interpreted as lack of weight bearing imposed by the clinician.																							
Results of scoring																							
 <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~1.00%</td> </tr> <tr> <td>2</td> <td>~7.00%</td> </tr> <tr> <td>3</td> <td>~1.00%</td> </tr> <tr> <td>4</td> <td>~1.00%</td> </tr> <tr> <td>5</td> <td>~13.00%</td> </tr> <tr> <td>6</td> <td>~19.00%</td> </tr> <tr> <td>7</td> <td>~42.00%</td> </tr> <tr> <td>8</td> <td>~13.00%</td> </tr> <tr> <td>9. Very Important</td> <td>~13.00%</td> </tr> <tr> <td>Unable to score</td> <td>~1.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~1.00%	2	~7.00%	3	~1.00%	4	~1.00%	5	~13.00%	6	~19.00%	7	~42.00%	8	~13.00%	9. Very Important	~13.00%	Unable to score	~1.00%
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5	~13.00%																						
6	~19.00%																						
7	~42.00%																						
8	~13.00%																						
9. Very Important	~13.00%																						
Unable to score	~1.00%																						

TABLE 90: RESOLUTION OF PAIN

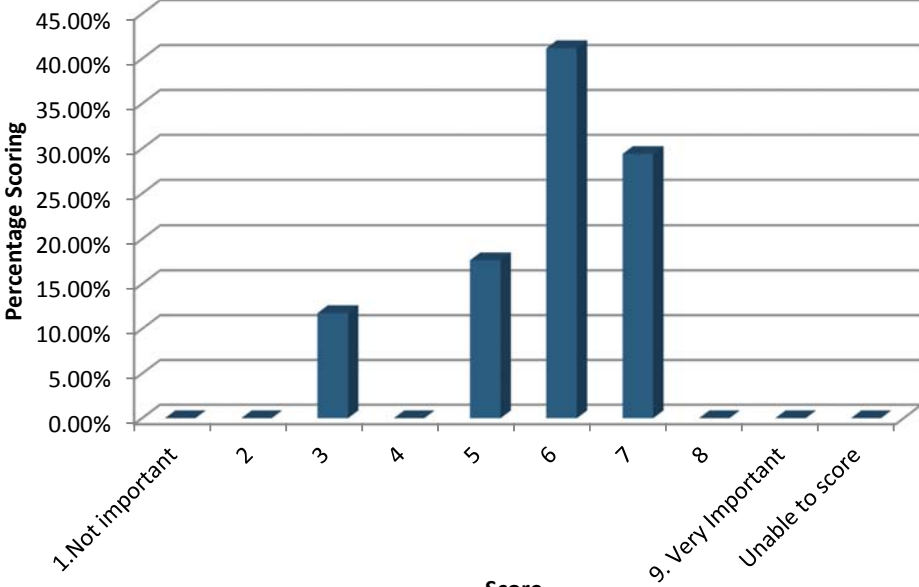
Switch Criterion	<u>Resolution of pain (pain completely better)</u>																						
Number of participants scoring 1-9	17																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. As above, SF confirmed that when scoring participant should exclude pain following surgery.																							
Results of scoring																							
 <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr><td>1. Not important</td><td>1.00%</td></tr> <tr><td>2</td><td>1.00%</td></tr> <tr><td>3</td><td>12.50%</td></tr> <tr><td>4</td><td>1.00%</td></tr> <tr><td>5</td><td>18.75%</td></tr> <tr><td>6</td><td>42.50%</td></tr> <tr><td>7</td><td>31.25%</td></tr> <tr><td>8</td><td>1.00%</td></tr> <tr><td>9. Very Important</td><td>1.00%</td></tr> <tr><td>Unable to score</td><td>1.00%</td></tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	1.00%	2	1.00%	3	12.50%	4	1.00%	5	18.75%	6	42.50%	7	31.25%	8	1.00%	9. Very Important	1.00%	Unable to score	1.00%
Score	Percentage Scoring																						
1. Not important	1.00%																						
2	1.00%																						
3	12.50%																						
4	1.00%																						
5	18.75%																						
6	42.50%																						
7	31.25%																						
8	1.00%																						
9. Very Important	1.00%																						
Unable to score	1.00%																						

TABLE 91: TOLERATING ORAL INPUT

Switch Criterion	<u>Tolerating oral input (can eat and drink)</u>																						
Number of participants scoring 1-9	17																						
Number of participants unable to score	0																						
Notes																							
There was some misunderstanding of tolerating oral input. A participant was anxious responses could have been made on the basis of children being able to take oral antibiotics only rather than the ability to eat and drink. It was also suggested that if the patient had a feeding tube they could then also tolerate oral input.																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~2.00%</td> </tr> <tr> <td>2</td> <td>~2.00%</td> </tr> <tr> <td>3</td> <td>~2.00%</td> </tr> <tr> <td>4</td> <td>~2.00%</td> </tr> <tr> <td>5</td> <td>~2.00%</td> </tr> <tr> <td>6</td> <td>~2.00%</td> </tr> <tr> <td>7</td> <td>~15.00%</td> </tr> <tr> <td>8</td> <td>~8.00%</td> </tr> <tr> <td>9. Very Important</td> <td>~85.00%</td> </tr> <tr> <td>Unable to score</td> <td>~2.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~2.00%	2	~2.00%	3	~2.00%	4	~2.00%	5	~2.00%	6	~2.00%	7	~15.00%	8	~8.00%	9. Very Important	~85.00%	Unable to score	~2.00%
Score	Percentage Scoring																						
1. Not important	~2.00%																						
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5	~2.00%																						
6	~2.00%																						
7	~15.00%																						
8	~8.00%																						
9. Very Important	~85.00%																						
Unable to score	~2.00%																						

TABLE 92: PARENTAL OPINION REGARDING IMPROVEMENT OR WORSENING OF CONDITION

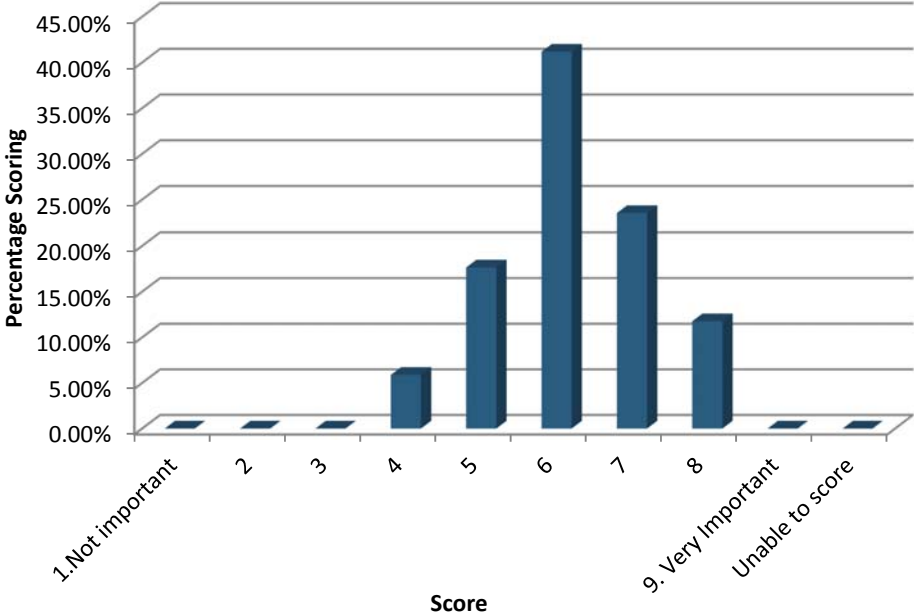
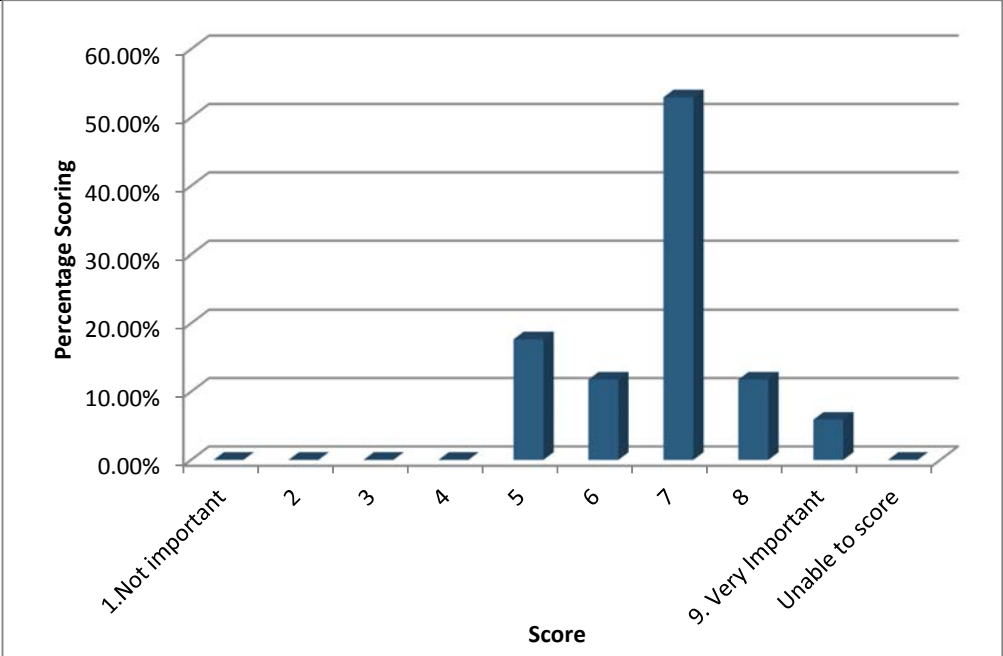
Switch Criterion	<u>Parental opinion regarding improvement or worsening of condition</u>																						
Number of participants scoring 1-9	17																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. At this stage queries were raised about the scoring categories and definition of consensus. These were reiterated to the group.																							
Results of scoring																							
 <table border="1"> <caption>Data for Parental Opinion Bar Chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~1.00%</td> </tr> <tr> <td>2</td> <td>~1.00%</td> </tr> <tr> <td>3</td> <td>~1.00%</td> </tr> <tr> <td>4</td> <td>~7.00%</td> </tr> <tr> <td>5</td> <td>~19.00%</td> </tr> <tr> <td>6</td> <td>~42.00%</td> </tr> <tr> <td>7</td> <td>~25.00%</td> </tr> <tr> <td>8</td> <td>~13.00%</td> </tr> <tr> <td>9. Very Important</td> <td>~1.00%</td> </tr> <tr> <td>Unable to score</td> <td>~1.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~1.00%	2	~1.00%	3	~1.00%	4	~7.00%	5	~19.00%	6	~42.00%	7	~25.00%	8	~13.00%	9. Very Important	~1.00%	Unable to score	~1.00%
Score	Percentage Scoring																						
1. Not important	~1.00%																						
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5	~19.00%																						
6	~42.00%																						
7	~25.00%																						
8	~13.00%																						
9. Very Important	~1.00%																						
Unable to score	~1.00%																						

TABLE 93: PAIN IMPROVEMENT

Switch Criterion	<u>Pain improvement (rather than resolution)</u>																						
Number of participants scoring 1-9	17																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only.																							
Results of scoring																							
 <table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>1.00%</td> </tr> <tr> <td>2</td> <td>1.00%</td> </tr> <tr> <td>3</td> <td>1.00%</td> </tr> <tr> <td>4</td> <td>1.00%</td> </tr> <tr> <td>5</td> <td>19.00%</td> </tr> <tr> <td>6</td> <td>13.00%</td> </tr> <tr> <td>7</td> <td>54.00%</td> </tr> <tr> <td>8</td> <td>13.00%</td> </tr> <tr> <td>9. Very Important</td> <td>7.00%</td> </tr> <tr> <td>Unable to score</td> <td>1.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	1.00%	2	1.00%	3	1.00%	4	1.00%	5	19.00%	6	13.00%	7	54.00%	8	13.00%	9. Very Important	7.00%	Unable to score	1.00%
Score	Percentage Scoring																						
1. Not important	1.00%																						
2	1.00%																						
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5	19.00%																						
6	13.00%																						
7	54.00%																						
8	13.00%																						
9. Very Important	7.00%																						
Unable to score	1.00%																						

6.2 Outcomes

TABLE 94: BREAKDOWN OF INDIVIDUAL OUTCOME DISCUSSIONS AND SCORES

Outcomes	Discussion	Number voting
<i>What outcomes should be measured to assess whether treatment has been effective?</i>		16

TABLE 95: NEED FOR NON-DIAGNOSTIC SURGICAL PROCEDURE

Outcome Name	<u>Need for non-diagnostic surgical procedure (surgery for treatment of the infection itself e.g. decompression, debridement)</u>																						
Number of participants scoring 1-9	15																						
Number of participants unable to score	1																						
Notes																							
Discussed and voted. Discussion whether this would differ between cases of OM and SA.																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>6.7%</td> </tr> <tr> <td>2</td> <td>6.7%</td> </tr> <tr> <td>3</td> <td>13.3%</td> </tr> <tr> <td>4</td> <td>13.3%</td> </tr> <tr> <td>5</td> <td>19.3%</td> </tr> <tr> <td>6</td> <td>13.3%</td> </tr> <tr> <td>7</td> <td>19.3%</td> </tr> <tr> <td>8</td> <td>0.7%</td> </tr> <tr> <td>9. Very Important</td> <td>6.7%</td> </tr> <tr> <td>Unable to score</td> <td>6.7%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	6.7%	2	6.7%	3	13.3%	4	13.3%	5	19.3%	6	13.3%	7	19.3%	8	0.7%	9. Very Important	6.7%	Unable to score	6.7%
Score	Percentage Scoring																						
1. Not important	6.7%																						
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3	13.3%																						
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6	13.3%																						
7	19.3%																						
8	0.7%																						
9. Very Important	6.7%																						
Unable to score	6.7%																						

TABLE 96: RE-HOSPITALISATION OR RECURRENCE OF SYMPTOMS WHILE ON ORAL ANTIBIOTICS

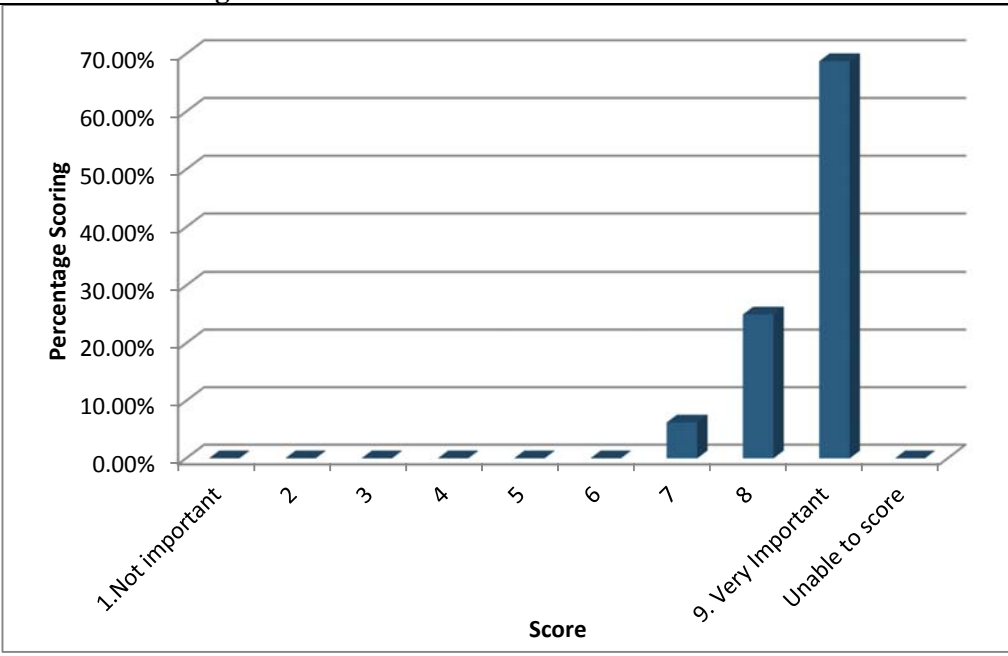
Outcome Name	<u>Re-hospitalisation or recurrence of symptoms while on oral (by mouth) antibiotics</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only.																							
Results of scoring																							
 <table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr><td>1</td><td>1.25%</td></tr> <tr><td>2</td><td>1.25%</td></tr> <tr><td>3</td><td>1.25%</td></tr> <tr><td>4</td><td>1.25%</td></tr> <tr><td>5</td><td>1.25%</td></tr> <tr><td>6</td><td>1.25%</td></tr> <tr><td>7</td><td>1.25%</td></tr> <tr><td>8</td><td>26.25%</td></tr> <tr><td>9</td><td>70.00%</td></tr> <tr><td>Unable to score</td><td>1.25%</td></tr> </tbody> </table>		Score	Percentage Scoring	1	1.25%	2	1.25%	3	1.25%	4	1.25%	5	1.25%	6	1.25%	7	1.25%	8	26.25%	9	70.00%	Unable to score	1.25%
Score	Percentage Scoring																						
1	1.25%																						
2	1.25%																						
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6	1.25%																						
7	1.25%																						
8	26.25%																						
9	70.00%																						
Unable to score	1.25%																						

TABLE 97: TREATMENT FAILURE – RECURRENCE OF INFECTION

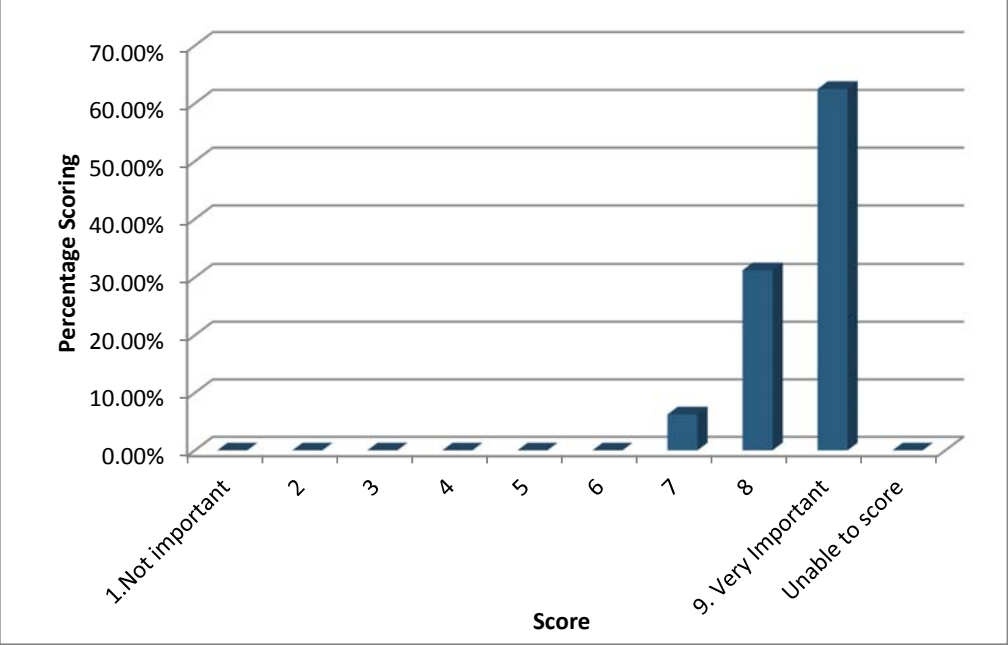
Outcome Name	<u>Treatment failure – recurrence of infection (either at original site or at new site)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. Discussion included presentation of possible treatment failures and the results of the service evaluation.																							
Results of scoring																							
 The bar chart displays the distribution of scores for treatment failure recurrence of infection. The x-axis represents the score from 1 to 9, with 1 being 'Not important' and 9 being 'Very Important'. The y-axis represents the percentage of participants scoring in each category. The data is as follows: <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~2.00%</td> </tr> <tr> <td>2</td> <td>~2.00%</td> </tr> <tr> <td>3</td> <td>~2.00%</td> </tr> <tr> <td>4</td> <td>~2.00%</td> </tr> <tr> <td>5</td> <td>~2.00%</td> </tr> <tr> <td>6</td> <td>~2.00%</td> </tr> <tr> <td>7</td> <td>~8.00%</td> </tr> <tr> <td>8</td> <td>~33.00%</td> </tr> <tr> <td>9. Very Important</td> <td>~65.00%</td> </tr> <tr> <td>Unable to score</td> <td>~2.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~2.00%	2	~2.00%	3	~2.00%	4	~2.00%	5	~2.00%	6	~2.00%	7	~8.00%	8	~33.00%	9. Very Important	~65.00%	Unable to score	~2.00%
Score	Percentage Scoring																						
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4	~2.00%																						
5	~2.00%																						
6	~2.00%																						
7	~8.00%																						
8	~33.00%																						
9. Very Important	~65.00%																						
Unable to score	~2.00%																						

TABLE 98: PAIN WHILE ON ANTIMICROBIAL TREATMENT

Outcome Name	<u>Pain while on antimicrobial treatment</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. Discussion noted pain differs dependent on whether the child is in a cast or not.																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>1.25%</td> </tr> <tr> <td>2</td> <td>1.25%</td> </tr> <tr> <td>3</td> <td>38.75%</td> </tr> <tr> <td>4</td> <td>26.25%</td> </tr> <tr> <td>5</td> <td>20.00%</td> </tr> <tr> <td>6</td> <td>13.75%</td> </tr> <tr> <td>7</td> <td>7.50%</td> </tr> <tr> <td>8</td> <td>1.25%</td> </tr> <tr> <td>9. Very Important</td> <td>1.25%</td> </tr> <tr> <td>Unable to score</td> <td>1.25%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	1.25%	2	1.25%	3	38.75%	4	26.25%	5	20.00%	6	13.75%	7	7.50%	8	1.25%	9. Very Important	1.25%	Unable to score	1.25%
Score	Percentage Scoring																						
1. Not important	1.25%																						
2	1.25%																						
3	38.75%																						
4	26.25%																						
5	20.00%																						
6	13.75%																						
7	7.50%																						
8	1.25%																						
9. Very Important	1.25%																						
Unable to score	1.25%																						

TABLE 99: ONGOING PAIN AT FOLLOW-UP

Outcome Name	<u>Ongoing pain at follow-up</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted.																							
Follow up clarified as orthopaedic follow up at outpatient appointments.																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>6.25%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>12.50%</td> </tr> <tr> <td>5</td> <td>25.00%</td> </tr> <tr> <td>6</td> <td>25.00%</td> </tr> <tr> <td>7</td> <td>12.50%</td> </tr> <tr> <td>8</td> <td>18.75%</td> </tr> <tr> <td>9. Very Important</td> <td>0.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	6.25%	3	0.00%	4	12.50%	5	25.00%	6	25.00%	7	12.50%	8	18.75%	9. Very Important	0.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
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8	18.75%																						
9. Very Important	0.00%																						
Unable to score	0.00%																						

TABLE 100: DISABILITY AT FOLLOW-UP

Outcome Name	<u>Disability at follow-up (any functional movement problems due to the original infection)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. Discussion on question of whether “disability” should be separate from “functionality”. SF confirmed that for purposes of scoring disability should be read as impairment of function at orthopaedic follow-up appointment, not long-term disability. Cross reference was made to the qualitative research presentation.																							
Results of scoring																							
<table border="1"> <caption>Data for Disability at Follow-up Bar Chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>0.00%</td> </tr> <tr> <td>5</td> <td>20.00%</td> </tr> <tr> <td>6</td> <td>0.00%</td> </tr> <tr> <td>7</td> <td>20.00%</td> </tr> <tr> <td>8</td> <td>45.00%</td> </tr> <tr> <td>9. Very Important</td> <td>20.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	20.00%	6	0.00%	7	20.00%	8	45.00%	9. Very Important	20.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	20.00%																						
6	0.00%																						
7	20.00%																						
8	45.00%																						
9. Very Important	20.00%																						
Unable to score	0.00%																						

TABLE 101: SYMPTOM FREE AT 1 YEAR

Outcome Name	<u>Symptom free at 1 year</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. CG noted that one group was close to achieving consensus and two groups were in consensus in following Round 1 of the Delphi Survey. SF reminded the group that they should not be thinking about how these would be recorded at this point but the importance of the outcome.																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>0.00%</td> </tr> <tr> <td>5</td> <td>0.00%</td> </tr> <tr> <td>6</td> <td>0.00%</td> </tr> <tr> <td>7</td> <td>12.50%</td> </tr> <tr> <td>8</td> <td>75.00%</td> </tr> <tr> <td>9. Very Important</td> <td>12.50%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	0.00%	6	0.00%	7	12.50%	8	75.00%	9. Very Important	12.50%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	0.00%																						
6	0.00%																						
7	12.50%																						
8	75.00%																						
9. Very Important	12.50%																						
Unable to score	0.00%																						

TABLE 102: LIMB SHORTENING OR DEFORMITY

Outcome Name	<u>Limb shortening or deformity</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>0.00%</td> </tr> <tr> <td>5</td> <td>0.00%</td> </tr> <tr> <td>6</td> <td>0.00%</td> </tr> <tr> <td>7</td> <td>0.00%</td> </tr> <tr> <td>8</td> <td>20.00%</td> </tr> <tr> <td>9. Very Important</td> <td>32.50%</td> </tr> <tr> <td>Unable to score</td> <td>51.25%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	0.00%	6	0.00%	7	0.00%	8	20.00%	9. Very Important	32.50%	Unable to score	51.25%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	0.00%																						
6	0.00%																						
7	0.00%																						
8	20.00%																						
9. Very Important	32.50%																						
Unable to score	51.25%																						

TABLE 103: DURATION TO CRP <5

Outcome Name	<u>Duration to CRP <5</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted.																							
Clarification given that less than 5 referred to the value of CRP and not days.																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>13.33%</td> </tr> <tr> <td>3</td> <td>33.33%</td> </tr> <tr> <td>4</td> <td>20.00%</td> </tr> <tr> <td>5</td> <td>7.14%</td> </tr> <tr> <td>6</td> <td>13.33%</td> </tr> <tr> <td>7</td> <td>13.33%</td> </tr> <tr> <td>8</td> <td>7.14%</td> </tr> <tr> <td>9. Very Important</td> <td>0.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	13.33%	3	33.33%	4	20.00%	5	7.14%	6	13.33%	7	13.33%	8	7.14%	9. Very Important	0.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	13.33%																						
3	33.33%																						
4	20.00%																						
5	7.14%																						
6	13.33%																						
7	13.33%																						
8	7.14%																						
9. Very Important	0.00%																						
Unable to score	0.00%																						

TABLE 104: DURATION TO RESOLUTION OF FEVER

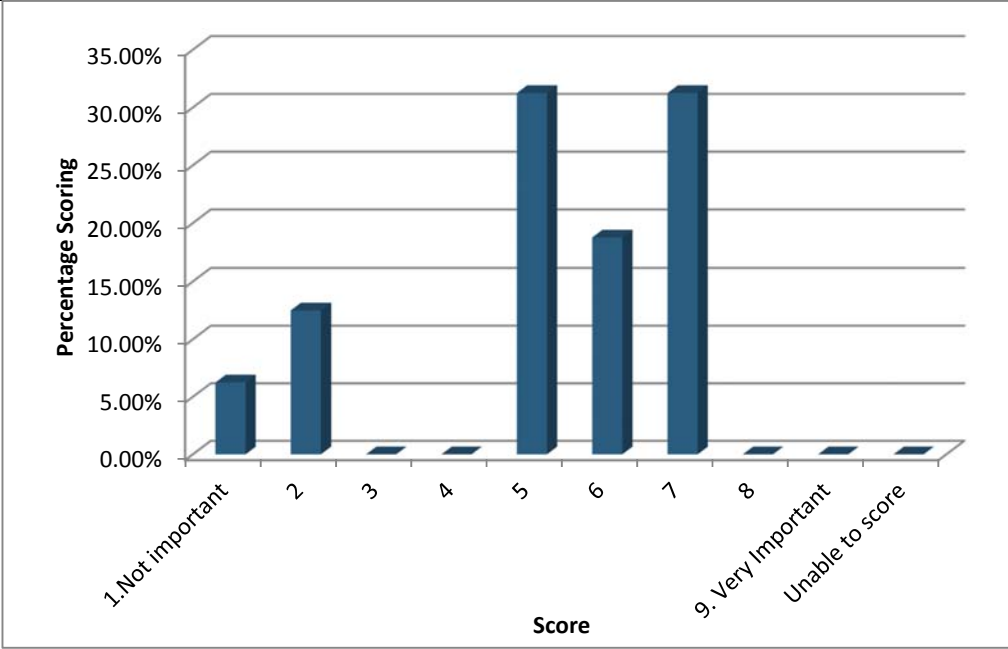
Outcome Name	<u>Duration to resolution of fever (number of days for fever to get better)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
 <table border="1"> <caption>Data for Results of Scoring Bar Chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~7.00%</td> </tr> <tr> <td>2</td> <td>~13.00%</td> </tr> <tr> <td>3</td> <td>~1.00%</td> </tr> <tr> <td>4</td> <td>~1.00%</td> </tr> <tr> <td>5</td> <td>~32.00%</td> </tr> <tr> <td>6</td> <td>~20.00%</td> </tr> <tr> <td>7</td> <td>~32.00%</td> </tr> <tr> <td>8</td> <td>~1.00%</td> </tr> <tr> <td>9. Very Important</td> <td>~1.00%</td> </tr> <tr> <td>Unable to score</td> <td>~1.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~7.00%	2	~13.00%	3	~1.00%	4	~1.00%	5	~32.00%	6	~20.00%	7	~32.00%	8	~1.00%	9. Very Important	~1.00%	Unable to score	~1.00%
Score	Percentage Scoring																						
1. Not important	~7.00%																						
2	~13.00%																						
3	~1.00%																						
4	~1.00%																						
5	~32.00%																						
6	~20.00%																						
7	~32.00%																						
8	~1.00%																						
9. Very Important	~1.00%																						
Unable to score	~1.00%																						

TABLE 105: DURATION TO RESOLUTION OF PAIN

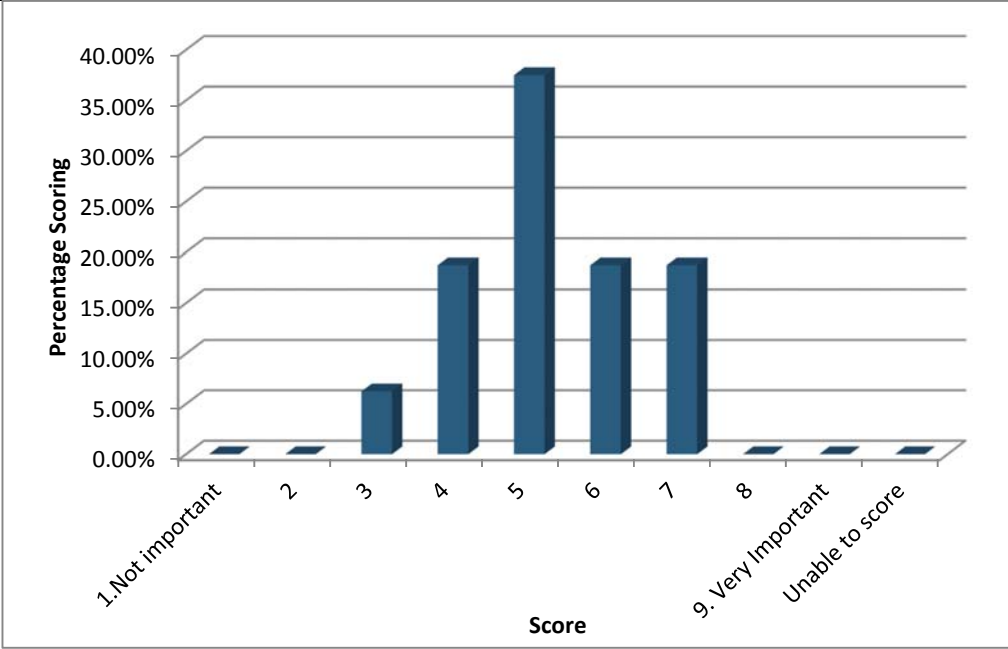
Outcome Name	<u>Duration to resolution of pain (number of days for pain to get better)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
 <table border="1"> <caption>Data for Results of Scoring Bar Chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>1.25%</td> </tr> <tr> <td>2</td> <td>1.25%</td> </tr> <tr> <td>3</td> <td>7.50%</td> </tr> <tr> <td>4</td> <td>20.00%</td> </tr> <tr> <td>5</td> <td>38.75%</td> </tr> <tr> <td>6</td> <td>20.00%</td> </tr> <tr> <td>7</td> <td>20.00%</td> </tr> <tr> <td>8</td> <td>1.25%</td> </tr> <tr> <td>9. Very Important</td> <td>1.25%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	1.25%	2	1.25%	3	7.50%	4	20.00%	5	38.75%	6	20.00%	7	20.00%	8	1.25%	9. Very Important	1.25%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	1.25%																						
2	1.25%																						
3	7.50%																						
4	20.00%																						
5	38.75%																						
6	20.00%																						
7	20.00%																						
8	1.25%																						
9. Very Important	1.25%																						
Unable to score	0.00%																						

TABLE 106: DURATION OF HOSPITAL STAY

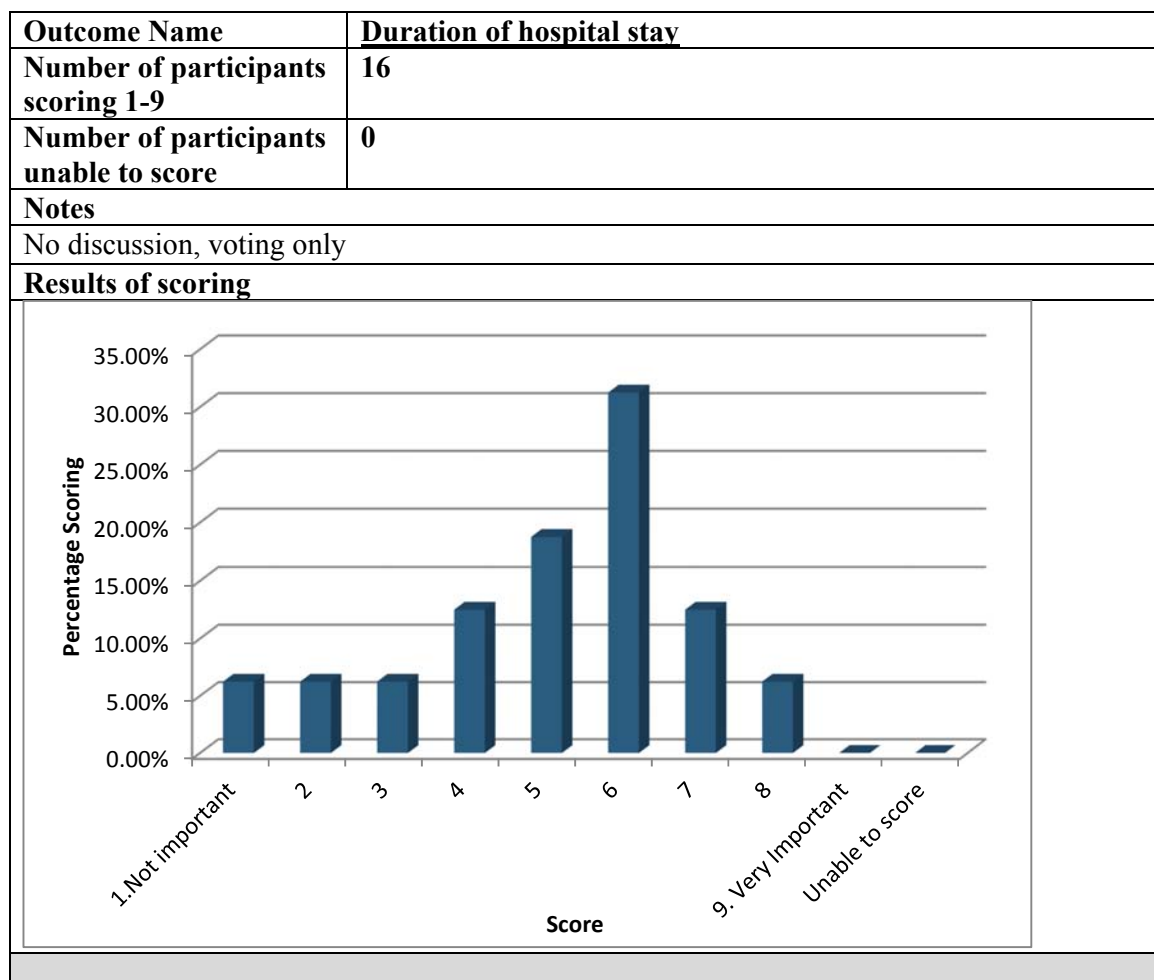


TABLE 107: FRACTURE AT OR NEAR SITE OF INFECTION

Outcome Name	<u>Fracture at or near site of infection</u>
Number of participants scoring 1-9	16
Number of participants unable to score	0
Notes	
Discussed and voted. Fracture definition clarified as direct consequence of infection rather than unrelated injury. One participant reflected that this might have been misinterpreted in the Delphi.	
Results of scoring	

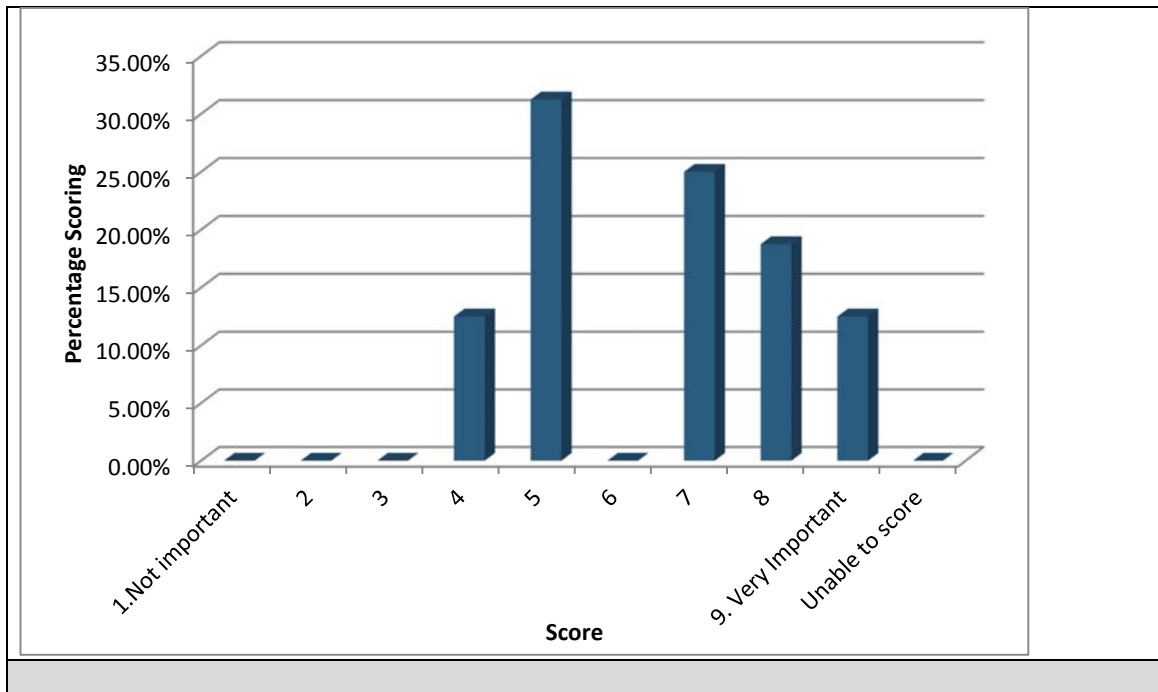


TABLE 108: PROLONGED ANTIBIOTIC THERAPY

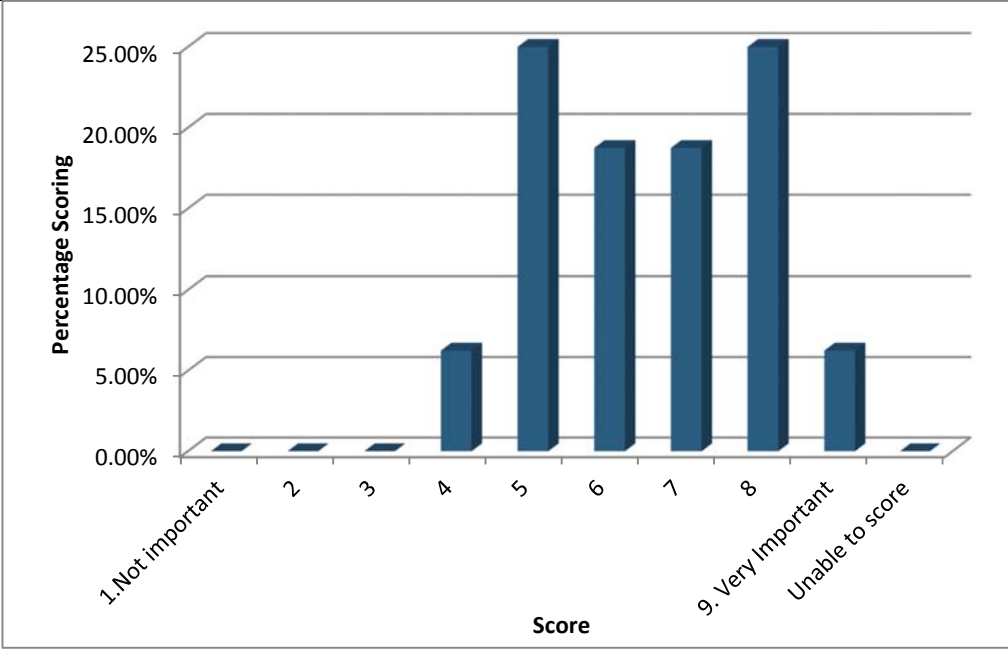
Outcome Name	<u>Prolonged antibiotic therapy</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
 <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~0.6%</td> </tr> <tr> <td>2</td> <td>~0.6%</td> </tr> <tr> <td>3</td> <td>~0.6%</td> </tr> <tr> <td>4</td> <td>~7.1%</td> </tr> <tr> <td>5</td> <td>~25.6%</td> </tr> <tr> <td>6</td> <td>~19.4%</td> </tr> <tr> <td>7</td> <td>~19.4%</td> </tr> <tr> <td>8</td> <td>~25.6%</td> </tr> <tr> <td>9. Very Important</td> <td>~7.1%</td> </tr> <tr> <td>Unable to score</td> <td>~0.6%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~0.6%	2	~0.6%	3	~0.6%	4	~7.1%	5	~25.6%	6	~19.4%	7	~19.4%	8	~25.6%	9. Very Important	~7.1%	Unable to score	~0.6%
Score	Percentage Scoring																						
1. Not important	~0.6%																						
2	~0.6%																						
3	~0.6%																						
4	~7.1%																						
5	~25.6%																						
6	~19.4%																						
7	~19.4%																						
8	~25.6%																						
9. Very Important	~7.1%																						
Unable to score	~0.6%																						

TABLE 109: QUALITY OF LIFE

Outcome Name	<u>Quality of life</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes Discussion regarding how to define quality of life as may mean different things to clinicians as it does to patients/parents. Participants became concerned with when and how quality of life should be measured and so it was clarified that the purpose of this meeting was to agree “what” was important and that the how and the when would need to be considered later. Needs further discussion with parents/PPI engagement for future trial.																							
Results of scoring <table border="1"> <caption>Data for Results of scoring</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>0.00%</td> </tr> <tr> <td>5</td> <td>20.00%</td> </tr> <tr> <td>6</td> <td>20.00%</td> </tr> <tr> <td>7</td> <td>7.50%</td> </tr> <tr> <td>8</td> <td>26.00%</td> </tr> <tr> <td>9. Very Important</td> <td>32.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	20.00%	6	20.00%	7	7.50%	8	26.00%	9. Very Important	32.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	20.00%																						
6	20.00%																						
7	7.50%																						
8	26.00%																						
9. Very Important	32.00%																						
Unable to score	0.00%																						

TABLE 110: CHRONIC OSTEOMYELITIS

Outcome Name	<u>Chronic osteomyelitis (infection that does not get better with treatment)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr><td>1. Not important</td><td>0.00%</td></tr> <tr><td>2</td><td>0.00%</td></tr> <tr><td>3</td><td>0.00%</td></tr> <tr><td>4</td><td>0.00%</td></tr> <tr><td>5</td><td>0.00%</td></tr> <tr><td>6</td><td>0.00%</td></tr> <tr><td>7</td><td>0.00%</td></tr> <tr><td>8</td><td>32.50%</td></tr> <tr><td>9. Very Important</td><td>70.00%</td></tr> <tr><td>Unable to score</td><td>0.00%</td></tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	0.00%	6	0.00%	7	0.00%	8	32.50%	9. Very Important	70.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	0.00%																						
6	0.00%																						
7	0.00%																						
8	32.50%																						
9. Very Important	70.00%																						
Unable to score	0.00%																						

TABLE 111: CHRONIC ARTHRITIS

Outcome Name	<u>Chronic arthritis (joint inflammation that does not get better with treatment)</u>																					
Number of participants scoring 1-9	16																					
Number of participants unable to score	0																					
Notes	Discussed and voted. Discussion indicated that the outcome wording may have been better clarified. It was not clear to some if this outcome related to diagnosing chronic arthritis specifically as a result of the acute infection.																					
Results of scoring	<table><thead><tr><th>Score</th><th>Percentage Scoring</th></tr></thead><tbody><tr><td>1</td><td>12.5%</td></tr><tr><td>2</td><td>0.0%</td></tr><tr><td>3</td><td>0.0%</td></tr><tr><td>4</td><td>0.0%</td></tr><tr><td>5</td><td>0.0%</td></tr><tr><td>6</td><td>0.0%</td></tr><tr><td>7</td><td>12.5%</td></tr><tr><td>8</td><td>37.5%</td></tr><tr><td>9</td><td>56.2%</td></tr></tbody></table>		Score	Percentage Scoring	1	12.5%	2	0.0%	3	0.0%	4	0.0%	5	0.0%	6	0.0%	7	12.5%	8	37.5%	9	56.2%
Score	Percentage Scoring																					
1	12.5%																					
2	0.0%																					
3	0.0%																					
4	0.0%																					
5	0.0%																					
6	0.0%																					
7	12.5%																					
8	37.5%																					
9	56.2%																					

TABLE 112: CHRONIC MYOSITIS

Outcome Name	<u>Chronic myositis (muscle inflammation that does not get better with treatment)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted.																							
Results of scoring																							
<table border="1"> <caption>Results of scoring data</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>7.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>25.00%</td> </tr> <tr> <td>5</td> <td>0.00%</td> </tr> <tr> <td>6</td> <td>19.00%</td> </tr> <tr> <td>7</td> <td>25.00%</td> </tr> <tr> <td>8</td> <td>19.00%</td> </tr> <tr> <td>9. Very Important</td> <td>7.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	7.00%	2	0.00%	3	0.00%	4	25.00%	5	0.00%	6	19.00%	7	25.00%	8	19.00%	9. Very Important	7.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	7.00%																						
2	0.00%																						
3	0.00%																						
4	25.00%																						
5	0.00%																						
6	19.00%																						
7	25.00%																						
8	19.00%																						
9. Very Important	7.00%																						
Unable to score	0.00%																						

TABLE 113: AMPUTATION OR FASCIOTOMY

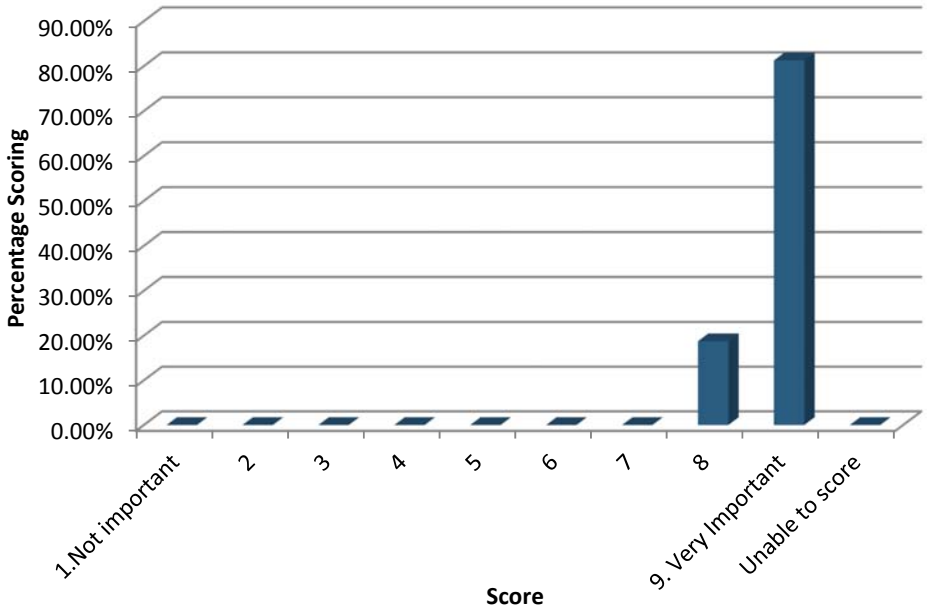
Outcome Name	<u>Amputation or Fasciotomy (when the skin and muscle have to be cut by a surgeon to relieve pressure between the skin and bone)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
 The bar chart displays the distribution of scores for the outcome 'Amputation or Fasciotomy'. The x-axis represents the score from 1 to 9, with labels '1. Not important', '2', '3', '4', '5', '6', '7', '8', '9. Very Important', and 'Unable to score'. The y-axis represents the percentage of participants, ranging from 0.00% to 90.00% in 10.00% increments. The data shows that 80.00% of participants scored 9 (Very Important), 20.00% scored 8, and 0.00% scored 1-7. The 'Unable to score' category is also shown with 0.00%. <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>0.00%</td> </tr> <tr> <td>5</td> <td>0.00%</td> </tr> <tr> <td>6</td> <td>0.00%</td> </tr> <tr> <td>7</td> <td>0.00%</td> </tr> <tr> <td>8</td> <td>20.00%</td> </tr> <tr> <td>9. Very Important</td> <td>80.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	0.00%	6	0.00%	7	0.00%	8	20.00%	9. Very Important	80.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	0.00%																						
6	0.00%																						
7	0.00%																						
8	20.00%																						
9. Very Important	80.00%																						
Unable to score	0.00%																						

TABLE 114: DEATH

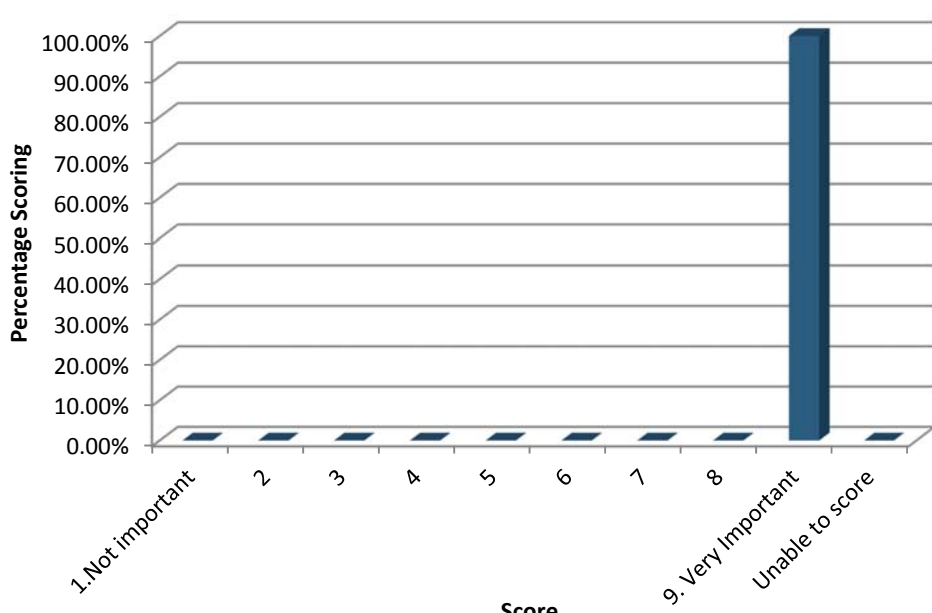
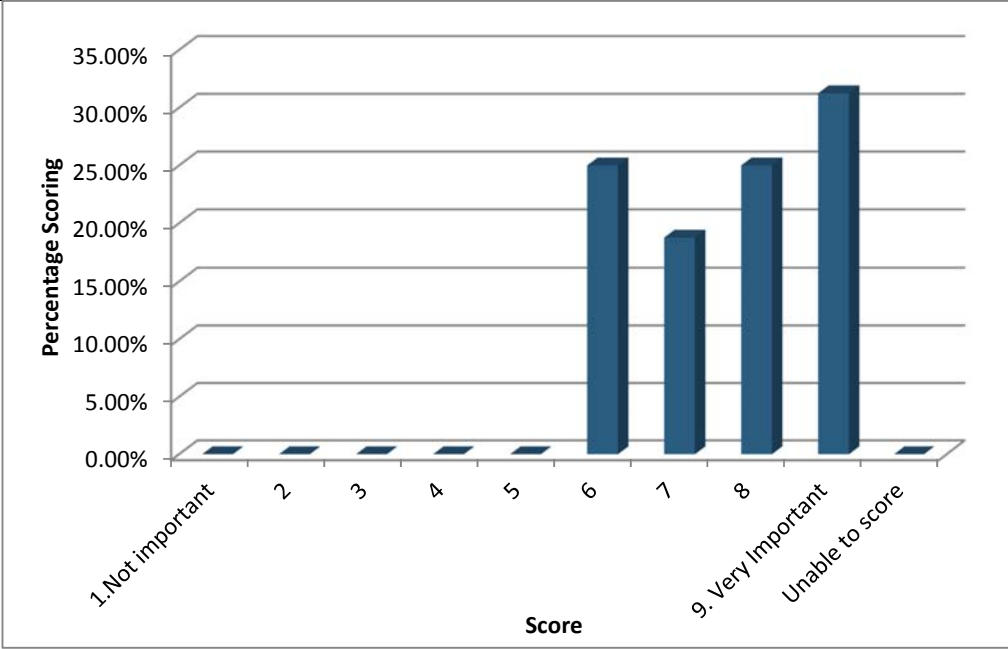
Outcome Name	<u>Death</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
 The chart displays the distribution of scores for the outcome 'Death'. The Y-axis represents the percentage of participants, ranging from 0.00% to 100.00% in 10% increments. The X-axis represents the scores, ranging from 1 (Not important) to 9 (Very Important), plus an 'Unable to score' category. The data shows that 100% of participants scored 9 (Very Important), and 0% of participants were unable to score. <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>0.00%</td> </tr> <tr> <td>5</td> <td>0.00%</td> </tr> <tr> <td>6</td> <td>0.00%</td> </tr> <tr> <td>7</td> <td>0.00%</td> </tr> <tr> <td>8</td> <td>0.00%</td> </tr> <tr> <td>9. Very Important</td> <td>100.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	0.00%	6	0.00%	7	0.00%	8	0.00%	9. Very Important	100.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	0.00%																						
6	0.00%																						
7	0.00%																						
8	0.00%																						
9. Very Important	100.00%																						
Unable to score	0.00%																						

TABLE 115: PICU REQUIREMENT

Outcome Name	<u>PICU (paediatric intensive care) requirement (e.g. PICU-free days at day 30, if admitted)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
 <table border="1"> <caption>Results of scoring data</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>1.25%</td> </tr> <tr> <td>2</td> <td>1.25%</td> </tr> <tr> <td>3</td> <td>1.25%</td> </tr> <tr> <td>4</td> <td>1.25%</td> </tr> <tr> <td>5</td> <td>1.25%</td> </tr> <tr> <td>6</td> <td>26.25%</td> </tr> <tr> <td>7</td> <td>19.38%</td> </tr> <tr> <td>8</td> <td>26.25%</td> </tr> <tr> <td>9. Very Important</td> <td>32.50%</td> </tr> <tr> <td>Unable to score</td> <td>1.25%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	1.25%	2	1.25%	3	1.25%	4	1.25%	5	1.25%	6	26.25%	7	19.38%	8	26.25%	9. Very Important	32.50%	Unable to score	1.25%
Score	Percentage Scoring																						
1. Not important	1.25%																						
2	1.25%																						
3	1.25%																						
4	1.25%																						
5	1.25%																						
6	26.25%																						
7	19.38%																						
8	26.25%																						
9. Very Important	32.50%																						
Unable to score	1.25%																						

Treatment/Line Related

TABLE 116: AGRANULOCYTOSIS / NEUTROPAENIA

Outcome Name	<u>Agranulocytosis / neutropaenia (abnormal white cell count)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>1.25%</td> </tr> <tr> <td>2</td> <td>1.25%</td> </tr> <tr> <td>3</td> <td>1.25%</td> </tr> <tr> <td>4</td> <td>13.75%</td> </tr> <tr> <td>5</td> <td>20.00%</td> </tr> <tr> <td>6</td> <td>13.75%</td> </tr> <tr> <td>7</td> <td>51.25%</td> </tr> <tr> <td>8</td> <td>7.50%</td> </tr> <tr> <td>9. Very Important</td> <td>1.25%</td> </tr> <tr> <td>Unable to score</td> <td>1.25%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	1.25%	2	1.25%	3	1.25%	4	13.75%	5	20.00%	6	13.75%	7	51.25%	8	7.50%	9. Very Important	1.25%	Unable to score	1.25%
Score	Percentage Scoring																						
1. Not important	1.25%																						
2	1.25%																						
3	1.25%																						
4	13.75%																						
5	20.00%																						
6	13.75%																						
7	51.25%																						
8	7.50%																						
9. Very Important	1.25%																						
Unable to score	1.25%																						

TABLE 117: DERANGED LIVER FUNCTION TESTS

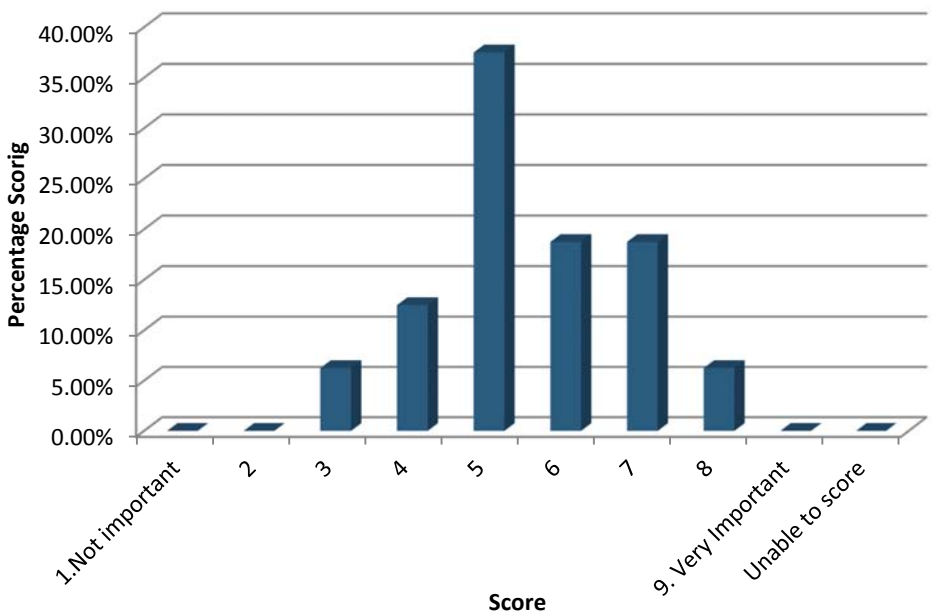
Outcome Name	<u>Deranged (abnormal) liver function tests</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. Discussion comments included that deranged liver function would not be informative for the effectiveness of the treatment and therefore should not be in the core outcome set.																							
Results of scoring																							
 <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~1.00%</td> </tr> <tr> <td>2</td> <td>~1.00%</td> </tr> <tr> <td>3</td> <td>~7.00%</td> </tr> <tr> <td>4</td> <td>~13.00%</td> </tr> <tr> <td>5</td> <td>~38.00%</td> </tr> <tr> <td>6</td> <td>~20.00%</td> </tr> <tr> <td>7</td> <td>~20.00%</td> </tr> <tr> <td>8</td> <td>~7.00%</td> </tr> <tr> <td>9. Very Important</td> <td>~1.00%</td> </tr> <tr> <td>Unable to score</td> <td>~1.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~1.00%	2	~1.00%	3	~7.00%	4	~13.00%	5	~38.00%	6	~20.00%	7	~20.00%	8	~7.00%	9. Very Important	~1.00%	Unable to score	~1.00%
Score	Percentage Scoring																						
1. Not important	~1.00%																						
2	~1.00%																						
3	~7.00%																						
4	~13.00%																						
5	~38.00%																						
6	~20.00%																						
7	~20.00%																						
8	~7.00%																						
9. Very Important	~1.00%																						
Unable to score	~1.00%																						

TABLE 118: CLOSTRIDIUM DIFFICILE INFECTION

Outcome Name	<u>Clostridium difficile infection (infectious complication of prolonged antibiotic treatment, unusual in children and not able to be diagnosed in children under 2 as the infection is carried by young children as a normal finding without causing problems)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
<table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>13.33%</td> </tr> <tr> <td>4</td> <td>25.00%</td> </tr> <tr> <td>5</td> <td>19.44%</td> </tr> <tr> <td>6</td> <td>25.00%</td> </tr> <tr> <td>7</td> <td>13.33%</td> </tr> <tr> <td>8</td> <td>6.67%</td> </tr> <tr> <td>9. Very Important</td> <td>0.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	13.33%	4	25.00%	5	19.44%	6	25.00%	7	13.33%	8	6.67%	9. Very Important	0.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	13.33%																						
4	25.00%																						
5	19.44%																						
6	25.00%																						
7	13.33%																						
8	6.67%																						
9. Very Important	0.00%																						
Unable to score	0.00%																						

TABLE 119: RASH OR ALLERGIC REACTION

Outcome Name	<u>Rash or allergic reaction</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. Comment raised that this could be a non-specific rash. Also that this should be scored as separate outcomes “rash” and “allergic reaction”.																							
Results of scoring																							
<table border="1"> <caption>Percentage Scoring by Score</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>7.50%</td> </tr> <tr> <td>5</td> <td>32.50%</td> </tr> <tr> <td>6</td> <td>26.25%</td> </tr> <tr> <td>7</td> <td>20.00%</td> </tr> <tr> <td>8</td> <td>20.00%</td> </tr> <tr> <td>9. Very Important</td> <td>0.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	7.50%	5	32.50%	6	26.25%	7	20.00%	8	20.00%	9. Very Important	0.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	7.50%																						
5	32.50%																						
6	26.25%																						
7	20.00%																						
8	20.00%																						
9. Very Important	0.00%																						
Unable to score	0.00%																						

TABLE 120: SUSPECTED DRUG-RELATED FEVER

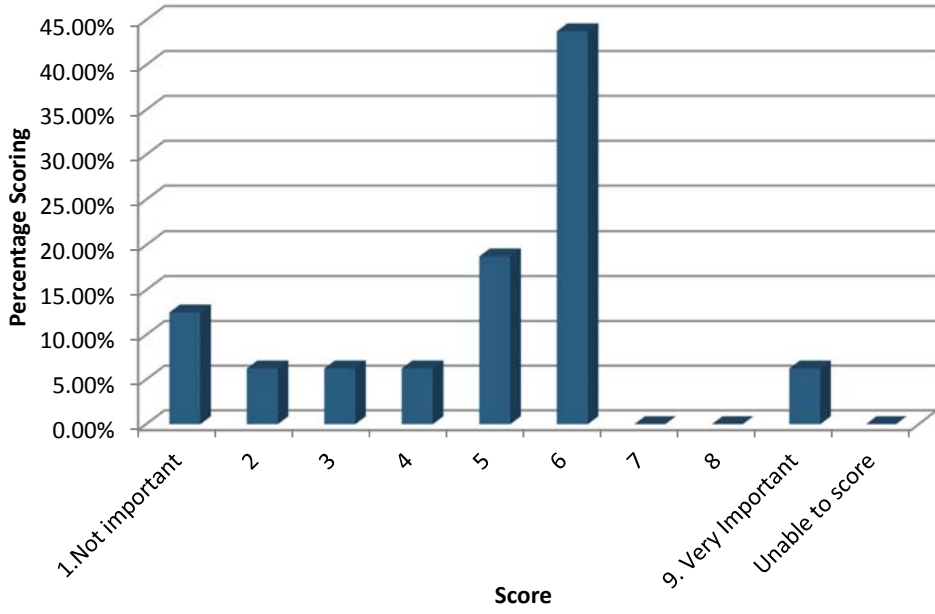
Outcome Name	<u>Suspected drug-related fever</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. Discussion that this was an uncommon side effect and that this might be captured as a drug reaction. CaP put forward her and her child's experience of drug related fever.																							
Results of scoring																							
 <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>13.3%</td> </tr> <tr> <td>2</td> <td>7.5%</td> </tr> <tr> <td>3</td> <td>7.5%</td> </tr> <tr> <td>4</td> <td>7.5%</td> </tr> <tr> <td>5</td> <td>20.0%</td> </tr> <tr> <td>6</td> <td>44.4%</td> </tr> <tr> <td>7</td> <td>0.0%</td> </tr> <tr> <td>8</td> <td>0.0%</td> </tr> <tr> <td>9. Very Important</td> <td>7.5%</td> </tr> <tr> <td>Unable to score</td> <td>0.0%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	13.3%	2	7.5%	3	7.5%	4	7.5%	5	20.0%	6	44.4%	7	0.0%	8	0.0%	9. Very Important	7.5%	Unable to score	0.0%
Score	Percentage Scoring																						
1. Not important	13.3%																						
2	7.5%																						
3	7.5%																						
4	7.5%																						
5	20.0%																						
6	44.4%																						
7	0.0%																						
8	0.0%																						
9. Very Important	7.5%																						
Unable to score	0.0%																						

TABLE 121: LINE INFECTION

Outcome Name	<u>Line infection (infection of the drip line itself)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. SF referred to a more recent paediatric paper here that described complications of PIC lines in and out of hospital.																							
Results of scoring																							
<table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.00%</td> </tr> <tr> <td>2</td> <td>0.00%</td> </tr> <tr> <td>3</td> <td>0.00%</td> </tr> <tr> <td>4</td> <td>0.00%</td> </tr> <tr> <td>5</td> <td>13.33%</td> </tr> <tr> <td>6</td> <td>7.78%</td> </tr> <tr> <td>7</td> <td>33.33%</td> </tr> <tr> <td>8</td> <td>33.33%</td> </tr> <tr> <td>9. Very...</td> <td>20.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.00%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	0.00%	4	0.00%	5	13.33%	6	7.78%	7	33.33%	8	33.33%	9. Very...	20.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	0.00%																						
4	0.00%																						
5	13.33%																						
6	7.78%																						
7	33.33%																						
8	33.33%																						
9. Very...	20.00%																						
Unable to score	0.00%																						

TABLE 122: LINE OCCLUSION

Outcome Name	<u>Line occlusion (block of the drip line)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
<table border="1"> <caption>Data for Line Occlusion Scoring Results</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>7.00%</td> </tr> <tr> <td>2</td> <td>0.50%</td> </tr> <tr> <td>3</td> <td>0.50%</td> </tr> <tr> <td>4</td> <td>13.00%</td> </tr> <tr> <td>5</td> <td>19.00%</td> </tr> <tr> <td>6</td> <td>13.00%</td> </tr> <tr> <td>7</td> <td>19.00%</td> </tr> <tr> <td>8</td> <td>19.00%</td> </tr> <tr> <td>9. Very Important</td> <td>13.00%</td> </tr> <tr> <td>Unable to score</td> <td>0.50%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	7.00%	2	0.50%	3	0.50%	4	13.00%	5	19.00%	6	13.00%	7	19.00%	8	19.00%	9. Very Important	13.00%	Unable to score	0.50%
Score	Percentage Scoring																						
1. Not important	7.00%																						
2	0.50%																						
3	0.50%																						
4	13.00%																						
5	19.00%																						
6	13.00%																						
7	19.00%																						
8	19.00%																						
9. Very Important	13.00%																						
Unable to score	0.50%																						

TABLE 123: VOMITING / DIARRHOEA

Outcome Name	<u>Vomiting / diarrhoea</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
No discussion, voting only																							
Results of scoring																							
<table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>7.5%</td> </tr> <tr> <td>2</td> <td>7.5%</td> </tr> <tr> <td>3</td> <td>38.5%</td> </tr> <tr> <td>4</td> <td>20.0%</td> </tr> <tr> <td>5</td> <td>13.5%</td> </tr> <tr> <td>6</td> <td>13.5%</td> </tr> <tr> <td>7</td> <td>7.5%</td> </tr> <tr> <td>8</td> <td>1.0%</td> </tr> <tr> <td>9. Very Important</td> <td>1.0%</td> </tr> <tr> <td>Unable to score</td> <td>1.0%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	7.5%	2	7.5%	3	38.5%	4	20.0%	5	13.5%	6	13.5%	7	7.5%	8	1.0%	9. Very Important	1.0%	Unable to score	1.0%
Score	Percentage Scoring																						
1. Not important	7.5%																						
2	7.5%																						
3	38.5%																						
4	20.0%																						
5	13.5%																						
6	13.5%																						
7	7.5%																						
8	1.0%																						
9. Very Important	1.0%																						
Unable to score	1.0%																						

TABLE 124: IV ANTIBIOTIC NECESSITATED INSERTION OF PICC OR OTHER CENTRAL LINE

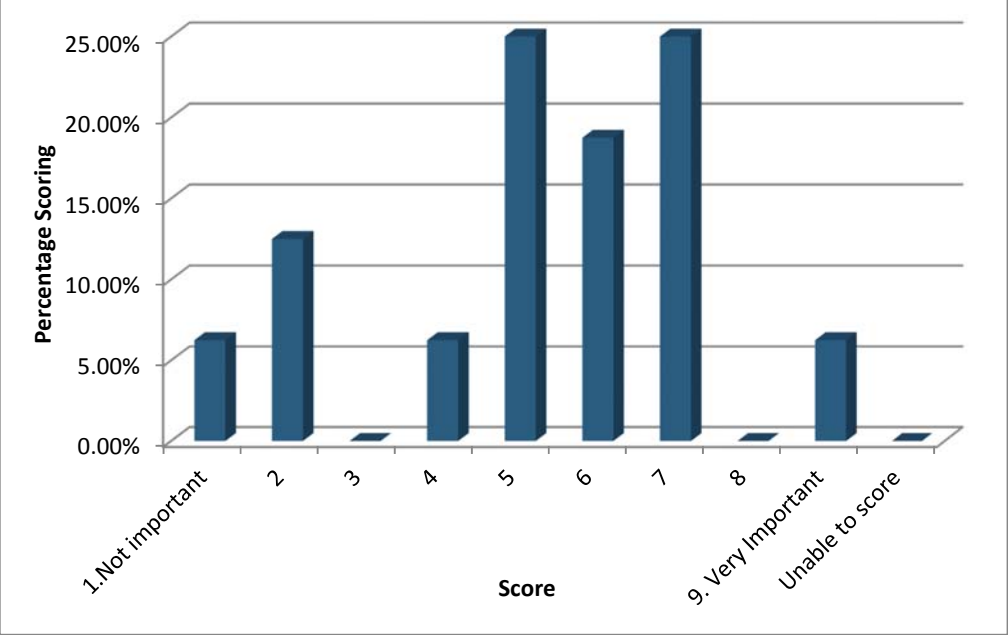
Outcome Name	<u>IV antibiotic necessitated insertion of PICC or other central line (need to insert another longer term intravenous drip)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussion over whether this should be classified as an outcome. Some confusion about what the outcome meant. Was a PICC needed because of the need for long term antibiotics (ie part of treatment plan, becoming more common in routine NHS care of bone and joint infections in children) or because of difficulty with access in the initial period of illness. There is a possibility that the time to PICC insertion at an institution could affect the response. One person suggested re-wording the outcome.																							
Results of scoring																							
 <table border="1"> <caption>Data for Results of scoring bar chart</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>~7.0%</td> </tr> <tr> <td>2</td> <td>~13.0%</td> </tr> <tr> <td>3</td> <td>~0.5%</td> </tr> <tr> <td>4</td> <td>~7.0%</td> </tr> <tr> <td>5</td> <td>~26.0%</td> </tr> <tr> <td>6</td> <td>~19.5%</td> </tr> <tr> <td>7</td> <td>~26.0%</td> </tr> <tr> <td>8</td> <td>~0.5%</td> </tr> <tr> <td>9. Very Important</td> <td>~7.0%</td> </tr> <tr> <td>Unable to score</td> <td>~0.5%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	~7.0%	2	~13.0%	3	~0.5%	4	~7.0%	5	~26.0%	6	~19.5%	7	~26.0%	8	~0.5%	9. Very Important	~7.0%	Unable to score	~0.5%
Score	Percentage Scoring																						
1. Not important	~7.0%																						
2	~13.0%																						
3	~0.5%																						
4	~7.0%																						
5	~26.0%																						
6	~19.5%																						
7	~26.0%																						
8	~0.5%																						
9. Very Important	~7.0%																						
Unable to score	~0.5%																						

TABLE 125: INFILTRATION OR EXTRAVASATION EVENT

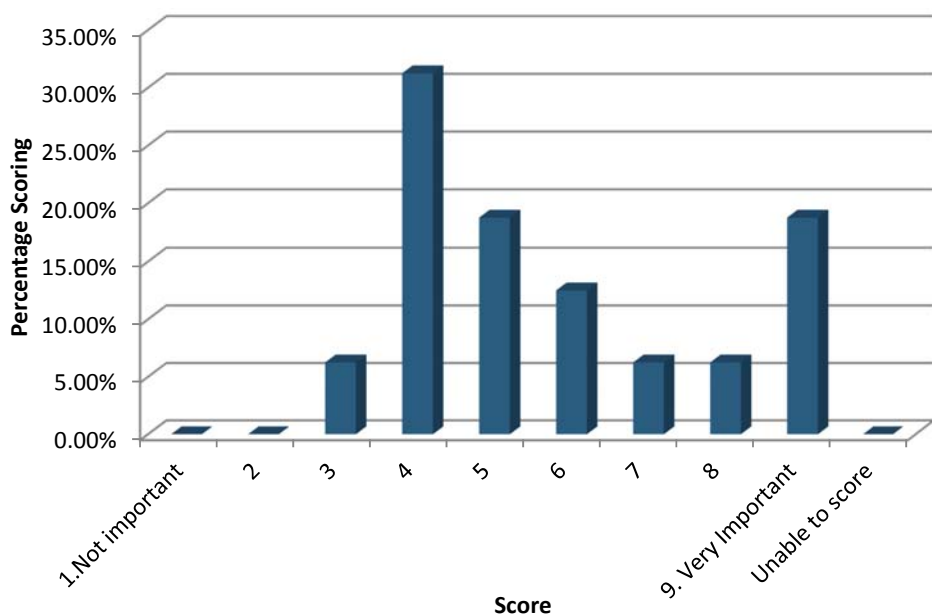
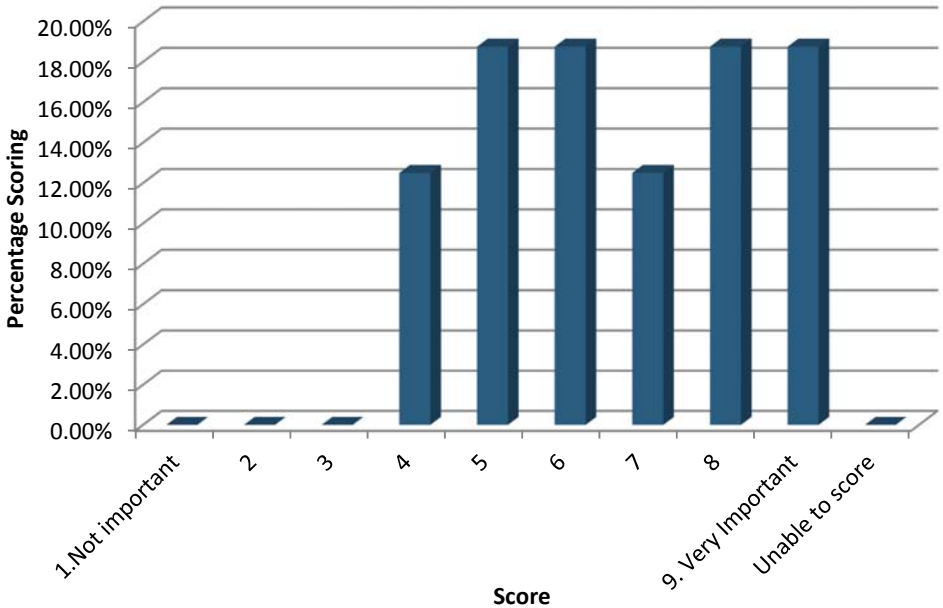
Outcome Name	<u>Infiltration or extravasation event (medicine being given into the veins accidentally is delivered to the tissues due to the drip coming out of the blood vessel)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Lay summary was verbally read for clarity. No discussion, voting only																							
Results of scoring																							
 <table border="1"> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr><td>1. Not important</td><td>0.00%</td></tr> <tr><td>2</td><td>0.00%</td></tr> <tr><td>3</td><td>7.00%</td></tr> <tr><td>4</td><td>32.00%</td></tr> <tr><td>5</td><td>20.00%</td></tr> <tr><td>6</td><td>13.00%</td></tr> <tr><td>7</td><td>7.00%</td></tr> <tr><td>8</td><td>7.00%</td></tr> <tr><td>9. Very Important</td><td>20.00%</td></tr> <tr><td>Unable to score</td><td>0.00%</td></tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.00%	2	0.00%	3	7.00%	4	32.00%	5	20.00%	6	13.00%	7	7.00%	8	7.00%	9. Very Important	20.00%	Unable to score	0.00%
Score	Percentage Scoring																						
1. Not important	0.00%																						
2	0.00%																						
3	7.00%																						
4	32.00%																						
5	20.00%																						
6	13.00%																						
7	7.00%																						
8	7.00%																						
9. Very Important	20.00%																						
Unable to score	0.00%																						

TABLE 126: ANY COMPLICATION OF VASCULAR ACCESS

Outcome Name	<u>Any complication of vascular access (any complication of the drip itself)</u>																						
Number of participants scoring 1-9	16																						
Number of participants unable to score	0																						
Notes																							
Discussed and voted. Explanation given that it's important to look at complications across arms of the trial.																							
Results of scoring																							
 <table border="1"> <caption>Data for Results of scoring</caption> <thead> <tr> <th>Score</th> <th>Percentage Scoring</th> </tr> </thead> <tbody> <tr> <td>1. Not important</td> <td>0.6%</td> </tr> <tr> <td>2</td> <td>0.6%</td> </tr> <tr> <td>3</td> <td>0.6%</td> </tr> <tr> <td>4</td> <td>13.0%</td> </tr> <tr> <td>5</td> <td>19.0%</td> </tr> <tr> <td>6</td> <td>19.0%</td> </tr> <tr> <td>7</td> <td>13.0%</td> </tr> <tr> <td>8</td> <td>19.0%</td> </tr> <tr> <td>9. Very Important</td> <td>19.0%</td> </tr> <tr> <td>Unable to score</td> <td>0.6%</td> </tr> </tbody> </table>		Score	Percentage Scoring	1. Not important	0.6%	2	0.6%	3	0.6%	4	13.0%	5	19.0%	6	19.0%	7	13.0%	8	19.0%	9. Very Important	19.0%	Unable to score	0.6%
Score	Percentage Scoring																						
1. Not important	0.6%																						
2	0.6%																						
3	0.6%																						
4	13.0%																						
5	19.0%																						
6	19.0%																						
7	13.0%																						
8	19.0%																						
9. Very Important	19.0%																						
Unable to score	0.6%																						

Appendix 7: Service evaluation statistical analysis plan, 18/12/2014



DINOSAUR: Service Evaluation Study

**Duration of Intravenous antibiotic therapy for Septic Arthritis or acUte
osteomyelitis in a paediatRic population**

Statistical Analysis Plan

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Barbara Arch	Carrol Gamble	Carrol Gamble
Title	Trial Statistician	Professor Medical Statistics	Professor Medical Statistics
Date	18 th December 2014		
Protocol Version and Date	Protocol Service Evaluation v2_1 26 th April 2013		

Change Control

Updated SAP version no.	Section number changed	Description of change	Date changed	Initials
1.4	8.2	Fundamental change to definition of case types	20/10/14	BA
1.5	Appendix	Changes made to several tables arising from web meeting with CI going through each table in detail.	26/11/14	BA

Table of Contents

1.	Introduction	369
2.	Definitions	369
3.	Study Aim	370
4.	Study Design	370
5.1	Participating centres	370
5.2	Participant selection criteria	370
5.3	Sample size calculations	371
5.4	Data Collection	371
6	Study Objectives	371
7.	Description of the study population	374
7.1	Representativeness of cases accrued	374
7.2	Sample characteristics and initial categorisation of types of cases	374
7.3	Completeness of follow-up	375
8.	Study Outcomes	375
9.	Analysis	377
9.1	Objective 1	377
9.2	Objective 2	378
9.3	Objective 3	379
10.	Analyses of missing data / withdrawals	379
11.	Setting results in context of previous research	379
12.	References	380
	Appendix A: Template Results Tables	381

Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned analyses for the service evaluation study DINOSAUR.

These planned analyses will be performed by the study statistician. The analysis results will be described in a statistical analysis report, to be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS v9). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP TM021 Archiving procedure in CTRC. The testing and validation of the statistical analysis programs will be performed following SOP ST001.

Definitions

OM	Acute Osteomyelitis
SA	Septic Arthritis
IV	Intra-venous
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
Hb	Haemoglobin
Plt	Platelets
WCC	White blood-cell count
N	Neutrophils [or if a statistic then Number]
PICC	Peripherally inserted central catheter

Study Aim

Currently there is little international or UK consensus regarding the route or duration of antibiotic treatment for acute osteomyelitis (OM)/septic arthritis (SA) in children. Data regarding paediatric bone and joint infections in the UK are scarce and outdated. This service evaluation will be used to:

1. Assess current case load, disease spectrum & clinical practice in the diagnosis & treatment of OM/SA in secondary & tertiary UK care
2. Determine whether a randomised controlled trial to investigate shorter duration of intravenous antibiotic therapy for bone and joint infections in children is feasible in the future.

This will be achieved in conjunction with a future component of the study (analysis plan of which not included in this document) obtaining qualitative & quantitative data on:

- a) willingness of clinicians to randomise to proposed protocol
- b) willingness of patients & parents to be randomized
- c) number of patients seen;
- d) clinical stakeholder & consumer perception of relevant outcomes

Study Design

This service evaluation is a descriptive study, examining routinely collected clinical data for all eligible paediatric cases of OM and SA presenting at participating tertiary and secondary healthcare centres over a minimum of a 6 months period.

Participating centres

All Tertiary and Secondary centres routinely treating cases of OM or SA from across England will be invited to participate in this national service evaluation. They will record data on all cases accrued over at least a 6 month period.

Participant selection criteria

All eligible patients presenting to participating centres with a diagnosis of bone and joint infection will be enrolled with no maximum, and data will be entered into a web based database.

Inclusion Criteria

All children from birth to 16 years with a clinical diagnosis of osteomyelitis or septic arthritis admitted to participating hospitals from home, or referred from another centre.

Exclusion Criteria

Patients whose parents have specifically requested for their child not to be included in the study.

Participant identification and recruitment

Posters displayed on admitting wards notify parents and patients that the centre is participating in a national service evaluation of children's bone and joint infections. Parents will have the opportunity to inform a member of their child's care team if they do not want their child's information entered into the database.

Sample size calculations

The study is funded to enable a maximum of 1,000 cases of OM or SA to be entered into the database. In order to get an accurate national evaluation, all participating centres will be asked to record cases for at least six months. It is estimated that at least 500 cases will be accrued by around 50 centres over a 6-12 month period. All eligible cases at participating centres will be recorded.

Data Collection

We will record demographic details and details of hospitalisation(s) including transfers between hospitals; type and site of disease; routine haematology, biochemistry and microbiology; radiological procedures; surgical procedures; length of IV therapy; antimicrobials used, route and duration; reason/criteria; used for oral switch (if any); and clinical outcomes at 3 months.

These data are to be collected from the patients' clinical notes. Training will be provided for teams at participating centres. The study will use a password protected web based data collection form that can be accessed at all participating hospitals.

Study Objectives

The study has three major objectives:

1. What are the clinical, biochemical and radiological criteria used by UK paediatricians / orthopaedic surgeons / radiologists to diagnose osteomyelitis?
2. What is the range of durations of intravenous and oral antibiotics used to treat osteomyelitis? What factors affect durations (e.g. surgery / blood tests / microbiology results)?
3. What are the rates of treatment failures / complications for different:
 - (a) Antibiotic regimes used at participating centres?
 - (b) Surgery types used at participating centres?

and what actions were taken following a complication at participating centres?

These objectives are broken down into further sub-objectives:

- 1A:** Describe the study sample: demographics; past medical history; presenting limbs/joints affected; and diagnosis types aiming to identify factors predisposing children to bone and joint infections. Describe pre-presentation variables that affect drug choice, dosage and duration, in particular age, allergies and co-morbidities.
- 1B:** Describe the clinical time-line for diagnosis: summarising the number of days from presentation when key clinical actions (1st imaging, surgery and initiation of IV antibiotics) occur.
- 1C:** Describe the surgical procedures carried out prior to diagnosis.
- 1D:** Summarise the types of microbiological tests carried out and the types of samples taken. Specifically, find the proportion of centres that are performing PCR tests, and testing for Panton-Valentine Leukocidin producing *Staphylococcus aureus*.
Calculate the proportion of children testing positive for: at least one micro-organism; and each specific micro-organism (using conventional techniques, ie not PCR).
- 1E:** Describe the combinations of blood-tests carried out at presentation and summarise the test results. Find the proportion of children with elevated results for each blood-test type at presentation (results above centre-specific normal ranges), and the proportion of children with CRP_{max} occurring at presentation. Describe the types of samples.
- 1F:** Summarise CRP_{max} by age-group and micro-organisms detected.
- 1G:** Describe the imaging methods routinely used to aid diagnosis. What proportions of each method gave an abnormal result..
- 2A:** Describe the clinical time-line for antibiotic treatment (specifically when antibiotics are started) Describe the types of antibiotic regimes prescribed. Summarise the number of different antibiotics given as initial treatment, and the total number of different antibiotics patients receive over the durations of treatment by each route. Summarise the numbers of children being given different types of regime: early vs

normal length of time to oral switch; dosage – how many were given normal doses throughout; shortened vs standard length of time on antibiotics.

- 2B:** Describe the IV and oral antibiotics prescribed during hospital stay. For each antibiotic: which were prescribed at least once; which were part of the initial treatment; what was the average daily dose; with what frequency were doses given; and was the duration greater than 1 week. Were there differences in initial IV antibiotic prescriptions between secondary and tertiary site types; between children with and without penicillin allergy; and with and without sickle cell disease?
- 2C:** Describe the combinations of blood-tests carried out immediately prior to oral switch and summarise the test results. Calculate the average CRP at oral switch as a proportion CRP_{max} . Summarise blood test results over time: from presentation through to last test.
- 2D:** Describe the surgical procedures carried out post diagnosis but prior to discharge, i.e. therapeutic procedures. How many children had only one procedure, two procedures or more than two?
- 2E:** Summarise the length of time spent in hospital: from hospitalisation to discharge.
- [2F]:** Summarise imaging carried out after initiation of IV, split by site type and image type. For each imaging type, identify cases that had at least one image carried out.
- 2G:** Describe the antibiotic regimes prescribed at discharge (drug, dose, frequency and duration). As part of this – what percentage went home on IV as opposed to oral?
- 2H:** Were discharge antibiotic regimes adhered to? Percentages of treatments shortened or changed post discharge, split by who made the decision: parent, hospital or GP. Describe the main reasons for non-adherence or change of regime post discharge.
- 3A:** Describe rates of different types of complication, and cross-tabulate with types of action taken.
- 3B:** Describe rates of Treatment Failure (Yes/No) and Any Complications (Yes/No) for different antibiotic regimes types. Measure associations between regime types and the two outcomes: Treatment Failure; and Any Complications.
- 3C:** Describe rates of Treatment Failure (Yes/No) and Any Complications (Yes/No) for different surgery types carried out post presentation. Measure associations between surgery types undertaken and the two outcomes: Treatment Failure; and Any Complications.

Description of the study population

Representativeness of cases accrued

The participating centres will be summarised and checked that they broadly represent all areas of the country. The numbers of cases withdrawn will be recorded.

Sample characteristics and initial categorisation of types of cases

The demographics of the sample (age, gender, medical history) will be described using summary statistics. Based on past medical history, cases will be categorised into four groups:

1. Simple cases
2. Complex cases
3. Current presentation due to infected implant or infected surgery from past orthopaedic surgery. (Subset of complex cases)
4. Misdiagnosed

Any children not falling into any of these categories will be excluded from the analysis.

Definitions

1. Simple cases

Children presenting with SA or OM for the first time, and with no chronic comorbidities. Specifically:

- No orthopaedic surgery 6 months prior to presentation on same limb/joint
- No chronic co-morbidities (sickle cell disease, known immunocompromise, indwelling central venous catheter or PICC, cystic fibrosis, or cerebral palsy).

2. Complex cases

Children presenting with SA or OM who already have a diagnosis of SA or OM and/or have chronic comorbidities, but who are not presenting because of an infected implant from previous orthopaedic surgery. Specifically:

- Not presenting because of an infected implant
- Any orthopaedic surgery in 6 months prior to presentation on same limb/joint
- Any chronic co-morbidities (sickle cell disease, known immunocompromise, indwelling central venous catheter or PICC, cystic fibrosis, or cerebral palsy).

3. Infected implants

Children presenting with SA or OM who already have a diagnosis of SA or OM and who are presenting because of an infected implant from previous orthopaedic surgery.

4. Incorrect diagnosis of SA/OM

Some children captured by the database were treated for SA/OM but were later found to have a different diagnosis.

Completeness of follow-up

Follow-up data are collected at a follow-up visit at around 3 months post discharge. The number lost to follow up will be reported and the reasons where known will be documented. Any deaths and their causes will be reported separately.

Study Outcomes

This study examines many measurements routinely made in the diagnosis, treatment, and aftercare of children with SA or OM. There are three areas of key interest: Diagnosis (Objective 1); Treatment (Objective 2); and Complications Arising and/or Treatment Failures (Objective 3). The key endpoints are:

Diagnosis:

- Bones and joints affected
- Time taken from first presentation to:
 1. Referral to hospital
 2. Having surgery
 3. Initiation of IV antibiotics [this time-point used also as a proxy for a diagnosis being made]
- Surgical procedures carried out prior to diagnosis
- Imaging types used (X-ray, CT scan, ultrasound, bone scan, MRI), and results obtained
- Diagnostic blood tests carried out (Hb, WBC, N, Plt, CRP, ESR) and their outcomes
- Microbiological tests carried out (presence of any of 8 named micro-organisms)

Antibiotic Treatment in and post hospital stay:

- Length of time on IV antibiotics
- Length of time on oral antibiotics
- Total length of time on antibiotics
- Length of time from presentation to discharge
- Blood tests carried out and their results
- Antibiotics prescribed (during hospital stay and at discharge)
- Dosage (Normal / High as defined in Children's British National Formulary)
- Adherence to discharge prescription
- Reasons for non-adherence or changes to prescribed regimes.

Complications / Failure of treatment

- Complication types
- Actions arising from complications
- Treatment failure (Y/N)

Analysis

The primary interest are the sub-group of children with acute SA / OM and no chronic comorbidities (simple cases). All analyses described below will therefore be carried out for this sub-group in the first instance. The other two sub-groups (chronic SA/OM and infections arising from previous orthopaedic surgery) will be analysed separately as a secondary analysis. See *Appendix A: Template Results Tables* for tables referred to in the following analysis plan.

Objective 1

[1A] See Section 8.2 above for demography and definition of diagnosis groups. Numbers and percentages will be calculated and results tabulated separately for: demographics; diagnosis groups; presentation; history of orthopaedic surgery; medical history; and antibiotics prescribed prior to presentation. See Tables 1A-1,2,3,4,5,6 below

[1B] The clinical time-line from first presentation through to diagnosis will be explored. Time to hospital referral, first imaging, surgery, radiological diagnosis, and initiation of IV antibiotics will all be summarised using appropriate descriptive statistics [see Table 1B-1].

[1C] The number and percentage of cases undergoing different types of surgery prior to diagnosis will be reported [see Table 1C-1].

[1D] The number and percentage of cases testing positive for at least one micro-organism, and each of 8 unique micro-organisms will be reported, split by centre type (Tertiary / Secondary). Any other micro-organisms detected will be categorised and reported as “Other”. Of cultures testing positive for *Staphylococcus aureus*, the number and percentage where PVL is tested for will be reported. The number and percentage of cases where a PCR test is also carried out will be calculated by centre type. [See Table 1D-1].

The number and percentage of types of sample for micro-biological testing (e.g. blood, pus, etc.) that are typically taken from children will be reported [see Table 1D-2].

[1E] The number and percentage of cases with test results at presentation for: each of 6 blood tests; and the combinations ‘CRP & ESR’ and ‘CRP & no ESR’ will be reported, split by centre type (Tertiary / Secondary) [see Table 1E-1]. A boxplot for each of the six blood test measures at presentation will be created to show the distribution of results. Proportions with elevated results (above centre-specific normal ranges) will be calculated for each blood test type [see Table 1E-2].

The blood test result ‘CRP_{max}’ will be summarised for culture-positive and culture negative cases and a box plot created to compare these. This analysis will be split by age-group. This is to explore whether a higher CRP_{max} is associated with particular organisms. Differences that are clinically significant will be tested for statistical significance using appropriate hypothesis tests [see Table 1E-3].

[1F] There are five imaging methods that could be requested by clinicians to aid diagnosis. The number and percentage of cases for each imaging type used prior to diagnosis will be reported, split by centre type (Tertiary / Secondary) and of these the number and percentage abnormal [see Table 1F-1].

Objective 2

Treatment of children with SA or OM takes the form of antibiotic treatment and additionally for some cases, surgical intervention. Initially antibiotics are given intravenously. At a later date, antibiotics are given orally – the timing of the switch is based on clinical judgement that the child has recovered sufficiently and is capable of taking drugs orally.

- [2A] The lengths of time on IV antibiotics, oral antibiotics, and total antibiotic duration will be summarised using appropriate descriptive statistics. (Note that these times are based on what happened during hospital stay and what was **planned** at discharge. It is not possible to obtain data for the actual date when antibiotics were stopped post discharge.) Results will also be split by centre type, whether there was at least one surgical procedure after initiation of IV antibiotics, if CRP_{max} occurred at presentation, and by microbes detected. [See Table 2A-1].

Antibiotic regimes will be further summarised for the sample: Number of antibiotics given in the initial treatment; timing of oral switch (<1 wk, 1-2 wks and >2 wks)); total course of antibiotics (shortened vs standard); dose (augmented at least once vs standard dose throughout where ‘augmented at least once’ is defined as having at least one high dose of IV antibiotics); and total number of different antibiotics prescribed over the full treatment period [see Table 2A-2].

- [2B] Antibiotics prescribed during hospital stay will be summarised using frequencies and percentages. There are a large number of antibiotics that could be prescribed by either route. Of these, 4 named IV antibiotics and 5 named oral antibiotics are of particular interest. A category labelled ‘other’ will be used to define all other antibiotics given by each route. For each antibiotic and route, summary statistics will be reported for whether it was part of the initial prescription; given at least once; frequency of administration of doses during a day; daily dose per kg weight of child; and duration of course (> 1 week Y/N). This will give an overview of the most commonly prescribed antibiotics during hospital stay [see Table 2B-1].

Initial IV antibiotic prescriptions will be compared between secondary and tertiary site types; between children with and without penicillin allergy; and with and without sickle cell disease [see Table 2B-2].

- [2C] Blood test results are routinely used to aid the decision to stop giving antibiotics via IV (ie. oral switch). The combinations of blood tests carried out immediately prior to (on the day before or on the day of) the oral switch will be reported as numbers and percentages. CRP as a proportion of CRP_{max} will be summarised [see Table 2C-1].

The change in blood test results over time will be explored graphically using boxplots. For each blood test type, a plot will be produced showing the distribution of results at: presentation; initial of IV; and on each day following start of IV.

- [2D] The number and percentage of cases undergoing different types of surgery post diagnosis will be reported [see Table 2D-1].
- [2E] Appropriate summary statistics will be used to describe length of hospital stay for cases – overall, and split by age-group and centre type [see Table 2E-1].
- [2F] The number and percentage of cases with imaging after initiation of IV will be reported split by site type and image type, with results given.
- [2G] Antibiotics prescribed at discharge will be summarised using frequencies and percentages. There are a large number of antibiotics that could be prescribed by either

route. Of these, 4 named IV antibiotics and 5 named oral antibiotics are of particular interest. A category labelled 'other' will be used to define all other antibiotics given by each route. For each antibiotic and route, summary statistics will be reported for whether it was given at least once; daily dose per kg weight of child; and planned duration of course. This will give an overview of the most commonly planned antibiotic regimes at discharge [see Table 2F-1].

- [2H] Antibiotic regimes post discharge are not always adhered to. The number and percentage of those stopped early will be reported, split by who took the decision (Parent / Hospital / GP). In the same way the number and percentage of patients who had a change to the planned regime will be reported split by who made the change (Hospital / GP). The frequencies of 5 possible reasons for shortening or changing regime will be explored [see Table 2G-1].

Objective 3

- [3A] The number and percentages of cases experiencing a complication of any kind will be reported. These will be further split by 'Complication Type', and cross-tabulated with 'Action Taken' (None / Surgery / Change of antibiotic regime / Re-admission to hospital / Other) [see Table 3A-1].
- [3B] Treatment failure is determined by complications that result in certain actions. e.g. Surgery. The outcomes 'Treatment Failure' (Y/N) and 'Any Complication' (Y/N) will be cross-tabulated with three antibiotic regime variables: Timing of oral switch (Early / Standard); Total course of antibiotics (Shortened / Standard); and Overall dose (High / Normal). Associations between regime types and outcomes will be measured using odds-ratios and 95% CIs. This will give an overview of whether treatment failure and complications may be more likely for certain types of regime [see Table 3B-1].
- [3C] Treatment Failure (Y/N) and Any Complication (Y/N) will be cross-tabulated with surgery undertaken (limited to surgery post presentation). Associations between surgery types and outcomes will be measured using odds-ratios and 95% CIs. This will give an overview of whether treatment failure and complications may be more likely for certain types of surgery [see Table 3C-1].

Analyses of missing data / withdrawals

As this is a service evaluation, there should be only a small number of withdrawals. Those that do occur will be documented. It may be of importance if withdrawals are clustered by centre.

Missing data will be noted and wherever possible, the reasons reported. If a large amount of data critical to the analysis are missing, some changes to the analysis plan may be needed.

Setting results in context of previous research

Once the service evaluation has been completed the results will be set in context of the existing evidence base.

References

1. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. [Ann Int Med 2010;152](#). Epub 24 March.
2. ICH E3 chapter 12.

Appendix A statistical analyses plan: Template Results Tables

1A: Demographics, past medical history, and presenting limbs/joints affected.

TABLE 1A-1

Demographics	Appropriate Summary Statistics
Age (years)	
Male	
Ethnicity	
European North/East/Mid	
European South (Mediterranean)	
European Roma	
African/Caribbean North African	
African/Caribbean Sub Saharan	
African/Caribbean Afro-caribbean	
Asian Indian Subcontinent	
Asian SE (Vietnam, Thailand, Indonesia, Malaysia, Phillipines)	
Asian East Asia (China, Japan, Korea)	
Asian West Asia (Afghanistan, Iranian)	
Middle Eastern Turkish	
Middle Eastern Arab peninsula	
Other/Mixed	

TABLE 1A-2

Diagnosis Group	Appropriate Summary Statistics
Simple ^(a)	
OM	
SA	
Complex ^(b)	
OM	
SA	
Presentation due to infected implant or surgery from previous orthopaedic surgery	
Misdiagnosed	
Types of diagnoses for misdiagnosed:	
Cellulitis	
Discitis	
Reactive arthritis	
Infective arthritis	
Joint effusion	
Abscess	
Other	
Unknown/Undecided	

^(a)Acute SA/OM with no co-morbidities; ^(b) 'Chronic SA/OM' or 'Acute SA/OM with co-morbidities'

TABLE 1A-3

Presentation	All	Simple (n=?)	Complex (n=?)
Presenting to:			
Outpatient Clinic			
Inpatient			
GP			
Emergency Department			
Walk-In Centre			
Not known			
Limbs/Joints affected*:			
Hip			
Shoulder			
Knee			
Ankle			
Wrist			
Skull			
Mandible			
Humerous			
Clavicle			
Radius			
Ulna			
Pelvis			
Rib			
Femur			
Tibia			
Fibia			
Sternum			
Elbow			
Foot			
Calcaneum			
Lumbar vertebrae			
Cervical vertebrae			
Thoracic vertebrae			
Sacrum vertebrae			

*Categories not mutually exclusive, so more than one bone/joint can be recorded per patient.

TABLE 1A-4

History of Orthopaedic Surgery	Any	In 6 months prior to presentation (same bone/joint as at presentation)
Yes?		
Bone/joint affected*:		
Knee		
Clavicle		
Radius		
Ulna		
Humerus		
Tibia		
Femur		
Ankle		
Side:		
Right		
Left		
Both		

TABLE 1A-5

Medical History	Yes	No	Not tested / unknown
Co-morbidities indicating complex case:			
Sickle cell disease			
Known immunocompromise			
Indwelling central venous catheter or PICC			
Cystic Fibrosis			
Cerebral Palsy			

TABLE 1A-6

Medical History	Simple	Complex	Other
Other Medical Conditions:			
Congenital cardiac disease			
Diabetes Mellitus			
Purpura Fulminans			
Malnutrition			
Other			
Immune modulating treatment in last 6 calendar months?			
Steroid			
Radiotherapy			
Chemotherapy			
Azathioprine			
Cyclosporin			
Cyclophosphamide			
Rituximab			
Leflunomide			
Tacrolimus			
Sirolimus			
Other			
Infection History in the last 12 calendar months?			
Pneumonia			
Septicaemia			
Pyelonephritis			
Cellulitis / soft tissue infection			
Meningitis			
Osteoarticular infection			
Abdominal sepsis			
Varicella			
Other			

History of Trauma in the last month?
Other Surgery in 12 months prior to presentation?

Pre-presentation variables that affect drug choice, dosage and duration. (Simple cases only)

TABLE 1A-7

Antibiotic Medical History	N(%)	Route		Duration
		IV	Oral	> 1 week
Penicillin allergy		-	-	-
Antibiotics (1 month pre-presentation)				
Any				
Flucloxacillin				
Clindamycin				
Cefuroxime				
Ceftriaxone				
Amoxicillin				
Co-Amoxiclav				
Rifampicin				
Vancomycin				
Fusidic Acid				
Teicoplanin				
Other				

1B: The clinical time-line for diagnosis

TABLE 1B-1

Diagnostic and hospital stay Time-line (Days)	Appropriate Summary Statistics
From first presentation to:	
Hospital Referral	
1 st Imaging	
Pre-diagnosis surgery	
Radiological diagnosis	
Initiation of IV antibiotics	
(proxy for diagnosis of OM/SA)	

1C: Surgical procedures carried out post presentation and prior to diagnosis (before or on the same day as initiation of IV antibiotics).

TABLE 1C-1

Surgery types	Rate n (%)
Any	
Aspiration	
Incision and drainage	
Drill decompression	
Curettage/excision	
Arthrotomy	
Arthroscopy	
Amputation	
Debridement	
Fasciotomy	
Compartment decompression	
Secondary closure	
Skin graft	
Other plastic surgery	

1D: Summary of range of tests carried out and sensitivity of conventional microbiological tests. (Simple cases only)

TABLE 1D-1

N(%)
Children with at least one conventional test carried out
At least one micro-organism detected
Specific mirco-organisms detected by conventional testing:
Staphylococcus Aureus
<i>PVL tested for?</i>
Kingella Kingae
Streptococcus pyogenes
Pseudomonas
Group b Streptococcus
Salmonella
Candida
Tuberculosis
Other
PCR testing carried out

Types of sample used for conventional microbiological testing. (Simple cases only)

TABLE 1D-2

N(%)
Number of different sample types taken
0
1
2
>2
Sample types. Children that had at least one:
Pus (periosteal)
Bone biopsy
Pus/Wound swab
Joint aspirate

Other

1E: Blood-tests carried out at presentation. (Simple cases only)

TABLE 1E-1

Blood tests at presentation	N(%) with at least one measurement on day of presentation	Summary statistic for test results	% with elevated* results
Hb			
WCC			
N			
Plt			
CRP			
ESR			
CRP & ESR		-	-
CRP & <i>not</i> ESR		-	-
CRP _{max}		-	-
occurring at presentation			

*Above the centre specific normal range

1F: Comparing average CRP_{max} for each culture negative vs. positive, by age-group. (PCR and conventional test results combined; Simple cases only).

TABLE 1F-1

Microbe	Summary statistics for CRP _{max}					
	< 1 year		1-6 years		6-16 years	
	+ve	-ve	+ve	-ve	+ve	-ve
Staphylococcus Aureus						
Kingella Kingae						
Streptococcus pyogenes						
Pseudomonas						
Group b Streptococcus						
Salmonella						
Candida						
Tuberculosis						
Other						

1G: Imaging types routinely used to aid diagnosis (On day of or prior to initiation of IV; Simple cases only).

TABLE 1G-1

Imaging Type	N(%) with at least one image	Number (%) Abnormal
X-ray		
CT scan		
Ultrasound		
MRI		
Bonescan		

What is the range of durations of intravenous and oral antibiotics used to treat osteomyelitis?

2A: The clinical time-line for antibiotic treatment.

TABLE 2A-1

Antibiotic Treatment Time-line (Days)	Appropriate Summary Statistics
Length of time on:	
IV	
Oral ^(a)	
Total ^(b)	

^(a)Use time on oral antibiotics pre-discharge plus planned duration, as proxy for actual duration.

^(b) Length of time treated with any antibiotic (for some children oral antibiotics were given concurrently to IV. So the Total length of time is not necessarily the time on IV plus the time on Oral)

Types of antibiotic regimes experienced.

TABLE 2A-2

Antibiotic Regime	All	Centre Type	
		Tertiary	Secondary
Number of different antibiotics given at initiation of treatment			
1			
2 or more			
Timing of oral switch			
Very Early (< 1 week)	Also report median & IQR for each category here		
Early (1-2 wks)			
Standard / Late (> 2 wks)			
Total course of antibiotics			
Shortened (< 6 weeks)			
Standard (> 6 weeks)			
Dose			
Augmented at least once ^(a)			
Standard throughout			

Total number of antibiotics
prescribed

IV:

1
2
>2

Oral:

1
2
>2

^(a)At least one IV antibiotic given at a high dose

2B: IV and oral antibiotics prescribed prior to discharge.

TABLE 2B-1

Antibiotic	Given at least once	Part of initial prescription	Daily dose per kg weight of child	Frequency					Duration (> 1 week)
				6 hourly	8 hourly	12 hourly	Once daily	Other	
IV									
Flucloxacillin									
Clindamycin									
Cefuroxime									
Ceftriaxone									
Other									
Oral									
Flucloxacillin									
Clindamycin									
Amoxicillin									
Co-Amoxiclav									
Rifampicin									
Other									

TABLE 2B-2

Antibiotics given as part of first treatment	Centre Type		Given had a penicillin allergy	Given had sickle cell disease
	Tertiary	Secondary		
IV				
Flucloxacillin				
Clindamycin				
Cefuroxime				
Ceftriaxone				
Other				
Oral				
Flucloxacillin				
Clindamycin				
Amoxicillin				
Co-Amoxiclav				
Rifampicin				
Other				

2C: Blood-tests carried out immediately prior to oral switch

TABLE 2C-1

Blood tests	Number (%) of cases with test results immediately prior to switch		Summary statistic for test results	As a proportion of CRP _{max}
	Tertiary	Secondary		
Hb				-
WCC				-
N				-
CRP				-
ESR				-
CRP & ESR			-	-
CRP & <i>not</i> ESR			-	-

2D: Surgery occurring after the initiation of IV antibiotics (post diagnosis).

TABLE 2D-1

Surgery types	Rate n (%)
All	
Aspiration	
Incision and drainage	
Drill decompression	
Curettage/excision	
Arthrotomy	
Arthroscopy	
Amputation	
Debridement	
Fasciotomy	
Compartment decompression	
Secondary closure	
Skin graft	
Other plastic surgery	

2E: Length of stay in hospital by age-group and site type.

TABLE 2E-1

Centre type	Age group			
	All	< 1 year	1-6 years	6-16 years
All				
Tertiary				
Secondary				

2F: Imaging types routinely used post diagnosis.

TABLE 2F-1

Imaging Type	Number (%) of cases imaged at least once post-diagnosis		Number (%) Abnormal
	Tertiary	Secondary	

X-ray
CT scan
Ultrasound
MRI
Bonescan

2G: Antibiotic regimes prescribed at discharge. As part of this – what percentage went home on IV as opposed to oral antibiotics.

TABLE 2G-1

Antibiotic	N(%)	Daily dose per kg weight of child	Planned Duration
Went home on			
IV		-	-
Oral		-	-
IV			
Flucloxacillin			
Cefuroxime			
Ceftriaxone			
Benzyl Penicillin			
Other			
Oral			
Flucloxacillin			
Cefalexin			
Co-Amoxiclav			
Other			

2H: Were discharge antibiotic regimes adhered to? Percentages of treatments shortened or changed post discharge, split by who made the decision: parent, hospital or GP. What were the main reasons for non-adherence or change of regime post discharge?

TABLE 2H-1

Adherence to prescribed antibiotic regimes	Number (%)
Stopped early by:	
Parent	
Hospital	
GP	
Changed by:	
Hospital	
GP	
Reason for shortening / change of regime:	
Unpalatable antibiotic	
Diarrhoea	
Rash	
Resolution of symptoms	

Recurrence of infection

3A: Complication types by action taken.

TABLE 3A-1

Complication	N (%)	Action taken				
		None	Surgery	Change of antibiotic regime	Re-admission to hospital	Other action
Any Complications						
Complication type:						
Fever						
Recurrence of Infection						
Dislocation						
Subluxation						
Pathological Fracture						
Sinus						
Other						

3B: Treatment failures and complications by type of antibiotic regime.

TABLE 3B-1

Antibiotic Regime	Treatment Failure?			Any complication?		
	Yes	No	Odds ratio	Yes	No	Odds Ratio
Timing of oral switch						
Early (< 2 weeks)						
Standard / Late (> 2 wks)						
Total course of antibiotics						
Shortened (< 6 weeks)						
Standard (> 6 weeks)						
Dose Repeated for IV and oral separately						
High						
Majority Lower range						

3C: Treatment failures and complications by type of surgery.

TABLE 3C-1

Surgery	Treatment Failure?			Any complication?		
	Yes	No	Odds ratio	Yes	No	Odds Ratio
Surgery undertaken after date of 1 st presentation						
Aspiration						
Incision and drainage						
Drill decompression						
Curettage/excision						
Arthrotomy						
Arthroscopy						
Amputation						
Debridement						
Fasciotomy						
Compartment decompression						
Secondary closure						
Skin graft						
Other plastic surgery						

Appendix 8: Additional statistical analyses carried out surplus to SAP 1.5 Service Evaluation

Additional statistical analyses carried out surplus to SAP¹ 1.5

- (1) Blood test results at presentation were summarised in the same way as for at diagnosis., using descriptive statistics.
- (2) Characteristics (age-group, sex, place that children presented, joints/limbs affected, diagnosis, and whether treated with oral antibiotics) were summarised by Simple/Complex case type as frequencies.
- (3) Conventional microbiology test results were originally designed to summarise results of all samples, but were later limited to results arising from bone, blood, joint or periosteal pus samples, for reasons of clinical relevance.
- (4) Time to maximal CRP was investigated and summarised using descriptive statistics.
- (5) The number of MRI scans carried out were further split by bone/joint affected.
- (6) Time-to-switch, split by case type and diagnosis was further presented using Kaplan-Meier curves.
- (7) Children that had only one surgical procedure post diagnosis were identified and the types of surgery the received were summarised.
- (8) All analyses were further split by diagnosis category (SA/OM).

Note that some analyses in the SAP were not carried – this was because clinical relevance was questioned. E.g. Blood test results were not split by centre type and microbiology results were not split by age-group.

¹ Statistical Analysis Plan