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Supplementary Material

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Investigating childhood hip diseases (Slipped capital femoral epiphysis and Perthes' disease) as childhood precursors to osteoarthritis of the hip in adulthood:

A nationwide service evaluation, and nested-cohort study.

Final Analysis: Part 1

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Date	19/09/2018	
Protocol Version and Date	v5.0 30/03/2017	

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3. Introduction

This report presents the results of pre-planned analyses of baseline aspects of the BOSS study, outlined in the Statistical Analysis Plan (SAP): Analysis Part 1. The analysis is undertaken using version 1.0 of the SAP, dated 08/02/2018.

The SAP planned for a presentation of baseline data for the nested cohort from whom consent is obtained to measure patient reported outcomes (PROMs). At the time of writing, queries were outstanding regarding consent validity for a handful of participants. Therefore it has been decided to postpone the reporting of the nested cohort baseline data, and move this to the second BOSS statistical report: Final Analysis Part 2, which is due in February 2020.

A handful of analyses have been added that were not in the v1.0 of the SAP. These are included in version 1.1, dated 05/09/2018. For ease of reference, these are also listed in the change control section of that document.

4. Case Ascertainment and Recruitment

Case ascertainment and data entry were the responsibility of clinicians. There were inevitably cases created in error, and duplicate entries for some children. Verified record creation errors and duplicates were deleted from the database. Of the remaining cases identified by clinicians, some exclusions were made. Types of exclusions are given, with more detail regarding these on the next page.

Figure 4-1: SCFE baseline CONSORT chart

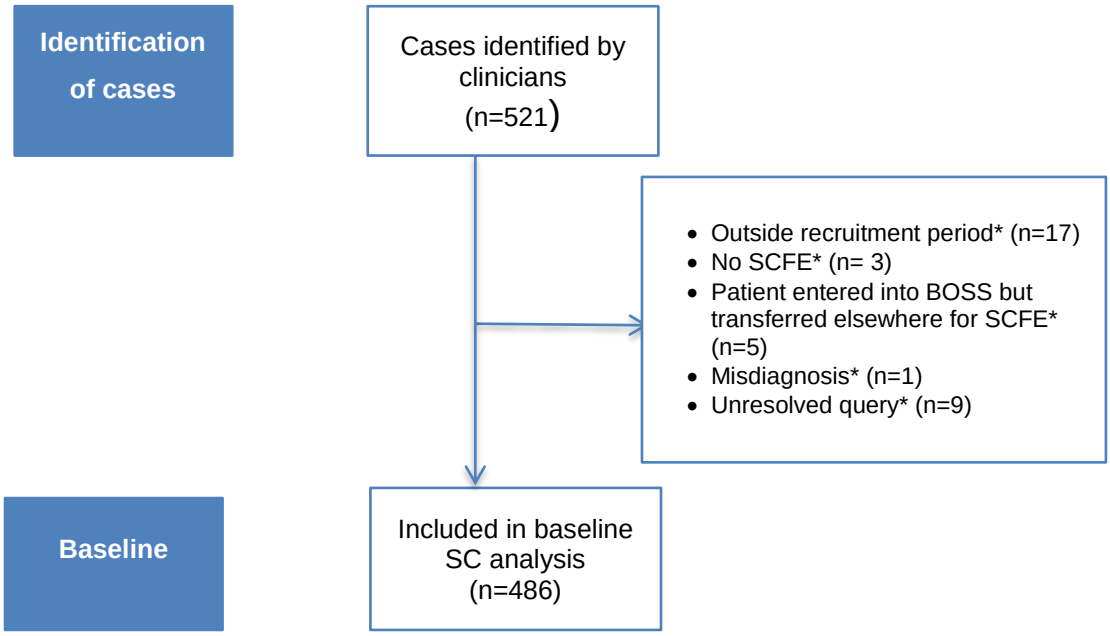
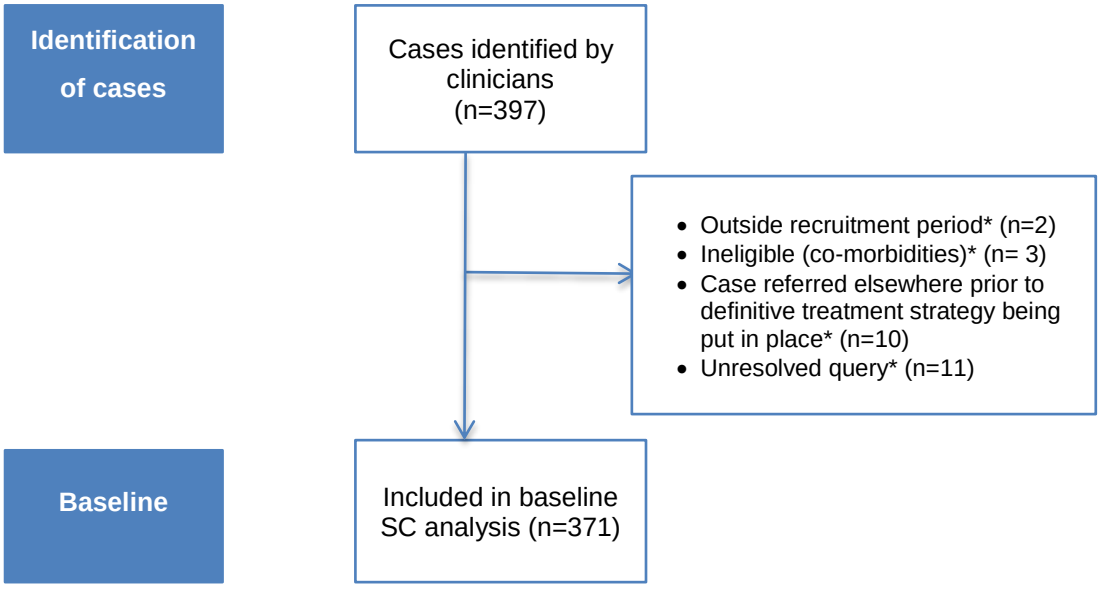


Figure 4-2: Perthes' baseline CONSORT chart



*Notes on exclusions

1. 'Outside recruitment period': At the start of recruitment, a number of children with SCFEs that were carried out prior to 04/04/2016 were input into the database. A handful of records were created after the recruitment period finished – retrospective case ascertainment was permitted till December 2017, but only to identify presentations of SCFE/Perthes prior to 01/10/2017. Presentations on or after that date are considered ineligible.
2. 'No SCFE': Occasionally potential SCFE patients were entered into the database - they had not yet had their surgery. At the start of data entry for SCFE patients, there is a question to check eligibility: 'Has the patient had a SCFE'. Most went on to have the operation, and the database was updated by clinicians. There are three where the database remained unchanged, and querying verified that no SCFE was carried out.
3. 'Patient entered into BOSS but transferred elsewhere for SCFE': this is similar to 'No SCFE', except that that the patient was transferred elsewhere, and they may been entered as a new case by the new site. These records could also be classified as 'created in error'. They are classed as exclusions, rather than ineligibles.
4. 'Misdiagnosis': one case in initially (wrongly) included as a SCFE. They were transferred to another site, who disagreed with the diagnosis. In a clinical trial, they may have gone on to be randomised, however for the purpose of this study, it was decided at an SMG to exclude the patient.
5. 'Unresolved query': These are records that are suspected to be created in error (little or no data input) or duplicates (another child exists in the database with the same gender, month of birth, year of birth and centre). A query is unresolved when a site either does not respond, or cannot confirm that a true case has been identified.
6. 'Ineligible (co-morbidities)': Perthes patients should not be included if certain comorbidities are present. In a handful of cases, clinicians created a record for such a patient – they then ticked 'Yes' to at least one comorbidity, and the system indicated no further data collection was required due to ineligibility. Note that the number recorded with comorbidities is not necessarily the total number of Perthes' patients presenting during the recruitment period with comorbidities.
7. 'Case referred elsewhere prior to definitive treatment strategy being put in place': for Perthes' patients, a diagnosis may be made at a hospital, but the patient is then transferred on to a specialist centre to be given a definitive treatment plan. Occasionally clinicians at the diagnostic centre entered the patient into BOSS – but the treating centre did not enter them. These patients are excluded from the study, as strictly speaking they are not eligible and we do not have a baseline date (date seen by definitive treatment provider).

4.1 Recruitment

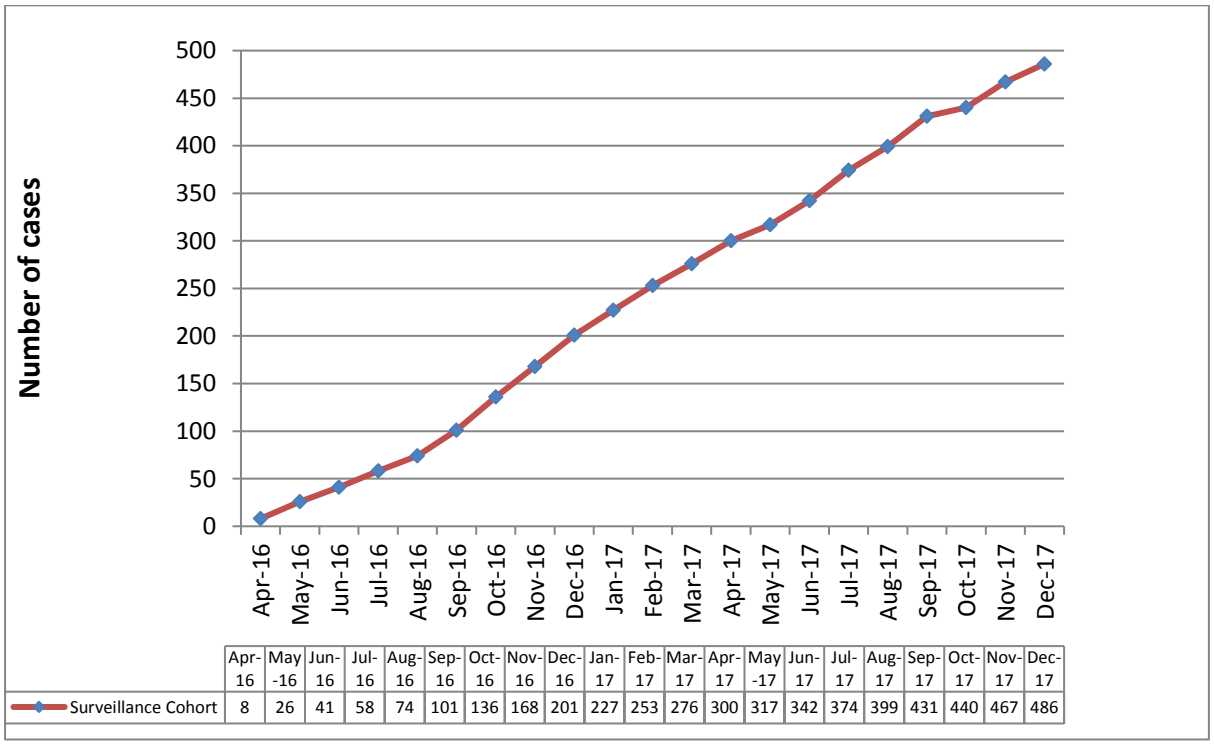
A total of 144 sites are taking part in the surveillance study.

Recruitment to the surveillance cohort began on 4th April 2016 and finished on 14th December 2017. This cohort represents all new presentations of SCFE and Perthes' from participating sites throughout England, Scotland and Wales between 4th April 2016 and 30th September 2017 inclusive. (Cases recruited after 30th September 2017 represent retrospective case ascertainment.)

486 confirmed cases of SCFE were identified in the surveillance cohort.

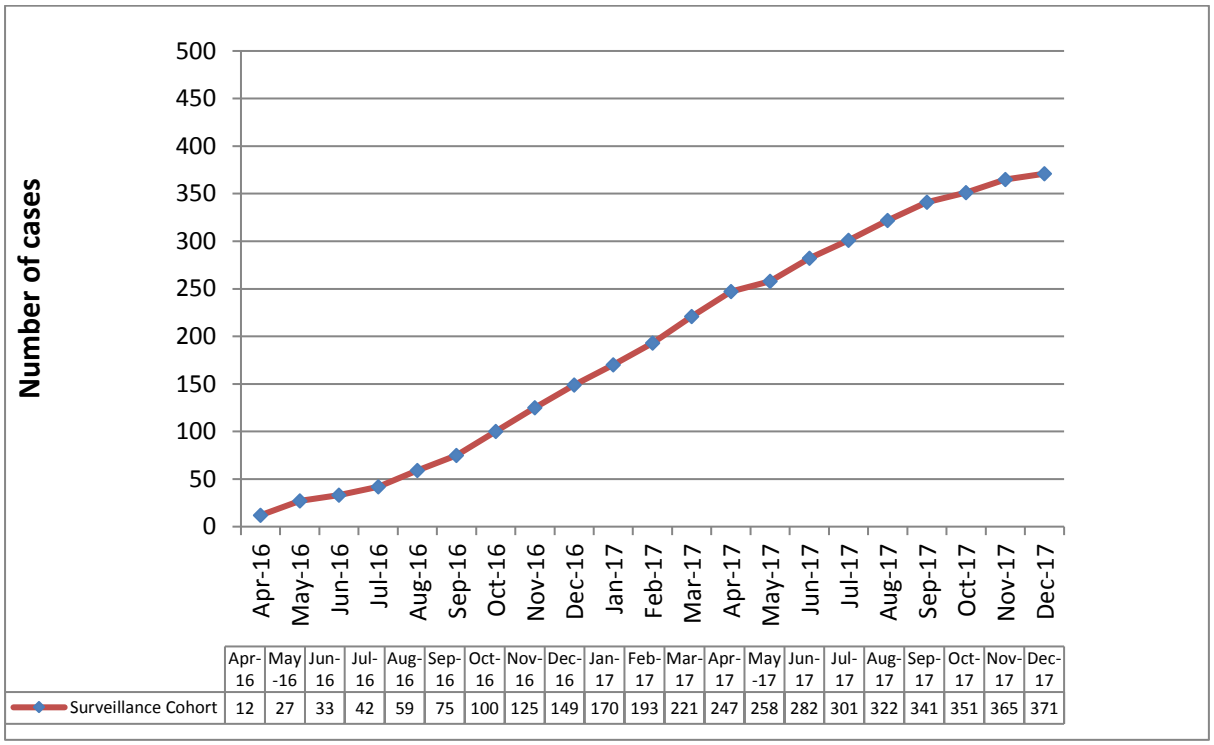
371 confirmed cases of Perthes' were identified in the surveillance cohort.

Figure 4-3: SCFE surveillance cohort recruitment over time



	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17
Surveillance Cohort	8	26	41	58	74	101	136	168	201	227	253	276	300	317	342	374	399	431	440	467	486

Figure 4-4: Perthes' surveillance cohort recruitment over time



	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17
Surveillance Cohort	12	27	33	42	59	75	100	125	149	170	193	221	247	258	282	301	322	341	351	365	371

Table 4-1: BOSS Recruitment to the Surveillance cohort (SC) by country, region and site.

Country, Region & Site Name	SCFE SC	Perthes' SC
England		
London & Surrounding Boroughs		
Barking Havering and Redbridge	8	3
Barnet and Chase Farm	-	-
Bart's	13	3
Basildon and Thurrock	7	2
Chelsea and Westminster Hospital NHS Foundation Trust	6	-
East Kent Hospitals University NHS Foundation Trust (QEQMH)	8	2
Epsom and St Helier University Hospitals NHS Trust	1	3
Great Ormond Street Hospital for Children NHS Foundation Trust	1	2
Guys and St Thomas NHS Foundation Trust	8	1
Hillingdon Hospitals NHS Foundation Trust	4	1
Homerton University Hospital NHS Foundation Trust	1	-
Imperial College Healthcare NHS Trust	3	2
Kings College Hospital NHS Foundation Trust	5	-
Maidstone and Tunbridge Wells NHS Trust	-	4
Medway NHS Foundation Trust	-	-
North Middlesex University Hospital NHS Trust	1	-
North West London Hospitals NHS Trust (also includes Ealing above)	-	-
Queen Elizabeth Hospital Woolwich	-	-
Royal Free London NHS Foundation Trust	4	1
Royal National Orthopaedic Hospital NHS Trust	17	9
Royal Surrey County NHS Foundation Trust	1	-
St Georges Healthcare NHS Trust	9	7
The Whittington Hospital NHS Trust	3	-
University College London Hospitals NHS Foundation Trust	-	-
University Hospital Lewisham	2	-
West Middlesex University Hospital NHS Trust	1	3
Whipps Cross University Hospital	-	-
London & Surrounding Boroughs Total	**103**	**43**
Central England		
Bedford	3	-
Birmingham Children's	23	-
Cambridge	6	4
Chesterfield Royal Hospital NHS Foundation Trust	-	-
Colchester Hospital University NHS Foundation Trust	4	-
Derby Hospitals NHS Foundation Trust	4	2
East and North Hertfordshire NHS Trust	2	-
Heart Of England NHS Foundation Trust	-	-
Hinchingbrooke Health Care NHS Trust	-	1
Ipswich Hospital NHS Trust	1	3
James Paget University Hospitals NHS Foundation Trust	-	-
Kettering General Hospital NHS Foundation Trust	2	1
Luton and Dunstable Hospital NHS Foundation Trust	2	-
Mid Essex Hospital Services NHS Trust	-	1
Norfolk and Norwich University Hospitals NHS Foundation Trust	6	9
Northampton General Hospital NHS Trust	2	2
Nottingham University Hospitals NHS Trust	12	8
Peterborough and Stamford Hospitals NHS Foundation Trust	10	1
Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust	7	10
Sandwell and West Birmingham Hospitals NHS Trust	4	1
Shrewsbury and Telford Hospital NHS Trust	-	-
The Dudley Group NHS Foundation Trust	-	3
The Princess Alexandra Hospital NHS Trust	2	3
The Royal Wolverhampton NHS Trust	-	-
United Lincolnshire Hospitals NHS Trust	2	1
University Hospitals Coventry and Warwickshire NHS Trust	7	9
University Hospitals Of Leicester NHS Trust	9	1
University Hospitals of the North Midlands	10	11
West Hertfordshire Hospitals NHS Trust	1	-
West Suffolk NHS Foundation Trust	5	3

Country, Region & Site Name	SCFE SC	Perthes' SC
Worcestershire Acute Hospitals NHS Trust	4	1
Wye Valley NHS Trust	1	-
Central England Total	**129**	**75**
Northern England		
Airedale	2	1
Alder Hey	23	40
Barnsley Hospital	-	2
Blackpool	-	-
Bolton	-	1
Bradford	3	-
Calderdale and Huddersfield	3	3
Central Manchester University (Manchester Children's)	18	8
City Hospitals Sunderland NHS Foundation Trust	1	2
Countess Of Chester Hospital NHS Foundation Trust	1	-
County Durham and Darlington NHS Foundation Trust	4	1
Doncaster and Bassetlaw Hospitals NHS Foundation Trust	-	1
East Lancashire Hospitals NHS Trust	6	11
Harrogate and District NHS Foundation Trust	-	-
Hull and East Yorkshire	5	5
Lancashire Teaching Hospitals NHS Foundation Trust	3	7
Leeds General Infirmary	4	9
Mid Cheshire Hospitals NHS Foundation Trust	-	-
Mid Yorkshire Hospitals NHS Trust	2	6
North Cumbria University Hospitals NHS Trust	-	-
Northern Lincolnshire and Goole Hospitals NHS Foundation Trust	-	-
Northumbria Healthcare NHS Foundation Trust	3	6
Pennine Acute Hospitals NHS Trust (North Manchester)	2	-
Pennine Acute Hospitals NHS Trust (Oldham)	3	-
Scarborough and North East Yorkshire Health Care NHS Trust	-	-
Sheffield Children's NHS Foundation Trust	18	2
South Tees Hospitals NHS Foundation Trust	3	9
Southport and Ormskirk Hospital NHS Trust	-	3
St Helens and Knowsley Hospitals NHS Trust	-	-
Stockport NHS Foundation Trust	1	2
Tameside Hospital NHS Foundation Trust	-	1
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	10	5
The Rotherham NHS Foundation Trust	-	2
University Hospital Of South Manchester NHS Foundation Trust	-	-
University Hospitals Of Morecambe Bay NHS Foundation Trust	1	1
Warrington and Halton Hospitals NHS Foundation Trust	-	-
Wirral University Teaching Hospital NHS Foundation Trust	1	-
Wrightington, Wigan and Leigh NHS Foundation Trust	-	1
York Teaching Hospital NHS Foundation Trust	-	-
Northern England Total	**118**	**129**
South of England		
Basingstoke	-	-
Brighton and Sussex	7	-
Buckinghamshire	3	1
Dorset County Hospital NHS Foundation Trust	1	-
East Sussex Healthcare NHS Trust	1	2
Frimley Park Hospital NHS Foundation Trust	2	2
Gloucestershire Hospitals NHS Foundation Trust	7	-
Great Western Hospitals NHS Foundation Trust	1	2
Milton Keynes Hospital NHS Foundation Trust	3	1
Northern Devon Healthcare NHS Trust	2	-
Oxford University Hospitals NHS Trust	7	11
Plymouth Hospitals NHS Trust	3	4
Poole Hospital NHS Foundation Trust	-	2
Queen Alexander Hospital, Portsmouth	3	11

Country, Region & Site Name	SCFE SC	Perthes' SC
Royal Berkshire NHS Foundation Trust	3	7
Royal Cornwall Hospitals NHS Trust	1	5
Royal Devon and Exeter NHS Foundation Trust	7	-
Royal United Hospital Bath NHS Trust	2	1
Salisbury NHS Foundation Trust	-	-
South Devon Healthcare NHS Foundation Trust	2	-
Taunton and Somerset NHS Foundation Trust	-	2
University Hospital Southampton NHS Foundation Trust	25	20
University Hospitals Bristol NHS Foundation Trust	6	2
Wexham Park	2	6
Winchester	-	-
Worthing And Southlands Hospitals NHS Trust	2	2
South of England Total	**90**	**81**
England Total	**440**	**328**
Scotland		
Borders General	-	-
Dumfries and Galloway Royal Infirmary	-	1
Forth Valley	2	3
Glasgow	11	1
Hairmyres Hospital	-	-
Inverclyde Royal	-	-
Monklands Hospital	-	1
Raigmore Hospital	2	1
Royal Aberdeen Children's Hospital	4	5
Royal Alexandria Hospital	2	1
Royal Hospital for Sick Children (Edinburgh)	8	9
Tayside	8	-
University Hospital Crosshouse	-	2
Western Isles Hospital	-	-
Wishaw General	1	2
Scotland Total	**38**	**26**
Wales		
Aneurin Bevan Health Board	3	2
Betsi Cadwaladr	-	-
Cardiff and Vale University Local Health Board	4	5
Cwm Taf Health Board	1	4
Swansea	1	6
Wales Total	**9**	**17**
Overall Total	**486**	**371**

4.2 Study population

4.2.1 Data sets analysed

Table 4-2: Data sets analysed

Population	n
SCFE Surveillance cohort:	
Patient-level	486
Hip-level*	514
First presentations included in incidence calculation*	397
At risk of contralateral SCFE*	345
Perthes' Surveillance cohort:	
Patient-level	371
Hip-level*	396
First presentations included in incidence calculation*	304
At risk of contralateral disease*	360

*Explanatory notes

1. 'Hip-level': In some analyses, we summarise data for each newly affected hip. Some children newly present with bilaterally, and therefore the total number of hips newly affected is greater than the total number of patients.
2. 'First presentations included in incidence calculation': for SCFE, the calculation of incidence is based on the recruitment window of 01/06/16 – 31/08/2017. The first two months had a large number of potential missed cases according to HES, and rather than attempt to check all these, it was deemed that an allowance of two months was needed as a run-in period for the study for the purpose of an incidence calculation. For the last month no HES data could be made available in time to carry out in-depth checking of potential missed cases, so this month is excluded as well. For Perthes', the calculation of incidence is based on the recruitment window of 01/09/16 – 30/09/2017. The first five months were not as well captured due to there being a fairly long run-in period for the study, and as there were no HES data available that could be used to identify potential missed cases. Also excluded from the incidence calculations, are cases with a history of contralateral SCFE/Perthes' at baseline.
3. 'At risk of contralateral SCFE': At the end of the study, we will be measuring the incidence of contralateral SCFE. The total number at risk at baseline is therefore of interest. This is defined as patients with: (a) no history of contralateral SCFE; (b) a unilateral 1st presentation; and (c) no prophylactic fix.
4. 'At risk of contralateral disease': At the end of the study, we will be measuring the incidence of contralateral Perthes'. The total number at risk at baseline is therefore of interest. This is defined as patients with: (a) no history of contralateral Perthes'; and (b) a unilateral 1st presentation.

5. Results: SCFE

5.1 Cohort characteristics

Table 5-1: SCFE baseline demographics

	Surveillance cohort (N=486)
Age (years)	
Mean (SD)	12.6 (1.8)
Min, Max	6.3, 18.7
Missing	0
Age-group (years)	
6 - <11	90 (18.5%)
>=11 - <19	396 (81.5%)
Gender	
Male	277 (57.0%)
Female	209 (43.0%)
Ethnicity	
White - British	320 (68.5%)
White - Irish	1 (0.2%)
White - Other white background	20 (4.3%)
Mixed - White & black Caribbean	13 (2.8%)
Mixed - White & black African	4 (0.9%)
Mixed - White & Asian	3 (0.6%)
Mixed - Other mixed background	5 (1.1%)
Indian	13 (2.8%)
Pakistani	17 (3.6%)
Bangladeshi	4 (0.9%)
Asian - Other Asian background	12 (2.6%)
Black Caribbean	12 (2.6%)
Other Black African	33 (7.1%)
Black - Other black background	5 (1.1%)
Chinese	2 (0.4%)
Any other ethnic group	3 (0.6%)
Missing	19
BMI	
n	140
Mean (SD)	26.4 (6)
Min, Max	14.2, 48.9
Missing	346

Table 5-2: Line listings of free-text entries for 'Any other ethnic group' (as they appear in the database)

Reported ethnic groups (N missing = 1)
• *Arabic* • *Not Sure*

5.2 Incidence

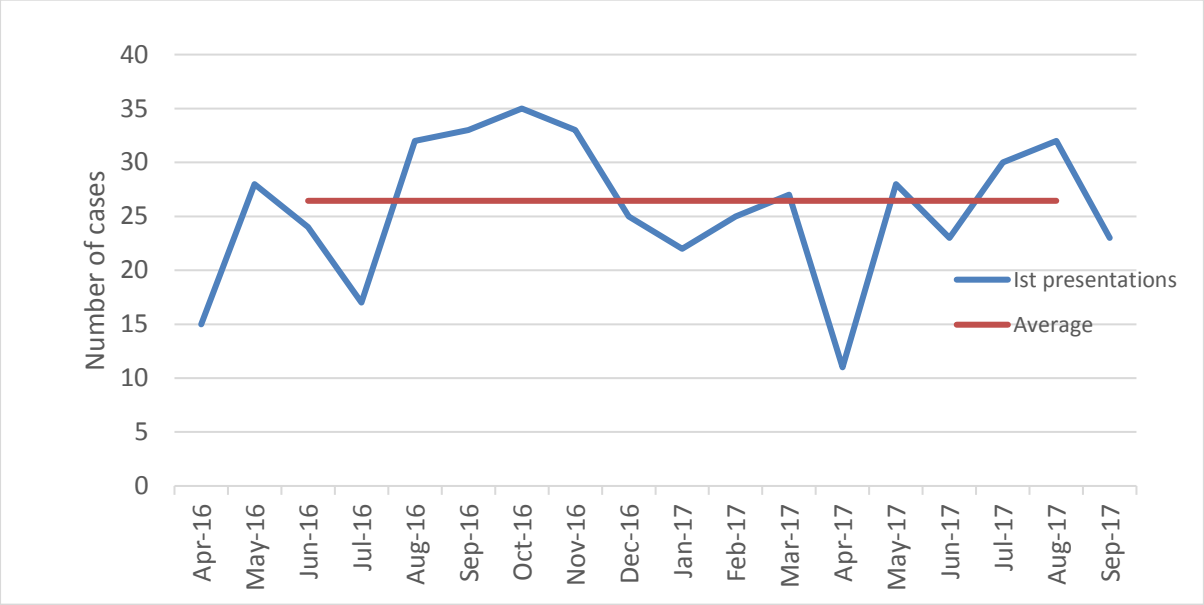
Table 5-3 gives incidence of first presentation of SCFE using the data collected in BOSS. See Section 5.2.1 below for a sensitivity analysis of incidence adding in potential missed cases identified by HES.

Table 5-3: Annual Incidence per 100,000 at-risk population of first presentations of SCFE (based on cases identified during the period 01/06/16 to 31/08/17, with no prior SCFE carried out on either hip)

	At-risk Population[(a)] (Mid-year estimate 2016[(b)])	First presentation of SCFE		
	n	n	Incidence	95% CI
All[(a)]	9,499,724	397	3.34	(3.01,3.67)
By Country & Region:				
England	8,301,394	357	3.44	(3.08,3.8)
London & Surrounding Boroughs	1,851,204	81	3.5	(2.78,4.35)
South	1,696,467	69	3.25	(2.53,4.12)
Northern	2,280,272	99	3.47	(2.79,4.16)
Central	2,473,451	108	3.49	(2.83,4.15)
Wales	454,551	7	1.23	(0.5,2.54)
Scotland	743,779	33	3.55	(2.44,4.98)
By age-group:				
6-10 years	3,850,071	79	1.64	(1.3,2.05)
11-18 years	5,649,653	318	4.5	(4.01,5)
By sex:				
Male	4,867,679	225	3.7	(3.21,4.18)
Female	4,632,045	172	2.97	(2.53,3.41)

[(a)]6-18 year-olds, England, Scotland & Wales; [(b)] Source: ONS

Figure 5-1: Number of first presentations[(a)] of SCFE per month surgery took place, with average[(b)] monthly case-load.



[(a)] No history of prior contralateral SCFE; [(b)] The plotted average is derived from the national incidence estimate calculated from these data, for the time-interval 01/06/16 to 30/08/17 (see Table 5-3).

5.2.1 Sensitivity analysis

Data from HES England, and equivalent sources for Scotland and Wales were extracted identifying all records within these databases of SCFE. A total of 596 records were extracted with operations between 1st June 2016 and 31st August 2017. Of these, 222 were confirmed 'not a case' by sites. A further 6 could be eliminated as duplicated records, leaving a total of 368 potential unique cases identified by HES. NB, Welsh data was only available up until mid April 2017, so a couple of additional cases may have been identified if the analysis were to be re-run.

These 368 were checked for a match to BOSS cases by operation date, sex, month of birth (England only) and year or birth; and through a process of checking and looking for potential data entry errors 336 of the HES cases could be matched to a BOSS case. Not all BOSS cases had a match in HES – there were 61 without a match. This shows that HES does not record all cases.

We are left with 32 cases, 5 of which are known to be true cases that did not get entered into BOSS. Querying during recruitment via e-mail click-and-confirm notifications and direct e-mailing was very successful in both recruiting cases to BOSS and identifying non-cases. The 27 that remain are mostly from sites that were not able to respond to the queries. Nearly one

third come from Scottish or Welsh sites – as populations are small in those countries, the sensitivity analysis has a larger impact on incidence estimates.

The querying process identified some serious flaws in HES data. There are duplicate entries, data-entry errors particularly with demographics, operations recorded for the same child sometimes appear at more than one site, and some sites' SCFEs were recorded at sites that do not do not even treat children or have no surgical capability. It is also difficult to identify first presentations from HES. The 27 potential additional SCFEs may represent contralateral presentations, may represent follow-up operations, or may not be cases at all.

Table 5-4 shows re-calculated incidence estimates adding in the 32 cases. These represent an upper bound on the estimate of incidence of SCFE.

Table 5-4: Sensitivity analysis re-calculations of annual Incidence per 100,000 at-risk population of first presentations of SCFE (based on cases identified during the period 01/06/16 to 31/08/17, with no prior SCFE carried out on either hip): assuming additional cases found in HES are first presentations.

	At-risk Population[(a)] (Mid-year estimate 2016[(b)])	**First presentation of SCFE**		
	n	**n**	**Incidence**	**95% CI**
All[(a)]	9,499,724	429	3.61	(3.27,3.95)
By Country & Region:				
England	8,301,394	379	3.65	(3.28,4.02)
London & Surrounding Boroughs	1,851,204	89	3.85	(3.09,4.73)
South	1,696,467	75	3.54	(2.78,4.43)
Northern	2,280,272	102	3.58	(2.88,4.27)
Central	2,473,451	113	3.65	(2.98,4.33)
Wales	454,551	12	2.11	(1.09,3.69)
Scotland	743,779	38	4.09	(2.89,5.61)
By age-group:				
6-10 years	3,850,071	82	1.70	(1.36,2.11)
11-18 years	5,649,653	347	4.91	(4.4,5.43)
By sex:				
Male	4,867,679	243	3.99	(3.49,4.50)
Female	4,632,045	186	3.21	(2.75,3.67)

[(a)]6-18 year-olds, England, Scotland & Wales; [(b)] Source: ONS

5.3 Medical history

Table 5-5: Medical history at recruitment into BOSS

	Surveillance cohort (N=486)
Previous contralateral disease	
Yes	22 (4.7%)
No	447 (95.3%)
Missing	17
Any family history of SCFE (1st degree family members only)	
No	359/374 (96.0%)
Yes: At least one 1st degree family member	15/374 (4.0%)
Family history not known	109/483 (22.6%)
Missing	3
Family member affected	
Father	3 (20%)
Mother	5 (33.3%)
Sister(s)	6 (40%)
Brother(s)	2 (13.3%)
Co-morbidities	
None	319 (68.2%)
At least one	149 (31.8%)
Missing	18
Co-morbidity types	**(n=468)***
Hypothyroidism	9 (1.9%)
Down's Syndrome	4 (0.9%)
Renal failure due to dialysis	0 (0%)
Obesity	123 (26.3%)
Previous radiotherapy	1 (0.2%)
Endocrinopathy	7 (1.5%)
Not specified	5 (1.1%)

*Denominator is total that answered *None/At least one* to Comorbidity question.

Table 5-6: Line listings of reported endocrinopathy (free-text entries in the database).

Reported endocrinopathy type (N missing = 2)
• *Previous bone marrow transplant for an auto-immune condition, long term steroids, marked growth retardation* • *Suspected - to be investigated* • *Idiopathic juvenile osteoporosis* • *Panhypopituatrism* • *Sudo HPT and vit D deficiency*

5.4 Presentation

5.4.1 Clinical time-line

Table 5-7: SCFE baseline clinical time-line (see also, explanatory notes on next page)

	Surveillance cohort (N=486)					
	All	Clinical Stability (n=482)				
		Stable (N=380)				Unstable (n=102)
		All Stable	Severity of worst affected hip (n=366)			
			Mild (n=188)	Moderate (n=104)	Severe (n=74)	
From onset of symptoms to seeking advice (months)						
n	414	320	166	79	62	92
Median (IQR)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.5 (0, 2)	0 (0, 1)
Min, Max	0, 24	0, 24	0, 12	0, 24	0, 12	0, 13
Missing	73	60	22	25	12	10
From onset of symptoms to diagnosis (months)						
n	442	345	173	91	68	95
Median (IQR)	1 (0, 3)	1 (0, 4)	1 (0, 2)	2 (1, 8)	3 (0, 6)	1 (0, 2)
Min, Max	0, 32	0, 32	0, 14	0, 24	0, 32	0, 15
Missing	44	35	15	13	6	7
From diagnosis to admission to hospital (days)						
n	479	374	184	103	73	101
Median (IQR)	0 (0, 4)	0 (0, 6)	0 (0, 5)	0 (0, 6)	1 (0, 11)	0 (0, 0)
Min, Max	0, 256	0, 256	0, 136	0, 131	0, 256	0, 43
Missing	7	6	4	1	1	1
From admission to hospital to surgery (days)						
n	478	375	186	103	73	100
Median (IQR)	1 (0, 3)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 5)	2 (1, 7)
Min, Max	0, 75	0, 47	0, 47	0, 17	0, 18	0, 75
Missing	8	5	2	1	1	2

*Explanatory notes:

1. Clinical stability missing for n=4 patients.
2. Of the 380 stable SCFEs, severity of worst affected hip is missing for n=14 patients.
3. Maximum number of days between admission and surgery: this is large (>30) in two patients. 75 days delay was incurred for one patient who was diagnosed and admitted at one hospital but then transferred at a later date to another hospital for surgery – they may have been discharged home in between, but if so, the re-admission date is not captured. 47 days delay was incurred by a patient whose presented with a head injury and diagnosed with SCFE at the same time. The head injury delayed surgery.

5.4.2 Diagnosis and Admission

Table 5-8: Factors relating to diagnosis and admission

	Surveillance cohort (N=486)
Health professional first sought advice from	
GP	228 (48.7%)
Physiotherapist	16 (3.4%)
Emergency Doctor	198 (42.3%)
Other	26 (5.6%)
Missing	18
Transferred from another hospital	
Yes	129 (26.8%)
No	352 (73.2%)
Missing	5
Delay of more than one week between first seeking professional advice and admission	
Yes	344 (72.4%)
No	131 (27.6%)
Missing	11
Sudden deterioration in symptoms precipitated presentation (e.g. trip or fall)	
Yes	210 (44.1%)
No	266 (55.9%)
Missing	10

Table 5-9: Line listings of 'Other health professionals' first sought advice from (free-text entries in the database).

Reported other health professionals (N missing = 1)
Surgeons/consultants • *Orthopaedic surgeon* (n=4) • *Orthopaedic surgeon clinic follow up* • *Paediatric orthopaedic surgeon* (n=3) • *Self-referral to ortho consultant as prev SCFE* • *Surgeon* Clinics • *Endocrine clinic* • *Metabolic bone team clinic* • *Minor injuries* Paediatricians • *Paediatrician* (n=2) • *Paediatric SpR* Multiple professionals • *All of physio, orthotist, GP, orthopaedic surgeon* • *All the above* [ie GP, Emergency Doctor, Physio] Other • *Consultant haematologist* • *General Practice Nurse Practitioner*

Table 5-10: Summary of factors contributing to delay between first seeking professional advice and admission to hospital (categorisation of free-text entries in the database)

Reported reasons (311 text entries summarised, N missing =33)	**N (%) (n=344*)**
Delay by family - commonly attributed to a sporting injury "pain after a football injury"	104 (37.8%)
Multiple healthcare attendances - commonly thought to be a "muscle sprain" or "growing pains" or given "a trial of rest and analgesia “or investigated for "knee pain"	96 (34.9%)
System delays (i.e. cancelled op, cancelled opd, delayed reporting of XR)	33 (12.0%)
Poor understanding of urgency once diagnosis made. "The diagnosis was made in A&E and the patient discharged to the outpatient clinic"	28 (10.2%)
Initial XR normal, or reported as normal	18 (6.5%)
Planned delayed elective admission for fixation	11 (4.0%)
Radiologist/doctor missed diagnosis	9 (3.3%)
Family declined advice for admission immediately	9 (3.3%)
No thought to diagnosis – e.g. thought to be growing pains	9 (3.3%)
Initial XR normal, or reported as normal and AP only	3 (1.1%)
Complex Patient	2 (0.7%)
Patient transferred after attempted fixation as unable to perform	1 (0.4%)
Medical Condition Delayed Op	1 (0.4%)
Response not relevant/not specific/not code-able	36

*A total of 344 out of 486 patients experienced a delay. Of these, 311 an additional text field was filled in giving details of the reasons.

Table 5-11: Pre-operative Imaging modalities available to treating surgeons

	Surveillance cohort (N=486)
At least one imaging modality reported	
Yes	480 (98.8%)
Missing*	6 (1.2%)
Imaging available (n=480)	
Plain radiographs	475 (99.0%)
CT	32 (6.7%)
MRI	85 (17.7%)
Radioisotope Bone Scan	5 (1.0%)

*Each imaging modality is set up in the database as default 'No'. 6 patients had 'No' ticked for all 4 imaging modalities. We may assume therefore that this question was not answered as we would expect there to be at least one imaging modality available.

5.4.3 Disease factors

Table 5-12: SCFE disease factors at presentation (newly affected hips)

	Surveillance cohort (N=486)
Clinical stability: patient able to walk (with crutches) at admission?	
Yes	380 (78.8%)
No	102 (21.2%)
Missing	4
No. of hips newly affected per child	
Unilateral	428 (90.9%)
No prior contralateral SCFE	*406 (94.9%)*
Prior contralateral SCFE	*22 (5.1%)*
Bilateral	43 (9.1%)
Missing	15
Total no. of hips newly affected	
n	514
Radiographic severity (n=514 hips)	
Mild	229 (44.9%)
Moderate	134 (26.3%)
Severe	147 (28.8%)
Missing	4

Table 5-13: Radiographic severity by clinical stability (all affected hips)

	Clinical stability: patient able to walk (with crutches) at admission?		
	Stable (hips=402)	**Unstable (hips=109)**	**Unknown (n=3)**
Radiographic severity (n=514 hips)			
Mild	213 (53.3%)	15 (13.9%)	1
Moderate	110 (27.5%)	24 (22.2%)	0
Severe	77 (19.3%)	69 (63.9%)	1
Missing	2	1	1

5.4.4 PROMs

The analysis of PROMs at baseline will be reported in the statistical analysis report Part 2, due in February 2020.

6. Results: Perthes'

6.1 Cohort characteristics

Table 6-1: Perthes' baseline demographics

	Surveillance cohort (N=371)
Age (years)	
Mean (SD)	6.3 (2.6)
Min, Max	1.8, 14.4
Missing	0
Age-group (years)	
0 - < 6	198 (53.4%)
>= 6 - <11	146 (39.4%)
>=11 - <15	27 (7.3%)
Gender	
Male	288 (77.6%)
Female	83 (22.4%)
Ethnicity	
White - British	329 (90.6%)
White - Irish	-
White - Other white background	14 (3.9%)
Mixed - White & black Caribbean	1 (0.3%)
Mixed - White & black African	-
Mixed - White & Asian	2 (0.6%)
Mixed - Other mixed background	-
Indian	-
Pakistani	5 (1.4%)
Bangladeshi	-
Asian - Other Asian background	6 (1.7%)
Black Caribbean	-
Other Black African	1 (0.3%)
Black - Other black background	2 (0.6%)
Chinese	1 (0.3%)
Any other ethnic group	2 (0.6%)
Missing	8
BMI	
n	144
Median (IQR)	17.2 (15.9, 19.4)
Min, Max	13.6, 49.7
Missing	227

Table 6-2: Line listings of other ethnic groups (free-text entries in the database)

Reported groups (N missing = 2)
[No data to report]

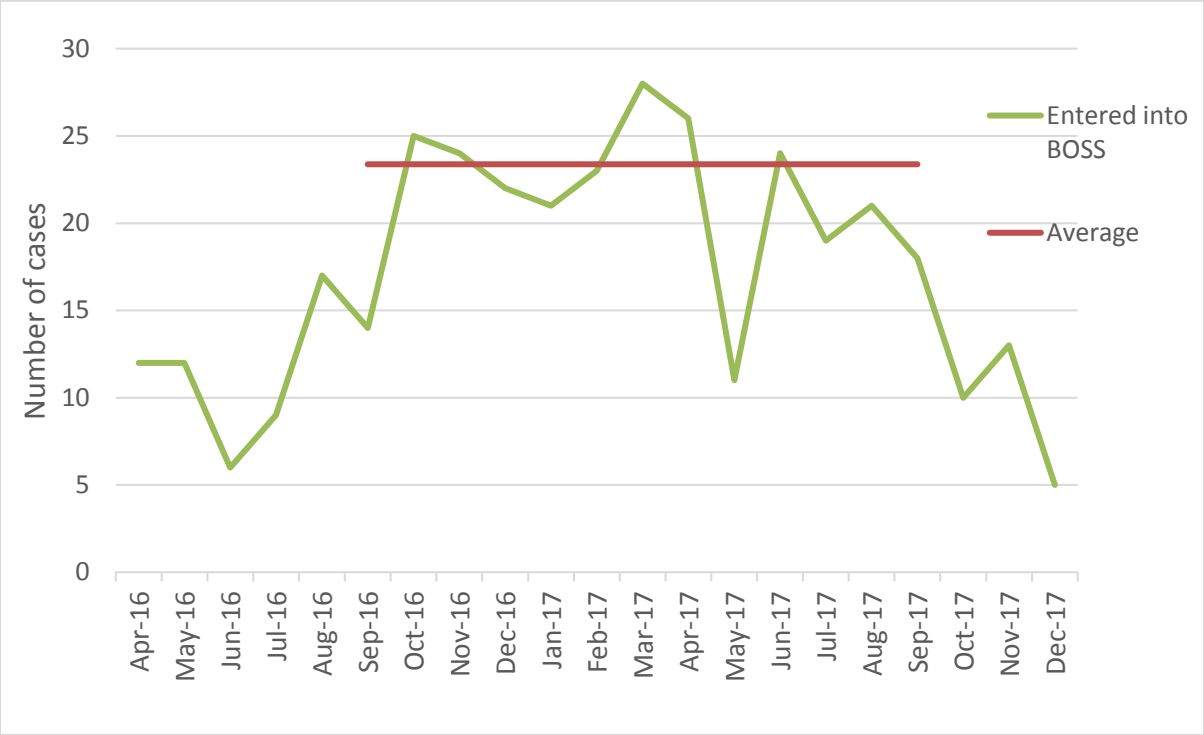
6.2 Incidence

Table 6-3: Annual Incidence per 100,000 population of first presentations of Perthes' disease (based on cases identified during the period 01/09/16 to 30/09/17, with no prior history of the disease in either hip, and no comorbidities that may mimic Perthes' disease)

	Population[(a)] (Mid-year estimate 2016[(b)])	First presentation of Perthes'		
	n	n	Incidence	95% CI
All[(a)]	11,311,227	304	2.48	(2.20,2.76)
By Country & Region:				
England	9,927,566	262	2.44	(2.14,2.73)
London & Surrounding Boroughs	2,323,067	38	1.51	(1.07,2.07)
South	1,982,386	63	2.93	(2.25,3.75)
Northern	2,698,410	101	3.46	(2.78,4.13)
Central	2,923,703	60	1.89	(1.45,2.44)
Wales	523,183	16	2.82	(1.61,4.58)
Scotland	860,478	26	2.79	(1.82,4.09)
By age-group:				
0-5 years	4,692,365	166	3.27	(2.77,3.76)
6-10 years	3,850,071	117	2.81	(2.30,3.31)
11-14 years	2,768,791	21	0.7	(0.43,1.07)
By sex:				
Male	5,793,959	231	3.68	(3.21,4.15)
Female	5,517,268	73	1.22	(0.96,1.54)

[(a)]0-14 year-olds, England, Scotland & Wales; [(b)] Source: ONS;

Figure 6-1: Number of Perthes' first presentations[(a)] per month entered into BOSS, with average[(b)] monthly case-load.



[(a)] No history of prior contralateral disease; [(b)] The plotted average is derived from the national incidence estimate calculated from these data, for the time-interval 01/09/16 to 30/09/17 (see Table 6-3).

6.3 Medical history

Table 6-4: Medical history at recruitment into BOSS

	Surveillance cohort (N=371)
Previous contralateral disease	
Yes	11 (3.2%)
No	333 (96.8%)
Missing	27
Any family history of Perthes (1st degree family members only)	
No	306/326 (93.9%)
Yes: At least one 1st degree family member	20/326 (6.1%)
Family history not known	45/371 (12.1%)
Missing	0
Family member affected	
Father	9 (45.0%)
Mother	4 (20.0%)
Sister(s)	-
Brother(s)	5 (25.0%)
Not specified	2 (10.0%)

6.4 Presentation

6.4.1 Diagnosis

Table 6-5: Clinical time-line

	Surveillance cohort (N=371)
From onset of symptoms to first seeking professional advice (months)	
n	311
Median (IQR)	0 (0, 2)
Min, Max	0, 18
Missing	60
From seeking advice to radiographic diagnosis (months)	
n	342
Median (IQR)	2 (1, 5)
Min, Max	0, 29
Missing	29

Table 6-6: Factors relating to diagnosis

	Surveillance cohort (N=371)
First sought advice from:	
GP	198 (55.9%)
Physiotherapist	4 (1.1%)
Emergency Doctor	123 (34.7%)
Other	29 (8.2%)
Missing	17
Delay of more than one week between first seeking professional advice and radiographic diagnosis	
Yes	230 (65.2%)
No	123 (34.8%)
Missing	18

Table 6-7: Summary of factors contributing to delay between first seeking professional advice and diagnosis (categorisation of free-text entries in the database)

Reported reasons (214 text entries summarised) (N missing = 16)	**N (%) (n=230)**
Multiple visits to GP prior to diagnosis.	113 (57.4%)
Waiting to get appointment, or for results of imaging	55 (27.9%)
Initially diagnosed for something else / x-rayed in wrong place	45 (22.8%)
1st X-ray or examination normal, or reported as normal	45 (22.8%)
Patient referred from another hospital	8 (4.1%)
Incidental finding of Perthes - patient not symptomatic	3 (1.5%)
Administrative – error in appointment booking	2 (1.0%)
GP did not refer to specialist care once diagnosed	2 (1.0%)
Parents not happy with advice at one hospital and switched to another	1 (0.5%)
Reason not relevant / unclear	17

*A total of 230 out of 371 patients experienced a delay. Of these, 214 an additional text field was filled in giving details of the reasons.

Table 6-8: Imaging modalities used/requested during assessment

	Surveillance cohort (N=371)
Plain radiographs	
AP only	105 (29.2%)
AP and lateral	254 (70.8%)
Missing	12
CT	
Yes	3 (1.0%)
No	296 (99.0%)
Missing	72
MRI	
Yes	66 (20.8%)
Conventional	*64 (100.0%)*
Perfusion	*0 (0.0%)*
Missing	*2*
No	252 (79.2%)
Missing	53

6.4.2 Disease factors

Table 6-9: Perthes' disease factors at presentation (newly affected hips)

		Surveillance cohort (N=371)
No. of hips newly affected per child		
	Unilateral	346 (93.3%)
	Bilateral	25 (6.7%)
Total no. of hips newly affected		
	n	396
Examination (n=396 hips)		
	Stiff hip (significantly limited abduction)	154 (40.7%)
	Minimal or no stiffness (minimal limitation of abduction)	224 (59.3%)
	Missing	18
Radiographic stage (n=396 hips)		
0:	No radiographic change – MRI only	11 (2.8%)
1A:	Sclerosis (early, normal height)	63 (16.2%)
1B:	Sclerosis (late, flattened)	134 (34.4%)
2A:	Fragmentation (early, 1 or 2 fissures)	93 (23.8%)
2B:	Fragmentation (late, no new bone)	51 (13.1%)
3A:	Reossification (early, new bone but texture not normal)	16 (4.1%)
3B:	Reossification (late, new bone of normal texture covering over 1/3 epiphysis)	15 (3.8%)
4:	Healed (no evidence of avascular bone)	7 (1.8%)
	Missing	6
Radiographic severity: Collapse of lateral column (n=357 with AP radiograph)		
	No collapse	104 (26.5%)
	< 50% collapse	158 (40.3%)
	Exactly 50% collapse	29 (7.4%)
	> 50% collapse	62 (15.8%)
	Missing	4
Radiographic severity: Head involvement of lateral radiograph (n=249 with lateral radiograph)		
	> 50% of head involved	154 (61.8%)
	< 50% of head involved	95 (38.2%)
	Missing	0

6.4.3 PROMs

The analysis of PROMs at baseline will be reported in the statistical analysis report Part 2, due in February 2020.

Investigating childhood hip diseases (Slipped capital femoral epiphysis and Perthes' disease) as childhood precursors to osteoarthritis of the hip in adulthood:

A nationwide service evaluation, and nested-cohort study.

Final Analysis Report

Analysis Part 2 (v2.0)

	ORIGINATED BY	APPROVED BY
Name	Barbara Arch	Paula Williamson
Title	Study Statistician	Professor of Biostatistics
Date	10/05/2021	
Protocol Version and Date	v7.0 20171220	

Change Control

Updated version no.	Section changed	Description of change	Date changed	Initials
2.0	5.2.2	Correction to statistic in Figure 5-2	10/05/2021	BA
2.0	5.4.1	Corrections made to Table 5-16	10/05/2021	BA
2.0	5.6.1	Corrections made to Table 5-21: Hips with AVN statistics	10/05/2021	BA
2.0	6.7.1	Figure 6-10 previously included graphs for SCFE in this section, and not Perthes. These have now been replaced with the correct graphs.	10/05/2021	BA

1. Table of Contents

2. List of Tables and Figures

2.1 Tables

2.2 Figures

3. Introduction

Slipped Capital Femoral Epiphysis (SCFE) and Perthes' disease are the most common acquired hip diseases of childhood. Although they are relatively rare conditions, both accelerate the development of osteoarthritis, and precipitate many patients requiring a hip replacement in early adulthood.

The evidence that underpins both diseases is limited to case reports and case series, therefore surgical techniques are largely determined through the 'experience' of the treating surgeon. The poor quality of evidence is attributed largely to the rarity of cases within any individual centre.

BOSS is a nationwide surveillance study. A surveillance cohort (SC) of SCFE and Perthes' disease was identified to determine the disease incidence, case mix, risk factors, variations in surgical interventions, and to determine the safety and efficacy of different surgical strategies. Findings will be used to inform national policy on SCFE in association with NICE.

Alongside the surveillance cohort, a subgroup - nested cohort (NC) was consented to be given questionnaires at baseline and during follow-up to provide patient reported outcomes (PROMs).

Key objectives were outlined in the protocol:

1. What is the incidence of SCFE and Perthes' disease in the UK?
2. How does this vary by region?
3. What is the case-mix variation (patient factors, SCFE - radiographic severity and clinical stability, Perthes' disease - radiographic stage and radiographic severity)?
4. What is the UK variation in surgical management, and is this related to patient, disease or surgeon factors (i.e. surgeon volume)?
5. What influence do patient, disease and surgeon factors have on radiographic outcomes at 2-years?
6. What influence do patient, disease and surgeon factors have on PROMs at 2-years?
7. Is there correlation between radiographic measures and PROMs at 2 years?
8. Do patient, disease or radiographic factors predict subsequent contralateral disease?

This statistical report is Part 2 of the analysis of BOSS. Part 1 was produced on 06/03/18 in accordance with the BOSS Statistical Analysis Plan v1.0, and provides baseline statistics regarding incidence, medical history, and presentation of cases of SCFE and Perthes' disease recruited into BOSS. Part 2 is produced in accordance with the BOSS Statistical Analysis Plan v2.0, and completes the remaining analyses: treatment/treatment strategies; clinical time-line;

follow-up outcomes; analysis of PROMs; and multivariate analyses linking baseline characteristics with outcomes.

4. Case Ascertainment and Recruitment

Figure 4-1 and Figure 4-2 below show how many cases of SCFE and Perthes' disease were identified during the recruitment period (4/4/16 to 30/9/17) and included in each surveillance cohort. Some of the cohort were lost to follow-up during the course of the study. Whilst every effort was made to recruit patients into the consented cohort at baseline, these flowcharts also illustrate that seeking permission to collect PROMs continued throughout follow-up. Figure 4-3 and Figure 4-4 show case-accrual over time.

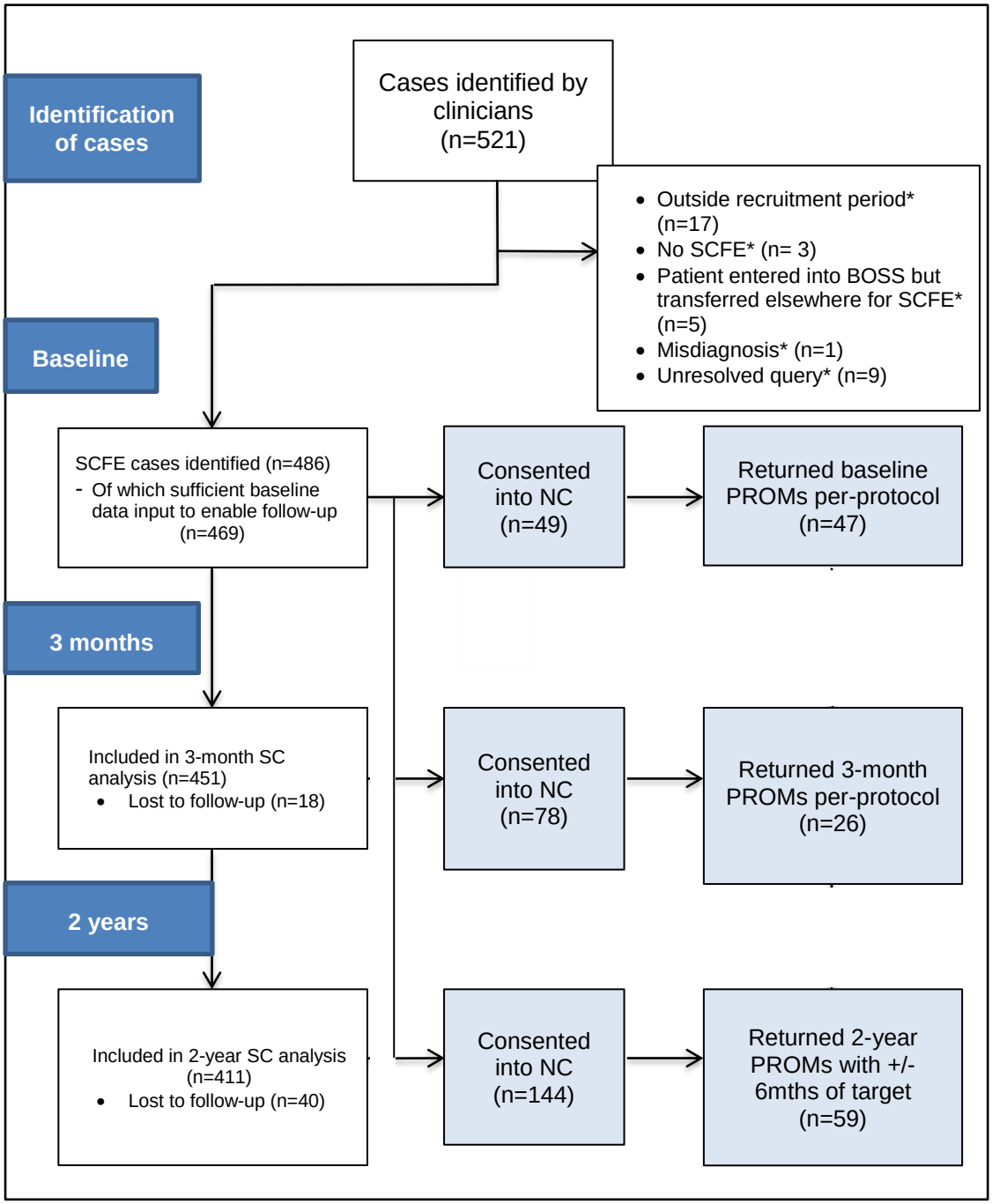
A total of 144 sites took part in the surveillance study. 50 of these enrolled to collect patient reported outcomes for children that consented to be part of a nested cohort. Table 4-1 shows how these cases are distributed across a large number of UK hospitals, with many seeing at most a handful of cases over the course of a year.

486 cases of SCFE were identified in the surveillance cohort. Of these, 144 (30%) were consented into a sub-cohort (consent was sought to collect patient reported outcomes and for NHS number to be stored to enable future data linkage).

371 cases of Perthes' disease were identified in the surveillance cohort. Of these, 172 (46%) were consented into a sub-cohort (consent was sought to collect patient reported outcomes and for NHS number to be stored to enable future data linkage).

4.1 SCFE

Figure 4-1: SCFE CONSORT chart



SC: Surveillance Cohort; NC: Nested Cohort. *See Final Analysis Report Part 1 p6, for notes regarding exclusions.

Notes:

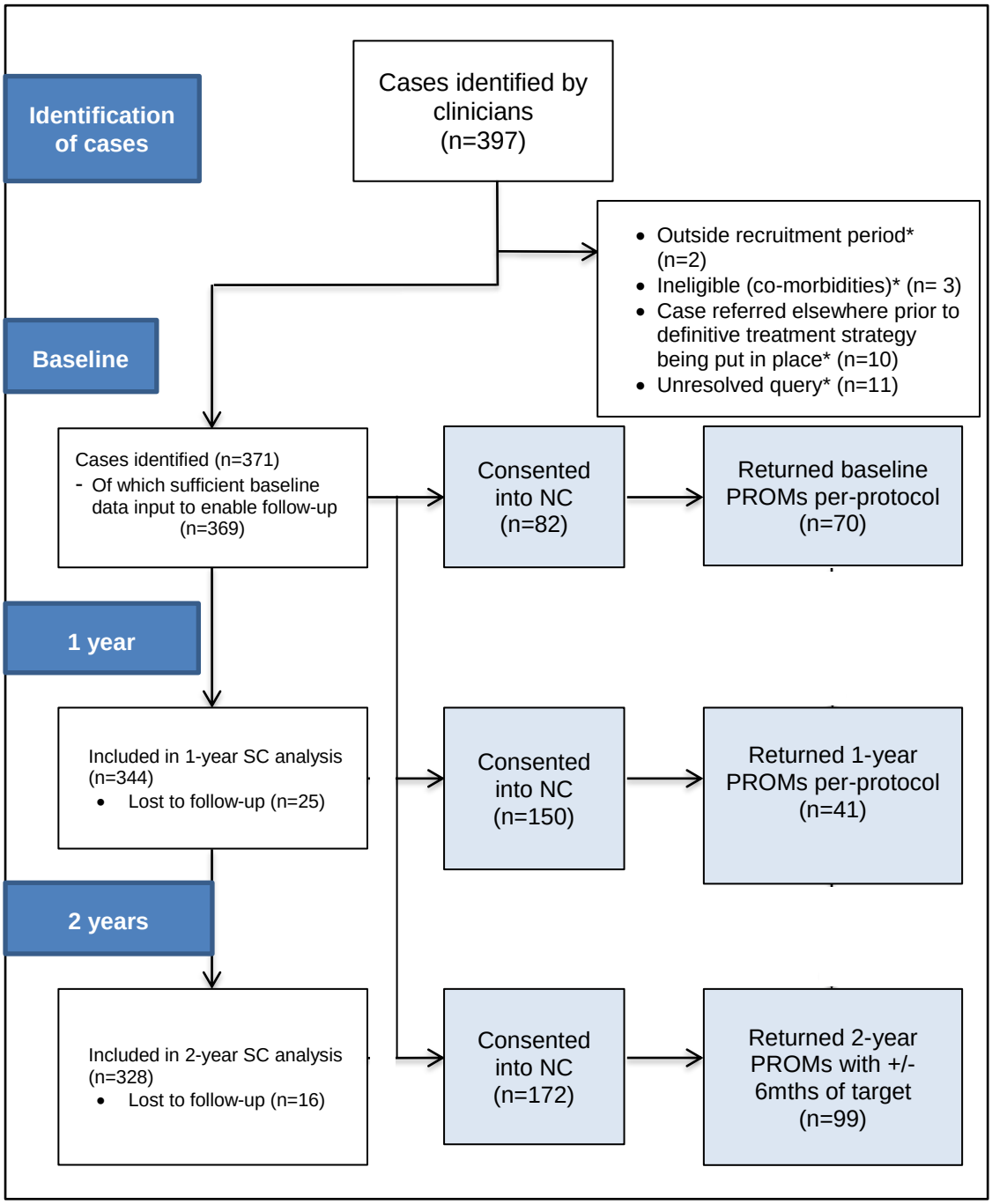
1. 17 cases could be confirmed true SCFEs, but there were insufficient baseline data regarding presentation to enable meaningful follow-up.
2. Some cases were lost to follow-up. Some were transferred to other hospitals, but were not followed up within BOSS at the new site. At 3 months, 12 were transferred, and 6 reported lost to follow-up (n=18). At 2 years, 8 were reported transferred, and 32 lost to follow-up (n=40). NB: 4 cases were reported as lost to follow-up at 3-months, but 2-year follow-up data was

uploaded – these were recoded as having missing data at 3-months rather than lost to follow-up.

3. For some cases, sites did not enter any follow-up data (29 at 3 months, and 42 at 2 years) – we do not know whether these patients were followed up. These will be included as 'missing' in the follow-up results tables. Every effort was made to encourage sites to upload follow-up to BOSS, even if just to inform us that patients were lost to follow-up.

4.2 Perthes' Disease

Figure 4-2: Perthes' disease CONSORT chart



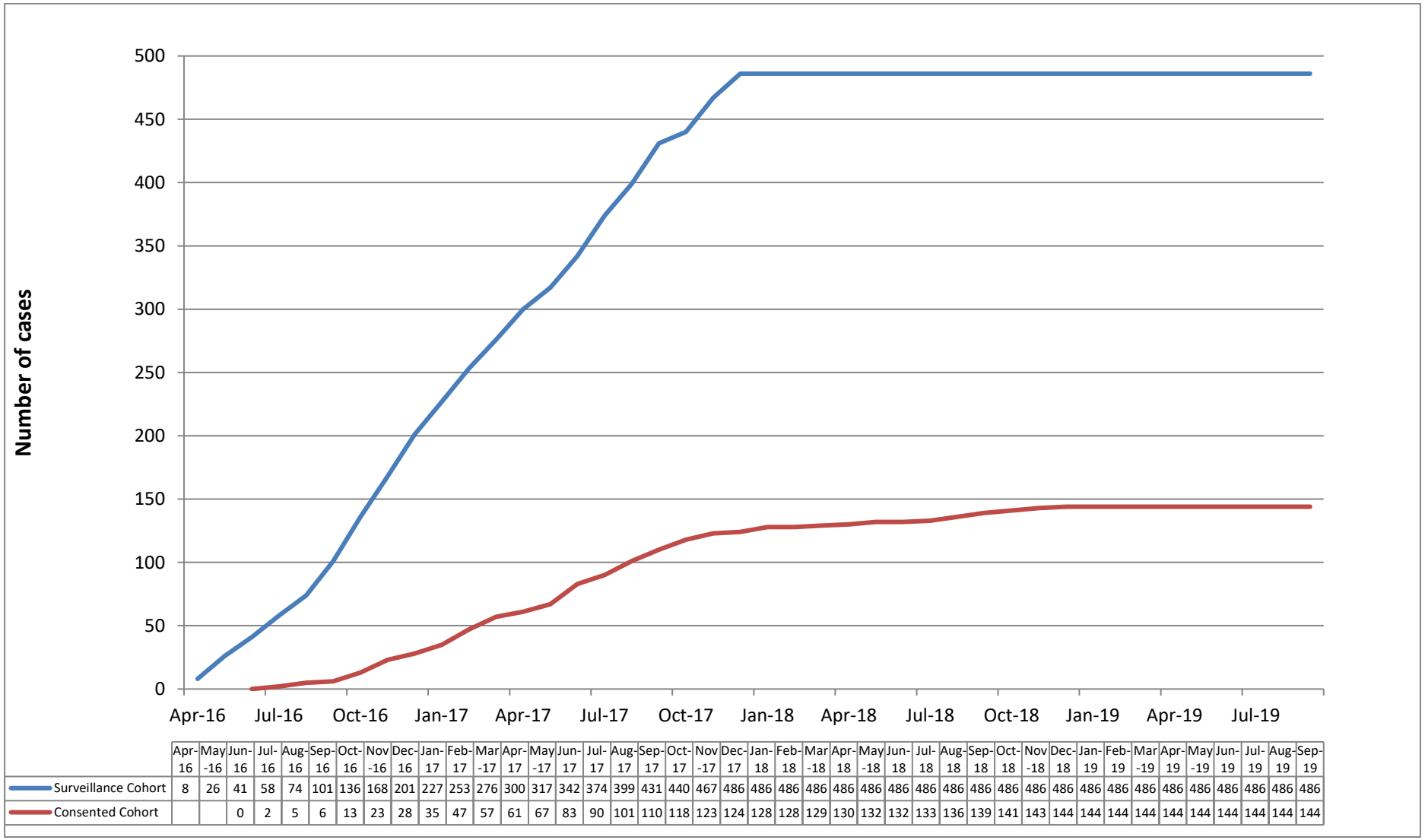
SC: Surveillance Cohort; NC: Nested Cohort. *See Final Analysis Report Part 1 p6, for notes regarding exclusions.

Notes:

1. 2 cases could be confirmed true Perthes' disease cases, but there were insufficient baseline data regarding presentation to enable meaningful follow-up.
2. Some cases were lost to follow-up. Some were transferred to other hospitals, but were not followed up within BOSS at the new site. At 1 year, 13 were transferred, 9 reported lost to follow-up, and 3 were found to be misdiagnoses (n=26). At 2 years, 4 were reported transferred, 10 lost to follow-up, and 2 cases had not been seen in clinic yet to enable a 2-year follow-up to be completed for BOSS (n=16).
3. For some cases, sites did not enter any follow-up data (21 at 1 year, and 27 at 2 years) – we do not know whether these patients were followed up. These will be included as 'missing' in the follow-up results tables.

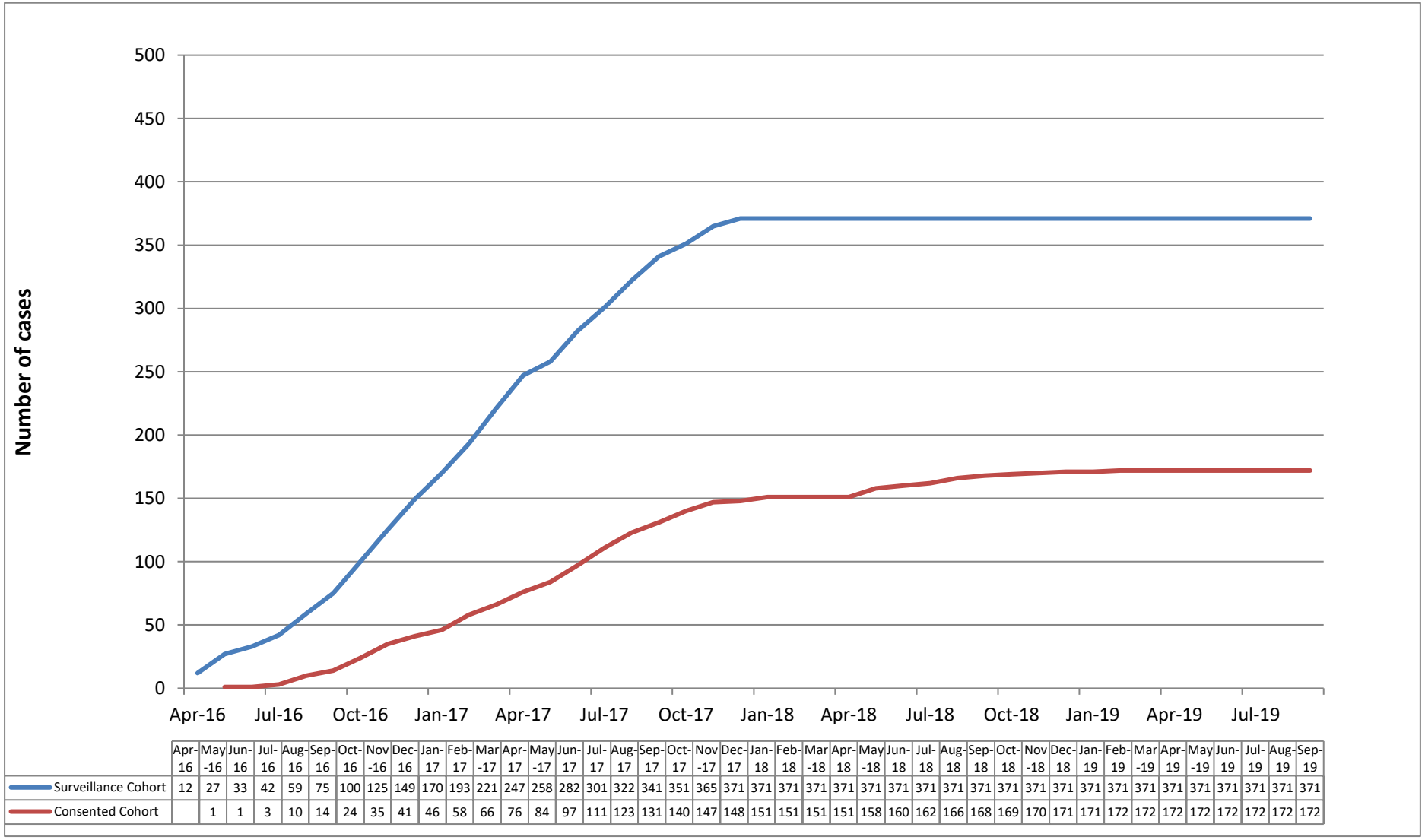
4.3 Recruitment

Figure 4-3: SCFE recruitment over time



	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19
Surveillance Cohort	8	26	41	58	74	101	136	168	201	227	253	276	300	317	342	374	399	431	440	467	486	486	486	486	486	486	486	486	486	486	486	486	486	486	486	486	486	486	486	486	486
Consented Cohort			0	2	5	6	13	23	28	35	47	57	61	67	83	90	101	110	118	123	124	128	128	129	130	132	132	133	136	139	141	143	144	144	144	144	144	144	144	144	144

Figure 4-4: Perthes' disease recruitment over time



	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19
Surveillance Cohort	12	27	33	42	59	75	100	125	149	170	193	221	247	258	282	301	322	341	351	365	371	371	371	371	371	371	371	371	371	371	371	371	371	371	371	371	371	371	371	371	371
Consented Cohort		1	1	3	10	14	24	35	41	46	58	66	76	84	97	111	123	131	140	147	148	151	151	151	151	158	160	162	166	168	169	170	171	171	172	172	172	172	172	172	172

Table 4-1: BOSS Recruitment to the Surveillance cohort (SC) and Nested consented cohort (NC) by country, region and site

Country, Region & Site Name	SCFE		Perthes' Disease	
	SC	**NC**	**SC**	**NC**
England (124 sites)				
London & Surrounding Boroughs (27 sites)				
Barking Havering and Redbridge	8	1	3	0
Barnet and Chase Farm	0	0	0	0
Barts	13	11	3	2
Basildon and Thurrock	7	0	2	0
Chelsea and Westminster Hospital NHS Foundation Trust	6	0	0	0
East Kent Hospitals University NHS Foundation Trust (QEQMH)	8	0	2	0
Epsom and St Helier University Hospitals NHS Trust	1	0	3	0
Great Ormond Street Hospital for Children NHS Foundation Trust	1	0	2	0
Guys and St Thomas NHS Foundation Trust	8	0	1	0
Hillingdon Hospitals NHS Foundation Trust	4	0	1	0
Homerton University Hospital NHS Foundation Trust	1	0	0	0
Imperial College Healthcare NHS Trust	3	0	2	1
Kings College Hospital NHS Foundation Trust	5	0	0	0
Maidstone and Tunbridge Wells NHS Trust	0	0	4	4
Medway NHS Foundation Trust	0	0	0	0
North Middlesex University Hospital NHS Trust	1	0	0	0
North West London Hospitals NHS Trust (also includes Ealing above)	0	0	0	0
Queen Elizabeth Hospital Woolwich	0	0	0	0
Royal Free London NHS Foundation Trust	4	0	1	0
Royal National Orthopaedic Hospital NHS Trust	17	11	9	9
Royal Surrey County NHS Foundation Trust	1	0	0	0
St Georges Healthcare NHS Trust	9	0	7	1
The Whittington Hospital NHS Trust	3	0	0	0
University College London Hospitals NHS Foundation Trust	0	0	0	0
University Hospital Lewisham	2	0	0	0
West Middlesex University Hospital NHS Trust	1	1	3	3
Whipps Cross University Hospital	0	0	0	0
London Total	**103**	**24**	**43**	**20**

Country, Region & Site Name	SCFE		Perthes' Disease	
	SC	NC	SC	NC
Central England (32 sites)				
Bedford	3	3	0	0
Birmingham Childrens	23	1	0	0
Cambridge	6	0	4	0
Chesterfield Royal Hospital NHS Foundation Trust	0	0	0	0
Colchester Hospital University NHS Foundation Trust	4	3	0	0
Derby Hospitals NHS Foundation Trust	4	0	2	0
East and North Hertfordshire NHS Trust	2	0	0	0
Heart Of England NHS Foundation Trust	0	0	0	0
Hinchingbrooke Health Care NHS Trust	0	0	1	0
Ipswich Hospital NHS Trust	1	0	3	0
James Paget University Hospitals NHS Foundation Trust	0	0	0	0
Kettering General Hospital NHS Foundation Trust	2	1	1	0
Luton and Dunstable Hospital NHS Foundation Trust	2	0	0	0
Mid Essex Hospital Services NHS Trust	0	0	1	0
Norfolk and Norwich University Hospitals NHS Foundation Trust	6	6	9	9
Northampton General Hospital NHS Trust	2	1	2	0
Nottingham University Hospitals NHS Trust	12	7	8	3
Peterborough and Stamford Hospitals NHS Foundation Trust	10	1	1	0
Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust	7	5	10	8
Sandwell and West Birmingham Hospitals NHS Trust	4	0	1	0
Shrewsbury and Telford Hospital NHS Trust	0	0	0	0
The Dudley Group NHS Foundation Trust	0	0	3	0
The Princess Alexandra Hospital NHS Trust	2	0	3	0
The Royal Wolverhampton NHS Trust	0	0	0	0
United Lincolnshire Hospitals NHS Trust	2	0	1	0
University Hospitals Coventry and Warwickshire NHS Trust	7	4	9	8
University Hospitals Of Leicester NHS Trust	9	1	1	0
University Hospitals of the North Midlands	10	7	11	9
West Hertfordshire Hospitals NHS Trust	1	0	0	0
West Suffolk NHS Foundation Trust	5	4	3	3
Worcestershire Acute Hospitals NHS Trust	4	0	1	1
Wye Valley NHS Trust	1	0	0	0

Country, Region & Site Name	SCFE		Perthes' Disease	
	SC	NC	SC	NC
Central England Total	**129**	**44**	**75**	**41**
Northern England (39 sites)				
Airedale	2	0	1	0
Alder Hey	23	20	40	37
Barnsley Hospital	0	0	2	0
Blackpool	0	0	0	0
Bolton	0	0	1	0
Bradford	3	0	0	0
Calderdale and Huddersfield	3	1	3	1
Central Manchester University (Manchester Childrens)	18	0	8	0
City Hospitals Sunderland NHS Foundation Trust	1	0	2	0
Countess Of Chester Hospital NHS Foundation Trust	1	0	0	0
County Durham and Darlington NHS Foundation Trust	4	3	1	1
Doncaster and Bassetlaw Hospitals NHS Foundation Trust	0	0	1	0
East Lancashire Hospitals NHS Trust	6	6	11	9
Harrogate and District NHS Foundation Trust	0	0	0	0
Hull and East Yorkshire	5	2	5	1
Lancashire Teaching Hospitals NHS Foundation Trust	3	2	7	6
Leeds General Infirmary	4	3	9	5
Mid Cheshire Hospitals NHS Foundation Trust	0	0	0	0
Mid Yorkshire Hospitals NHS Trust	2	1	6	0
North Cumbria University Hospitals NHS Trust	0	0	0	0
Northern Lincolnshire and Goole Hospitals NHS Foundation Trust	0	0	0	0
Northumbria Healthcare NHS Foundation Trust	3	0	6	0
Pennine Acute Hospitals NHS Trust (North Manchester)	2	0	0	0
Pennine Acute Hospitals NHS Trust (Oldham)	3	0	0	0
Scarborough and North East Yorkshire Health Care NHS Trust	0	0	0	0
Sheffield Childrens NHS Foundation Trust	18	0	2	1
South Tees Hospitals NHS Foundation Trust	3	2	9	4
Southport and Ormskirk Hospital NHS Trust	0	0	3	1
St Helens and Knowsley Hospitals NHS Trust	0	0	0	0
Stockport NHS Foundation Trust	1	0	2	0
Tameside Hospital NHS Foundation Trust	0	0	1	0
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	10	8	5	3
The Rotherham NHS Foundation Trust	0	0	2	0

Country, Region & Site Name	SCFE		Perthes' Disease	
	SC	NC	SC	NC
University Hospital Of South Manchester NHS Foundation Trust	0	0	0	0
University Hospitals Of Morecambe Bay NHS Foundation Trust	1	1	1	1
Warrington and Halton Hospitals NHS Foundation Trust	0	0	0	0
Wirral University Teaching Hospital NHS Foundation Trust	1	0	0	0
Wrightington, Wigan and Leigh NHS Foundation Trust	0	0	1	0
York Teaching Hospital NHS Foundation Trust	0	0	0	0
Northern England Total	**117**	**49**	**129**	**70**
South of England (26 sites)				
Basingstoke	0	0	0	0
Brighton and Sussex	7	2	0	0
Buckinghamshire	3	0	1	0
Dorset County Hospital NHS Foundation Trust	1	0	0	0
East Sussex Healthcare NHS Trust	1	0	2	1
Frimley Park Hospital NHS Foundation Trust	2	0	2	0
Gloucestershire Hospitals NHS Foundation Trust	7	1	0	0
Great Western Hospitals NHS Foundation Trust	1	0	2	0
Milton Keynes Hospital NHS Foundation Trust	3	0	1	0
Northern Devon Healthcare NHS Trust	2	0	0	0
Oxford University Hospitals NHS Trust	7	4	11	7
Plymouth Hospitals NHS Trust	3	3	4	3
Poole Hospital NHS Foundation Trust	0	0	2	0
Queen Alexander Hospital, Porstsmouth	3	0	11	0
Royal Berkshire NHS Foundation Trust	3	2	7	6
Royal Cornwall Hospitals NHS Trust	1	0	5	0
Royal Devon and Exeter NHS Foundation Trust	7	0	0	0
Royal United Hospital Bath NHS Trust	2	0	1	0
Salisbury NHS Foundation Trust	0	0	0	0
South Devon Healthcare NHS Foundation Trust	2	0	0	0
Taunton and Somerset NHS Foundation Trust	0	0	2	0
University Hospital Southampton NHS Foundation Trust	25	13	20	18
University Hospitals Bristol NHS Foundation Trust	6	0	2	0
Wexham Park	2	0	6	0
Winchester	0	0	0	0
Worthing And Southlands Hospitals Nhs Trust	2	0	2	0
South of England Total	**90**	**25**	**81**	**35**

Country, Region & Site Name	SCFE		Perthes' Disease	
	SC	NC	SC	NC
England Total	**439**	**142**	**328**	**166**
Scotland (15 sites)				
Borders General	0	0	0	0
Dumfries and Galloway Royal Infirmary	0	0	1	0
Forth Valley	2	0	3	0
Glasgow	11	1	1	0
Hairmyres Hospital	0	0	0	0
Inverclyde Royal	0	0	0	0
Monklands Hospital	0	0	1	0
Raigmore Hospital	2	0	1	0
Royal Aberdeen Childrens Hospital	4	0	5	0
Royal Alexandria Hospital	2	0	1	0
Royal Hospital for Sick Children (Edinburgh)	8	0	9	0
Tayside	8	0	0	0
University Hospital Crosshouse	0	0	2	0
Western Isles Hospital	0	0	0	0
Wishaw General	1	0	2	0
Scotland Total	**38**	**1**	**26**	**0**
Wales				
Aneurin Bevan Health Board	3	0	2	0
Betsi Cadwaladr	0	0	0	0
Cardiff and Vale University Local Health Board	4	0	5	0
Cwm Taf Health Board	1	0	4	0
Swansea	1	1	6	6
Wales Total	**9**	**1**	**17**	**6**
Overall Total	**486**	**144**	**371**	**172**

4.4 Study population

4.4.1 Data sets analysed

The sample size varies through the report, due to loss to follow-up. Table 4-2 gives the key populations of interest within the study. Some analyses relate to children, and many relate to hips. All results tables indicate denominators and specify whether these are children or hips.

Table 4-2: Data sets analysed

Population	N
SCFE Surveillance cohort:	
Patients at baseline	486
Patients to be followed up	469
Hips	513
Hips fixed prophylactically at baseline	120
Patients at risk of contralateral SCFE	286
SCFE Nested cohort:	
Patients	144
Perthes' disease Surveillance cohort:	
Patients at baseline	371
Patients to be followed up	369
Hips	393
Patients at risk contralateral disease	333
Perthes' disease Nested cohort:	
Patients	172

Notes:

1. Of the 486 cases of SCFE identified in BOSS, 469 had sufficient data entered at baseline to enable meaningful follow-up.
2. Of the 371 cases of Perthes' disease identified in BOSS, 369 had sufficient data entered at baseline to enable meaningful follow-up.
3. 'Hips': In some analyses, we summarise data for each newly affected hip. Some children newly present bilaterally, and therefore the total number of hips newly affected is greater than the total number of patients.
4. 'At risk of contralateral SCFE': the total number at risk of contralateral SCFE at baseline. This is defined as patients with: (a) no history of contralateral SCFE; and (b) a unilateral 1st presentation, and (c) no prophylactic fix. There are 5 patients included in this at-risk group for whom we do not know prophylactic fix status – these have been included in the at-risk group.
5. 'At risk of contralateral disease': we are measuring the risk of contralateral Perthes' disease. The total number at risk at baseline is therefore of interest. This is defined as patients with: (a) no history of contralateral Perthes' disease; and (b) a unilateral 1st presentation.

4.4.2 Protocol deviations

Table 4-3: Protocol deviations

Protocol deviations	
SCFE Surveillance data:	**(n=469)**
3-month surveillance data entered > 2 weeks prior to 3-month target date	8 (1.7%)
2-year surveillance data entered > 3 months prior to 2 year target date	5 (1.1%)
SCFE PROMs:	**(n=144)**
Any PROMs protocol deviation	99 (68.8%)
Baseline PROMs recorded > 2 weeks prior to SCFE surgery	0
Baseline PROMs recorded > 2 weeks after SCFE surgery	6 (4.2%)
3-month PROMs recorded > 2 weeks prior to 3-month target date	15 (10.4%)
3-month PROMs recorded > 2 weeks after 3-month target date	4 (2.8%)
2-year PROMs recorded > 3 months prior to 2-year target date	45 (31.3%)
2-year PROMs recorded > 1 month later than 2-year target date	19 (13.2%)
Perthes' Disease Surveillance data:	**(n=369)**
1-year surveillance data entered > 1 month prior to 1-year target date	11 (3.0%)
2-year surveillance data entered > 3 months prior to 2 year target date	7 (1.9%)
Perthes' Disease PROMs:	**(n=172)**
Any protocol deviation	108 (62.8%)
Baseline PROMs recorded > 4 weeks prior to baseline	0
Baseline PROMs recorded > 4 weeks after baseline	15 (8.7%)
1-year PROMs recorded > 4 weeks prior to 1-year target date	44 (25.6%)
1-year PROMs recorded > 4 weeks after 1-year target date	16 (9.3%)
2-year PROMs recorded > 3 months prior to 2-year target date	13 (7.6%)
2-year PROMs recorded > 1 month later than 2-year target date	31 (18.0%)

Notes:

1. Perthes' disease baseline was originally planned to be 'date of diagnosis', but once the study was underway, it was realised that the date that a patient first met with a treating physician at a hospital was more meaningful as a baseline – this date was not captured by the study. Diagnosis may have been made weeks or months prior to this. It was decided that for most Perthes' disease cases, we would use 'date entered BOSS' as the baseline date, as this was likely to be closer to the date that the patient's treatment plan was decided than the diagnosis date. Cases that were entered retrospectively after the end of recruitment were given 'diagnosis date' as the baseline date, as 'date entered BOSS' would certainly be too late, and outside our recruitment window. This problematic definition of 'baseline' gives rise to a level of uncertainty surrounding protocol deviations.
2. The number of protocol deviations were presented at the SSC meeting on 22/10/2019. It was recognised that compliance had been poor, and the number of 2-year PROMs that were per-protocol was small. It was decided to widen the window for 2-year PROMs to within +/- 6 months of the target date.

5. Results: SCFE

5.1 Baseline demographics

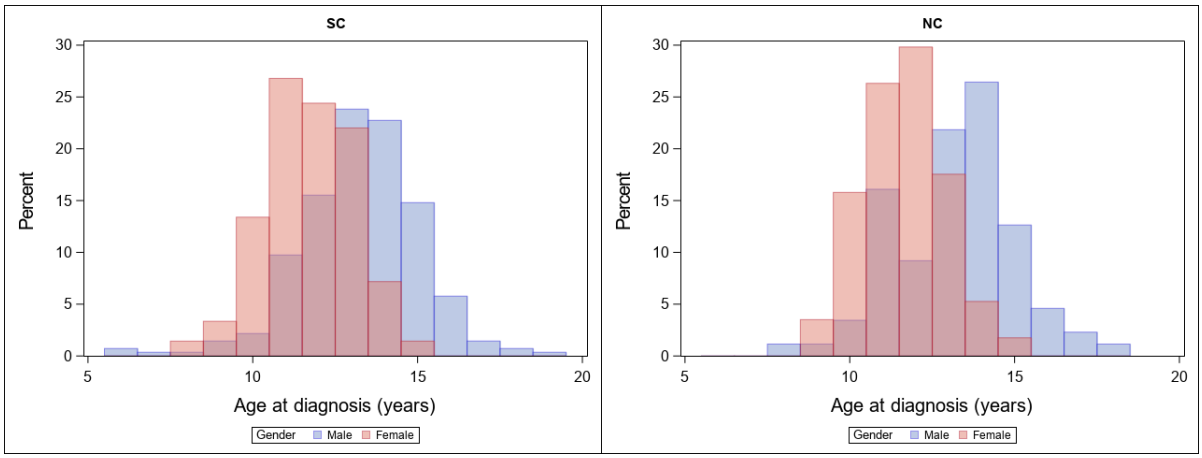
Table 5-1: Final SCFE baseline demographics of NC compared with SC

	Surveillance cohort	All consented cohort	Baseline PROMs	2-year PROMs
Children				
n	486	144	47	59
Age (years) at surgery				
n	485	144	47	59
Mean (SD)	12.6 (1.8)	12.5 (1.8)	12.2 (1.5)	12.2 (2)
Median (IQR)	12.7 (11.4, 13.8)	12.5 (11.2, 13.8)	11.8 (11, 13.3)	12.1 (10.7, 13.6)
Min, Max	6.3, 18.7	7.8, 17.8	9.6, 15.5	7.8, 17.8
Missing	1	0	0	0
Age-group (years)				
6 - <11	90 (18.6%)	29 (20.1%)	10 (21.3%)	17 (28.8%)
>=11 - <18	395 (81.4%)	115 (79.9%)	37 (78.7%)	42 (71.2%)
Missing	1	0	0	0
Sex				
Male	277 (57.0%)	87 (60.4%)	27 (57.4%)	36 (61.0%)
Female	209 (43.0%)	57 (39.6%)	20 (42.6%)	23 (39.0%)
Ethnicity				
White - British	320 (68.5%)	103 (72.5%)	35 (76.1%)	45 (78.9%)
White - Irish	1 (0.2%)	3 (2.1%)	0	0
White - Other white background	20 (4.3%)	6 (4.2%)	0	1 (1.8%)
Mixed - White & black Caribbean	13 (2.8%)	2 (1.4%)	1 (2.2%)	2 (3.5%)
Mixed - White & black African	4 (0.9%)	1 (0.7%)	1 (2.2%)	0
Mixed - White & Asian	3 (0.6%)	1 (0.7%)	0	1 (1.8%)
Mixed - Other mixed background	5 (1.1%)	2 (1.4%)	0	0
Indian	12 (2.6%)	4 (2.8%)	1 (2.2%)	1 (1.8%)
Pakistani	17 (3.6%)	2 (1.4%)	3 (6.5%)	1 (1.8%)
Bangladeshi	4 (0.9%)	8 (5.6%)	1 (2.2%)	0
Asian - Other Asian background	11 (2.4%)	1 (0.7%)	1 (2.2%)	3 (5.3%)
Black Caribbean	12 (2.6%)	6 (4.2%)	1 (2.2%)	0
Other Black African	33 (7.1%)	1 (0.7%)	1 (2.2%)	2 (3.5%)
Black - Other black background	5 (1.1%)	2 (1.4%)	1 (2.2%)	0
Chinese	2 (0.4%)	0	0	0
Any other ethnic group	5 (1.1%)	2 (1.4%)	0	1 (1.8%)
Missing	19	2	1	2
BMI				
n	140	55	14	20
Mean (SD)	26.4 (6)	24.8 (4.7)	25.3 (5)	24.6 (4.2)
Median (IQR)	25 (22.5, 29.3)	24.1 (21.4, 26.1)	25.1 (21.4, 29.1)	24.3 (21.1, 27.1)
Min, Max	14.2, 48.9	15.5, 39.7	15.5, 33.3	18.4, 33.3
Missing	346	89	33	39

Notes:

1. The baseline statistical analysis report (see BOSS Final Analysis Report: Part 1) summarised age at diagnosis. This report summarised age at surgery – this is the 1st SCFE surgery that is used to define the baseline date. One case had missing date of surgery – there was minimal data entered for this case, but a date of diagnosis was provided.
2. BMI is missing for most cases – this is generally because height was not routinely measured.

Figure 5-1: Histograms showing the distribution of age at diagnosis of BOSS SCFE cases in the surveillance cohort (SC) and the nested consented cohort (NC).



5.2 Treatment of SCFE

This section summarises the initial treatment of SCFE (at baseline). We report pre-operative imaging that was available, decisions made regarding surgical management (timing, type of surgery and techniques employed, experience in the room during surgery, and whether prophylactic fixation was used), and post-operative planning that was put in place.

5.2.1 Pre-operative imaging

Table 5-2: Pre-operative imaging reported to be available

	Surveillance cohort at baseline
Children	
n	486
Imaging type	
Plain radiographs	475 (99.0%)
CT	32 (6.7%)
MRI	85 (17.7%)
Radioisotope bone scan	5 (1.0%)
Missing	6

Notes:

1. For 6 cases, no imaging options were ticked – this is treated as missing data, and not interpreted as 'No imaging available'.

5.2.2 Surgical management

Table 5-3: Surgical management of each patient with respect to timing

	Clinical stability at baseline*	
	Stable	**Unstable**
Children		
n	380	102
How was timing of surgery decided?		
Emergency surgery	30 (8.0%)	21 (20.6%)
Routine trauma case	299 (79.9%)	44 (43.1%)
Deliberate delay	45 (12.0%)	37 (36.3%)
Missing	6	0
If deliberate delay, how many days?		
n	45	36
Mean (SD)	7.7 (6.2)	8.8 (4.8)
Median (IQR)	6 (3,10)	8.5 (5.5,10)
Min, Max	1, 21	1, 21
Missing	0	1

*Stable at baseline = was able to walk at admission with or without the use of crutches; Unstable = was not able to walk unaided at admission. 4 cases' stability were unclassified due to missing data – these are excluded from this table.

For all subsequent, hip-specific SCFE tables or follow-up tables, the analysis population is the 469 children (513 hips) from whom sufficient baseline data were available.

Table 5-4: Type of surgical management of unaffected hips

	Children presenting unilaterally
Unaffected hips, with no historical SCFE	
n	406
Was there a prophylactic fix of the opposite hip?	
No	279 (69.9%)
Yes	120 (30.1%)
Missing	7
Reason for prophylactic fix:	
n	120
Standard protocol	57 (47.9%)
Age of patient	33 (27.7%)
Obesity	27 (22.7%)
Other risk factors	34 (28.6%)
Missing	1

Table 5-5: Line listings of risk factors (other than standard protocol, age of patient or obesity) justifying a prophylactic fix (free-text entries in the database)

Reason (n=35)
• *Extent of L SUFE* • *Severe SCFE on opposite hip* • *Severe SCFE on opposite side* • *Severe unstable left SUFE, prophylactic pinning in case of 'silent' slip.* • *Severity of contra-lateral slip* • *Severity of contralateral slip. Patient immaturity. Poor compliance with follow-up.* • *Large slip of symptomatic side*
• *Low vit D* • *Low Vitamin D* • *Low Vitamin D levels*
• *Endocrine* • *Hypothyroid* • *Hypothyroidism* • *Metabolic bone sudo HPT*
• *Behavioural disorder* • *Downs* • *Downs syndrome* • *Ehler Dahlos syndrome Type I* • *Learning difficulties, epilepsy* • *On long term steroids*
• *Complained of some pain / waddling gait* • *Intermittent ache right hip, so fixed on 08.11.2017* • *Occasional left hip pain but not symptomatic at right hip presentation* • *Pain*
• *Active* • *Due to unusual presentation of Left slip / pre-slip. Right side fixed to avoid potential future confusion / delay* • *Had not presented for a year with symptoms on the left* • *Non compliance, continued to weight bear without crutches against advice given when seen at Northwick Park Hospital on 2nd June, mother requested prophylactic fixation* • *There was evidence of previous slip other side (no symptoms)*
• *Family history* • *Option given to parents whether they wanted the normal side fixing prophylactically* • *Previous left SCFE* • *Posterior Sloping Angle* • *Retroverted femoral head*
N=1: no details given

Table 5-6: Type of surgical management of each affected hip [*Definitions in notes below]

	Surveillance cohort at baseline		
	All	**Stable**	**Unstable**
Hips n	513	402	109
Was an open reduction performed?			
No	409 (81.2%)	355 (89.6%)	53 (50.0%)
Yes	95 (18.8%)	41 (10.4%)	53 (50.0%)
Missing	9	6	3
Open reduction not performed: further details			
n	409	355	53
In-situ fixation without reduction	367 (90.4%)	331 (94.0%)	35 (66.0%)
In-situ fixation with serendipitous reduction	31 (7.6%)	14 (4.0%)	17 (32.1%)
In-situ fixation with intentional reduction manoeuvre	8 (2.0%)	7 (2.0%)	1 (1.9%)
Technique type not reported	3	3	0
Capsular decompression performed	21 (5.3%)	17 (4.9%)	4 (7.8%)
No capsular decompression performed	378 (94.7%)	330 (95.1%)	47 (92.2%)
Missing	10	8	2
Surgical management strategy at baseline*			
Fix now	410 (80.9%)	343 (86.6%)	66 (60.6%)
Fix later	97 (19.1%)	53 (13.4%)	43 (39.4%)
Missing	6	6	0
Reduce and fuse	134 (26.6%)	62 (15.7%)	71 (66.4%)
Fix and fuse	339 (67.4%)	303 (76.9%)	35 (32.7%)
Fix and grow	25 (5.0%)	24 (6.1%)	1 (0.9%)
No reduction, no wires and no screws	5 (1.0%)	5 (1.3%)	0 (0.0%)
Missing	10	8	2

Notes:

1. Fix now: Timing of surgery = Emergency or a routine trauma case.
2. Fix later: Timing of surgery = A deliberate delay between diagnosis and surgery. (97 hips from the 83 patients that had a deliberate delay)
3. Reduce and fuse: Open reduction, or in-situ fix with serendipitous reduction, or in-situ fix with intentional reduction manoeuvre.
4. Fix and fuse: No reduction, screws used, and screw type = conventional.
5. Fix and grow: No reduction, screws allowing growth used and/or wires used.
6. No reduction, no wires and no screws: 4 hips had an in-situ fixation without reduction, and it was recorded that neither screws nor wires were used.
7. Missing: insufficient data collection to enable classification. Two hips' stability at baseline was not reported.

Table 5-7: Management of open reductions (n=90 children)

	Open reductions at baseline
Hips with open reduction	
n	95
Surgical dislocation performed?	
Yes	39 (43.3%)
No	51 (56.7%)
Unreported	5
No. of times the senior surgeon has performed a surgical dislocation or similar in past year	
n	83
Median (IQR)	5 (3,7)
Min, Max	1, 7
Unreported	12
Femoral neck osteotomy used to facilitate the reduction?	
Yes	62 (71.3%)
No	25 (28.7%)
Unreported	8
Blood flow to femoral head compromised?	
No	49 (54.4%)
Yes	13 (14.4%)
Did not assess	28 (31.1%)
Unreported	5
Blood flow to femoral head compromised = NO: how was this determined?	
Gross appearance of the epiphysis	14 (30.4%)
Drill/wire hole to observe bleeding from the epiphysis	38 (82.6%)
Transduced blood flow	5 (10.9%)
Unreported	3
Blood flow to femoral head compromised = YES: how was this determined?	
Gross appearance of the epiphysis	3 (25.0%)
Drill/wire hole to observe bleeding from the epiphysis	12 (100.0%)
Transduced blood flow	1 (8.3%)
Unreported	1

Table 5-8: Seniority of most senior surgeon in theatre

	Surveillance cohort at baseline
No. of hips	
n	513
Most senior surgeon present	
Consultant	466 (91.6%)
Non consultant career grade	16 (3.1%)
Senior trainee (ST8+)	10 (2%)
ST6/7	5 (1%)
ST5 or below	7 (1.4%)
Other	5 (1%)
Unreported	4
No. of SCFEs that senior surgeon has operated on in last year	
0	40 (8.5%)
1	47 (10%)
2	48 (10.2%)
3	74 (15.7%)
4	58 (12.3%)
5-10	145 (30.8%)
>10	42 (8.9%)
Unreported	59

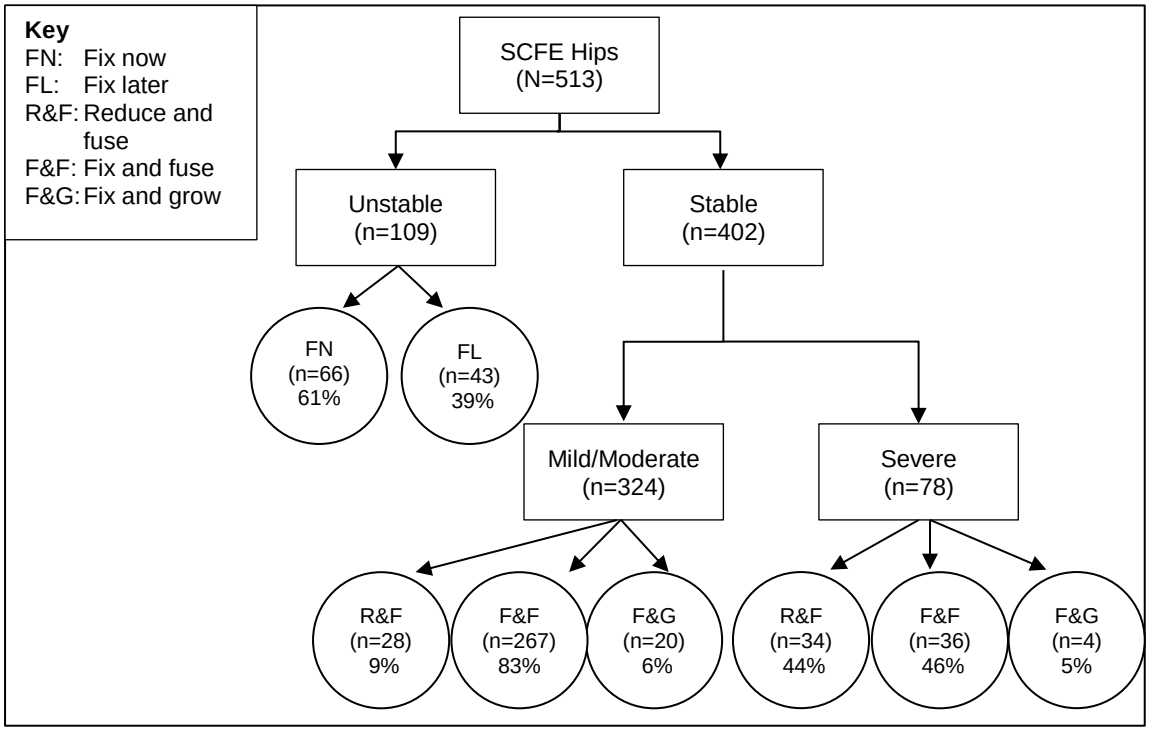
Notes:

1. Where the senior surgeon present was recorded as ‘other’, one was a non-training registrar with 2-years’ experience at that level, and one was a senior clinical fellow. The rest were described as ‘unknown’.

Table 5-9: Fixation technique

	Surveillance cohort at baseline
Hips	
n	513
Screws used?	
Yes	496 (98.0%)
No	10 (2.0%)
Missing	7
Number of screws used	
1	433 (87.7%)
2	56 (11.3%)
3	3 (0.6%)
≥ 4	2 (0.4%)
Missing	2
Size (mm) of screws used	
7.3	122 (25.3%)
7.0	61 (12.6%)
6.5	275 (56.9%)
5.5	6 (1.2%)
5.0	3 (0.6%)
4.5	1 (0.2%)
4.0	14 (2.9%)
3.5	1 (0.2%)
Unreported	13
Type of screws used	
Conventional fully threaded	99 (20.4%)
Conventional partially threaded	361 (74.3%)
Screw design enabling growth of the epiphysis	26 (5.3%)
Unreported	10
Wires used?	
Yes	24 (4.8%)
No	481 (95.2%)
Unreported	8
Did the guide wire, drill or screw penetrate the joint at any stage?	
Yes	48 (9.7%)
Penetration with drill	*6 (12.5%)*
Penetration with wire	*42 (87.5%)*
Penetration with screw	*4 (8.3%)*
No	446 (90.3%)
Unreported	19

Figure 5-2: Flow chart showing number and percentage[(a)] of types of surgical management according to clinical stability and radiographic severity at baseline



[a)] Parent nodes are represented with rectangles and leaves with circles. Percentages at leaves are calculated using a denominator of *n* reported at their parent node. Where surgical management data are unknown or do not belong to the categories of interest, percentages below a node will not sum to 100%.

5.2.3 Post-operative planning

Table 5-10: Planning for post-op period

	Surveillance cohort at baseline
Children	
n	469
Protected weight bearing planned?	
No	45 (9.8%)
Yes	416 (90.2%)
Unreported	8
Duration of protected weight bearing (weeks):	
n	410
Median (IQR)	6 (6,6)
Min, Max	1, 24
Unreported	6
Long-term restrictions on activities (such as sports) planned?	
No	301 (66.2%)
Yes	154 (33.8%)
Unreported	14

Table 5-11: Categorisation of text-entry responses where long-term restrictions on activities such as sport are planned

	Restriction planned (N=154 children)	Planned Duration							
		6 weeks / 2 months / 10 weeks	3 mths	4 mths / 5 mths	6 mths / 8 mths	1 yr	Until physis has fused / healed	Until clinical review	Not specified
Details for nature and duration of any restriction planned									
Details provided	152	23 (15.1%)	50 (32.9%)	3 (2.0%)	25 (16.4%)	4 (2.6%)	24 (15.8%)	9 (5.9%)	16 (10.5%)
Unanswered	2								
Nature of restriction planned									
No (impact) sports	130 (85.5%)	18 (13.8%)	46 (35.4%)	3 (2.3%)	21 (16.2%)	4 (3.1%)	21 (16.2%)	6 (4.6%)	12 (9.2%)
Restriction to range of movement allowed	3 (1.9%)	2 (67%)	1 (33%)	0	0	0	0	0	0
None specified	20 (13.1%)	3 (15%)	3 (15%)	0	4 (20%)	0	3 (15%)	3 (15%)	4 (20%)

Notes:

1. Text entries could generally be classified into one ’Planned Duration’ and one ‘Nature of restriction planned’. But in a couple of examples, two categories were possible.

5.3 Clinical time-line

Table 5-12: SCFE clinical time-line

	Surveillance cohort at baseline (N=469 children)					
	All	Clinical Stability (n=467)				
		Stable				Unstable
		All Stable	Severity of worst affected hip (n=367)			
			Mild	Moderate	Severe	
Children						
n	469	367	189	103	75	100
From onset of symptoms to seeking advice (months)						
n	401	310	167	80	63	90
Median (IQR)	1 (0,2)	1 (0,2)	1 (0,2)	1 (0,2)	1 (0,2)	0 (0,1)
Min, Max	0, 24	0, 24	0, 12	0, 24	0, 12	0, 13
Missing	68	57	22	23	12	10
From onset of symptoms to diagnosis (months)						
n	431	335	176	90	69	94
Median (IQR)	1 (0,3)	1 (0,4)	1 (0,2)	2 (1,8)	3 (0,7)	1 (0,2)
Min, Max	0, 32	0, 32	0, 14	0, 24	0, 32	0, 15
Missing	38	32	13	13	6	6
From diagnosis to admission to hospital (days)						
n	457	356	185	98	73	99
Median (IQR)	0 (0,5)	0 (0,6)	0 (0,4)	0 (0,6)	1 (0,11)	0 (0,0)
Min, Max	0, 192	0, 192	0, 136	0, 131	0, 192	0, 43
Missing	12	11	4	5	2	1
From admission to hospital to surgery (days)						
n	458	357	186	98	73	99
Median (IQR)	1 (0,3)	1 (0,2)	1 (0,2)	1 (0,2)	1 (0,4)	2 (1,7)
Min, Max	0, 75	0, 47	0, 47	0, 8	0, 12	0, 75
Missing	11	10	3	5	2	1
From surgery to diagnosis of contralateral SCFE (months)						
n	32	27	19	5	3	5
Median (IQR)	7.7 (3.9,11.9)	7.8 (3.9,11.4)	7.7 (3.4,10.5)	11.4 (9.9,12.3)	6.7 (3.9,15.3)	7.6 (7.5,18.9)
Min, Max	0.7, 28	2.2, 28.0	2.2, 28.0	3.9, 19.0	3.9, 15.3	0.7, 20.4
Missing	1	0	0	0	0	1

Notes:

1. In bilateral presentations, results are split by severity of worst affected hip.
2. 17 children had no severity reported for either hip at presentation – these are excluded from this analysis.
3. 1 case of contralateral SCFE had missing date of diagnosis of the contralateral slip.

5.4 Post-operative complications

In this section we report on key complications post SCFE/prophylactic fix: surgical site infections, avascular necrosis, and chondrolysis. We also report any other complications that were recorded (contralateral SCFE is reported separately in Section 5.10). We examine whether AVN is more likely in unstable hips or following an open reduction; and if an open reduction is carried out, does higher experience in the room during surgery result in lower AVN rates.

Table 5-13: Site infections arising from baseline surgery [first presentations & prophylactic fixes]

	Surveillance cohort at 3 months	
	1st presentations	**Prophylactic fixes**
Hips		
At presentation	513	120
Lost to follow-up at 3 months	20	3
Analysed	493	117
Surgical site infection		
No	450 (99.1%)	107 (96.4%)
Yes	4 (0.9%)	4 (3.6%)
Missing	39	6
When was the infection identified?		
At admission	0	0
Other post-discharge follow-up	2 (50%)	3 (75%)
Post discharge patient reported only	2 (50%)	1 (25%)
Missing	0	0
Criteria used to diagnose the infection		
Abscess or other evidence of infection at re-operation	0	0
Antibiotics prescribed by GP for SSI (patient reported only)	2 (50%)	1 (25%)
Aspirated fluid/swab of surgical site yield organisms and pus cells are present	0	0
Clinician's diagnosis	1 (25%)	3 (75%)
Fever	0	0
Heat	0	0
Incision opened by surgeon or spontaneously dehiscence	0	0
Localised pain and tenderness	1 (25%)	0
Localised swelling	0	0
Purulent drainage	0	1 (25%)
Redness	2 (50%)	3 (75%)
None ticked	0	0
Type of surgical site infection		
Deep incisional	0	0
Superficial incisional	4 (100%)	4 (100%)
Missing	0	0

Notes:

1. This table is hip-specific. 18 patients were lost to follow-up at 3 months, and two of these were a bilateral presentation.
2. 37/513 (7%) 1st presentation hips, and 5/120 (4%) prophylactically fixed hips had no 3-month follow-up data entered, but were not confirmed lost-to-follow-up.

Table 5-14: Other complications relating to hips fixed at baseline [first presentations & prophylactic fixes]

	1st presentations			Prophylactic fixes		
	Baseline to 3 months	**3 months to 2-years**	**All follow-up**	**Baseline to 3 months**	**3 months to 2-years**	**All follow-up**
Hips						
At presentation	513	513	513	120	120	120
Lost to follow-up	20	62	60	3	14	14
Analysed	493	451	453	117	106	106
Avascular necrosis						
Yes	17 (3.7%)	24 (6%)	29 (7.1%)	0	1 (1%)	1 (1%)
No	437 (96.3%)	378 (94%)	377 (92.9%)	111 (100%)	100 (99%)	100 (99%)
Missing	39	49	47	6	5	5
Chondrolysis						
Yes	0	3 (0.8%)	3 (0.8%)	0	0	0 (0%)
No	453 (100%)	397 (99.3%)	397 (99.3%)	110 (100%)	101 (100%)	101 (100%)
Missing	40	51	53	7	5	5
Other complications						
Osteomyelitis	0	1 (0.2%)	1 (0.2%)	0	1 (0.9%)	1 (0.9%)
Post-operative or peri-prosthetic fracture of the femur	1 (0.2%)	1 (0.2%)	2 (0.4%)	1 (0.9%)	0	1 (0.9%)
Hip dislocation	2 (0.4%)	1 (0.2%)	2 (0.4%)	0	0	0
Implant penetration	5 (1.0%)	1 (0.2%)	6 (1.3%)	1 (0.9%)	0	2 (1.9%)
Re-slip	3 (0.6%)	3 (0.7%)	5 (1.1%)	0	0	0
Other	15 (3.0%)	31 (6.9%)	43 (9.4%)	1 (0.9%)	4 (3.8%)	5 (4.7%)

Notes:

1. This table is hip-specific, and records whether patients had these complications during each follow-up period. 18 patients were lost to follow-up at 3 months, and two of these were a bilateral presentation. 58 patients were lost to follow-up at 2 years – four of these were bilateral presentations.
2. The total number of hips analysed in the 'All follow-up' column includes two hips that had AVN during the first 3 months, but were subsequently lost to follow-up. Counts in this column may not equate to the sum of counts in each follow-up period – this is because a small number of hips have complications reported in both periods, and these are not counted twice when looking at the whole of follow-up.
3. 37/513 (7%) 1st presentation hips, and 5/120 (4%) prophylactically fixed hips had no 3-month follow-up data entered. 47/513 (9%) 1st presentation hips, and 4/120 (3%) prophylactically fixed hips had no 2-year follow-up data entered.
4. 'Missing' denotes hips where no follow-up data were uploaded, or hips where the question was unanswered.
5. The denominator for the percentages of other complications is: Total number of hips analysed minus the number with no response recorded for the question.

Table 5-15: Line listings of other reported complications (free-text entries in the database)

Other complication during 1st 3-months post baseline: 1st presentations (n=15)

Screw backout:

- *SCFE screw backed out (fixation lost)*
- *Screw backed out. Re-implantation 28/9/2016*
- *Unfortunately the left sided fixation has backed out, possibly as a result of him weight bearing through the left leg. The slip has worsened slightly compared to pre op x-rays as a result of the screw backing out.*

Screw failure requiring revision:

- *Screw bent due to failure to comply with restricted weight bearing*
- *The screw does not appear to cross the physis!! He was discharged from clinic by the Consultant responsible at this visit who stated 'the radiograph showed good alignment of the SUFE'*
- *Failure of compliance fully weight bearing symptom free but broken internal fixation and re slip with implant migration. Implants removed slip repositioned on tration and single screw re-fixation performed*

Other:

- *She has been experiencing some further pain over the anterolateral left thigh. Further x-rays today show her fixation screw in optimal position. This has been inserted through the base of the anterior aspect of the femoral neck and slightly proud and could possibly be creating some soft tissue impingement. 03/05/17: She still experiences slight ache from around the left hip.*
- *Growth plate not closed*
- *Premature proximal femoral physeal closure - planning epiphyseodesis as skeletally dysmature - likely to be perform before end 2017 as predicted LLD is 2.7 cm*
- *Premature proximal femoral physeal closure - probable cam impingement & restricted range of motion*
- *Recurrent right hip pain.*
- *Limp and slight leg length discrepancy*
- *Minimal limb length discrepancy*
- *Minor heterotopic calcification not causing restriction of movement*
- *Small amount of hip pain - which seems to be settling - hence decision for follow-up in 3 months time*

Other complication during 2 years post baseline: 1st presentations (n=31)

Screw failure requiring revision:

- *Screw significantly prominent. Continued slipping of epiphysis despite previous fixation*
- *Screw that had bent broke and an additional screw had to be inserted*

Screw backout:

- *Loosening of screw*
- *Outgrown the screw*

Other:

- *'Significant CAM deformity'*
- *1.5cm leg length discrepancy*
- *CAM lesion*
- *Cam with ? narrowing of lat joint space. Screw close to joint surface but not penetrating - for planned removal and arthrogram.*
- *Coxa Breva & LLD managed by contralateral epiphyseodesis femur and tibia Removal of internal fixation or femoral neck lengthening and restoration trochanteric offset declined - despite Trendelenberg gait*
- *Deformation of head and neck*

- *Had a fall while playing football and developed left hip pain*
- *Hip discomfort*
- *Hip impingement*
- *Impingement*
- *LH: Pain and reduced range of movement*
- *Leg length discrepancy*
- *Leg length discrepancy, shorter on the right side*
- *Osteoarthrits leading to THR*
- *Osteopenia*
- *Painful right hip*
- *Painless hip impingement with restriction of ROM. Referred to Ed Bache in Birmingham for consideration of further surgery. Outcome of this clinic appointment not known.*
- *Patient developed pain in the left hip esp. after activity. MRI should that the head of the screw was impinging on the illopsosas. pain was discussed in the MDT and because the physis was closed, plan was made for screw exchange. last thing patient was seen i clinic the pain has subsided and the decision was made to watch and wait.*
- *Presented with pain in left hip ?FAI*
- *Prominence of the right femoral head and neck transition with associated subcortical cystic bone bruising, which may be associated with CAM type femoroacetabular impingement*
- *When reviewed in July 2019 - Femoroacetabular impingement with evidence of CAM lesion on x-rays from which she is symptomatic*
- *coxa vara shortening of left lower limb*
- *experiences occasional episodes pf aching pain around anterior aspect when walking distance. Slight prominence fixation screw*
- *persistant pain*
- *stitch abcess post-operatively, no deep sepsis*
- *very retroverted femoral head. MR arthrogram requested*

n=1: no details given

Other complication during 3 months post baseline: prophylactic fixes (n=1)

- *right hip pain*

Other complication during 2 years post baseline: prophylactic fixes (n=4)

- *Grown off screw. Discussed revising screw, though family not keen and observing closely.*
- *Growth disturbance leading to short femoral neck*
- *Leg length discrepancy (approx. 3cm) requiring epiphysiodesis*
- *Valgus of femoral head*

5.4.1 Risk of AVN

Table 5-16: Risk of avascular necrosis (AVN) with respect to risk factors (Model 1: risk of AVN adjusted for baseline use of open reduction and stability of hip; Model 2: risk of AVN in open reductions adjusted for experience of most senior surgeon. All models include a random effect for child in if any children included present bilaterally)

Covariate		Hips	N (%) with any AVN during follow-up	Odds Ratio of AVN	95% confidence interval for odds ratio
Model 1 (N=397 hips, from 363 children):					
Stability of hip at presentation	Stable	310	9 (2.9%)	1	-
	Unstable	87	20 (23.0%)	4.4	(1.7,11.4)
Open reduction carried out at baseline	Yes	79	21 (26.7%)	7.5	(2.4,23.2)
	No	318	8 (2.5%)	1	-
Hips excluded from model (N=116):	*Stability/open reduction status missing*	11			
	AVN status unknown	47			
	Confirmed lost to follow-up at 2 years	58			
Model 2 (N=72 hips with open reduction, from 68 children):					
Experience of most senior surgeon - number of similar procedures performed in past year by senior surgeon	Fitted as continuous:	72	19 (26.4%)	1.0	(0.8,1.2)
	Summary for each category: 0	5	2 (40%)		
	1	7	2 (29%)		
	2	12	4 (33%)		
	3	10	3 (30%)		
	4	6	0		
	5-10	13	2 (15%)		
	>10	19	6 (32%)		
Hips excluded from model (N=23):	*Experience of surgeon missing*	12			
	Followed up, but AVN status unknown	2			
	Lost to follow-up	9			

Notes:

1. The reference categories for the odds ratio of AVN in Model 1 are: ‘Open reduction=No’, and ‘Stability at baseline=Stable.
2. It was decided to fit ‘Experience of most senior surgeon’ as a continuous variable (the 5-10 category was modelled numerically as 7.5 procedures, and the >10 category was modelled as 12.5 procedures. From this model, the odds ratio represents the effect that each additional procedure undertaken has on the odds of AVN.
3. Models were fitted using logistic regression with random effects, including all hips with complete data collection for the variables fitted. Random effects were included so that both hips from bilateral presentations could be included (39 bilateral cases in the ‘all hips’ model, and 4 in the ‘Open reductions’ model).

5.5 Other surgery

In this section we report on what other related surgery took place during follow-up, and whether any surgery was planned for the future.

5.5.1 Surgery during follow-up

Table 5-17: Surgery following baseline fixation

	1st presentations			Prophylactic fixes		
	Baseline to 3 months	**3 months to 2 years**	**All follow-up**	**Baseline to 3 months**	**3 months to 2 years**	**All follow-up**
Hips						
At presentation	513	513	513	120	120	120
Lost to follow-up	20	62	62	3	14	14
Analysed	493	451	451	117	106	106
Related surgery						
Any	26 (5.7%)	61 (15.4%)	74 (18.5%)	2 (1.8%)	9 (9.1%)	11 (11.1%)
No	428 (94.3%)	335 (84.6%)	326 (81.5%)	107 (98.2%)	90 (90.9%)	88 (88.9%)
Missing	39	55	51	8	7	7
Related surgery type						
Fracture fixation	1 (0.2%)	1 (0.2%)	2 (0.4%)	1 (0.2%)	0	1 (0.9%)
Removal of screw(s) / wire(s)	6 (1.2%)	24 (5.3%)	27 (6.0%)	1 (0.2%)	5 (4.3%)	6 (5.7%)
Exchange or adjustment of screw(s) / wires(s)	10 (2.0%)	15 (3.3%)	23 (5.1%)	1 (0.2%)	2 (1.7%)	3 (2.8%)
Realignment osteotomy	3 (0.6%)	6 (1.3%)	8 (1.8%)	0	0	0
Intracapsular	*2 (0.4%)*	*1 (0.2%)*	*3 (0.7%)*	-	-	-
Extracapsular	*1 (0.2%)*	*5 (1.1%)*	*5 (1.1%)*	-	-	-
Impingent surgery, not realignment osteotomy (i.e. hip head / neck osteochondroplasty)	1 (0.2%)	1 (0.2%)	2 (0.4%)	0	0	0
Arthroscopic	*1 (0.2%)*	*0*	*1 (0.2%)*	-	-	-
Open	*0*	*1 (0.2%)*	*1 (0.2%)*	-	-	-
Hip arthroplasty	0	8 (1.8%)	8 (1.8%)	0	0	0
Epiphysiodesis for limb length discrepancy	1 (0.2%)	7 (1.6%)	8 (1.8%)	0	2 (1.7%)	2 (1.9%)
Other hip surgery	11 (2.2%)	7 (1.6%)	18 (4.0%)	0	1 (0.9%)	1 (0.9%)
Missing	0	0		1	0	

Notes:

1. The counts in each column represent the data collected at each follow-up time-point.
2. Denominators for percentages of types of related surgery is the total number of hips followed up.
3. One patient had two realignment osteotomies reported: the one at 3 months was extracapsular, and the one reported at 2 years was intracapsular.

Table 5-18: Line listings of other reported related surgery (free-text entries in the database)

Other related surgery during 1st 3 months post baseline (1st presentations) (n=11)
Dislocated Hip: • *Hip dislocated post-op day 2. Surgery involved re-exploring joint, repositioning and suture of capsule and re-attachment of trochanteric fragment. No signs of AVN 3 months later.* • *On 10.06.2016 underwent closed reduction of the dislocated left hip and application of a hip spica On 15.9.2016 screws partially withdrawn as one had penetrated articular surface after avascular necrosis.* Hinged distraction of avascular hip on MR: • *Unstable severe grade SCFE. Pre-op subtraction scan showed reduced perfusion. Had staged hinged distraction.* • *Hinged distraction on 13/12/2016 for pre=-op AVN and poor vascularity detected on pre-op perfusion MRI scan.* • *Patient had unstable SUFE pinned in situ developed AVN proven on subtraction MRI and revised on 14th Dec 17 to alignment and then staged hinged distraction* • *Severe unstable SUFE. Pre-op Subtraction MRI scan show no perfusion of right femoral head. had staged hinged distraction.* Other: • *Patient had severe grade unstable SUFE. Pre-op subtraction showed very poor perfusion. One screw was removed in March 2018* • *Patient had stabilisation of SCFE, then subsequently transferred to Exeter for realignment osteotomy as a planned procedure. Initially pinning in-situ used as a temporary measure for a couple of weeks only to transfer the patient to definitive care.* • *Prophylactic pinning of the left hip 3 weeks later.* • *Percutaneous fixation with single screw* • *Left hip arthroscopy- trimming labral tear, resection head neck bump*
Other related surgery during 2 years post baseline (1st presentations) (n=7)
Failed attempt at screw removal: • *Attempted removal of screws however, these were unable to be removed on either side and surgery was abandoned.* • *Attempted screw removal - failed on 13.02.2018* Hinged distraction for AVN: • *hinged distraction in December 2016* • *hip distractor for 5 months following development of early AVN* Other: • *Removal of I Plates from Epiphysiodesis of Right Distal Femur and right proximal tibia epiphysiodesis* • *STEROID INJECTION AND EUA* • *curettage of screw tract and local antibiotics*
Other related surgery during 2 years post baseline (Prophylactic fixes) (n=1)
Failed attempt at screw removal: • *Attempted removal of screws however, these were unable to be removed on either side and surgery was abandoned.*

5.5.2 Planned surgery beyond 2 years' follow-up

Table 5-19: Future surgery planned

	1st presentations at 2 years (N=411 children)	Prophylactic fixes at 2 years (N=106 children)
No. of hips		
At presentation	513	120
Lost to follow-up	62	14
Analysed	451	106
Further surgery planned?		
Yes	43 (10.8%)	5 (5%)
No	356 (89.2%)	95 (95%)
Missing	52	6
Planned surgery: further detail		
Fracture fixation	0	0
Removal of screw(s) / wire(s)	27 (62.8%)	4 (80%)
Exchange or adjustment of screw(s) / wires(s)	4 (9.3%)	1 (20%)
Realignment osteotomy	2 (4.7%)	0
Intracapsular	*0*	*0*
Extracapsular	*2 (100%)*	*0*
Impingent surgery, not realignment osteotomy (i.e. hip head / neck osteochondroplasty)	2 (4.7%)	0
Arthroscopic	*2 (100%)*	*0*
Open	*0*	*0*
Hip arthroplasty	3 (7.0%)	0
Epiphysiodesis for limb length discrepancy	1 (2.3%)	0
Other hip surgery	7 (16.3%)	1 (20%)

Table 5-20: Line listings of other reported planned surgery (free-text entries in the database)

Other planned surgery (1st presentations) (n=7)
• *Arthrogram* • *Has been referred to Mr Katchburian at Maidstone by the treating surgeon* • *Possible removal of metalwork* • *Referred to adult hip surgeons for management of cam deformity Has had arthrogram* • *further debridement of screw tract* • *potentially planned for a Southwick osteotomy - but awaiting arthrogram results*
Other planned surgery (Prophylactic fixes) (n=1)
• *curettage of screw tract and antibiotic injection*

5.6 Radiographic outcomes

5.6.1 2-year hip shape

In this section we report on the 2-year hip shape of our cohort. This is the alpha-angle measured on lateral radiographs.

Of the potential 513 hips available for analysis, at 2-year follow-up, 62 had been lost to follow-up, 78 hips did not have a routine radiograph recorded, and 29 hips were excluded owing to AVN. Of the remaining 344 hips, 159 (46%) did not send x-rays that were at least 1 year post baseline – these are treated as missing, reason unknown. This leaves 185 hips that could be included in the analysis of 2-year hip shape, and represents 36% of the 513 newly presenting hips recorded in BOSS.

Radiographs were difficult to obtain, and not always available at 2 years. It was decided to include radiographs that were taken at least one year after baseline, as it is considered that the shape would not change greatly after than time. The median, IQR, min and max from baseline of radiographs included in this analysis was: 2.0 (1.6, 2.2) (1.0, 3.5) years.

In terms of demographics, the sample is representative of the surveillance cohort (SC): of the 185 hips, 107 are from males (58%), and the mean (SD) age was 12.3 (1.7), with BMI 26.2 (6.3). In terms of presentation, they are also fairly representative: 149 (81%) were stable at baseline – compared with 78% in the SC.

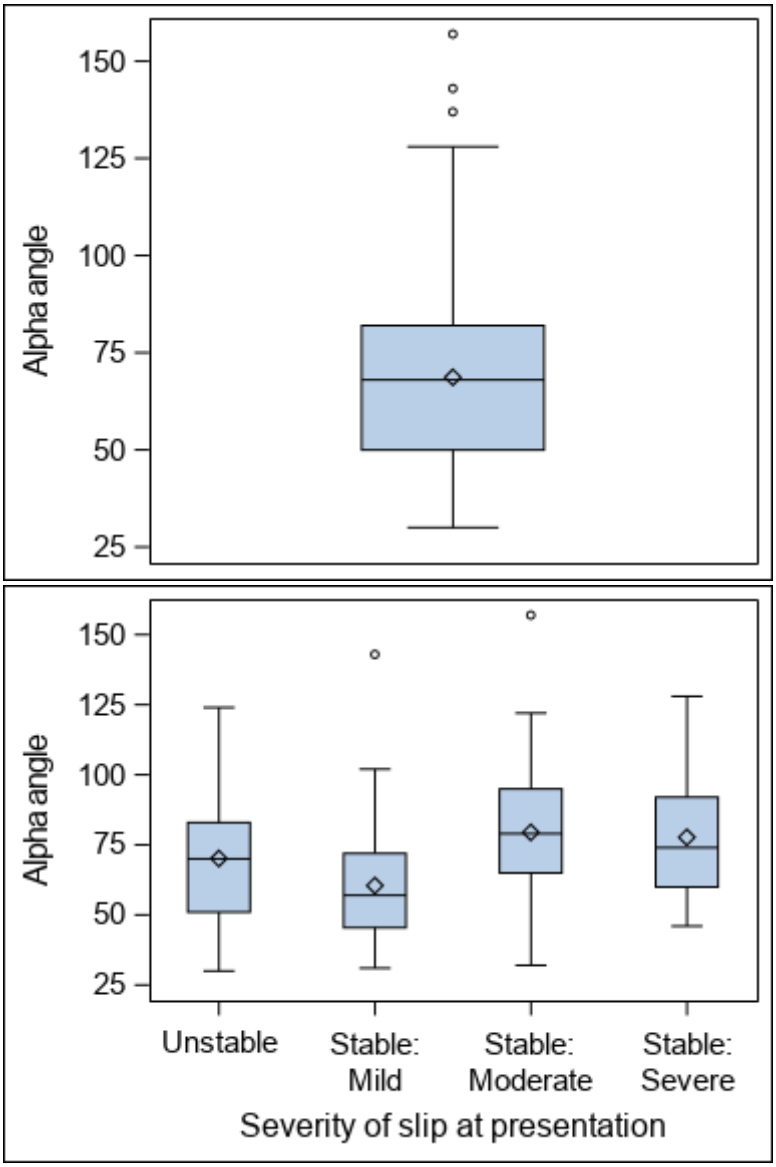
Table 5-21: Hip shape at 2 years*

	Surveillance cohort at 2 years				
	All	Baseline Stability/Severity*			
		Unstable	Stable: Mild	Stable: Moderate	Stable: Severe
Hips					
n	451*	98	190	92	70
Alpha angle					
n	185	35	84	36	29
Mean (SD)	68.6 (23.2)	70.2 (23.9)	60.5 (19.0)	79.5 (25.4)	77.7 (21.8)
Median (IQR)	68 (49,82)	70 (51,83)	57 (46,72)	79 (65,95)	74 (60,92)
Min, Max	30, 157	30, 124	31, 143	32, 157	46, 128
Hips with AVN	29	20	2	2	5
No lateral radiograph	78	24	27	13	14
Missing*	159	30	77	40	12

* Notes:

1. Radiographs were difficult to obtain, and not always available at 2 years. For each child, it was decided to include the radiograph closest to 2-years, and at least one year post baseline.
2. One hip was unclassified for stability at baseline.
3. 62 of the 513 hips presenting at baseline were known to be lost to follow-up. This analysis had a potential sample size of 451 hips.
4. Missing: we do not have a measurement, but the reason is unknown. A 2-year radiograph was not received, and we do not know if this is because there were none taken, or if it just wasn't sent.

Figure 5-3: Boxplot of hip-shape (sphericity alpha angle) at 2 years: overall for n=185 hips; and split by severity of hip at baseline [Unstable n= 35, Stable Mild n=84, Stable Moderate n=36, and Stable Severe: n=29]



Notes:

1. One hip was not classified at baseline for stability.

5.6.2 Baseline factor prediction of hip shape

In this section we explore the potential association between baseline factors and 2-year hip shape. A univariate analysis is carried out initially to examine effects of each factor, and a multivariate model is then fitted including age, sex, clinical stability and radiographic severity together with any other factor that was found to be significantly associated. Surgical management types have not been examined – these depend on clinical stability and severity, and so independent contributions of these factors are difficult to incorporate with this analysis approach.

5.6.2.1 Univariate analysis

Table 5-22: Univariate analysis of hip shape (sphericity alpha angle) at 2 years with respect to potential baseline predictors. [Parameter estimates are derived by fitting random effects linear regression models for each covariate]

Predictor	n	Median (IQR) Alpha angle	Parameter estimate	
			Estimate	95% CI
Hips	185	-	-	-
Age (continuous)*	185	-	2.08	(-0.13,4.29)
Sex				
Male	107	68 (53,80)	0	-
Female	78	67.5 (46,83)	-1.36	(-9.11,6.40)
BMI	57	-	0.82	(-0.49,2.13)
Severity of slip at presentation				
Unstable	35	70 (51,83)	-	-
Stable: Mild	84	57 (45.5,72)	-10.53	(-20.72,-0.35)
Stable: Moderate	36	79 (65,95)	7.54	(-4.43,19.51)
Stable: Severe	29	74 (60,92)	7.31	(-5.36,19.99)
Time-lag from onset of symptoms to diagnosis (days)	165	-	1.12	(0.14,2.09)
Treating centre case-load				
Low (1-2 cases per year)	34	73.5 (56,85)	1.01	(-9.23,11.25)
Medium (3-5 cases per year)	45	58 (48,78)	-5.42	(-14.73,3.90)
High (>5 cases per year)	105	69 (49,82)	0	-

Notes:

1. There is no evidence of a non-linear relationship between 2-year EQ-5D-Y and age [scatterplot not shown]. Age is therefore presented as continuous rather than categorised into groups.
2. Clinical stability (Stable/Unstable) and Radiographic Severity (Mild/Moderate/Severe) were planned to be examined separately, but it was decided that combining these into a single 4-category descriptor of severity would make more sense clinically.

5.6.2.2 Multivariate analysis

Table 5-23 gives the results of the final multivariate random effects linear regression model chosen to represent how baseline variables relate to 2-year hip shape. Age, and sex are fitted as *a priori* choices. Clinical stability and radiographic severity were also *a priori* choices, but are combined into single descriptor of severity. Time-lag is also fitted, as this was found to be significant at the univariate level.

Table 5-23: Multivariate analysis of hip shape at 2 years with respect to baseline covariates.

Covariate	Parameter estimate		Overall significance of covariate as a predictor of 2-year Alpha Angle
	Estimate	95% CI	
Hips			
n	164		
Age at baseline (years)			0.354
	1.1	(-1.6, 3.8)	
Sex			0.666
Male	0	-	
Female	1.7	(-7.6, 11.1)	
Severity of slip at presentation			0.047
Unstable	0	-	
Stable: Mild	-10.3	(-22.0, 1.3)	
Stable: Moderate	4.0	(-9.8, 17.7)	
Stable: Severe	4.8	(-10.2, 19.8)	
Time-lag from onset of symptoms to diagnosis (days)			0.204
	0.6	(-0.4, 1.7)	

Notes:

1. Clinical stability (Stable/Unstable) and Radiographic Severity (Mild/Moderate/Severe) were planned to be examined separately, but it was decided that combining these into a single 4-category descriptor of severity would make more sense clinically.

5.7 PROMs

BOSS was designed to collect surveillance data for all known cases of SCFE in the UK during a discrete time-period. At the same time, it was planned that a subset of SCFE cases would be approached and asked to be part of a consented cohort. This cohort would fill in questionnaires at three time-points during the study: baseline, 3 months post baseline, and 2 years post baseline, and their NHS number would be stored by BOSS to enable future data linkage. A total of 57/144 sites were enrolled to invite their SCFE cases to consent to being part of the consented cohort. The questionnaires filled in by patients are referred to in the study as Patient Reported Outcome Measures (or PROMs).

In practice, there was a low rate of accrual of cases into the consented cohort (see Figure 4-3: SCFE recruitment over time). There was also a difficulty in collecting PROMs within the time-windows specified in the protocol (see Table 4-3: Protocol deviations). The reasons for this are most likely to be related to a lack of research nurse expertise available in this field of surgery, rather than a reluctance on the part of cases to take part. Some sites were clearly very successful at consenting patients (e.g. Alder Hey, 20/23 SCFE cases were consented).

An electronic system for collecting consent and PROMs was developed to make the process easier for both clinicians and patients. Unfortunately, this was introduced too late in the study, and only yielded a small number of additional consentees.

Low sample sizes and low per-protocol PROMs completion has impacted the methods of analysis possible. The planned multivariable analyses are not possible, and it is also not possible to examine within-patient changes in PROMs over time. However, Table 5-1 does show that the consented cohort is representative of the surveillance cohort (SC); and that the subsets that completed baseline PROMs and 2-year PROMs are also representative in terms of demographics. We also have a similar case-mix in terms of stability at baseline: 43 (73%) were stable at baseline – compared with 78% in the SC; but different in terms of severity of slip: 19 (32%) were mild and 14 (24%) were moderate, compared with 45% and 26% respectively in the SC - i.e. we have a slightly larger proportion of severe slips reporting 2-year PROMs compared with the SC.

5.7.1 Patient reported baseline presentation

SCFE cases consented at baseline were asked to fill in a patient CRF. Although 47 cases were consented at baseline, we have a patient CRF for 38 of these. A further 27 completed patient CRFs outside the baseline window.

Table 5-24 Patient reported presentation factors

	Consented cohort	
	All	**Consented at baseline**
Children n	144	49
Completed questionnaires n	65 (45%)	38 (78%)
What was the main reason for seeking medical care? (you can select more than one reason)		
Hip or groin pain	33 (51%)	20 (53%)
Thigh pain	19 (29%)	15 (39%)
Knee pain	27 (42%)	14 (37%)
Limp	36 (55%)	22 (58%)
Unable to walk	14 (22%)	12 (32%)
No reason given	0	0
How did your child get to hospital on the day of admission?		
Walked without help	33 (51%)	17 (45%)
Walked with support (e.g. crutches)	13 (20%)	9 (24%)
Wheelchair	10 (15%)	7 (18%)
Carried	4 (6%)	2 (5%)
Stretcher	5 (8%)	3 (8%)
No response given	0	0
Was your child admitted to hospital for surgery soon after symptoms began? (i.e. within 2-3 weeks)		
Yes	26 (41%)	17 (46%)
No	38 (59%)	20 (54%)
No response given	1	1
If no, please give details of any test of treatments that they received before the Slipped Epiphysis was identified:		
Physio	6 (22%)	6 (38%)
Medication	1 (4%)	1 (6%)
Insoles	1 (4%)	1 (6%)
Response given, but does not give any details of test treatments	20 (74%)	9 (56%)
No response given	11	4

Notes:

1. Although 47 sets of PROMs were completed at baseline, 9 of these did not include the patient CRF summarised in this table.
2. Most children were consented post baseline, but 27 of these were given the baseline patient CRF to complete.

5.7.2 Descriptive results: PROMs progression over time

Table 5-25: Summary statistics for SCFE PROMs

	Consented cohort Questionnaire completed:		
	Within 2 weeks of baseline	**At 3 months +/-2 weeks**	**At 2 years +/-6 months**
Consented cohort			
n	49	78	144
Questionnaires completed			
n	47 (96%)	26 (33%)	59 (41%)
EQ-5D-Y: score [*1.0 = Perfect health*]			
n	47	26	59
Mean (SD)	0.14 (0.44)	0.64 (0.36)	0.82 (0.22)
Median (IQR)	0.1 (-0.2,0.6)	0.8 (0.3,0.9)	0.9 (0.8,1.0)
Min, Max	-0.6, 1.0	-0.5, 1.0	0.0, 1.0
Missing	0	0	0
EQ-5D-Y: VAS [*100 = Perfect health*]			
n	46	26	57
Mean (SD)	60.3 (18.4)	75.1 (23.0)	81.3 (17.5)
Median (IQR)	60 (50,75)	82 (60,90)	85 (70,95)
Min, Max	10,100	20,100	40,100
Missing	1	0	2
PedsQL Total Score [*100 = Excellent quality of life*]			
n	46	25	59
Mean (SD)	53.5 (16.2)	66.0 (17.2)	77.6 (17.3)
Median (IQR)	52.7 (43.5,66.3)	65.2 (53.4,73.9)	82.6 (63.0,92.4)
Min, Max	13.0, 82.1	30.4, 100.0	29.3, 100.0
Missing	1	1	0
PedsQL: Physical factors [*100 = Excellent physical quality of life*]			
n	46	25	59
Median (IQR)	31.3 (15.6,50.0)	56.3 (40.6,68.8)	83.3 (62.5,90.6)
Min, Max	3.1,79.2	15.6, 100	9.4, 100
Missing	1	1	0
PedsQL: Emotional factors [*100 = Excellent emotional quality of life*]			
n	46	25	59
Median (IQR)	60 (50,80)	85 (60,100)	85 (65,100)
Min, Max	0, 100	0, 100	30, 100
Missing	1	1	0

PedsQL: Social factors	[*100 = Excellent social quality of life*]		
n	47	25	59
Median (IQR)	65 (55,85)	70 (60,90)	90 (75,100)
Min, Max	30, 100	45, 100	20, 100
Missing	0	1	0
PedsQL: School factors	[*100 = Excellent quality of life with reference to school*]		
n	47	25	58
Median (IQR)	70 (50,80)	60 (55,70)	80 (65,90)
Min, Max	5, 100	35, 100	5, 100
Missing	0	1	1
Wong Baker Faces Scale	[0 = *No pain*]		
n	45	24	51
Mean (SD)	4.2 (2.3)	1.8 (2.5)	1.7 (1.9)
Median (IQR)	4 (2,6)	1 (0,3)	2 (0,2)
Min, Max	0, 10	0, 10	0, 8
Missing	2	2	8

Notes:

1. The per-protocol window for 2-year PROMs was set as between -3 months and +1 month from the 2-year target. At the SSC meeting which took place in November 2019, it was decided to widen the window of acceptability for 2-year PROMs to +/-6 months.
2. One case returned two sets of PROMs within the +/-6 month window for 2 years. Only the PROMs that were completed closest to the 2-year target were included in the analysis above.
3. Recent research [1]has indicated that regular EQ-5D-3L value sets cannot be used for children and adolescents. The main reason is that health states are valued differently when described for an adult or a child. Research is currently ongoing, partly funded by the EuroQol Research Foundation, to ultimately produce EQ-5D-Y value sets for use in children and adolescents. For the purpose of this study, EQ-5D-Y has been evaluated using Dolan 1997. [2] NB. The valuation method incurs the possibility of a negative score for some health states. Health state index scores generally range from 0 (where 0 is a health state equivalent to death) and 1 (perfect health).

[1] *Kind P, et al. Can adult weights be used to value child health states? Testing the influence of perspective in valuing EQ-5D-Y. Qual Life Res 2015 Oct;24(10):2519-2539*
[2] *Dolan P. Modelling valuations for EuroQol health states. Med Care 1997;35(11):1095-108*

Figure 5-4: Scatterplot of EQ-5D-Y overall score by time-point

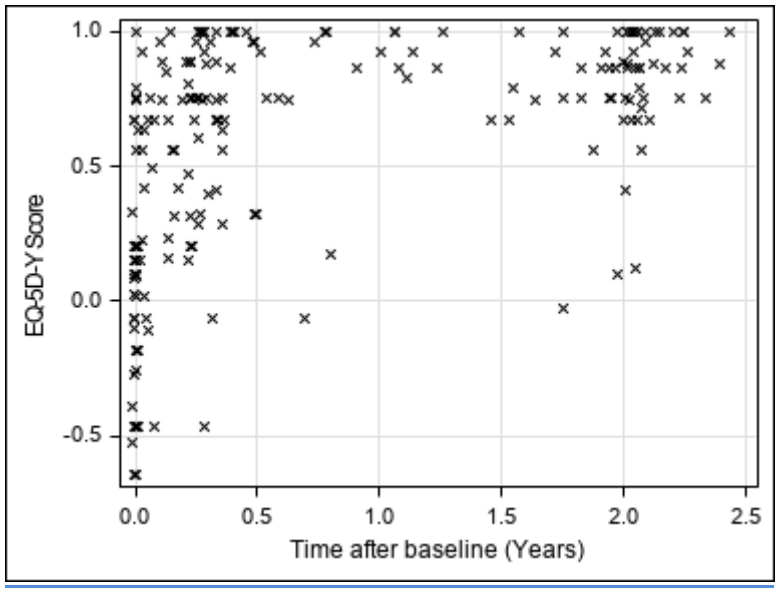


Figure 5-5: Scatterplot of EQ-5D-Y VAS score by time-point

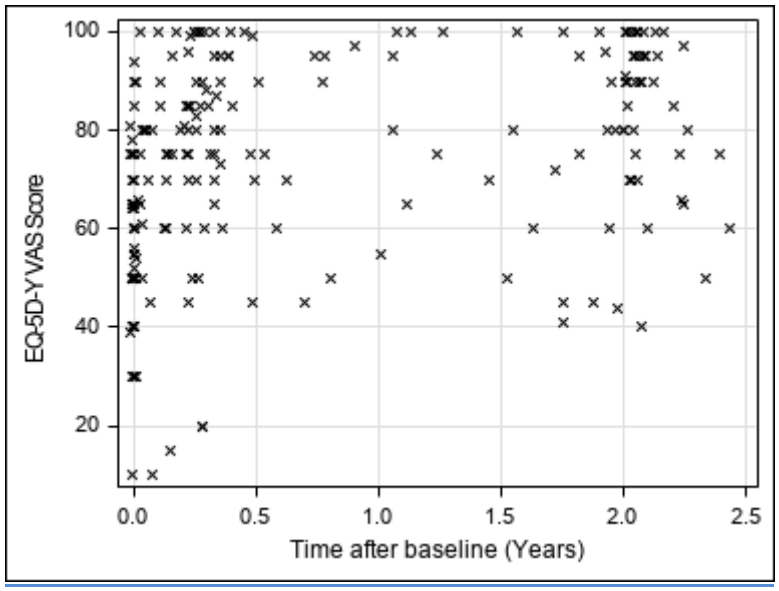


Figure 5-6: Scatterplot of total PedsQL score by time-point

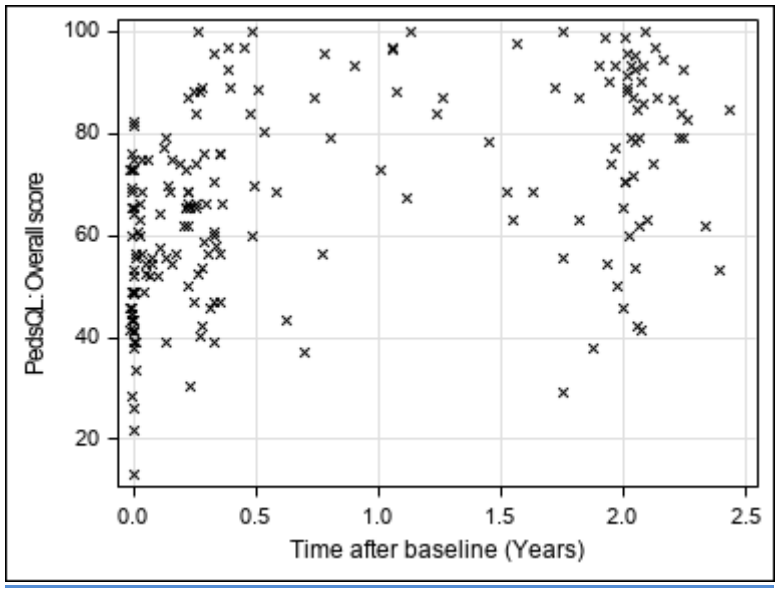
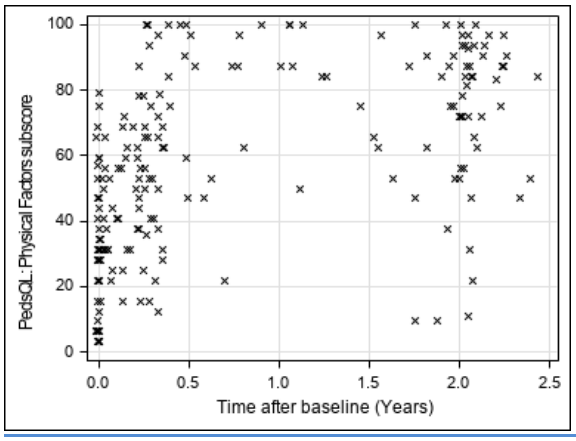
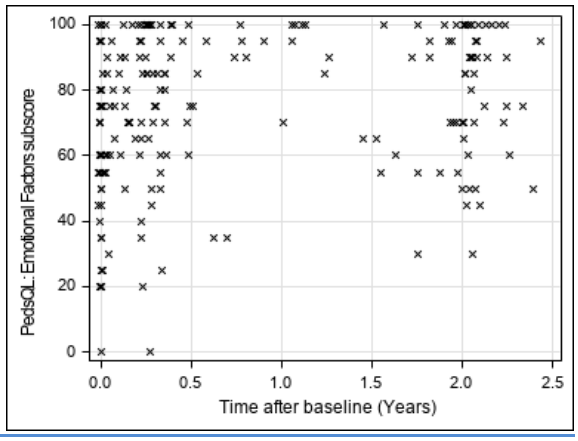
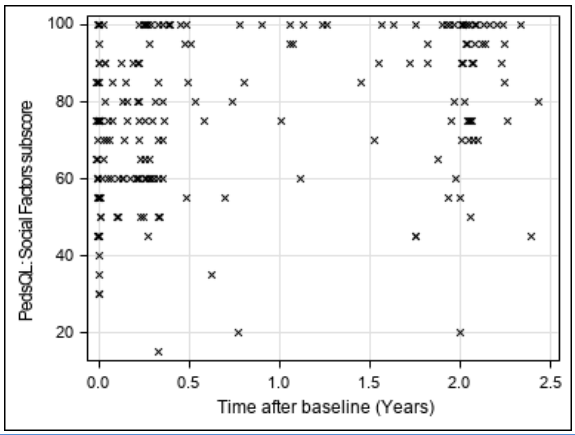


Figure 5-7: Scatterplot of PedsQL sub-scores by time-point







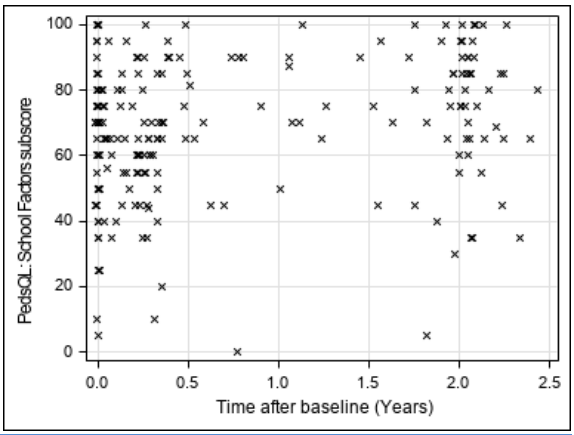


Figure 5-8: Scatterplot of Wong-Baker Faces score by time-point

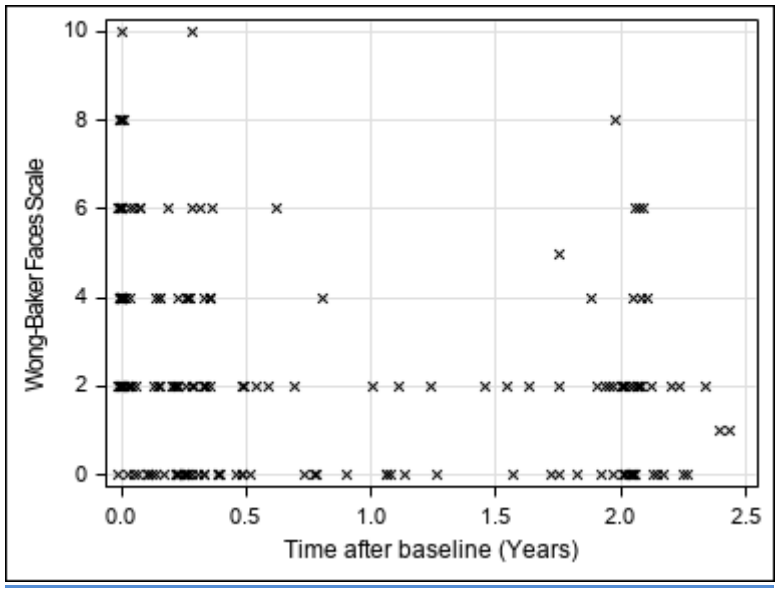
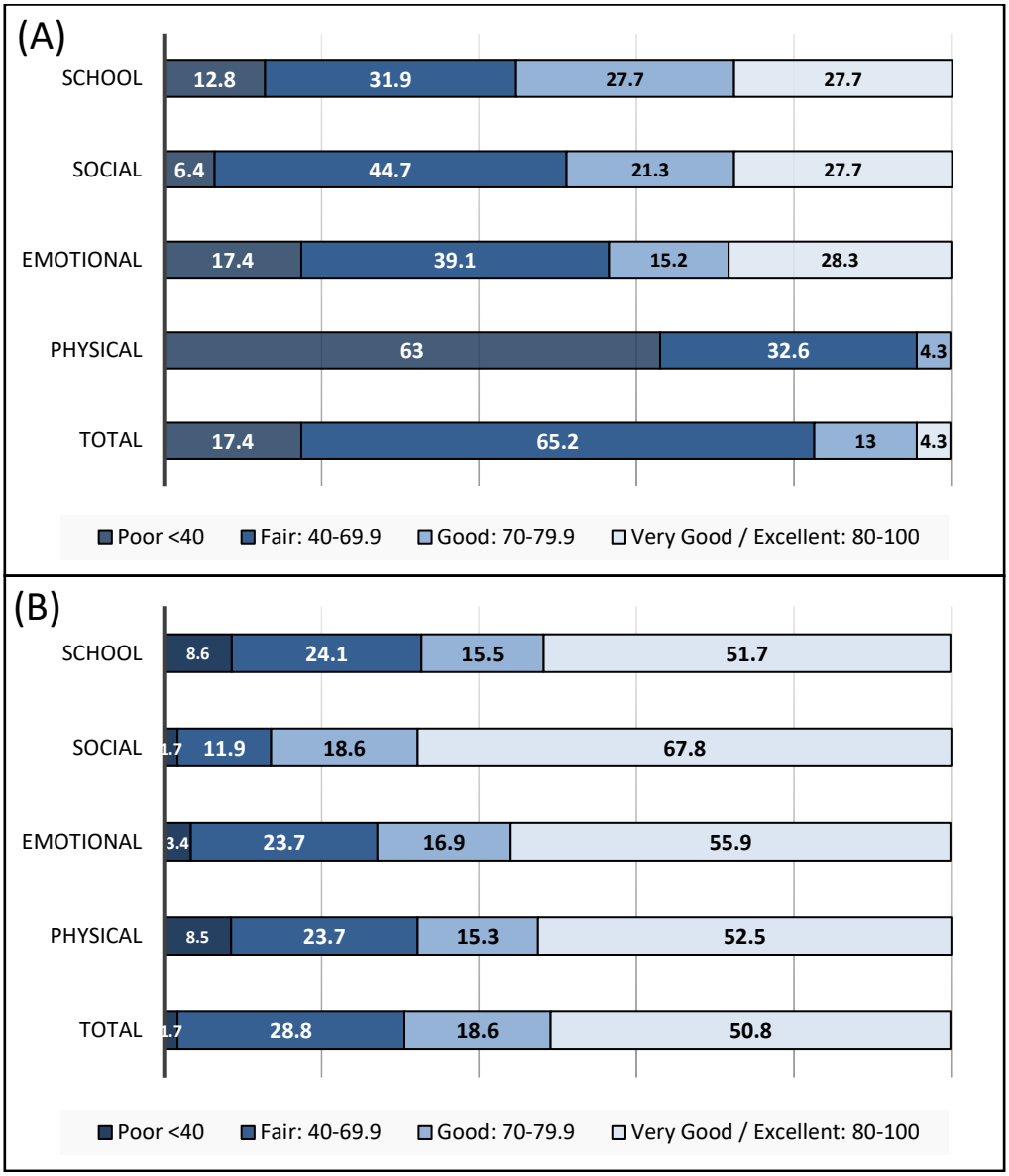


Figure 5-9: Distribution of PedsQL in SCFE patients at (A) baseline (n=47), and (B) 2 years (n=59). Categorisations as suggested by Huang *et al* (2009)[3].



Notes:

1. Most cases (47/49) that consented at baseline provided baseline PROMs, however 26 of these did not provide 2-year PROMs. Of the 59 2-year PROMs analysed, 21 provided baseline PROMs, and the remaining 38 consented later in the study. This means that the two charts above represent slightly different samples. Demographics of each are given in Table 5-1.

[3] Huang IC, Thompson LA, Chi YY, et al. The linkage between pediatric quality of life and health conditions: establishing clinically meaningful cutoff scores for the PedsQL. *Value Health*. 2009;12(5):773–781. doi:10.1111/j.1524-4733.2008.00487.x

5.7.3 Baseline factor prediction of 2-year PROMs

In this section, we explore the potential association between baseline factors and 2-year PROMs. A univariate analysis is carried out initially to examine effects of each factor, with the purpose of fitting a multivariate model including age, sex, clinical stability and radiographic severity together with any other factor that was found to be significantly associated at the univariate level. Surgical management types have not been examined – these depend on clinical stability and severity, and so independent contributions of these factors are difficult to incorporate with this analysis approach. Where baseline data are hip-specific, and a child presents bilaterally, the baseline assessment for the worst affected hip is used.

5.7.3.1 Univariate analysis

Table 5-26: Univariate analysis of EQ-5D-Y at 2 years with respect to potential baseline predictors. [Parameter estimates are derived by fitting random effects linear regression models for each covariate]

Predictor	N	Median (IQR) EQ-5D-Y	Parameter estimate	
			Estimate	95% CI
Questionnaires	59	-	-	-
Age at surgery (years)	59	-	0.01	(-0.02,0.04)
Sex				
Male	36	0.9 (0.8,1.0)	0	-
Female	23	0.9 (0.8,0.9)	0.0	(-0.1,0.1)
BMI	20	-	-0.01	(-0.04,0.02)
Severity of slip at presentation				
Unstable	15	0.9 (0.8,0.9)	0	-
Stable: Mild	19	0.9 (0.8,1.0)	0.0	(-0.1,0.2)
Stable: Moderate	12	0.9 (0.8,1.0)	0.1	(-0.1,0.2)
Stable: Severe	12	0.8 (0.7,1.0)	-0.1	(-0.2,0.1)
Time-lag from onset of symptoms to diagnosis (months)	59	-	0.00	(-0.01,0.01)
Treating centre case-load				
Low (1-2 cases per year)	9	0.9 (0.8,0.9)	0.1	(-0.1,0.2)
Medium (3-5 cases per year)	11	0.9 (0.9,1.0)	0.1	(0.0,0.3)
High (>5 cases per year)	39	0.9 (0.7,1.0)	0	-

Notes:

1. There is no evidence of a non-linear relationship between 2-year EQ-5D-Y and age [scatterplot not show]. Age is therefore presented as continuous rather than categorised into groups.
2. Where total counts do not add up to 59, the baseline status of the predictor is unknown/missing.
3. Clinical stability (Stable/Unstable) and Radiographic Severity (Mild/Moderate/Severe) were planned to be examined separately, but it was decided that combining these into a single 4-category descriptor of severity would make more sense clinically.

Table 5-27: Univariate analysis of PedsQL at 2 years with respect to potential baseline predictors.

Predictor	N	Median (IQR) PedsQL	Parameter estimate	
			Estimate	95% CI
Questionnaires	59	-	-	-
Age at surgery (years)	59	-	-0.11	(-2.45,2.23)
Sex				
Male	36	84.8 (69.6,90.8)	0.0	-
Female	23	79.3 (63.0,93.5)	-5	(-14.0,4.4)
BMI	20	-	-0.16	(-2.48,2.16)
Severity of slip at presentation				
Unstable	15	70.7 (59.7,92.4)	0	-
Stable: Mild	19	86.8 (79.3,92.4)	8.3	(-3.7,20.2)
Stable: Moderate	12	85.3 (77.2,90.2)	9.3	(-4.1,22.7)
Stable: Severe	12	72.3 (58.7,90.2)	1.0	(-12.4,14.4)
Time-lag from onset of symptoms to diagnosis (months)	59	-	-0.31	(-1.24,0.62)
Treating centre case-load				
Low (1-2 cases per year)	9	91.3 (73.9,93.5)	4.9	(-8.1,17.8)
Medium (3-5 cases per year)	11	79.3 (62.0,89.1)	-0.9	(-12.9,11.0)
High (>5 cases per year)	39	83.7 (63.0,90.2)	0	-

Notes:

1. There is no evidence of a non-linear relationship between 2-year PedsQL and age [scatterplot not show]. Age is therefore presented as continuous rather than categorised into groups.
2. Where total counts do not add up to 59, the baseline status of the predictor is unknown/missing.
3. Clinical stability (Stable/Unstable) and Radiographic Severity (Mild/Moderate/Severe) were planned to be examined separately, but it was decided that combining these into a single 4-category descriptor of severity would make more sense clinically.

Table 5-28: Univariate analysis of Wong-Baker at 2 years with respect to potential baseline predictors.

Predictor	N	Median (IQR) Wong-Baker	Parameter estimate	
			Estimate	95% CI
Questionnaires	51	-	-	-
Age (continuous)*	51	-	-0.16	(-0.47,0.14)
Sex				
Male	32	1.5 (0.0,2.0)	0	-
Female	19	2.0 (0.0,2.0)	0.8	(-0.3,1.9)
BMI	17	-	0.07	(-0.14,0.28)
Severity of slip at presentation				
Unstable	12	2.0 (0.5,2.0)	0.0	-
Stable: Mild	16	2.0 (0.0,2.0)	0	(-2.0,1.0)
Stable: Moderate	11	2.0 (0.0,4.0)	0	(-1.5,1.8)
Stable: Severe	11	2.0 (0.0,2.0)	0	(-1.9,1.4)
Time-lag from onset of symptoms to diagnosis (months)	46	-	0.01	(-0.09,0.12)
Treating centre case-load				
Low (1-2 cases per year)	8	2.0 (0.0,2.0)	-0.3	(-1.8,1.3)
Medium (3-5 cases per year)	10	1.5 (0.0,2.0)	-0.2	(-1.6,1.2)
High (>5 cases per year)	33	2.0 (0.0,2.0)	0	-

Notes:

1. There is no evidence of a non-linear relationship between 2-year Wong-Baker and age [scatterplot not show]. Age is therefore presented as continuous rather than categorised into groups.
2. Where total counts do not add up to 51, the baseline status of the predictor is unknown/missing.
3. Clinical stability (Stable/Unstable) and Radiographic Severity (Mild/Moderate/Severe) were planned to be examined separately, but it was decided that combining these into a single 4-category descriptor of severity would make more sense clinically.

5.7.3.2 Multivariate analysis

Tables 5-29 to 5-31 would have given the results of the final multivariate models chosen to represent how baseline variables relate to 2-year PROMs. However, as the univariate analyses indicated no significant predictors of these outcomes, these analyses were not carried out.

Table 5-29: Multiple linear regression analysis of EQ-5D-Y at 2 years with respect to baseline covariates

<No Results>

Table 5-30: Multiple linear regression analysis of PedsQL at 2 years with respect to baseline covariates

<No Results>

Table 5-31: Multiple linear regression analysis of Wong Baker Faces at 2 years with respect to baseline covariates

<No Results>

5.9 Association between 2-year hip shape and 2-year PROMs

In this section we explore whether there is any correlation between two 2-year outcomes: hip shape and PROMs. Spearman's' rank correlation is used to assess this, as the PROMs we have measured are generally pseudo-continuous, being inherently subjective and not necessarily linear in nature. For correlation to be represent a clinically relevant association, r_S should be larger than 0.6 or smaller than -0.6.

Table 5-32: Correlation between 2-year hip shape and 2-year PROMs

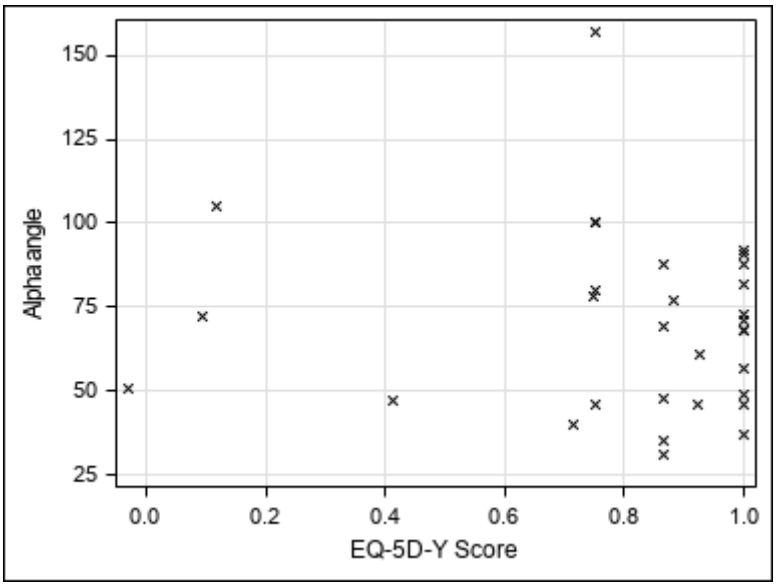
2-year PROMs	**Number of 2-year PROMs**	**Number 2-year PROMs where corresponding 2-year radiographs are available and alpha angle can be measured**	**Spearman's rank correlation (r_S)**
EQ-5D-Y			
Score	59	31	-0.06
VAS	57	29	0.33
PedsQL			
Total Score	59	31	0.02
Physical factors	59	31	0.02
Emotional factors	59	31	-0.08
Social factors	59	31	-0.09
School factors	59	31	0.17
Wong Baker Faces	51	27	-0.13

Notes:

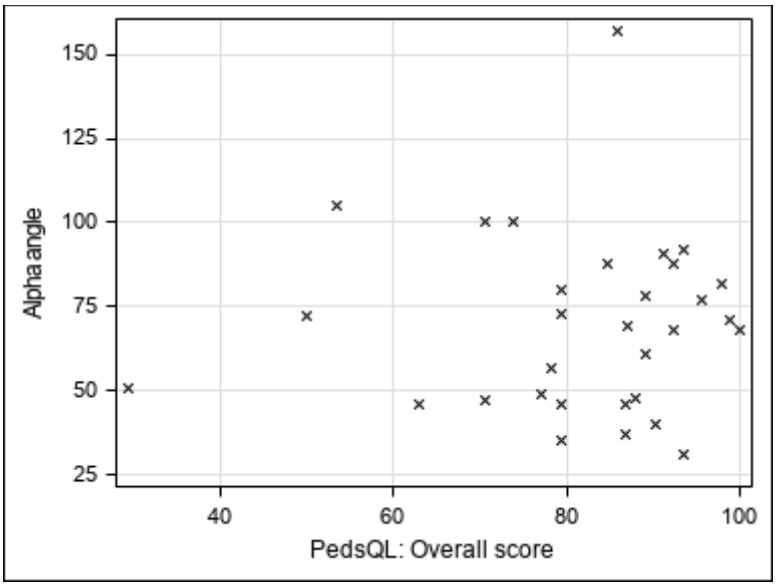
1. 28/59 (47%) of the 2-year PROMs could not be included in this analysis due to unavailable/missing 2-year radiographs. Four had AVN at 2 years, and therefore the alpha angle could not be reported [these patients were fairly homogeneous in most aspects of their PROMs – mean (SD) scores were: EQ_5D-Y score 0.8 (0.1), EQ-5d-Y VAS 71 (14), PedsQL total score 62 (5.3), and Wong-Baker 1.7 (0.6). These are slightly poorer outcomes than the averages for 2-year PROMs (see Table 5-25 above).]; 13 were followed up, but no lateral x-ray was taken; and 11 are missing, reason unknown.
2. For this table, and in Figures 5-10 to 5-12 below, if children presented at baseline bilaterally, then 2-year hip shape of the hip that was worst affected at baseline was used. If both hips were equal in presentation at baseline, the least normal alpha-angle (furthest from 60^O) at two years was used.

Figure 5-10: Scatterplot of 2-year hip-shape with (a) EQ5DY, (b) PedsQL and (c) Wong-Baker Faces

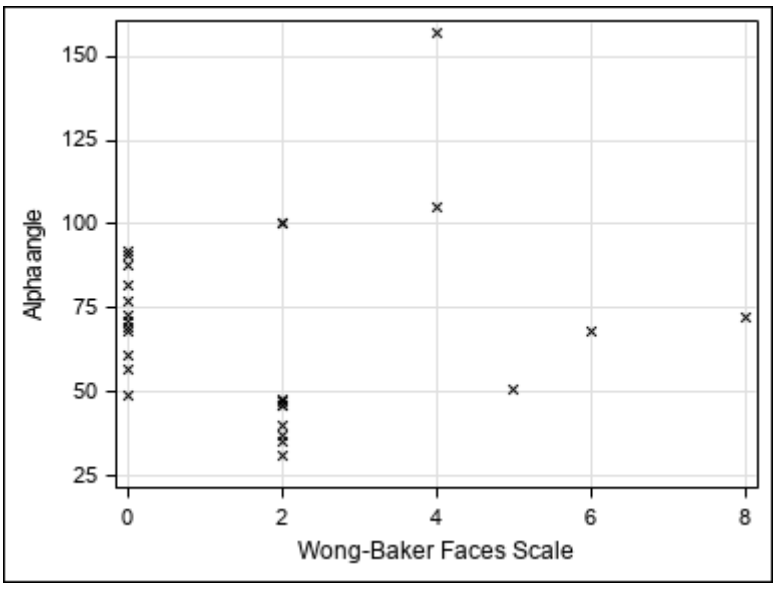
(a)



(b)



(c)



5.10 Contralateral SCFE

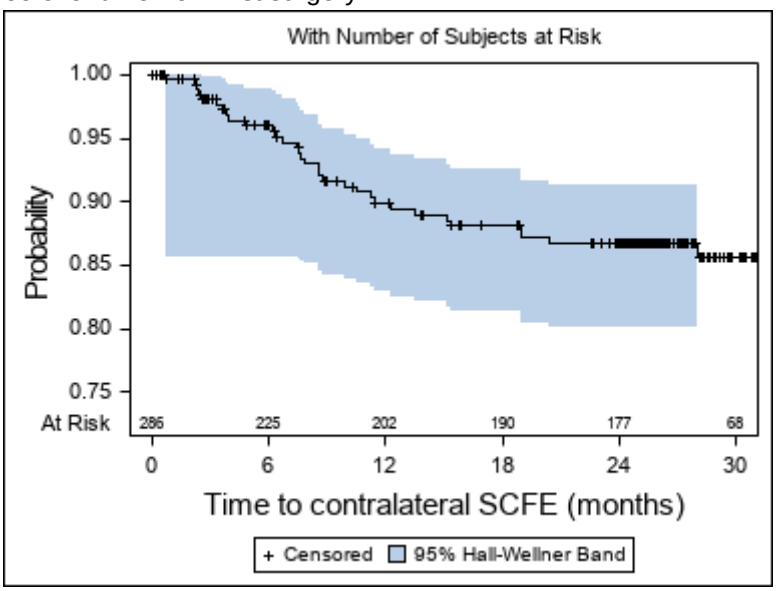
5.10.1 Risk

A total of 286 children in BOSS entered the study 'at risk of contralateral SCFE'. These are children that presented unilaterally, with no history of prior contralateral SCFE and were not known to have received a prophylactic fix. Of these, a total of 33 contralateral SCFE were recorded during the study. The risk of contralateral SCFE was therefore found to be 11.5%, 95%CI: (7.8%, 15.2%).

5.10.2 Time to contralateral SCFE

The time from first presentation (surgery for first SCFE) to diagnosis of a contralateral SCFE is presented in the Kaplan-Meier graphs below. Each step down in the curve represents the time at which a contralateral event occurred. The small vertical lines on the curve represent the last known follow-up for patients that, as far as we know, did not experience a contralateral event.

Figure 5-11: Kaplan-Meier plot with 95% confidence bands showing probability of remaining contralateral slip free over time from first surgery.



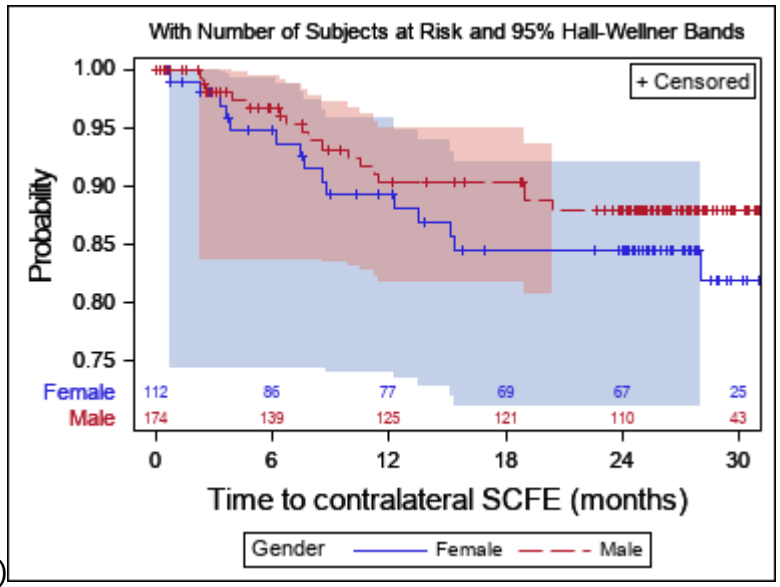
Notes:

1. Where no contralateral slip is recorded, cases are censored the last known date that the hip can be assumed to be normal: For those that were recorded as lost to follow-up, this date is the last clinic follow-up; otherwise we make the assumption that whilst follow-up data are uploaded, the status of the contralateral hip remains normal, and we use the final date of data-upload.

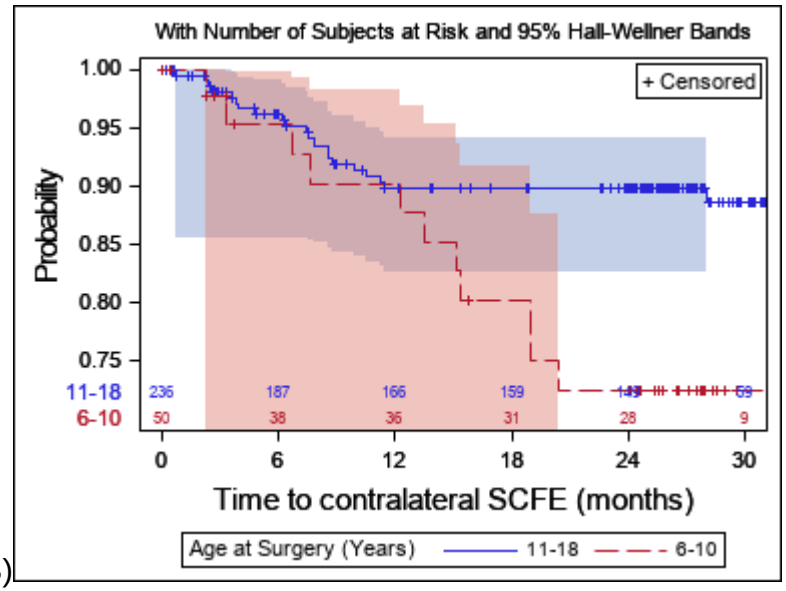
2. In one case, a contralateral slip is recorded, but the date of diagnosis is missing. The month and year that professional help was sought is known, and therefore this case is censored at the beginning of that month.
3. The scale on the vertical axis does not start at 0. This is to allow the detail of the graph to be seen, but can mislead the reader into seeing a high risk of contralateral SCFE. All graphs can be reproduced with the full vertical axis if required.

Figure 5-12: Kaplan-Meier plots with 95% confidence bands showing probability of remaining contralateral slip free over time from first surgery, split by (A) sex; and (B) age-group at baseline.

(A)



(B)



5.10.3 Predictors of contralateral SCFE at 2 years

In this section we explore the potential association between baseline factors and contralateral SCFE. A univariate analysis is carried out initially to examine effects of each factor, with the purpose of fitting a multivariate model including age, sex, clinical stability and radiographic severity together with any other factor that was found to be significantly associated at the univariate level.

5.10.3.1 Univariate analysis

Table 5-33: Univariate analysis of risk of contralateral SCFE at 2 years with respect to potential baseline predictors: at risk population where no prophylactic fix was performed. [Parameter estimates are derived by fitting Cox proportional hazards models for each covariate]

Baseline variable	N	No. of contralateral SCFE	Hazard Ratio	
			HR	95% CI
Children at risk	286	-	-	-
Age (years)*	286	32		
0-6.4 months post baseline	286	11	0.90	(0.19, 4.16)
6.4-11 months post baseline	223	11	0.92	(0.20,4.28)
> 11 months post baseline	205	10	0.09	(0.02, 0.34)
Sex				
Male	174	17	1	-
Female	112	15	1.44	(0.72,2.88)
BMI	70	9	1.03	(0.93,1.14)
Severity of slip at presentation				
Unstable	60	5	1	-
Stable: Mild	122	19	1.98	(0.74,5.30)
Stable: Moderate	62	5	1.02	(0.29,3.52)
Stable: Severe	40	3	0.87	(0.21,3.63)
Time-lag from onset of symptoms to diagnosis (days)	267	31	0.96	(0.86,1.07)
Treating centre case-load type				
Low (1-2 cases per year)	92	12	1.58	(0.67,3.76)
Medium (3-5 cases per year)	90	11	1.41	(0.58,3.39)
High (>5 cases per year)	104	9	1	-

Notes:

1. These analyses pertain to the 'at-risk' population as defined in the Statistical Analysis Plan v1.0. This includes unilateral presentations, where a prophylactic fix was not undertaken on the unaffected hip.

2. This univariate analysis was originally planned in the SAP as modelling the risk of contralateral SCFE at 2 years. However, as there was considerable loss to follow-up and missing 2-year

data, it was decided to change the methodology to a time-to-event analysis, so that all 286 at risk patients could be included.

3. Clinical stability (Stable/Unstable) and Radiographic Severity (Mild/Moderate/Severe) were planned to be examined separately, but it was decided that combining these into a single 4-category descriptor of severity would make more sense clinically.
4. The proportional hazards assumption does not hold over the full follow-up period, therefore hazard ratios are presented for three distinct periods post baseline, in which approximately equal numbers of contralateral SCFE were recorded. The hazard ratio represents the increase in risk of contralateral SCFE for each additional year of age of child.

5.10.3.2 Multivariate analysis

Table 5-34 would have given the results of the final multivariate model chosen to represent to what extent baseline variables are predictors of contralateral SCFE. However, the total number of events is too small to fit a model with more than one covariate, and only age was found to be a significant predictor at the univariate level.

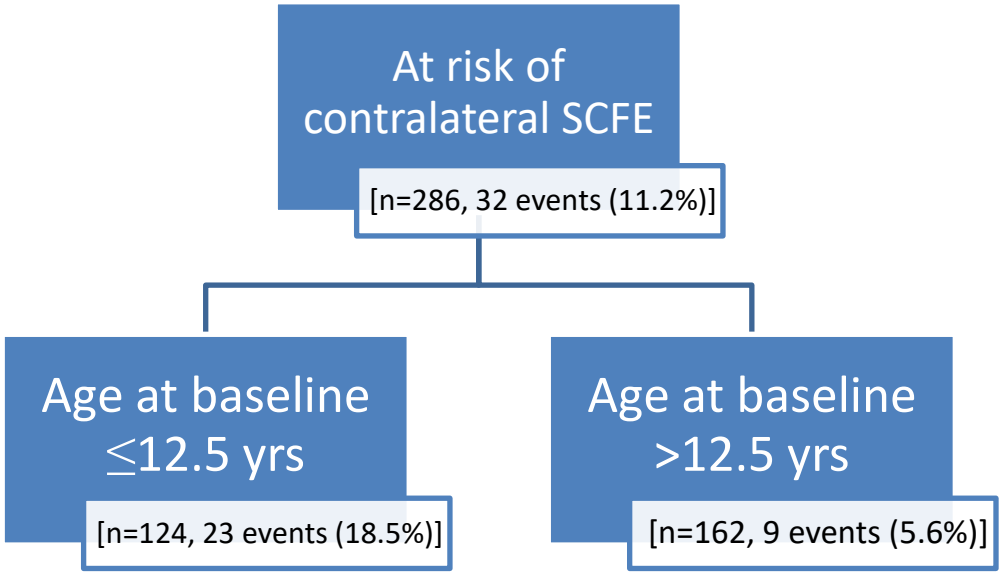
Table 5-34: Cox proportional hazards multivariable model of time-to-contralateral SCFE, with respect to baseline covariates

<No Results>

5.10.3.3 Recursive partitioning

Decision trees were obtained for the full 'at risk' cohort, using the methodology described in Leblanc and Crowley (1992)[4], which uses recursive partitioning incorporating the time-to-event nature of the outcome. Figure 5-12 gives the results – pruned to minimise the cross-validation error. Note: these results are descriptive, and are an intuitive visual method for showing which subgroups may be at most risk.

Figure 5-13: Results of recursive partitioning applied to all cases 'at-risk of contralateral SCFE' fitting the potential baseline predictors: age, sex, BMI, clinical stability, time-lag from onset of symptoms to diagnosis, and centre type



[4] LeBlanc, M., & Crowley, J. (1992). Relative Risk Trees for Censored Survival Data. *Biometrics, 48*(2), 411-425. doi:10.2307/2532300

6. Results: Perthes' Disease

6.1 Baseline demographics

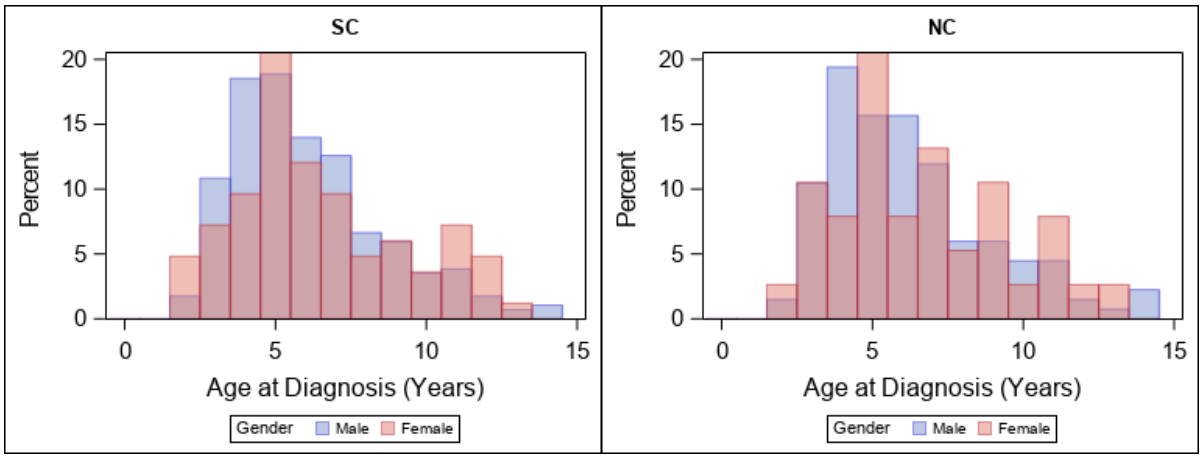
Table 6-1: Final Perthes' disease baseline demographics

	Surveillance cohort	All consented cohort	Baseline PROMs	2-year PROMs
Children				
n	371	172	70	99
Age at diagnosis (years)				
Mean (SD)	6.1 (2.6)	6.3 (2.7)	6.1 (2.5)	6.6 (2.8)
Median (IQR)	5.4 (4.2, 7.4)	5.7 (4.2, 7.8)	5.6 (4.2, 7.4)	6 (4.3, 8.8)
Min, Max	1.7, 14.1	2.3, 14.1	2.4, 14.1	2.7, 14.1
Missing	2	0	0	0
Age at baseline (years)				
Mean (SD)	6.3 (2.6)	6.5 (2.7)	6.3 (2.5)	6.8 (2.8)
Median (IQR)	5.8 (4.4, 7.7)	5.9 (4.5, 8.1)	5.7 (4.4, 7.5)	6.2 (4.6, 8.8)
Min, Max	1.8, 14.4	2.3, 14.4	2.4, 14.1	2.8, 14.1
Missing	0	0	0	0
Age-group at baseline (years)				
0 - < 6	199 (53.6%)	87 (50.6%)	37 (52.9%)	47 (47.5%)
>= 6 - <11	146 (39.4%)	70 (40.7%)	29 (41.4%)	41 (41.4%)
>=11 - <=14	26 (7.0%)	15 (8.7%)	4 (5.7%)	11 (11.1%)
Missing	0	0	0	0
Gender				
Male	288 (77.6%)	134 (77.9%)	53 (75.7%)	78 (78.8%)
Female	83 (22.4%)	38 (22.1%)	17 (24.3%)	21 (21.2%)
Ethnicity				
White - British	329 (90.6%)	157 (93.5%)	61 (89.7%)	91 (93.8%)
White - Other white background	14 (3.9%)	4 (2.4%)	3 0	3 (3.1%)
Mixed - White & black Caribbean	1 (0.3%)	0	0	0
Mixed - White & Asian	2 (0.6%)	0	0	0
Pakistani	5 (1.4%)	3 (1.8%)	2 (2.9%)	1 (1.0%)
Asian - Other Asian background	6 (1.7%)	2 (1.2%)	1 (1.5%)	1 (1.0%)
Other Black African	1 (0.3%)	0	0	0
Black - Other black background	2 (0.6%)	1 (0.6%)	0	0
Chinese	1 (0.3%)	0	0	0
Any other ethnic group	2 (0.6%)	1 (0.6%)	1 (1.5%)	1 (1.0%)
Missing	8	4	2	2
BMI				
n	144	91	47	53
Mean (SD)	18.4 (4.2)	18.2 (3.3)	18.1 (3)	17.4 (3)
Median (IQR)	17.2 (15.9, 19.4)	17.4 (15.9, 19.4)	17.1 (15.9, 19.4)	16.6 (15.7, 18.6)
Min, Max	13.6, 49.7	13.6, 30.6	14.4, 30.6	13.6, 29.2
Missing	227	81	23	46

Notes:

1. This table has been reduced by removing rows defining the following 6 ethnic groups, with no cases of Perthes' disease identified by BOSS: White - Irish; Mixed - White & black African; Mixed - Other mixed background; Indian; Bangladeshi; and Black Caribbean.
2. Baseline for Perthes' patients is defined as date of entry into BOSS which is taken as a proxy for the first appointment in hospital with a consultant orthopaedic specialist. Baseline is often close to the date of diagnosis, but may have taken place months or years prior to patients being seen at a hospital.

Figure 6-1: Histograms showing the distribution of ages of BOSS Perthes' disease in the surveillance cohort (SC) and the nested consented cohort (NC).



6.2 Clinical time-line

Table 6-2: Perthes' disease clinical time-line

	Surveillance cohort at baseline
Children	
n	371
From onset of symptoms to first seeking professional advice (months)	
n	311
Median (IQR)	1 (0,2)
Min, Max	(0,18)
Missing	60
From onset of symptoms to radiographic diagnosis (months)	
n	342
Median (IQR)	2 (1,5)
Min, Max	(0,29)
Missing	29
From radiographic diagnosis to diagnosis of contralateral disease (months)	
n	7
Median (IQR)	11.9 (3.5,22.8)
Min, Max	(2.9,23.5)
Missing	0

6.3 Treatment of Perthes' disease

This section summarises the decision making process regarding the treatment of Perthes' disease. Baseline is ideally the time at which a patient is first seen by a consultant, and at which a treatment strategy is put in place. It is not necessarily the same time as diagnosis. We report on what was planned at baseline (surgical and non-surgical interventions) and what was actually done.

Note: For all subsequent, hip-specific Perthes' disease tables, or follow-up tables, the analysis population is reduced to 393 hips from 369 children.

6.3.1 Surgical versus non-surgical

The primary treatment strategy planned for each affected hip at baseline can be dichotomised into two approaches: surgical and non-surgical. The number and percentage of patients with each strategy planned overall and split by stage of disease of hip at presentation is presented in Table 6-3. A chi-squared test for trend, testing the null hypothesis that stage of disease at presentation is not associated with type of treatment planned, gave the result: p=0.7.

Table 6-3: Initial primary treatment strategy type split by stage of disease at presentation

	Surveillance cohort at baseline									
		Stage of disease at presentation								
Hips	**All**	Missing	0	1A	1B	2A	2B	3A	3B	4
n	393	14	11	63	133	93	51	14	13	1
Type planned										
Surgical	67 (26.9%)	1	3 (42.9%)	10 (25%)	22 (25.9%)	18 (31.6%)	7 (18.9%)	4 (36.4%)	2 (22.2%)	0
Non-surgical	182 (73.1%)	2	4 (57.1%)	30 (75%)	63 (74.1%)	39 (68.4%)	30 (81.1%)	7 (63.6%)	7 (77.8%)	0
No definitive strategy	134	2	4	22	48	36	14	3	4	1
Missing	10	9	0	1	0	0	0	0	0	0

The number and percentage of hips with each strategy planned overall is reported in Table 6-4 together with the number and percentage with types of treatment confirmed by 1 and 2 years of follow-up.

Of the 249 hips with a planned treatment strategy, 207 had a confirmed actual treatment recorded. Of these, 56/61 (92%) of hips that were planned surgical treatment were confirmed as surgical; 127/146 (87%) of hips that were planned non-surgical were confirmed as non-surgical. A McNemar's test, testing the null hypothesis that primary treatment received (as assessed at 2 years) is not different to primary treatment planned, gave the result: p=0.0043.

[NB The subgroup included in this hypothesis test - 207/393 (53%) hips with an *a priori* treatment strategy and a confirmed actual treatment recorded - have similar demographics to the surveillance cohort (SC): 76% male, with median (IQR) age at baseline 5.7 (4.4, 7.4) years. The casemix was also similar to the SC: 45% presenting stiff, compared with 41% in the SC; and a similar distribution of disease stage at presentation (17%, 35%, and 23% at stage 1A, 1B and 2A compared with 16%, 34% and 24% in the SC). So whilst we have only half of hips represented in this analysis, the hypothesis test conclusion can be considered as generalizable to the SC.]

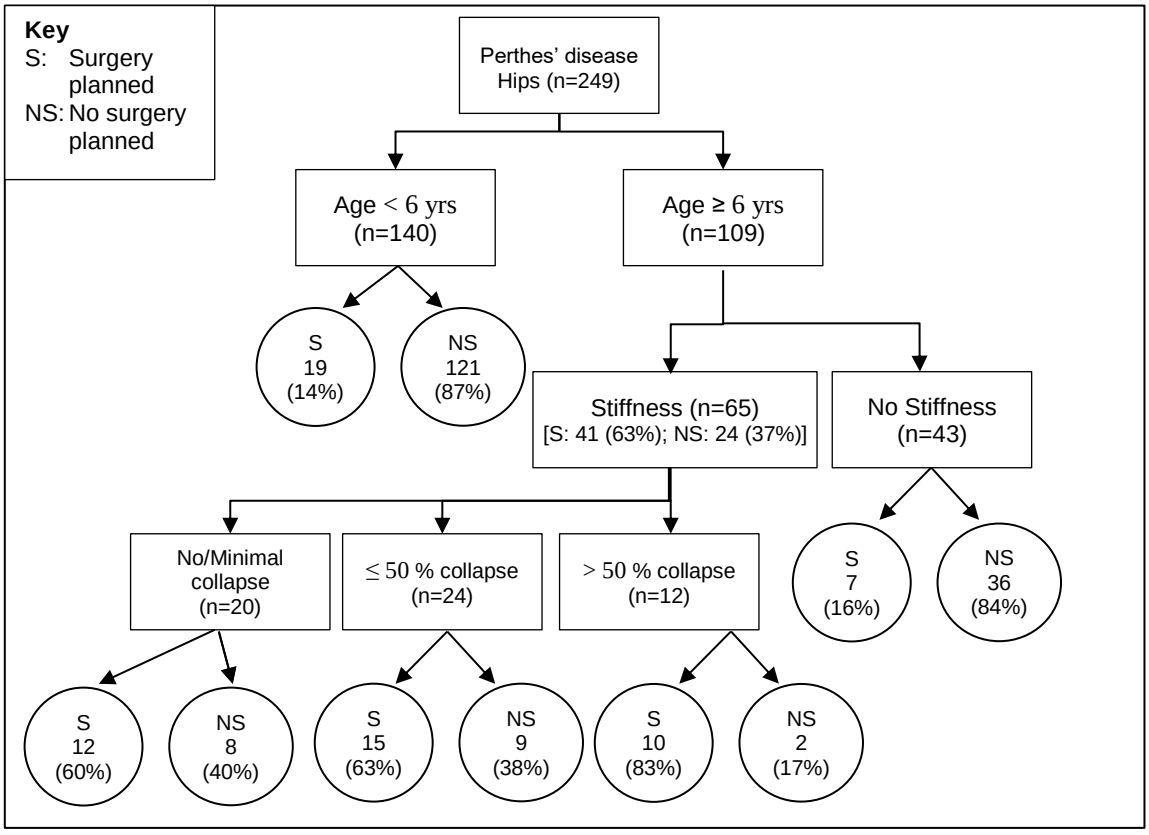
Table 6-4: Types of treatment (surgical vs non-surgical) planned at baseline, and types confirmed at 1 and 2 years follow-up.

	Baseline	**1 year**	**2 years**		
Hips (n)					
First presentations	393	393	393		
Lost to follow-up	-	26	45		
Analysed	393	367	348		
Treatment type	**Planned strategy**	**Actual treatment**	**Actual treatment**		
Surgical	67 (26.9%)	109 (31.9%)	117 (36.4%)		
Non-surgical	182 (73.1%)	233 (68.1%)	204 (63.6%)		
No definitive strategy	134	-	-		
Missing	10	25	27		
Planned versus actual			**Actual treatment**		
Planned			**Surgical**	**Non-surgical**	**Unknown**
Surgical			56 (91.8%)	5 (8.2%)	6
Non-surgical			19 (13.0%)	127 (87.0%)	36
No definitive strategy			42 (36.8%)	72 (63.2%)	20
Missing			1	4	5

6.3.1.1 *A priori* decision-tree

The following decision flow-chart shows the observed number and proportion of surgical vs non-surgical treatment strategies planned split by an *a priori* constructed decision tree. N.B. descriptive statistics relating to presentation characteristics of Perthes' disease such as stiffness of hip and degree of collapse of the lateral column are described in the baseline analysis report (Statistical Analysis Report: Part 1).

Figure 6-2: Likelihood of a surgical vs non-surgical strategy according to an *a priori* constructed decision tree



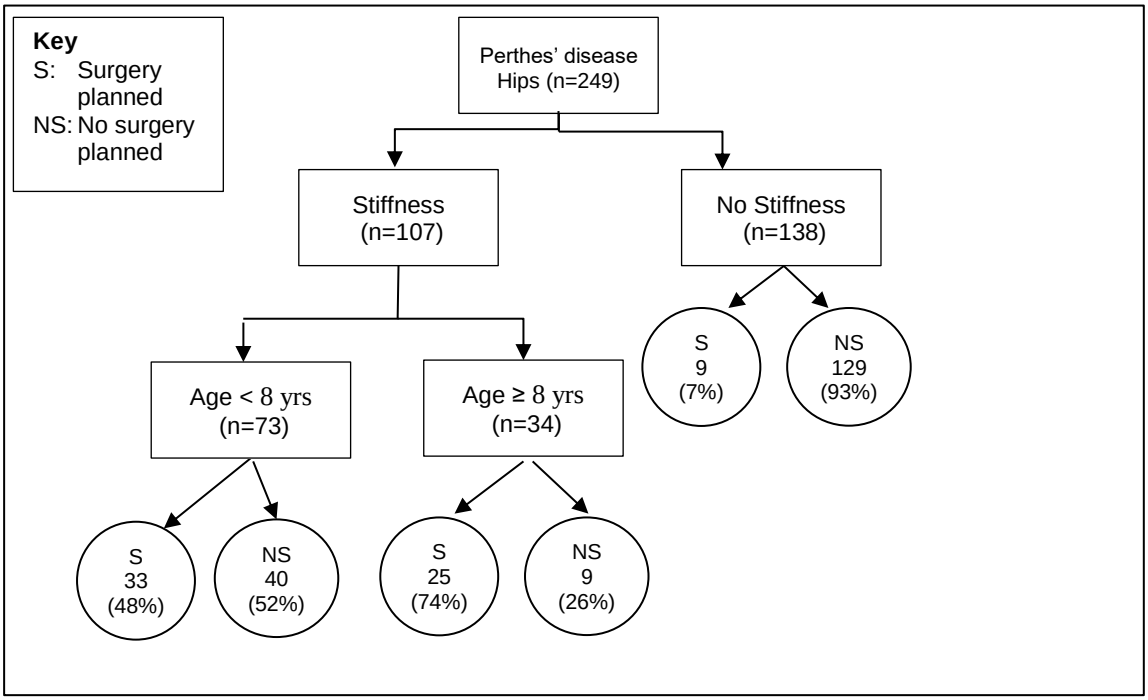
Notes:

1. Of 393 hips, 249 (63%) had a planned strategy recorded at baseline. 239 (61%) could be classified as 'S' or 'NS' within this decision tree – for nine hips the degree of collapse was not recorded, and for another hip, stiffness at baseline was not recorded.
2. The cohort with a strategy in place at baseline had the following casemix: 190/249 (76%) male, 140/249 (56%) < 6 years of age at baseline, 138/245 (56%) with minimal or no stiffness, 96/228 (42%) with < 50% collapse of the lateral column, 64/228 (28%) with no collapse of the lateral column. This is similar to the full Perthes' cohort, so can be considered representative.
3. Age is 'Age at baseline'.
4. Stiffness: there was significantly limited abduction; No stiffness: minimal limitation of abduction.
5. Degree of collapse relates to AP radiographs

6.3.1.2 Actual decision tree

The following decision flow-chart is derived using recursive partitioning. It shows an optimal decision tree structure for predicting which cases would be likely to have a surgical treatment plan and which would have a non-surgical treatment plan. Comparing these results with Figure 6-2, we can see that the stiffness of the hip is the primary guide to strategical decision making, followed by, to a lesser extent, whether a child is older than 8.

Figure 6-3: Likelihood of a surgical vs non-surgical strategy according to a derived decision tree structure



Notes:

1. Of 393 hips, 249 (63%) had a planned strategy recorded at baseline. 239 (61%) could be classified as 'S' or 'NS' within this decision tree – for nine hips the degree of collapse was not recorded, and for another hip, stiffness at baseline was not recorded.

2. See points 2 and 3 on p79 above.

3. This decision tree is a pruned version of the optimal tree resulting from fitting the variables: age at baseline, stiffness of hip at baseline (Stiff / Not stiff), and collapse of the lateral column (None / ≤ 50% collapse / >50% collapse). Additional branches from the optimal tree further differentiate age for <8 year olds into smaller and smaller age-bands. The tree presented is the most parsimonious, and has a minimum complexity parameter (cp) of 0.1.

6.3.2 Non-surgical treatment

Planned and actual non-surgical treatment duration and type are presented in Table 6-5.

Table 6-5: Non-surgical strategies: planned versus actual

	Non-surgical treatment planned at baseline	Confirmed non-surgical treatment given during 1st year
Hips		
n	182	233
Treatment type:		
Observation	159 (88.3%)	207 (90%)
Non-weight bearing	19 (10.6%)	19 (8.3%)
Spica/Orthosis	2 (1.1%)	4 (1.7%)
Missing	2	3
Length of time (weeks) non-weight bearing / Spica / Orthosis		
n	19	16
Mean (SD)	19.2 (16.8)	39.5 (16.9)
Median (IQR)	12 (6,26)	50 (26,52)
Min, Max	2,52	6,55
Missing	2	7

6.3.3 Surgical treatment

Summaries of planned and actual surgical treatment types are presented in Tables 6-6 and 6-7.

Table 6-6: Surgical strategies (hips planned and hips confirmed as having surgery)

	Surgical treatment planned at baseline	Confirmed surgical treatment given during follow-up
Hips		
n	67	117
Bony procedures?		
Yes	62 (93.9%)	111 (96.5%)
No	4 (6.1%)	4 (3.5%)
Missing	1	2
Bony procedure type:		
Varus osteotomy	29 (47.5%)	63 (57.8%)
Blade plate	*13 (45%)*	*20 (31.7%)*
Locking plate	*14 (48%)*	*34 (54%)*
Other	*2 (7%)*	*9 (14.3%)*
Salter Osteotomy	3 (4.8%)	5 (4.6%)
Other acetabular redirectional Osteotomy	0	2 (1.8%)
Shelf Osteotomy	28 (45.2%)	35 (32.1%)
Hip distraction using external fixator	0	2 (1.8%)
Other salvage procedure (pelvis)	0	0
Core decompression / drilling of the femoral head	1 (1.6%)	1 (0.9%)
Other surgical procedure	2 (3.2%)	0
None specified	0	2
Soft tissue procedures?		
Yes	30 (44.8%)	41 (35%)
None specified	37 (55.2%)	79 (67.5%)
Soft tissue procedure type:		
Adductor release	20 (64.5%)	33 (80.5%)
Psoas release	19 (61.3%)	16 (39%)
Other	6 (19.4%)	4 (9.8%)

Table 6-7: Line listings of other bony and soft-tissue procedures (free-text entries in the database)

Other procedures planned
Bony procedures: (n=2 hips) • *Arthorgram for investigation. Likely valgus osteotomy. He was diagnosed aged 3 and a half years. Treated with supervised neglect. Now is in reossification and has coxa magna and likely hinge abduction. Symptomatic and referred from Frimley to Southampton. Initial diagnosis was pre BOSS starting, but pt is new to this centre and is still in the decision making stage of the disease. So included on BOSS but you may want to exclude.* • *Arthrogram & trochanteric epiphysiodesis*
Soft tissue procedures: (n=6 hips) • *Arthrogram first to exclude hinge abduction. As none was present, then proceeded to Shelf.* • *Arthrogram of hip, to exclude hinge abduction.That would then confirm the surgical containment plan, supplemented by physiotherapy and activity modification advice.* • *As required* • *arthrogram* • *Arthrogram first to exclude hinge abduction.* n=1: no details given
Other procedures actually received
Soft tissue procedures: (n=4 hips) • *APPLICATION OF HIP SPICA TO ENFORCE NON-WEIGHT BEARING* • *Botox* • *EUA, Arthrogram & steroid injection* • *Application of 1-legged hip spica for 6 weeks - as child has learning difficulties and would not have complied with WB status post-op*

6.3.4 Medical therapies and physiotherapy

Summaries of planned and actual medical therapies and physiotherapy are presented in Tables 6-8 and 6-9.

Table 6-8: Medical therapies and physiotherapy

	Surveillance cohort	
	Planned strategy at baseline	**Actual treatment reported at 1 year follow-up**
Hips		
First presentations	393	393
Lost to follow-up	-	26
Analysed	393	367
Additional drug therapies?		
Yes	3 (1.2%)	12 (3.6%)
No	244 (98.8%)	325 (96.4%)
No treatment strategy in place	134	-
Missing	12	30
Therapy type:		
Botox	0	1 (0.3%)
Steroids	2 (0.5%)	4 (1.2%)
Bisphosphonates	1 (0.3%)	0
Other	1 (0.3%)	7 (2.1%)
Physiotherapy in treatment plan?		
Yes	166 (53.5%)	207 (61.2%)
No	83 (33.3%)	131 (38.8%)
Missing	144	29

Table 6-9: Line listings of other medical therapies (free-text entries in the database)

Other medical therapies
Planned (n=1): • *Partial weight - bearing,walking frame for resting & wheelchair for long distances* **Actual (n=7):** • *Calpol & Ibuprofen for pain (needed daily)* • *Fanconi Anaemia - Previous Stem cell transplant Currently on Folic Acid, Ondansetron, Growth Hormone & Penicillin V NB non specific for AVN of Hip* • *Multivitamins and Vitamin D recommended* • *Vitamin D* • *Vitamin D Supplements* • *Vitamin D recommended* • *vitamin D*

6.4 Radiographic outcomes

In this section we report how hips with Perthes' disease change over time. They are assessed for radiographic stage at Baseline, 1 year and 2 years. At each time-point, hips that are at stages 1A to 3A are assessed for radiographic severity; hips at stages 3B or 4 are assessed for shape.

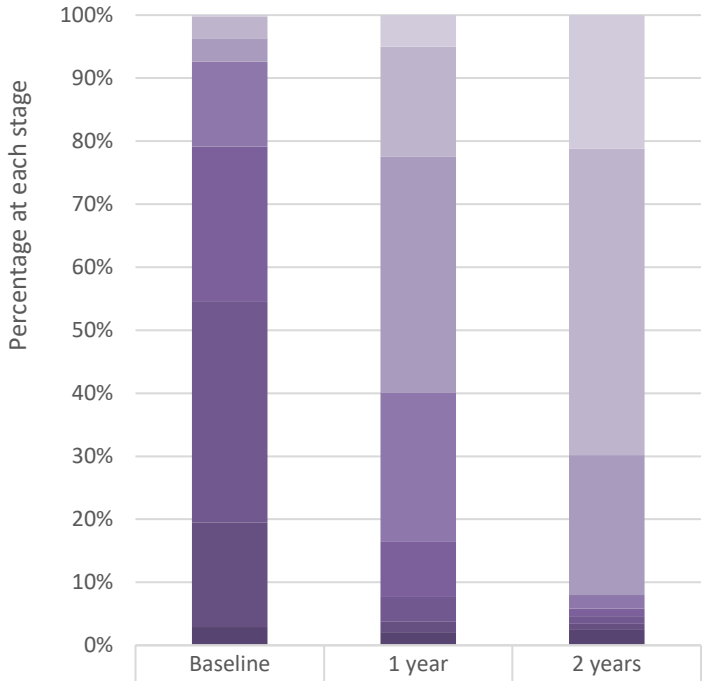
6.4.1 Disease progression

6.4.1.1 Radiographic stage

Table 6-10: Perthes' disease radiographic stage of hips at each time-point

		Surveillance cohort		
		Baseline	**1 year**	**2 years**
Hips				
	1st presentations	393	393	393
	Lost to follow-up	-	26	45
	Analysed	393	367	348
Radiographic stage				
0:	No radiographic change on MRI	11 (2.9%)	7 (2.1%)	8 (2.5%)
1A:	Sclerosis (early, normal height)	63 (16.6%)	6 (1.8%)	3 (0.9%)
1B:	Sclerosis (late, flattened)	133 (35.1%)	13 (3.8%)	4 (1.2%)
2A:	Fragmentation (early, 1 or 2 fissures)	93 (24.5%)	30 (8.8%)	4 (1.2%)
2B:	Fragmentation (late, no new bone)	51 (13.5%)	80 (23.6%)	7 (2.2%)
3A:	Reossification (early, new bone but texture not normal)	14 (3.7%)	127 (37.5%)	72 (22.2%)
3B:	Reossification (late: new bone covering over 1/3 epiphysis)	13 (3.4%)	59 (17.4%)	158 (48.6%)
4:	Healed	1 (0.3%)	17 (5%)	69 (21.2%)
	Missing	14	14	28

Figure 6-4 Stacked barchart showing Perthes' disease radiographic stage of hips at each time-point



	Baseline	1 year	2 years
4: Healed	1	17	69
3B: Reossification (late: new bone covering over 1/3 epiphysis)	13	59	158
3A: Reossification (early, new bone but texture not normal)	14	127	72
2B: Fragmentation (late, no new bone)	51	80	7
2A: Fragmentation (early, 1 or 2 fissures)	93	30	4
1B: Sclerosis (late, flattened)	133	13	4
1:A Sclerosis (early, normal height)	63	6	3
0: No radiographic change on MRI	11	7	8

6.4.1.2 Radiographic severity

Table 6-11: Perthes' disease radiographic severity of hips assessed to be at stages 1A to 3A, at each time-point

	Surveillance cohort		
	Baseline	**1 year**	**2 years**
No. of hips			
1st presentations	393	393	393
Lost to follow-up	-	26	45
Analysed	393	367	348
No. of hips at stages 1A to 3A			
n	354 (90.1%)	256 (69.8%)	90 (25.9%)
Radiographic severity: Collapse of lateral column			
No collapse	103 (29.5%)	27 (10.5%)	9 (10%)
< 50% collapse	157 (45%)	99 (38.7%)	27 (30%)
Exactly 50% collapse	29 (8.3%)	21 (8.2%)	9 (10%)
> 50% collapse	60 (17.2%)	109 (42.6%)	45 (50%)
Unreported / Missing	5	0	0
Radiographic severity: Head involvement of lateral radiograph			
> 50% of head involved	152 (61.8%)	145 (77.5%)	56 (81.2%)
< 50% of head involved	94 (38.2%)	42 (22.5%)	13 (18.8%)
Lateral radiograph not performed	99	69	21
Unreported / Missing	9	0	0

6.4.1.3 Hip shape

Table 6-12: Perthes' disease radiographic shape of hips assessed to be at stage 3B or 4 during follow-up

	Surveillance cohort	
	1 year	**2 years**
Hips		
1st presentations	393	393
Lost to follow-up	26	45
Analysed	367	348
No. of hips at stage 3B or 4		
n	76 (20.8%)	227 (65.2%)
Shape of hip at follow-up		
Spherical	37 (50%)	98 (43.9%)
Ovoid	20 (27%)	84 (37.7%)
Flat	17 (23%)	41 (18.4%)
Missing	2	4
Spherical		
Coxa Magna	7 (19.4%)	52 (53.6%)
Steep Acetabulum	1 (2.8%)	4 (4.1%)
Short Neck	5 (13.9%)	24 (24.7%)
None	25 (69.4%)	38 (39.2%)
Missing	1	1
Flat		
Acetabulum incongruent	6 (35.3%)	20 (48.8%)
Acetabulum congruent	11 (64.7%)	21 (51.2%)
Missing	0	0
No Coxa Magna	3 (17.6%)	13 (31.7%)
Coxa Magna	14 (82.4%)	28 (68.3%)
Missing	0	0

Table 6-13: Perthes' disease radiographic shape of hips assessed to be at stage 3B or 4 at the end of follow-up (SDS and Stulberg grade)

		2 years
No. of hips		
	1st presentations	393
	Lost to follow-up	45
	Analysed	348
No. of hips at stage 3B or 4 at 2 years		227 (65.2%)
AP Roundness error (%)		
	n	141
	Mean (SD)	11.5 (12.2)
	Median (IQR)	7.1 (1.2, 20.0)
	Min, Max	0.0, 56.7
	Missing	86
Stulberg grade		
I	Spherical congruency	39 (17.5%)
II	Spherical congruency, < 2mm loss of head shape	59 (26.5%)
III	Aspherical congruency (not flat)	84 (37.7%)
IV	Aspherical congruency (flat head and acetabulum)	26 (11.7%)
V	Aspherical incongruency	15 (6.7%)
	Missing	4

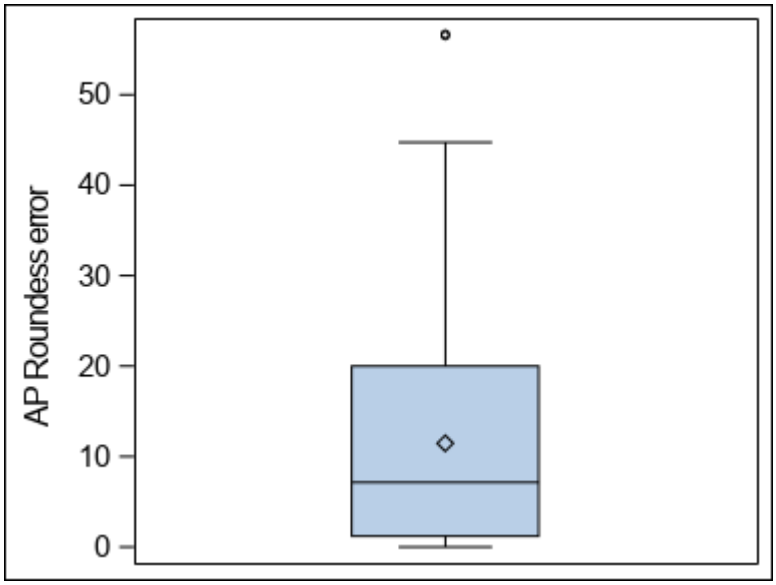
Notes:

1. The measure of shape was planned to be sphericity deviation score (SDS) – however this requires both AP and lateral radiographs. In practice, only AP radiographs are routinely taken at 2 years, so we have taken the AP element of SDS: AP roundness error, and summarised this a proxy measure of roundness. NB a roundness error of 0 indicates a perfect circle, and the larger the % error, the less circular the hip is.

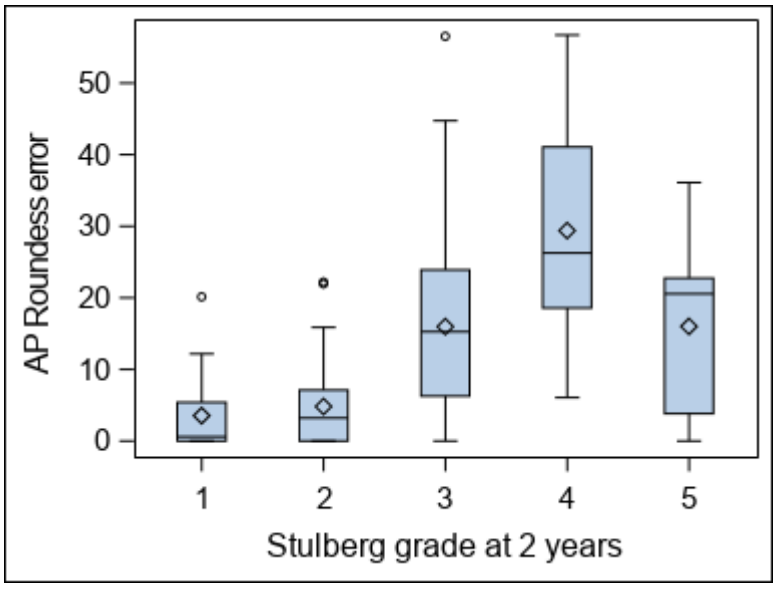
2. 17 X-rays were received, but dated as being less than 18 months post baseline. These were excluded.

Figure 6-5: Boxplot of 2-year hip-shape (AP roundness error) restricted to hips that reached stage 3B and 4. (A): all grades (n=141); (B): all hips measured split by 2-year Stuhlberg grade (Grade 1: n=20; Grade 2: n=41; Grade 3: n=52; Grade 4: n=11; Grade 5: n=11)

(A)



(B)



Notes:

1. 6 hips are excluded from graph (B) – missing data make them ungradable by Stulberg.

6.4.2 Baseline factor prediction of 2-year hip shape

In this section we explore the potential association between baseline factors and 2-year hip shape. Hip shape is assessed numerically using measurements from radiographs, and with a grading dependent on clinical radiograph based judgements. This means that different methods are needed for each measure.

227 hips were known to have reached stages 3B or 4 at 2 years. Of these, 141 radiographs were received and an AP roundness error was measured. [The numeric measure of hip shape was planned to be sphericity deviation score (SDS) – however this requires both AP and lateral radiographs. In practice, only AP radiographs are routinely taken at 2 years, so we have taken the AP element of SDS: AP roundness error, and summarised this a proxy measure of roundness. NB a roundness error of 0 indicates a perfect circle, and the larger the % error, the less circular the hip is.] 223/227 hips could be assigned a Stulberg grade.

Univariate analyses are carried out initially to examine effects of each factor, with the purpose that multivariate models will then be fitted including age, sex, stiffness of hip, degree of collapse and treatment type, together with any other factor that was found to be significantly associated at the univariate level.

6.4.2.1 Univariate analysis

Univariate analyses of AP roundness errors are presented in Table 6-14. The modelling method incorporates random effects so that within-person correlations can be accounted for in bivariate presentations.

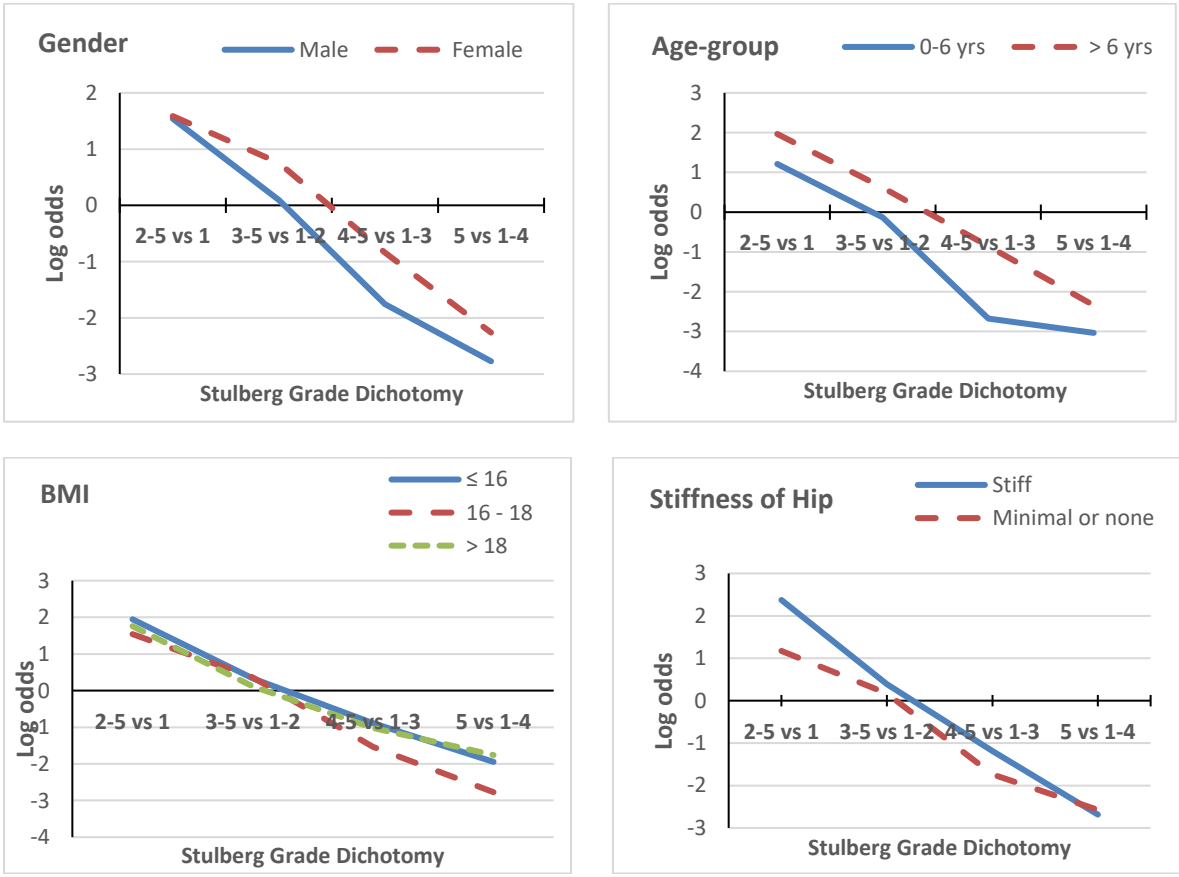
Table 6-14: Univariate analysis of hip shape (AP roundness error) at 2 years with respect to potential baseline predictors. [Parameter estimates are derived by fitting random effects linear regression models for each covariate]

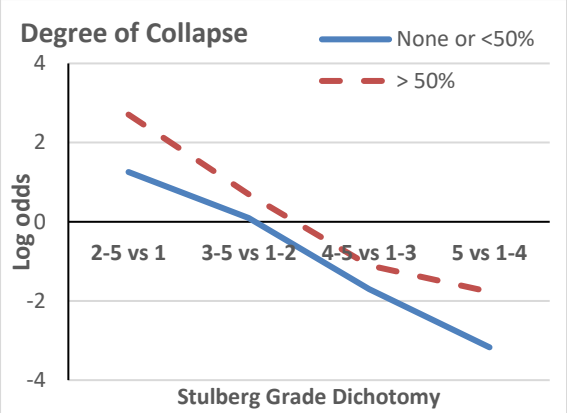
Predictor	N	Median (IQR) Roundness Error	Odds Ratio	
			Estimate	95% CI
Hips	141	-	-	-
Age at diagnosis	141	-	2.4	(1.5,3.3)
Sex				
Male	107	6.3 (0.0,18.6)	0	-
Female	34	12.2 (3.9,20.7)	5.9	(-0.2,12.0)
BMI	62	-	0.4	-*
Stiffness of hip at baseline**				
Stiff	60	7.2 (3.3,21.7)	3	(-3.3,8.4)
Minimal or no stiffness	79	6.3 (0.0,17.4)	0	-
Degree of collapse of lateral column				
None	36	6.1 (0.0,20.1)	0	-
< 50%	58	6.0 (1.2,15.9)	-1.4	(-34.2,31.3)
Exactly 50% collapse	12	4.4 (0.0,17.4)	1.8	(-49.6,53.2)
> 50%	19	18.3 (7.1,25.9)	5.2	(-40.1,50.4)
Head involvement of lateral column				
> 50%	55	5.6 (1.1,15.8)	0	-
< 50%	31	6.3 (0.0,20.2)	0.6	(-11.7,13.0)
Definitive treatment				
Surgical	76	6.9 (0.0,16.1)	0	-
Non-surgical	58	7.3 (2.2,22.2)	-3.7	(-12.8,5.4)
Time-lag from onset of symptoms to diagnosis (months)	132	-	0.3	(-1.4,0.3)
Treating centre case-load				
Low (1-2 cases per year)	17	15.9 (9.3,24.7)	4.4	(-3.8,12.7)
Medium (3-5 cases per year)	31	4.3 (0.0,13.6)	-2.2	(-8.7,4.3)
High (>5 cases per year)	93	6.5 (2.1,18.6)	0	-

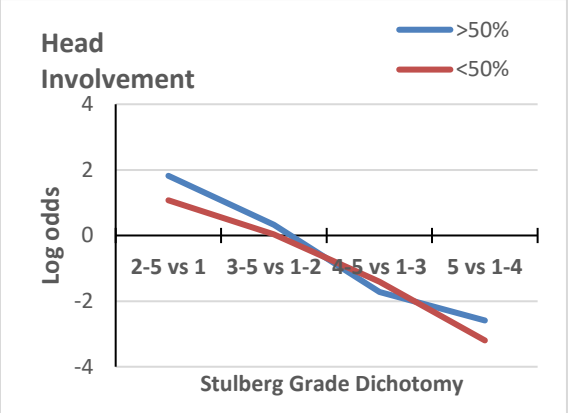
*A confidence interval for BMI was not calculable due to insufficient data to estimate a variance structure. **Stiffness of hip was added to this analysis *post hoc*

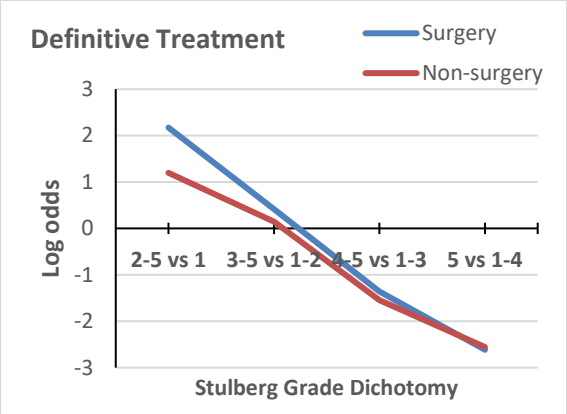
The planned method of analysis for investigating the effect of baseline covariates on 2-year Stulberg grade was ordinal regression with random effects. This is subject to an assumption of proportional odds (that the effect of baseline covariates on the odds of a hip being in a particular grade or higher, is similar across all grades of hip). Figure 6-6 presents a graphical assessment of the proportional odds assumption. Lines should ideally be parallel, and should not cross. These graphs show that (a) gender, age-group and degree of collapse clearly differentiate the outcome, and proportional odds looks reasonable; (b) head involvement, BMI, time-lag between onset of symptoms and diagnosis, and treating centre caseload do not differentiate the outcome; (c) stiffness of hip and definitive treatment may have a small role in differentiating the outcome. Note that degree of collapse of the lateral column was simplified into two groups (None or <50%, and ≥50%) which differentiated the outcome more clearly than the original four categorisations. Age was examined as two groups: the *a priori* groups of interest are 0-6, 6-11 and 11-14 years. However in the hips that were gradable at 2 years, there were only 21 in the oldest category, therefore we combined these into the category below.

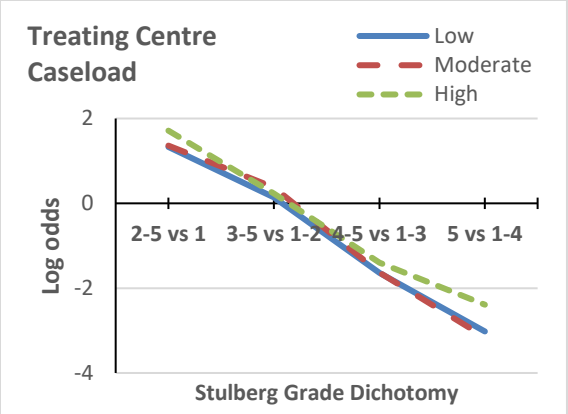
Figure 6-6: Univariate analysis of Stulberg Grade – assessment of proportional odds. (Log-odds of classification into each Stulberg Grade or higher vs all lower grades, split by baseline factor)




Degree of Collapse
None or <50%
> 50%
Log odds
4
2
0
-2
-4
2-5 vs 1
3-5 vs 1-2
4-5 vs 1-3
5 vs 1-4
Stulberg Grade Dichotomy


Head Involvement
>50%
<50%
Log odds
4
2
0
-2
-4
2-5 vs 1
3-5 vs 1-2
4-5 vs 1-3
5 vs 1-4
Stulberg Grade Dichotomy


Definitive Treatment
Surgery
Non-surgery
Log odds
3
2
1
0
-1
-2
-3
2-5 vs 1
3-5 vs 1-2
4-5 vs 1-3
5 vs 1-4
Stulberg Grade Dichotomy


Treating Centre Caseload
Low
Moderate
High
Log odds
2
0
-2
-4
2-5 vs 1
3-5 vs 1-2
4-5 vs 1-3
5 vs 1-4
Stulberg Grade Dichotomy

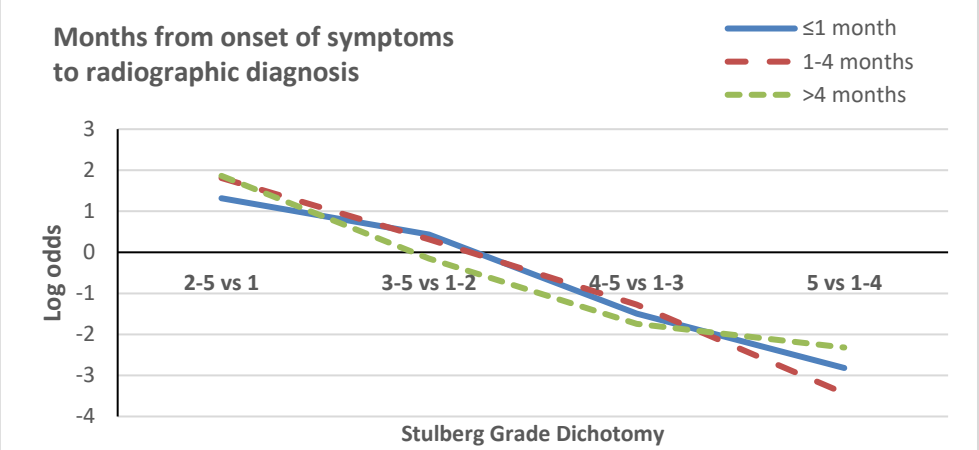

Months from onset of symptoms to radiographic diagnosis
≤1 month
1-4 months
>4 months
Log odds
3
2
1
0
-1
-2
-3
-4
2-5 vs 1
3-5 vs 1-2
4-5 vs 1-3
5 vs 1-4
Stulberg Grade Dichotomy

Table 6-15: Univariate analysis estimating baseline covariate effects of being in a particular Stulberg grade or higher (at 2 years), expressed as odds ratios with 95% CIs. [N=227 hips]

Covariate	N	Median (IQR) Grade	Proportional Odds Ratio	95% CI
Gender				
Male	170	3 (2, 3)	0.52	(0.29, 0.93)
Female	53	3 (2, 4)	1	-
Age group at baseline				
≤ 6 yrs	109	2 (2, 3)	1	-
> 6 yrs	114	3 (2, 4)	2.62	(1.60, 4.28)
BMI	92	3 (2, 3)	0.98	(0.91, 1.07)
Stiffness of hip				
Stiff	94	3 (2, 3)	1.64	(0.93, 2.90)
Minimal or no stiffness	127	3 (2, 3)	1	-
Degree of collapse				
None or < 50%	149	3 (2, 3)	1	-
≥ 50%	48	3 (2, 3.5)	2.34	(1.04, 5.26)
Head involvement				
>50%	86	3 (2, 3)	0.76	(0.39, 1.47)
<50%	51	3 (1, 3)	1	-
Definitive treatment				
Surgery	88	3 (2, 3)	1	-
No surgery	125	3 (2, 3)	0.69	(0.40, 1.18)
Time-lag from onset of symptoms to diagnosis (months)	195	3 (2, 3)	0.96	(0.91, 1.01)
Treating centre case-load				
Low	43	3 (2, 3)	1	-
Moderate	49	3 (2, 3)	1.13	(0.53, 2.40)
High	131	3 (2, 3)	1.24	(0.65, 2.34)

Notes:

1. Stiffness of hip was added to this analysis *post hoc.*
2. Age is fitted as categorical, as in exploratory analyses, it could not be assumed that age had a linear effect on the outcome, and also the proportional odds assumption may not have held. Using clinically relevant age-categories also gives results that are easier to interpret.

6.4.2.2 Multivariate analysis

Table 6-17 gives the results of the final multivariate model chosen to represent how baseline variables affect hip shape (AP roundness error) at 2 years. Included are all hips newly affected at baseline. A random effect is added for 'child' to account for within-patient correlation for bilateral presentations.

Table 6-18 gives the results of the final multivariate ordinal regression model fitted for Stulberg Grade. A random effect is added for 'child' to account for within-patient correlation for bilateral presentations.

Table 6-16: Multiple linear regression of AP roundness error at 2 years with respect to baseline covariates

Covariate	Odds Ratio		Overall significance of covariate as a predictor of AP roundness error
	Estimate	95% CI	
Hips	141	-	
Age at baseline (years)	2.4	(0.8, 4.0)	0.0223
Sex			0.116
Male	0	-	
Female	5.6	(-3.4, 14.7)	
Stiffness of hip*			0.779
Stiff	-0.7	(-9.9, 8.5)	
Minimal or no stiffness	0	-	
Definitive treatment			0.971
Surgery	0	-	
No surgery	0.1	(-9.2, 9.4)	

*Stiffness of hip was added to this analysis *post hoc*

Notes:

1. The model includes random effects to allow for bilateral presentations.
2. Degree of collapse was initially included, but this resulted in a saturated model. As this is the most complex of the covariates fitted, it was decided to remove it and re-fit the model.

Table 6-17: Chosen multivariate ordinal regression model fitting Stulberg grade at 2 years with respect to baseline covariates (N=223 hips)

Covariate	Proportional Odds Ratio	95% CI	Overall significance of covariate as a predictor of Stulberg Grade
Gender			0.012
Males	0.44	(0.23, 0.84)	
Females	1	-	
Age-group at baseline			0.007
≤ 6 yrs	1	-	
> 6 yrs	2.62	(1.30, 5.28)	
Stiffness of hip*			0.656
Stiff	1.16	(0.61, 2.20)	
Minimal or no stiffness	1	-	
Degree of collapse			0.052
None or < 50%	1	-	
≥ 50%	2.19	(0.99, 4.83)	
Definitive treatment			0.923
Surgery	1	-	
No surgery	0.97	(0.51, 1.83)	

*Stiffness of hip was added to this analysis *post hoc*

Notes:

1. The model includes random effects to allow for bilateral presentations.
2. The chosen covariates fitted are the three significant variables from the univariate analysis (Gender, Age-group and Degree of collapse). Also fitted, because they are of clinical interest and do not violate proportional odds at the univariate level, are Stiffness of hip and Definitive treatment
3. Interpretation of proportional odds ratios: overall effect of covariate on odds of being in a particular grade or higher. Odds ratios < 1 imply a better outcome for a category compared with the reference category (as lower grades represent a better outcome). E.g. A male is around twice as likely to be categorised into a lower grade at 2 years than a comparable female. Older children are 2.5 times more likely to be categorised into a higher group than comparable younger children.

6.5 Complications

In this section we report on two key complication types during follow-up: the need for any surgery other than the primary treatment, and a fixation of an associated fracture. More detail about what surgery was used is given in Section 6.6.

Table 6-18: Complications (all affected hips)

	Surveillance cohort	
	1 year	**2 years**
Hips		
First presentations	393	393
Lost to follow-up	26	45
Analysed	367	348
Any surgery (not including primary treatment)		
Yes	14 (4.1%)	48 (14.8%)
No	326 (95.9%)	277 (85.2%)
Missing	27	23
Need for a fixation of an associated fracture		
Yes	0	0
No	340 (100.0%)	325 (100.0%)
Missing	27	23

6.6 Other surgery

6.6.1 Other Surgery during follow-up

Table 6-19: Other surgery during follow-up

	Surveillance Cohort during following up
Hips	
First presentations	393
Lost to follow-up*	43
No data uploaded in Y2 / question unanswered	23
Analysed*	327
Hips with other surgery	
n	48 (14.8%)
Surgery type	
Removal of metalwork	40 (12.2%)
Epiphysiodesis for limb length discrepancy	2 (0.6%)
Fixation of associated fracture	0
Realignment osteotomy	5 (1.5%)
Impingent surgery, not realignment osteotomy (i.e. hip head / neck osteochondroplasty)	0
Arthroscopic	-
Open	-
Trochanteric advancement	0
Head reshaping osteotomy	0
Via surgical dislocation	-
Not via surgical dislocation	-
Redirectional acetabular osteotomy	0
Arthroplasty	1 (0.3%)
Other hip surgery	10 (3.1%)
Unreported	0

*****Two 'removals of metalwork' were identified after one year, and then these patients were subsequently lost to follow-up. They are removed from the 'lost-to-follow-up' total and added into the denominator of those analysed.

6.6.2 Related surgery planned post follow-up

Table 6-20: Related surgery planned post follow-up prior to discharge

	Surveillance cohort at 2 years
Hips	
First presentations	393
Lost to follow-up	45
No data uploaded in Y2 / question unanswered	26
Analysed	322
Any related surgery planned	
Yes	26 (8.1%)
No	296 (91.9%)
Surgery type	
Removal of metalwork	14 (4.3%)
Epiphysiodesis for limb length discrepancy	3 (0.9%)
Fixation of associated fracture	0
Realignment osteotomy	1 (0.3%)
Impingent surgery, not realignment osteotomy (i.e. hip head / neck osteochondroplasty)	1 (0.3%)
Arthroscopic	*0*
Open	*1*
Trochanteric advancement	0
Head reshaping osteotomy	0
Via surgical dislocation	-
Not via surgical dislocation	-
Redirectional acetabular osteotomy	0
Arthroplasty	4 (1.2%)
Other hip surgery	7 (2.2%)
None ticked	0

Table 6-21: Line listings of other surgery reported (free-text entries in the database)

Other surgery
During follow-up (n=10) • *Distal femur periosteal release* • *drilling of femoral head* • *Examination under anaesthetic and Arthrogram* • *Exchange of external fixator pin 13/10/2016.* • *Further soft tissue release (adductor release) on the 13/4/2017 as the hip remained very stiff and painful.* • *L hip arthrogram & Staheli shelf acetabuloplasty 3/12/2018* • *steroid injection to the hip to help with flare of symptoms and stiffness* • *trochanteric apophyseodesis 15-12-17* • *trochanteric epiphysiodesis* • *Very stiff. Had an arthrogram to consider if any other treatments can be done. Considering whether a Total Hip Replacement will be required in the longer term.*
Planned post follow-up (n=7) • *?shelf acetabuloplasty for head coverage* • *Arthrogram* • *Awaiting arthrogram* • *Depending on how hip progresses and symptoms - child still young and currently has LLD with high-riding GT. May require limb equalisation surgery +/- tranchanteric advancement.* • *Partial remodelling of acetabulum evident current - if not does not remodel further and child becomes symptomatic, to consider further surgery (femoral +/- pelvic osteotomy if appropriate; otherwise THR)* • *Potential for arthrodesis rather than arthroplasty in the first instance. She is meeting the adult hip team to discuss. Plus has had a few hip blocks in the interim.* • *Scar Revision by plastic surgeons*

6.7 PROMs

BOSS was designed to collect surveillance data for all known cases of SCFE in the UK during a discrete time-period. At the same time, it was planned that a subset of SCFE cases would be approached and asked to part of a consented cohort. This cohort would fill in questionnaires at three time-points during the study: baseline, 1 year post baseline, and 2 years post baseline, and their NHS number would be stored by BOSS to enable future data linkage. A total of 57/144 sites were enrolled to invite their SCFE cases to consent to being part of the consented cohort. The questionnaires filled in by patients are referred to in the study as Patient Reported Outcome Measures (or PROMs).

In practice, there was a low rate of accrual of cases into the consented cohort (Figure 4-4: Perthes' disease recruitment over time). There was also a difficulty in collecting PROMs within the time-windows specified in the protocol (see Table 4-3: Protocol deviations). The reasons for this are most likely to be related to a lack of research nurse expertise available in this field of surgery, rather than a reluctance on the part of cases to take part. Some sites were clearly very successful at consenting patients (e.g. Alder Hey, 37/40 Perthes' disease cases were consented).

An electronic system for collecting consent and PROMs was developed to make the process easier for both clinicians and patients. Unfortunately, this was introduced too late in the study, and only yielded a small number of additional consentees.

Low per-protocol PROMs completion has impacted the methods of analysis possible. The sample sizes achieved are not quite large enough to examine within-patient changes in PROMs over time. However, Table 6-1 does show that the consented cohort is representative of the surveillance cohort; and that the subsets that completed baseline PROMs and 2-year PROMs are also representative.

6.7.1 Descriptive results: progression over time

Table 6-22: Summary statistics for Perthes' disease PROMs

	Consented cohort Questionnaire completed:		
	Within 2 weeks of baseline	**At 1 year +/-1 months**	**At 2 years +/-6 months**
Consented cohort			
n	82	150	172
Questionnaires completed			
n	70 (85%)	41 (27%)	99 (58%)
EQ-5D-Y: score [*1.0 = Perfect health*]			
n	70	41	99
Mean (SD)	0.50 (0.42)	0.68 (0.37)	0.76 (0.30)
Median (IQR)	0.7 (0.1,0.8)	0.8 (0.7,0.9)	0.8 (0.7,1.0)
Min, Max	-0.4, 1.0	-0.4, 1.0	-0.6, 1.0
Missing	0	0	0
EQ-5D-Y: VAS [*100 = Perfect health*]			
n	60	41	96
Mean (SD)	71.1 (19.0)	81.2 (15.6)	82.9 (18.6)
Median (IQR)	74 (56,85)	85 (70,95)	88 (79,95)
Min, Max	25,100	50,100	0,100
Missing	10	0	3
PedsQL Total Score [*100 = Excellent quality of life*]			
n	70	40	99
Mean (SD)	59.4 (19.0)	70.6 (18.6)	72.8 (20.5)
Median (IQR)	57.6 (45.0,73.9)	72.3 (56.0,87.0)	76.1 (57.6,91.3)
Min, Max	22.6, 96.7	18.5, 100.0	15.2, 100.0
Missing	0	1	0
PedsQL: Physical factors [*100 = Excellent physical quality of life*]			
n	70	40	99
Median (IQR)	46.9 (31.3,62.5)	65.6 (53.1,78.1)	75.0 (53.6,90.6)
Min, Max	9.4, 100.0	9.4, 100.0	0.0, 100.0
Missing	0	1	0
PedsQL: Emotional factors [*100 = Excellent emotional quality of life*]			
n	70	40	98
Median (IQR)	60 (45,80)	83 (63,100)	80 (55,95)
Min, Max	10, 100	20, 100	15, 100
Missing	0	1	1

PedsQL: Social factors	[*100 = Excellent social quality of life*]		
n	69	40	99
Median (IQR)	70 (55,90)	78 (63,95)	80 (60,95)
Min, Max	10, 100	20, 100	10, 100
Missing	1	1	0
PedsQL: School factors	[*100 = Excellent quality of life with reference to school*]		
n	66	38	99
Median (IQR)	66 (50,85)	70 (55,85)	75 (55,95)
Min, Max	10, 100	30, 100	20, 100
Missing	4	3	0
Wong Baker Faces Scale	[0 = *No pain*]		
n	68	38	93
Mean (SD)	3.5 (2.8)	2.4 (2.6)	2.1 (2.2)
Median (IQR)	2 (2,6)	2 (0,4)	2 (0,3)
Min, Max	0, 10	0, 10	0, 10
Missing	2	3	6

Notes:

1. The per-protocol window for 2-year PROMs was set as between -3 months and +1 month from the 2-year target. At the SSC meeting which took place in November 2019, it was decided to widen the window of acceptability for 2-year PROMs to +/-6 months.
2. Four cases returned two sets of PROMs within the +/-6 month window for 2 years. Only the PROMs that were completed closest to the 2-year target were included in the analysis above.
3. Recent research [5]has indicated that regular EQ-5D-3L value sets cannot be used for children and adolescents. The main reason is that health states are valued differently when described for an adult or a child. Research is currently ongoing, partly funded by the EuroQol Research Foundation, to ultimately produce EQ-5D-Y value sets for use in children and adolescents. For the purpose of this study, EQ-5D-Y has been evaluated using Dolan 1997. [6] NB. The valuation method incurs the possibility of a negative score for some health states. Health state index scores generally range from 0 (where 0 is a health state equivalent to death) and 1 (perfect health).

[5] *Kind P, et al. Can adult weights be used to value child health states? Testing the influence of perspective in valuing EQ-5D-Y. Qual Life Res 2015 Oct;24(10):2519-2539*
[6] *Dolan P. Modelling valuations for EuroQol health states. Med Care 1997;35(11):1095-108*

Figure 6-7: Scatterplot of EQ-5D-Y score by time-point

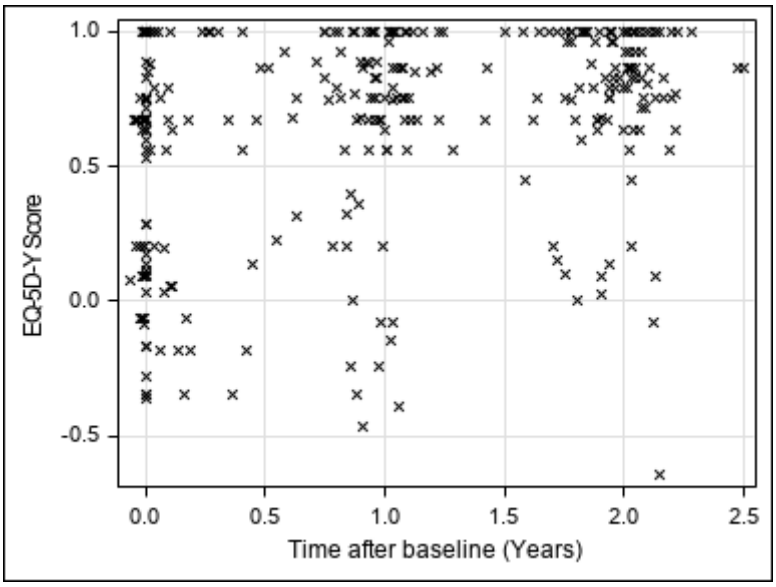


Figure 6-8: Scatterplot of EQ-5D-Y VAS score by time-point

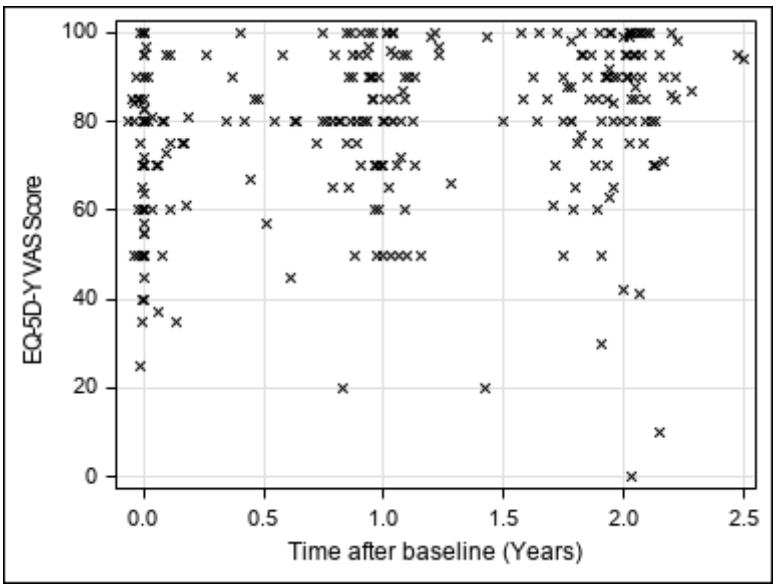


Figure 6-9: Scatterplot of total PedsQL score by time-point

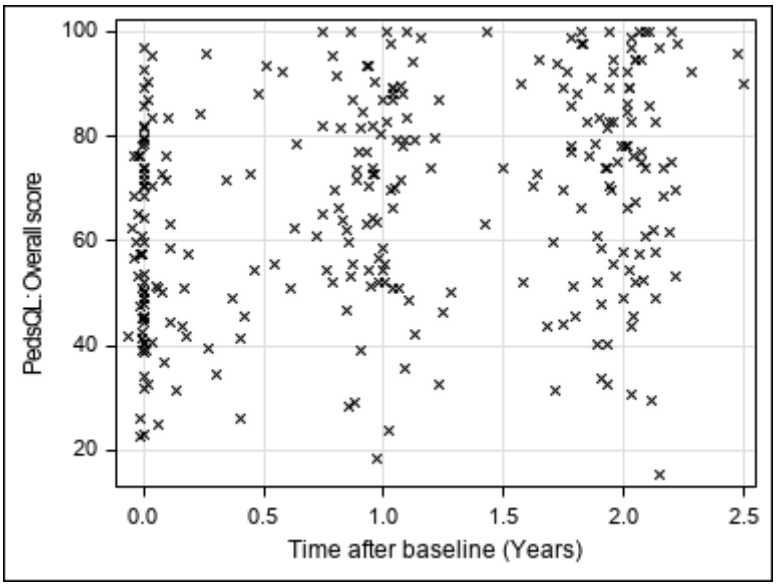
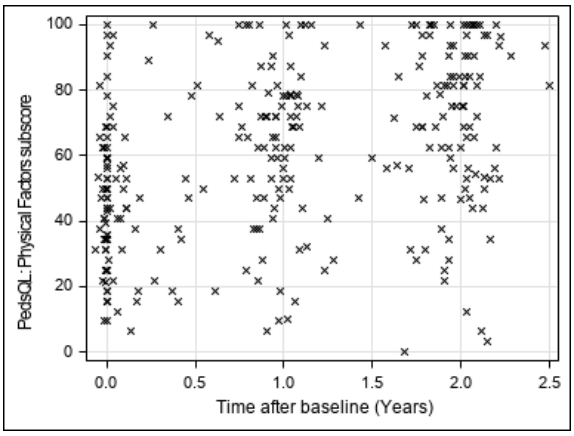
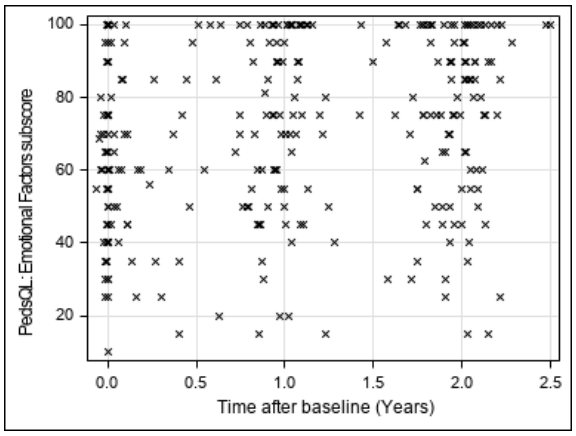
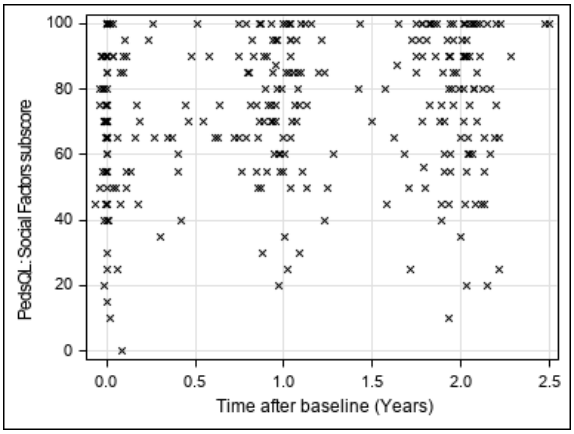


Figure 6-10: Scatterplot of PedsQL sub-scores by time-point







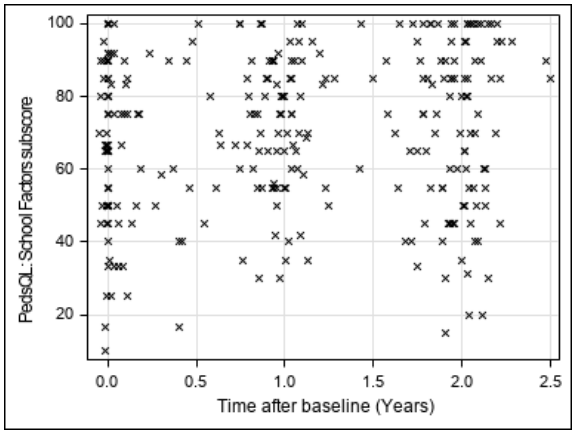


Figure 6-11: Scatterplot of Wong-Baker Faces score by time-point

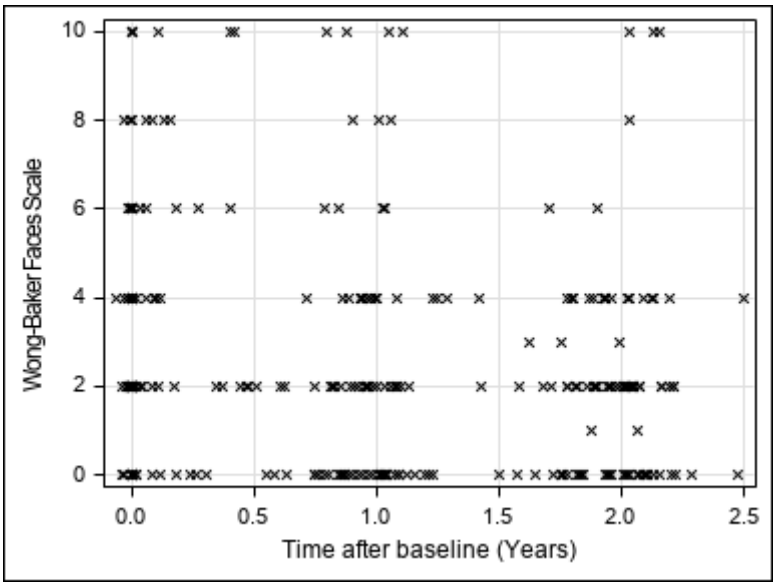
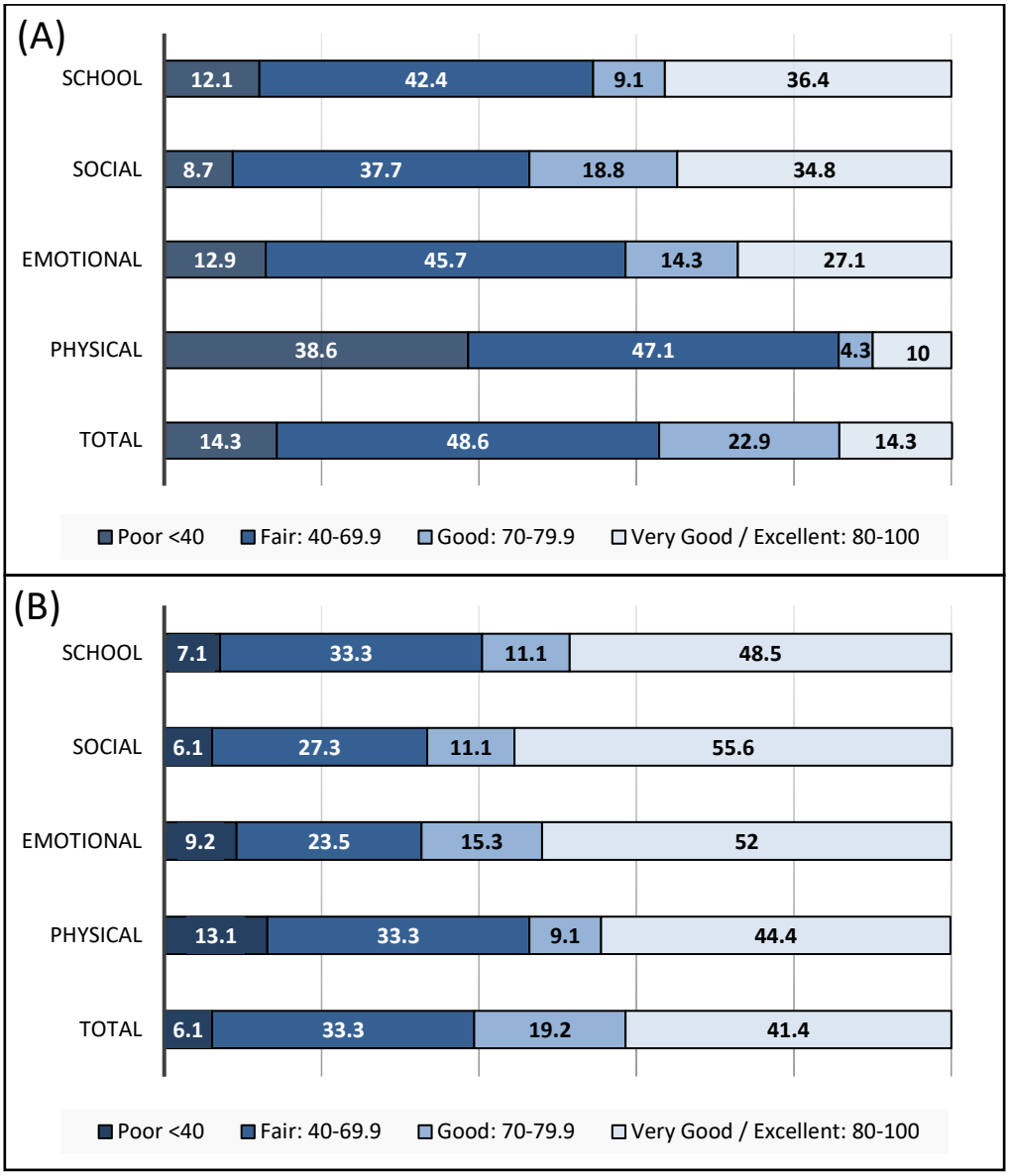


Figure 6-12: Distribution of PedsQL in Perthes' disease patients at (A) baseline (n=70), and (B) 2 years (n=99). Categorisations as suggested by Huang *et al* (2009) [7].



[7] Huang IC, Thompson LA, Chi YY, et al. The linkage between pediatric quality of life and health conditions: establishing clinically meaningful cutoff scores for the PedsQL. *Value Health*. 2009;12(5):773–781. doi:10.1111/j.1524-4733.2008.00487.x

6.7.2 Baseline factor prediction of 2-year PROMs

In this section, we explore the potential association between baseline factors and 2-year PROMs. A univariate analysis is carried out initially to examine effects of each factor, with the purpose of fitting a multivariate model including age, sex, stiffness of hip, degree of collapse of the lateral head and treatment type, together with any other factor that was found to be significantly associated at the univariate level. Where baseline data are hip-specific, and a child presents bilaterally, the baseline assessment for the worst affected hip is used.

6.7.2.1 Univariate analysis

Table 6-23: Univariate analysis of EQ-5D-Y at 2 years with respect to potential baseline predictors. [Parameter estimates are derived by fitting random effects linear regression models for each covariate]

Predictor	N	Median (IQR) EQ-5D-Y	Parameter estimate	
			Estimate	95% CI
Age at diagnosis	99	-	-0.02	(-0.04,0.00)
Sex				
Male	78	0.8 (0.7, 1.0)	0	-
Female	21	0.8 (0.7, 1.0)	0.0	(-0.2,0.1)
BMI				
	53	-	-0.01	(-0.04,0.02)
Stiffness of hip at baseline*				
Stiff	53	0.9 (0.7, 1.0)	0	-
Minimal or no stiffness	46	0.8 (0.6, 1.0)	-0.05	(-0.16,0.06)
Degree of collapse of lateral column				
None	25	0.8 (0.6, 1.0)	0.1	(-0.1,0.3)
< 50%	42	0.9 (0.7, 1.0)	0.1	(-0.1,0.2)
Exactly 50% collapse	9	1.0 (0.6, 1.0)	0.0	(-0.2,0.2)
> 50%	14	0.8 (0.7, 0.9)	0	-
Head involvement of lateral column				
> 50%	36	0.9 (0.7, 1.0)	-0.1	(-0.3,0.0)
< 50%	21	0.8 (0.6, 1.0)	0	-
Actual treatment type				
Surgical	52	0.9 (0.7, 1.0)	0	-
Non-surgical	43	0.8 (0.8, 1.0)	0.1	(-0.1,0.2)
Time-lag from onset of symptoms to diagnosis (months)				
	99	-	0.01	(-0.01,0.03)
Treating centre case-load				
Low (1-2 cases per year)	5	0.8 (0.8, 1.0)	0.1	(-0.2,0.4)
Medium (3-5 cases per year)	16	0.8 (0.7, 0.9)	-0.1	(-0.2,0.1)
High (>5 cases per year)	78	0.9 (0.7, 1.0)	0	-

*Stiffness of hip was added to this analysis *post hoc*

Notes:

1. There is no evidence of a non-linear relationship between 2-year EQ-5D-Y and age [scatterplot not show]. Age is therefore presented as continuous rather than categorised into groups.

Table 6-24: Univariate analysis of PedsQL at 2 years with respect to potential baseline predictors.

Predictor	N	Median (IQR) PedsQL	Parameter estimate	
			Estimate	95% CI
Age (continuous)*	99		-0.75	(-2.21,0.72)
Sex				
Male	78	76.1 (58.0, 89.1)	0	-
Female	21	75.0 (57.6, 94.6)	0.0	(-10.1,10.0)
BMI	53		-1.82	(-3.72,0.08)
Stiffness of hip at baseline*				
Stiff	53	78.3 (54.3, 94.6)	0	
Minimal or no stiffness	46	74.5 (59.8, 85.9)	-0.05	(-0.16,0.06)
Degree of collapse of lateral column				
None	25	73.9 (52.2, 84.8)	4.9	(-10.5,20.3)
< 50%	42	79.9 (59.8, 92.4)	6.2	(-3.8,16.2)
Exactly 50% collapse	9	77.2 (67.4, 94.6)	-1.6	(-14.8,11.7)
> 50%	14	70.1 (55.4, 82.6)	0	-
Head involvement of lateral column				
> 50%	36	71.7 (52.2, 85.9)	-0.3	(-11.4,10.8)
< 50%	21	70.5 (59.8, 82.6)	0	-
Actual treatment type				
Surgical	52	73.9 (52.2, 92.4)	0	-
Non-surgical	43	77.2 (60.9, 91.3)	4.1	(-4.4,12.6)
Time-lag from onset of symptoms to diagnosis (months)	99		0.81	(-0.37,1.99)
Treating centre case-load				
Low (1-2 cases per year)	5	78.4 (77.2, 82.6)	7.3	(-11.6,26.2)
Medium (3-5 cases per year)	16	71.7 (52.7, 87.7)	-1.8	(-13.1,9.4)
High (>5 cases per year)	78	75.5 (57.6, 92.4)	0	-

*Stiffness of hip was added to this analysis *post hoc*

Notes:

1. There is no evidence of a non-linear relationship between 2-year PedsQL and age [scatterplot not show]. Age is therefore presented as continuous rather than categorised into groups.

Table 6-25: Univariate analysis of Wong-Baker at 2 years with respect to potential baseline predictors.

Predictor	N	Median (IQR) Wong-Baker	Parameter estimate	
			Estimate	95% CI
Age (continuous)*	93	-	0.05	(-0.11,0.21)
Sex				
Male	72	2 (0, 3.5)	0	-
Female	21	2 (0, 2)	0.1	(-1.0,1.2)
BMI				
	50	-	-0.03	(-0.21,0.15)
Stiffness of hip at baseline*				
Stiff	50	2 (0, 4)	0	-
Minimal or no stiffness	43	2 (0, 3)	0.3	(-0.7,1.2)
Degree of collapse of lateral column				
None	23	2 (1, 2)	0.4	(-1.2,1.9)
< 50%	39	2 (0, 3)	-0.2	(-1.3,0.8)
Exactly 50% collapse	9	2 (0, 2)	1.7	(0.3,3.1)
> 50%	13	2 (2, 4)	0	-
Head involvement of lateral column				
> 50%	31	2 (0, 4)	-0.1	(-1.4,1.2)
< 50%	20	2 (0, 2.5)	0	-
Actual treatment type				
Surgical	50	2 (0, 4)	0	-
Non-surgical	39	2 (0, 3)	-0.2	(-1.0,0.7)
Time-lag from onset of symptoms to diagnosis (months)				
	99	-	0.01	(-0.13,0.14)
Treating centre case-load				
Low (1-2 cases per year)	4	1.5 (0.5, 2)	-0.9	(-3.2,1.4)
Medium (3-5 cases per year)	15	2 (0, 4)	-0.1	(-1.3,1.2)
High (>5 cases per year)	74	2 (0, 3)	0	-

*Stiffness of hip was added to this analysis *post hoc*

Notes:

1. There is no evidence of a non-linear relationship between 2-year Wong-Baker and age [scatterplot not show]. Age is therefore presented as continuous rather than categorised into groups.

6.7.2.2 Multivariate analysis

Tables 6-27 to 6-29 would have given the results of the final multivariate models chosen to represent how baseline variables relate to 2-year PROMs. However, as the univariate analyses indicated no significant predictors of these outcomes, these analyses were not carried out.

Table 6-26: Multiple linear regression analysis of EQ-5D-Y at 2 years with respect to baseline covariates

<No Results>

Table 6-27: Multiple linear regression analysis of PedsQL at 2 years with respect to baseline covariates

<No Results>

Table 6-28: Multiple linear regression analysis of Wong Baker Faces at 2 years with respect to baseline covariates

<No Results>

6.8 Association between 2-year hip shape and 2-year PROMs

In this section we explore whether there is any correlation between two 2-year outcomes: hip shape and PROMs. Spearman's' rank correlation is used to assess this, as the PROMs we have measured are generally pseudo-continuous, being inherently subjective and not necessarily linear in nature. For correlation to be represent a clinically relevant association, r_S should be larger than 0.6 or smaller than -0.6.

Table 6-29: Correlation between 2-year hip shape (AP roundness error) and 2-year PROMs

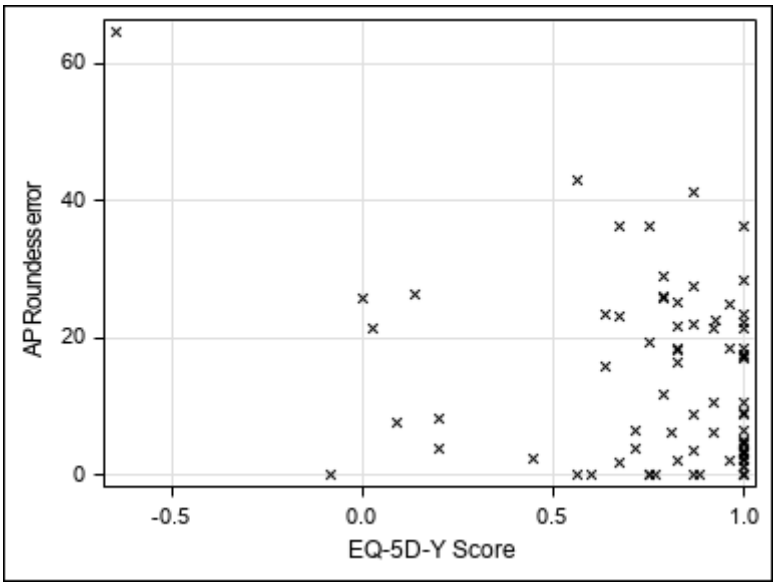
2-year PROMs	Number of 2-year PROMs	Number 2-year PROMs where corresponding 2-year AP radiographs are available	Spearman's rank correlation (r_S)
EQ-5D-Y			
Score	99	75	-0.14
VAS	96	73	-0.24
PedsQL			
Total Score	99	75	-0.08
Physical factors	99	75	-0.24
Emotional factors	98	74	0.04
Social factors	99	75	-0.05
School factors	99	75	-0.06
Wong Baker Faces	93	71	0.16

Notes:

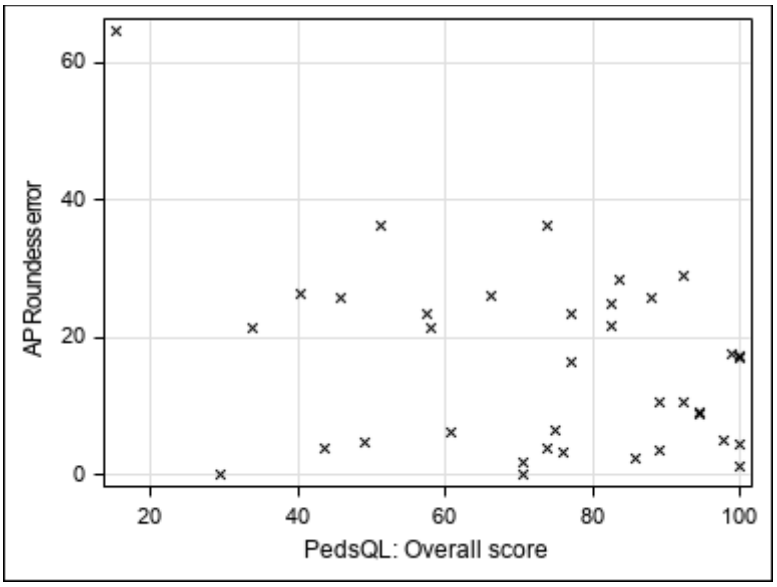
1. 24/99 (24%) of the 2-year PROMs could not be included in this analysis. For 20 of the children that completed 2-year PROMs, no 2-year radiographs were transferred. In addition, one child's x-ray was lateral and not AP; and three had early reossification, meaning that measurements could not be made.
2. There were no bilateral presentations among the hips included in this analysis.

Figure 6-13: Scatterplot of 2-year hip-shape with (a) EQ5DY, (b) PedsQL and (c) Wong-Baker Faces

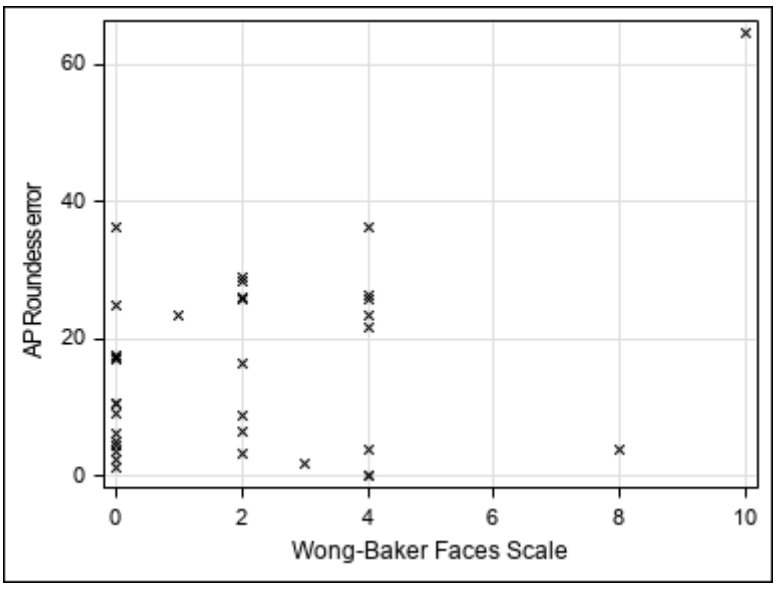
(a)



(b)



(c)



6.9 Contralateral Perthes' disease

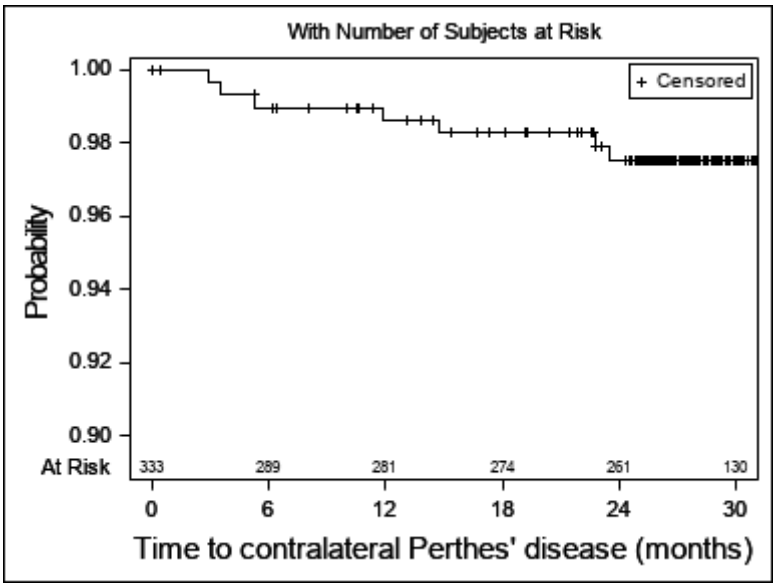
6.9.1 Risk

A total of 333 children in BOSS entered the study 'at risk of contralateral Perthes' disease'. These are children that presented unilaterally, and with no history of prior contralateral Perthes' disease. Of these, a total of 7 contralateral diagnoses were recorded during the study. The risk of contralateral Perthes' disease was therefore found to be 2.1% 95%CI: (0.6%, 3.6%).

6.9.2 Time to contralateral Perthes' disease

The time from first presentation (entry into BOSS/first diagnosis) to diagnosis of contralateral disease is presented in the Kaplan-Meier graphs below. Each step down in the curve represents the time at which a contralateral event occurred. The small vertical lines on the curve represent the last known follow-up for patients that, as far as we know, did not experience a contralateral event.

Figure 6-14: Kaplan-Meier plot showing time from entry into BOSS/first diagnosis to diagnosis of contralateral disease. [Confidence bands not displayed – these cover the whole graph when we restrict the y-axis to the range 0.9-1.0].



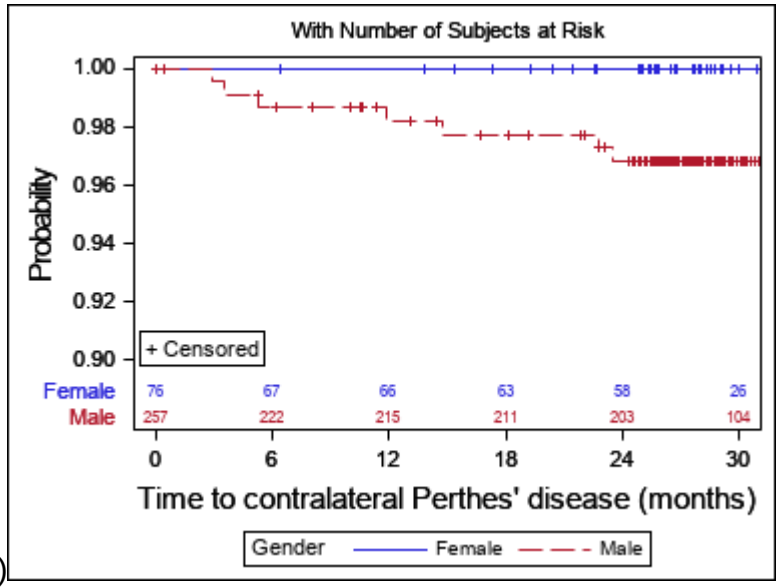
Notes:

1. Where no contralateral disease is recorded, cases are censored the last known date that the hip can be assumed to be normal: For those that were recorded as lost to follow-up, this date is the last clinic follow-up; otherwise we make the assumption that whilst follow-up data are uploaded, the status of the contralateral hip remains normal, and we use the final date of data-upload.

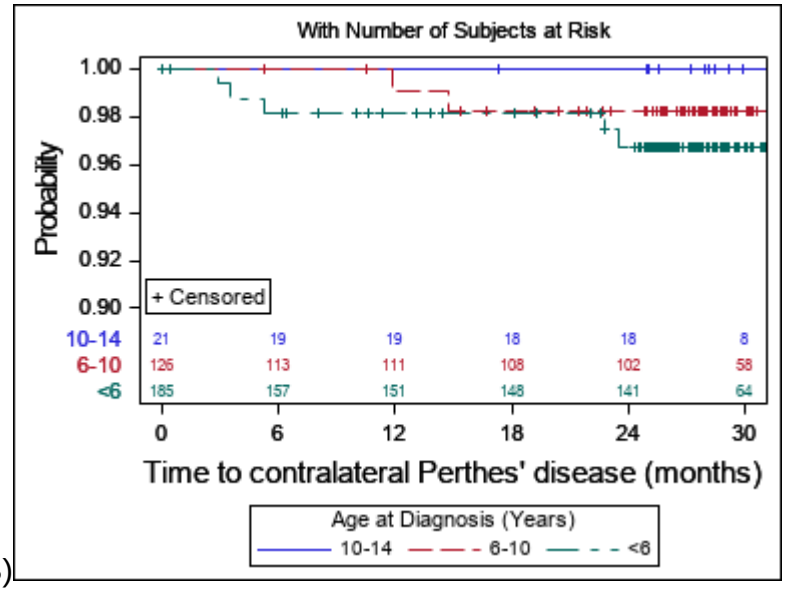
4. The scale on the vertical axis does not start at 0. This is to allow the detail of the graph to be seen, but can mislead the eye. All graphs can be reproduced with the full vertical axis if required.

Figure 6-15: Kaplan-Meier plots showing time from entry into BOSS/first diagnosis to diagnosis of contralateral disease split by (A) sex; and (B) age-group. [Confidence bands not displayed – these cover the whole graph when we restrict the y-axis to the range 0.9-1.0, and there is no separation by strata].

(A)



(B)



Notes:

1. As there are only 7 contralateral Perthes' disease events recorded in BOSS, splitting the plots by group is of limited value. No contralateral events were in females, and none were observed in the 10-14 year-old age category.

6.9.3 Predictors of contralateral Perthes' disease

In this section we explore the potential association between baseline factors and contralateral Perthes' disease. A univariate analysis is carried out initially to examine effects of each factor, with the purpose of fitting a multivariate model including age, sex, stiffness of hip, degree of collapse of the lateral column and type of treatment received, together with any other factor that was found to be significantly associated at the univariate level.

6.9.3.1 Univariate analysis

Table 6-30: Univariate analysis of risk of contralateral Perthes' disease at 2 years with respect to baseline variables: at risk population only. [Parameter estimates are derived by fitting Cox proportional hazards models for each covariate]

Baseline variable	N	No. of contralateral diagnoses	Hazard Ratio	
			HR	95% CI
Age	332	7	0.8	(0.58,1.15)
Sex				
Male	257	7	1	-
Female	76	0	-	-
BMI	132	3	1.1	(0.88,1.47)
Stiffness of hip at baseline*				
Stiff	139	2	1	-
Minimal or no stiffness	181	5	2.0	(0.39,10.48)
Degree of collapse of lateral column				
No collapse	93	2	1.6	(0.22,11.05)
< 50% collapse	136	2	1	-
Exactly 50% collapse	24	0	-	-
> 50% collapse	46	2	3.2	(0.45,22.58)
Head involvement of lateral column				
> 50%	130	2	2.4	(0.41,14.64)
< 50%	82	3	1	-
Actual treatment type				
Surgical	113	3	1.5	(0.30,7.42)
Non-surgical	163	3	1	-
Time-lag from onset of symptoms to diagnosis (months)	313	7	0.8	(0.62,1.15)

Treating centre type				
Low	83	1	0.8	(0.05,13.00)
Medium	76	1	1.7	(0.20,14.63)
High	173	5	1	-

*Stiffness of hip was added to this analysis *post hoc*

Notes:

1. These analyses pertain to the 'at-risk' population as defined in the Statistical Analysis Plan v1.0. This includes unilateral presentations, where a prophylactic fix was not undertaken on the unaffected hip.
2. This univariate analysis was originally planned in the SAP as modelling the risk of contralateral Perthes' disease at 2 years. However, as there was considerable loss to follow-up and missing 2-year data, it was decided to change the methodology to a time-to-event analysis, so that all 333 at risk patients could be included.
3. As there are only 7 contralateral events recorded from cases that entered BOSS 'at-risk', calculation of hazard-ratios is of limited value. No events were observed in females, and none were observed in the 10-14 year-olds.
4. For 4 contralateral events, at least one of the baseline factors investigated are unknown.

6.9.3.2 Multivariate analysis

Table 6-31 would have given the results of the final multivariate model chosen to represent to what extent baseline variables are predictors of contralateral Perthes' disease. However, the total number of events is too small to fit a model with more than one covariate, and no covariates were found to be a significant predictor at the univariate level.

Table 6-31: Cox proportional hazards multivariable model of time-to-contralateral Perthes' disease, with respect to baseline covariates.

<No Results>

6.9.3.3 Recursive partitioning

In this section we would have presented a decision tree derived using recursive partitioning, using the methodology described in Leblanc and Crowley (1992)[8]. However, the observed event rate was too low to enable a meaningful analysis.

Figure 6-16: Results of recursive partitioning applied to all cases 'at-risk of contralateral Perthes' disease fitting the potential baseline predictors: age, sex, BMI, degree of collapse of lateral column, and d

<No Results>

[8] LeBlanc, M., & Crowley, J. (1992). Relative Risk Trees for Censored Survival Data. *Biometrics, 48*(2), 411-425. doi:10.2307/2532300

7. Appendix

At the analysis stage, a number of additional analyses were identified that had not been pre-planned in the statistical analysis plan. All additional analyses are listed here.

7.1 SCFE additional analyses

1. The definition of the 'at-risk of contralateral SCFE' was amended to exclude children that received a prophylactic fix at baseline.
2. Columns added to Table 5-1 to describe baseline demographics for two further sub-groups of interest.
3. Additional histogram describing the age at diagnosis of children within the consented cohort.
4. Columns added to Table 5-3 in order to split results by baseline clinical stability.
5. Additional table created to describe surgical management of affected and unaffected hips separately.
6. Columns added to Table 5-12 (previously 5-11) so that the clinical time-line is split by baseline clinical stability.
7. Columns added to Table 5-14 (previously 5-13) so that complications can be described for two sub-periods of follow-up and for all follow-up.
8. The analysis of the risk of AVN was extended to adjust for baseline clinical stability. Table 5-16 (previously 5-15) was re-ordered to clarify that two distinct models were fitted.
9. Columns added to Table 5-17 (previously 5-16) so that complications can be described for two sub-periods of follow-up and for all follow-up.
10. Columns added to Table 5-21 (previously 5-20) so that results could be split by baseline clinical stability and severity.
11. Additional boxplot (Figure 5-3) created to split results by baseline clinical stability and severity.
12. Median (IQR) was added as a column to all univariate analysis tables describing continuous outcomes.
13. Additional table created to summarise patient reported presentation factors. (Table 5-24)
14. Scatterplots added to describe the four sub-scales for PedsQL. (Figure 5-7)
15. Distribution graphs added to aid comparison of PROMs between baseline and PROMs.
16. The analysis of risk factors for contralateral SCFE was changed from the logistic regression modelling a binary 2-year outcome, to a Cox Proportional Hazards model, modelling a time-to-event. This was because there was considerable loss to follow-up, and incomplete data collection. A time-to-event analysis enabled all available data to be used for patients that we did not have complete follow-up data for.

7.2 Perthes' disease additional analyses

1. Columns added to Table 6-1 to describe baseline demographics for two further sub-groups of interest.
2. Additional histogram describing the age at diagnosis of children within the consented cohort.
3. Rows added to Table 6-4 to describe planned versus actual treatment types.
4. Two columns in Table 6-6 where combined so that all treatment during follow-up is summarised together.
5. Additional graph added (Figure 6-4) to give a graphical representation of Table 6-10.
6. Additional boxplot added to Figure 6-5 (previously Figure 6-4) to summarise measured roundness error by Stulberg grade.
7. The binary baseline factor 'stiffness of hip' was added to all univariate and multivariate analyses. This is a key clinical baseline factor that was overlooked and not included in the SAP.
8. Median (IQR) was added as a column to all univariate analysis tables describing continuous outcomes.
9. An additional table (Table 6-15) was added to provide descriptive statistics regarding the proposed univariate analysis of factors affecting 2-year Stulberg grade.
10. Two columns were combined in Table 6-20 (previously 6-19), so that 'Other Surgery' would be summarised for all follow-up instead of split by year of follow-up.
11. Scatterplots added to describe the four sub-scales for PedsQL. (Figure 6-9)
12. Distribution graphs added to aid comparison of PROMs between baseline and PROMs. (Figure 6-11)