Follow us @BoneJointOpen

Freely available online OPEN ACCESS

BJO

CHILDREN'S ORTHOPAEDICS

A protocol for a nationwide multicentre, prospective surveillance cohort and nested-consented cohort to determine the incidence and clinical outcomes of slipped capital femoral epiphysis

D. C. Perry,
B. Arch,
D. Appelbe,
P. Francis,
C. Spowart,
M. Knight,
On behalf of the BOSS Collaborative

From University of Liverpool, UK

Aims

Slipped capital femoral epiphysis (SCFE) is one of the most common hip diseases of adolescence that can cause marked disability, yet there is little robust evidence to guide treatment. Fundamental aspects of the disease, such as frequency, are unknown and consequently the desire of clinicians to undertake robust intervention studies is somewhat prohibited by a lack of fundamental knowledge.

Methods

The study is an anonymized nationwide comprehensive cohort study with nested consented within the mechanism of the British Orthopaedic Surgery Surveillance (BOSS) Study. All relevant hospitals treating SCFE in England, Scotland, and Wales will contribute anonymized case details. Potential missing cases will be cross-checked against two independent external sources of data (the national administrative data and independent trainee data). Patients will be invited to enrich the data collected by supplementing anonymized case data with patient-reported outcome measures. In line with recommendations of the IDEAL Collaboration, the study will primarily seek to determine incidence, describe case mix and variations in surgical interventions, and explore the relationships between baseline factors (patients and types of interventions) and two-year outcomes.

Discussion

This is the first disease to be investigated using the BOSS Study infrastructure. It provides a robust method to determine the disease frequency, and a large unbiased sample of cases from which treatment strategies can be investigated. It may form the basis for definitive robust intervention studies or, where these are demonstrated not to be feasible, this may be the most robust cohort study.

Cite this article: *Bone Joint Open* 2020;1-3:35–40.

Keywords: Slipped capital femoral epiphysis, Cohort study

Strengths and Limitations

- This large cohort seeks to define the incidence of disease, with linked national administrative data to identify any potentially missing cases.
- This study will form a large unbiased sample of cases from all relevant UK hospitals, providing results that are readily generalizable.
- The study will readily be able to determine variation in practice, and provide key information for intervention studies.
- The study is an observational cohort study of standard care. Therefore, selection bias is inherent to the study design.

Introduction

Slipped capital femoral epiphysis (SCFE) is the most common hip disease of adolescence. In the short-term it always requires surgery to stabilize the epiphysis onto the femoral neck, and typically results in deformity at the level of the growth plate. In the long-term, SCFE

Correspondence should be sent to Daniel C Perry; email: danperry@liverpool.ac.uk

doi: 10.1302/2633-1462.13.BJO-2020-0002

Bone Joint Open 2020;1-3:35–40.

accelerates the development of osteoarthritis, and many patients have disability necessitating hip arthroplasty in early adulthood.[1] It typically presents to the clinician with knee, thigh or hip pain, or a limp,[2] and there is strong evidence to suggest that obesity is the major cause.[3]

The incidence is reported to be approximately five to seven cases per 100,000 children aged six to 18 years,[2,4] though the true incidence is unknown. Estimates are based on hospital administrative data, in which the validity of the diagnoses is not confirmed.

While SCFE is the most common hip disease of adolescence, robust evidence to support effective management and intervention is poor, with no clinical trials to guide treatment decisions. Administrative data are unable to be used to guide management, so as such databases do not provide detail regarding the severity and type of management strategies, nor the clinical characteristics of the individual. Consequently, treatment strategies vary by country, by hospital, and even by surgeon. These differences have been illustrated in surveys of the membership of the British, Dutch, European, and North American Paediatric Orthopaedic Societies.[5-7] The uncertainty has prompted members of the British Society of Children's Orthopaedic Surgery to prioritize questions pertaining to SCFE as two of the top five research priorities across the whole of children's orthopaedic surgery.[8]

The IDEAL Framework outlines a methodological approach to research in surgery.[9-11] Research relating to SCFE has not yet reached 'stage 2b' within IDEAL: "co-operative prospective evaluation of the techniques". The proposed study is a 2b design, focusing on identifying the case mix, technical intervention variables, and clinical outcomes. The study uses the British Orthopaedic Surgery Surveillance (BOSS) Study, a nationwide UK mechanism for investigating rare orthopaedic disease, the basis for which is described separately, develops a nationwide cohort of SCFE to determine the disease incidence, case mix, risk factors, variations in surgical interventions, and to determine the safety and efficacy of different surgical strategies.

Specific objectives

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

Methods

A national prospective comprehensive surveillance cohort study of SCFE will be formed in two parts:

Anonymized surveillance cohort. A consecutive anonymized comprehensive cohort encompassing all UK cases of SCFE. Individual consent is not sought for this element of the study. In a study of a rare disorder, in which the number of cases is small, refusal to contribute data by one or two individuals will result in under-ascertainment of cases and incorrect calculation of incidence. Seeking consent would therefore reduce case ascertainment and introduce bias; for example, certain groups or types of individual might be more likely to refuse consent. The consecutive surveillance cohort is important to minimize selection bias, in accordance with recommendations of the IDEAL framework,[9] and this method of case ascertainment has been established in similar surveillance programmes.[12,13]

Consented cohort. An identified cohort formed from those within the surveillance cohort that consent to the collection of PROMs, and future data linkage.

The cohort will be collected from all UK orthopaedic units treating children and adolescents, with sites acting as data collection centres. All orthopaedic units treating children have agreed to participate as part of their audit and risk management activities, with encouragement from the British Orthopaedic Association, and British Society for Children's Orthopaedic Surgery. This follows similar methodology to the successful UK Obstetric Surveillance Study (UKOSS).[12]

The study is underpinned by bespoke software that automates many aspects of the follow-up and communication with sites. The software is built around the REDCap Electronic Data Capture platform (Vanderbilt University, Nashville, Tennessee, USA), with bespoke elements adding to the functionality to facilitate the study. This is described in detail elsewhere as the BOSS Study.

In brief, reporting clinicians upload case details including only minimal identifiers of individuals, including sex, and month and year of birth, with monthly electronic prompts to clinicians inviting them to confirm case ascertainment and to prompt follow-up. Given that SCFE is rare, other data sources (nationwide administrative data, such as hospital episode statistics) can be periodically linked to the BOSS records using the minimal identifiers, to identify potential missing cases at each site.

Individuals and their families will be informed about the BOSS Study, and will be invited to consent to provide patient reported outcomes to enrich the data collected. Patients can consent on paper at participating hospitals, or will be given a unique code allowing them to consent and participate in the study online at the study website.

Table I. ICD-10 and OPSC codes used in routine administrative data to identify cases.

Any of the following ICD-10 codes		Any of the following OPSC codes entered during the same admission
M93.0 Slipped capital femoral epiphysis (this ICD-10 code may be used in isolation as long as the episode of care is associated with an operation date)		
M92.8 Other specified osteochondrosis	**AND**	**W241** Closed reduction of intracapsular fracture of neck of femur and fixation using nail or screw
M93.8 Osteochondropathy, unspecified		**W275** Temporary fixation of epiphysis
M93.9 Osteochondropathy		**W278** Other specified fixation of epiphysis
S72.0 Fracture of the neck of the femur		**W279** Unspecified fixation of epiphysis

Case definition

Inclusions. Patients must fulfil all of the following criteria:

1. Skeletally immature individuals;
2. Radiological confirmation of displacement of the epiphysis relative to the metaphysis occurring at the proximal femoral physis;
3. Newly presenting to secondary/tertiary care during the study period with the above radiological changes in either hip (patients will be included if the other side has been affected outside the study period, but the opposite hip is newly affected);
4. Undergoing surgical stabilization during hospital admission; and
5. A resident within the England, Scotland, or Wales.

Exclusions. Previous attempts at stabilization of the currently affected hip.

Denominator population. The denominator population will be defined as the population of children aged six to 18 years within the geographical boundaries of England, Scotland, and Wales.

Potential missing cases may be identified from two sources; national administrative data and an independent trainee reporting system. Potential missing cases are flagged to reporting clinicians each month when prompted to upload true cases, or to click a hyperlink to identify erroneous cases.

For national administrative data, cases of SCFE routinely undergo urgent surgery; therefore, the use of the data is ideal to supplement case ascertainment. ICD-10 codes pertaining to SCFE were identified in a prior study using administrative data (Table I).[2] Diagnostic and interventional SCFE codes will be searched within the admission codes within the hospital episode statistics for England (supplied by NHS Digital), the Patient Episode Database for Wales, and the Scottish Morbidity Record.

Cases from administrative data will be matched to cases within the BOSS Study based on sex, month and year of birth, and date of surgery. (A seven-day window around the surgery date is permitted to allow for errors in coding within administrative datasets.) National databases are updated monthly, with a lead-time of three months after the completion of the care episode. A monthly extract will be sought from each of the administrative databases until three months after the end of case identification to accommodate the lead-time for data upload.

For the National Orthopaedic Surgery Trainee Research Network, the British Orthopaedic Network Environment (BONE) will function as a reporting network to highlight potential cases. If a trainee becomes aware of a case in the hospital where they are working, they will enter the date of admission, date of surgery, sex, and hospital trust onto a secure electronic REDCap database, which is separate from the main study database. Data entered into the trainee's system does not capture full case details and is intended to maximize recruitment to the main database only; data entered into the trainee database is not a substitute for data entered into the main study. At the end of each month, the trainee will be prompted to electronically verify that cases they have recorded truly reflect the activity they experienced over this period.

Data collected. Demographics including height and weight, disease chronicity and severity, surgical intervention (including co-interventions), and intraoperative monitoring techniques (fluoroscopy/blood flow) were collected (Tables II and III).

The healthcare team reported the following outcomes at three months and two years: complications (such as infection, fracture, avascular necrosis, and chondolysis); subsequent operative interventions; planned operative interventions; contralateral SCFE; and radiological sphericity, measured using α angle (at two years only).

Consented cohort. Several PROMs were used, including the Wong-Baker Faces pain rating scale, EQ-5D-Y (EuroQol), and paediatric quality of life (PedsQL; Mapi Research Trust, Lyon, France).

The Wong-Baker Faces scale[14] is a validated self-reported tool. It is an ordinal assessment of pain using a series of six facial expressions to illustrate the degree of pain intensity. A numerical rating is assigned to each face (with 0 being 'no hurt' to 10 being 'hurts worst'). It has been validated for use among children aged over three years.[15] It is highly correlated to the visual analogue scale ($r = 0.90$; $p < 0.001$). Test-retest reliability is excellent ($r = 0.90$, $p < 0.001$).[16] The Wong-Baker scale is widely used in clinical practice, forming part of the Royal College of Emergency Medicine 'composite tool for the assessment of pain in children' produced in 2013 as part of a best practice guidelines.[17]

Table II. Schedule of observations for the anonymized surveillance cohort.

Detail	Admission	3 months postoperative	2 years postoperative	Admission for opposite sided SCFE at any stage
Surgeon case report (case details)	X	X	X	X
Most recently available routinely collected radiographs of relevant hip or pelvis.* (AP and lateral as per standard care; pre- and postoperative (or intraoperative if postoperative unavailable))	X		X	X

*The BOSS Study does not require that radiographs be taken for the purpose of the study. It is routine practice to undertake radiographs in the treatment and follow-up of SCFE. The BOSS Study requests the anonymized routinely collected images from the medical record for use by the study team.

Table III. Schedule of observations for the nested consented cohort.

Questionnaire	Admission (± 2 weeks)	3 months (± 2 weeks)	2 years (-3 months/ + 1 month)	Admission for opposite-sided SCFE (± 2 weeks)*
Initial admission, questions for parents/guardians (case details)	X			X
EQ-5D-Y (proxy if aged > 4 years and < 8 years)	X	X	X	
PedsQL (proxy if aged < 8 years)	X	X	X	
Wong Baker Faces Pain Scale (aged 4+ years)	X	X	X	

*This will be collected if a patient already enrol in the study presents with a SCFE in the opposite hip.

EQ-5D-Y is the youth version of the EQ-5D-3L, which is a validated, generalized, health-related quality of life questionnaire consisting of five domains related to daily activities with a three-level answer possibility. EQ-5D-Y has been especially adapted in terms of language for children aged eight to 18 years.[18,19] A proxy version is available for younger children. Its age appropriateness in terms of feasibility, reliability, and validity in children and adolescents has been established.[19] There is currently ongoing work to produce EQ-5D-Y value sets for use in children and adolescents. Our interim solution is to apply adult EQ-5D value sets to the EQ-5D-Y classification.

PedsQL is a well-validated, widely-used quality of life tool for use in children.[20] It provides a general measure of quality of life, in addition to three summary scores, including a total scale score, a physical health score, and a psychosocial health score.

Long-term follow-up. The strength of UK data linkage offers an efficient means for a population cohort to be tracked to 'definitive outcomes'; requiring minimal intrusion to the patient, and minimal attrition and follow-up costs. Subsequent arthroplasty is regarded as 'failure' of the hip, and is therefore the definitive long-term outcome and can be ascertained via linkage to the National Joint Registry.[21] Measurement is proposed after ten years, and at five yearly intervals. Consent will be broad for future linkage to healthcare and other administrative datasets, in line with recommendations of the recent Medical Research Council report concerned with maximizing the utility of cohorts.[22]

All patients entered into the surveillance cohort can participate in the consented cohort. Consent can be obtained at any time in the patient's follow-up, but questionnaires should only be completed at the time-points specified in the schedule of observations.

Sample size, statistics, and analysis. Incomplete existing data means it is not possible to accurately predict the number of cases expected. National administrative data demonstrates an incidence of approximately five to seven cases per 100,000 of children aged six to 18 years.[2,4] If we assume this approximates to the rest of the UK and use population data from the 2001 census (9.1 million six- to 18-year-olds), this suggests there would be 615 annual new cases of SCFE (530 in England, 55 in Scotland, and 30 in Wales). The resulting 95% Poisson confidence intervals would allow the incidence to be estimated in the range 6.43 to 7.52 cases per 100,000 of children aged six to 18 years per year.

The surveillance cohort will recruit for a period of 18 months to identify the incidence of disease. The nested consented cohort will require 300 cases to enable meaningful comparisons to be made within subgroups (approximately 60% of those thought to be eligible).

The full statistical analysis plan, including dummy tables, is available on request. Key planned analyses are defined as:

1. Incidence rates will be estimated using reported new cases of SCFE, and denominators from UK census data. Rates will be stratified by country, region, age, and sex, and 95% confidence intervals will be calculated based on an assumed Poisson distribution for counts.
2. Variations in case-mix will be reported using descriptive statistics.
3. Variations in surgical management will be reported using descriptive statistics. Surgical management decisions are likely to vary by hospital, patient, and disease. In order to better understand this process, decision trees will be constructed to characterize overall management practices and highlight variation by centre.
4. Subsequent contralateral disease in SCFE is a binary outcome; therefore, logistic regression will be used to assess the importance and quantify the effects of a range of patient, disease, and radiological risks factors on this outcome, after adjusting for known confounders; recursive partitioning will be used to understand the most likely combinations of subgroups of baseline factors in predicting contralateral SCFE. Time to contralateral SCFE will be displayed using Kaplan-Meier plots, overall and split by age group and sex.
5. Univariate and multivariate analyses including random effects will be used to explore the relationship between baseline factors and two-year outcomes. Logistic regression for binary outcomes (such as AVN), and linear regression for continuous outcomes (e.g. α angle and two-year PROMs).
6. Associations between hip shape and PROMs at two years will be quantified using Spearman's rank *r* and displayed with scatterplots.

Ethical considerations and approval

The ethical approach for the anonymized surveillance study has broadly been described elsewhere.

Among those entering the consented study, informed written/electronic consent will be obtained from parents or legal guardians (if participants are younger than 16 years). Patients who become aged 16 years while in the study will be asked to provide a written/electronic consent to affirm their willingness to continue participation in the study.

Assent will be sought from competent minors over eight years of age, where the research team assesses competence and relevance to do so. Where possible, the minor should personally write their name and date the assent form themselves. The form is then countersigned by the parent/legal representative and the researcher taking consent. Assent forms do not substitute for the consent form. Assent should be taken where appropriate; however, the absence of assent does not exclude the patient from the study if consent has been obtained from the parent/legal representative.

This programme of work complies with the Helsinki Declaration and was reviewed and approved by the National Research Ethics Service Committee London – City and East (REC ref 15/LO/2202) and the Health Research Authority (ref 190754). The release of national administrative data for this purpose was approved by the Public Benefit and Privacy Panel (PBPP) in Scotland (ref - 1617 to 0030) and the Data Access Advisory Group (DAAG) in England (ref NIC-362142-K9C7P). There was no similar process in Wales.

Patient and public involvement

Representatives of Steps UK, the primary charitable support group for children and young people with limb disorders, were consulted in the development of the funding application for this programme of work. Members of this group will sit on the study management group. The National Institute for Health Research Young Person's Advisory Group, a group of children and young people involved in improving the conduct of research in children, assisted in the development of the participant information materials.

Discussion

The framework proposed by the IDEAL collaboration forms the basis for the study.[9] The evidence in the treatment of SCFE is such that the current evidence is not mature enough to support the development of randomized clinical trials. The intention of this large surveillance cohort and nested-consented cohort is to provide robust feasibility data for randomized trials, and if such trials are not feasible, then the intention is that this will form the definitive cohort.

References

1. **Metcalfe D**, **Peterson N**, **Wilkinson JM**, **Perry DC**. Temporal trends and survivorship of total hip arthroplasty in very young patients: a study using the National joint registry data set. *Bone Joint J*. 2018;100-B(10):1320–1329.
2. **Perry DC**, **Metcalfe D**, **Costa ML**, **Van Staa T**. A nationwide cohort study of slipped capital femoral epiphysis. *Arch Dis Child*. 2017;102(12):1132–1136.
3. **Perry DC**, **Metcalfe D**, **Lane S**, **Turner S**. Childhood obesity and slipped capital femoral epiphysis. *Pediatrics*. 2018;142(5):e20181067.
4. **Murray AWA**, **Wilson NILN**. Changing incidence of slipped capital femoral epiphysis: a relationship with obesity? *J Bone Joint Surg Br*. 2008;90(1):92–94.
5. **Witbreuk M**, **Besselaar P**, **Eastwood D**. Current practice in the management of acute/unstable slipped capital femoral epiphyses in the United Kingdom and the Netherlands: results of a survey of the membership of the British Society of children's orthopaedic surgery and the Werkgroep Kinder Orthopaedie. *J Pediatr Orthop B*. 2007;16(2):79–83.
6. **Mooney JF**III, **Sanders JO**, **Browne RH**, **et al**. Management of unstable/acute slipped capital femoral epiphysis: results of a survey of the POSNA membership. *J Pediatr Orthop*. 2005;25(2):162–166.
7. **Sonnega RJA**, **van der Sluijs JA**, **Wainwright AM**, **Roposch A**, **Hefti F**. Management of slipped capital femoral epiphysis: results of a survey of the members of the European paediatric orthopaedic Society. *J Child Orthop*. 2011;5(6):433–438.
8. **Perry DC**, **Wright JG**, **Cooke S**, **et al**. A consensus exercise identifying priorities for research into clinical effectiveness among children's orthopaedic surgeons in the United Kingdom. *Bone Joint J*. 2018;100-B(5):680–684.
9. **Ergina PL**, **Barkun JS**, **McCulloch P**, **et al**. IDEAL framework for surgical innovation 2: observational studies in the exploration and assessment stages. *BMJ*. 2013;346:f3011–f1.
10. **Cook JA**, **McCulloch P**, **Blazeby JM**, **et al**. IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage. *BMJ*. 2013;346:–f2820–f0.

11. **McCulloch P**, **Cook JA**, **Altman DG**, **et al**. IDEAL framework for surgical innovation 1: the idea and development stages. *BMJ*. 2013;346:f3012–f2.
12. **Knight M**, **Kurinczuk JJ**, **Tuffnell D**, **Brocklehurst P**. The UK obstetric surveillance system for rare disorders of pregnancy. *BJOG*. 2005;112(3):263–265.
13. **Bradnock TJ**, **Marven S**, **Owen A**, **et al**. BAPS-CASSGastroschisis: one year outcomes from national cohort study. *BMJ*. 2011;343:d6749–d9.
14. **Wong DL**, **Baker CM**. Pain in children: comparison of assessment scales. *Pediatr Nurs*. 1988;14(1):9–17.
15. **Garra G**, **Singer AJ**, **Taira BR**, **et al**. Validation of the Wong-Baker faces pain rating scale in pediatric emergency department patients. *Acad Emerg Med*. 2010;17(1):50–54.
16. **Keck JF**, **Gerkensmeyer JE**, **Joyce BA**, **Schade JG**. Reliability and validity of the faces and word descriptor scales to measure procedural pain. *J Pediatr Nurs*. 1996;11(6):368–374.
17. **No authors listed**. Management of Pain in Children. The Royal College of Emergency Medicine (RCEM). Best Practice Guideline. 2017. https://www.rcem.ac.uk/docs/RCEM%20Guidance/RCEM%20Pain%20in%20Children%20%20Best%20Practice%20Guidance%20(REV%20Jul%202017).pdf (date last accessed 15 January 2020).
18. **Eidt-Koch D**, **Mittendorf T**, **Greiner W**. Cross-Sectional validity of the EQ-5D-Y as a generic health outcome instrument in children and adolescents with cystic fibrosis in Germany. *BMC Pediatr*. 2009;9(1):55.
19. **Wille N**, **Badia X**, **Bonsel G**, **et al**. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res*. 2010;19(6):875–886.
20. **Varni JW**, **Seid M**, **Kurtin PS**. PedsQL 4.0: reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. *Med Care*. 2001;39(8):800–812.
21. **No authors listed**. National Joint Registry for England, Wales, and Northern Ireland (NJR). 10th Annual Report. 2013. http://www.njrcentre.org.uk/njrcentre/Portals/0/Documents/England/Reports/10th_annual_report/NJR%2010th%20Annual%20Report%202013%20B.pdf (date last accessed 15 January 2020).
22. **No authors listed**. Maximising the value of UK population cohorts: MRC Strategic review of the largest UK population cohort studies. Medical Research Council (MRC). 2014. https://mrc.ukri.org/publications/browse/maximising-the-value-of-uk-population-cohorts/ (date last accessed 15 January 2020).

Author information:
- D. C. Perry, MB ChB (Hons), MA (Oxon), FRCS (Orth), PhD, Consultant Orthopaedic Surgeon and NIHR Clinician Scientist
- B. Arch, BSc, Medical Statistician
- P. Francis, BSc, Study Manager
- C. Spowart, BSc, Senior Study Manager
  University of Liverpool, Institute of Translational Medicine, Alder Hey Hospital, Liverpool, UK.
- D. Appelbe, MSc, PhD, Senior Information Analyst, NDORMS, University of Oxford, Kadoorie Centre, John Radcliffe Hospital, Oxford, UK.
- M. Knight, MA, MBChB MPH, Dphil, FFPH, FRCPE, Professor of Maternal and Child Population Health, Nuffield Department of Population Health, University of Oxford, Oxford, UK.

Author contributions:
- D. C. Perry: Drafted the initial manuscript, Iterative edits to the text, Approval of the final document.
- B. Arch: Advised on statistical elements of the manuscript, Iterative edits to the text, Approval of the final document.
- D. Appelbe: Advised on information technology elements of the manuscript, Iterative edits to the text, Approval of the final document.
- P. Francis: Advised on regulatory elements, Iterative edits to the text, Approval of the final document.
- C. Spowart: Oversight of on regulatory elements of the manuscript, Iterative edits to the text, Approval of the final document.
- M. Knight: Advised on study design, Iterative edits to the text, Approval of the final document.

Funding statement:
- This article presents independent research funded by the National Institute for Health Research (NIHR) to Daniel C Perry through an NIHR Clinician Scientist Fellowship (CS-2014-14-012). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

ICMJE COI statement:
- D.Appelbe, B. Arch, P. Francis, and C. Spowart also report a grant paid to their institutions from the NIHR.