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Orthotic management of instability of the knee in neuromuscular disease

Project protocol 1.0

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SUMMARY OF RESEARCH

The project aims to address the commissioned research question of which orthotic devices are in use in the NHS for instability of the knee, for which neuromuscular conditions and what further research is needed. There are four key objectives:

1) To assess the evidence-base for the effectiveness of orthotic devices for management of instability of the knee in adults who have neuromuscular disease (NMD) including knee instability related to central nervous system (CNS) disorders.

2) To identify the types of orthotic devices currently being used by the NHS for the management of instability of the knee in adults with neuromuscular disease (including CNS disorders), the frequency of their use, and their cost.

3) To identify the most important outcomes for patients.

4) To identify any implications for clinical practice, any gaps in the evidence and future research needs.

To meet the first objective a systematic review will be undertaken of the best available evidence on the effectiveness of orthotic devices in this population. A database of published and unpublished literature will be assembled from systematic searches of electronic sources, hand searching, reference checking and contacting manufacturers. Studies will be assessed for risk of bias. Standard systematic review methods will be used to reduce error and bias in the review processes. Given the nature of the available data it is likely that a narrative synthesis will be the most appropriate approach to synthesis. In addition to the synthesis of effectiveness data, data will also be mapped in relation to the condition where the orthotic devices have been evaluated, details of the specific designs of the devices being evaluated, and the types of outcome measures used.

To meet the second objective a survey of orthotists and physiotherapists will be undertaken and audit data will be sought. We intend to distribute the electronic questionnaire through relevant professional bodies: the Association of Chartered Physiotherapists Interested in Neurology (ACPIN) and the British Association of Prosthetists and Orthotists (BAPO). A range of sources and methods will be used to derive information on the two key elements of cost: the devices and the staff and other resource costs related to fitting (number of fittings and length of appointment) and ongoing monitoring and maintenance. Sources will include orthotists, list prices and manufacturers.

To meet the third objective we will use qualitative research methods to collate the views of people with NMD (including knee instability related to CNS disorders) who have been fitted with an orthotic device for knee instability. 25-30 people will be interviewed. Purposive sampling will be used to ensure that a diverse sample of conditions, age, length of time using orthoses, high and low usage and regions is achieved. Focus groups will be undertaken with 2-4 prevalent populations, to allow more in-depth examination of important outcomes and associated factors. A predominantly thematic analysis will be used.

To meet the fourth objective the three sources of evidence - healthcare professionals, patients and the systematic review - will be interrogated and the different sources will be integrated. For example we will compare outcomes of importance to patients (derived through the qualitative study) with the outcomes that are being used to measure effectiveness in clinical trials (derived through the systematic review) with any formal outcome measures that are being used to assess patient outcomes in clinical practice (derived through the survey of healthcare professionals). Similarly we will explore whether there are any disparities between the devices being used in clinical practice and those being evaluated in research studies. Implications for practice, evidence gaps and future research needs will be clearly linked to the evidence source/s from which they have been derived.

BACKGROUND AND RATIONALE

Neuromuscular disease

Neuromuscular diseases (NMD) are a heterogeneous group of conditions and terminology can vary. Neurology practice in the UK recognises neuromuscular disease as conditions that primarily affect the peripheral nerve, muscle and neuromuscular junction. Hilton-Jones et al. describe the term as covering any condition caused by dysfunction of the motor unit (the motor nerve and the muscle it controls).[1] They identify four anatomical sites: the anterior horn cell/motor neuron (e.g. polio and motor neuron disease); the peripheral nerve (e.g. Charcot Marie Tooth disease); the neuromuscular junction (e.g. myasthenia gravis) and the muscle (e.g. muscular dystrophy).[1] There is a wide variety of pathologies, motor impairments and co-morbidities across these neuromuscular disorders. For instance, peripheral nerve conditions which may be sensory as well as motor; neuromuscular junction conditions where there may be a large element of variability and physiological fatigue; and muscle conditions which will vary in co-morbidities such as cardiomyopathy and respiratory impairment. The exact muscle groups affected will vary both between and within individual conditions. However, there are common factors, particularly fatigue as well as weakness, affecting mobility and lower limb function. There are some NMDs that also have central nervous system signs e.g. Amytrophic Lateral Sclerosis and Myotonic Dystrophy, but the lower motor neuron features of flaccid weakness, loss of reflexes and muscle wasting are predominant.

The term neuromuscular disease is sometimes used in a more inclusive way, encompassing upper motor neurone conditions that have a common end point of affecting muscle function. This would therefore include CNS disorders such as multiple sclerosis and stroke. Clinical management of people with primarily central nervous system conditions will often differ from the conditions described above due to the effect of upper motor neuron features on lower limb function; for example in conditions such as multiple sclerosis spasticity will influence the prescription of orthoses; in patients who have experienced a stroke issues such as spasticity, neglect and spatial awareness will impact, plus there is acute onset usually with improvement and plateau, unlike many neuromuscular diseases where ongoing disease progression is a feature. Following feedback from the board the scope includes a broad patient population using this wider definition of neuromuscular disease.

Knee instability in neuromuscular disease

There are several mechanisms that may lead to knee instability in NMD. The knee is a hinge joint that also has a rotatory action, with articular surfaces between the femur and the tibia, and the patella and femur. The muscle groups that have a direct effect on the knee are the knee extensors comprising of quadriceps femoris and tensor fascia latae, and the knee flexors that include the hamstring group, sartorius, gracilis and gastrocnemius. One mechanism that may lead to knee instability is weakness in any of these muscles. This would be particularly common in muscle conditions that are predominantly limb girdle in origin; peripheral nerve conditions that affect these muscles, such as diabetic amyotrophy or poliomyelitis; or in upper motor neurone conditions that affect the lower limb. This could be uni or bilateral according to condition. Weakness in these muscle groups, or in more remote muscle groups, may also lead to secondary impairment of the tendons, ligaments and cartilage associated with the knee due to altered alignment and redistribution of force across the joints and soft tissue**.** Muscle weakness or over-activity remote from the muscles directly affecting the knee may also cause knee instability due to the secondary effects on posture, such as excessive plantar flexion leading to anterior progression of the ground reaction force under the foot. Excessive plantar flexion could be by relative over-activity of soleus and gastrocnemius in comparison to tibialis anterior and peroneals or be a compensation for weakness of the gluteal muscles hip extensors. Sensory impairment, either proprioceptive affecting control of knee position, or pain/cutaneous sensory modalities due to pressures from an orthosis, may be an added complication to consider. Knee instability itself may be in any of the planes that the knee can move, so antero-posterior, medial-lateral and rotational. Initial instability due to weakness in NMD, as opposed to structural, is more commonly seen in the antero-posterior plane, which is where the direct effect of muscle action occurs. The main problems seen in neuromuscular conditions are those affecting the posterior structures of the knee, which would lead to a *genu recurvatum,* or the knee 'giving way' anteriorly, potentially leading to falls.

KAFO and other orthotics for this condition

Knee instability due to muscle weakness or ligamentous laxity is often treated using orthoses. Knee-ankle-foot orthoses (KAFOs) span the knee, ankle and foot to stabilize the joints and assist safe ambulation. They can be used alone or can form part of a more extensive type of orthosis known as hip-knee-ankle-foot orthoses (HKAFOs) that also provides hip control. "Conventional" KAFOs made of metal and leather have been used

for centuries. Modern KAFOs made from thermoplastics are lighter and fit more closely, affording better control of the limb. Some KAFOs offload the body weight from the leg by means of an ischial seat. Most KAFOs incorporate knee joints that lock the knee straight during walking and unlock when the user sits. Recent years have seen the introduction of Stance Control knee joint technology, where mechanical or microprocessor controlled knee joints allow the knee to bend when walking, but lock when weight is borne through the leg to provide stability to the knee in order to allow a more normal walking pattern. Knee stability can also be improved by the use of knee braces/orthoses (KO) or in some cases by a type of ankle-foot orthosis (AFO) known as a Ground Reaction AFO (GRAFO).

The clinical effectiveness of the various orthotic options is unclear. Diagnosis is a poor predictor of the type of orthosis that will be most effective. Orthosis design should be driven by the specific biomechanical deficits of each individual patient. Analysis of effectiveness of orthoses must be based on the functional deficit rather than diagnosis.

Patient acceptance and preferences

User opinion towards orthoses has been highlighted as an important factor in acceptance and use of prescribed devices. In lower motor neurone conditions, this issue has mainly been explored with regard to the use of ankle-foot orthoses (AFOs). The first paper to address this was in people with Charcot Marie Tooth disease. Vinci et al. (2008) reported on interviews with 25 people, five of whom used AFOs.[2] They reported negative feelings about wearing the devices. The people who did not wear them felt they were not ready to accept them or wanted to manage without them. Phillips et al. (2011) used the nominal group technique and individual interviews to explore the opinions of people with Charcot Marie Tooth disease.[3] Although the improvements in walking with orthoses were noted, people reported practical issues and restrictions as well as concerns about comfort and the appearance of the device. A third study of walking function in people with Charcot Marie Tooth disease compared 11 AFO users with 21 non-users.[4] Six of the non-users had been prescribed AFOs but chose not to wear them. Their physical characteristics resembled the non-AFO group more than the AFO group for measures of muscle strength and disease severity. This study raised the question as to whether AFOs can be prescribed too early in some cases and people with Charcot Marie Tooth disease self-select their use when there is greater physical need.

Acceptance of orthoses crossing the knee has had less investigation. A study of boys with Duchenne muscular dystrophy explored the opinions of knee-ankle-foot orthoses (KAFO) users.[5] Using KAFOs could be distressing for boys and parents as it signified deterioration in their condition. They did recognise, however, the functional improvements as a result of using the devices. A study of stance control orthoses in Inclusion Body Myositis had mixed views from users.[6] They reported improved stability and falls prevention but all complained about issues such as size, bulkiness and appearance.

Having an understanding of patients' views and experience of orthotic devices and the impact on adherence is important to designing appropriate interventions for evaluation in clinical trials. Expected adherence also influences the likely sample size required for a trial. In addition, any trial of orthoses should include user views and indications of acceptance. Even if a trial demonstrates biomechanical improvements, this is secondary if people are not willing to use the device regularly. Involvement of people in the prescription process is also paramount but at the same time recognising that it is ultimately their choice. This should help build trust to promote optimum use of orthotics devices, so enabling people and ensuring cost effectiveness.[7]

Orthotic services

Orthotists in the NHS work closely with several clinical specialities ranging from orthopaedics to diabetes care, rheumatology and a range of other conditions including neuromuscular diseases. There are an estimated 1.2 million people using orthotic services in the NHS.[8] An Audit Commission report in 2000 estimated that 15% of a typical Trust's expenditure on orthoses was related to lower limb devices. At that time there was also wide variation in the prices quoted by different suppliers for identical products.[9] A survey of clinicians running specialist clinics for adults with neuromuscular disease found that the availability of specialist orthotics in the form of an orthotist with experience in neuromuscular diseases was low in the 32 clinics surveyed.[10]

Previous research on effectiveness

Scoping searches found no previous systematic reviews assessing the effectiveness of orthotic devices in the specific population of interest: knee instability in adults with neuromuscular disease. A search for guidelines did not identify any guidance related to use of knee-ankle-foot orthoses (KAFO) or other orthotics for people with neuromuscular disorders in the UK setting. Quality Improvement Scotland has issued a Best Practice Statement

on use of ankle-foot orthoses (AFO) following stroke, though that condition is outside the scope of the proposed work.[11]

A number of related reviews in paediatric populations were found. There were two systematic reviews of KAFO in the treatment of children with Duchenne muscular dystrophy.[12 13] Bakker et al. concluded that the use of KAFO in this population can prolong assisted walking and standing but there is uncertainty about whether it can prolong functional walking. The evidence-base was described as weak; no RCTs were found and in the four non-randomised controlled studies that they included there was a risk of bias in the selection of patients for the studies and in how outcome was measured. Dos Anjos Fernandes et al. also concluded there was benefit for children with Duchenne muscular dystrophy from use of KAFO; and this more recent review included an RCT.[13]

Related to adult populations, a Cochrane review has investigated any intervention for Charcot Marie Tooth disease and identified a single controlled study of foot orthoses (FO); however, while FO can influence the alignment of the knee on the coronal plane, they do not correct knee instability.[14] A review of non-surgical interventions for this condition did not identify any orthotics studies.[15] The literature searches for these reviews were undertaken in 2007 and 2006 respectively and therefore need to be updated. An overview of the evidence on KAFOs and hip-knee-ankle foot (HKAFO) orthoses for all conditions in 2006 concluded that the level of evidence was generally low and consisted mainly of small study sample sizes and inadequate study design, though these aspects were not addressed in any detail.[16] Two Cochrane reviews were identified that assessed interventions for ankle instability or reduced range of motion in the ankle in people with neuromuscular disease, but did not investigate knee instability.[17, 18] A search of PROSPERO did not identify any relevant ongoing reviews.

In addition to uncertainty about effectiveness, there is uncertainty about the acceptability of these devices to patients, the extent to which prescribed devices are used, and factors which determine their usage. Long-term rejection rates of KAFOs are high in people with paraplegia and with spinal cord lesions.[19] In a trial only 50% of stroke patients wore their ankle foot orthosis.[20] However, information on acceptability and use has not been collated systematically in relation to people with neuromuscular conditions that lead to knee instability.

One of the few studies of the patient perspective investigated the views of people with Charcot Marie Tooth disease in relation to wearing ankle-foot-orthoses.[3] This study found a difference between male and female users in the barriers to use of their orthosis. Comfort, choice and being listened to were key issues for females; the top ranking barrier was that the orthotic restricted the space available in shoes. Male users focused on functional use; the top ranking barrier was the way in which working life and specific work tasks were disrupted.[3]

There is likely to be a close relationship between patient expectations about outcomes and use of orthoses. The reasons for non-use or under use of orthoses are of particular importance in designing any future trial and further understanding of this issue is required. Identifying the most important outcomes and benefits to users and providers establishes a more informed foundation upon which to compare and evaluate current research and identify implications for future research.

AIMS AND OBJECTIVES

The project aims to address the commissioned research question of which orthotic devices are in use in the NHS for instability of the knee in adults, for which neuromuscular conditions and what further research is needed. It is our understanding from the advertised scope that the purpose of this commissioned work is to inform future research addressing the question of the clinical and cost-effectiveness of different types of orthotic management of the knee in people with neuromuscular disease.

There are four key objectives:

1) To assess the evidence-base for the effectiveness of orthotic devices for management of instability of the knee in adults who have neuromuscular disease, including knee instability related to central nervous system (CNS) disorders.

2) To identify the types of orthotic devices currently being used by the NHS for the management of instability of the knee in adults with neuromuscular disease (including CNS disorders), the frequency of their use, and their cost.

3) To identify the most important outcomes for patients.

4) To identify any implications for clinical practice, any gaps in the evidence and what the research questions to be answered next are.

RESEARCH PLAN

Study objective 1: To assess the evidence-base for the effectiveness of orthotic devices for management of instability of the knee in people who have neuromuscular disease.

Based on our knowledge of the area and screening of a sample of records from the draft searches, there are likely to be very few, if any RCTs available, therefore the review will aim to identify the best evidence that is currently available. While the strength of the evidence for effectiveness is likely to be limited, the information from the studies in the review will be important in informing future research; for example, we will collate and map information from the primary studies on the outcomes investigated and how they have been measured. This will allow an exploration of how well outcomes important to patients are currently being addressed in research evaluating the effectiveness of orthotics.

The main components of the systematic review are outlined below. These will be finalised and described in detail in the protocol which will be registered on PROSPERO. We will also plan to work with the Cochrane Neuromuscular Disease (CNMD) Group with the aim of producing a Cochrane systematic review from this HTA.

Inclusion/exclusion criteria

Studies meeting the following criteria will be included:

- Population – adults (16 years and older) with a neuromuscular disorder who have impaired walking ability due primarily to instability of the knee. Neuromuscular disorder will include conditions that primarily affect the peripheral nerve, muscle and neuromuscular junction e.g. motor neurone disease, muscular dystrophy, myasthenia gravis, spinal muscular atrophy, Charcot Marie Tooth disease, polio, myopathies, inclusion body myositis. Knee instability related to CNS conditions will also be included e.g. spinal cord injury, spina bifida, stroke.

- Intervention – Orthoses with the clinical aim of controlling knee instability for example, knee-ankle-foot orthoses (KAFO), ankle-foot orthoses (AFO) and knee orthoses (KO) or mixed designs. Orthoses of any design or material, custom or pre-fabricated; locked knee joint, eccentric knee joint or stance-control design (KAFO), with and without an electronic component will be eligible. Studies evaluating the use of functional electrical stimulation will be excluded.

- Comparator – Studies using any of the above orthotics as a comparator (KAFO, AFO; Foot Orthoses (FO), KO; or a mixed design (AFO and KO or FO and KO), including studies comparing different designs of the same orthotics; or no intervention.

  For comprehensiveness we have included all the interventions and comparators listed in the brief, though it is unlikely that a KAFO would be considered as a treatment option for the same population as a FO. In addition, there is a view that a KAFO is normally used when AFO or KO are considered insufficient to control knee instability, regardless of the condition;[19, 21] however there is currently not a consensus on this and we understand that all three are treatment options in the UK.

- Study design – randomised controlled trials (RCTs) and controlled trials. In the absence of evidence from controlled studies, studies without a control group will be used.

The following outcomes will be assessed:

- Condition specific or generic patient-reported outcomes measures assessing function, disability, independence, activities of daily living, quality of life or psychosocial outcomes.
- Pain
- Walking ability
- Other functional ability e.g. sit to stand, short turns in confined spaces
- Biomechanical analysis
- Adverse effects e.g. tissue damage, falls
- Usage
- Patient satisfaction and the acceptability of a device

- Resource utilisation data such as number of follow-up appointments, device malfunction or other problems

Two researchers will independently screen studies for relevance based on the inclusion criteria.

Search Strategy

A database of published and unpublished literature will be assembled from the systematic searches of electronic sources, hand searching, reference checking, contacting manufacturers and consultation with experts in the field. Searches will be undertaken by an experienced information specialist and the search strategy will be peer reviewed by a second information specialist. There will be three components to the searches:

- Studies will be identified be searching several electronic databases including MEDLINE, MEDLINE In-Process, Cumulative Index to Nursing & Allied Health (CINAHL), EMBASE, PASCAL, Science Citation Index, BIOSIS Previews, PEDro, Recal Legacy, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, Cochrane Central Register of Controlled Trials (CENTRAL).
- Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including Conference Proceedings Citation Index: Science, Health Management Information Consortium (HMIC), ClinicalTrials.gov and NTIS; and contacting manufacturers. Selected websites will also be searched such as those of the International Society for Prosthetics and Orthotics (ISPO), British Association of Prosthetists and Orthotists (BAPO), American Orthotic and Prosthetic Association and the American Academy of Orthotists and Prosthetists and the associated Journal of Prosthetics and Orthotics.
- The reference lists of all included studies, any related systematic reviews and key background papers will be checked.

A draft search strategy is provided in Appendix A, devised for MEDLINE in the OVID interface. The strategy combines indexed keywords (MeSH) terms for neuromuscular diseases and terms for the orthotic devices. The strategy will be further developed for example to include free text terms for different neuromuscular diseases, and to identify populations with knee instability related to CNS conditions, and converted to run appropriately on other databases.

Data extraction

A data extraction form will be developed, piloted on a small selection of studies and adjusted as necessary. Data extracted will include details of the study methods, country and setting, patient characteristics, intervention, comparators, outcome measures and results. Data will be extracted to allow calculation of between group differences and confidence intervals, as appropriate for the specific outcome measure (e.g. relative risk, hazard ratio, mean difference). For studies without a control group, data will be extracted to allow calculation of change from baseline and/or post-intervention outcomes and associated confidence intervals depending on the data available. Standard data imputation methods will be used where necessary and appropriate. Where possible, measures will be taken to maximise the possibility of between study comparisons, for example through use of the standardised mean difference. Data will be extracted by one researcher and checked by a second researcher.

Assessment of risk of bias

There is a lack of consensus about how risk of bias should be assessed in non-randomised studies and there is no gold standard tool for assessing risk of bias of case series or other observational designs. [22 23] However, there is a broad consensus in the methodological literature that selection bias and confounding are a key source of bias in observational study designs.[22 23] We will use a similar approach to that of Siegfried and colleagues who adapted domains similar to the Cochrane Risk of Bias Tool for observational designs.[24] Central to this is the assessment of control for confounding. We will develop an *a priori* list of key potential sources of confounding. Each study will be assessed as to whether they have adjusted for these confounders and the adequacy of the methods used. Assessment of risk of bias will be undertaken independently by two researchers. Should we identify any RCTs the Cochrane Risk of Bias Tool will be used to assess the risk of bias.

Synthesis

First a narrative and tabular summary of key study characteristics will be undertaken. This will include baseline population details (e.g. disease characteristics, severity of knee instability); intervention (e.g. type of orthoses, material); study methods (e.g. how outcomes were measured, length of follow-up); and risk of bias. This

information will underpin the assessment of clinical and methodological heterogeneity and will inform the interpretation of the study results as well as judgements about external validity.

Given the nature of the available data it is likely that a narrative synthesis will be the most appropriate approach to synthesis. Studies will be grouped by type of intervention and comparator; where comparative studies are not available studies will be grouped by type of intervention. In addition to undertaking a synthesis of any effectiveness data, data will also be mapped in relation to the types of conditions where these devices have been evaluated, details of the specific designs of the devices being evaluated and the types of outcomes measures used.

Should such sufficient data be available, meta-analyses will be undertaken where appropriate (based on clinical and statistical heterogeneity), using approaches recommended in the Cochrane Handbook and CRD's guidance for undertaking systematic reviews in healthcare.

Study objective 2: To identify the types of orthotic devices currently being used by the NHS in the management of instability of the knee in neuromuscular disease, the frequency of their use, and their cost.

To meet this objective a survey of orthotists and physiotherapists who provide orthotics to people with NMD will be undertaken. As part of the survey they will also be asked whether they have any audit or prescribing data already collected that can be anonymised and provided for the study on types of orthoses being provided for people with neuromuscular disease and patient adherence. We will also check whether any relevant data have been collected through professional bodies such as the British Association of Prosthetists and Orthotists (BAPO) Supplementary information will be sought from manufacturers of devices, if necessary.

The survey methods, questionnaire design and piloting as well as reporting will follow published guidance.[25, 26]

Sampling

Based on previous work in this area,[8, 9] and the knowledge of the clinical co-applicants, we expect that there may be regional variations in the types of orthotic devices being prescribed and the care pathways of patients. Therefore, we will aim to obtain as wide a geographical coverage as possible. The target population for the survey is orthotists and physiotherapists who fit orthotic devices. The sampling frame for the survey will be the membership of the Association of Chartered Physiotherapists Interested in Neurology (ACPIN) and the British Association of Prosthetists and Orthotists (BAPO).

ACPIN is one of the largest Professional Networks recognised by the Chartered Society of Physiotherapy. It is concerned with all aspects of physiotherapy related to the needs of neurologically impaired adults and their relatives and carers. There are currently 2700 members which will comprise a significant percentage of physiotherapists working with adults with neurological impairment. BAPO was established to encourage high standards of prosthetic and orthotic practice. It is the only UK body that represents the interests of prosthetic and orthotic professionals and a high majority of the profession are members. We do not have a precise number for membership currently but expect it to be in the region of 700. The questionnaire will be emailed to the mailing list of both organisations.

The use of this sampling frame will allow the response rate to the survey to be calculated. Because of how orthotic services are arranged in the NHS, with orthotists in some hospitals employed by private organisations and others by the NHS, as well as variations in which directorate orthotic services come under in different hospitals, any other approach to identifying these professionals would be very resource intensive. Although the proposed approach provides an incomplete sampling frame, as not all relevant orthotists and physiotherapists are members of either organisation, we believe it will provide reasonable coverage of regions and types of orthotic services (e.g. specialist neurological clinics and general clinics).

Response rates in surveys of healthcare professionals vary greatly. A recent systematic review and meta-analysis estimated a mean response rate of 38% by health professional to online surveys.[27] An earlier systematic review reported response rates ranging from 9% to 94%. We have taken a conservative estimate of 30% to estimate what an appropriately powered sample would be.[28] The primary purpose of the survey is to provide descriptive information on current NHS practice and the sample size has been calculated on that basis.[29, 30]

Based on a 95% confidence level and a 10% margin of error (which would seem reasonable given the exploratory nature of the survey) the estimated minimum sample size required would be 96 and assuming a more ideal 5% margin of error the sample size required is 384. Assuming an overall response rate of 30% we would have a sample of 1100 participants and even a response rate of 20% would provide a sufficiently powered sample for descriptive analysis and allow some sub-group analysis.

Recruitment

To help ensure the highest possible participation rate the survey will be promoted through a range of channels including BAPO, ACPIN, and the NHS Orthotics Network (www.networks.nhs.uk/nhs-networks/orthotics) and their national conferences (if timing is appropriate). Where practical we will take an evidence-based approach to ensure as high a response rate as possible;[27, 31] including at least two follow-up questionnaires.

Data collection

To inform the survey, in particular to develop a structured list of the different possible types of orthotic devices used for knee instability, and possible care pathways, focus groups will be undertaken in at least two locations in England. The questionnaire will then be developed, piloted and amended as necessary. This will use predominantly structured questions and responses. Depending on the findings from the focus groups, we will consider using a patient vignette approach to eliciting information about what devices are used in which circumstances, The survey will be conducted using SurveyMonkey. Key aspects covered will be:

- Demographic characteristics including years of post-qualification, experience in neuromuscular diseases and centre characteristics.
- The types of orthoses being used for people with neuromuscular diseases who have knee instability and what determines the type of device used, including how knee instability is assessed and what factors are taken into account when trying to treat it with an orthosis.
- Main sources of referral and care pathways.
- Whether they use any formal outcome measure to assess patient outcomes and what these are.
- Most important treatment outcomes from their perspective.
- Factors influencing the effectiveness of devices and their acceptability to patients.
- Whether they have any audit data on adherence or related issues that can be anonymised and provided for the study.

Analysis

Data will be downloaded from SurveyMonkey into Excel. Standard checks will be undertaken to identify and remove errors, for example for outliers, inconsistencies and omissions. The survey is exploratory and the analysis will be primarily descriptive. The response rate to the survey will be calculated and descriptive analysis undertaken of respondent characteristics to allow exploration of the representativeness of the sample. Descriptive analyses will be undertaken of responses to questions; frequency tables, summary statistics and cross-tabulations will be presented. Appropriate statistical tests for comparison of groups such as chi-squared will be utilised as appropriate. Where relevant, data will be sub-grouped by professional grouping, type of provider, for example orthotic services being provided as part of a multidisciplinary NMD service compared to orthotic services in a more generalist environment. Any free-text responses will be analysed using thematic analysis (see qualitative study for details). Any audit data will be collated and synthesised using systematic review approaches to collating data from different sources.

Costs of devices

A costing analysis of orthoses for knee instability will be undertaken. In order for costs to be appropriately assessed, both the device costs and the resources used need to be estimated. Although the fundamental cost of interest is the cost of the orthoses, there are a number of other key elements to the costing of the orthoses. Given that orthoses can be custom-made or pre-fabricated, information regarding the number of fittings required, the useful life of the device and any replacements and maintenance required will be essential. The time required from other health care professionals, such as physiotherapists, nurses, etc. will also need to be estimated and included in the costing analysis.

There are several combinations of orthoses available and the pricing of these devices can be quite varied. In addition there is likely to be variation in patient care pathways. The relevant cost categories will be identified and measured through direct elicitation from orthotists delivering services within the NHS, and other sources where necessary. A sample of orthotists, from the survey described earlier, will be identified by asking at the end of the survey whether they would be willing to provide contact details to be approached for further information.

A semi-structured interview, structured around a series of patient profiles will be used to elicit the information. The patient profiles, covering key aspects of patient pathways and the key types of orthotics used for knee instability in the NHS will provide a useful guide to ensure that all resources used and costs are included in the estimation. They will be developed based on information collected from the patients' focus groups and

interviews, and the orthotist/physiotherapist survey and focus groups. This direct elicitation should provide a clear insight into the useful life of the orthotic devices, the number of patient visits and the resources required to fit the devices, the number of fittings and refits required as well as the costs associated with the service provided.

Once all of the relevant cost categories have been identified and the identified costs have been measured, for example in time required, values will be placed on each of the cost categories to provide estimates for the relevant costs. Values for the costs will be estimated through a number of sources as relevant:

- Orthotists working in the NHS, clinic finance staff and manufacturers.
- The report compiled by the Personal Social Services Research Unit in the University of Kent Unit, "Costs of Health and Social Care 2012", will provide values for the cost of time required by other health care professionals, such as physiotherapists, nurses, etc.
- Up until 2010, the NHS Purchasing and Supply Agency (PASA) was the main health service purchasing organisation and would have provided estimates for the device costs under consideration here. This organisation has since been subsumed into various organisations, including the Government Procurement Service. For this report, the relevant organisation will be identified and the unit costs estimated from this source, or, if necessary, if the archived reports from NHS PASA become available (we have made initial enquiries and this is a possibility), the unit costs they contain can be inflated and actualised into 2014 prices.

Study objective 3: To identify the most important outcomes for patients

This objective will be met by using qualitative research methods to collate the views of people who have been fitted with an orthotic device for knee instability about what the important physical and psycho-social treatment outcomes are for them. Factors influencing the likely achievement of those outcomes within the context of the person's illness and care pathway will be explored.

Overview of approach

Building on the findings of the survey and systematic review in this complex and under-researched field, this exploratory qualitative research aims to:

i. Identify important outcomes among people who have been fitted with an orthotic device for knee instability across a broad range of diverse neuromuscular diseases;

ii. Explore the factors influencing the perceived likelihood of achieving the outcomes for those individuals within the context of their condition and care pathway;

iii. Undertake an in-depth examination of important outcomes and associated factors among people who have been fitted with an orthotic device for knee instability in 2-3 highly prevalent neuromuscular disease populations, for example, post-polio.

Aims i and ii will be achieved using one-to-one interviews in the participant's own home to collect data from a larger, diverse sample of participants in terms of their type of condition (and mobility), types of orthotic device(s) and demographic characteristics.

Aim iii will be achieved via a small number of focus groups (2-4) among a small sample of participants' experiencing a particular neuromuscular condition with instability of the knee.

Sampling

A total of 25-30 people with different types of neuromuscular disease (including CNS conditions) who are using an orthosis to manage knee instability will be interviewed. Purposive sampling will be used for the individual interviews to reflect a range of conditions, age, sex, length of time using an orthosis, high and low usage and region. The proposed sample of interviewees is likely to achieve data saturation whereby similar themes emerge.[32]

A total of two to four focus groups will be set up to examine the issues in more depth for a specific condition. Each focus group will include 5-8 people with one particular type of neuromuscular disease who are using an orthosis to manage knee instability. The final number of individual interviews and focus groups conducted will be determined by the need to achieve data saturation on the diversity and complexity of issues across and within conditions. A recent study investigating the experiences of lower limb prosthetic users, which used similar methods, found that saturation was achieved after six focus groups and 10 interviews.[33]

Recruitment

To help ensure that a range of views are captured, participants will be recruited from a range of sources: charities such as Muscular Dystrophy Campaign, Polio Survivors Network, British Polio Fellowship, Charcot-Marie-Tooth UK and through NHS orthotics clinics that the co-applicants are connected with. A patient information sheet will be developed providing details of the study, together with a consent form and a form to elicit demographic characteristics.

Data collection

The protocol and topic guides will be subject to standard research ethics and governance approvals. The interviews and focus groups will be conducted in person in accordance with the study protocol by experienced qualitative researchers. Under exceptional circumstances, an interview may be conducted by telephone if necessary. The protocol will detail introductory procedures, appropriate use of prompts, strategies to overcome literacy difficulties and mechanisms to encourage discourse between group members as well as participation from all participants within the focus group.

A topic guide will be developed for the focus groups and interviews. The guide will be developed in consultation with the patient advisors on the project and then piloted with a user of orthotics for knee instability and amended as necessary.

The topic guide will be designed to elicit information on people's experience of wearing an orthosis for knee instability within the context of their own condition and their care pathway. Two key aspects on which views will be sought are what the important treatment goals and outcomes are for them and factors related to usage and perceived acceptability and effectiveness of the device.

With the permission of participants interviews and focus groups will be recorded.

Analysis

Recordings will be transcribed verbatim by approved transcribers and anonymised. Data will be transferred using secure, password protected and encrypted methods in accordance with the Data Protection Policy for University of York. A thematic analysis will be undertaken using the six phases outlined by Braun & Clark (2006).[34] In summary this will involve reading and re-reading the transcripts and coding line by line in a systematic way, collating data relevant to each code. Codes will be collated into potential themes, reviewed and a thematic map developed. This is an under-researched area and the views and experiences of this group of patients are not well known. Therefore, an inductive approach will be undertaken which identifies themes in an inductive or "bottom-up" way as opposed to a theoretical or "top-down" way.[34] The Braun & Clarke (2000) checklist of criteria for a good thematic analysis will be followed.[34]

Where appropriate, data from the in-depth interviews will also be examined on a case-by-case basis using phenomenological research methods to examine the perspective and experience of the individual in relation to their own condition and care experience.[35 36]

A second researcher will check for accuracy a sample of data transcripts against the audio recordings and will interrogate the validity of the codes against the raw data. Data will be entered into Atlas-ti for thematic and phenomenological analysis.

Write-up

Methods and findings will be described and presented by theme and individual case-studies in accordance with data reporting requirements for the HTA Programme. Subject to funders' approval, the protocol and key findings will be published in peer reviewed journals. A short summary of study findings will be distributed to study participants and other patient and interest groups.

Study objective 4: To identify any implications for clinical practice, any gaps in the evidence and what the research questions to be answered next are

To meet this objective the three sources of evidence, from healthcare professionals, patients and the systematic review, will be interrogated and the different sources will be integrated. For example we will compare outcomes of importance to patients (derived through the qualitative study) with the outcomes that are being used to measure effectiveness in clinical trials (derived through the systematic review) with any formal outcome measures that are being used to assess patient outcomes in clinical practice (derived through the survey of

healthcare professionals). Similarly we will explore whether there are any disparities between the devices being used in clinical practice and those being evaluated in research studies.

In order to inform the substantive future research question identified in the research brief ("What is the clinical and cost-effectiveness of different types of orthotic management of the knee in people with neuromuscular disease") implications for future research will be informed by gaps in the effectiveness evidence (systematic review), the care pathways currently being used in clinical practice, the types of devices in use in the NHS for knee instability and their associated costs (survey and healthcare professional focus groups), factors determining whether prescribed devices are used, and important outcomes to patients (qualitative study).

Implications for practice, evidence gaps and future research priorities will be clearly linked to the evidence source from which they have been derived.

PROJECT MANAGEMENT

The project will be undertaken at the University of York led by the principal investigator. The York research team will have formal project meetings on at a monthly basis and other meetings as and when required. The Project Steering Group/Advisory Group will consist of the York research team, the other co-applicants and 2-3 patient public members. This group will meet face-to-face on three occasions with other meetings as required by tele-conferencing. During the first months of the project the research protocols for the individual components will be finalised and registered with the appropriate bodies (PROSPERO for the systematic review and ISRCTN for the qualitative study).

Project Timetable: 1 April 2014 to 31 March 2015

TASK	1	2	3	4	5	6	7	8	9	10	11	12
Systematic review												
Protocol development (including PROSPERO registration	■											
Literature searches		■										
Screening and study selection		■	■									
Data extraction, quality assessment, checking			■	■								
Synthesis					■							
Write up						■						
Survey												
Focus groups and design survey		■	■	■								
Publicise and undertake survey				■	■	■						
Analysis							■					
Costing							■	■				
Write up									■			
Interviews & focus groups with patients												
Protocol development (ethical approval & ISRCTN registration)	■	■	■	■								
Identify and recruit sample					■	■						
Undertake fieldwork						■	■	■	■			
Transcription, coding and analysis							■	■	■	■		
Write up											■	
Report												
Collate evidence from each element and draft overarching report											■	■
Draft other outputs												■
PROJECT MANAGEMENT												
Project Group Meetings	*	*	*	*	*	*	*	*	*	*	*	*
Steering Group Meetings	*					*					*	

ETHICAL APPROVALS

We will recruit users of orthotic devices mainly through patient groups and charities. However we may recruit some patients through the NHS and we will therefore seek NHS Research Ethics Committee (REC) approval and any relevant research governance requirements. We will prepare patient information leaflets and consent forms which comply with latest guidance from the National Research Ethics Service (NRES).

Based on the NRES guidance as to what constitutes research requiring review by a REC, we understand that the data we will be obtaining from orthotists is classified as clinical audit and does not require REC review. The systematic review does not raise any ethical issues and does not require REC review.

DISSEMINATION AND PROJECTED OUTPUTS

The groups who should be interested in this project include those involved in the prescribing, supplying, and training in the use of orthoses; those using an orthosis, carers, support organisations; researchers; and those making policy and commissioning decisions related to practice or future research.

It is anticipated that within this diverse target audience the level of understanding of the research methods to be used will vary considerably, presenting the opportunity to use an innovative approach. Our dissemination activities will aim to engage with the audiences throughout the project to promote understanding of the aims and methods, involvement where appropriate, and culminating in dissemination of the findings. The key vehicle for this engagement will be a project specific blog which anyone can sign up to read, receive email or tweet alerts to new content, and which can also be linked to organisational sites such as charity websites. The blog site will include a lay overview of the whole project, updates on progress from different perspectives, and finally the summary of findings on completion.

The blog will be coordinated by a specialist in dissemination and written by members of the research team, with potential for inviting guest blogs from relevant parties. The aims of the blog will be to:

- Raise awareness of the project. The blog will be used to promote and encourage orthotist and physiotherapist participation in the survey (Study objective 2) and provide support information for patients considering taking part in the one to one interviews or focus groups (Study objective 3).
- Provide an ongoing update of progress
- Provide a focus for developing a project specific network of interested individuals, groups and organizations
- Promote a feeling of being part of the research and encourage a high response rate when asking for information about current practice
- Raise awareness of how systematic reviews are carried out
- Potentially provide a mechanism for moderated feedback and comment
- Provide a mechanism for distributing a summary of the findings with links to the full report on completion
- Potentially offer the opportunity to follow up on the impact of the results
- Potentially establish a network for future research in this area

Details of the blog will be sent to relevant networks and organisations, such as the British Association of Prosthetists and Orthotists (BAPO), Association of Chartered Physiotherapists Interested in Neurology (ACPIN); and the NHS Orthotics Network; to relevant charities such as Muscular Dystrophy Campaign, Polio Survivors Network, British Polio Fellowship, and Charcot-Marie-Tooth UK. We plan to evaluate whether this approach to engagement and dissemination is useful by assessing usage and obtaining the views of users at the end of the project in order to inform future projects. On completion of the project we will produce:

- A short lay summary giving brief background details, information about the quality of evidence, the results and implications to inform all relevant parties. Distribution of this summary report will use the networks already identified, those developed through the blog and any other groups who may have a general interest in the topic (e.g. GPs, neurologists, orthopaedic surgeons).
- The publication of the findings will be news released.
- The potential for short articles on the websites of interested organisations and in other relevant lay media will be explored.

Additional dissemination activities will include the submission of papers for peer-reviewed publication and submission of abstracts to conferences, including one international conference. All dissemination activities will involve signposting those interested in further details to the full NIHR HTA report.

PATIENT AND PUBLIC INVOLVEMENT

We plan to recruit 2-3 patients to our advisory group. Neuromuscular disease covers a wide range of conditions and we recognise that it will be important not to focus on a single condition at the expense of others. We will aim to have people with a range of conditions on the advisory group where knee instability is a prevalent problem. A role description will be developed and advertised through relevant charities and support groups.

We will ask patient members to give their views on (i) the survey questionnaire of healthcare professionals and the topic guide and patient information leaflet for the qualitative study; (ii) lay summaries of the project; (iii) the implications for clinical practice and future research; and (iv) the planned non-technical summary. People who join the group will receive an induction informing them about the team and the planned project. They will be offered the support of a mentor from the advisory group, if they wish.

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Appendix A: Draft search terms

	Term	***No. of hits***
1	exp Neuromuscular Diseases/	(236745)
2	exp Orthotic Devices/ or Braces/ or Splints/	(16004)
3	Knee/ or Knee Joint/ or Ankle/ or Ankle Joint/ or Foot/ or Foot Joints/ or Foot Orthoses/	(75592)
4	2 and 3	(1782)
5	("knee ankle foot" or KAFO or KAFOs or SCKAFO or SCKAFOs or AFO or (((KAF and system*) or knee or "ankle foot" or foot) and (device* or brace* or bracing or sling* or splint* or orthos* or orthot*))).ti,ab.	(7297)
6	4 or 5	(8061)
7	1 and 6	(384)