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SIRJIA

Steroid Induction Regimen for Juvenile Idiopathic Arthritis

Protocol

Version 5.0, 26th September 2018

Trial Sponsor:
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1. Full title of project:

Steroid Induction Regimen for Juvenile Idiopathic Arthritis (JIA)

2. Summary of Research:

Background

In the UK, JIA is the most common inflammatory disorder in childhood. Arthritis activity is measured using a combination of clinical variables known as the core outcome set (COS) and this study will build on a previous published literature review (1) and work from the Single Hub Access for Rheumatology in Europe (SHARE) (http://www.ped-rheum.com/content/11/1/5) European Union work package specifically focusing on JIA and its treatment. We are co-investigators in the Childhood Arthritis Prospective Study (http://www.caps-childhoodarthritisprospectivestudy.co.uk/), the largest incident cohort study of JIA worldwide, which has delivered one publication on the Health Economics of treating arthritis (2) from those study data with a second follow up paper in preparation. From this we believe that it is important to understand why and how clinicians and patients together choose to use, or even more importantly, to reject different modalities of steroid treatments in JIA without a firm evidence base and where some delivery methods may be more costly than others. An example of the need for this concerns intra-muscular Depot-Medrone. We are aware it is currently rarely used in childhood JIA and yet is a main remission induction modality used in adult RA treatment (3).

Early and as complete a remission inducing treatment as possible in inflammatory presentations and disease flares has been shown to be important in reducing the perpetuation of chronic disease and prevention of long-term damage (4) Although DMARDS, especially methotrexate, are well established in the treatment of JIA they are slow to act if used alone. This can leave the inflammatory process essentially unchecked for 6-12 weeks. Biologic drugs may be highly effective in early disease but there are no guidelines that include immediate use of these agents at diagnosis or as intermittent pulsed treatments to control flares. This is because of a combination of the cost of the biologic drugs as well as possible long-term, as yet unknown, safety issues leading to the reasonable reserving of these drugs for second-line treatment. The concept of TIGHT control (5-8) is established in adult rheumatoid arthritis treatment with additional agents or increased doses of existing drugs added at frequent clinic review until remission is established where all regimes include the use of steroids. It is not known how many UK centres treating JIA adopt this approach. Routes and doses of corticosteroids (CS) are all based on physician preference. Some units use high dose methylprednisolone IV infusions from 1-3 consecutive days on 1-2 consecutive weeks. Patients may then be changed to oral steroids or intra-articular injections to treat joints remaining active. In adult RA, treatment flares are often treated with IM injections of CS. In paediatric practice the IM route is not used very often but the reasons for this are not clear: clinicians who use this route anecdotally describe good treatment responses and excellent patient acceptability, but the extent of such practice is currently not known. It is possible that the IM route would be rated as too painful for use in childhood but this has not been formally studied. Conversely, the IM route may provide better long-term remission, being the cheaper route with the lowest steroid adverse event burden. However, this is uncertain in the paediatric clinical setting so this study will include addressing the acceptability of including the IM modality in a final trial protocol.

Intra-articular steroid injections (IACIs) are frequently used to control individual joints but it is not known whether the steroid in this method is functioning as a *defacto* steroid depot to distant joints as well acting directly on injected joints. In some patients multiple IACIs are performed and repeated without the use of additional DMARDs. Upwards of 20 joints are injected at one time in some patients. IACIs are sometimes performed with conscious sedation (inhaled nitrous oxide – Entonox) but multiple injections require a general anesthetic in theatre, often with X-ray or ultrasound guidance.

It is not known whether the best steroid route for long-term remission is either the direct IACI route given to any inflamed joint or a larger IV "pulse" dose (rapidly effective but with shorter duration of action). The moderate oral dose route may give a smoother steroid profile but it is not known whether the response is as complete and/or whether the side effect profile is higher. IM use is intended to act as a slow release preparation. Views on these different routes will be obtained in this study as well as the choice of the steroid dosing regimes to be followed in each delivery route.

There have been no studies of patient preference in the choice of routes. There have been no head-to-head studies of steroid induction regimes to assess non-inferiority in efficacy terms, patient acceptability, PK/PD of different routes, overall steroid burden and the frequency of steroid related side effects between the different routes of administration.

3. Research Methodology

This study will encompass:

a) A national survey with stakeholders including healthcare professionals (HCPs) (paediatric rheumatologists, paediatricians with a specialist interest in rheumatology, adolescent rheumatologists with expertise in JIA, specialist nurses in paediatric rheumatology).
i. Current practice including: criteria for starting CS, the proportion of patients with JIA receiving CS, the timing of reviews and dosing criteria with any systemic CS reduction regimes as well as the number receiving more than one CS modality.
ii. Capability, including: the proportion of GCP-trained nursing/medical staff, out-of-hours consultant/ research nurse and clinical nurse specialist cover, number of available day case facilities for in-hospital CS delivery needed for the IM, IV and IACI routes (occupancy, staffing ratios, etc.).
iii. Acceptability, in broad terms, of a randomized clinical trial on use of each of the four CS delivery methods in different JIA subtypes and patient age groups. This component will also assess the barriers perceived by HCPs (identified from Survey Monkey) to accepting a treatment regime as a trial arm when this is not part of the current treatment choice for the team.

b) Determining the choice of primary outcome and CS treatment regimes for the future clinical trial in JIA through:
i. Review of literature, review of the latest revision of the EMA guideline on JIA trial design, review of the outcomes of the SHARE conclusions
ii. Stakeholder Consultation

- Survey and Stakeholder Consensus Process of parents/patients and HCPs to achieve consensus on the primary outcome, inclusions/ exclusion criteria and treatment modalities
- Stakeholder Meeting (using Formal Consensus Techniques) to present and discuss the findings from the structured survey on the parameters of the proposed trial. Combined HCP and Consumer/PPI consensus meeting will be held to identify the primary outcome measure, acceptability and treatment decisions around choice of CS induction

regime, aspects of the feasibility trial design including type and timing of intervention, barriers to recruitment.

iii. Qualitative study of patient/parent experience in the use of CS and a future trial involving randomization between deliver routes. Patients (>8 years) and parents will be sampled from the co-applicant centres where one or more of the delivery routes are used.

c) Conducting a prospective feasibility study collecting data on newly diagnosed JIA patients receiving CS treatments focusing on the JIA disease subtype, the doses and routes given, and on data relevant to the primary outcome results at baseline and at 6 weeks and 12 weeks post commencement of the steroid therapy with assessment of chosen definitions of remission from changes in primary outcome measure over the 12 week study period. The number of newly treated patients with CS in each JIA subtype will be determined to allow for accurate power calculations to be made for a potential future randomized trial.

d) Preparation of a Project Report concluding whether a definitive trial is feasible based on defining the appropriate eligibility, sample size, primary outcome, and choice of CS interventions and the route for the control arm, based on **a**-**c** above.

4. Background and Rationale:

Compliance with HTA Commissioned Brief:

This application addresses directly the HTA commissioned brief arising from the important clinical question of the initial treatment to induce remission of JIA initially and in management of significant disease flares. CS have been used in the treatment of JIA since the 1950s. It is well known that CS can transform disease activity in JIA and that the majority of JIA patients receive CS during their care. However, the clinical practice of using high dose CS for a limited period, to downgrade the inflammatory response aiming to induce initial remission, is not evidence-based although it is in widespread use. A literature search and horizon scan for this application found only 4 intervention studies of CS in JIA all relating to IACI with only 2 RCTs. No intervention studies and only 13 observational studies were identified for other forms of steroid treatment with 2 prospective studies examining the current management of JIA including oral steroids (9, 10). Damage in JIA occurs from joint erosions leading to cartilage loss and bony eburnation with resultant pain, functional disability and increased need for early joint replacement (11). Disorders of local bone growth as well as overall growth in height are frequent in inadequately controlled disease (12, 13). CS would be used as part of most tight control regimes and yet in a relatively recent evidence summary it was concluded that there is a "near complete lack of published evidence" for the use of systemic glucocorticoids in JIA (14). Additionally Dueckers (15) states that "There are no controlled trials and no standardized therapeutic regimes for the use of systemic glucocorticoids". It is well known and reported that CS are used frequently in induction of remission in JIA (16). Most clinical trials of therapeutic agents in JIA have attempted to control for CS effect by controlling the allowed changes in CS dosing. However, no trials have directly compared the different steroid induction regimes themselves while controlling for other DMARDs and/or biologic agents.

Route of CS administration:

There are currently four routes by which CS are administered; orally, IV, IM or IACI: the only informative evidence-base of effectiveness and efficacy is for IACI. However, the above routes, either alone or as a combination of delivery routes, are widely used on the basis that that the initial systemic CS suppress the severity of inflammatory response and reduce the number of active joints that eventually require IACIs. Many patients receive more than one route of CS

delivery but selection of route and the comparative outcome of the different routes and dose are not supported by a robust evidence-base.
Although there are non-evidenced-based statements in the literature that systemic CS are rarely used in JIA, the Childhood Arthritis Prospective Study (CAPS) (17) provides valuable data. In total, 1477 new cases of JIA from six UK centres have been recruited and followed up and 340 of 759 (45%) with 3 years of follow up received oral, IM or IV steroids. However very few patients are treated with IM injections (n=8) compared with oral steroids (n=265), IV steroids (n=191) or IACIs (n=603) (Professor Thomson, Chief Investigator, personal communication).
Patient/family acceptability and physician decision-making processes play a large part in differences of route of administration. A RCT comparing the different routes of CS administration is unlikely to succeed unless the reasons behind treatment decisions are understood along with willingness to randomize patient treatment choice. There is paucity of robust data for the most commonly used CS regime used nationally which would be chosen as the comparator arm.

Safety, Clinical and Cost Effectiveness of CS in JIA:

High dose CS and CS given for protracted periods result in significant adverse drug reactions (ADRs) including reduction in growth in height, weight gain, facial puffiness, striae, acne, behavioural issues and sleep alteration, immuno-suppression, increased blood pressure, hirsutism, propensity for diabetes, cardiovascular complications and osteoporosis. Subcutaneous fat atrophy occurs in approximately 8% of IACI, but rates of ADRs from other routes of CS administration are not known. It is essential to optimise the CS dosage to maximise benefit with minimum cumulative dose-related ADRs.

CS have a significant effect on halting radiological progression of rheumatoid arthritis. There are still large differences in doses, health care costs & patient burden between the different CS treatment regimes across the UK. There are no head-to-head comparisons of CS with studies controlling for other treatment modalities such as DMARDS or biologic agents, although steroids are frequent concurrent medications in clinical trials in JIA. There has been no systematic data collection of ADRs associated with different routes of treatment and yet this is an important part of the risk benefit ratio needed in clinical choices of treatment.

Available evidence includes:

(1) A Cochrane review (18) included 15 RCTs (1,414 patients receiving steroids in the first 2 years of treatment). A small RCT in 22 patients with systemic onset JIA found that IV methyl prednisolone in combination with low dose oral prednisolone had a better response than with oral prednisolone alone (19).

(2) Data from a study of the treatment of JIA by IACI demonstrated that IACI triamcinolone hexacetonide was superior to triamcinolone acetonide with a longer duration of action & a lower relapse rate (20).

(3) A British Society of Paediatric and Adolescent Rheumatology (BSPAR)-led audit of steroid use in 2006 received data from 3 of the then 12 tertiary paediatric rheumatology referral centres approached and 2 of 7 DGHs with paediatric rheumatology clinics approached. Results noted that amongst 86 cases of all JIA subtypes receiving steroids in the previous 2 years, 68 cases (79%) received IACIs and 9 cases (10%) received oral steroids alone. Only one case (1%) received IV steroids and 2 cases (2%) received IM alone with the remaining 25 cases (29%) receiving a combination of steroid delivery routes. Of 39 treatment episodes of IV methylprednisolone the doses used were uniform. Three cases (3%) received different doses and types of IM steroid. However with such a low response to this audit the results are not

generalisable. The low response rate also highlights difficulties with busy units supporting clinical studies, something that this feasibility study seeks to address.

Poor disease control in JIA is linked to long-term joint damage and secondary physical and emotional debility. The long-term HE costs are significantly increased if eventual joint replacements are required. There is a documented reduction in employment prospects for patients with JIA despite higher than average educational attainments, probably linked to long-term joint damage. There is a window of opportunity in inflammatory arthritis to permanently downgrade the inflammatory response. Early aggressive treatment regimes using CS are frequently employed in JIA in an effort to achieve "tight control" and prevent joint damage. There is wide variability between centres, clinicians and patients in CS regimes used with no head-to-head comparison of efficacy and patient acceptability. It is not known whether different steroid regimes are more or less effective in any of the 7 JIA disease subtypes. Good control of arthritis reduces immediate patient morbidity improving mobility and skeletal health reducing joint damage and systemic complications such as secondary coronary artery disease (known to be significantly raised in adult rheumatoid arthritis & with some suggestion of similar risks in childhood disease). The clinical aim of using steroids for short high dose treatment courses at initial induction of remission and subsequent flares is to reduce the duration and cumulative steroid dose of lower dose but longer lasting steroid courses (usually given by mouth).

It is possible that the long-term concurrent use of DMARDS or the very expensive biologic drugs could be reduced or avoided in some patients by repeated short courses of systemic steroids or by the use of multiple and repeated IACIs but this has not been studied. The advent of DMARD and biologic treatment has led to an impression of a reduced role for steroids in JIA but available databases such as CAPS show that steroids are still commonly used in JIA. The annual cost of the average biologic drug is over £10,000 (21). If even a few patients were prevented from needing biologic treatments by satisfactory suppression of inflammation from timely steroid doses with or without cheaper DMARDS then the HE effect of evidence-based CS use would be marked.

Important Outputs of Proposed Feasibility Study

Many randomized controlled trials find recruitment difficult if clinical teams are not involved in the development of study protocols and therefore are not committed to the study through the ownership of the study questions and need for the evidence. The design of this feasibility study has been planned to maximise HCP 'buy in' to a final RCT by adapting the protocol and outcome measure choice following literature review, extensive surveys, qualitative interviews and structured survey and Stakeholder Consensus process of opinions and refining agreements in areas of difference.

A head-to-head RCT of different CS regimes is the eventual goal. However, the difficulties in achieving such a study are such that a detailed feasibility study as planned is essential to discover whether such a RCT is acceptable and achievable and whether the results will be meaningful.

Irrespective of whether the findings of the feasibility study suggest that a future full trial is possible, this study will generate significant outputs of value and impact to the wider national and international research community and the NIHR in terms of the joint consumer and HCP choice of primary outcome, treatment preferences, and a wider UK paediatric rheumatology unit engagement with research by the active engagement with the research question and protocol development. Although a subsequent definitive trial is essential, benefit to patients and the NHS from this feasibility study will contribute additionally in the following ways:

i. Definitive evidence-based guidelines will be produced on how and when to initiate CS treatment in the different subgroups of JIA based on their efficacy as remission inducing agents. This will enable evidence-based clinical care pathways to be written, which should result in

standardised treatment and care. This should reduce disparities in the treatment of JIA especially between tertiary and secondary care settings.
ii. Definitive guidelines could potentially decrease the long-term disease related damage and potentially reduce the need for escalating treatment to include biologic treatments in some patients by timely and complete induction of remission using steroids and DMARDS alone. Reducing disease severity could also decrease post-inflammation joint damage, reducing pain and disability. This would directly benefit patients and families, and the NHS by reducing healthcare utilization in adult life particularly in terms of the need to joint replacements and possibly by reducing the need for long-term use of biologic agents in JIA patients.

5. Evidence explaining why this research is needed now:

This research is needed now because:

a) This study question was one of the first research questions prioritised by the Paediatric Rheumatology CSG research strategy in May 2009. This widely used treatment modality has side effects inducing the most anxiety in patients and families. This priority has been re-emphasised in revisions of the CSG Research Strategy in 2011, and again in 2014 including direct input from the CSG consumers.

b) Standardisation of JIA treatment is needed as the delay in disease control is linked to speed of remission induction. There is large variation in JIA treatment rates and actual choice of CS treatment regimes as expected from the lack of evidence-base. Consensus treatment guidelines in JIA are being produced by the SHARE process but do not include the steroid regimes to be used. The differences cause confusion and complicate analysis of outcome data from other studies such as the biologic drug long-term safety registry studies.

c) An assessment of the effectiveness of the four CS delivery routes with possible combinations of routes is needed, and their respective indications and acceptability established.

d) A well-run feasibility study is needed before any definitive trial particularly in an area with so many potential variables. Undertaking a definitive RCT is inherently costly. Undertaking a definitive study where national practice is so varied, stakeholder acceptability unknown and without an agreed primary outcome therefore poses significant and unnecessary risk when this feasibility study will directly address these questions. The patient numbers in each group may prove to be too small to make a full trial justifiable. The numbers of possible treatment combinations and JIA subtypes will require a clear rationalization made possible by a final Discussion and Consensus Meeting. This detailed feasibility study, undertaken before a definitive trial is an absolute prerequisite and will provide important outputs whatever the final recommendations regarding a full trial.

6. Aims and Objectives:

Specific study aims include:

***Research Aim I*:**

Establishing current practice to establish the numbers of patients with varying severities of JIA attending hospital and requiring CS treatment and HCP capacity to deliver a RCT.

Objective research questions (RQ):

RQ 1: What types, routes and doses of CS are used?
RQ 2: What clinical criteria are used for commencing CS and choosing route of administration?

RQ 3: What are key issues/concerns with regards to capacity and capability in the conduct of a future randomised clinical trial?

RQ4: How many potentially eligible children and young people attend hospital in the UK with varying severities of JIA requiring CS treatment who could be randomised in a comparative treatment study?

Fulfilling the commissioning brief: This will characterise current practice and inform an estimate of eligible patients for a future RCT.

Research Aim II

To determine the control, intervention and patient group(s) for a future RCT and establish HCP willingness to randomise and likely consent rate

RQ 5: What characteristics would HCPs and parents/patients want to see included in a future RCT on CS in JIA? Which patients should be included/excluded? What would be the most appropriate control in a future trial? How would active disease or a disease flare be defined?

RQ 6: How willing would patients/parents be to consent to be randomised in a future clinical trial and how willing would HCPs be to randomise?

RQ 7: How would patients/parents preference for mode of CS delivery influence their willingness to participate in a future RCT?

Fulfilling the commissioning brief: This will identify clinician- and patient-directed control and intervention for a RCT and inform randomisation and consent rates in a RCT.

Research Aim III

To choose the primary outcome for use in a future clinical trial of CS in JIA

RQ 8: What primary outcome is important to HCPs?

RQ 9: What primary outcome is important to parents/patients?

RQ 10: What would a minimally important clinical difference be for any potential primary outcome?

Fulfilling the commissioning brief: This will identify the primary outcome.

Research Aim IV

To conduct a prospective observational study of newly diagnosed patients with JIA fulfilling the proposed inclusion/exclusion criteria who naturalistically receive proposed control or treatment arms, to observe change and variance in primary outcome over a 12 week period in order to inform the precision of the sample size calculation.

Fulfilling the commissioning brief: This will inform the sample size estimate for the RCT and further characterise the estimate of eligible patients for the RCT.

Research Aim V

To develop a report for the HTA Programme on the feasibility for a definitive study defining design, control and intervention arms, with recommendations to the inclusion and exclusion criteria, primary outcome, sample size based on primary outcome and subtypes of JIA to be included.

Fulfilling the commissioning brief: This will define the feasibility (yes/no) of a future RCT and the key parameters to prepare a full RCT proposal if feasible.

7. Research Plan

We intend to use a mixed methods study design in order to address the research aims and questions (Flowchart) in developing and delivering a national feasibility study.

This feasibility study will include:

a) A comprehensive assessment of current UK practice as regards JIA CS treatment, and potential trial capability and acceptability. A national survey of current clinical practice among HCPs (paediatric rheumatologists, paediatricians with a specialist interest in rheumatology, adolescent rheumatologists with expertise in JIA, specialist nurses in paediatric rheumatology) involved in the care of children and young people with JIA delivering informative data on:

Survey of current practice including routine care of patients with JIA, types of steroid regimes in use, criteria for starting CS, numbers and proportions of patients with different subgroups of JIA attending paediatric rheumatology services who receive CS (RQ 1, 2, 3, 4) and data on the number children and young people with different severities of disease and disease duration pre-treatment, duration of flare pre-treatment will also be collated from purposively chosen hospitals (RQ 1,4) through prospective screening logs .

Capacity and capability questionnaire including proportion of GCP-trained nursing/medical staff (RQ 3).

b) Ascertainment of HCP views on the most appropriate patient group(s) and control and intervention arms for a future RCT investigating the effectiveness of and optimal thresholds for CS use (RQ 5). This will be collected through:

i. A structured survey (linked to a) above)

ii. Stakeholder* Consensus meeting on any aspects not achieving consensus in the structured survey and will be agreed through a Stakeholder Consensus Process.

c) A qualitative study of parent and patient perspectives of future RCT of CS including: parent/patient perspective on the most appropriate modes of CS delivery to include in a RCT (RQ 5); acceptability in broad terms for a clinical trial on CS use of children and young people with JIA (RQ 6,7). A specific output will be knowledge of family acceptability of randomisation to different regimes in a final RCT.

d) The choice of a primary outcome measure for a clinical trial in children and young people with JIA through:

i. Updated review of literature - (RQ 8-10)

ii. Structured survey of HCPs and PPI partners to establish candidate primary outcome measures for the future RCT (RQ 8-10).

iii. Stakeholder* Discussion Groups of parents and young people to achieve understanding of the choice of primary outcome measure to be considered for the future RCT (RQ 8-10) prior to Stakeholder Consensus Process of HCPs and PPI partners.

* Engagement with HCPs and parents to address Aims II/III will use the qualitative interviews and the same structured survey of outcome measures completed by HCPs and PPI partners.

The PPI discussion group with be followed by a Stakeholder Consensus meeting aiming for equal numbers of professional and PPI partners having equal voting rights to establish the primary outcome important to HCPs and to parents/ patients. PPI discussion group will meet prior to the full Stakeholder Consensus meeting to allow for full explanation of the aspects to be voted on in the final round of combined PPI and HCP consensus process.

A final Discussion and Consensus Meeting will have PPI consumers' representation, and health care professionals. This will also be used to feedback the summary results of the study to participants and where appropriate a consensus approach will be used again to finalise any remaining areas of lack of agreement on the final trial design to be recommended. This meeting will be multi-disciplinary and will cover aspects of trial design including capability, capacity, randomisation, type and timing of intervention, definition of usual standard care to be comparator arm, treatment threshold criteria, minimally important differences in potential outcomes, need for pilot study, 'blinding' etc. It will discuss methods to address any identified potential barriers to participation in a larger study as well as the acceptability of a future randomised trial.

e) Undertake a prospective feasibility study for the early induction of remission in children and young people with JIA testing chosen primary outcome, treatment arms and JIA subgroups to be studied. (Research Aim IV)

f) Writing of outcomes of feasibility study including a report to HTA with assessment of the proposed intervention and control arms for definitive study based on a)-e) above (Research Aim V).

Study Team expertise:

The assembled team has extensive multidisciplinary paediatric rheumatology clinical expertise (EM, MWB, HF, FMc, MR, AR,) and includes patient and public involvement (PPI) representative (SS). Our team has extensive, highly relevant methodological experience in: feasibility studies/structured surveys of practice (CTU/PW, HG, AJ), qualitative research assessing parental perceptions and experiences in challenging settings (BY); consensus methods (MWB, HF, MP).

8. Health technologies being assessed:

To determine the feasibility of a RCT to compare efficacy of potential CS delivery regimens (namely IACI, oral, IV pulsed, or depot IM injections or a combination of routes) in induction of treatment response and remission in patients with newly diagnosed or flaring JIA. Total CS exposure, development of CS side effects, acceptability to patients /families for each treatment regime will all be important secondary outcomes.

9. Design and theoretical/conceptual framework:

We will use a mixed method design to enable data triangulation (22, 23). This will provide different forms of data from multiple perspectives and will allow the production of a complete picture to help address the research aims (24). Methods will include: a national survey of -practice, screening logs, qualitative interviews with patients and parents, choice of primary outcome measure through structured survey, discussion group and Stakeholder Consensus meeting with equal HCP and PPI involvement and a feasibility study of data collection using the chosen primary outcome. Convergence of qualitative and quantitative research methods involving patients, parents and HCPs will enable us to produce data, which is both complementary and corroborative. A pragmatic approach will be used to synthesize the different types of data.

10. Target population for the pilot study:

Target populations: Patients <16 years with JIA requiring CS treatment for induction of remission at initial presentation or during future disease flares.

11. Inclusion/Exclusion Criteria for the Prospective Feasibility Study:

Inclusion criteria for the feasibility study

Participants: We will include children and young people up to 16 years of age with a new diagnosis of JIA or with flaring disease requiring induction of remission. Subtypes of JIA to be included will be confirmed by the consensus process.

Exclusion criteria for the feasibility study

a) Any patient with arthritis as part of another disorder such as a connective tissue disease

b) Any patient with JIA and haemophagocytic lymphohistiocytosis complicating their JIA where current standard of care will be used as treatment. Details and reasons for exclusion will be noted on the screening log.

c) Any patient with JIA and severe infection complicating their JIA at the time of disease flare. Details and reasons for exclusion will be noted on the screening log.

12. Setting/context:

This study will take place in any of the UK's tertiary or secondary paediatric rheumatology centres that have access to NIHR CRN research support staff to enable data collection or where a nominated research lead will commit to data collection.

13. Search strategy:

We will be undertaking review of literature, review of the latest revision of the EMA guideline on JIA trial design, review of the outcomes of the SHARE conclusions. As described in our response to the Board's comments, this will not be a systematic review.

14. Sampling

Overall Sampling Strategy: Sampling strategies designed by this research team for mixed method feasibility and pilot studies have already proven successful (e.g. NIHR funded UKCRN 10194). Eligible parents and patients who meet the inclusion criteria (Section 11), will be identified and approached by local NIHR CRN nurses or research lead or on the basis of previous involvement in previous NIHR CRN listed studies in rheumatology.

a) ***National Survey of Clinical Practice and HCP views on the most appropriate patient group(s) and control and intervention arms for a future RCT***

We will purposively sample HCPs (medical, nursing, AHP) with expertise in JIA from NHS Acute Trusts. We will identify a lead HCP at each site to ensure optimal penetration among JCPs for the survey.

b) Prospective Screening log

Paediatric rheumatologists at tertiary and secondary sites identified in 14 a) will be invited to provide screening log data on JIA patients treated with CS. These sites will be chosen to reflect different types of hospital (secondary/tertiary centre) in different regions. Completion of screening logs will entail identifying all patients who meet the inclusion criteria, treated with CS in the study period. The study will increase the opportunities for patients with all subtypes

of JIA including oligoarticular JIA to be included in a research study where most DMARD and biologic RCTs have excluded them. Sample size cannot be determined prior to data collection as this will be dependent on admission/attendance rates.

c) Stakeholder involvement in Structured surveys and Discussion Group and Stakeholder Consensus Meetings

The aim of sampling for the structured surveys and stakeholder consensus meeting is not to achieve generalisability or statistical representativeness but to explore a wide range of viewpoints amongst a diverse group of people who have relevant experience. The consultation process will be a sequential process with the issues identified through a structured survey, which require a consensus meeting obvious through the process. If areas of significant disagreement remain towards the end of the study with regard to the final protocol recommendations then a second survey process and second consensus meeting will be used after all results are known. We will identify and select potential participants for structured surveys and the consensus meeting in the following ways:

i. Eligible parents and young people for all aspects of the study: We will identify from interested sites and through our PPI co-applicant's links to consumers websites. Sites will display posters in clinical areas advertising the study to facilitate recruitment, as well as clinician approaches to suggest involvement. Parents will be supplied with the following:

- Information on how the findings from this research will be used to inform the development of a clinical trial.
- Participant information sheet (PIS) and consent form.

Parents and patients who register interest will be purposively sampled (e.g. patient's age, gender, experience of CS treatment and subtype of JIA). Options of involvement include a structured survey, patient discussion groups and Stakeholder Consensus Meeting, or qualitative interview. The consensus meetings will take place in North West England so the option of taking part in either an interview or structured survey has been provided to encourage the involvement of parents and patients from other parts of the country. Parents will be informed that childcare will be provided at the consensus meeting. Contact details of parents who wish to participate will be obtained on the consent form and a member of the study team will contact parents at a later date to confirm attendance. **HCPs:** We will sample HCPs with experience in the use of CS in JIA by profession, grade, clinical speciality and geographical location aiming to cover the main tertiary centres and centres with established paediatric rheumatology services with access to all routes of CS administration. There is currently no standard method for sample size calculation for a structured survey and Stakeholder Consensus process, so a pragmatic approach will be undertaken. For this study we will purposively sample 40-50 relevant HCPs identified by research nurses through NIHR CRN: Children or from the BSPAR membership mailing. For the consensus meeting an expert from each of the paediatric rheumatology centres expressing interest in the feasibility study will be invited in conjunction with 4-8 PPI participants aiming for not less than 10 and not more than 20 attendees. These attendees do not need to have been part of the structured survey process increasing the sampling of opinion. This meeting will provide a nominal group technique derived consensus on areas not agreed through the structured survey process.

d) Patient and parent qualitative interviews

We will recruit patients and parents to participate in semi-structured qualitative interviews. We will ensure that participants for interview have had relatively recent experience of CS treatment (e.g. within the last 3-4 months). This will be especially important for the younger patients, who might otherwise struggle to remember the treatment.

Where patients are 8 years or older both they and their parents will be interviewed; where patients are 7 years or younger only their parents will be interviewed. Sampling of families will aim for diversity in terms of patient age, JIA subtype and severity, experience of CS delivery (to include participants with experience of one or more of each of the proposed treatment delivery routes), and family socio-economic characteristics (via postcodes). Face-to-face interviews are likely to facilitate the most naturalistic presentation and discussion of the future trial, and be more suitable for younger children. Therefore, for logistical reasons sampling to the qualitative interviews will largely focus on participants who live within a day's return travel of Liverpool, although we will sample from more distant sites where it is necessary to achieve our purposive sampling targets and data saturation. Based on previous studies we anticipate that a sample of approximately 16 families will be sufficient to achieve data saturation (i.e. when no more new themes are identified during data analysis) (25).

15. Data collection:

a) National Survey of Clinical Practice, Screening Log and HCP Stakeholder Views

The national survey of clinical practice amongst HCPs will be devised by the research team and include both open and closed questions, and comment boxes. Topic guides for stakeholder survey will be developed by the Trial Management Group (TMG) to explore: acceptability of the proposed trial; identification of potential barriers for participation in a trial and how these could be addressed; feasibility trial design.

A draft survey will be circulated to the TMG to review ease of use, comprehension and interpretation, and refined based on its comments/suggestions. The survey will then be pilot tested on a group of paediatricians and modified further if required. The survey will be produced using Survey Monkey software. A hyperlink to the survey will be generated which can be embedded and emailed to selected paediatric rheumatology-linked HCPs inviting them to participate. HCPs who do not respond within two weeks will be sent a follow-up email and telephone reminders if required.

A further smaller national survey of HCPs as well as PPI partners will cover the choice of primary outcome measure as well as inclusion criteria to the study. This will be held prior to the Discussion Groups and Stakeholder Consensus Meetings so that the results can be fed into the consensus process. For the final Stakeholder Consensus Meeting the second national survey will only be with HCPs in view of the complexity of the medical questions to be decided.

b) Patient/Parent Qualitative Interviews

Findings from the literature review and national survey of practice will be used to inform the interview topic guides as part of an iterative approach to research. We anticipate that interviews will begin by exploring participants' experiences of early treatment and understanding of different CS delivery routes, whether the choice of CS delivery route was discussed with families (and if so, how the decision was made, what factors influenced it and who was involved), other factors influencing families' preferences for the different CS treatment routes and reasons for these preferences (e.g. perceived clinician preferences, side-effects, treatment effectiveness and the burden, familiarity, experience of pain and discomfort and inconvenience of the modes of treatment delivery). Exploration of parent/patient perspectives on important outcomes will be integrated within this section of the interview by eliciting how they judged whether or not CS treatment had made a difference.

The interviewer will then describe the proposed future trial in a way and using language that resembles as closely as possible how a trial would usually be presented to families in a clinic setting (although making in clear that the trial is still in planning and that consent in not actually being sought). At this stage the key parameters of the trial will not have been agreed, but the

interviews will reflect the possible treatment arms and modes of CS delivery. Verbal explanation of the trial will be supplemented by prototype information materials and participants will be given time to read and digest these. The interviewer will then explore participants' views on a future trial, the different CS treatment routes, potential willingness to receive a randomised treatment delivery, perceptions of the proposed trial design, questions about the trial, potential barriers to recruitment, possible adaptations to remove or minimise such barriers and views of the information materials. All interviews will be conversational and participant-centred to ensure that interview content reflects their own priorities and views on the proposed trial design; parents and children will also be encouraged to discuss their views of the trial with each other. An experienced qualitative researcher will conduct all interviews with patients and parents face-to-face in their home or other setting of their choice having first explained his/her independence from the trial and clinical team and confidentiality of the interviews. To resemble as closely as possible the usual sequence of presenting a trial to families, the interviewer will arrange a brief follow-up telephone call with families 1-2 weeks following the main interviews. These brief follow-up interviews will explore, whether, after having had time to further reflect on the trial, families have additional questions or concerns about the trial, whether their views of the trial have changed since the first interview, and if so, how their views have changed and the reasons for this.

c) Modified Structured Survey with Stakeholder Consensus Meeting and Discussion Groups
A Structured Survey to evaluate outcomes of importance and to choose the primary outcome for the final trial recommendation will be completed by both HCPs and parents/patients. Engagement of stakeholder groups is essential. As this is a feasibility study for all aspects of recommendations for a final study protocol, many aspects will be covered. It is likely that the consultation process will be a sequential process with the issues that require clarification at a consensus meeting becoming obvious through the process. However, as the final protocol choice will be based on highly complex medical questions necessitating the need for PPI partners to only be involved on appropriate protocol aspects. The qualitative interviews will be the source of detailed PPI information.

d) Discussion Groups and Stakeholder Consensus meetings*:*
Experts from the centres identified as being willing to be involved in the feasibility study will be invited to attend a first discussion group and stakeholder meeting to agree the primary outcome and feasibility study inclusion criteria. (There will be a second and final discussion and consensus meeting to agree all aspects of the final trial to be proposed after collation of data from the rest of the study.) Equal numbers of PPI participants (parents and patients over the age of 14 years) and HCPS will be included in the initial discussion and consensus meeting. An overview of findings from each discrete data collection approach and the survey of primary outcome measure and study inclusion criteria will be brought together and summarised and presented to the Discussion Groups for clarity prior to the Stakeholder Consensus Process. This will cover the final choice of primary outcome and agreement on the minimally important clinical difference in one session.

The final agreed aspects of the study voted for by clinicians will be reported back and discussed with PPI consumers on the day of the final discussion and consensus meeting. The PPI involvement approach in the discussion and consensus meeting will occur to ensure that the choices for the trial design have PPI inclusion.

Discussion groups will be held initially to ensure that all patient and HCP important outcomes have been considered. Following on there will be a formal Stakeholder Consensus Meeting run according to the Nominal Group Technique (NGT) to decide on the primary outcome to be

evaluated in the feasibility study. The Nominal Group Technique is a structured group meeting that follows a prescribed sequence of problem-solving steps and follows a set of rules for the decision making process overseen by a moderator. These steps include: 1) silent generation of ideas 2) further thought and listening during the round robin procedure 3) serial discussion for clarification of the opinion of each group member 4) preliminary vote with consensus levels chosen, typically between 70-85%, 5) brief discussion of preliminary vote and 6) final vote (27, 31). The NGT process forces equal participation among members in generating information and achieving outcomes. A non-voting chair will ensure the process is not overtaken by any one individual with strong views. The total number of participants will not exceed 20 and be more than 10 with recommendations from the Health Technology Assessment 1998 (31).
The list of generated outcomes will be reviewed and written in lay language with reading age considered so that the discussion group is accessible to all parents and patients. The survey will delivered online and will follow the same format as the HCP survey.

Definition of consensus: The definition of consensus will be specified prior to round one. Each outcome will be classified as 'consensus in', 'consensus out' or 'no consensus' according to the following criteria;

- Consensus In: >70% participants scoring as 7-9 AND <15% participants scoring as 1-3.
- Consensus Out: >70% participants scoring as 1-3 AND <15% participants scoring as 7-9.
- No consensus: anything else.

***e) Prospective Feasibility Study*:**
The final part of this mixed methods study is the feasibility study. The two main objectives are to collect further information on the number of eligible patients and to determine the potential sample size for any future trial. In addition the outcome measures chosen in the first consensus process (both primary and secondary), to be used in a future trial, data will be collected to allow for a power calculation for a final trial. The 6 week and 12 week visits would not necessarily be part of routine clinical practice, and therefore the feasibility study will be used to assess the response to steroids at the early time point of 6 weeks(for initial induction of disease control) and for maintenance of control at 12 weeks from initiation of steroid treatment.
Teams will be asked to treat patients as normal but to focus recruitment for patients to reflect as many treatment routes as possible for this part of the study, with the route chosen and doses used to be in keeping with their prior clinician decision.

There will be completion of the Childhood Health Assessment Questionnaire (CHAQ) at baseline, 6 and 12 weeks in clinic (32). The CHAQ is used as part of the calculation of composite outcome measure in JIA. The parent CHAQ will be completed by parents for patients below the age of 11 and the validated adolescent CHAQ by young people aged 11-16.

Consent will be obtained from parents/legal representative for patients with JIA requiring CS within national paediatric rheumatology centres. Patients will contribute to the prospective feasibility study with data collected before the commencement of treatment, at 6 weeks (with a 1 week window either side) and at 12 weeks after CS treatment is started.

- ***Informed Consent:***

  Informed consent is a process initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. In obtaining and

documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki

The consent form will request permission for personnel involved in the research (responsible individuals from the sites research team, CTRC (part of the University of Liverpool), Regulatory Authorities, Sponsor and the applicable NHS Trust) to have access to the individuals medical records. Both the person taking consent and the parent or legal representative must personally sign and date the form. The original copy will be filed in the participant's medical notes and a copy of the signed informed consent will be given to the parent or legal representative for their records. One further copy will be filed in the investigator site file and one final copy of the consent form should be sent to the MC CTU.

The parent/legal representative may, without being subject to any resulting detriment, withdraw from the study at any time by revoking the informed consent. The rights and welfare of the participants will be protected by emphasizing to them that the quality of medical care will not be adversely affected if they decline to participate in this trial.

- ***Assent form:***
  Assent will be obtained by young people aged 6 years and upwards. Any 15 year old turning 16 before the final study outcome visit will not be reconsented due to the short and "care as usual" nature of the study.

The agreed inclusion and exclusion criteria will be applied to patients at each of the included centres to identify participants who would be eligible for the proposed RCT. The minimum data set from which the possible candidate primary outcome can be calculated, which are required to be obtained for the sample size calculation, will be collected using paper CRFs that will also collect demographic and anonymized data on patients such as age, doses of steroid preparations, types of JIA, routes of CS administered and pattern of joint involvement.
In order to refine estimates of potentially eligible patients identified in the previous prospective screening logs, factoring in the HCP and PPI-informed estimates of randomization and consent rates to observed patient eligibility will help estimate the actual proportion of eligible patients who would be studied as per protocol. These data combined with the sample size estimate will inform the time required to recruit the necessary number of patients into a proposed RCT.

16. Data analysis:

a) National Survey of Clinical Practice & Screening Log

Both national survey and screening log data will be analysed using statistical software. Categorical data will be summarised using percentages and frequencies. Mean and standard deviation will be used to present continuous data. Where estimable, 95% confidence intervals will be presented. Qualitative, free text, questionnaire data will be coded, indexed and thematically analysed using QSR NVivo (V10).

b) Parent and patient qualitative interviews

The qualitative researcher will lead the data analysis. Interviews and will be transcribed, checked and anonymised as the study progresses. Respondent validation will be used so that

previously unanticipated topics will be added to the topic guide and discussed with participants as interviewing and analyses progress. Analysis will draw on the Framework approach (28, 29). This approach to qualitative data analysis is suited to facilitating the involvement of multidisciplinary research teams in the analysis. Such involvement will be crucial to interpreting the data and ensuring the wider team's ownership of findings. Epistemologically, our overall approach to the study and analysis will be broadly interpretive, that is, we will not regard interviews as providing direct access to participants' perspectives but will treat these as accounts of their views and experiences and interpret them in their social context. For example, we will be alert to the tendency of interviews to elicit justifications of views and behaviours rather than straightforward descriptions. Analysis will combine both deductive and inductive approaches. For example, we will interrogate data for evidence pertinent to our specific questions about CS treatment and the acceptability of the future trial. However, as in previous research (30), our analysis will not be constrained by such questions and pre-defined categories, and we will be open to following up unanticipated lines of enquiry and to the unexpected ways that participants assign meaning to their experiences of treatments.

Procedurally, the Framework approach involves initial steps common to other methods of qualitative analysis: 'familiarization' with the data; using a mix of deductive and inductive (open coding) approaches to 'identify' or generate a framework of categories and sub-categories; and 'indexing' the data according to these categories. Open coding will occur at multiple levels from detailed line-by-line coding to a more holistic approach (e.g. taking account of a participant's overall stance towards a future trial) and thereby helping to contextualize the analysis. The remaining elements of the Framework approach are more unique: 'charting', whereby we will arrange summaries of the data into matrices according to the framework categories. This facilitates the final step, 'mapping', which involves exploring patterns within the data in ways that connect to the aims of the feasibility study. BY will provide overall leadership of the analysis and supervision of the qualitative research associate but other members of the team will be involved to discuss interpretations of the data and 'test' the developing analysis. Parent and patient representatives will be also be involved by reviewing summary presentations or reports of the ongoing analysis. QSR NVivo (V10) software will be used to assist in the organisation and indexing of qualitative data. Beyond the above procedures, the qualitative study will be informed by guidance on quality in qualitative research (31, 33). Nevertheless, we are aware that in qualitative research, procedures do not guarantee quality (34). Our overarching criterion for judging the quality of the analysis will consider its catalytic validity (35) - its contribution to informing questions about the feasibility, design and implementation of a future trial.

c) Synthesis of qualitative and quantitative data

A pragmatic approach will be used to synthesize data, which will involve working back and forth between different data types (22, 36). This will involve cross-referencing qualitative themes with subject related quantitative SPSS output in order to present overall findings on a given topic (e.g. views on primary outcome measure from interviews and surveys). No one type of data or perspective will be given precedence [37]. Where qualitative and quantitative findings on an issue do not corroborate, or there is divergence between accounts on the same key issue we will explore the data sets further, or note the issue as one for special attention at the final consensus and discussion meeting.

d) Final Stakeholder Discussion and Consensus meeting

After analysis of all the results a report will be prepared with a conclusion on the outputs below. These results will be presented to a final meeting of Stakeholders with the intention that any

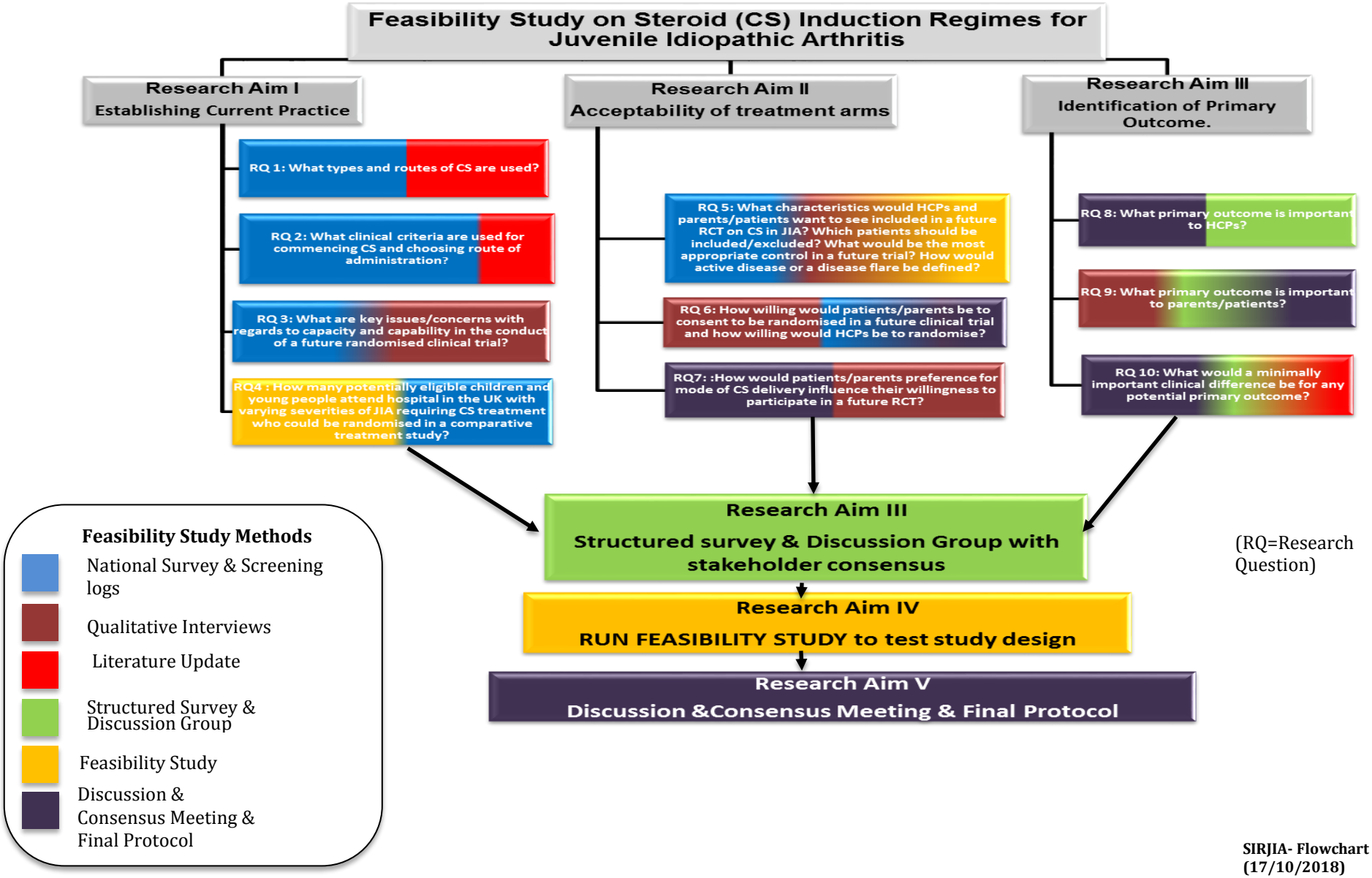
final areas of major uncertainty be subject to a final Consensus process. If the results suggest that an RCT would be feasible then significant aspects of the RCT protocol would also be agreed. This will include the inclusion, exclusion criteria, the routes of steroids to be compared, the primary and secondary outcome measures to be used as well as the power calculations for the likely interventions to be chosen.

17. Dissemination and projected outputs:

The projected outputs arising from this feasibility study will be:

- Consensus on the feasibility of a RCT comparing CS with multiple treatment route options
- A comprehensive and quantitative overview of current practice for treatment of newly diagnosed JIA
- An overview of infrastructure in the NHS to support RCTs in JIA
- Data on numbers of eligible JIA patients available in the UK for the RCT
- Identification of the control treatment arm
- A consensus on the primary outcome to be used in a future RCT
- Feasibility study data on the early change in primary outcome
- An estimate of a sample size for a future RCT of the agreed treatment arms and primary outcome
- Estimates of the likely randomisation and consent rates to further inform feasibility of delivering a future RCT
- Insights into the practical aspects of how to deliver a future definitive trial
- Preliminary patient information and consent materials
- A summary report for consideration by the HTA Programme on the feasibility of a RCT including data on all critical parameters required for a definitive assessment
- Study findings submitted for publication in open access peer reviewed medical journals. This will inform the design of future trials conducted in challenging settings. This will also inform best practice and likely impact on service development and delivery in paediatric rheumatology commissioned services
- Presentation of findings at relevant national and international meetings and conferences (including the RCPCH annual meeting).

Study Flowchart



(RQ=Research Question)

19. Project management

a) Sponsorship

The study will be sponsored by Alder Hey Children's Foundation NHS Trust as the lead NHS centre, using a model established for other NIHR funded studies.

b) Project Management

The study team already has extensive experience in project managing research studies, particularly on JIA. CTU will provide expertise with the coordination of the study at various sites, trial design, data management and analysis. The management of the study will be overseen by the TMG and Trial Steering committee (SSC). A clinical trial manager will be appointed. The TMG will consist of the following: CI, project manager, statistician, trial coordinator and co-applicants. The purpose of the TMG will be to oversee the day-to-day management and overall conduct and progress of the trial, to ensure that the study complies with GCP principles, relevant regulations and adherence to the study protocol. It will meet at monthly intervals throughout the duration of the study and will review progress of all study work streams against the study Gantt.

An independent person who is not named as a co-applicant on the funding application will chair the SSC. The SSC will consist of a number of independent and non-independent members. Independent members will include sponsor representatives, doctor, nurse and parent representative, whilst non-independent members will include the CI and two study co-applicants. The purpose of the SSC will be strategic overview of progress of the study and be informed by the TMG of any major issues on participant safety and overall delivery, which need a decision on whether or not to continue or make major changes to the protocol in consultation with the funder. The SSC will meet at six monthly intervals throughout the duration of the study.

Two parents will be invited to become actively involved by joining the SSC. Furthermore, both parents will be welcome to attend monthly TMG meetings and will be given copies of TMG agenda and minutes. Parents may need to be consulted over particular management issues related to PPI.

c) Communication

This study will involve co-applicants from Liverpool, Newcastle, Bristol and Belfast. Regular and timely communication and update will be through email, Skype and teleconferences. However, face-to-face meetings with co-applicants from the different centres will be needed at various time-points during the study.

20. Approval by ethics committees

We anticipate that this study will be eligible for a proportionate ethical review. Potential ethical issues include:

a) Collection of Participant Demographic Data in Prospective Screening Log, Prospective Feasibility Study and Qualitative Interviews.

Steps will be taken to ensure anonymisation of data in keeping with the Data Protection Act and Caldicott principles. Data will be collected and stored either in locked cupboards, in locked offices or on the 'M' drive on password protected computers, in accordance with local university and hospital research governance policies. Following the template for similar studies conducted by this team, collection of demographic, disease phenotype, treatment data and recording of the agreed primary outcome at baseline and at 3 months after administration of the chosen steroid will not require informed consent. Centres will be free to choose any route of

steroid administration as per existing clinical decision making. The qualitative interview participant demographic data will be subject to data collection and storage requirements within the approvals provided by a research ethics committee.

b) Informed consent/assent

All participants in the qualitative and prospective feasibility study workstreams (parents/legal guardians and patients) will receive study information sheet and will be asked to sign a consent form prior to participation. The assent form will be completed by age appropriate participants (6-10 and 11-15). The information sheet will outline the nature of the study and the level of their involvement. Participants will be made aware that their contribution with the study is at their own discretion. If they do agree to participate they will be informed that they can withdraw at any point without giving reason and this will not affect their legal rights or infants medical care.

Advice has previously been sought from the National Research Ethics Service on the requirement for ethical approval for completion of a structured survey. As the structured survey is seeking opinion only ethical approval will not be required. Consent for participation in both the online structured survey and the consensus meeting will be implied by submission of a response or attendance. The discussion group topic guide for patients/parents will be submitted to ethics for approval to ascertain that they will be no risks or burdens by asking the questions.

c) Risks, Burdens and Benefits

There are no anticipated risks, burdens or benefits for any of the participants involved in the study. Parents/legal guardians participating with the discussion group workshop will receive payment in line with the INVOLVE guidance and interviews will receive a £20 voucher for a high street store as a token of gratitude for participating with the study. Furthermore, all participants will be provided with a certificate to acknowledge their contribution to the research for their professional development portfolios.

21. Patient and Public Involvement

The research team will incorporate the principles of good practice guidance for promoting public involvement in research as set out in the INVOLVE guidance. The research team is already extremely experienced with service user involvement with other successful NIHR funded studies (UKCRN 10320 (Sycamore study), UKCRN 2635 (CAPS study), UKCRN 7725 (The Long-term Safety and Efficacy of Biologic Therapies in Children with Rheumatic Disease), UKCRN 3836 (UK JSLE Cohort Study).

a) Aims of active involvement in this research

PPI and consultation will be fundamental to all stages of the proposed study to ensure a successful outcome. Additionally, PPI will inform future trial development by identifying barriers and potential solutions to successful recruitment in a challenging setting. We aim to undertake PPI within this study in the following ways;

- Co-applicant
- Study management
- Study oversight through membership of the TMG and SSC
- Study design
- Development of participant information leaflets
- Advising on data analysis
- Advising on lay summaries

- Dissemination of research outputs (publications/newsletters/conferences)

b) Description of patients, carers or members of the public to be involved

As mentioned previously (Section 14), we will invite parents/carers to be involved in the research if they have had child or young person with JIA.

c) Description of methods of involvement

Preliminary PPI work had already commenced prior to and as part of the outline application submission. We have a parent and a young person with arthritis as co-applicants on this study who will help us to identify further participants for the feasibility study. A payment will be given in recognition for their time, skills and expertise, calculated using the INVOLVE Cost Calculator.

They will also be offered a variety of training opportunities tailored to their own individual needs. This will enable them to fully engage with the research study and to effectively undertake their roles. An informal meeting will be arranged for a training needs assessment of their initial training requirements, although assessment of their needs will be on-going throughout the duration of the study. The initial meeting will be used to identify their current level of knowledge, skills and experiences and how we can develop these further. Consideration will also be given to their role within in the research study and identification of any potential challenges where further training or support may be required. Training could involve bespoke sessions on treatments for JIA and on steroid regimens or facilitating discussion groups and would be provided by a research team member. It could also include more formalised teaching/courses on: Good Clinical Practice, Obtaining Informed Consent, and Understanding Evidence-based Healthcare: A Foundation for Action. Other training opportunities will include conference attendance. Furthermore, the consumer co-applicants and subsequently identified additional consumers will be offered a research team member to act as a mentor for them throughout the study. The mentor will be able to provide both parents with informal support and guidance, for instance, briefing them before and after TMG/SSC meetings, one-to-one feedback, help developing good relationships between the parents and the other members of the research team, providing a point of contact for parents who have encountered problems with their involvement in the study.

d) Co-applicant

A young person with arthritis has kindly agreed to be a co-applicant for the study.

References

1) McErlane, F., Beresford, M.W., Baildam, E.M., Thomson, W., Hyrich, K.L. Recent developments in disease activity indices and outcome measures for juvenile idiopathic arthritis. Rheumatology (Oxford) 2013 Nov; 52(11):1941-51. Review.
2) Thornton, J.A., Lunt, M., Ashcroft, D.M., Baildam, E.M., Foster, H., Davidson, J., Gardner-Medwin, J., Beresford, M., Symmons, D., Thomson, W., Elliott, R. (2008). Costing juvenile idiopathic arthritis: examining patient-based costs during the first year after diagnosis. Rheumatology (Oxford), 47(7), 985-90.
3) Choy, E.H., Kingsley, G.H., Khoshaba, B, Pipitone N, Scott, D.L., the Intramuscular methylprednisolone Study Group. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. Ann Rheum Dis 2005; 64: 1288-1293.
4) Wallace, C.A., et al. Extension study of participants from the trial of early aggressive therapy in juvenile idiopathic arthritis. J Rheumatol 2014 Dec; 41(12):2459-65.
5) Grigor, C., Capell, H., Stirling, A., et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004; 364:263-9.
6) Hetland, M.L., Stengaard-Pedersen, K., Junker, P. et al. Radiographic progression and remission rates in early rheumatoid arthritis- MRI bone oedema and anti-CCP predicted radiographic progression in the 5 year extensions of the double-blind randomised CIMESTRA trial. Ann Rheum Dis 2010; 69: 1789-95.
7) Smolen, J.S., Aletaha, D., Bijlsma, J.W. et al Treating Rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010; 69:631-7.
8) Rantalaiho V, Kautiainen H, Korpela M, Puolakka K, Blåfield H, Ilva K, Hannonen P, Leirisalo-Repo, M., Möttönen, T.; FIN-RACo Study Group. Physicians' adherence to tight control treatment strategy and combination DMARD therapy are additively important for reaching remission and maintaining working ability in early rheumatoid arthritis: a sub-analysis of the FIN-RACo trial. Ann Rheum Dis. 2014 Apr; 73(4):788-90.
9) Oen, K., Duffy, C.M., Tse, S.M., Ramsey, S., Ellsworth, J., Chédeville, G., Chetaille, A.L., Saint-Cyr, C., Cabral, D.A., Spiegel, L.R., Schneider, R., Lang, B., Huber, A.M., Dancey, P., Silverman, E., Rosenberg, A.M., Cameron, B., Johnson, N., Dorval J, Scuccimarri R, Campillo S, Petty, R.E., Duffy, K.N., Boire, G., Haddad, E., Houghton, K., Laxer, R., Turvey, S.E., Miettunen P, Gross K, Guzman, J., Benseler, S., Feldman, B.M., Espinosa, V., Yeung, R.S., Tucker, L. Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicentre inception cohort. Arthritis Care Res (Hoboken). 2010 Apr; 62(4):527-36. doi: 10.1002/acr.20044.
10) Shen, C.C.I., Yao, T.C., Yeh, K.W., Huang, J.L. Association of disease activity and anti-rheumatic treatment in juvenile idiopathic arthritis with serum lipid profiles: a prospective study. Semin Arthritis Rheum. 2013 Jun; 42(6):590-6.
11) Ga¨re, B.A. & Fasth, A. The natural history of juvenile chronic arthritis: a population based cohort study: I. Onset and disease process. J Rheumatol 1995; 22:295– 307.
12) Weiss, J.E. & Ilowite, N.T. Juvenile idiopathic arthritis. Rheum Dis Clin North America2007; 33(3); 441-70.
13) Cannizzaro, E. et al Temporomandibular joint involvement in children with juvenile idiopathic arthritis. J Rheumatol 2011; 38 (3):510-5.
14) Beukelman, T, et al 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res 2011; 63(4):465-482.
15) Dueckers G, Guellac N, Arbogast M, Dannecker G, Foeldvari I, Frosch M, Ganser G,Heiligenhaus A, Horneff G, Illhardt A, Kopp I, Krauspe R, Markus B, Michels H, Schneider M, Singendonk W, Sitter H, Spamer M, Wagner, N. & Niehues T. Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. Clin Immunol. 2012 Feb; 142(2):176-93. doi: 10.1016/j.clim.2011.10.003. Epub 2011 Oct 26.
16) Hashkes, P.J. & Laxer, R.M. Medical treatment of juvenile idiopathic arthritis. JAMA 2005; 294(13):1671-84.)
17) Kimme, L. Hyrich, Sham D. Lal, Helen E. Foster, Judith Thornton, Navid Adib, Eileen Baildam, Janet Gardner-Medwin, Lucy R. Wedderburn, Alice Chieng, Joyce Davidson, Wendy Thomson. Disease

activity and disability in children with juvenile idiopathic arthritis one year following presentation to paediatric rheumatology. Results from the Childhood Arthritis Prospective Study. Rheumatology 2010; 49:116–122.
18) Kirwan, J.R., Bijlsma, J.W., Boers, M. & Shea, B.J. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007 Jan 24; (1): CD006356. Review.
19) Picco Gattorna, M., Buoncompagni, A., Pistoia, V. & Borrone, C. Scand J Rheumatol. 1996; 25(1):24-7. 6-methylprednisolone 'mini-pulses': a new modality of glucocorticoid treatment in systemic onset juvenile chronic arthritis.
20) Zulian, F., Martini, G., Gobber, D, Plebani, M., Zacchello, F. & Manners, P. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology (Oxford) 2004 Oct; 43(10):1288091.
21) National Institute for Health and Care Excellence (2010) Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. NICE technology appraisal guidance 195.
22) Cresswell, J.W. Research Design: Qualitative and Quantitative, and Mixed Methods Approaches. London: Sage Publications, 2009
23) Bryman, A. Quality and Quantity in Social Research. London: Routledge, 1988
24) Cresswell, J.W. & Plano Clark, V.L. Designing and Conducting Mixed Methods Research London: Sage Publications, 2007
25) Tong, A., Sainsbury, P. & Craig, J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care 2007; 19 (6):349-57.
26) Guyatt, G.H. GRADE guidelines: 2- Framing the question and deciding on important outcomes. J Clin Epidemiol 2011; 64:395-400.
27) Cantrill, J.A., Sibbald, B. & Buetow, S. The Delphi and nominal group techniques in health services research. Int J Pharm Pract. 1996; 1:67–71.
28) Ritchie, J. & Spencer, L. (2002). Qualitative data analysis for applied policy research. The qualitative researcher's companion, 305-329.
29) Gale, N. K., Heath, G., Cameron, E., Rashid, S. & Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC medical research methodology, 13(1), 117.
30) Young, B., Ward, J., Salmon, P., Gravenhorst, K., Hill, J. & Eden, T. (2011) Parents' experiences of children's presence in consultations with physicians: qualitative study in leukemia. Pediatrics vol 127 issue 5 pp 1230-1238.
31) Murphy, E., Dingwall, R., Greatbatch, D., Parker, S. & Watson, P. Qualitative research methods in health technology assessment: a review of the literature. Health Technol Assess 1998; 2: iii-ix, 1-274
32) Ghiannini, E, H., Ruperto, N., Ravelli, A., Lovelli, D.J., Felson, D.T. & Martini, A. Prelinimary Definition of Improvement in Juvenile Arthritis. Arthritis and Rheumatism, vol 40(7) 1997, p1202-1209.
33) Stige, B., Malterud, K. & Midtgarden, T. Toward an agenda for evaluation of qualitative research. Qualitative Health Research 2009; 19: 1504-1516
34) Chamberlain, K. (2000). Methodolatry and qualitative health research. Journal of Health Psychology, 5(3), 285-296.
35) Guba, E.G. & Lincoln, Y.S. Fourth generation evaluation. Newbury Park, CA: Sage; 1989
36) Glaser, B. The Constant Comparative Method of Qualitative Analysis. Social Problems 1965; 12(4):436-45
37) Erzberger, C. & Kelle, U. Making inferences in mixed methods: the rules of integration. In: Tashakkori, A., Teddlie, C., editors. Handbook of mixed methods in social and behavioural research. London: Sage Publications, 2003:457-88

Protocol Amendments

Summary of Amendments from Protocol V1.0, 15/01/2015 to Protocol v2.0, 17/06/2016

Protocol Section Number	Protocol Section Title	Summary Changes
22	Expertise and justification of support required.	Finance details removed pages 17-19.

Summary of Amendments from Protocol V2.0,17/06/2016 to Protocol v3.0, 30/05/2017

Protocol Section Number/Page	Protocol Section Title	Summary Changes
Section 3, Page 5	Project Timelines	Removed as Gantt no longer included has been replaced by study flowchart diagram.
7d	The choice of a primary outcome measure.	The process of achieving the primary outcome has been revised to replace the Delphi process with structured survey and discussion Group. HCPs and Patient/Parent Consumers.
15e, pages 16-17	Prospective Feasibility Study	Informed consent will be taken a change requested by clinicians as there is an extra study visit at week 6 which is not a routine visit. Assent will be taken for children between 6 and 15 and when children turn 16 they will not be required to reconsent as adults due to the shortness of study and usual care nature of study.
Throughout the protocol	Delphi Process	The section has been deleted since it has now been replaced by structured survey and discussion Group.
17b, Pages 21-22	Plan of Investigation and Milestones	Gant Chart has been removed and replaced with study flow diagram.

Summary of Amendments from Protocol V3.0, 30/05/2017 to Protocol v4.0, 05/02/2018

Protocol Section Number	Protocol Section Title	Summary Changes
15e, pages 16-17	Prospective Feasibility Study	CHAQ to be completed at baseline, 6 and 12 weeks in clinic by parents and children above 11 years old.

Summary of Amendments from Protocol V4.0, 05/02/2018 to Protocol v5.0, 26/09/2018

Protocol Section Number	Protocol Section Title	Summary Changes
Throughout the protocol	Final Discussion and Consensus Meeting	The final consensus meeting has been revised to Discussion and Consensus Meeting.
Throughout the protocol	Final Discussion and Consensus Meeting	The Discussion and Consensus Meeting process has been revised as PPI Consumers will not vote on all aspects of the future protocol. Only clinicians without research nurses will be attending the consensus meeting. The role of PPI consumers has been revised due to the complexity of some aspects of the protocol.
15, page 14	Data Collection	PPI consumers will not participate in the E-survey on choosing a future protocol for a RCT.
22, pages 23	Definition of End of Study	Definition of end of study has been added.
24- 25	References	References have been added to the protocol.