Detailed Project Description

1. Full title of project:

Steroid Induction Regimen for Juvenile Idiopathic Arthritis (JIA)

2. Response to board feedback:

In the feedback letter from the HTA Board dated 14th November 2014 the research team were asked to consider the following comments when preparing the full proposal:

a) The board considered the study to be ambitious for the costs and time requested and this should be carefully reviewed. In particular the applicants should consider whether the systematic review is both necessary and realistic within the timeframe;

The study team is grateful to the Board for its helpful comments and is pleased to be in the position to submit a second phase detailed project description and to clarify the study methodology. The team has experience of this type of feasibility study and the design. Associated costs and milestones are based on both previous experience in successful delivery and the specific requirements of the commissioned call. We acknowledge the Board's concerns and have modified the application as outlined below; we are confident that the project can be fully addressed, accommodated and delivered to time and target.

Response a.1 Systematic Literature Review

In our initial application we had included a full systematic review as part of the Core Outcome Set (COS) choice because of methodological guidance (COMET; OMERACT) that a detailed literature review is always the starting point for COS development. On review, we will not be developing new outcome measures as part of this study but instead choosing the appropriate primary outcome based on the opinions of health care practitioners (HCP) and parents/patients from pre-existing sets already described in the literature. The choice will then be refined as part of the feasibility study. In accordance therefore also with our methodologists we believe it is justifiable to reduce the extent of a literature review, as advised by the Board, to the most recent publications only for the following reasons:

First, the European Medicines Agency (EMA) has recently produced, and circulated for comment, a draft plan for the expected trial designs, including outcome measures, to be used in studies of JIA. We would therefore, refer to these recommended outcomes. Our specific requirement is to assess the sensitivity of the chosen measures to the potential rapid change expected in an induction of remission study.

Second, there is a Single Hub Access for Rheumatology in Europe (SHARE) (http://www.ped-rheum.com/content/11/1/5) European Union work package specifically focussing on JIA underway where standards of care and treatment in JIA are being agreed through a Delphi consensus after full systematic review of the available literature including COS measures that many of our Team are either leading or participating in. We are confident therefore that this work package will report prior to the commencement of this feasibility study and therefore a much reduced literature search concentrating on the most recent publications would be all that would be required.

Third, the team has continued to work in the area of COS in JIA as NIHR CRN: Children Paediatric Rheumatology Clinical Study Group's (CSG's) Topic Specific Group for JIA. As part of the work facilitated by the CSG, the team is fully integrated with a comprehensive UK-wide paediatric rheumatology community initiative specifically focussing on COS in JIA, which will directly inform the need for any specific updates of her previous literature review (1).

A review of previous trials and/or systematic reviews will provide evidence on which outcome domains have been measured, the measurement instruments that have been used, and on timings of measurement. The final decision on the primary outcome will be based on the results of the national survey, Delphi process, stakeholder meeting and the qualitative interviews and will balance the importance, power and feasibility issues. In particular, to assess early response to treatment it is necessary to know that the chosen primary outcome measure is measurably sensitive enough to change. For example active and limited joint counts are measured in many JIA trials. However, the term 'active joint count' is not always clearly defined or used consistently between studies. The composite "core set criteria for JIA" includes measures such as physician and parent/patient global visual analogue scales of disease activity, as well as measures of function and inflammation, but clinical decision to treat may not include reference to such measures.

The initially proposed systematic review will therefore be downgraded to a literature review on specific study linked questions, for the reasons stated above. We have been able accordingly to readjust the costs commensurately in favour of the actual survey and clinical pilot feasibility study. By refining the timelines we have also increased time at the end of the study to allow rigorous data cleaning, data analysis and write up. We are unable to shorten the study time lines but also have not needed to increase them by reducing the initial set up/

systematic review delivery period. This fits with the Board's specific concerns of the ambitious nature of the proposal in terms of the value of another systematic review of the literature.

Response a.2 Health Economics

The second area in which we recognise the outline proposal may have appeared over-ambitious was in the proposed health economic (HE) component. Although included initially, we are aware of the paucity of published studies on HE outcomes in treatment of JIA in general. The Childhood Arthritis Prospective Study (http://www.caps-childhoodarthritisprospectivestudy.co.uk/), the largest incident cohort study of JIA worldwide, has delivered one HE publication (2) from those study data and a second follow up paper in preparation. The output of a HE systematic review would be limited and HE assessments as part of the feasibility study would be small. HE analysis will not be therefore, undertaken in the feasibility study. This will form part of a future full trial and will primarily involve analysis of the hospital costs accrued for the various treatment regimens and societal costs (loss of work days, etc).

There are methodological and practical challenges to eliciting preference-based outcomes in the steroid treatment of JIA. There is no evidence-based guideline on the advantages and disadvantages of each regime, their age-appropriateness, and relevance to core outcomes in the context of JIA. Identifying the most appropriate preference-based outcome measure will inform the HE evaluation component of a future definitive trial comparing the cost effectiveness of different remission induction regimes in JIA under investigation. The main HE implications will not be because of the cost of steroid component as such, but rather the costs of the hospital stay for each comparator, the potential for reduction in use of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and in particular in the potential for a reduced need for biologic drugs. None of this will be addressed in the feasibility study.

b) The proposal to measure the best way to make a diagnosis went beyond the commissioning brief and was not supported by the board.

Following receipt of our feedback letter we wrote to clarify with the Chair of the Board, the second point of the feedback namely "the proposal to measure the best way to make a diagnosis went beyond the commissioning brief and was not supported by the board".

We wrote to clarify this point as we believe that the concept of a diagnostic component to the study was specifically not within our proposal and it is not our intention to look at any aspect of diagnosis. We apologise if we gave that impression in our outline application. However, we considered that the Board meant to refer to the section in our proposal under the Overall Aim where we refer to " Patient acceptability and physician decision – making will be studied…". This aspect is planned as a small part of the Survey Monkey component of the study as we believe that it is important to understand why clinicians and patients together choose to use, or even more importantly, to reject different modalities of steroid treatments in JIA.

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). Few paediatric rheumatologists use it and there is *ad-hoc* personal feedback from clinicians about potential benefits of this modality of treatment, although without an evidence-base for its use. We sense a perspective amongst paediatric rheumatologists against this modality because of perceived painful injections and short duration of action. However, this route may be the easiest to administer, the cheapest to use, with the lowest cumulative corticosteroid dose and potentially the most effective responses. It is possible that intramuscular (IM) steroids have a role in certain patients groups (eg older adolescents with active arthritis affecting many joints). From a patient perspective the IM route may offer an effective, rapid way to alleviate symptoms, administered in the outpatient environment rather than as a day case admission or risking delays in accessing joint injections or intravenous (IV) steroids. It is an important part of the feasibility study to explore the opinions of clinicians and their current practice, patients and families for their preferences and rationale for treatment choices and to explore the cost comparisons of treatment options – this information may well inform innovative and cost effective new treatment strategies in paediatric rheumatology and indeed through exploring the perceived concerns of paediatric rheumatologists, inform the community about how these concerns can be addressed.

In order to keep the qualitative component of the study within the brief and within the deliverable costs and timelines we clarify that the full interviews will be with parents and patients (8 years or over) where the patient experience of the various treatments will be explored. In addition their views will be sought on the proposal that a future trial would randomise between delivery routes. The HCP component will only be through structured on-line questions to explore the decision making process in respect of the choice of steroid treatments in JIA.

On discussing with the Chair of the HTA Board on 1.12.14 it was clarified that on reading this explanation the rationale is understandable and that we should proceed as planned with the detailed application.

3. Summary of Research:

In the UK, JIA is the most common inflammatory disorder in childhood. 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 repeatedly 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.

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

- Delphi process of parents/patients and HCPs to achieve consensus on the primary outcome and treatment modalities
- Stakeholder Meeting (using Formal Consensus Techniques) to present and discuss the findings from the Delphi 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 regular time points up to 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 newly treated with CS in each JIA subtype will be determined to allow for accurate power calculations to be made 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.

Project timelines: The study will be completed in 21 months. Individual components (see Gantt Chart) are: contracting, set-up and literature review – 6 months; surveys of practice - 6 months; qualitative interviews 7 month; Delphi process and consensus meeting 10 months; prospective feasibility – 10 months; final report for HTA – 1 month. Individual components run in parallel.

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 systematic review, extensive surveys, qualitative interviews and Delphi processing 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 Delphi consensus. 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 Delphi 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 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. Delphi process* of HCPs and parents and young people to achieve consensus on outcome measures for the future RCT (RQ 8-10).

iii. Stakeholder* Consensus meeting on any aspects not achieving consensus in the Delphi process.

* Engagement with HCPs and parents to address Aims II/III will use the same Delphi processes and HCP and PPI Delphi and Stakeholder Consensus meeting. The Consensus meeting will be multi-disciplinary and 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, Delphi process, qualitative interviews with patients and parents, a consensus meeting with HCPs with 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 a 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 Delphi surveys and consensus meeting. The aim of sampling for the Delphi 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. We will identify and select potential participants for Delphi 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. 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 in a Delphi survey, consensus meeting, or qualitative interview. Participants can choose which elements they wish to take part in by ticking the appropriate box on the consent form. The consensus meeting will take place in North West England so the option of taking part in either an interview or Delphi 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, to arrange interviews or forward the Delphi survey.

ii. 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 Delphi process, so a pragmatic approach will be undertaken. Critical to a successful Delphi process is the retention of participants between the 2 rounds. 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 2-4 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 Delphi process increasing the sampling of opinion. This meeting will provide a nominal group technique derived consensus on any remaining areas not agreed through the Delphi 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 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.

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) Delphi Process

A Delphi process to evaluate outcomes of importance will be completed by both HCPs and parents/patients. Engagement of stakeholder groups is essential. All HCPs and parents/ patients who complete all two rounds of the Delphi process will be entered into a prize draw to win an iPad mini. This prize has been chosen based on a Cochrane review of ways to improve recruitment to surveys, which demonstrated that a non-monetary incentive improved response rate.

Method: We will undertake a two round Delphi process with each stage building on the preceding one, with HCPs and PPI participants to achieve consensus over the primary outcome as well as aspects of the feasibility study. The results from the literature review will inform the development of an initial list of potential outcomes to include in the survey. Outcomes identified as patient-reported outcome measures or other validated scoring instruments will be reviewed and the domains used within the instrument used as an outcome instead of the instrument itself. Where there is uncertainty about how to present these outcomes, the advice of two relevant clinicians who are members of the TMG will be sought. Software developed by CTU specifically for Delphi surveys will be used. This software will produce a hyperlink for the survey, which can be embedded into an email and sent directly to each participant. An initial draft of the survey will be circulated around the TMG who will complete the Delphi survey and provide comments, advise on ease of use, comprehension and interpretation. The Delphi survey will be refined further based on their comments/suggestions prior to circulation to a wider audience.

- **Round One**

  In round one, participants will be provided with a unique identifier, which will be stored on a separate database, in order to anonymise survey responses. Participant demographic data will be collected such as profession type, grade, clinical speciality, and length of service. In the first round of the Delphi process participants will be shown the list of outcomes, identified from systematic review of the literature, focus groups and interviews and will be asked to score each outcome using the Grading of Recommendations, Assessment, Development and Evaluations scale of 1 to 9. In the Delphi process the scale will be presented in the format 1 to 9, with 1 to 3 labelled 'not important', 4 to 6 labelled 'important but not critical' and 7 to 9 labelled 'critical' (26). Participants will be provided with an option to add additional outcomes that they think are relevant together with a score for each outcome added.

- **Round Two**

  All participants who have provided scores in round one will be invited to participate in round two. In round two, results from round one will be presented. Each participant will be presented with the number of respondents and distribution of scores for each outcome for their particular stakeholder group together with their own score from round one. In round two, participants will be asked to review each outcome and re-score. Any changes to scores in light of the stakeholder group or overall response will be documented. Those who have not taken part in round one and have not provided a score will not be invited to participate in round two.

  Participants will be asked to complete each survey in the Delphi process within three weeks of receipt of the email. All participants will be sent a follow-up email reminder two weeks following the initial email to improve response rates. Participant contact details will be collected upon registration allowing further telephone or text follow-up to improve response rate if needed.

The list of generated outcomes will be reviewed and written in lay language with reading age considered so that the survey is accessible to all parents. 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

d. Consensus meeting: Experts from each of the centres identified as being willing to be involved in the feasibility study will be invited to attend a final consensus meeting. In addition 2-4 PPI participants will be included in the consensus process. An overview of findings from each discrete data collection approach will be brought together and summarised. This will cover the final choice of primary outcome and agreement on the minimally important clinical difference in one session. The Nominal Group Technique (NGT) 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).

e. Prospective Feasibility Study:

The two main objectives of the feasibility study are to collect further information of the number of eligible patients and to determine the potential sample size for any future trial.

Patients with JIA requiring CS within national paediatric rheumatology centres will contribute to the prospective feasibility study with data collected before the commencement of treatment and again after three months. This will be an observational study of existing, clinician-led practice and will not require informed consent. 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 primary outcome data 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 (31,32). Nevertheless, we are aware that in qualitative research, procedures do not guarantee quality (33). Our overarching criterion for judging the quality of the analysis will consider its catalytic validity (34) - its contribution to informing questions about the feasibility, design and implementation of a future trial.

c) Delphi Process

Each round of the Delphi process will be analysed to review attrition bias. In round one, free text responses will be reviewed by two members of the study team to find out whether new outcomes have been identified for inclusion in round two. In round two, the number of participants who have scored each outcome together with the distribution of scores will be summarised by stakeholder group. Results of the stakeholder group response will be compared with the whole group response and the percentage agreement used to determine the structure and focus of the final consensus meeting. Each outcome will be classified as 'consensus in', 'consensus out ' or 'no consensus' according to pre-defined classifications (see above).

d) 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 (22,35). 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 [36]. 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 consensus meeting.

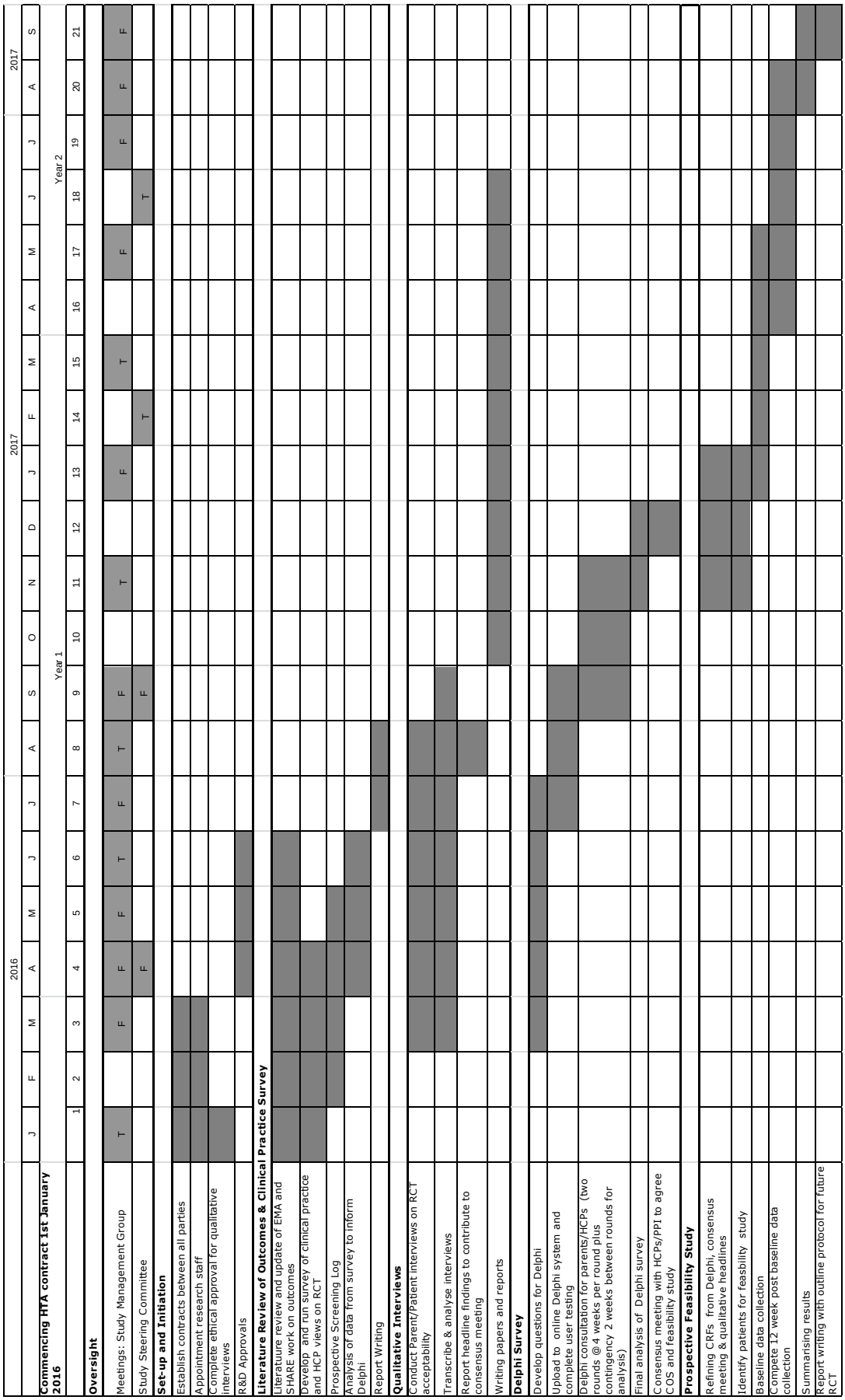
17. Dissemination and projected outputs:

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).

18. Plan of Investigation and Milestones

a) Gantt Chart (F = face-to-face; T = teleconference)



b) Estimated milestones

Milestones are estimated based on date of outcome of review of full submission. Month 1 of the project is expected to commence 1th January 2016.

Pre-award	Apply for ethical approval for qualitative study development of participant information. Develop HCP survey of current practice and views on key RCT parameters
Month 1 – 3	Study set up including protocol development, and contracting between parties. Appointment of staff, finalise protocol, service evaluation data collection forms completion of R&D approval for NHS sites involved in recruitment for qualitative interviews.
Month 1-3	Complete literature review and identify list of outcomes used in previous research.
Month 1-4	Deliver HCP survey of current practice and views on key RCT parameters.
Months 2-5	Prospective screening log
Month 4-6	Finalise list of outcomes from previous literature, analyse survey of clinical practice
Month 2-7	Complete interviews with parents and or/ patients
Month 2-8	Transcribe and fully analyse qualitative interviews
Month 3-7	Develop questions for Delphi
Month 7-9	Upload questions for Delphi
Month 9-11	Initiate Delphi consultation rounds as online Delphi survey with healthcare professionals and PPI participation – two rounds; complete qualitative analysis and data synthesis
Month 12	Final consensus meeting with Nominal Group Technique. Agreement on key parameters for proposed RCT
Months 13-20	Prospective feasibility study (5 months identification of newly diagnosed JIA patients; 3 months to complete all observed measurements of primary outcome measure)
Month 21	Preparation of final report for HTA with recommendations on RCT feasibility.

19. Project management

a) Sponsorship

Sponsorship will be organised within the framework of the Liverpool Health Partners Joint Research Office (http://www.liverpoolhealthpartners.org.uk/research.html). The study will be sponsored by the University of Liverpool and 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 (TSC). 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 TSC. The TSC 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 TSC 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 TSC will meet at six monthly intervals throughout the duration of the study.

Two parents will be invited to become actively involved by joining the TSC. 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

All participants in the qualitative workstream (parents/legal guardians and patients) will receive study information sheet and will be asked to sign a consent form prior to participation. 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 Delphi survey. As the Delphi is seeking opinion only ethical approval will not be required. Consent for participation in both the online Delphi and the consensus meeting will be implied by submission of a response or attendance.

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 focus group workshop and interviews will receive a £20 voucher for a high street store as a token of gratitude for participating with the study. All participants (HCPs and parents) completing all Delphi questionnaire rounds will be entered into a prize draw to win an *iPad mini*. 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 TSC
- 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 focus 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, 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/TSC 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 (SS) has kindly agreed to be a co-applicant for the study.

22. Expertise and justification of support required

a) Expertise

Baildam (0.15 FTE) Chief Applicant/Investigator an experienced Consultant Paediatric Rheumatologist at Alder Hey Children's Hospital and Honorary Senior Lecturer at Liverpool University and Associate Director of the UK's Experimental Arthritis Treatment Centre for Children (EATC) with a long track record of JIA research. She is co-applicant for The Long-term Safety and Efficacy of Biologic Therapies in Children with Rheumatic Disease (Arthritis Research UK) and co-applicant for the Arthritis Research UK Experimental Arthritis Treatment Centre for Children. She is a co-investigator on the CAPS study as well as UK PI for the Study of Belimumab in Juvenile Systemic Lupus Erythematosus and UK CI for the Arthur Study of Tocilizumab in systemic JIA.

Beresford (0.02 FTE) is Professor of Child Health at Liverpool University, Theme Lead of the NIHR CRN: Children, Chair of the UK's Paediatric Rheumatology CSG, Director of the EATC and of the NIHR Alder Hey Clinical Research Facility. He has successfully developed (with Ramanan) two funded clinical trials in JIA-associated uveitis one of which is well into study recruitment. He will advise on the practicalities of trial design and development and Chair the consensus conference. In addition to the role of other co-applicants he will support the CI and represent the University of Liverpool in oversight of the academic aspects of the study and Chair the Consensus meeting.

Stones (0.016 FTE) is a patient with JIA who is applying for an NIHR Doctoral research fellowship. He is member of the CSG and a co-applicant on a mobile app research development project. He will facilitate patient surveys and workshops.

Ramanan (0.016 FTE) is Professor of Paediatric Rheumatology, Co-CI on HTA/ARUK funded trial in JIA and CI of several industry studies and is Associate Director of the EATC. His expertise includes clinical trial design and delivery in paediatric rheumatology.

Foster (0.016 FTE) Experienced paediatric rheumatologist since 1995, with major interest in transition and clinical outcomes, and Honorary Consultant Great North Children's Hospital, Newcastle upon Tyne. Professor Paediatric Rheumatology, Newcastle University with extensive experience in clinical research and track record of collaborative working. She is NHS England Commissioning lead for paediatric rheumatology, Speciality group lead for paediatrics North East North Cumbria LCRN and former member of paediatric rheumatology CSG. She brings skills and experience from various perspectives to add value to the project team. She will help construct the exploration of current practice using mixed methodologies.

Young (0.05FTE) has over 20 years' published research experience with children and families about heath, clinical care, medicines and clinical research, including experience of trial feasibility projects. She is an experienced qualitative methodologist and co-lead of the Patient Perspectives Theme of the North West Hub for Trials Methodology Research (NWHTMR) and a member of the Nuffield Council of Bioethics working party on Children and Clinical Research (http://nuffieldbioethics.org/project/children-research/). Her cumulative research grant income is approaching £14 million and she has authored 70 peer-reviewed publications.

McErlane (0.016 FTE) Consultant Paediatric Rheumatologist Great North Children's Hospital, Newcastle upon Tyne and lead of the NIHR CRN: Children JIA topic specific group which was part of the process prioritising this particular study. The link with units in the UK will facilitate involvement in this and a future study. In addition her MSc project was on outcome measures in JIA and she will lead the primary outcome component of this study with Williamson.

Rooney (0.016FTE) is a Senior Lecturer in Paediatric Rheumatology in Queens University of Belfast and has led the only UK multi-centre clinical trial of the prevention of steroid induced osteoporosis in paediatric

rheumatology. This study is completed and results under analysis. She will advise on the practicalities of trial design and will assist in developing a method of assessing steroid induced ADRs.
Peak (0.01FTE) Director of NIHR CRN: Children NW Coast and Co-Director of the EATC has extensive experience in research delivery, Delphi process and optimising use of NIHR CRN resources.

The Medicines for Children (MCRN) Clinical Trials Unit (CTU) is part of the University of Liverpool Clinical Trials Research Centre (CTRC) has full UKCRC registration. The CTU has a strong portfolio of publicly funded clinical studies and trials, including feasibility studies and COS development. **Williamson (0.01FTE)**, Director of the CTU and **Helen Gillard (0.107FTE)**, Research Associate/Senior Trials Manager, will provide expertise in study management and administrative, logistical and biostatistical support for the development, implementation, and successful completion of the feasibility study. **Williamson** is lead for the COMET Initiative, and will also provide expertise in using the Delphi technique to achieve consensus on the appropriate primary outcome measure. **Jones (0.1FTE)** is an experienced statistician in multiple NIHR-funded studies.

b) Justification of support requested

The proposed costs in the outline were £248,040. The costs included in this application total £274,776 with the increase being primarily due to an increase in costs for CI time which was not included in the first assessment.

i. Staff costs (£232,519)

Costs for the co-applicants with details of percentage FTE commitment are detailed above. Costs have also been included for the following study specific staff. **Supervising Trials Manager (0.107FTE)** will provide management advice and supervision of the study coordinator.

- **Study coordinator (0.641FTE)**. The study coordinator will be involved throughout the study and, together with the Supervising Trials Manager, will take a leading role in planning, coordinating and completing the study and in its day to day management (e.g. coordination of meetings, distribution of surveys, prospective screening log and Delphi).
- **Information Systems Developer Support (0.054 FTE)**. The average FTE is based on variable input depending on the stage of the study, Resource will be required for 3 months during set up and for 5 months to deliver the Delphi'.
- **The statistical research associate (0.33 FTE)** will compile and analyse the results of the Delphi survey and will offer statistical support for the survey of practice and HCP responses.
- **PPI support role (0.027 FTE)**. The study design includes two PPI representatives on the TMG and two on the TSC. Costs have been included to ensure that PPI reps are given adequate support and training for their role and also to evaluate PPI involvement and impact in the study.
- **IT support (0.316 FTE).** IT support will vary over the duration of the study with highest input during finalisation and testing of the online Delphi survey. Although software currently exists some modifications will be required to meet study specific requirements.
- **Qualitative Research Associate (1FTE 7 months)** will prepare the materials for qualitative interviews, arrange and conduct interviews with parents and patients, organize transcription, check and anonymise transcripts, assist with data analysis and prepare a preliminary report on the analysis.

ii. PPI costs (£2,568)

PPI costs have been included based on the INVOLVE guidance for payments.

Patient and public involvement for this study will be via representation at TMG meetings (two members), and the TSC meetings (two members); a fee of £40 per PPI rep per meeting has been included based on half day involvement to include preparation time. In addition members of the TMG will act as facilitators at the final consensus meeting.

iii. Travel and Subsistence (£9,756)

Travel and subsistence costs have been requested to include TMG and TSC meetings, attendance at the consensus meeting and costs associated with conducting the qualitative interviews.

iv. Equipment (£1,566)

Costs for 2 PCs, a digital audiorecorder (for the qualitative interviews) plus mobile telephone and plan are requested. Consumables (£2,513)

Ethical and ICH GCP requirements demand that an audit trail of all trial records and essential documents are maintained. Office consumables associated with maintenance of a study master file and preparation of study specific documentation for the consensus meeting have been included; this includes printing, photocopying and postage costs. All study documents will be maintained in accordance with GCP.

Consumables costs also include the cost of leaflet and poster printing for presentation at local and national conferences.

vi. Other direct costs (£20,586)

- **Research Nurse (RN) Support** at study sites will provide data collection support for the prospective screening log, prospective feasibility study and will be paid as a payment for each patient identified. Based on £36.12 per hour of RN time. 150 cases (screening log) at 60 mins each: 50 cases for prospective feasibility at 120 mins each. Total = £9,030.
- Teleconference costs have been requested to facilitate TMG and TSC meetings. These are a trial specific cost requiring multiple lines and are not covered within indirect costs.
- IT costs related to the online Delphi have been included to cover hosting of the website and provision of a helpdesk.
- Other direct costs include, manuscript publication (HTA report and main paper), transcription of qualitative interviews, childcare for parents attending the consensus meeting, room hire for the consensus meeting and, a £20 high street voucher for parents attending the consensus meeting.

vii. Indirect/Estate Costs (£58,880)

As per HEFCE policy, provision for Estates and Indirect charges are recorded in this section, broken down by organisation.