STAR-JIA
STEROID TREATMENT TRIAL IN JUVENILE IDIOPATHIC ARTHRITIS

STAR-JIA PROTOCOL

Steroid TreAtment tRial in JIA: A randomised trial to compare effectiveness, safety and cost-effectiveness of intravenous versus oral corticosteroid induction regimens for children and young people with juvenile idiopathic arthritis.

V1.0, 12/07/2023

Trial Sponsor:

Alder Hey Children's NHS Foundation Trust

Eaton Road

Liverpool

L12 2AP

Trial Registry ID:

Sponsor Reference: AH23-05-006

IRAS Reference: 1007610

Funder Reference: NIHR134350

CTA Reference: To be confirmed

Ethics Reference: To be confirmed

FUNDED BY NIHR | National Institute for Health and Care Research

NHS Alder Hey Children's NHS Foundation Trust

UNIVERSITY OF LIVERPOOL

LIVERPOOL CLINICAL TRIALS CENTRE LCTC

This study is funded by the NIHR Health Technology Assessment Programme (HTA) (NIHR134350). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

PROTOCOL APPROVAL

I, the undersigned, hereby approve this clinical trial protocol:

Authorised by Chief Investigator:

Signature: Clare Pain box SIGN 4LW7LRPQ-4KW8K7R6 **Date:** Jul 12, 2023

Associate Professor Clare Pain

Consultant Paediatric Rheumatologist

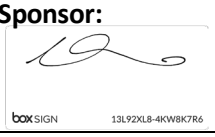
Authorised by Co-Chief Investigator:

Signature: A. V. Ramanan box SIGN 4L88J2X4-4KW8K7R6 **Date:** 12 Jul 2023

Professor Athimalaipet Ramanan

Consultant Paediatric Rheumatologist

Authorised on behalf of Sponsor:

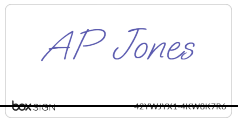
Signature: 

Date: 12 Jul 2023

Mrs Kelly Davies

Research Governance Manager

Authorised on behalf of the Lead Statistician:

Signature: 

Date: 12 Jul 2023

Dr Ashley Jones

Head of Statistics

General Information

This document describes the STAR-JIA trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the Liverpool Clinical Trials Centre (LCTC) to confirm they have the most up to date version.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority (HRA) guidance. Regulatory and ethical compliance information is located in section 17.

The Liverpool Clinical Trials Centre brings together a wealth of expertise built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration Clinical Trials Unit (UKCRC CTU) network since its establishment in 2007 (www.ukcrc.org).

Randomisation: web access *http://www.xxxxxxxxx (Web address to be confirmed)*

If there are any problems with the randomisation systems contact

*LCTC via email on **star-jia@liverpool.ac.uk***

(Note that the LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays and University of Liverpool closed days)

Clinical Queries

Clinical queries relating to this trial should be referred to the
Chief Investigator, Dr Clare Pain via LCTC by emailing to **star-jia@liverpool.ac.uk**

SAE Reporting

Where the adverse event meets one of the serious categories, it must be recorded in the database immediately and in no circumstances later than 24 hours of becoming aware of the event (See section 11 for more details).

Contact details: star-jia@liverpool.ac.uk

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**	**Clinical Laboratory:**
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Health Economics:	**Statistics:**	
Professor Dyfrig Hughes Professor in Pharmacoeconomics Bangor University Bangor, Gwynedd, LL57 2DG, UK Tel: +44 1248 351 151 E-mail: D.A.Hughes@liverpool.ac.uk	Liverpool Clinical Trials Centre University of Liverpool Block C, Waterhouse Building Brownlow Street, Liverpool L69 3GL Tel: 0151 794 8974 E-mail: star-jia@liverpool.ac.uk	

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	Chief Investigator (CI)	Co-Chief Investigator (CI):
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In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:	Medical Expert who will Evaluate SAE Reports:	
Prof Athimalaipet Ramanan Consultant Paediatric Rheumatologist Co-chief Investigator University Hospitals Bristol NHS Foundation Trust Marlborough Street Bristol BS1 3NU E-mail: avramanan@hotmail.com	Prof Athimalaipet Ramanan Consultant Paediatric Rheumatologist Co-chief Investigator University Hospitals Bristol NHS Foundation Trust Marlborough Street Bristol BS1 3NU E-mail: avramanan@hotmail.com	

Additional Contacts:

The contact details for the trial oversight committee members and participating sites are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1 TABLE OF CONTENTS

2 GLOSSARY

AE	Adverse Event
ALC	Adult Lacking Capacity
AR	Adverse Reaction
BP	Blood pressure
CAG	Confidentiality Advisory Group
CHAQ	Childhood Health Assessment Questionnaire
CHU-9D	Child Health Utility 9D Questionnaire
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case Report Form
CS	Corticosteroids
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTU	Clinical Trials Unit
CYP	Children and Young People
DPA	Data Protection Act
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HCP	Healthcare Professionals
HES	Hospital Episode Statistics
HR	Heart Rate
HRA	Health Research Authority
HRQOL	Health-related Quality of Life
IA	Intra-articular
IB	Investigator's Brochure
ICO	Information Commissioner's Office
IDSMC	Independent Data and Safety and Monitoring Committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IPD	Individual Participant Data
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IV	Intravenous
IWRS	Interactive Web Response System
JIA	Juvenile Idiopathic Arthritis
LCTC	Liverpool Clinical Trials Centre
medDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Health Care Products Regulatory Agency
MTX	Methotrexate
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
PBPP	Public Benefit & Privacy Panel for Health & Social Care
Pain VAS	Pain Visual Analogue Scale

pcJIA	Polyarticular course Juvenile Idiopathic Arthritis
PhGA-VAS	Physician Global Assessment of Disease Activity Visual Analogue Scale
PGA-VAS	Patient/Parent Global Assessment of Well-Being Visual Analogue Scale
pGTI	Paediatric Glucocorticoid Toxicity Index
PI	Principal Investigator
PLICS	Patient Level Information and Costing System (PLICS)
POCBP	Participants of child-bearing potential
PREM	Patient-reported Experience Measures
PROM	Patient-reported Outcome Measures
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
RUAE	Related Unexpected Adverse Event
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischaemic Attacks
TMF	Trial Master File
TMG	Trial Management Group
TPN	Total Parenteral Nutrition
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
USM	Urgent Safety Measure
VAS	Visual Analogue Scale

3 PROTOCOL OVERVIEW

Full Title:	Steroid TreAtment tRial in JIA: a randomised trial to compare effectiveness, safety and cost-effectiveness of intravenous versus oral corticosteroid induction regimens for children and young people with juvenile idiopathic arthritis.
Acronym:	STAR-JIA
Phase:	IV
Target Population:	Patients aged 1- 18 years inclusive with new onset polyarticular course Juvenile Idiopathic Arthritis (pcJIA)
Sample size:	130
Inclusion Criteria:	1. Participants must be between 1-18 years of age inclusive. 2. New onset pcJIA diagnosed by a paediatric rheumatologist (to include polyarticular rheumatoid factor (RF+) positive, polyarticular RF negative, enthesitis-related arthritis, psoriatic arthritis and extended oligo-articular). This includes new diagnosis of JIA with at least 5 joints affected and patients previously categorised as oligoarticular JIA (with 4 joints or less) who have extended to at least 5 joints. 3. Participants are expected to be able to commence allocated treatment within 1 week of randomisation. 4. Written, informed consent and where appropriate, assent obtained from participant or their legal representative. 5. Participants of child-bearing potential must be willing to abstain from sexual intercourse from consent to their final visit and/or use another acceptable contraception method as described in section 9.10.5 of this protocol.
Exclusion Criteria:	1. Any contraindication to starting corticosteroids. 2. Any contraindication to starting methotrexate. 3. Pregnancy. 4. Treatment with systemic corticosteroids within 4 weeks preceding screening (includes intravenous, intraarticular, intramuscular and oral).

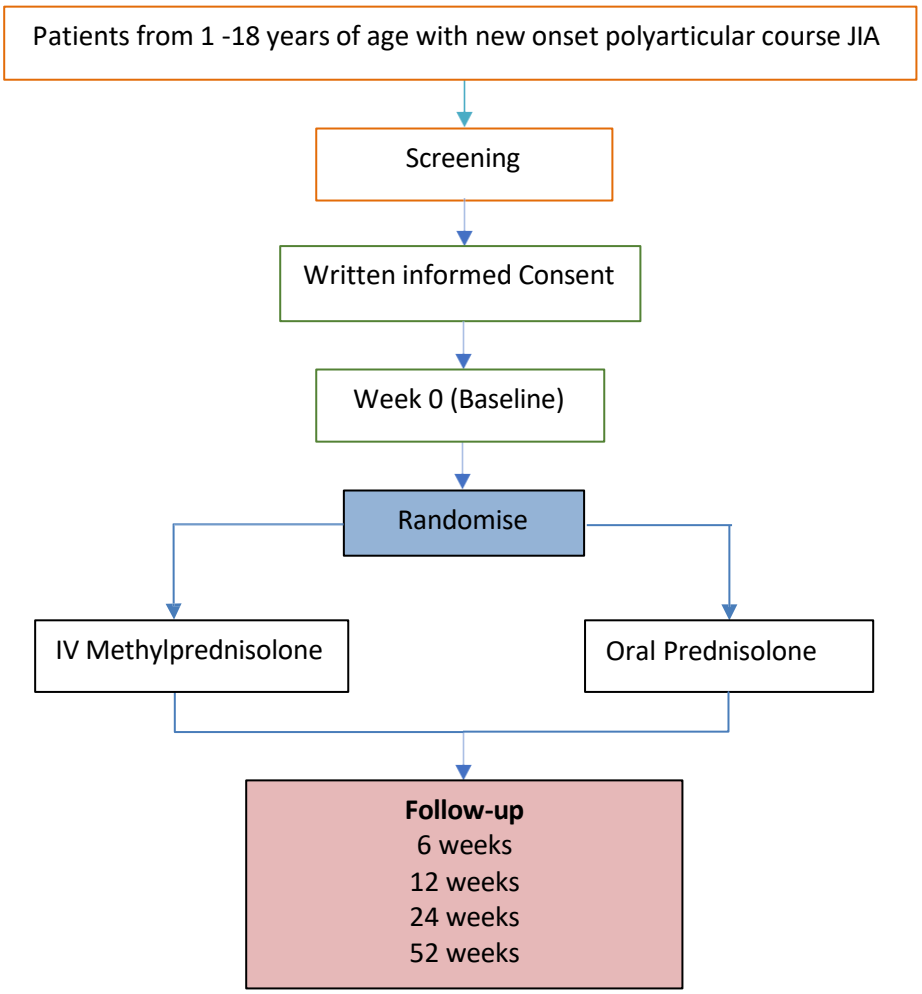
<table>
<tr><td></td><td>5. Treatment with methotrexate within 12 weeks preceding screening.

6. Any co-morbidity which in view of the treating clinician makes participation inappropriate.</td></tr>
<tr><td>Study Centres and Distribution:</td><td>A minimum of 14 Paediatric Rheumatology Centres in the UK</td></tr>
<tr><td>Treatment duration:</td><td>Participants will be randomised to either:
(i) A 6-week course of oral prednisolone (tablet or solution), taken at home.
OR
(ii) A 3-day course of intravenous methylprednisolone on a hospital day-case unit.</td></tr>
<tr><td>Visits</td><td>0 weeks (Baseline)
6 weeks ± 1 week
12 weeks ± 2 weeks
24 weeks ± 2 weeks
52 weeks ± 2 weeks
Total duration of follow-up: 52 weeks</td></tr>
<tr><td></td><td>IMP: Methylprednisolone
Route: IV
Form: For Intravenous administration
Dose: 30mg/kg per day for 3 consecutive days (Maximum dose: 1g per day)</td></tr>
<tr><td></td><td>Control: Prednisolone
Route: Oral
Form: Tablet or solution
Dose: The initial dose of prednisolone will be 1mg/kg per day with a maximum dose of 40mg. For participants weighing ≥40kg, the weaning will be a reduction in line with the percentage decrease used for lighter patients.
<table>
<tr><th>Week of oral prednisolone</th><th>Dose (patient <40kg)</th><th>Dose (patient ≥40kg)</th></tr>
<tr><td>1</td><td>1mg/kg per day</td><td>40mg</td></tr>
<tr><td>2</td><td>0.75mg/kg per day</td><td>30mg</td></tr>
<tr><td>3</td><td>0.5mg/kg per day</td><td>20mg</td></tr>
<tr><td>4</td><td>0.375mg/kg per day</td><td>15mg</td></tr>
<tr><td>5</td><td>0.25mg/kg per day</td><td>10mg</td></tr>
<tr><td>6</td><td>0.125mg/kg per day</td><td>5mg</td></tr>
</table></td></tr>
</table>

Objectives	
Primary objectives	1. To compare the clinical effectiveness of intravenous methylprednisolone versus oral prednisolone for controlling new onset polyarticular JIA in JIA Core Outcomes.
Secondary objectives	2. To compare the differences in JIA Core Outcomes for intravenous methylprednisolone versus oral prednisolone for the following domains: a. Pain b. Function c. Health-related Quality of Life (HRQOL) 3. To assess the effectiveness of intravenous versus oral corticosteroids in minimising the need for additional treatments including all corticosteroid routes and additional disease-modifying anti-rheumatic drugs (DMARDs)/biologics. 4. To evaluate short/medium term safety and tolerability of IV versus oral corticosteroids, with regards to adverse reactions, serious adverse events, laboratory assessments and paediatric glucocorticoid toxicity index (pGTI). 5. To determine if a dose response relationship can be identified in the efficacy/adverse responses to corticosteroids across all participants by secondary analysis, normalising corticosteroids received for dose, bioavailability and potency using previously published data.
Economic objectives	6. To determine the cost effectiveness of intravenous compared to oral corticosteroids from the perspective of the National Health Service and Personal Social Services. [20-23] 7. To estimate the resource use, cost and health utilities associated with intravenous and oral corticosteroids.
Exploratory/ Translational objective	8. To collect a fully-consented collection of biological blood samples that will be transferred to the Liverpool University Biobank for future ethical approved research. Blood samples will be collected and processed to plasma, serum and PBMCs with downstream extraction of protein and nucleic acid (RNA and DNA).

Outcomes:		**Corresponding objective number:**
Primary outcome:	Change in JADAS10 score between week 0 (baseline) and week 6.	1
Secondary Outcomes:	American College of Rheumatology (ACR) Pediatric Response Criteria • 30 • 50 • 70 • 90 • 100	1
	Juvenile Arthritis Disease Activity Score (JADAS) • 10 • 27 • 71	1
	Disease activity as measured by JADAS-10 cut-off Scores.	1
	Pain	2a.
	Function	2b
	Health-related Quality of Life (HRQOL)	2c.
	Requirement for additional treatment for JIA due to failure to respond to study treatment.	3
	Paediatric Glucocorticoid Index (pGTI) scores.	4
Economic outcomes	Incremental cost per quality-adjusted life year (QALY) gained.	6
	Resource use, cost and health utilities.	7

3.1 Schematic of Trial Design



3.2 Trial Lay Summary

The aim of this study is to compare two different routes of corticosteroid treatment in children and young people with JIA to find out which is best. Both are currently prescribed to treat JIA.

JIA causes significant pain and joint stiffness which can have a major impact on daily life and education. It is important to treat quickly and effectively to ensure children can return to normal activities and prevent long-term joint damage. Medications for long-term control take around 12 weeks to start working. Steroids act quickly to reduce inflammation whilst the other medications start to work.

Despite the benefits of steroids, there are many potential side-effects. There are no studies comparing giving steroids by tablet or solution versus via a drip. We don't know which route is most effective or tolerable for patients.

Children and young people aged 1-18 years with newly diagnosed polyarticular JIA (pcJIA) will be invited to take part.

They will be randomised to either:

1) A 6-week course of oral prednisolone taken at home

OR

2) A 3-day course of IV Methylprednisolone given via a drip on a hospital day-case unit.

Participants will be assessed at week 0 (baseline) before starting treatment and at four other visits at 6 weeks, 12 weeks, 24 weeks and 52 weeks. These appointments are in line with standard NHS appointments for JIA.

The main difference in taking part in this study compared to standard care is that the choice of steroid will be selected by random. In addition to standard care assessments, there will be additional assessments and questionnaires including assessment of steroid toxicity and side-effects. Questionnaires which assess the impact of JIA on quality of life and cost of treatment including time missed from usual activities by participants and carers. Participants may need to stay up to an hour longer than standard care appointments.

4 ROLES AND RESPONSIBILITIES

4.1 Sponsor

Alder Hey Children's NHS Foundation Trust is the Sponsoring organisation and is legally responsible for the trial. They will formally delegate specific duties to the Chief Investigator and Liverpool Clinical Trials Centre.

4.2 Funder

This trial is funded by NIHR Health Technology Assessment (HTA) Programme. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Table 1: Trial Funding

Funder(s)	Financial and Non-financial Support Given	Role
NIHR Health Technology Assessment Programme	Non-commercial financial support for delivery of project	The funders organised independent peer review of the study design, will approve protocol amendments, monitor trial progress, and appoint independent members of the trial oversight committees.
Alder Hey Children's Charity	Non-commercial financial support for collection of blood samples for future use	This funding source is allowing the collection and storage of blood samples for future research
Experimental Arthritis Treatment Centre for Children (supported by Versus Arthritis)	Non-commercial financial support for collection of blood samples for future use	This funding source is allowing the collection and storage of blood samples for future research

4.3 Chief Investigator (CI)

Associate Professor Clare Pain is the CI and Professor Ramanan the Co-CI for the trial and both are responsible for overall design and conduct of the trial in collaboration with other members of the trial team.

4.4 Principal Investigators (PIs)

In each participating site a PI will be identified to be responsible for identification, recruitment and data collection, along with follow up of trial participants and adherence to trial protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

4.5 Clinical Trials Unit (CTU)

The Liverpool Clinical Trials Centre (LCTC) is part of the University of Liverpool. In collaboration with the CI, the LCTC will have overall management responsibility and will be responsible for trial management activities including (but not limited to) trial planning, budget administration and Trial Master File (TMF) management (limited to budget and duties delegated to LCTC), safety reporting, data management, randomisation, statistical analysis, participating site initiation and monitoring and IMP management.

4.6 Health Economists at Bangor University

The Health Economist team are responsible for the production of patient-reported resource use measure questionnaires, cleaning and analysis of data collected in patient-reported resource use measure questionnaires and Patient Level Information and Costing System (PLICS) data and analysis.

4.7 Liverpool University Biobank

The Liverpool University Biobank will be responsible for:

- Providing SOPs and resources for the collection, shipment and receipt of samples for the biobank.
- Organising shipment and receipt of the samples.
- Monitoring consent provided by participants for collection of the samples - an optional part of this study.
- Maintaining records relating to the storage of the samples.
- Storage of all biobank samples including the spinning of human peripheral blood mononuclear cells (PBMC) samples before storage in the biobank.

4.8 Oversight Committees

4.8.1 Trial Management Group (TMG)

A TMG will be formed comprising the CI, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management. The TMG will meet regularly as defined in their terms of reference.

4.8.2 Trial Steering Committee (TSC)

The TSC will consist of an independent chairperson, two independent experts in the field of Rheumatology, an independent biostatistician, patient and public contributors, and the CI and Co-CI. Other non-member individuals may be invited to meetings to provide trial progress reports and updates, or as observers. The role of the TSC is to provide oversight for the trial and provide advice through its independent Chairperson. The TSC will consider recommendations of the Independent Data and Safety Monitoring Committee (IDSMC). The TSC assessment of IDSMC recommendations for the continuation or amendment of the trial will be communicated to the trial Sponsor and funder. The TSC will meet throughout the trial in accordance with their terms of reference.

4.8.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC will consist of at least three independent members encompassing expertise in biostatistics and Rheumatology. The IDSMC will receive and review monitoring reports for the trial and provide recommendations on the conduct of the trial to the TSC in accordance with their terms of reference.

5 INTRODUCTION

5.1 Background

Juvenile Idiopathic Arthritis (JIA) is a chronic inflammatory disease affecting 1 in 1000 children with around 12,000 children with JIA in England and Wales [1,2]. Delay in diagnosis and under-treatment lead to joint damage, disability and reduced quality of life [3]. In the UK and most of the world, children and young people with new-onset poly-articular Juvenile Idiopathic Arthritis (pcJIA) are commenced on corticosteroids and methotrexate [2, 4, 5]. As methotrexate can take several months to have an effect, corticosteroids are used to rapidly control inflammation with aims of reducing symptoms such as pain, stiffness, improving function and reducing damage [6]. Limited evidence informs optimal route or dose of corticosteroids in this group and practice varies hugely including administration via intravenous (IV), oral, intra-articular (IA) and intra-muscular (IM) routes [4, 5, 7].

The UK paediatric rheumatology clinical community and consumer representatives have strongly stated that further work should be conducted in this area to determine the most effective induction treatment to inform clinical practice. This question formed the basis of a NIHR HTA funded feasibility study SIRJIA (Steroid Induction Regimen for Juvenile Idiopathic Arthritis), which showed that a definitive randomised controlled trial is feasible and needed. A literature review formed part of this feasibility report [7]. Using the same search terms, an updated search up until June 2021 did not identify any new controlled studies of corticosteroids use in pcJIA. A search of clinicaltrials.gov in June 2021 identified no ongoing trials. Several consensus treatment plans were identified highlighting clinician equipoise and lack of evidence to support oral versus intravenous corticosteroids in this group [4, 5].

Whilst comparison of multiple routes of corticosteroids are possible, we have chosen comparison of oral and intravenous corticosteroids when prescribed in combination with the non-interventional medicinal product, methotrexate, because there is more pressing urgency for evidence of their efficacy, safety and cost-effectiveness than intra-articular or intramuscular in pcJIA.

Specifically:

i) The feasibility study literature review (and our updated review 2021) shows ongoing lack of evidence for intravenous and oral corticosteroids but evidence to support use of intra-articular corticosteroids;

ii) There is a considerable delay from decision to treat with intra-articular corticosteroids (often requiring general anaesthetic (GA) in children and young people) to administration (unpublished data from co-applicants) leading clinicians to use additional oral or intravenous corticosteroids whilst awaiting theatre. Limited availability to timely theatre and potential randomisation to GA were identified as a source of risk in the intra-articular corticosteroid arm in SIRJIA; [7]

iii) Intramuscular administration of corticosteroids is uncommon and so less benefit will be gained from its inclusion in this study;

iv) Cost and impact on families is disproportionate between IV and oral (estimated cost IV £1400 vs £7 for oral and requires 3 days missed school/work, cannulation). Understanding the efficacy, safety and cost-effectiveness of oral corticosteroids versus IV corticosteroids will have the highest impact for the NHS and patients/families, as choices between these drugs are currently opinion and anecdotal rhetoric-based rather than evidence-based.

5.2 Rationale

Limited evidence informs optimal route or dose of corticosteroids in this group and practice varies hugely. Clinician equipoise exists with lack of evidence to inform comparative effectiveness, safety and cost-effectiveness of intravenous corticosteroids versus oral corticosteroids [7].

Despite the advent of biologics and small molecules for treatment of pcJIA, nearly all children with new-onset pcJIA still receive corticosteroids despite the limited evidence base. The lack of evidence to compare intravenous to oral corticosteroids means we could be subjecting children and young people to a corticosteroid regimen with less efficacy leading to worse outcomes, more toxicity or potentially more invasive/costly treatments.

The COVID19 pandemic has led to changes in service configuration which have made accessing theatre time for GA more difficult, anecdotally shifting practice from intra-articular corticosteroid treatment to greater use of oral and intravenous corticosteroids.

5.3 Risk and Benefits

This trial is categorised as Type A (No higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the Medicines & Healthcare products Regulatory Agency (MHRA).

The IMP, IV methylprednisolone, and the Comparator, oral prednisolone (tablets and solution) are licensed for the treatment of inflammatory arthritis in adults and prescribed off-label (supported by accredited evidence) as part of established practice and standard care treatment for Juvenile Idiopathic Arthritis (JIA) in paediatric patients.

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the TMF. The trial risk assessment is used to determine the intensity and focus of monitoring activity.

6 AIMS

The overall aim of this study is to compare the effectiveness, safety and cost-effectiveness of intravenous versus oral corticosteroid treatment for children and young people with new onset polyarticular JIA. We aim to provide evidence that can be used to inform corticosteroid-use in the treatment of JIA based on the findings of our study and use our health economics analysis to inform NHS commissioning.

6.1 Objectives

6.1.1 Primary Objective

1) To compare the clinical effectiveness of intravenous methylprednisolone versus oral prednisolone for controlling new onset polyarticular JIA in JIA Core Outcomes [8, 28].

6.1.2 Secondary Objective(s)

2) To compare the differences in JIA Core Outcomes [15] for intravenous methylprednisolone versus oral prednisolone for the following domains:

   a. Pain

   b. Function

   c. Health-related Quality of Life (HRQOL)

3) To assess the effectiveness of intravenous versus oral corticosteroids in minimising the need for additional treatments including all corticosteroid routes and additional disease-modifying anti-rheumatic drugs (DMARDs)/biologics.

4) To evaluate short/medium term safety and tolerability of IV versus oral corticosteroids, with regards to adverse reactions, serious adverse events, laboratory assessments and paediatric glucocorticoid toxicity index (pGTI).

5) To determine if a dose response relationship can be identified in the efficacy/adverse responses to corticosteroids across all participants by secondary analysis, normalising corticosteroids received for dose, bioavailability and potency using previously published data.

6.1.3 Economic Objectives

6) To determine the cost effectiveness of intravenous compared to oral corticosteroids from the perspective of the National Health Service and Personal Social Services [20-23].

7) To estimate the resource use, cost and health utilities associated with IV and oral corticosteroids [24].

6.1.4 Exploratory / Translational Objectives

To collect a fully-consented collection of biological blood samples that will be transferred to the Liverpool University Biobank for future ethical approved research. Blood samples will be collected and processed to plasma, serum and PBMCs with downstream extraction of protein and nucleic acid (RNA and DNA).

6.2 Outcomes

Outcomes	Timing of measurement	Method of measurement	Objective *Section 6.1*
Primary outcome			
Change in JADAS10 score	0 and 6 weeks	JADAS composite score [8, 28]	1
Secondary outcomes			
American College of Rheumatology (ACR) Pediatric Response Criteria • 30 • 50 • 70 • 90 • 100	0, 6, 12 ,24 and 52 weeks	ACR Pediatric Response Criteria [15]	1
JADAS • 10 • 27 • 71	0, 6, 12, 24 and 52 weeks	JADAS composite score [12]	1
Disease activity as measured by JADAS-10 cut-off scores	0, 6, 12, 24 and 52 weeks	JADAS cut-off scores [8]	1
Pain	0, 6, 12, 24 and 52 weeks	Pain Visual Analogue Scale (Pain VAS) [33]	2a
Function	0, 6, 12, 24 and 52 weeks	Childhood Health Assessment Questionnaire (CHAQ) [13, 15]	2b
Health-related quality of life (HRQOL))	0, 6, 12, 24 and 52 weeks	Child Health Utility 9D Questionnaire (CHU-9D) [13] CAPTURE-JIA PROM [28]	2c
Requirement for additional treatment for JIA due to failure to respond to study treatment.	6, 12, 24 and 52 weeks	Concomitant medications as specified in Section 9.10.4	3

Paediatric Glucocorticoid Index (pGTI) scores	0, 6, 12, 24 and 52 weeks	pGTI assessment and scoring [18, 19]	4
Primary economic outcomes			
Incremental cost per quality-adjusted life year (QALY) gained.	0, 6, 12, 24 and 52 weeks	CHU-9D [13] Resource use questionnaires	6
Resource use, costs and health utilities associated with IV and oral corticosteroids.	0, 6, 12 ,24 and 52 weeks	CHU-9D [13] Resource use questionnaires Patient Level Information and Costing Systems	7

7 TRIAL DESIGN

This trial is designed as a multi-centre, open-label randomised controlled trial with 1:1 allocation ratio, stratified by site.

7.1 Trial Setting

Potential participants will be identified and recruited from a minimum of 14 Paediatric Rheumatology Centres in the UK.

7.2 Internal Pilot

STAR-JIA incorporates an internal pilot phase from first site open for 36 weeks. We will employ the following traffic-light stop/go criteria with regards proceeding to the full trial.

	Red	Amber	Green
Average Recruitment rate/site/month	< 0.24	0.24- 0.47	≥0.48
Number of sites opened	<7	7-13	≥14
Retention	<60%	60 – 79 %	≥80%
Treatment adherence	<60%	60 – 79 %	≥80%
Primary outcome completeness	<70%	70 – 89 %	≥90%

8 ELIGIBILITY CRITERIA

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be emailed to star-jia@liverpool.ac.uk before randomisation.

8.1 Inclusion Criteria

1. Participants must be between 1-18 years of age inclusive.
2. New onset pcJIA diagnosed by a paediatric rheumatologist (to include polyarticular rheumatoid factor (RF+) positive, polyarticular RF negative, enthesitis-related arthritis, psoriatic arthritis and extended oligo-articular). This includes new diagnosis of JIA with at least 5 joints affected and patients previously categorised as oligoarticular JIA (with 4 joints or less) who have extended to at least 5 joints.
3. Participants are expected to be able to commence allocated treatment within 1 week of randomisation.
4. Written, informed consent and where appropriate, assent obtained from participant or their legal representative.
5. Participants of child-bearing potential must be willing to abstain from sexual intercourse from consent to their final visit and/or use another acceptable contraception method as described in section 9.10.5 of this protocol.

8.2 Exclusion Criteria

1. Any contraindication to starting corticosteroids
2. Any contraindication to starting methotrexate
3. Pregnancy
4. Treatment with systemic corticosteroids within 4 weeks preceding screening (includes IV, IA, IM and oral).
5. Treatment with methotrexate within 12 weeks preceding screening.
6. Any co-morbidity which in view of the treating clinician makes participation inappropriate.

8.3 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials during the first six weeks of their participation in STAR-JIA. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on STAR-JIA, it should first be discussed with LCTC by emailing star-jia@liverpool.ac.uk who will contact the Chief Investigator for their decision. Co-enrolment into clinical trials with biologic therapy, DMARDs or small molecules is only permitted after the follow-up visit at 6 weeks. Subsequent participation in any other trial should be noted.

9 TRIAL INTERVENTIONS

Eligible patients will be randomised between IV methylprednisolone and oral prednisolone. Participants allocated IV methylprednisolone will have this administered once daily over 3 consecutive days on a hospital day unit or ward and participants allocated oral prednisolone will receive 6 weeks of prednisolone taken once daily.

The trial is open label and no blinding will take place. The Investigational Medicinal Product (IMP) will be labelled appropriately (as it would be for standard care) because both the IMP and the comparator drug are already licensed to be given as standard NHS treatment for JIA. Both the IMP and comparator will be supplied by the NHS Trust where the participant has been diagnosed with pcJIA and is expected to receive care.

9.1 Description of the Interventions

All corticosteroids can cause profound and varied metabolic effects. They modify the body's immune responses to diverse stimuli.

9.1.1 IV Methylprednisolone

IV methylprednisolone is prescribed off label as part of conventional treatment for JIA in CYP at hospitals across the UK.

Participants randomised to IV methylprednisolone at baseline (0 weeks) will commence treatment over 3 consecutive days on a hospital day unit within 1 week of randomisation. It should be ensured that participants and/or their parent/guardian understand the process by which they will receive an appointment from the day unit and receive contact details for the day unit should they have a question or concern *(e.g., should the participant fail to receive an appointment within 1 week of randomisation)*. It should be made clear that failing to attend the day unit for treatment may limit the benefits of treatment and stopping treatment before the final day (day 3) of treatment may adversely affect health.

Follow-up visits will take place at 6, 12, 24 and 52 weeks. These visits are in line with standard care appointments.

Methylprednisolone is a potent anti-inflammatory steroid with greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention. Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. This is an excipient with known effects. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. Following the intravenous injection of methylprednisolone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. This preparation is also rapidly absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after intravenous injection.

Further information is provided by NICE by copying the URL https://bnf.nice.org.uk/drugs/methylprednisolone/#drug-action into a browser *(Google chrome is recommended).*

Pfizer's Solu-medrone (also packaged under the registered name Solu-medrol) (Methylprednisolone sodium succinate for intravenous administration) is the most common brand used in the NHS. Solu-medrol sterile powder is an anti-inflammatory glucocorticoid containing methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate is the sodium succinate ester of methylprednisolone, and it occurs as a white, or nearly white, odourless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

Contraindications and cautions regarding IV methylprednisolone are provided in the SmPC accessible via the link below.

Detailed information on the pharmacodynamic and pharmacokinetic properties of methylprednisolone sodium succinate can be found in the SmPC below.

IV Methylprednisolone - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

9.1.2 **Oral Prednisolone**

Participants randomised to a reducing dose regimen of oral prednisolone at the baseline visit will receive prednisolone tablets or solution at the same visit to commence treatment at home immediately. For children aged 1-15yrs, the reducing dose regimen should be explained to the parent/guardian accompanying the child. It should be ensured that participants and/or their parent/guardian understand the reducing dose regimen and what to do if a dose is missed before the end of the baseline visit. It should also be made clear that missing doses or immediately stopping treatment before the prescription end date may limit the benefits of treatment and adversely affect health.

Follow-up visits will take place at 6, 12, 24 and 52 weeks. These visits are in line with standard care appointments.

Oral prednisolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effects. It is rapidly and apparently almost completely absorbed after oral administration; it reaches peak plasma concentrations after 1-3 hours. There is, however, wide inter-subject variation suggesting impaired absorption in some individuals. Plasma half – life is about 3 hours in adults and somewhat less in children, initial absorption, but not overall bioavailability, is affected by food. Prednisolone has a biological half-life lasting several hours.

Detailed information on the pharmacodynamic and pharmacokinetic properties can be found in the SmPCs below.

Prednisolone 1mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Prednisolone 5mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Prednisolone 5mg Soluble Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Prednisolone 10 mg/ml Oral Solution - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Prednisolone is excreted in the urine as free and conjugated metabolites, together with small amounts of unchanged prednisolone.

In this study, prednisolone solution or tablets (soluble or non-soluble) will be prescribed based on the needs of each participant randomised to oral prednisolone.

Each prednisolone tablet contains the stated amount of prednisolone as the sodium phosphate ester. This is an excipient with known effects.

Further information is provided by NICE by copying the URL https://bnf.nice.org.uk/drugs/prednisolone/#drug-action into a browser *(Google chrome is recommended).*

9.2 Drug Storage and Supply

Local NHS stock of IV methylprednisolone and oral prednisolone will be used in the trial as this is provided as standard care treatment for JIA.
The IMP should be stored at controlled room temperature 20-25°C in a dry, locked cupboard. The comparator (tablets or solution) should also be stored at room temperature away from heat and sunlight.

A normal dispensing label can be used. This should comply with Schedule 5 of the Medicines for Human Use Regulations 1994.

The IMP and comparator drug have marketing authorisation (MA) in the UK and will be used in the marketed presentation and packaging bearing the MA number that is normally used by each site. There will not be any repackaging and trial labelling of the IMP or comparator for the trial.

The IMP and comparator are stock drugs at all sites in this trial. The IMP and comparator drug will be sourced locally by the research site pharmacy as part of standard care. There will be no additional drug ordering. prescription, dispensing or drug administration costs.

As the IMP and comparator are given as standard care treatment for JIA, sites will maintain accountability, destruction and return records in hospital pharmacy as per their local site policy.

9.3 Preparation, Dosage and Administration

The IMP and comparator will be prescribed in line with local site policies, procedures and guidelines.

9.3.1 Preparation, Dosage and Administration of IV Methylprednisolone

Methylprednisolone sodium succinate for intravenous administration is soluble in water; it may be administered in a small volume of diluent and is well suited for intravenous use in situations where high blood levels of methylprednisolone are required rapidly.

In this study, participants will receive IV methylprednisolone, once daily with a dose of 30mg/kg per day, with a maximum dose of 1g per day, for 3 consecutive days on a hospital day unit or ward.

IV methylprednisolone should be prepared and administered in accordance with the manufacturer's instructions and in line with local site policies, procedures and guidelines.

Solu-medrone (Solu-medrol) is available packaged with or without a dilutent. The manufacturer, Pfizer, states that either: bacteriostatic water for injection (available at sites) or the accompanying dilutent should be used. The manufacturer also states that solu-medrone is used within 48 hours after mixing, however, hospital policies usually dictate that intravenous medications should be mixed on the day of administration and commenced without any unnecessary delays after preparation to reduce risk of contamination or error.

9.3.2 Preparation, Dosage and Administration of oral Prednisolone

Prednisolone tablets or solution may be prescribed in line with the needs of the participant. The initial dose of prednisolone will be 1mg/kg, with a maximum dose of 40mg. For participants weighing over 40kg, the weaning will be a reduction in line with the percentage decrease used for lighter patients.

A reducing dose regimen over 6 weeks should be prescribed as follows:

Week of oral prednisolone	Dose (patient <40kg)	Dose (patient ≥40kg)
1	1mg/kg per day	40mg
2	0.75mg/kg per day	30mg
3	0.5mg/kg per day	20mg
4	0.375mg/kg per day	15mg
5	0.25mg/kg per day	10mg
6	0.125mg/kg per day	5mg

Doses can be rounded up or down to nearest 5mg/1mg dose for ease of administration. However, exact dosing regimens need to be recorded in source documentation.

9.4 Treatment Modifications

After the patient has entered the trial, the treating doctor is free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the intervention arm to which they have been allocated.

The clinician may prescribe alternative treatment for pcJIA at the six week follow up after trial treatment has been completed. These alternative treatments prescribed should be recorded with concomitant medications on the appropriate CRF.

Any additional treatments for pcJIA given between baseline and 6 weeks visit will be classed as a treatment failure and should be discussed with the CI and/or co-CI prior to commencement.

Similarly, the participant/parent/legal representative remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons, unless willing to do so, and without prejudicing further treatment of the participant.

9.5 Dose modifications

If a clinician has clinical reasons for modifying the dose of IV methylprednisolone or oral prednisolone outside the dosage specified in this protocol, it should be recorded as a protocol deviation.

Any dose modification must reflect the guidance on prescribing IV methylprednisolone and oral prednisolone tablets and solution in the British National Formulary for Children, accessible via the link, https://bnfc.nice.org.uk/ or the British National Formulary, accessible via the link https://bnf.nice.org.uk/ for participants 16yrs and over.

Participants randomised to oral prednisolone or where appropriate, their legal guardians should be asked to confirm they understand how to follow the reducing dose regime at home after having it explained by the clinician. Clinicians are expected to follow local policies, procedures and guidelines when explaining the reducing dose regime.

Participants randomised to IV methylprednisolone will have their dose calculated whilst on the hospital day unit.

Adverse reactions to either IV methylprednisolone or oral prednisolone will be recorded as detailed in Section 11.

9.6 Accountability Procedures

As the IMP, IV methylprednisolone and comparator, oral prednisolone, will be given in line with standard care, site stock will be used for this trial. Trial-specific pharmacy accountability logs are not required for this trial as treatment is in line with standard care however, each site must maintain records for traceability of the preparation, checking and dispensing the IMP, IV methylprednisolone and the comparator, oral prednisolone as would be expected when preparing, checking and dispensing the same medications for JIA in standard care. Each site must be able to provide evidence of traceability if requested at any point during the trial.

The IMP and comparator will be labelled in line with the local policies, regulations and procedures of each site. It is the responsibility of sites to ensure that local policies, regulations and procedures are followed and manage drug inventory as there will be no central drug management system in place.

Clinicians at each site are responsible for ensuring the prescribed dose for the IMP or the reducing dose regime of the comparator is clearly stated in each participant's medical records.

Each site is responsible for ensuring the IMP, IV methylprednisolone, is administered as prescribed in line with local policies, procedures and guidelines. Sites are also responsible for maintaining up-to-date, accurate electronic records of drug administration of the IMP. Further details are provided in the trial's Pharmacy Manual.

9.7 Assessment of Compliance

The Research Team at each site will be asked to enter compliance data onto an electronic CRF.

This data will include:

- Confirmation of whether or not the participant adhered to their randomised treatment arm.

No participant treatment diaries will be used to collect data in this study.

9.8 Dosing Errors (Overdose and Under dose)

Refer to Section 11 - Safety Reporting.

9.9 Trial Restrictions

Trial restrictions are stated in the eligibility criteria and section 9.10 below.

9.10 Concomitant Medications/ and Specific Restrictions

9.10.1 Medications permitted

(i) Medications permitted from baseline (Visit 0)

- Methotrexate (see section 9.10.3 below)
- Folic Acid

- Topical steroid treatments (creams, ointments, eyedrops)
- Non-steroid anti-inflammatory drugs (NSAIDs)
- Proton pump inhibitors (PPIs)[#]

[#]The use of gastroprotective agents such as PPIs is recommended with corticosteroid use and clinicians should follow local guidelines/policy.

(ii) Medications permitted after 6 weeks (Visit 1)

- Biologics, additional DMARDS and JAK inhibitors may be prescribed
- Any additional corticosteroids via any route
- Other medications that do not meet the criteria below

9.10.2 Medications not permitted / Precautions required

- Between enrolment in the trial and 6 week follow-up visit, no systemic corticosteroids are allowed (including intra-articular, intra-muscular, intravenous (IV) or oral) except those prescribed as per the trial protocol.
- Biologics, JAK inhibitors and additional DMARDS except for methotrexate (non-investigational medicinal product (NIMP)) are not permitted between enrolment and 6 week follow-up visit.
- Medications contraindicated in patients on corticosteroids or methotrexate (NIMP).
- Medications that have (or suspected to have) resulted in hypersensitivity or an allergic reaction previously.

Evidence of known or suspected allergies and hypersensitivity should be checked and documented in accordance with each site's policies and procedures.

9.10.3 Non-Investigational Medicinal Product - Methotrexate

As standard of care for pcJIA, includes commencement of methotrexate in combination with corticosteroids, all participants who enrol in STAR-JIA will be prescribed methotrexate (NIMP), 10mg-20mg/m2 (rounded to nearest 2.5mg dose, to a maximum dose of 25mg) either subcutaneously or oral. The first dose of the NIMP, methotrexate, should occur within one week of starting corticosteroids.

Safety monitoring of participants on methotrexate and supply of methotrexate should be in line with local monitoring regime, policies, procedures and guidelines for Rheumatology patients on methotrexate, taking account of the age of the participant.

The results of all standard care blood tests in this trial as listed in the Schedule of Assessments in Section 10.7.1 should be checked by clinicians at every visit as part of safety monitoring and to ensure it is safe for the participant to continue to receive methotrexate. If blood results are outside of the normal local reference ranges provided at the site, the clinician should review the results and follow local policies, procedures and guidelines.

In the case of intolerance to methotrexate, dose can be reduced or methotrexate stopped as deemed appropriate by the treating clinician. Start and end dates of methotrexate will be recorded and reason for starting or stopping should be recorded in the concomitant medication section of the CRF.

9.10.4 Data on Concomitant Medication

Disease-modifying anti-rheumatic drugs (DMARDs), biologics, JAK inhibitors, corticosteroids, topical or systemic agents for ocular hypertension and topical steroid eye drops commenced due to JIA or Uveitis that a participant is receiving at the time of enrolment, or commences after enrolment and before the 52 week follow-up visit, must be recorded on the appropriate CRF with the reason for use, dates of administration, dosage form, dose and dose frequency.

9.10.5 **Specific Requirements / Restrictions**

Pregnancy is part of the exclusion criteria for this trial. The SmPCs for both IV methylprednisolone and oral prednisolone indicate there is a risk of stillbirth from administration of these corticosteroids during pregnancy. Consequently, avoiding sexual intercourse whilst receiving these corticosteroids is recommended. Clinicians at all sites are expected to provide participants age >12yrs with age and developmental-appropriate counselling regarding the possible harms to an unborn child from the disease and study treatment.

Pregnancy Testing

Pregnancy testing will take place at baseline (Visit 0) for participants of child-bearing potential as complications in pregnancy may arise as a result of JIA itself or as a result of corticosteroid treatment or methotrexate [26]. Participants of appropriate age-groups and parents are informed of this in the following trial information sheets before enrolment:

- *STAR-JIA Parent Information Sheet*
- *STAR-JIA Participant Information Sheet for 16-18yr olds*
- *STAR-JIA Participant Information Sheet for children, 11-15yrs*

Sites will be expected to follow their local policies and procedures regarding pregnancy testing and monitoring from week 6 onwards. This includes pregnancy and blood test monitoring for methotrexate, any other DMARDs and biologic medications and communicating with GPs regarding prescription of these medications and monitoring. Sites are also expected to follow local policies and procedures regarding the prescription of other additional permitted medications, as described in section 9.10.1, and for the period of time that a participant receives this medication.

Participants of child-bearing potential who have begun menstruation will need to complete a urine pregnancy test after giving consent/assent to enrol in this trial. The clinical trials facilitation group (CTFG) guidance states that an individual is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile.

Participants under 16 years should be asked whether they wish for their legal guardian to be present when the result is given. Clinicians have a responsibility to ensure that participants who are confirmed as pregnant should be advised on the most suitable pathway of care and local policies and procedures followed.

Contraception

Participants of child-bearing potential should be advised to avoid pregnancy during this trial and agree to at least one of the acceptable contraception methods listed below until visit 4 at 52 weeks.

All participants of child-bearing potential will be asked which reliable form of contraception they would use during the study period.

As the trial's target population is 1-18yrs, participants of child-bearing potential who confirm that they will have '**complete abstinence'** of sexual intercourse during the entire period of risk associated with the trial treatments will be accepted as we have considered ethical implications regarding trial requisites of contraception in participants of

child-bearing potential who state they are not sexually active and do not wish to use other forms of contraception. However, '**periodic abstinence'** (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception [26].

A list of acceptable contraception methods are provided in 2014_09_HMA_CTFG_Contraception_guidance Version 1.1. pdf (legemiddelverket.no) [27] and listed below;

- Complete sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments.
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal and transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner

9.10.6 **Blinding**

This is an open label trial with no blinding requirements.

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

LCTC will provide a screening log for completion during the trial to document all patients who have been screened, this information is required for enrolling participants and for monitoring purposes.

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent must be obtained prior to trial participation.

Date(s) of informed consent (plus assent where appropriate and if obtained) processes (including date of provision of patient information, details of information provided (titles, version details), randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

The informed consent process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered.

In obtaining and documenting consent, the research team 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. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason.

10.2.1 Informed Consent Process

Written informed consent and age-appropriate assent will be sought from potential participants / Legal Representatives.

Potential participants / Legal Representatives will be approached by a member of the local research team during their routine appointment with a Consultant Rheumatologist at which the potential participant is diagnosed with pcJIA. An ethically approved age-appropriate written information sheet will be provided and an animation explaining the trial will be available. This includes a detailed explanation of the trial and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the assent/consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ensure that the potential participant / Legal Representative has fully understood all the information and will ask if they are happy to agree to participation in the trial.

Where this is the case, written informed consent will be obtained by means of a dated signature on the assent/consent forms by the potential participant / Legal Representative. This should be countersigned and dated by the person who obtained informed consent, i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the potential participant / Legal Representative for their information
- One copy securely transferred to the LCTC
- One copy filed in the participant's medical records paper/electronic.

Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

10.2.2 **Minors – Assent Processes & Information Provision**

All minors, 11-15yrs, 6-10yrs and 5yrs and under, will be provided with an age-appropriate ethically-approved trial Information Sheet, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks. Feedback on these information sheets was sought from the PPIE group and information sheets were modified taking account of the feedback.

Minors aged 6 years and above will be approached for assent, unless the site team deem the minor to be of insufficient developmental capacity. Where a minor is approached for assent, they will not be entered into the trial until assent (in addition to legal consent from an appropriate adult) is provided – an exception to this is made where the minor expresses a wish for the decision to be made solely by the appropriate adult.

Where a minor does provide assent, they must personally write their name and date the assent form, which is then also signed and dated by the researcher.

The original signed assent form will be retained in the trial site's ISF and copies will be made:

- One copy provided to the minor
- One copy securely transferred to the LCTC
- One copy filed in the participant's medical records paper/electronic.

Details of the assent process (date, persons involved, version and type of information sheet and assent form used) must also be recorded directly into the participant's medical records.

Assent forms do not substitute for the consent form signed by the minor's Legal Representative.

Regardless of whether or not assent is sought, if a minor expresses a wish NOT to participate in the trial, this should be respected and the minor should not be recruited.

Once a minor reaches the age of consent (16 years old), they should be approached for consent at their next trial visit in accordance with the above described consent process. This new consent will replace the original consent provided by their Legal Representative (and any assent they had previously provided).

10.3 **Eligibility Assessment and Confirmation**

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log and must not occur until fully informed consent is documented. Eligibility criteria are described in Section 8.

Eligibility confirmation must be documented in the participant's medical notes and then on the trial's Eligibility CRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation). Protocol eligibility waivers are not permitted.

10.4 **Baseline (Week 0) Assessments**

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.7) in order to accurately complete the baseline CRF and collect the necessary information for the trial analyses.

Routinely collected information e.g. medical history / vital signs / relevant blood test results etc. can be transcribed from the patient's medical notes into the CRF once appropriate consent has been obtained.

The patient can proceed to randomisation once all the baseline assessments have been completed.

10.5 Randomisation

10.5.1 Randomisation Process

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to receive either IV methylprednisolone or oral prednisolone in a ratio of 1:1. Randomisation should occur on the same day following:

a) Eligibility criteria have been fulfilled (and full eligibility confirmed by a medically qualified person)

b) Baseline assessments have been completed.

A personal login username and password, provided by the LCTC will be required to access the randomisation system. Designated research staff will be issued with their personal login and password upon completion of training in the use of the system. This training will be coordinated by the LCTC.

When the system requirements (i.e. eligibility, baseline assessments) are confirmed the participant's treatment allocation and a unique trial number (randomisation number) will be displayed on a secure webpage. An automated email confirmation will be sent to the authorised randomiser, Principal Investigator (PI), site pharmacy and LCTC central trial email.

It is the responsibility of the PI or delegated research staff to inform the pharmacy department at their site of impending randomisation to ensure there is sufficient supply of the trial treatments.

Following randomisation, participants should be notified of their allocation as soon as possible and then should receive their randomised treatment allocation as described in Section 9.

10.5.2 Randomisation System Failure

In the event of a randomisation system failure, the site should contact the LCTC (Monday to Friday between 9:00 to 17:00 excluding bank holidays and University of Liverpool closed days) to try to resolve the problem.

10.6 Trial Treatment

Once the research team are aware of treatment allocation, participants are expected to be able to commence allocated treatment within 1 week of randomisation. This will be administered as described in Section 9.3.

10.7 Schedule for Assessments and Follow-up

10.7.1 Schedule of Assessments

All assessments and follow up are to be conducted in line with the Schedule of Assessments below: please note that screening and baseline are likely to occur on the same visit in most cases.

			Follow-Up Schedule					
Procedures	Screening	0 weeks	6 weeks	12 weeks	24 weeks	52 weeks	Trial Completion	Premature Discontinuation
Assessment & confirmation of eligibility	X							
Written Informed Consent		X						
Pregnancy Test+		X						
Demographic data		X						
Medical History from 24 weeks before recruitment		X						
Compliance with treatment (Defined in Section 9.7)			X					
Adverse Reactions (Refer to section 11)		(X)	(X)	(X)				
Serious Adverse Events (SAEs) (Refer to section 11)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Height (in metres)		X	X	X	X	X		
Weight (in kilograms)		X	X	X	X	X		
Blood pressure		X	X	X	X	X		
Concomitant Medications as specified in section 9.10.4		X	X	X	X	X		
Physician Reported Clinical Assessments – Active and Restrictive Joint Count		X	X	X	X	X		
Physician Reported Clinical Assessments – ILAR subtype classification of JIA		X				X		
Physician Reported Clinical Assessments – pGTI Assessment (defined in section 10.7.10)		X	X	X	X	X		
Physician Reported Clinical Assessments – PhGA-VAS (defined in section 10.7.4)		X	X	X	X	X		
Patient/Parent reported questionnaires – PGA-VAS (defined in section 10.7.4)		X	X	X	X	X		
Patient/Parent reported questionnaires – Pain VAS (defined in section 10.7.5)		X	X	X	X	X		
Patient/Parent reported questionnaires – CHAQ (defined in section 10.7.6)		X	X	X	X	X		
Patient/Parent reported questionnaires – CAPTURE-JIA PROM (defined in section 10.7.7)		X	X	X	X	X		
Patient/Parent reported questionnaires – CHU-9D (defined in section 10.7.7)		X	X	X	X	X		
Patient/Parent reported questionnaires – Resource Use Questionnaire (defined in section 10.7.9)		X	X	X	X	X		

Procedures		Screening	0 weeks	Follow-Up Schedule: 6 weeks	12 weeks	24 weeks	52 weeks	Trial Completion	Premature Discontinuation
	Tanner Puberty Stage Self-Assessment ≥ 10 years (defined in section 10.7.4)		X				X		
Clinical Laboratory (Refer to section 10.7.11)	FBC including *Haemoglobin (g/dL)* *WBC (x 10^9/L)* *Neutrophils (x10^9/L)* *Lymphocytes (x10^9/L)* *Platelets (x10^9/L)*		X	X	X	X	X		
	ESR *(mm/hr)*		X	X	X	X	X		
	CRP (mg/dL)		X	X	X	X	X		
	Renal profile including: *Urea (mmol/L)* *Creatinine (µmol/L)* *Potassium (mmol/L)* *Sodium (mmol/L)*		X	X	X	X	X		
	Glucose (mmol/L)		X	X	X	X	X		
	Liver profile including *Albumin (g/L)* *Alanine Transaminase (ALT) (IU/L)* *Alkaline phosphatase (ALP) (IU/L)* *Aspartate aminotransferase (AST) (IU/L)* *Bilirubin (µmol/L)*		X	X	X	X	X		
	Lipids *LDL (mmol/L)*		X	X	X	X	X		
	HbA1C *(mmol/mol)*		X	X	X	X	X		
Biobank Samples[#]	Serum & PBMCs		X		X				
	DNA		X						
Randomisation			X						
Trial Intervention***			X						

(X) – As indicated/appropriate.

*At baseline, all procedures should be done before trial intervention.

[+] Pregnancy tests are only required for participants of child-bearing potential

[#] Optional blood samples for future research – please note DNA sample can be taken at any point in the trial if unable to be obtained at baseline.

*** Trial intervention to be commenced within 1 week of randomisation.

10.7.2 Summary of Visits

Participants will need to attend clinics for treatment visits at:

0 weeks (baseline) and randomisation
6 weeks ± 1 week
12 weeks ± 2 weeks
24 weeks ± 2 weeks
52 weeks ± 2 weeks

Participants need to attend clinics at 6 weeks ± 1 week and ± 2 weeks for 12, 24 and 52 weeks visits from randomisation. If possible, appointments should be arranged at the initial appointment when randomisation occurs. The following assessments should be performed at clinic visits and data collected as stated below.

Screening

Assessment and confirmation of eligibility criteria should take place when patients consent to screening at their standard care appointment at the site.

Baseline Visit – Week 0

If consent/assent is given to participate, the baseline visit will take place immediately. The screening and baseline visit including randomisation are likely to occur at the same visit. Data should be recorded from the following assessments.

Physician-reported events

- Written informed consent
- Pregnancy Test
- Demographic data

  Date of birth (Month and year only), Gender, Ethnicity, Postcode (Social Deprivation Index)
- Medical History

  *From 24 weeks before recruitment including uveitis. Previous surgery and vaccinations **not** required.*
- Adverse Reactions and SAEs
- Height
- Weight
- Blood Pressure
- Concomitant medication as specified in section 9.10.4

  DMARDs, biologics, JAK inhibitors, corticosteroids, topical or systemic agents for ocular hypertension and topical steroid eye drops.

Physician-reported clinical assessments

- Active and restricted joint count
- PhGA-VAS

- ILAR subtype classification of JIA
- Paediatric Glucocorticoid Toxicity Index Assessment (pGTI assessment)

Assessments for participant/parent completion

- PGA-VAS

  (Participants ≥11 years / Parent proxy <11 years)
- Pain VAS over the past week

  (Participants ≥11 years / Parent proxy <11 years)
- Tanner Puberty Stage Self-Assessment

  (Participants ≥ 10 years)

Questionnaires for participant/parent completion

- CHAQ

  (Participants ≥ 11 years / Parent proxy <11 years)
- CAPTURE-JIA PROM
- CHU-9D
- Resource Use Questionnaire

Clinical laboratory tests

- Collection of blood samples and recording of results
  Standard Care: FBC, ESR, CRP, Liver Profile, Renal Profile, Glucose (Refer to section10.8.1)
  Trial-specific tests required for pGTI Assessment: LDL, HbA1C
  Actual results of ESR, LDL and HbA1C blood tests should be recorded on the appropriate CRF.

Biobank samples

- Collection of Serum & PBMC samples
- Collection of DNA sample

  (If DNA sample cannot be obtained at baseline, seek consent to obtain DNA sample any visit during the trial)

Trial intervention

- Randomisation
- Prescription of Trial Intervention

<u>Follow-up Visit 1 at 6 weeks</u>

Physician-reported events

- Assessment of Compliance with study intervention
- Adverse reactions and SAEs
- Height
- Weight
- Blood Pressure
- Concomitant medication as specified in section 9.10.4

  DMARDs, biologics, JAK inhibitors, corticosteroids, topical or systemic agents for ocular hypertension and topical steroid eye drops.

Physician-reported clinical assessments

- Active and restricted joint count
- PhGA-VAS
- pGTI assessment

Assessments for participant/parent completion

- PGA-VAS

  (Participants ≥11 years / Parent proxy <11 years)
- Pain VAS over the past week

  (Participants ≥11 years / Parent proxy <11 years)

Questionnaires for participant/parent completion

- CHAQ
- *(Participants ≥ 11 years / Parent proxy <11 years)*
- CAPTURE-JIA PROM
- CHU-9D
- Resource Use Questionnaire

Clinical laboratory tests

- Collection of blood samples and recording of results
  Standard Care: FBC, ESR, CRP, Liver Profile, Renal Profile, Glucose (Refer to section10.8.1)
  Trial-specific tests required for pGTI Assessment: LDL, HbA1C
  Actual results of LDL and HbA1C blood tests should be recorded on the appropriate CRF.

Follow-up Visit 2 at 12 weeks

Physician-reported events

- Adverse Reactions and SAEs
- Height
- Weight
- Blood Pressure
- Concomitant medication as specified in section 9.10.4

  DMARDs, biologics, JAK inhibitors, corticosteroids, topical or systemic agents for ocular hypertension and topical steroid eye drops.

Physician-reported clinical assessments

- Clinical examination including active and restricted joint count
- PhGA-VAS
- pGTI assessment

Assessments for participant/parent completion

- PGA-VAS

  (Participants ≥11 years / Parent proxy <11 years)
- Pain VAS over the past week

  (Participants ≥11 years / Parent proxy <11 years)

Questionnaires for participant/parent completion

- CHAQ

  (Participants ≥ 11 years / Parent proxy <11 years)
- CAPTURE-JIA PROM
- CHU-9D
- Resource Use Questionnaire

Clinical laboratory tests

- Collection of blood samples and recording of results
  Standard Care: FBC, ESR, CRP, Liver Profile, Renal Profile, Glucose (Refer to section10.8.1)
  Trial-specific tests required for pGTI Assessment: LDL, HbA1C
  Actual results of ESR, LDL and HbA1C blood tests should be recorded on the appropriate CRF.

Biobank samples

- Collection of Serum & PBMC samples
- Collection of DNA sample if not taken already

  (If DNA sample cannot be obtained at baseline, seek consent to obtain DNA sample any visit during the trial)

Follow-up Visit 3 at 24 weeks

Physician-reported events

- Adverse reactions and SAEs
- Height
- Weight
- Blood Pressure
- Concomitant medication as specified in section 9.10.4

  DMARDs, biologics, JAK inhibitors, corticosteroids, topical or systemic agents for ocular hypertension and topical steroid eye drops.

Physician-reported clinical assessments

- Active and restricted joint count
- PhGA-VAS
- pGTI assessment

Assessments for participant/parent completion

- PGA-VAS

  (Participants ≥11 years / Parent proxy <11 years)
- Pain VAS over the past week

  (Participants ≥11 years / Parent proxy <11 years)

Questionnaires for participant/parent completion

- CHAQ

  (Participants ≥ 11 years / Parent proxy <11 years)
- CAPTURE-JIA PROM
- CHU-9D
- Resource Use Questionnaire

Clinical laboratory tests

- Collection of blood samples and recording of results
  Standard Care: FBC, ESR, CRP, Liver Profile, Renal Profile, Glucose (Refer to section10.8.1)
  Trial-specific tests required for pGTI Assessment: LDL, HbA1C
  Actual results of ESR, LDL and HbA1C blood tests should be recorded on the appropriate CRF.

Follow-up Visit 4 at 52 weeks

Physician-reported events

- Assessment of Adverse Events
- Height
- Weight
- Blood Pressure
- Concomitant medication as specified in section 9.10.4

  DMARDs, biologics, JAK inhibitors, corticosteroids, topical or systemic agents for ocular hypertension and topical steroid eye drops.

Physician-reported clinical assessments

- Clinical examination including active and restricted joint count
- PhGA-VAS
- ILAR subtype classification of JIA
- pGTI assessment

Assessments for participant/parent completion

- PGA-VAS

  (Participants ≥11 years / Parent proxy <11 years)
- Pain VAS over past week

  (Participants ≥11 years / Parent proxy <11 years)
- Tanner Puberty Stage Self-Assessment

  (Participants ≥ 10 years)

Questionnaires for participant/parent completion

- CHAQ

  (Participants ≥ 11 years / Parent proxy <11 years)

- CAPTURE-JIA PROM
- CHU-9D
- Resource Use Questionnaire

Clinical laboratory tests

- Collection of blood samples and recording of results
  Standard Care: FBC, ESR, CRP, Liver Profile, Renal Profile, Glucose (Refer to section10.8.1)
  Trial-specific tests required for pGTI Assessment: LDL, HbA1C
  Actual results of ESR, LDL and HbA1C blood tests should be recorded on the appropriate CRF.

10.7.3 Guidance for different types of assessments

10.7.4 Efficacy Assessments

(i) JADAS10

JADAS10 is a Juvenile Arthritis Disease Activity Score is designed to measure the level of disease activity in non-systemic juvenile idiopathic arthritis by providing a single numerical score [28]. Disease activity in joints will be assessed in all participants at every visit to determine the efficacy of the IMP and comparator. It is distinguished from the clinical JADAS10 (cJADAS10) by its inclusion of the erythrocyte sedimentation rate (ESR). Employing the JADAS10 rather than cJADAS10 score will not impact on the accuracy of calculations since previous validation work has confirmed that the statistical performances of the different JADAS scores are comparable [28]. Whilst the JADAS10 is the primary outcome, a complete active and restricted joint count will be undertaken to calculate the secondary outcome. JADAS27 and 71 will also be calculated as will the number of participants that reach cut-offs for inactive disease, minimal/moderate and high disease activity according to JADAS scores [8].

(ii) American College of Rheumatology (ACR) Pediatric Response Criteria

The ACR Pediatric Response Criteria consists of six core variables: PhGA VAS, PGA VAS, functional ability measured using CHAQ, active joint count, restrictive joint count and ESR [12]. The criteria will be used in the clinical assessment of each participant at every visit to determine the efficacy of IMP and comparator.

(iii) Physician Global Assessment of Disease Activity Visual Analogue Scale (PhGA-VAS)

The physician global assessment of disease activity visual analogue scale (PhGA-VAS) is a single question assessment tool used by physicians in standard care to measure disease activity (in this case, JIA) on a 0-10 visual analogue scale where 0=no activity and 10=maximum activity. [12]

(iv) Patient Global Assessment of Well-being Visual Analogue Scale (PGA-VAS)

The patient global assessment of well-being visual analogue scale (PGA-VAS) is a single question assessment completed by patients (or if appropriate, their parent) in standard care to score the extent to which disease (in this case, JIA) is affecting their health on a 0-10 visual analogue scale where 0 = very well and 10 = very poor [12]. All participants (or if appropriate, their parent/legal guardian) will be asked to complete this assessment at every visit. Participants 11 years of age and over will be asked to complete the PGA-VAS. Parents/legal guardians will be asked to complete this assessment for children under 11 years.

10.7.5 Pain Assessment

(i) Pain VAS

The pain visual analogue scale (Pain-VAS) is a single question assessment completed by patients (or if appropriate, their parent) in standard care to score the severity of their pain over the last one week on a 0-10 visual analogue scale where 0=no pain and 10= very severe pain [33]. All participants (or if appropriate, their parent/legal guardian) will be asked to complete this assessment at every visit. Participants 11 years of age and over will be asked to complete the Pain VAS. Parents/legal guardians will be asked to complete this assessment for children under 11 years. The Pain-VAS will be the participant's self-assessment of pain or, if the participant is under 11 years, parental assessment of the participant's pain over the past week.

10.7.6 Functioning Assessment

(i) Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ is the most widely used functional measure of disability in JIA, both in standard care throughout the UK and clinical trials. It consists of eight domains enquiring about the child or young person's ability to manage a range of activities of daily living on a 5 point scale [13, 15]. Permission to use the CHAQ has been obtained from Professor Gurkirpal Singh at Stanford University. Parents/legal guardians will be asked to complete the CHAQ for participants under 11 years, however, participants 11 years of age and over will be asked to complete the CHAQ themselves. Completion of the questionnaire will be checked by site staff.

10.7.7 Quality of Life Assessment

(i) Child Health Utility-9D Questionnaire

The CHU-9D [13] is an instrument that measures health and calculates QALYs for children and adolescents. It is a paediatric generic preference-based measure of health-related quality of life (HRQOL) which children 11 years of age and over will be asked to complete. Parents or legal guardians will be asked to complete a proxy version of CHU-9D for children under 11 years of age. It consists of a short questionnaire and a set of preference weights giving utility values for each health state described by the descriptive system, allowing the calculation of quality-adjusted life years (QALYs) for use in cost utility analysis. The questionnaire has 9 questions with 5 response levels per question and is self-completed by the child. A license to use the CHU-9D has been obtained from University of Sheffield. Completion of the questionnaire will be checked by local site staff.

(ii) CAPTURE-JIA Patient Reported Outcome Measure (PROM)

The CAPTURE-JIA PROM questionnaire consists of three core themes: physical, social and emotional wellbeing [28]. Permission to use the CAPTURE-JIA PROM has been obtained from Dr Flora McErlane at Newcastle-upon-Tyne University Hospitals NHS Trust. Completion of the questionnaire will be checked by local site staff. Participants age 11 years and over to complete in clinic. Parents/legal guardian of participant to complete parent proxy if participant is under 11 years of age.

10.7.8 Safety Assessments

An assessment of adverse reactions and serious adverse events will be undertaken at each study visit from baseline to the last trial visit. These reviews will be carried out by the PI or other delegated staff member conducting the visit. Requirements for adverse event reporting are detailed fully in Section 11.

10.7.9 **Resource Use Questionnaire**

The University of Bangor will provide a resource use questionnaire for the trial's health economic outcomes. This may be completed by participants age 11 years or over, or parent/legal guardian of the participant if under 11 years of age [31].

Whilst the premise of this trial is to define the most effective treatment regimen as per the primary outcome, primary economic evaluation will determine the comparable cost effectiveness of the two treatments regimens.

Understanding the efficacy, safety and cost-effectiveness of oral vs IV will have the highest impact for the NHS and patients/families, as choices between these drugs are currently opinion and anecdotal rhetoric-based rather than evidence-based. The cost and impact on families is disproportionate between treating JIA with IV methylprednisolone and treating JIA with oral prednisolone. IV methylprednisolone is administered at an estimated cost of £1400 and involves cannulation and 3 days missed from school or work whilst oral prednisolone has an estimated cost of £7 per patient without any need for cannulation or missed school or work.

Benefits may also exist in terms of healthcare experience, longer-term outcomes or quality of life between the two corticosteroid regimens which will enable informed decisions with families about the choice of treatment. We will use our health economics analysis to inform NHS commissioning.

10.7.10 **Paediatric Glucocorticoid Toxicity Index (pGTI) Assessment**

The pGTI is a standardized, weighted clinical outcome assessment which measures change in glucocorticoid toxicity over time [18, 19]. It is an aggregate assessment of common, important glucocorticoid toxicities that are organized into health domains graded as minor, moderate, or major and weighted according to severity. Two quantitative scores comprise the overall toxicity profile derived from pGTI data: 1) the Cumulative Worsening Score; and 2) the Aggregate Improvement Score. The pGTI also includes a qualitative, unweighted record of glucocorticoid side-effects known as the Damage Checklist, which documents less common toxicities unlikely to change with varying glucocorticoid dosing. As part of this study, pGTI assessment data will be collected from participants at baseline, 6, 12, 24 and 52 weeks respectively and recorded on an electronic pGTI CRF developed by a third party company.

10.7.11 **Tanner Puberty Stage Self-Assessment (included to support calculation of the pGTI scores)**

The Tanner Puberty Stage Assessment [30] will be used to support the physician's confirmation of the participant's stage of puberty required for the physician's completion of the pGTI assessment. The Tanner Stage Puberty Assessment is a self-assessment questionnaire for assessing the onset of puberty in children [29, 30]. Children aged 10 and upwards will be asked to respond to questions regarding stage of puberty using pictures to support this. This assessment will only be done at baseline and 52 weeks.

10.8 **Sample Management**

10.8.1 **Collection of standard care blood samples and bloods required for pGTI assessment**

Participants will have blood tests as part of standard care and for pGTI calculation at every visit as shown in table 2. These will be ordered by the clinician who is examining the participant and taken by staff trained and competent to undertake venepuncture in accordance with site's policies and procedures. Please note it is acceptable, if a participant is randomised to IV arm, to collect baseline bloods at time of insertion of cannula for IV methylprednisolone administration.

10.8.1.1 Processing and analysis

Standard care and pGTI blood samples (LDL and HbA1c) will be processed and analysed at each site's hospital laboratories.

10.8.1.2 Recording of blood results

All blood results will be available in each participant's medical records however, only the actual results from ESR, LDL and HbA1C blood tests should be recorded on the appropriate CRF at every visit.

The clinician who examines the participant will be responsible for monitoring the participant's blood results as well as responding to and reporting clinically significant abnormal results in accordance with section 11.

The schedule for standard care blood tests can be found in the Schedule of Events in section 10.7.1

10.8.1.3 Volume of blood to be collected

For participants age 16yrs and under, the maximum volume of blood collected for standard care blood tests and research-specific blood tests will be a maximum of 12mls.

For participants over 16 years, the maximum volume of blood collected for standard care blood tests and research-specific blood tests will be a maximum of 15mls.

10.8.2 Collection and shipment of blood samples for future research (OPTIONAL)

Participants and where appropriate, their legal guardian(s), will be provided with written information to explain that, as part of this study, participants are invited to provide blood samples at the baseline visit and 3 month visit for future research. Participants can still take part in the clinical trial if they do not consent/assent to blood samples being taken for future research. This includes a one-off DNA sample (ideally at baseline but can be taken at any time during the study) and samples for serum and PBMCs at baseline and 12 weeks. If a sample cannot be taken at baseline or the 3month visit, participants should be asked if they are willing to provide it at a later visit. Written informed consent (with assent where appropriate) will be sought. Blood samples for future research will be collected where consent/assent is obtained and deposited into the Liverpool University Biobank (LUB). A detailed description of sample collection, packaging and shipping is provided in the STAR-JIA Sample Collection Manual. In brief, samples will be collected at trial sites using pre-labelled sample collection kits, blood will be posted to the Liverpool University Biobank where they will be processed to plasma, red cell pellet, serum and PBMCs and where required to protein and nucleic acids.

A detailed description of processes for sample collection, packaging, shipment and ordering kits is provided in the STAR-JIA Sample Collection Manual. Samples should be collected as early in the day as possible to allow for next day delivery to the Liverpool University Biobank (LUB). If possible, arrange blood sample collection times between Monday and Thursday to avoid deliveries over the weekend when lab staff will not be available to process samples. For enquiries regarding samples collected for future research, please email LUB at: **Biobanking@liverpool.ac.uk** or telephone LUB on: **0151 794 9100**.

10.8.3 Custodianship

The optional blood samples collected as part of the STAR-JIA trial will be considered as a gift and adopted by Liverpool University Biobank and stored for release to researchers for future approved research.

10.9 Intervention Discontinuation and Participant Discontinuation / Withdrawal

In consenting to the trial, participants / Legal Representatives agree to all trial activities including administration of trial intervention and treatment and follow-up assessments, visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.9.1 Premature Discontinuation of Trial Intervention

Participants may discontinue treatment for reasons including, but not limited to:

- Participant-led, i.e. request by the participant / Legal Representative
- Unacceptable side effects (see Section 11 for Adverse Event reporting)
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.
    - Participant meets an exclusion criterion (either newly developed or not previously recognised)

10.9.2 Premature Trial Intervention Discontinuation Procedures

Discontinuation from trial intervention should be reported to LCTC using the 'Premature Discontinuation of Trial Intervention' CRF. This does not mean discontinuation of the trial altogether, and the remaining trial procedures, follow up visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn). Data to be collected at the time of discontinuation will include the following:

- Reason for the premature trial intervention discontinuation should be documented on the appropriate CRF.
- All baseline data will be collected and should have already been completed on the appropriate CRF.
- All queries relating to baseline data should be dealt with within two weeks of being raised.
- The participant should be asked if are happy to remain in this trial.
- LCTC should be informed if a participant requests to withdraw from this trial.

10.9.3 Participant Withdrawal

Participants / Legal Representatives are free to withdraw at any time without providing a reason, though a reason should be recorded if one is given. LCTC should be informed via email to the LCTC and via completion of a Withdrawal CRF to be returned to LCTC within 7 days.

If participants / Legal Representatives express a wish to withdraw from further trial activities, the research team at site should ascertain if this is for all elements of trial follow-up, or if for example data from routine assessments can still be collected for the trial. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable.

Where a participant / Legal Representative decides that they do not want any further data to be provided for trial purposes, data already collected up to the point of withdrawal will still be used in trial reports and analyses, but no further data will be collected unless required by law (e.g. safety reporting regulatory requirements).

10.9.4 Participant Transfer

If a participant moves from the area, every effort should be made for them to be followed-up at another participating trial site and for this trial site to take over responsibility for the participant.

A copy of the participant's CRFs should be provided to the new site. The participant remains the responsibility of the original site until the new site PI has signed the Transfer CRF.

10.9.5 **Loss to Follow-up**

A participant will be considered lost to follow up if they fail to return for three scheduled visits and are not contactable by the site research team.

If a participant fails to attend/facilitate a required trial visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit (be conscious of acceptable windows for collecting valid data) and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. three telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the participant's medical notes.)
- If the participant continues to be unreachable, they should be considered withdrawn from the trial with a primary reason of lost to follow up and this should be recorded on the appropriate CRF.

10.10 **End of Trial**

The End of the Trial is defined to be the database lock. Trial closure activities will begin once all participant treatment and follow-up are complete. Alternatively, the trial may be closed prematurely by the TSC, on the recommendation of the IDSMC. Site and trial closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely.

10.10.1 **Trial Discontinuation**

In the event that the study is discontinued, all participants will be followed-up post treatment and adverse events will continue to be collected as per protocol (see section 9). The treating clinician will be responsible for deciding the best treatment locally for each participant.

11 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

For the purposes of this study, Adverse Reactions (AR) related to the interventions, IV methylprednisolone and oral prednisolone and JIA-related Uveitis and **all** Serious Adverse Events (SAEs) are reportable.

ARs will be collected at 6 weeks and 12 weeks **only** due to the short half-life of corticosteroids and that most adverse reactions occur whilst on or shortly after stopping corticosteroids.

All Serious Adverse Events (SAEs) will be recorded throughout the study and must be reported immediately (and within 24 hours of knowledge of the event) by entry into the trial database and signed off by the PI.

This includes SAEs related to IMPs and Non-Investigational Medicinal Products (NIMPs). Any trial specific SAE reporting exceptions are detailed in section 11.4.

11.1 Terms and Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
Serious Adverse Reaction (SAR)	An adverse reaction which meets the definition of serious (see Section 11.3) is a SAR. A SAR event that has been assessed as 'expected' (see Section 11.7 Expectedness) according to the Reference Safety Information (see below) will remain classified as a SAR only, however some Serious Adverse Reactions that are considered 'unexpected' will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is classed in nature as serious and "unexpected" (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

11.2 Adverse Events

Only adverse events that meet the definition of seriousness are reportable see section 11.3

11.3 Assessment of "Seriousness"

The assessment of seriousness of safety events must be performed by an appropriately delegated, medically qualified member of the site research team.

An Adverse Event or Adverse Reaction is assessed as serious if it:

- Results in death.
- Is life-threatening.
    - (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death)
- Requires hospitalisation or prolongation of existing hospitalisation.
    - (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE)
    - The above excludes admission to a Day Unit for treatment.
- Results in persistent or significant disability or incapacity.
    - (i.e. substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect.
    - (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis)
- Is another important medical event.
    - (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

11.4 Trial Specific SAE Reporting Requirements

SAEs must be entered into the trial database within 24 hours of the site becoming aware.

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11.5 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator (or medically trained delegate) responsible for the care of the participant using the definitions in the table below.

Table 2: Severity Grading

Severity	Description

Mild	Does not interfere with routine activities
Moderate	Interferes with routine activities
Severe	Impossible to perform routine activities

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 11.3). Hence, a severe safety event need not necessarily be a "serious" safety event.

11.6 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assessment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. Assessment should be made against the IMP or comparator administered to a participant.

Table 3: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be classed as "Related" (i.e. having a reasonable possibility of being a causal relationship), and events assessed as unrelated or unlikely will be classed as "Unrelated" (i.e. having no reasonable possibility of being related).

Assessment of causality should be made based on known safety profiles of the IMPs in question (e.g. SmPC) or of other drugs in the same class.

In the case of discrepant views on causality between the treating investigator and others, **the causality assessment of the treating investigator will never be downgraded** and the MHRA & REC will be informed of both points of view.

11.7 Assessment of "Expectedness"

Assessments of expectedness are the Sponsor's responsibility and are delegated to the LCTC and Medical Reviewer. There is no requirement for a reporting investigator to assess expectedness.

An event will be considered unexpected if it is not listed within the relevant document as detailed in the table below, which is current and approved for the trial at the time of the event's onset.

Intervention	Document to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Brand name: Solu-Medrone Manufacturer: Pfizer Active Substance: Methylprednisolone Sodium Succinate Dose: 1g Formulation: Powder for injection	SmPC	Section 4.8
Brand name: Prednisolone Manufacturer: Wockhardt UK Ltd Active substance: Prednisolone Dose: 1mg Formulation: Tablet	SmPC	Section 4.8

Side-effects of the trial interventions that are listed in the SmPCs will be regarded as expected.

The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI, the event will be assessed as unexpected. Fatal or life-threatening events related to the IMP/Intervention by nature, are deemed unexpected (unless specified in the RSI as such).

11.8 Time Period for Active Monitoring of Safety Events

Active monitoring of safety events experienced by trial participants will be from the period of IMP administration to last dose of IMP and up to their 12 weeks follow-up visit.

IMPORTANT: Any serious adverse event occurring in a trial participant after the end of the "active monitoring" period must continue to be reported by sites to the LCTC if the PI becomes aware of them. Reporting should be in accordance with the timeframes and procedures described in section 11.12.

11.9 Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)

- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- Pregnancy (See section 11.10 for more details)

Do not record:

- Non-related Adverse Events
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication **without signs or symptoms**
- The disease being treated or associated symptoms/signs unless more severe than expected for the participant's condition

*N.B. If overdose occurred **with** resulting signs and symptoms that meet the protocol criteria for SAE (i.e., requiring hospitalisation) then they should be reported accordingly (see section 11.4 for more information) and the overdose highlighted to the LCTC team.

The events above do not need recording as the trial is considered low risk. Both the IMP and Comparator are given in standard care for new onset pcJIA. This is documented in the Risk Assessment.

11.10 Reporting of Pregnancy

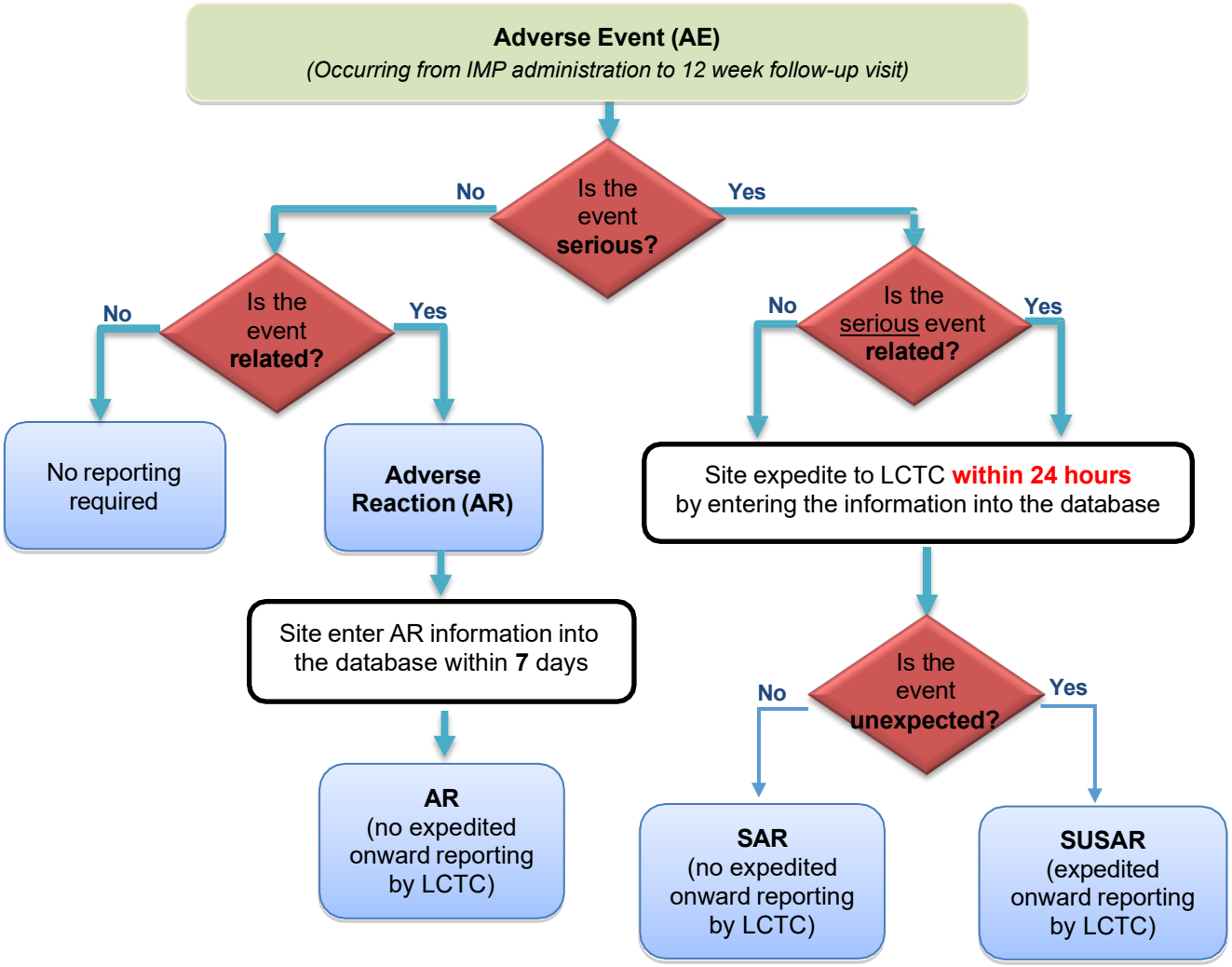
Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. If pregnancy occurs within the active monitoring period described in section 11.8, this must be reported via the database to the LCTC, within 24 hours of the research team becoming aware. All pregnancies and outcomes reported to LCTC will be notified to the trial Sponsor and monitored by trial oversight committees.

11.11 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified reported via the database to the LCTC within 24 hours of becoming aware. Deaths occurring within the active monitoring period described in section 11.8 are reportable.

11.12 Reporting Procedures

All safety events which are recorded for the trial should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine trial visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. SAEs are to be reported to LCTC in an expedited manner). Any questions concerning safety reporting should be directed to the LCTC in the first instance. A flowchart is given below as an overview of reporting procedures for different types of safety events.


Adverse Event (AE)
(Occurring from IMP administration to 12 week follow-up visit)
Is the event serious?
No
Yes
Is the event related?
No
Yes
No reporting required
Adverse Reaction (AR)
Site enter AR information into the database within 7 days
AR (no expedited onward reporting by LCTC)
Is the serious event related?
No
Yes
Site expedite to LCTC within 24 hours by entering the information into the database
Is the event unexpected?
No
Yes
SAR (no expedited onward reporting by LCTC)
SUSAR (expedited onward reporting by LCTC)

11.12.1 **Site Responsibilities**

Initial Reports

In addition to below requirements to report to the LCTC, safety events should also be reported to the site R&D team in accordance with local policy.

The site PI is responsible for ensuring that all adverse events (whether or not assessed as serious / related / expected) which the local research team becomes aware of are recorded on CRFs for trial purposes and reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events.

All adverse events should be recorded in the database within 7 days of the site becoming aware of the event.

Events which are assessed as "serious" must **also** be recorded in the database **immediately and in no circumstances later than 24 hours from becoming aware**.

The assessments of seriousness and causality must be performed by an appropriately authorised medically qualified doctor. The following is considered the regulatory minimum reporting information and must be provided in initial reports:

- Participant study number
- Study site identifier and name of reporting site staff member
- Description of the event, including date of onset
- For CTIMPs: Suspect IMP
- Seriousness assessment
- Causality assessment

N.B. In the absence of a delegated medically qualified doctor the SAE CRF must be assessed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE and make amendments as appropriate. The initial report shall be followed by detailed follow-up reports.

Follow-up Reports

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable. Where additional information on a SAE is received by site this must be entered into the database within 24 hours of becoming aware of the information.

Sites must respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event.

11.12.2 **LCTC Responsibilities**

The trial Sponsor, Alder Hey Children's NHS Foundation Trust have delegated to LCTC the duty of onward reporting of safety events to REC, MHRA and Sponsor.

Safety events which are assessed as "serious", "related" and "unexpected", will be classed as SUSARs and will be onward reported in an expedited manner to MHRA and REC within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** of receipt at the LCTC. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of receipt at the LCTC

Additionally, SUSARs will be reported to the trial Sponsor within agreed timelines.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline as per LCTC Safety Processing Plan.

The LCTC will submit annual reports containing safety information to REC and MHRA.

Information on safety events will also be reported to TSC/IDSMC. Inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported safety events in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

11.13 **Urgent Safety Measures (USMs)**

An USM is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA via the usual amendment process.

The LCTC will notify the REC and MHRA immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a temporary halt, or permanent termination of the trial.

Following notification of a USM, a substantial amendment should be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the trial is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the trial is halted or permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), LCTC will notify the REC and MHRA within 15 days of the date of halt/termination.

11.14 **Contact Details and Out-of-hours Medical Cover**

As this trial is low risk and the IMP and comparator are given in standard NHS practice and have a well-established safety profile emergency, out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size

12.1.1 Sample Size Calculation

The sample size calculation is based on the recommendations by Borm [32]. The method by Borm uses a two-step approach, firstly calculating the required sample size as if a t-test were to be used then the number of patients is multiplied by a 'design factor' to give the number of patients required for the analysis using ANCOVA.

Based on data from the HTA feasibility study [7], the mean change from baseline to six weeks in cJADAS10 in those patients who had oral corticosteroids was -6.37 with SD 5.05 and the correlation between baseline and six weeks was 0.55.

Applying the first step, a sample size of 87 in each group (174 patients in total) is required to have 90% power to detect a difference in means of 2.5 (which equates to an effect size of 0.50), assuming that the common within group SD is 5.05, using a two group t-test with a 5% two-sided significance level. Assuming 5% missing data the total required sample size would be 184.

Stage 2 applies the design factor (which is equal to 0.6975 (1-0.552) to the sample size obtained in Stage 1, which then gives a total number of required patients to be 130.

12.2 Method of Randomisation

12.2.1 Allocation Sequence Generation

Participants/legal guardians who give their informed consent for the randomised controlled trial will complete baseline processes and outcome measures before being individually randomised. The randomisation will be performed by the site team using 24-hour web-based randomisation system to protect against subversion whilst ensuring that the trial maintains good balance to the allocation ratio of 1:1 both within each stratum and across the trial. This system will be set up, maintained and monitored independently of the trial statistician or other trial staff.

12.2.2 Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all baseline measurements have been completed.

12.3 Interim Analyses

There are no planned interim analyses for this trial.

Analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an IDSMC. These analyses will be performed at the LCTC. The IDSMC will be asked to give recommendations to the TSC on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

12.4 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Analyses will be by 'intention to treat' for the primary and secondary outcomes on all randomised participants, in the group to which they were allocated, and for whom the outcomes of interest have been observed or measured.

Demographic and baseline characteristics will be summarised separately using descriptive statistics for each randomised group to allow assessment of whether balance was achieved between randomised groups. This will include sex, age, ethnicity, JIA subtype (ILAR classification) and other relevant characteristics. No statistical testing of demographic and baseline differences between groups will be performed.

Primary and secondary outcomes at 0 weeks (baseline), 6 weeks, 12 weeks, 24 weeks and 52 weeks will be summarised for each treatment group using descriptive statistics at each time point.

If normally distributed the primary analyses will report the difference between group means (with 95% confidence intervals) using an analysis of covariance (ANCOVA), adjusting for baseline and the stratification factor (recommend by ICH E9), this will permit greater power to detect the minimum important difference than the t- test.

Binary outcomes will be reported using relative risks and 95% confidence intervals. Continuous outcomes will be reported using a linear mixed effects method including all patients, all time-points and adjusting for the stratification factor. Time to event outcomes will be summarised by Kaplan-Meier curves and compared overall using log-rank tests and survival regression methods.

13 DATA MANAGEMENT

13.1 Source Documents

The case report form (CRF) will be considered the source document for data where the information cannot be obtained from the medical records and is recorded directly in the trial specific CRF.

The trial Source Data Checklist will document where the source data for the trial is routinely held. The investigator is required to confirm that the information held in the checklist is an accurate reflection of data collection practices at site. A copy of this checklist should be retained in the Investigator Site File

13.2 Data Collection Methods

Data are to be entered into an electronic secure web-based trial specific system by approved members of the research team at site.

The following CRFs are subject to expedited reporting and need to returned to LCTC in paper format/secure data transfer:

- Serious Adverse Event

13.2.2 Questionnaires and Assessments

These are described in section 10.7 Participants or if appropriate, a parent/legal guardian of the participant will be given the following questionnaires and assessments to complete: CHAQ, CHU-9D, CAPTURE-JIA PROM, pain VAS, PGA-VAS, Tanner self-assessment and the Resource Use Questionnaire. These are described in section 10.7. The research team will enter data from these questionnaires and assessments onto the electronic secure web-based trial-specific system. The questionnaires and assessments will then be stored in the ISF.

13.2.3 PLICS data

PLICS data will be collected, analysed and stored by the University of Bangor. Participants will be asked to consent to the data on their NHS hospital attendances and treatment to be collected for the purpose of this study commencing 24 weeks before.

Responsibility for the PLICS data collection and anonymization will rest with the site research nurse who will supply their site Finance Departments with the necessary details to ensure only information on consented participating patients are provided. It is the responsibility of the site Finance Departments to provide the site research nurses with the data in a timely fashion and should the site research nurse so request, to ensure all patient identifying data have been replaced with the patient trial number. Pseudo-anonymised PLICS data will be transferred securely from each site to Bangor University for analysis.

13.2.4 Biobank Sample Data

DNA, PBMC and serum samples will be collected from participants who consent to this optional part of the study at the baseline visit and again at 3-month follow-up visit for PBMC and serum samples. Further detailed information can be found in section 10.7.10 for further detail. These samples are pseudonymised and labelled with the trial randomisation number. The physical samples and transfer forms and copies of consent forms will be sent by sites to the Liverpool University Biobank. Participants are informed of, and agree to, this transfer as part of their trial consent process. Liverpool University Biobank will check that written consent has been provided with each sample received by the Biobank and upload these for secure electronic storage on a University of Liverpool server. LCTC will also monitor consent for samples.

14 MONITORING

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, whether central or on site and what level of detail monitoring will be conducted.

Site monitoring visits may be 'triggered' in response to concerns regarding trial conduct, participant recruitment, outlier data or other factors as appropriate. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the trial protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- source data verification.

15 CONFIDENTIALITY & DATA PROTECTION

This trial will collect and process Personal Data of participants. All data will be handled in accordance with applicable data protection legislation, including the UK General Data Protection Regulation (GDPR) and Data Protection Act (DPA) 2018.

The Data Controller organisations for this trial are Alder Hey NHS Foundation Trust, University of Liverpool and Bangor University. The Data Processors for this trial include all trial sites.

LCTC is part of the University of Liverpool, which is registered as a Controller with the Information Commissioner's Office (ICO). The University of Bangor and Alder Hey Children's Hospital NHS Foundation Trust are also ICO registered.

Data will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.), thereby ensuring data minimisation and purpose limitation. At all times, this data will be handled confidentially and securely.

Data collected at sites and transferred to LCTC will include direct identifiers. These identifiers will be participant names on Consent Forms, contact details on Contact Forms and Special Category data on CRFs. Medical data is subject to a duty of confidence under Common Law. Trial participants consent to the disclosure of their data to researchers as part of the trial's recruitment and consent process.

Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to LCTC by recruiting sites. This transfer of identifiable data is disclosed in the Participant Information.

The CRFs collecting special category data including health, gender, date of birth, post code and ethnicity data and each participant's questionnaire data will be pseudonymised and labelled with a unique trial randomisation number. This data will be collected and stored separately to direct identifiers to ensure pseudonymisation.

Participants who consent to donate DNA, PBMC and serum samples for future research will have their samples labelled with the participant's trial randomisation number and date collected. A copy of the participant's consent form will accompany their samples when they are sent to Liverpool University Biobank (LUB) where LUB staff will check consent has been given for the sample collection and ensure confidentiality and data protection in relation to the samples and consent forms.

Breaches of data protection principles or regulations identified by LCTC will be notified to the trial Sponsor and applicable Data Protection Officers.

16 QUALITY ASSURANCE & CONTROL

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each site will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated.
- The Trial Manager at the LCTC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended the trial-specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual site.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG may monitor screening and consent rates between sites and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

16.1 Records Retention

All essential documents created for this trial will be retained for the trial-specific archive period as defined in the trial contracts. This archive period will begin on the official End of Trial date (defined in section 10.10 above).

The PI at each site is responsible for ensuring their site-specific records (trial files, data and source documents) are securely and confidentially retained during the full archive period. If a PI leaves their site (e.g. retires or changes employer) before the end of the archive period, they must transfer responsibility, in accordance with the local site processes and in compliance with the trial contract.

In addition to sites, each team who are delegated duties for the trial will be responsible for securely and confidentially retaining their own trial records for the whole archive period, unless their contracts with Sponsor permit different arrangements (e.g. provision of records to Sponsor for archiving).

17 REGULATORY & ETHICAL CONSIDERATIONS

Statement of Compliance

This trial will be run in accordance with all applicable legislation, including, but not limited to:

- Principles of GCP
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended)
- UK GDPR & DPA 2018
- UK Policy Framework for Health & Social Care Research
- Human Tissue Act 2004

17.1 Ethical Considerations

The trial will abide by the principles of GCP and Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone peer review and ethical and regulatory review by an independent REC and by MHRA.

17.1.1 Ethical Considerations regarding Consent, Assent & Enrolment

Participation in this trial is voluntary. The risks to participants in this trial are no greater than the risks to patients receiving the same treatment as standard of care for Juvenile Idiopathic Arthritis.

For children under 16 years of age, consent will be sought from the person with parental responsibility for the child. If a participant reaches the age of 16 before the end of the follow-up period (52 week visit), consent will be sought at the study visit on or following the child's sixteenth birthday.

Assent will be sought from children between 6 and 15 years of age. If a child between 6 and 15 years of age states that they do not want to participate in this trial, it will be recorded as 'no consent obtained' and the child will not be included in the trial.

17.1.2 Ethical Considerations regarding Pregnancy Testing & Monitoring

Pregnancy testing for participants of child-bearing potential before prescribing these medications is not performed in standard care, however, it has been included in this trial based on the risks to unborn children described in the SmPCs for IV Methylprednisolone and oral Prednisolone and taking account of the biological half-life of these drugs.

For Methotrexate (a NIMP) and medications that are permitted after visit 1 at week 6 of this trial, sites will be expected to follow their local policies and procedures regarding pregnancy testing and monitoring (including blood testing) before the prescription of additional permitted medications.

Information about the study being unsuitable for pregnant patients and that participants of child-bearing potential will be asked to do a urine pregnancy test after consenting to participate in the study is in the following documents:

- *STAR-JIA Parent Information Sheet*
- *STAR-JIA Information Sheet for Young Adults, 16-18yrs*
- *STAR-JIA Information Sheet for Children, 11-15yrs*

It is reasonable to suggest that a participant under 16yrs of age with child-bearing potential and their parent will be aware of the urine pregnancy test and if it is confirmed that they are pregnant, or may be pregnant, before treatment in this trial, they will no longer be able to participate and will need to discuss standard care treatment options with their doctor. It is also reasonable to suggest that a participant under 16yrs of age of child-bearing potential will have opportunity to ask any questions they wish and can ask whether the results of the pregnancy test may be disclosed to their parent or legal guardian before they give assent to participate in the study. If a patient is dissatisfied with the Clinician's answer, they can say that they do not wish to participate and will not be enrolled in this study.

17.2 Approvals

The protocol, participant information & consent/assent materials and any proposed public-facing material will be submitted to an appropriate REC, the Health Research Authority (HRA) and MHRA, and trial sites for approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

17.3 Non-Compliances

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical e.g. MHRA and REC requirements are handled based on their nature and severity.

17.3.1 Protocol Deviations

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees. The handling of protocol deviations will be documented in the SAP.

Protocol deviations and other non-serious breaches of GCP, etc. will be managed according to local site and LCTC procedures as appropriate.

17.3.2 Serious Breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants. The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within 7 days by LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

18 INDEMNITY

Alder Hey Children's NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated trial, the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation may therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as: "A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process ".

19 PUBLICATION AND DISSEMINATION

19.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

19.2 Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the STAR-JIA Consortium which will also be named at the manuscript head.

19.3 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and results will be submitted to the MHRA and REC. The trial results will be published regardless of the magnitude or direction of effect. A Lay Summary will be produced and made available via the HRA website.

19.4 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers.

All requests for access to the anonymised IPD will be assessed by the Sponsor and discussed with the Chief Investigator in accordance with the Sponsor policy on data sharing.

20 AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version

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