NETSCC, HTA

6 February 2012

A Randomised Controlled Trial of the Clinical Effectiveness, **S**afet**Y** and **C**ost Effectiveness of **A**dalimumab in Combination with **M**eth**O**t**RE**xate for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis (**SYCAMORE**)

Version 1.1, 08 September 2011

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Clinical Trials Research Centre

HTA
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Arthritis Research UK

Providing answers today and tomorrow

Protocol Authorisation

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General Information

This document describes the SYCAMORE trial and provides information about procedures for entering patients into it. 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. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Clinical Trials Unit or Liverpool Cancer Trials Unit) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the CTU.

This protocol defines the participant characteristics required for study 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 and waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Research Network Clinical Trials Unit; MCRN CTU), cancer (The Liverpool Cancer Trials Unit; LCTU), epilepsy, oral health and obstetrics and gynaecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The NIHR Medicines for Children Research Network and National Cancer Research Network is part of the National Institute for Health Research Clinical Research Network.

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2 CONTENTS

Glossary

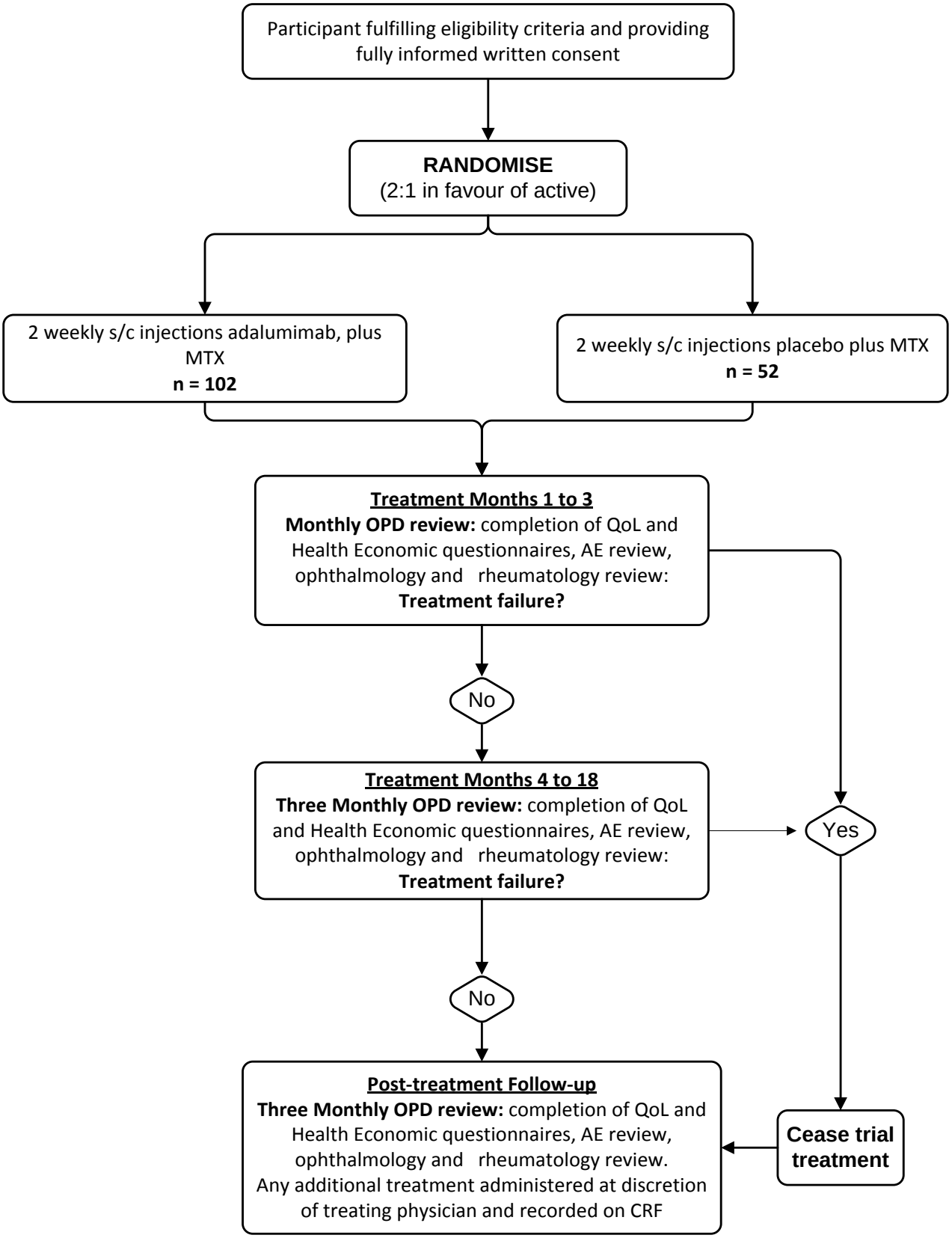
ACR	American College of Rheumatology
AE	Adverse Event
AR	Adverse Reaction
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Childhood Health Questionnaire
CI	Chief Investigator
CMO	Cystoid Macular Oedema
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
DMARD	Disease Modifying Anti-Rheumatic Drugs
GP	General Practitioner
HUI2	Health Utilities Index 2
IB	Investigator's Brochure
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
LREC	Local Research Ethics Committee
MCRN CTU	Medicines for Children Research Network Clinical Trials Unit
MREC	Main Research Ethics Committee
NIHR CRN	National Institute for Health Research Clinical Research Network
OCT	optical coherence tomography
PI	Principal Investigator
R&D	Research & Development
S/C MTX	Subcutaneous Methotrexate
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of product characteristics
SUN	Standardisation of the Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal

3 PROTOCOL SUMMARY

Title of Study:	Randomised controlled trial of the clinical effectiveness, safety and cost effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis
Study Design:	Randomised, double-blind, placebo-controlled, multicentre, trial of adalimumab in combination with methotrexate (MTX) in patients with active uveitis in association with JIA refractory to MTX monotherapy. Participants will be randomised applying a ratio of 2:1 (in favour of adalimumab).
Population	154 patients with persistently active JIA-associated uveitis (despite optimised methotrexate (MTX) treatment for at least 12 weeks)
Number of Sites	The study will be carried out in at least 16 tertiary care centres throughout the UK
Study Duration	All participants will be treated for 18 months, with follow up for a total of 3 years from randomisation (continuing on MTX throughout)
Description of Agent/Intervention	Adalimumab. All participants will receive a stable dose of MTX and in addition either adalimumab (20mg/0.8ml for patients <30kg or 40mg/0.8ml for patients weighing ≥30kg, s/c injection every 2 weeks based on body weight), or placebo (0.8ml as appropriate according to body weight) s/c injection every 2 weeks.
Primary Objective	To compare the clinical effectiveness of adalimumab in combination with MTX versus placebo with MTX alone, with regard to controlling disease activity in refractory uveitis associated with juvenile idiopathic arthritis (JIA)
Secondary Objectives	• To evaluate short term safety and tolerability of adalimumab in combination with MTX versus MTX alone, with regards ocular complications of treatment, adverse events and laboratory assessments • To determine quality of life and cost effectiveness of adalimumab in combination with MTX versus MTX alone in severe uveitis associated with JIA • To determine the clinical effectiveness of adalimumab in combination with MTX versus MTX alone, with regard underlying JIA disease activity • To determine the durability and magnitude of adalimumab efficacy response in sustaining inactive disease and achieving complete clinical remission • To determine the long term safety of adalimumab in combination with MTX versus MTX alone • To assess the efficacy of treatment with adalimumab to permit concomitant medication reduction, in particular regional and parenteral steroids • To assess clinical implications of anti-adalimumab antibody (HAHA) development in relation to efficacy / hypersensitivity • To develop a fully consented, trial-related biobank for subsequent investigation

Protocol Summary - continued

Schematic of Study Design:



4 BACKGROUND INFORMATION

4.1 Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Children with JIA also are at risk of inflammation of the uvea in the eye (uveitis). Overall, 20-25% of all paediatric uveitis is associated with JIA[1,2] but a greater proportion are seen in referral cohorts. The major risk factors for development of uveitis in JIA are oligoarticular pattern of arthritis, an age at onset of arthritis of less than seven years of age, and antinuclear antibody positivity [3]. In the initial stages of mild to moderate inflammation the uveitis is entirely asymptomatic. This has led to the current practice of screening all children with JIA regularly for uveitis. Approximately 12-38% of patients with JIA will develop uveitis in the seven years following the onset of arthritis [4,5]. In 30-50% of children with JIA associated uveitis structural complications are present at diagnosis [6]. Furthermore about 50-75% of those with severe uveitis will eventually develop visual impairment secondary to ocular complications such as cataract, glaucoma, band keratopathy and macular pathology [7-9]. Defining the severity of inflammation and structural complications in uveitis patients can now be more consistently described following Standardised Uveitis Nomenclature (SUN) guidelines, allowing their incorporation into design of randomised controlled trials (RCT) and cohort studies [10]. Significant poor prognosticators of poor visual acuity include structural changes at presentation; the need for intraocular surgery, posterior segment inflammation, abnormal intraocular pressure and the failure to maintain long-term disease control as marked by persistent AC cell scores <1+ [6-8,11]. Despite current screening and therapeutic options (pre-biologics) 10-15 % of children with JIA associated uveitis may eventually develop bilateral visual impairment and are certified legally blind [12,13]. It is therefore critical to find more effective therapeutic interventions.

4.2 Rationale

Methotrexate (MTX) is well established as the first-line disease modifying agent in the management of JIA [14,15]. The current approaches to treatment of mild JIA-associated uveitis include use of topical steroids. MTX is also thought to be effective for JIA-associated uveitis in children with moderate-to-severe uveitis [16-18], but there have been no prospective randomised placebo-controlled trials of MTX or steroid regimens in JIA-associated uveitis. Systematic review of the evidence of MTX in JIA is restricted to joint involvement [14] but not in paediatric uveitis. Despite the scarce evidence, MTX has become the mainstay of treatment for JIA-uveitis [19]. However, up to 15-50% of children will have refractory uveitis in spite of optimal therapy with methotrexate [16-18]. De Boer found that 30% of patients started on MTX will not achieve control during the first year of therapy and even when remission is achieved on MTX 9/13 will later relapse suggesting only 4/22[18%] patients achieve total remission.IN the GOS cohort a similarly low proportion of 12% were found to be in total remission five years after starting MTX [74]. Several agents including ciclosporin and mycophenolate mofetil (MMF) have been shown to be of benefit in controlling JIA-uveitis in retrospective small case series[20,21]. However their use remains restricted due to intolerability due to adverse reactions and little evidence that they rescue methotrexate-refractory patients. In addition, neither ciclosporin nor MMF are very effective in controlling joint manifestations in the children [19]. More recently, animal models and corroborative human evidence [22], supports the role of tumor necrosis alpha (TNF-α) in the aetiopathogenesis of uveitis, and moreover the potential value of its inhibition as a therapeutic intervention [23].

Studies on experimental models of autoimmune uveitis have demonstrated that TNF plays a pivotal role in pathogenesis of intraocular inflammation [22], which has been borne out in

treatment of adult uveitis [23]. In mouse models of anterior uveitis, deleting p55 receptor as well as combined TNFR p55 and p75 knockout animals, results in reduced disease [24], more significantly than the effect of TNFR p55 fusion protein [25]. Furthermore, in an animal model of uveitis, infliximab reduced disease severity [26], albeit at doses of 20mg/kg. Translating this to humans, several case series have been published demonstrating the efficacy of infliximab and adalimumab in treatment of severe refractory uveitis in adults and children [27-32]. In contrast, etanercept has been reported not to halt onset of uveitis or be more effective than placebo [33,34], and less effective than infliximab in treating JIA-uveitis [30,35,36]. There are a number of reports of new-onset uveitis associated with etanercept use in JIA [37]. An adverse events register-based study examining these cases determined that whilst the frequency was greater for etanercept than for infliximab or adalimumab (n=20, 4 and 2 cases respectively), causality could not be established [38]. Etanercept is not considered to be effective in treating intraocular inflammation [30].

Adalimumab is a fully human monoclonal antibody engineered by gene technology that uses site-directed mutagenesis to enhance its binding efficiency to TNF. It does not contain non-human or artificial protein sequences. Adalimumab binds only to TNF-α and has a half life of approximately two weeks. The antibody has been extensively studied *in vitro* as well as *in vivo* and is non-toxic in animal toxicology experiments. Clinical trial of adalimumab as monotherapy or in combination with MTX in adult subjects with rheumatoid arthritis showed a significant clinical response [39]. In children with JIA, a multicenter randomised, double blind stratified parallel group trial has shown a significant benefit in children with active arthritis [40].
Studies in paediatric non-infectious uveitis have shown very promising results with adalimumab, with 21 out of 26 eyes from 14 children with JIA- or idiopathic-uveitis showing improvement in inflammation [41]. In another retrospective case series of 18 paediatric patients with uveitis, 88% had a substantial decrease in ocular inflammation and adalimumab showed corticosteroid-sparing potential [27].
There are no prospective studies of efficacy and safety of anti-TNF agents in JIA-associated uveitis. In the randomised controlled trial of adalimumab in JIA that demonstrated safety and efficacy, the most commonly reported adverse events were infections and injection-site reactions [40]. Serious adverse events considered possibly related to study drug by the investigator occurred in 14 patients. Seven of these included one case of: bronchopneumonia, herpes simplex infection, pharyngitis, and pneumonia, and two cases of herpes zoster infection. In this trial there were no deaths, malignant conditions, opportunistic infections, cases of tuberculosis, demyelinating diseases or lupus-like reactions [40]. The fixed dose model of 20 mg for children < 30 kg and 40mg for children ≥30 kg selected for this trial is based on the data generated in the above trial using the same dosing regimen [40]

4.3 Objectives

4.3.1 Primary objective:

To compare the clinical effectiveness of adalimumab in combination with methotrexate (MTX) versus MTX alone, with regard to controlling disease activity in refractory uveitis associated with juvenile idiopathic arthritis (JIA)

4.3.2 Secondary objectives:

- To evaluate short term safety and tolerability of adalimumab in combination with MTX versus MTX alone, with regards ocular complications of treatment, adverse events and laboratory assessments

- To determine quality of life and cost effectiveness of adalimumab in combination with MTX versus MTX alone in severe uveitis associated with JIA
- To determine the clinical effectiveness of adalimumab in combination with MTX versus MTX alone, with regard underlying JIA disease activity
- To determine the durability and magnitude of adalimumab efficacy response in sustaining inactive disease and achieving complete clinical remission
- To determine the long term safety of adalimumab in combination with MTX versus MTX alone
- To assess the efficacy of treatment with adalimumab to permit concomitant medication reduction, in particular regional and parenteral steroids
- To assess clinical implications of anti-adalimumab antibody (HAHA) development in relation to efficacy / hypersensitivity
- To develop a fully consented, trial-related biobank for collection of serum, DNA and RNA for subsequent investigation

4.4 Potential Risks and Benefits

JIA-associated uveitis is a severe, potentially sight-threatening condition, often inadequately treated using standard therapies. Advent of the biologic therapies offers significant anticipated benefits therefore to the patient. However, due care must be taken in determining the potential benefits of anti-TNF therapy, now being used in off-label manner in this condition, against the potential associated risks. Safety (short and long term) of the new biologic therapies in children and young people is of major importance, particularly in this study. The risk / benefit assessment of this intervention needs careful attention. Safety is therefore a key secondary outcome measure of the trial.

4.4.1Potential Risks

The long term follow up of children on etanercept and adalimumab from controlled studies have, to date, not shown any increased risk of malignancies. However the United States Federal Drug Administration (FDA) have recently issued an alert to healthcare professionals that their analysis has revealed that 48 children developed malignancies whilst on anti-TNF agents including eleven deaths [48]. The data is mainly for children and adolescents on etanercept and infliximab on account of limited follow up data available on adalimumab. The analysis includes in particular children with Crohn's disease. 88% of the 48 children were also on concomitant immunosuppressive medication including azathioprine and methotrexate. The complete details of the FDA analysis are not currently available. Importantly, these data do not provide comparative information on long term malignancy rates in JIA patients treated with methotrexate alone, or untreated JIA. Subsequent data presented at the American College of Rheumatology (2009) of 1168 patients over 16396 patient years indicates no increased risk of anti-TNF therapy in JIA (Abstract: Bernatsky, Rosenberg & Kiem, ACR, 2009). Recent data presented at EULAR emphasises the importance of comparing anti-TNF safety data to untreated disease (EULAR 2010, McCroskey P) and that current data does not indicate a significant relative increase with respect to controls (Southwood T et al. EULAR 2010 – Oral presentation). All these reports however emphasise the critical importance of making safety a major priority in this trial. This priority is both within the treatment and follow up duration of the trial, but also ensuring procedures are in place to continue this safety follow up longer term.
The risk of increased malignancy with azathioprine in patients with Crohn's disease on infliximab is well recognised [49,50]. As noted already, adverse events associated with the recent adalimumab trial in JIA was associated with minimal safety signals [40]. A recent retrospective cohort study evaluated overall mortality and cancer mortality in relation to immunosuppressive drugs exposure in adult patients with ocular inflammatory diseases

including anti-TNF drugs [51]. The study did show an increased overall and cancer mortality in adult patients exposed to anti-TNF agents. The authors acknowledge that this data needs interpreted with caution on account of the methodological issues associated with retrospective studies and prevalence of co-morbidity in patients on anti-TNF drugs.

From adult data, but also the growing evidence base from published data of long term follow up in biologic registries, clinical trials and cohort studies, a number of important safety signals need to be considered in this trial, Patients taking TNF-blockers are more susceptible to serious infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with adalimumab. Because the elimination of adalimumab may take up to five months, monitoring should be continued throughout this period.

Adverse events of the haematologic system, including medically significant cytopaenia (e.g. thrombocytopaenia, leucopaenia) have been reported with adalimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on adalimumab.

Adalimumab has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking adalimumab as monotherapy and those taking concomitant methotrexate. Antibody formation to the drug itself was lower when adalimumab was given together with methotrexate in comparison with use as monotherapy. Administration of adalimumab without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1). In patients with polyarticular juvenile idiopathic arthritis, adalimumab antibodies were identified in 27/171 subjects (15.8%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 22/86 (25.6%), compared to 5/85 (5.9%) when adalimumab was used as add-on to methotrexate[40].

Patients who develop a new infection while undergoing treatment with adalimumab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications. Serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia

Approximately 10-15% of participants can be expected to see injection site reactions at some time.

4.4.2Known Potential Benefits

In rheumatoid arthritis studies I-IV, all individual components of the adult ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo.
In rheumatoid arthritis studies I-IV, Adalimumab-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In polyarticular course JIA, adalimumab has been shown to have a significant clinical benefit in JIA on core paediatric ACR response criteria [46]. In the double-blind, withdrawal design phase of the trial of adamilumab in JIA[40], amongst patients not receiving MTX, there was significant increase in the number of disease flares in those subsequently receiving placebo compared to adalimumab (71% versus 43%, p=0.03) [75]. In those patients receiving concomitant MTX, flares occurred in 65% on placebo, compared to 37% receiving adalimumab (p=0.02). At 48 weeks, the percentage of patients treated with MTX who had ACR Pedi30, Pedi50, Pedi70 and Pedi90 responses were significantly greater for those receiving adalimumab than those receiving placebo (ACR Pedi 30: 63% versus 38%, p=0.03; ACR Pedi 50: 63% versus 38%, p=0.03; ACR Pedi70: 63% versus 27%, p=0.002). Open label extension of the studies showed sustained responses for up to 104 weeks of treatment. As outlined in the Protocol Rationale, its reported use in JIA-associated Uveitis warrants an RCT trial to assess its clinical effectiveness and safety.

5 SELECTION OF CENTRES/CLINICIANS

Study centres will be initiated once all their global (e.g. local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to MCRN CTU. Initiation meetings will cover the requirements outlined in the Clinical Trials Research Centre's Standard Operating Procedures relating to site training and set up.

5.1 Centre/Clinician Inclusion Criteria

a. Centres offering combined paediatric rheumatology/ophthalmology service
b. It is essential that all recruits should have regular and emergency access to a paediatric rheumatologist / ophthalmologist
c. Completion of calibration training in ophthalmology assessments
d. Sufficient demonstrated capacity of staff to carry out study assessments
e. Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI)
f. CV including a record of ICH GCP training – Other personnel on the delegation log
g. Completion and return of 'Signature and Delegation Log' to CTU
h. Positive SSI
i. Local R&D approval
j. Signed contract between site and sponsor
k. Receipt of evidence of completion of (h) to (j) by CTU
l. Sites must be able to perform Biochemical assessments as outlined in section 10.3.7

All sites would be expected to demonstrate ability to run paediatric clinical trials in accordance with Good Clinical Practice, and as such demonstrate support and infrastructure for all aspects of trial delivery including integration of the clinical research teams with pharmacy, clinical laboratory, and research support services; all centres will be expected to work in collaboration with Research Network support where present, including the NIHR MCRN Local Research Networks, the Comprehensive Local Research Network, and equivalent in Scotland, Wales and Northern Ireland.

5.2 Centre/Clinician Exclusion Criteria

Not meeting the inclusion criteria and expectations stated above

6 TRIAL DESIGN

6.1 Primary Endpoint

The primary endpoint is 'time to treatment failure'.

Treatment failure is defined by ONE or more of the following:

1) Anterior segment inflammatory score grade (SUN criteria)
   Following at least 3 months of therapy:
   i) 2-Step increase in SUN cell activity score (AC Cells) over 2 consecutive readings
   ii) Sustained non-improvement with entry grade of 3 or greater for 2 consecutive readings
   iii) Only partial improvement (1 grade) with sustained / development of other ocular co-morbidity*
   iv) Worsening of existing (on enrolment) ocular co-morbidity after 3 months
   v) Sustained scores as recorded at entry grade measured over 2 consecutive readings (grades 0.5 to 2) still present after 6 months of therapy.

2) Use of Concomitant Medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria (see section 9.8.1), or any of the concomitant medications not allowed (see section 9.8.2)

* Ocular co-morbidities are defined as:
   i) Disc swelling and/or Cystoid Macular Oedema (CMO) as gauged clinically and where possible by OCT evidence; and/or:
   ii) Sustained raised intraocular pressure (>25mm Hg) over 2 consecutive visits not responding to single ocular hypotensive agent, and/or:
   iii) Sustained hypotony (<6 mmHg) over 2 consecutive visits, and/or
   iv) Development of unexplained reduction in vision (LogMar) over two consecutive visits of 15 letters (in the event of cataract participants will remain in trial, also if cataract surgery is required. Failure will still remain as described in endpoints above).

6.2 Secondary Endpoint(s)

1) Number of participants failing treatment
2) Incremental cost-effectiveness and cost-utility of adalimumab added to MTX compared with MTX alone
3) Health status according to the multi-attribute health utility index, HUI2
4) Safety, tolerability and compliance
   a. Adverse events (AEs) and serious adverse events (SAEs)
   b. Laboratory parameters (haematological and biochemical analysis and urinalysis
   c. Development of anti-adalimumab antibody (HAHA) will be determined with samples collected at months 1, 6 and 18
   d. Participant diaries and dosing records will determine tolerability and compliance throughout the trial treatment period
5) Use of Corticosteroids over duration of study period and throughout follow up, including:
   a. Total oral corticosteroid dose
   b. Reduction in and rate of systemic corticosteroid dose from entry dose

   c. Topical corticosteroid use (frequency) compared to entry usage
   d. Need for pulsed corticosteroid
6) Optic and ocular
   a. Number of participants having disease flares (as defined by worsening on SUN criteria) following minimum 3 months disease control
   b. Number of participants having disease flares within the first 3 months.
   c. Visual acuity measured by Age-appropriate LogMar assessment
   d. Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography (OCT) (where available).
   e. Number of participants with disease control (defined as zero cells, with topical treatment for 3 and 6 months)
   f. Number of participants entering disease remission (defined as zero cells, without topical treatment for 3 and 6 months)
   g. Duration and magnitude in sustaining inactive disease (zero cells, with or without topical treatment)
7) Quality of Life assessment (Childhood Health Questionnaire (CHQ), Childhood Health Assessment Questionnaire (CHAQ))
8) American College of Rheumatology (ACR) Pedi core set criteria: at ACR30, ACR50, ACR70, ACR90 and ACR100 levels (see section 8.2)
9) Number of participants undergoing disease flare, in remission on and off medication [54] of their JIA and with minimum disease activity [55]
10) Number participants requiring change in biologic / Disease-modifying anti-rheumatic drugs (DMARDs) therapy due to failure to respond from arthritis

7 STUDY POPULATION

7.1 Inclusion Criteria

A participant is eligible for the trial based upon at least one eye fulfilling the eligibility criteria

1) Children and young people aged ≥ 2 and ≤18 years fulfilling ILAR diagnostic criteria for JIA (all subgroups that have uveitis).
2) At the time of trial screening the participant must have active anterior uveitis, defined as a "sustained grade of cellular infiltrate in anterior chamber of SUN criteria grade ≥1+ or more during the preceding 12 weeks therapy despite MTX and corticosteroid (both systemic and topical) therapy"
3) They must have failed MTX (minimum dose of 10-15mg/m^2, with a maximum dose of 25mgs). The participant must have been on MTX for at least 12 weeks* and have been on a stable dose for 4 weeks prior to screening visit.
4) No disease modifying immunosuppressive drugs, other than MTX, in the 4 weeks prior to screening
5) Written informed consent of participant or parent/legal guardian, and assent where appropriate.
6) Participant and parent/legal guardian willing and able to comply with protocol requirements.
7) For participants of reproductive potential (males and females), use of a reliable means of contraception throughout their trial participation. Post pubertal females must have a negative serum pregnancy test within 10 days before the first dose of trial drug.
8) Able to be randomised and commence trial treatment within 2 weeks of the screening visit.

* Omission of a maximum of 2 weeks methotrexate treatment within the 12 weeks is acceptable and will not render the patient ineligible unless they have been missed in the 4 weeks prior to the screening visit.

7.2 Exclusion Criteria

1) Uveitis without a diagnosis of JIA
2) Currently on adalimumab or has previously received adalimumab.
3) Have been on other biologic agent within previous 5 half-lives of agent (For other biologic agents and their wash out periods, (refer to protocol supplementary document #10)
4) More than 6 topical steroid eye drops per day prior to screening (this dose must have been stable for at least 4 weeks prior to screening visit)
5) For patients on Prednisone or Prednisone equivalent, change of dose within 30 days prior to screening
6) For patients on Prednisone or Prednisone equivalent with a dose >0.2mg/kg per day
7) Intra-articular joint injections within four weeks prior to screening
8) Any ongoing chronic or active infection (including infective uveitis) or any major episode of infection requiring hospitalisation or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to the screening evaluation
9) History of active tuberculosis of less than 6 months treatment or untreated latent TB
10) Participant has history of central nervous system (CNS) neoplasm, active CNS infection, demyelinating disease, or any progressive or degenerative neurological disease

11) Poorly controlled diabetes or persistently poorly controlled severe hypertension (>95th percentile for height / age) as deemed by the treating physician
12) Previous history of malignancy
13) Intraocular surgery within the 3 months prior to screening (cataract/ glaucoma/ vitrectomy)
14) Intra-ocular or peri-ocular corticosteroids within 30 days prior to screening.
15) History of ocular herpetic disease
16) Pregnant or nursing female
17) Demonstrations of clinically significant deviations in any of the following laboratory parameters:
    a. Platelet count < 100,000/mm^3
    b. Total white cell count < 4000 cells/mm^3
    c. Neutrophils < 1000 cells/mm^3
    d. AST or ALT > 2 x upper limit of normal (ULN) or serum bilirubin > 2x the ULN
    e. Glomerular filtration rate (GFR) of < 90 mL/min/1.73m^2 [GFR (ml.min/1.73 m^2 BSA) = 0.55 x height (cm)/plasma creatinine (mg/dl)]
    f. Hematocrit <24%
18) Having been administered a live or attenuated vaccine within three months prior to screening
19) Previous randomisation into the SYCAMORE trial to either arm of the trial.

7.3 Co-enrolment Guidelines

To avoid potentially confounding issues, patients should not be recruited into other interventional IMP trials. Individuals who have participated in previous trial testing of an IMP should will not be eligible for this trial until the appropriate washout period has outlined within Exclusion Criteria (Section 7.2) or in accordance with the respective half-life of the previous IMP.
Where recruitment into another trial or study is considered to be appropriate and without having any detrimental effect on either trial this must first be discussed with the coordinating centre (MCRN CTU) who will contact the Chief Investigator (Dr Athimalaipet Vaidyanathan Ramanan).
All patients however are eligible to be considered for recruitment to non-interventional studies relevant to their disorder or treatment, in accordance with the respective study protocols. In particular, longitudinal observational cohort, pharmacovigilance and efficacy, quality of life and mechanism of disease studies.

7.4 Patient Transfer and Withdrawal

7.4.1Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.
A copy of the patient CRFs should be provided to the new site. The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs,

the patient remains the responsibility of the original centre. The CTU should be notified in writing of patient transfers.

7.4.2Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

a. Parent/ legal representative (or, where applicable, the patient) withdraws consent.
b. Unacceptable adverse effects/ toxicity as determined by the treating clinician.
c. Intercurrent illness preventing further treatment.
d. Development of serious disease or any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 7.4). Upon discontinuation of trial intervention participants will be treated in accordance with usual local clinical practice.

7.4.3Withdrawal from Trial Completely

Patients are free to withdraw consent at any time without providing a reason.
In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient (or parent/legal representative, where applicable) should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

If consent is withdrawn completely then the reasons for withdrawal of consent will be collected (if possible) and reported for both groups. Participants who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses unless the patient explicitly states that this is not their wish. The patient will not contribute further data to the study and the CTU should be informed in writing by the responsible physician and a withdrawal CRF should be completed.

8 SCREENING, ENROLMENT AND RANDOMISATION

Several assessments are required to be undertaken as part of the research activity in order to establish eligibility, requiring that written informed consent (or proxy consent in the case of minors) is obtained prior to formal trial screening. For this reason, centres are encouraged to adopt a pre-screening procedure in order to identify potentially eligible patients prior to their attending clinic review.

8.1 Patient Identification, Provision of Information and Pre-screening

All teams will review on a regular and timely basis potentially eligible patients from within their clinical cohort(s). Potential recruits identified via these pre-screening exercises will be provided with an ethically approved summary of the trial prior to attending for clinical review.

At the time of clinical review the treating consultant and / or other designated individual (as identified on the site signature and delegation log) will subsequently ratify that they potentially meet these criteria and will approach identified patients to discuss the study further. If they wish to know more about the trial and to be considered for entry they will be supplied with a copy of the Patient Information Sheet and Consent form (PISC).

The time taken from initial contact and provision of information to obtaining written consent should be sufficient to enable appropriate discussions with the patient / family about the trial, explanation of the protocol and procedures, and seeking formal consent. Generally this will be a minimum period of 24 hours, although it is acknowledged that some patients / families may come to this decision sooner

A screening log will be maintained at each trial centre, recording all individuals considered and screened for the trial, assigning each a unique screening number, and recording the eventual outcome. Reasons for non-consideration of pre-screened patients, and non-recruitment of screened patients will be documented (e.g. not eligible, declined consent, etc.) and the information will be used for monitoring purposes.

8.2 Consent and Screening

Formal screening involves the collection of baseline data. All patients considered for the trial will be recorded on the screening log and have a unique screening number that will be used on trial documents until the randomisation number is allocated. Assessments for consideration of trial entry which are <u>not</u> undertaken as part of routine care should only be undertaken following provision of written consent. All screening assessments should be completed, and results collated to verify eligibility in a timely manner to ensure that randomisation and treatment can be commenced within 2 weeks of obtaining written consent.
Assessment activities are summarised here and detailed descriptions of assessments are provided in section 10. During screening you should:

1) Obtain or verify that written informed consent has been obtained from non-minors (aged 16-18 years inclusive) or proxy consent for minors (aged <16 years), with assent of minors, where appropriate.
2) Carry out assessments to confirm eligibility and determine baseline parameters:

a. Demographics / medical/ ophthalmic/ surgical history and past medical history
b. Detailed rheumatology assessments
c. Detailed ophthalmology assessments
d. Review concurrent medication and medication history in relation to eligibility
e. Detailed Systems Physical examination
f. Haematological laboratory assessments
g. Biochemical laboratory assessments
h. Tanner score
i. Height, weight and vital signs (heart & respiratory rate, temperature and blood pressure)
j. Standard ACR Pedi Core Set outcome variables
k. Urinalysis (microscopy)
l. Serum Pregnancy Test
m. PPD Tuberculin skin test or local equivalent
n. Completion of CHQ/CHAQ, HUI2 and CSRI

3) Eligible patients can now be randomised (Sections 8.4 and 9.2)
4) Consent/assent forms and the Baseline CRF of eligible patients should be submitted to the CTU within 7 days of the visit occurring
5) The outcome for patients found to be ineligible after completing assessments will be recorded on screening logs (CRFs do not require to forwarded to the CTU)
6) Patient's who fail screening may be re-screened after a minimum period of 1 week after their last screening. Patients who fail screening on three occasions are considered to be ineligible for the trial and should not be screened again.

8.3 Randomisation and Treatment Commencement

8.4 Requests for Randomisation

Randomisation and treatment commencement should occur within 2 weeks of the screening visit.

N.B. All screening assessments should be completed prior to randomising and commencing allocated treatment

1) Complete the appropriate documents to confirm eligibility, request randomisation and prescribe trial treatment. All documentation will carry the trial participants screening number
2) Trial prescriptions will detail the appropriate dose for the participants' weight and will indicate that Adalimumab or placebo are to be dispensed according to the treatment allocated at randomisation.
3) Deliver these documents to the pharmacy department in order that pharmacy can proceed with the randomisation (see Section 9.2).
4) Randomisations will be undertaken during normal working hours (Monday – Friday 0900 – 1700). Randomisation requests received outside of these times will be actioned on the next working day.
5) Commence allocated treatment

9 TRIAL TREATMENTS

9.1 Introduction

This is a randomised, double-blind, placebo controlled trial. The investigational medicinal products (IMPs) in this trial are adalimumab and placebo. Participants will be randomised to one of the following treatment arms:

Active arm: Adalimumab subcutaneous injection every 2 weeks for 18 months. The dose will be based on body weight (20mg for participants weighing <30kg or 40mg for participants weighing ≥ 30kg). Dose modifications are NOT permitted in participants whose bodyweight changes from less than 30 kg to greater than 30 kg or from greater than 30 kg to less than 30 kg during the 18 month treatment period.

Placebo arm: Placebo subcutaneous injection every 2 weeks for 18 months

All patients in both arms will continue to receive a stable dose of Methotrexate at a minimum dose of 10-15mg/m^2 and a maximum dose of 25mgs as a non-investigational medicinal product (NIMP) throughout the 18 month treatment period (refer to section 9.12).

After the 18 month treatment period participants will be followed up for a further 18 months to determine sustained effectiveness (remission) and safety over and above ongoing MTX therapy.

9.2 Randomisation

Randomisation will be undertaken during normal working hours (Monday – Friday 0900 – 1700) by the pharmacy departments of participating centres upon receipt of a randomisation request form and prescription from authorised clinicians. Pharmacy personnel will verify that these documents are appropriately completed before proceeding.

It is the responsibility of the PI or delegated research staff to:

1) Notify pharmacy of potential randomisations so that pharmacy can ensure adequate drug supplies are at site and
2) Complete the appropriate trial documents and deliver these to the pharmacy department at their centre in order that pharmacy can proceed with a randomisation.

Participants will be randomised using a secure (24-hour) web based randomisation programme. Randomisation lists will be generated in a 2:1 ratio in favour of the active therapy. The lists will incorporate random elements and the web randomisation programme will controlled centrally by the MCRN CTU; both measures to ensure allocation concealment.

Participant treatment allocation will be displayed on a secure webpage and an automated email confirmation sent to the authorised randomiser.
In the event of an internet connection failure between the centre and the randomisation system, the centre should contact the MCRN CTU immediately to try to resolve the problem. If this is not possible at the time MCRN CTU will provide the treatment allocation.

Randomisation: web access http://www.mcrnctu.org.uk/SYCAMORE/
If there are any problems with web randomisation please contact the MCRN CTU helpdesk on: 0845 68 00 951

Designated pharmacy staff will be trained to use the web randomisation system during the initiation process. After pharmacy staff are trained they will be issued with personal login and password details.

9.3 Delivery and storage of IMP at trial sites

Clinical trial supplies will only be delivered to an investigator site once the site has been initiated by MCRN CTU, acting on behalf of sponsor to ensure full ethical and regulatory approvals have been granted. The size of the shipments to each site will be pre-determined based on the participant recruitment target for that individual site. Recruitment will be monitored centrally and drug shipment dates will be tailored accordingly to ensure that pharmacies hold adequate supplies of trial treatment. Pharmacies must document all shipment receipts and will provide copies of this documentation to the MCRN CTU.

IMP stock must be received by a designated member of the pharmacy department and must be stored at 2-8°C with temperature monitoring and in accordance with IMP regulations. Records of all shipments must be kept in the drug accountability log. If IMP stock received from the distributor is unexpected, wrong, damaged or out of temperature range, the stock should be quarantined and MCRN CTU contacted for further actions.

9.4 Dispensing, Dosage and Administration of Study Treatments

9.4.1 Dispensing

IMPs will be supplied as bulk stock from the distributor to pharmacy in kits containing 2 vials. Authorised, trial trained pharmacy staff should select adalimumab or placebo vials (identified by corresponding kit numbers) according to the randomisation instruction, prescription and participant's body weight (20mg for participants weighing <30kg or 40mg for participants weighing ≥ 30kg). The number of vials to besupplied at each dispensing will be determined by the date of the next clinic visit, up to a maximum of three months' supply (i.e. 6 vials).

Pharmacy must enter the site and trial participant identifiers onto the vial and carton labels of each kit at dispensing, (refer to section 9.6) and must complete, sign and date their accountability log. A second member of the pharmacy team must counter-sign and date the log to document the dispensing. Pharmacy must ensure that the participant and the researcher remain blinded to the treatment allocation.

At each subsequent dispensing, the patient's randomised treatment allocation should be ascertained by pharmacy (adalimumab or placebo) and a corresponding kit dispensed on production of a valid trial prescription. Drug accountability logs must be maintained throughout.

9.4.2Dose Modifications (Adalimumab and placebo)

The dose of Adalimumab should remain the same as at trial entry, regardless of minor fluctuations in weight which may cause a participant to cross the 30kg threshold for the upper and lower doses.

9.4.3 Dosage and Administration

The allocated treatment (adalimumab or placebo) must be administered by subcutaneous injection as per local policy every 2 weeks based on the participant's body weight (20mg/0.8mL for participants <30kg or 40mg/0.8mL for participants weighing ≥30kg)
The first dose will be administered by the research / clinical team looking after the patient. All participants or a family member will be invited to self-administer the study treatment after the first dose and taught as such to do this under procedures in place within each participating centre for teaching this. The first dose they administer will also be under supervision of the clinical team, who will ensure they are confident and able to carry out all parts of the procedure appropriately and accurately. If they do not want to do this, then arrangements will be put in place on an individual basis for ensuring trial medication is administered as prescribed.

The exact date and time (24-hour clock) of all doses administered must be recorded on the administration record of the CRF. For participants who are self-administering this must be recorded in their trial medication diary.

9.5 Formulation and Packaging:

Two strengths of adalimumab and matching placebo will be manufactured by Abbott Laboratories Ltd and supplied in bulk to the distributor for distribution to trial centres. Shipment requests will be authorised by the MCRN CTU

9.5.1Adalimumab solution for subcutaneous injection:

- Adalimumab 20 milligrams/0.8mL is a clear, colourless solution presented in a single-use glass vial for subcutaneous injection.

- Adalimumab 40 milligrams/0.8mL is a clear, colourless solution presented in a single-use glass vial for subcutaneous injection.

- Excipients: Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dehydrate, Sodium dihydrogen phosphate dehydrate, Sodium Chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH.

- Each vial is intended for a single dose to a single patient. Discard any remaining solution in vials.

9.5.2Placebo solution for subcutaneous injection:

- The matching placebo solution is a clear, colourless solutions presented in a single-use vial for subcutaneous injection in volumes of 0.8mL.

- The composition and pH of the placebo is identical to that of the active vials but without adalimumab.

- Each vial is intended for a single dose to a single patient. Discard any remaining solution in vials

9.5.3Packaging:

- **Contents:** Each kit will consist of 2 vials of adalimumab or placebo in an outer carton. Both vials and outer carton will be labelled.

9.6 Labelling, Storage and Stability

Labelling: IMPs will be labelled in accordance with regulation 46 SI2004/1031 and the detailed guidance provided in annex 13 of the EU Good Manufacturing Practice (GMP) guide. Each kit will be identified by a kit number on the labelling. Blank sections will be provided on the vial label and outer label for site and patient specific details to be filled in by pharmacy during dispensing.

Storage and shelf life: The IMPs should be stored in a refrigerator at 2-8°C. Do not freeze. Keep the vials in the outer carton. The product has a shelf life of 24 months, cool bags with cool blocks will be provided to transport vials home by patients.

Temperature excursions: In the event of storage temperatures falling outside the range permitted, stock should be quarantined and the trial coordinator at the MCRN CTU notified for further instructions (see section 1 for trial coordinator contact details).

9.7 Expired and unused IMP stock

Any stock that has expired at the trial site during the trial and any stock remaining at trial closedown must be notified to the MCRN CTU who will authorise destruction. Stock will be destroyed locally according to site policy and records made in the drug accountability log. Any unused vials remaining at the patient's home at the end of the trial or on early withdrawal should be returned to the dispensing pharmacy at the participating trial site.

9.8 Concomitant Medications/Treatments

Any medication (including over the counter medicines such as paracetamol, antacids, mineral supplements, NSAIDs, anti-inflammatory eye drops and herbal preparations) that the participant is receiving at the time of enrolment, or receives during the study, must be recorded on the appropriate case report form (CRF) along with the reason for use, dates of administration, dosage form, dose and dose frequency.

9.8.1Medications Permitted

- Methotrexate – participants must be receiving at least 10-15mgs/m^2 with a maximum dose of 25mgs
- Low dose of steroids (≤0.2mg/kg/day of prednisone or prednisolone equivalent medication orally) are permitted prior to randomisation and during the active phase of the trial. Prednisone or prednisone equivalent dose must be unchanged for at least

30 days prior to enrolment. Weaning of systemic steroids whilst enrolled in the trial is at the discretion of the treating clinician.

- Topical steroid eye drops with maximum of 6 drops/ day at randomisation (this dose must have been stable for at least 4 weeks prior to screening visit).
    - Either within the first 3 months of being in the trial, or at the 3 month assessment visit, the drops should be reduced to a maximum of 2 drops/day (the rate at which the drops are reduced within the 3 month period will be determined by the treating clinician).
    - Failure to reduce eye drops to 2 drops/ day by or at the 3 month visit will be considered a treatment failure and the participant should be withdrawn from trial treatment.
    - After the 3 month time point the dose cannot be changed for the duration of the trial treatment phase.
- Maxidex, Predforte or equivalent – preparation to be stipulated at screening and to remain unchanged for individual throughout treatment-phase of trial
- Intra-articular joint injections- the participant must not receive more than two intra-articular joint injections in a single session and no more than a total of eight injections per year; no joint injections within 4 weeks of randomisation.
- Depot peri-ocular steroid injection but not within 30 days prior to screening.

9.8.2 Medications Not Permitted

- Intra-ocular or peri-ocular corticosteroids
- The introduction of oral steroids, or increase in oral steroids, is not permitted at any time during the trial.
- Intravenous methylprednisolone at any time
- Other biologic therapies, including: etanercept, infliximab, gonilumimab; rituximab, abatacept, anakinra, tocilizumab
- Ciclosporine, Mycophenolate Mofetil, Azathioprine, Lefunamide, Sulfazalazine, hydroxychloroquine, any other disease modifying, anti-rheumatic drug

9.9 Assessment of Compliance with Study Treatments

Participant diaries and dosing records will determine tolerability and compliance throughout the trial period (see section 10). The parent/guardian of a participant will maintain a diary for all trial and other medications that are administered outside of the trial visit (i.e. at home). In the diary, the date and time the drug is administered will be recorded. The dosing records will be reviewed and verified for compliance at each visit by the research personnel at the trial centre, and all relevant dosing information will be transcribed onto the CRF at each visit. Additionally, any discernible departure from the protocol regarding trial drug administration will also be recorded onto the CRF.

9.10 Early withdrawal of treatment

Patients meeting the criteria for “treatment failure” (section 6.1) or failing to comply with criteria of permitted and non-permitted medicines will be withdrawn from the trial. The decision to discontinue trial therapy is at the discretion of the treating physician. Doses may be discontinued at any point during the trial period for reasons such as unacceptable adverse effects, serious adverse events, intercurrent illness, development of serious disease or any change in the participant’s condition that the physician believes warrants a change in medication**.** Any changes must be documented in the CRF along with the justification for those changes.

9.11 Unblinding

Treatment allocation will be concealed unless knowledge is essential for ongoing care. Should knowledge of treatment allocation be required by the responsible investigator this shall be obtained via their pharmacy department who will complete an unblinding CRF and submit this to the MCRN CTU.

All children participating in this study during the active treatment phase of the study are immunosuppressed, in view of their concomitant MTX therapy and / or potentially corticosteroid therapy, irrespective of them being on IMP or placebo. Additionally, for the purpose of out-of-hours management of the patient, all patients should be presumed to be on anti-TNF therapy, and managed as such. In this way, in the event of an AE or SAE, such as an inter-current infection, the treating clinician should manage as patients presumed to be on anti-TNF therapy. For this reason, should unblinding be deemed necessary, this would be carried out via the local pharmacy department following the procedure described below. If out of hours unblinding is required, this will be accessed via the local pharmacy department on-call service.

9.11.1 Unblinding of Individual Participants During Trial Conduct

9.11.1.1 Upon completion of 18 months treatment

Although discouraged, it is acceptable to unblind participants upon completion of their trial treatment (18 months) if this is necessary to enable appropriate ongoing treatment.

9.11.1.2 Early withdrawal from treatment

Upon early withdrawal from trial therapy, breaking the statistical blind should generally be considered only when knowledge of the treatment assignment is deemed essential for the subject's care by the subject's physician or a regulatory body as it is considered that it may not always be necessary to know the allocation of these patients.

N.B. If simply ceasing study treatment is a viable option for the patient's care, it should not be necessary for unblinding to occur.

9.11.2 Procedure

a. The decision to unblind a single case should be made when knowledge of an individuals allocated treatment is essential to:
    i. Enable treatment of severe adverse event/s, or
    ii. Enable administration of another therapy that is contraindicated by the trial treatment
    iii. Enable appropriate ongoing care upon cessation of allocated trial therapy
b. *Where possible* (during office hours), consent for individual unblinding should be made via the trial coordinator at MCRN CTU who will seek agreement of one of the lead investigators (Ramanan and Beresford)
c. Pharmacy departments will be unblinded to the treatment allocations of patients within their centre. The PI should ensure that all research personnel are aware of contact details for obtaining details of treatment allocation should this be necessary.
d. The request for the allocated treatment should be made to the local pharmacy department
e. Only the individual patient is to be unblinded and the following is to be documented by pharmacy on the unblinding CRF:
    i. Date information needed
    ii. Detailed reason for unblinding

iii. Identity of recipients of the unblinding information

f. The local investigator will ensure all necessary CRFs to time of unblinding are completed and submitted to MCRN CTU (if possible, completed *before* unblinding is performed)
g. All instances of unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator, including the identity of all recipients of the unblinding information.
h. Allocation should not routinely be revealed to MCRN CTU personnel

9.11.3 Accidental Unblinding

All instances of inadvertent unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator. Reports to include:

a. Date of unblinding
b. Detailed explanation of circumstances
c. Recipients of the unblinding information
d. Action to prevent further occurrence
e. Allocation should not be routinely revealed to MCRN CTU personnel

9.11.4 Unblinding at Trial Closure

The end of the trial will be considered as the date of the final database lock. In the event that the trial is closed prematurely by the Trial Steering Committee, on the recommendation of the Independent Data and Safety Monitoring Committee, for reasons such as clear differences between safety of trial treatments, the end of the trial will still be considered as the date of the final database lock.
Upon trial closure the criteria for unblinding will remain in effect. Pharmacy departments will not disclose treatment allocations on an individual basis. Each participating pharmacy department will return unblinding codes, without breaking the seals to reveal allocation codes, to the MCRN CTU. MCRN CTU will notify local investigators in writing of unblinding information for patients under their care. A copy of this notification should be placed in the medical records and a copy retained in the site file. It is the responsibility of the local investigator to notify trial participants of their allocated treatment.

9.12 Non-Investigational medicinal Product (NIMP) - Methotrexate

All participants will be prescribed methotrexate in conjunction with their allocated trial treatment.

9.12.1 Dose range

All participants should, at trial entry, be on a stable dose of methotrexate, which should be in the dose range of 10-15mg/m^2, with a maximum dose of 25mgs. The participant must have been on a stable dose for at least 4 weeks prior to the screening visit.

Treatment with MTX will continue for the duration of participants continuing with randomised treatment.

9.12.2 Dose modifications - Methotrexate

Upon randomisation, all participants are to remain on a stable dose of MTX in combination with their allocated trial treatment. The MTX dose/route should remain within the parameters

10-15mg/m^2 (maximum dose of 25mgs) No dose reduction or change in route of administration is allowed after randomisation.
A dose increase is acceptable for growth (at same dose/m^2 as at trial entry) but must not be increased on clinical grounds.
Methotrexate treatment may be suspended for clinical reasons, however this can only be for up to a maximum cumulative period of 4 weeks throughout the duration of the protocol treatment phase. Patients requiring intermittent or continuous suspension of methotrexate treatment for a cumulative period longer than 4 weeks will be considered a treatment failure and should be withdrawn from trial treatment.

10 ASSESSMENTS AND PROCEDURES

After obtaining written consent (and assent where appropriate) from the parent or legal guardian, or from the trial participant, a medical/ophthalmic history will be taken and recorded on the appropriate CRF with particular emphasis on other disorders of relevance and allergies. Separate sections on the CRF will be provided to record the JIA and uveitis-specific medical/ophthalmic history and the participant's other medical/surgical history. Medication (prescription, over-the-counter, and herbal supplements) use over the four weeks prior to the screening visit will also be recorded. Physical examination, measures of disease activity and complications, medication history, surgical history and laboratory tests (haematological and biochemical analysis and urinalysis) will be performed at the screening visit and will be repeated at each subsequent trial visit.

10.1 Schedule for Follow-up

Table 1 summarises study visits and assessments:

Table 1: Study visits and assessments:

Time (months)		0^	1	2	3	6	9	12	15	18	21	24	27	30	33	36	
	Screening*	Randomisation & commence treatment								End of treatment						End of trial	Premature withdrawal
Written informed consent	X																
Confirm consent (verbal)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Assessment of Eligibility Criteria	X	X															
Review of Medical/ Opthalmic/ Surgical History	X																
Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)	X	(X)			X	X	X	X	X	X	X						
Purified protein derivative (PPD) Tuberculin Skin Test[1,2] / Test for latent TB as locally performed	X																
Urinalysis [3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation		X															
Study Intervention		X	X	X	X	X	X	X	X	X							
Compliance with study intervention		X	X	X	X	X	X	X	X	X							
Physical Exam - Complete	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (heart & Respiratory rate, temperature and blood pressure)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childhood Health Questionnaire (CHQ)		X	X	X	X	X	X	X	X	X							
Childhood Health Assessment Questionnaire (CHAQ)		X	X	X	X	X	X	X	X	X							
Health Utilities Index 2 Questionnaire		X			X	X	X	X		X			X			X	X
Client Service Receipt Inventory (CSRI)		X			X	X	X	X		X			X			X	X
Sample for DNA collection	(X)																
RNA and Serum/plasma	(X)				X					X							
Haematological analysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemical analysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for HAHA analyses **	X				X												
ANA, dsDNA and ENA	X							X									
Opthalmic assessments:																	
Vision assessment	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optical coherence tomography (optional)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Assessment of vitritis	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp bio-microscopy	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cataract scoring	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Goldmann tonometry or tonopen	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standard ACR Pedi Core Set outcome variables	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tanner Score	X				X			X			X	X	X	X	X	X	X
Review of Participant Diaries	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Assessment of Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

^ Visit 0 must be completed and treatment commenced within 14 days of the screening visit (10 days for pregnancy test)

* all procedures should be done before study intervention.

** to be done also as required if anaphylaxis occurs during trial.

(X) - As applicable/indicated/appropriate

[1] Participants who are PPD positive at screening will require a chest x-ray. Treatment of participants who have a positive PPD skin test and/or abnormal chest x-ray should be in accordance with regional/national guidelines, and initiated at least 4 weeks prior to receiving the first dose of trial medication

[2] Participants with recent (within 6 months of trial entry screen) positive PPD (≥ 5 mm) who are being treated with appropriate prophylaxis may request a waiver for a screening PPD from the MCRN CTU. Documentation of the positive PPD should be available as well as chest x-ray report from the date of the positive PPD and treatment/prophylaxis history from near the time of the participant's conversion.

[3] Microscopic urinalysis will be obtained at baseline and for other visits only if relevant abnormalities greater than trace are noted on the dipstick analysis.

10.2 Procedures for Assessing Efficacy

10.2.1 Ophthalmic Assessments

Ophthalmic assessment of disease activity and ocular complications will take place by slit lamp bio-microscopy for uveitis activity (at maximum illumination), including cells and flare in anterior and posterior chambers, using SUN criteria[10].

10.2.1.1 SUN Criteria

SUN Criteria is a quantitative assessment of cell number in the anterior chamber which is graded 0-4 (see table below adapted from Jabs *et al* [10]). With no fully validated measures in paediatric uveitis, SUN criteria are the most robust currently available; the investigators are currently engaged in international collaborative efforts to reach consensus on their use and complete their validation in paediatric uveitis.

The SUN Working Group Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field†
0	< 1
0.5+	1 - 5
1.0+	6 - 15
2.0+	16 - 25
3.0+	26 - 50
4.0+	> 50

SUN = Standardisation of Uveitis Nomenclature

† Field size is a 1mm by 1mm slit beam

Sun Working Group Grading Scheme for criteria for grading presence of AC flare:

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

10.2.1.2 Vision

Using age-appropriate LogMar visual acuity (Kays pictures and standard LogMar)

10.2.1.3 Fundoscopy

Fundoscopy to assess: Disc swelling, or macular oedema and other structural changes in macular (epiretinal membrane) and optic nerve (neovascularisation, glaucomatous neuropathy) and retina (neovascularisation, retinal detachment)

Fundoscopy is to be assessed at trial entry and then at trial exit. Additional dilated fundoscopy can be done in between if clinically indicated, if the participant is in anterior remission, then it is not mandatory to undertake this assessment for the purposes of the trial.

10.2.1.4 Optical coherence tomography (OCT)

Optical coherence tomography (OCT; at least stratus II) for macular oedema; where units available to do so (non invasive). Within units - same OCT to be used throughout study.

Vitritis

Assessment of vitritis and vitreous haze. Grading can be assessed through the binocular indirect ophthalmoscope (BIO SCORE) [44]

10.2.1.5 Cataract Score

Cataract score (LOCS III grading) Adapted from Chylack et al[45] (see Appendix B)

10.2.1.6 Intraocular pressure

Intraocular pressure by Goldmann tonometry or tonopen as clinically deemed appropriate at the clinical trial setting.

10.2.1.7 Other structural Changes

Presence or absence of other structural changes including extent of band keratopathy, synechiae, iris bombe, membrane formation and neovascularisation.

10.2.2 Physical Examination

A full musculoskeletal and systems physical examination will be performed at each trial visit including detailed joint count. If the full examination is completed at baseline then it does not need to be completed again at first treatment visit as little time will have elapsed between visits.

Vital Signs will also be measured including resting blood pressure and heart rate, with the participant in the sitting position, respiratory rate and oral body temperature.

Body weight and height: will be measured at screening and at each trial visit.

10.2.3 Rheumatology Assessments: American College of Rheumatology Pedi Core Set Criteria and related outcomes

Standard ACR Paediatric Core Set outcome variables [46] will be assessed at each study visit. The table below (adapted from Giannini *et al [46])* summarises the 6 core set variables.

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Paediatric Core Set Criteria
• Physician global assessment of disease activity (10 cm visual analogue scale)
• Parent/patient assessment of overall well-being (10 cm visual analogue scale)
• Functional ability (Childhood Health Assessment Questionnaire, CHAQ) [34]
• Number of joints with active arthritis
• Number of joints with limited range of movement
• Erythrocyte sedimentation rate, normalised to a 0-10 scale

From these core outcome variables, the following rheumatology outcome variables will be determined during data analysis, according to published methodology, namely:

- The ACR Paediatric 30, 50, 70, 90 and 100 levels. These are defined as 30%, 50%, 70%, 90% and 100% improvement respectively in a minimum of three variables in the core set with worsening of one variable by no more than 30% as defined in the ACR criteria (see reference [46]).
- Episode(s) of disease flare, defined as a minimum of 40% worsening in at least 2 out of 6 components, with no more than one component improving by >30% [75]
- Ability to achieve clinical remission as defined by standardised definitions of inactive disease, remission on medication and remission off medication [54] and with minimum disease activity [55] (see references)
- The Juvenile Arthritis Disease Activity Score, or JADAS [76]. The JADAS comprises four components: (1) physician global assessment of disease activity (2) parent/patient global assessment of well-being (3) active joint count, in 27, 71 or 10 joints; and (4) erythrocyte sedimentation rate (ESR). The JADAS is calculated as a sum of scores from its four components, giving global scores of 0-57, 0-101 and 0-40 for the JADAS-27, JADAS-71 and JADAS-10 respectively.

10.3 Procedures for Assessing Safety

10.3.1 Adverse Events

An assessment of adverse events will be undertaken at each study visit from baseline to study completion. These reviews will be carried out by the PI or other delegated staff member conducting the visit.

Requirements for adverse event reporting is detailed fully in Section 12 (Pharmacovigilance).

10.3.2 Screening for Tuberculosis

A test for latent tuberculosis infection (LTBI) must be performed within four weeks prior to the baseline visit according to local practice guidelines, including those with a prior history of BCG administration. Multiple puncture tests such as the Tine and Heaf tests are not acceptable. The purified protein derivative (PPD) tuberculin skin test and the QuantiFERON®-TB Gold (QFT-G) (or local equivalent) are acceptable screening assays for latent TB in this study.
The TB test results should be interpreted according to local guidelines for immunocompromised patients, even though the patients entering this study may or may not be immunocompromised at baseline. The purpose of using this definition is to maximize the likelihood of detecting latent TB.

- Participants who are PPD / QFT-G (or local equivalent) positive according to local guidelines at screening will require a chest x-ray.
- Participants with recent (within 6 months of screening visit) positive PPD (≥ 5 mm) who are being treated with prophylaxis may be eligible for trial entry. In these circumstances, documentation of:
    - The positive PPD
    - A chest x-ray report from the date of the positive PPD
    - Documentation of treatment detail and duration
- Treatment of participants who have a positive PPD skin test / QFT-G (or local equivalent) and/or abnormal chest x-ray should be managed in accordance with regional/national guidelines, and initiated at least 4 weeks prior to receiving the first dose of trial medication

- Treatment for latent tuberculosis must be started with anti-tuberculosis therapy in accordance with local/national recommendations. Those with positive PPD at screen must have been treated with anti-tuberculosis therapy for at least 4 weeks prior to receiving study medication and chest radiograph is negative for active tuberculosis.

10.3.3 Urinalysis

Urinalysis will also be carried out at each study visit, a fresh aliquot of urine will be tested for protein, glucose, blood, leukocyte esterase, specific gravity, and pH by dipstick. A microscopic urinalysis will be obtained at screening and the results recorded on the CRF.
Subsequently, microscopic urinalysis will be obtained only if relevant abnormalities greater than trace are noted on the dipstick analysis.

10.3.4 Serum pregnancy test

Designated trial personnel will perform a serum pregnancy test for all post-pubertal female participants at the screening visit. There must be evidence of a negative serum pregnancy test for all post pubertal females within 10 days before their first dose of trial drug.
Subsequently, serum pregnancy tests will be undertaken three monthly for the duration of treatment and a final test three months after their final dose of trial drug.

10.3.5 Tanner Score

Secondary sexual development will be measured at baseline and at weeks 12 and 48 during receipt of treatment. This will be done either by self- assessment or by clinical examination. The Tanner score [77] will also be assessed at early withdrawal from trial treatment and three monthly at post treatment follow visits. This will be done on participants of ALL ages, if the participant has reached full sexual maturity then this assessment will only take place at screening.

10.3.6 Haematological Laboratory Assessments

Routine haematological assessments of full blood count will be required for the study (to include haematocrit, haemoglobin, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils, platelet count and ESR), which will be analysed in local laboratories. If ESR is unable to be tested then plasma viscosity may be accepted.
For safety purposes, an auto- antibody screen (ANA, dsDNA and ENA) should also be carried out at the baseline and 12 month visits.

10.3.7 Biochemical laboratory Assessments

Routine biochemical assessments of renal and liver function tests) are required for the study (to include C- Reactive protein (CRP), urea, creatinine, sodium, potassium, calcium, inorganic phosphate, glucose, chloride, bicarbonate, total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST]), which will be assessed in local laboratories.

10.3.8 Compliance with Study Treatment

10.3.8.1 <u>Participant Diaries:</u>

The participant or the parent/guardian of a participant will maintain a diary for all trial and other medications that are administered outside of the trial visit (i.e. at home).

For *trial allocated treatment* the diary will collect information on:

(i) Vial number
(ii) Time/ date of administration
(iii) Volume/dose
(iv) Any problems with administration/ protocol adherence

For other *prescribed* medications the diary will record:

(i) Medicine name
(ii) Dose prescribed
(iii) Number of times per day medicine was taken
(iv) Number of days/ weeks supplied

For *over the counter* medicines, the diary will record:

(i) Name of medicine
(ii) Cost

10.3.8.2 Pharmacy/ Clinical accountability

Any discernible departure from the protocol regarding trial drug administration will be recorded onto the CRF (see section 9 for IMP accountability)

10.4 Quality of Life

Quality of, Life will be measured by the use of Childhood Health Questionnaire (CHQ) [78] and Childhood Health Assessment Questionnaire (CHAQ) [47]. Data collection will take place on a monthly basis for the first 3 months, then 3 monthly until withdrawal from the active phase of trial treatment.

10.4.1 Child Health Assessment Questionnaire

Childhood Health Assessment Questionnaire (CHAQ) is the most widely used functional measure of disability in JIA both in routine clinical practice throughout the UK and clinical trials. Translated into many languages and validated in respective cultures and countries, it is easily completed and scored. It consists of eight domains, enquiring about the child / young person's ability to manage a range of activities of daily living on a 5 point scale. Completion of the questionnaire will be checked by staff

10.4.2 Childhood Health Questionnaire

The Child Health Questionnaire (CHQ) is a generic measure of quality of life used in JIA. It explores a number of important domains including self esteem, emotional and behavioural difficulties, and family impact. Completion of the questionnaire will be checked by staff

10.5 Health Economics

The primary health outcome measure for the economic evaluation will be quality-adjusted life-years (QALY).

10.5.1 Health Utilities Index 2

Health Utilities Index 2 (HUI2) questionnaire will be administered to participants or their parents (guardians) where appropriate [59] for self completion.
Health utilities will be assessed at baseline and at 3, 6, 9, 12, 18, 27 and 36-months post randomisation (or at early trial withdrawal). The HUI2 is the only validated utility measure for children with UK preferences, and is specified as NICE's preferred method for this purpose [60]. The 6 attributes of the HUI2 (sensation, mobility, emotion, cognition, self-care, and pain) will be summarized into a single UK-derived preference-based utility score [61]. HUI2 is more likely to be sensitive to the quality of life decrement attributable to sensory (vision) loss than alternative generic measures of utility [62].

10.5.2 Hospital Episode Statistics

Patients' use of secondary care resources in English sites will be measured from routine hospital information systems via the NHS Information Centre (bespoke Hospital Episode Statistics (HES) Extract Service). Requests for anonymised extracts will be made according to standardised procedures at 18 and 36 months.

10.5.3 Client Service Receipt Inventory

Patients' use of primary care services, personal social services, non-scheduled clinic attendance and out-of-pocket expenditures will be collected at baseline and at 3, 6, 9, 12, 18, 27 and 36-months post randomisation by administering a specifically designed questionnaire (based on a modified Client Service Receipt Inventory) [56] to parents (guardians). Data on patients' use of medicines will be collected within patients' diaries.

10.6 Other Assessments

10.6.1 Special Assays or Procedures

To assess clinical implications of anti-adalimumab antibody (HAHA) development in relation to efficacy / hypersensitivity.

10.7 Establishment of JIA-associated Biobank

A Biobank will be developed, integral to the trial, in accordance with Arthritis Research UK's guidelines on detailed clinical and related material banks (http://www.arthritisresearchuk.org/). Written information will be provided to families for this part of the study and written informed consent (with assent where appropriate) obtained.

All blood samples will be gifted to the University of Bristol under the care of Professor Adam Finn and kept for a minimum of ten years. The Trial Management Committee will have first call on their use. The BioBank will include all children enrolled in this trial and will be under strict governance control according to Good Clinical Practice, and adherence to HTA licences where applicable. Samples will be identifiable by identifying number only and stored in a locked freezer. The laboratory has alarm systems and backups for all freezers containing samples and there is a high level of security for access to the building. The Biobank will be a resource open to all, UK-wide, through application and approval for use through the Trial Steering Committee. Application will need to be made to the Steering

Committee for access to parallel clinical data such that combined analysis would be possible.

The Biobank will serve as a resource to investigate the pharmacogenetics, aetiopathogenesis and identification of biomarkers of JIA-associated uveitis. Understanding the genetic basis of age-specific disease processes allows consideration of the unique and rapid period of human development through to adulthood. Pharmacologic modulation of developing gene networks may have unintended and unanticipated consequences that do not become apparent or relevant until later in life. Early predictors of response allow future personalised treatment prescription in children. The Biobank of DNA alongside the clinical data collection will make this a very real possibility in the near future. In addition, understanding the aetiopathogenesis of JIA-associated uveitis will offer insight and opportunity into novel therapeutic targets, especially in the new era of biologic therapies.
Blood samples will be collected pre and post treatment (at 2 months, 6 months and 18 months). Samples will be collected for DNA and RNA extraction, acDNA synthesis, serum and PBLs frozen for future analysis. Separate funding and ethical approval will be sought to support future pharmacogenetic and molecular biological investigations.
A range of state-of-the-art technologies will be adopted to interrogate the mechanisms and biomarker search and assessment. These will employ the ability to elaborate both epigenetic, genetic, transcriptomic and proteomic analyses as well as functional assays where appropriate or indicated.. For example, 560gene-array analysis looking for candidate cytokine polymorphisms (e.g. IL-17, IL-10 and steroid resistance [70-72]) and epigenetic control of cytokine responses ; investigation using qPCR and Western Blotting of RNA control of TNF translation via FxR1P to assess activation in population of responders or non-responders in the trial and thus validate possibilities of responsiveness to therapy. [73].

10.8 Loss to Follow-up

If any of the trial participants are lost to follow up contact will initially be attempted through the PI or designated research staff at each centre. If the lead investigator at the trial centre is not the participants usual clinician responsible for their specialist care then follow up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the participants GP will be asked to contact the patient or the participants' family to provide follow up information to the recruiting centre. This information will be included on the Patient Information Sheet.
Wherever possible, information on the reason for loss to follow up will be recorded.

10.9 Trial Closure

The end of the trial will be considered as the date of the final database lock. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (ISDMC). Should the trial be closed prematurely, all active participants (receiving treatment or in follow-up) will be called in for a final follow-up visit and assessments will be undertaken as per schedule (section 8). Ongoing care will be at the discretion of the treating clinician.

11 STATISTICAL CONSIDERATIONS

11.1 Method of Randomisation

Randomisation lists will be generated in STATA using simple block randomisation with random variable block length.

11.2 Outcome Measures

11.2.1 Primary

The primary endpoint is 'time to treatment failure'.

Treatment failure is defined by ONE or more of the following:

1) Anterior segment inflammatory score grade (SUN criteria)
   Following at least 3 months of therapy:
   i) 2-Step increase in SUN cell activity score (AC Cells) over 2 consecutive readings
   ii) Sustained non-improvement with entry grade of 3 or greater for 2 consecutive readings
   iii) Only partial improvement (1 grade) with sustained/development of other ocular co-morbidity*
   iv) Worsening of existing (on enrolment) ocular co-morbidity after 3 months
   v) Sustained scores as recorded at entry grade measured over 2 consecutive readings (grades 0.5 to 2) still present after 6 months of therapy.

2) Use of Concomitant Medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria section 9.8.1), or any of the concomitant medications not allowed (see section 9.8.2)

* Ocular co-morbidities are defined as:
   v) Disc swelling and/or Cystoid Macular Oedema (CMO) as gauged clinically and where possible by OCT evidence; and/or:
   vi) Sustained raised intraocular pressure (>25mm Hg) over 2 consecutive visits not responding to single ocular hypotensive agent, and/or:
   vii) Sustained hypotony (<6 mm Hg) over 2 consecutive, and/or
   viii) Development of unexplained reduction in vision (LogMar) over two consecutive visits of 15 letters (in the event of cataract participants will remain in trial, also if cataract surgery is required. Failure will still remain as described in endpoints above).

11.3 Secondary Endpoint(s)

1) Number of participants failing treatment
2) Incremental cost-effectiveness and cost-utility of adalimumab added to MTX compared with MTX alone
3) Health status according to the multi-attribute health utility index, HUI2
4) Safety, tolerability and compliance
   a. Adverse events (AEs) and serious adverse events (SAEs)
   b. Laboratory parameters (haematological and biochemical analysis and urinalysis

   c. Development of anti-adalimumab antibody (HAHA) will be determined with samples collected at months 1, 6 and 18
   d. Participant diaries and dosing records will determine tolerability and compliance throughout the trial treatment period
5) Use of Corticosteroids over duration of study period and throughout follow up, including:
   a. Total oral corticosteroid dose
   b. Reduction in and rate of systemic corticosteroid dose from entry dose
   c. Topical corticosteroid use (frequency) compared to entry usage
   d. Need for pulsed corticosteroid
6) Optic and ocular
   a. Number of participants having disease flares (as defined by worsening on SUN criteria) following minimum 3 months disease control
   b. Number of participants having disease flares within the first 3 months.
   c. Visual acuity measured by Age-appropriate LogMar assessment
   d. Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography (OCT) (where available).
   e. Number of participants with disease control (defined as zero cells, with topical treatment for 3 and 6 months)
   f. Number of participants entering disease remission (defined as zero cells, without topical treatment for 3 and 6 months)
   g. Duration and magnitude in sustaining inactive disease (zero cells, with or without topical treatment)
7) Quality of Life assessment (Childhood Health Questionnaire (CHQ), Childhood Health Assessment Questionnaire (CHAQ))
8) American College of Rheumatology (ACR) Pedi core set criteria: at ACR30, ACR50, ACR70, ACR90 and ACR100 levels (see section 8.2)
9) Number of participants undergoing disease flare, in remission on and off medication [54] of their JIA and with minimum disease activity [55]
10) Number participants requiring change in biologic / Disease-modifying anti-rheumatic drugs (DMARDs) therapy due to failure to respond from arthritis

11.3.1 Sample Size

The sample size was based on data on failure rates from 62 patients on MTX in a comparable population provided by Dr C Edelsten, Great Ormond Street Hospital. After three months 11 patients had disease control based on Grade 0 SUN criteria (18%) and therefore based on the trial inclusion criteria would not be eligible for the trial. At 15 months following the start of treatment with MTX, 23 patients of the 51 who had failed at 3 months had achieved disease control (45%), leaving 28 (55%) who had not. To detect a relative reduction of 50% between a failure rate of 60% to 30% with 90% power (there is unlikely to be a trial of this nature again in the near future and therefore we have increased the power to 90% from the conventional power of 80% to optimise the detection of a significant difference between treatment regimes if one truly exists)at a 5% significance level, using a 2:1 randomisation a total of 140 patients (93 adalimumab, 47 placebo) are required. A trial of adalimumab in JIA with or without MTX powered the study using a 40% absolute (57% relative) difference in the rate of flare between the placebo and the adalimumab groups [40]. The advent of biological therapies in JIA has led international investigators to a paradigm shift in the treatment of JIA and its related complications, leading to significantly more ambitious outcomes in clinical trials, including elimination of inflammation and normalisation of short-term and long-term function [15,52]. To this end, in JIA, instead of previously accepted clinical outcomes of 30% absolute difference in outcome between active agent and placebo [53], increasingly significant differences are being expected and regarded as significant, with

new definitions of response being established for use in clinical trials such as clinical remission and minimal disease activity [54,55]. Indeed, 40% of patients in the adalimumab-JIA trial were reported as showing an ACR Pedi 100% response (100% response rate) at 2 years [40].
The clinically relevant outcomes of JIA-uveitis may take years to develop and the relationship between isolated measures of clinical activity and long –term outcomes remains ill defined. Recent studies do suggest that the length of continuously controlled activity is likely to be of more clinical relevance than short term improvements in levels of activity.

In view of these factors, as well as the expectation expressed unanimously through consumer consultation in the development of this trial protocol, we have set a minimum 50% relative difference in failure rate between interventions. Based on the nature of the disease resulting potentially in loss of vision and a meeting of investigators representing participating centres, as well as consumer representatives, and their experience of compliance from current usage of biologic therapies in JIA-uveitis, it is estimated that loss to follow up will be approximately 10%. Therefore we have increased the sample size by approximately 10% to allow for this, giving a total number of patients 154 (102 adalimumab, 52 placebo).

The null hypothesis underlying this trial is that there is no significant difference between adalimumab and placebo in controlling disease activity of JIA-associated uveitis unresponsive to MTX therapy.

11.4 Interim Monitoring Reports

Interim monitoring reports of the accumulating data will be performed at regular intervals (at least annually) for review by an Independent Data Monitoring and Safety Committee (IDSMC). The IDSMC will be asked to give advice 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. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

11.5 Analysis Plan

A comprehensive statistical analysis plan will be developed before any formal statistical analyses will be carried out.

The primary analysis will use the principle of intention to treat based on all the randomised participants, as far as is practically possible. If consent for treatment is withdrawn but the participant is happy to remain in the study for follow-up, they will be followed up until completion. However if they decide to withdraw consent completely then the reasons for withdrawal of consent will be collected (if possible) and reported for both groups.

The primary outcome is ‘time to failure’ with detailed criteria as to what constitutes a treatment failure described in section 3.10. A participant is eligible for the trial based upon at least one eye fulfilling the eligibility criteria (see section 3.5). At baseline and all subsequent assessment visits both eyes will be assessed and decisions with regards to treatment failure

will be based on the worst eye, irrespective as to whether this was the original failing eye used to determine eligibility. Analysis of time to treatment failure will be summarised by Kaplan-Meier curves for each treatment group and compared overall using the logrank test and survival regression methods. For secondary outcomes continuous data will be reported as a difference in means and binary data will be reported in terms of the relative risk each with 95% confidence intervals. Missing data will be monitored and strategies developed to minimise its occurrence. Missing data will be handled by considering the robustness of the complete case analysis to sensitivity analyses using various imputation assumptions; however these will be informed by data collected on the reasons for missing data.

11.6 Economic Analysis Plan

The analysis will adopt the perspectives of the NHS and personal social service providers and patients, which approximates a societal perspective. Each item of resource use (see section 8) will be multiplied by the unit cost specific to that item. Unit cost data will be obtained from appropriate sources, including routine hospital data (NHS reference costs, published annually by the Department of Health) [57], the British National Formulary and nationally published data, e.g. Unit costs of health and social care published annually by the PSSRU, University of Kent [58]. Total costs per patient will be calculated.

Two analytic approaches will be used: a within trial analysis and an economic model. Trial-based estimates of cost-effectiveness will be calculated based on standard methods [63]. Uncertainty in parameter estimates being addressed through the application of non-parametric bootstrapping and the estimation of cost-effectiveness acceptability curves [63]. We will also apply regression (GLM) models of cost and outcomes, with age, baseline active anterior uveitis grade score and other covariates as deemed appropriate, to minimise bias in the ICER estimates.

A model-based extrapolation of the trial results will be performed to explore the impact of a longer analytic time horizon, and consideration of health outcomes on the treatment cost-effectiveness [64]. The impact of adalimumab on the development of cataract, glaucoma and blindness will be estimated by constructing risk equations based on epidemiological data [65,66]. Costs and health state utilities, derived from published sources, will be attached to these states for the development of a Markov model to assess the long-term costs and benefits of the two treatment arms.

Incremental cost-utility ratios will be estimated based on QALY estimates. Costs and benefits exceeding 1-year will be discounted at 3.5% per annum, according to NICE's current rate [60] . Estimates of ICERs will be compared with the £20,000 to £30,000 per QALY threshold for cost-effectiveness [60], and a range of uni- and multi-variate, as well as probabilistic sensitivity analyses will be conducted to assess the robustness of the analysis.

12 PHARMACOVIGILANCE

12.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:
In the case of a product with a marketing authorization, in the summary of product characteristics for that product
In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**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.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation 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

12.2 Notes on Adverse Event Inclusions and Exclusions

12.2.1 Include

- 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 study/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

12.2.2 Do Not Include

- 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 patient's condition

12.2.3 Reporting of Pregnancy

Designated trial personnel will perform a serum pregnancy test at the screening visit for all post-pubertal female participants. This will be repeated three monthly for the duration of treatment administration and a further test three months after administration of the last dose of study drug.

Any pregnancy which does occur during the course of the study should be reported to the MCRN CTU immediately as an SAE. The investigator should discuss the risks of continuing with the pregnancy with the participant and the possible effects on the foetus if they continue on trial treatment. It is at the investigator's discretion to decide whether the individual should be instructed to stop taking study drugs. All pregnancies that occur during trial treatment, or within 3 months of finishing treatment, need to be followed up until delivery and neonatal outcome (defined as 4 weeks from delivery) and reported separately.

12.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

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 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

12.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 2.
If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 2: 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.

12.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.
All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP, graded as serious and **unexpected** (see section 10.2 and SPC for list of Expected Adverse Events) should be reported as a SUSAR.

12.6 Follow-up After Adverse Events

All 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.
When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

12.7 Reporting Procedures

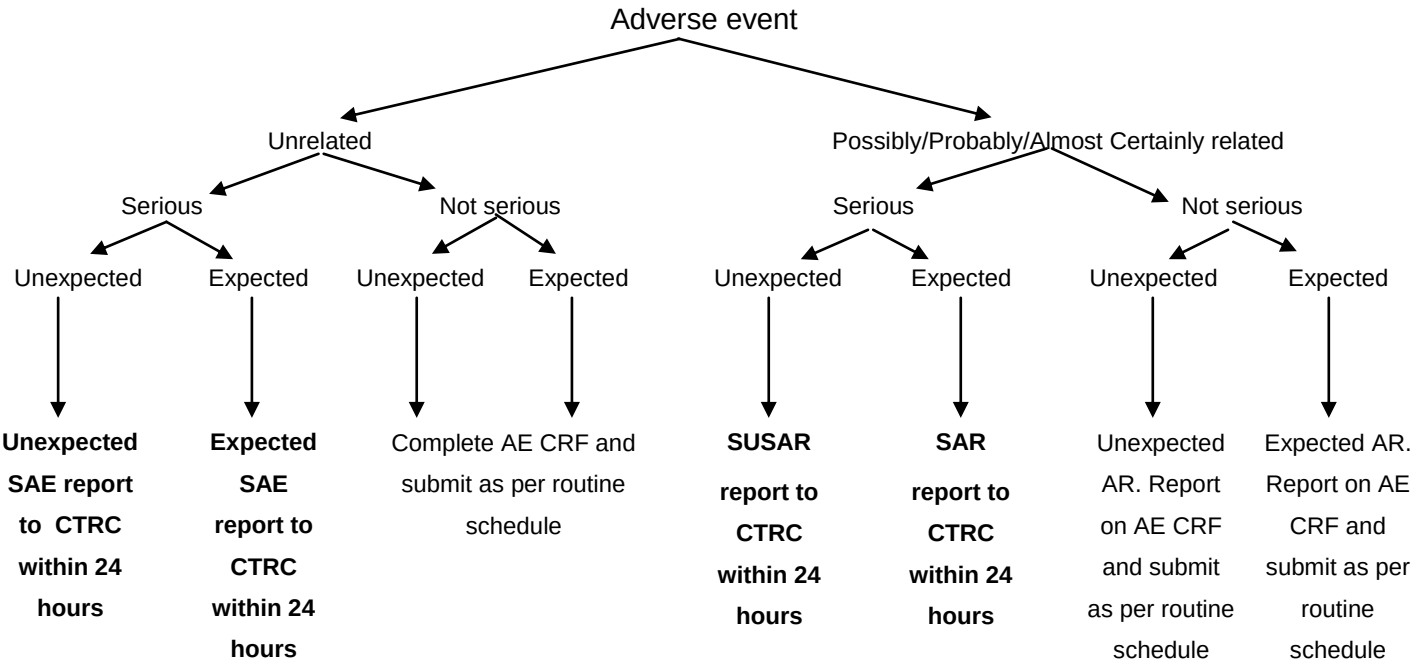
All adverse events fulfilling reporting criteria should be recorded on the CRF and submitted to the MCRN CTU within the defined timelines, beginning from the time that written informed consent is obtained (i.e. prior to to undergoing any study-related procedure and/or receiving investigational medicinal product) and continuing for 30 calendar days after cessation of the investigational medicinal product. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CTU in the first instance. A flowchart is given overpage to aid in determining reporting requirements.

12.7.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded on an Adverse Event Form, which should be transmitted to the CTU within seven days of the form being due.

12.7.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.
The CTU will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required locally.



12.8 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported immediately by the investigator to the CTU on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the CTRC. As soon as possible thereafter the responsible investigator should check

the SAE form, make amendments as appropriate, sign and re-send to the CTRC. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting an SAE to the CTRC research sites should also telephone the appropriate trial co-ordinator/data manager on telephone number **0151 282 4713** to advise that an SAE report has been submitted.

iii. Send the SAE form by fax (within 24 hours or next working day) to the CTU:

Fax Number: 0151 282 4721

iv. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

v. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

vi. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vii. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

12.9 Maintenance of Blinding

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness will be evaluated for active and excipents in placebo.

Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the clinical trials unit prior to reporting to the regulator.

12.10 Responsibilities – CTU

The CTU is undertaking duties delegated by the trial sponsor, University Hospitals Bristol NHS Foundation Trust, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The CTU will also send an annual safety report containing a list of all SARs to regulatory authorities and MREC. Copies of the report will be sent to the Principal Investigator at all institutions participating in the trial

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

12.10.1 SAE reporting – Abbott

In line with Abbott policies for the reporting of adverse events in connection with investigator-initiated studies supported by Abbott Laboratories, UK, the CTU will notify Abbott UK Pharmacovigilance of all SAEs that occur during the trial. These reports will remain blinded.

12.11 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE and ADR reporting rates across sites. The CTU will send annual safety reports containing a list of all SARS to regulatory authorities an MREC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTU to carry out site visits if there is suspicion of unreported AEs in

patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

13 ETHICAL CONSIDERATIONS

13.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

13.2 Ethical Approval

The trial protocol will not be initiated until it has received the favourable opinion of the a Main Research Ethics Committee (MREC). Subsequent to this it must also undergo review at the R&D offices at participating sites. The local R&D office should be sent the appropriate SSI form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to CTU before the site is initiated and patients recruited.

13.3 Informed Consent Process

13.3.1 General

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 is required for all trial participants. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. This trial will be recruiting minors and young people over the age of 16 years and informed consent processes will reflect the legal and ethical requirements to obtain valid informed consent for trial participants.

Information will be provided to potential participants and their families verbally and in writing. All will have the opportunity to discuss the project with the responsible investigator at site and/or a designated member of the research team. Discussions will be supported with detailed written and ethically approved Patient Information Sheets and Consent forms (PISC) provided directly to young people able to consent for themselves (defined in statutory instrument 2004 No.1031 as aged ≥16 years) and parents / legal guardian of minors (aged <16 years). Age and stage of development appropriate information leaflets will be provided to minors and their assent obtained, where appropriate. Careful presentation will be made of the known risks of the disease and trial medications, and possible benefits, as well as a detailed explanation of the trial procedures and protocol.

All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

Minors and young people eligible for this trial will have JIA-associated uveitis refractory to treatment with MTX. They may therefore be anxious about available treatments and the ultimate outcome for their sight if inflammation persists.

All of the recruiting investigators are experienced rheumatologists and ophthalmologists familiar with imparting information to families and young people. When potentially eligible minors and young people are identified, they/ their parent/ the person with parental responsibility will be approached by the investigator, or a designated member of the investigating team, during which an opportunity will be given to understand the objectives of the trial. The treatment schedule and trial visits are in line with standard clinical care, although they will be made aware that additional travel may be needed if the trial assessments require they be reviewed at their tertiary centre rather than their local hospital. The potential risks and benefits of the anti-TNF agent will be discussed, as will treatment failure criteria and what will happen if they choose not to enter the trial or have to withdraw from the trial for any reason. In addition, the rationale for the use of a placebo and the applied randomisation ratio will be explained.

Consent from the patient, or proxy consent in the case of minors, should be obtained by a designated member of the research team prior to their participation in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Verbal information should be reinforced with the implementation of the Patient Information and Consent Forms (PISC).

The right of the patient (non-minors) or parent/ legal guardian (for minors) to refuse consent to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

Adequate time to consider trial entry (at least 24 hours) will be allowed before written consent of the participant/ parent/ lrgal representative will be obtained by the responsible clinician or other designated team member (recorded on the signature and delegation log). The right of the individual to refuse participation without giving reasons will be respected.

13.3.2 Competent Adults (aged 16 – 18 years at time of consent)

Upon completion of the above, the patient will then sign and date the informed consent document. Both the person obtaining consent and the participant must personally sign and date the form. A copy of the informed consent document will be given to the patient for their records. The original copy will be filed in the participant's medical notes and a further copy of the signed consent form will be filed in the Investigators Site File. One final copy of the consent form should be sent to the CTU.

13.3.3 Minors (aged <16 years at time of consent)

The Medicines for Human use (Clinical Trials) Regulations 2004 define a person under the age of 16 years to be a minor. The regulatons require that informed consent for minors be provided by a person with parental responsibility* or a legal representative.

Upon completion of the above, proxy consent from the parent or legally acceptable representative should be obtained prior to each patient participating in the trial. Both the person obtaining consent and the parent/legal representative must personally sign and date the form. A copy of the informed consent document will be given to the parent/legal representative for their records. The original copy will be filed in the participant's medical notes and a further copy of the signed consent form will be filed in the Investigators Site File. One final copy of the consent form should be sent to the CTU.

* A mother automatically has parental responsibility for her child from birth. However, this is not the case for fathers. Conditions for fathers gaining parental responsibility varies throughout the UK and is summarised below. Practitioners should verify that the consenting parent has parental responsibility to do so.

For births registered in England and Wales
In England and Wales, if the parents of a child are married to each other at the time of the birth, or if they have jointly adopted a child, then they both have parental responsibility. Parents do not lose parental responsibility if they divorce, and this applies to both the resident and the non-resident parent.
This is not automatically the case for unmarried parents. According to current law, a mother always has parental responsibility for her child. A father, however, has this responsibility only if he is married to the mother when the child is born or has acquired legal responsibility for his child through one of these three routes:

- (from 1 December 2003) by jointly registering the birth of the child with the mother
- by a parental responsibility agreement with the mother
- by a parental responsibility order, made by a court

For births registered in Scotland
A father has parental responsibility if he is married to the mother when the child is conceived, or any time after that date. An unmarried father has parental responsibility if he is named on the child's birth certificate (from 4 May 2006). Alternatively, unmarried fathers can also be named following a re-registration of the birth.

For births registered in Northern Ireland
A father has parental responsibility if he is married to the mother at the time of the child's birth. However he does not have parental responsibility if he marries the mother after the birth. An unmarried father has parental responsibility if he is named on the child's birth certificate (from 15 April 2002). Alternatively, unmarried fathers can also be named following a re-registration of the birth.

For births registered outside the UK
If a child is born overseas and then comes to live in the UK, the parental responsibility rules apply for the UK country in which they live.

13.3.3.1 Assent in minors

If capable, and under appropriate circumstances, minors should approached to provide assent by a member of the research team experienced with minors. Age-and-state-of-development Patient information Sheet and Assent forms, approved by the independent ethical committee, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks should be used. The information leaflets will be developed in close collaboration with the consumer representatives on the trial team and with guidance from the MCRN young persons group.

The minor should personally write their name and date the assent form, which is then signed by the parent/legal representative and the researcher and copies retained/disseminated as for consent forms.

Assent should be obtained, where appropriate, and documented in the patient notes, however assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Whilst the absence of assent does not exclude the patient provided consent has been obtained from the parent/legal representative, the explicit wish of a minor who is capable of forming an opinion and assessing information in relation to the trial and who wishes to refuse participation in, or to be withdrawn from, the clinical trial at any time should be considered by the investigator. Reasons for absence of assent should therefore be recorded in the participant's medical notes.

13.3.4 Minors reaching 16 years during trial participation

For a participant involved in the study who reaches the age of 16 (and is therefore deemed competent to provide consent), the minor should be re-consented at their next scheduled visit after their 16th Birthday. The same process will be followed as for competent adults aged 16-18 at the time of consent (refer to section 11)

14 REGULATORY APPROVAL

This trial has been registered with the MHRA and will not be initiated until it has been granted a Clinical Trial Authorisation (CTA). The EUdraCT reference is 2010-021141-41**.**

15 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial coordinated by the CTU to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial.

15.1 Risk Assessment

In accordance with the CTRC Standard Operating Procedures this trial will undergo a risk assessment, completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Coordinator and supervising Trial Manager
- Trial Statistician and supervising Statistician
- MCRN CTU Director

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.
The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:

- Score ≤ 33% = Low risk
- Score ≥34 to ≤ 67% = Moderate risk
- Score ≥ 68 to ≤ 100% = High risk

The outcome of the SYCAMORE trial risk assessment has defined this to be a low risk trial and the level and nature of monitoring has been determined accordingly.

15.2 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF.

The data that is to be recorded in the CRF and should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes) and the data where no prior record exists and which is recorded directly in the CRF (i.e. where the CRF is considered the **source document**, unless otherwise indicated by the investigator) can be found in protocol supplementary document #6.

In addition to the above, date(s) of conducting informed consent (plus assent, where appropriate) process including date of provision of patient information, screening number, randomisation number and the fact that the patient is participating in a clinical trial of adalimumab versus placebo should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient. Further, study treatment allocation should also be noted in the patient's medical record after unblinding of the study.

15.3 Data Capture Methods

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. MCRN CTU will supply No Carbon Required Case Report Forms (NCR CRFs).and guidance on how the CRF should be completed (supplementary document #13).
Data stored at CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

15.4 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
Case report forms will be labelled with the participant's initials and unique trial screening and/or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.
The CTU will be undertaking activities requiring the transfer of identifiable data:
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 the CTU by recruiting centres, which requires that name data will be transferred to the CTU. This transfer of identifiable data is disclosed in the PISC.
The CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

15.4.1 Direct access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Participants will consent to allow the research time access to their data.

15.5 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the study is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. The level and nature of monitoring will be described in the trial monitoring plan, which will be fianlised upon completion of the trial risk assessment. To ensure the integrity of the data the following policies will be observed:

- The Principal Investigator, and designated staff from each centre will attend an initiation meeting, coordinated by CTU in conjunction with co-lead investigators to provide training in the trial protocol and procedures
- The trial coordinator will verify appropriate approvals are in place prior to the trial being initiated within the CTU
- The trial coordinator is to verify appropriate approvals are in place prior to the initiation of a site, and that the relevant personnel have attended study specific training
- The trial coordinator is to monitor screening, recruitment and withdrawal rates between sites and report to the TMG
- Regular QC checks will be performed on data already inputted to ensure data entered is of a high standard.
- Independent oversight of the study will be provided by the Independent Data and safety Monitoring Committee and the Trial Steering Committee.

15.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File and Pharmacy Site File, until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).
In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).
The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.
The MCRN CTU undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. Data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval. The MCRN CTU will archive the documents in compliance with ICH GCP utilising the Records Management Service of the

University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

16 INDEMNITY

The SYCAMORE trial is sponsored by University Hospitals Bristol NHS Foundation Trust and co-ordinated by the MCRN CTU in the University of Liverpool.

The University Hospitals Bristol NHS Foundation Trust cover for negligent harm is in place through the Clinical Negligence Scheme for Trusts. For NHS sponsored research HSG(96)48 reference no.2 refers 'If there is any negligent harm during the study when the NHS body owes a duty of care to their person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim'.

For the purposes of the study 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".

17 FINANCIAL ARRANGEMENTS

This study is funded by a joint venture between Arthritis Research UK and the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme. Contractual agreements will be in place between the sponsor and collaborating sites that will describe financial arrangements. IMP and Placebo are to be supplied by Abbott Laboratories.

17.1 Participant Payment

Participants and their parents / guardians will not be paid to participate in the trial and the schedule for study visits is in line with routine standard care where possible.
There is provision for reimbursement of travel expenses in the event that participants are required to travel to a tertiary centre for assessment at a visit that would otherwise take place at a centre closer to their home.

17.2 Collaborating Centre Payments

17.2.1 Research Team

Some tasks are to be undertaken during routinely scheduled clinic appointments that are directly related to the research and will impose a time demand on clinic staff, which is in addition to their usual clinical work. Financial support for these activities are split between NHS Service Support Costs and Research Costs.

17.2.1.1 NHS Service Support

This cost is estimated to be £1,738 per participant randomised and followed up as per protocol. This amount is calculated as a cost to the NHS, but is not necessarily reimbursed to the centre as such; resource to for NHS Service Support Costs can be accessed via the Local Comprehensive Research Network.

17.2.1.2 Research Support

Additionally, a per patient payment of £871 pounds per participant randomised and followed up as per protocol is available. This has been calculated to cover research-associated costs for the time of personnel at collaborating centres. Payment schedule details are specified in the Research Site Agreement (paid quarterly in arrears upon receipt of valid invoice).

17.2.2 Pharmacy Department

The pharmacy costs are to support the additional workload associated with the clinical trial and have been included as NHS Service Support Costs.

18 TRIAL COMMITTEES

18.1 Trial Management Group (TMG)

The composition of the Trial Management Group (TMG) is detailed in Appendix A
The TMG is be responsible for the day-to-day running and management of the trial and will convene at least monthly in the first year and at least quarterly thereafter.

18.2 Trial Steering Committee (TSC)

The TSC comprises three independent members (see section 1).
The role of the TSC is to provide overall supervision for the trial and provide advice through its Chairperson, who will be one of the independent members of the committee. Additionally, the TSC will be composed of TMG members, a consumer representative appointed by the MCRN/ARC Paediatric Rheumatology Clinical Studies Group (CSG), a representative of the MCRN/ARC Paediatric Rheumatology CSG (as per Arthritis Research UK requirements) and a nursing representative. The TSC will convene to approve the protocol and then at least annually thereafter. The ultimate decision for the continuation of the trial lies with the TSC

18.3 Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) consists of three independent members (see section 1).
The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety, trial conduct and external data. They will first convene to approve the protocol, agree their charter and define frequency of subsequent meetings (at least annually). The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the trial.

19 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.
The Trial Management Group will form the basis of the Writing Committee and 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 at least. 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 should be attached to any publications resulting from this trial.
The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

20 PROTOCOL AMENDMENTS

V1.0 25/02/2011 amended to **V1.1 08/09/2011 – Minor Amendment 1**

Page Number	Section	Change made
Throughout	Throughout	Header amended to update version and date
2		Professor Beresford's job title updated
6	1	Statistician changed from Lynne Cresswell to Andrew McKay. Senior statistician changed to include Gaynor Skotny
7	1	Trial steering committee member changed from Simon Harding to Carlos Pavesio
21	6.1	Point 1 iii typographical error corrected to add a '/' in between sustatined and development
21	6.1	Point 1 iv and v have been reversed so that points 1 i-iv refer to endpoints after 3 months and point v refers to endpoints after 6 months
21	6.1	Point 2 ii intraocular pressure has been changed from <25mm Hg to >25mm Hg due to a previous typographical error
21	6.1	Points 2 ii, 2 iii, and 2 iv have been changed from stating intervals from over 1 month to intervals over 2 consecutive visits as in some instances, monthly follow up isn't taking place within the trial protocol
22	6.2	Points 6 d and e have been deleted so that references to visual angle have been removed from the protocol, as these parameters are included within other assessments
23	7.1	Point 4 wording has been changed to remove reference to Adalimumab and state no Disease modifying immunosuppressive drugs, other than MTX, in the 4 weeks prior to screening
23-24	7.2	Points 4, 5, 7 and 14 have been changed from collecting data prior to randomisation to collecting data prior to screening, as this time point defines eligibility, or not
45	11.2	Points 2 ii, 2 iii, and 2 iv have been changed from stating intervals from over 1 month to intervals over 2 consecutive visits
45	11.2	Points 1 iii typographical error corrected to add a / in between sustatined and development
46	11.3	Points 6 d and e have been deleted so that references to visual angle have been removed from the protocol

V1.0 25/02/2011 – Original Submitted Version

21 REFERENCES

1. Edelsten C, Reddy MA, Stanford MR, Graham EM. Visual loss associated with pediatric uveitis in english primary and referral centers. *Am J Ophthalmol* 2003;**135**:676-80
2. Smith JA, Mackensen F, Sen HN, Leigh JF, Watkins AS, Pyatetsky D, Tessler HH, Nussenblatt RB, Rosenbaum JT, Reed GF, Vitale S, Smith JR, Goldstein DA. Epidemiology and course of disease in childhood uveitis. *Ophthalmology* 2009;**116**:1544-51, 1551
3. Kanski JJ. Uveitis in juvenile chronic arthritis: incidence, clinical features and prognosis. *Eye* 1988;**2 (Pt 6)**:641-5
4. Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. *Ophthalmology* 2001;**108**:2071-5
5. Saurenmann RK, Levin AV, Feldman BM, Rose JB, Laxer RM, Schneider R, Silverman ED. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. *Arthritis Rheum* 2007;**56**:647-57
6. Chia A, Lee V, Graham EM, Edelsten C. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. *Am J Ophthalmol* 2003;**135**:757-62
7. Holland GN, Denove CS, Yu F. Chronic anterior uveitis in children: clinical characteristics and complications. *Am J Ophthalmol* 2009;**147**:667-678
8. Woreta F, Thorne JE, Jabs DA, Kedhar SR, Dunn JP. Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol* 2007;**143**:647-55
9. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol* 2002;**86**:51-6
10. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;**140**:509-16
11. Thorne JE, Woreta F, Kedhar SR, Dunn JP, Jabs DA. Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. *Am J Ophthalmol* 2007;**143**:840-846
12. Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. *Ophthalmology* 1987;**94**:1242-8
13. de Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. *Br J Ophthalmol* 2003;**87**:879-84
14. Takken T, van der NJ, Helders PJ. Methotrexate for treating juvenile idiopathic arthritis. *Cochrane Database Syst Rev* 2001:CD003129
15. Beresford MW, Baildam EM. New advances in the management of juvenile idiopathic arthritis--1: Non-biological therapy. *Arch Dis Child Ed Pract* 2009;**94**:144-150
16. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005;**32**:362-365
17. Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. *J Pediatr* 1998;**133**:266-8
18. Yu EN, Meniconi ME, Tufail F, Baltatzis S, Foster CS. Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. *Ocul Immunol Inflamm* 2005;**13**:353-60
19. Sharma SM, Dick AD, Ramanan AV. Non-infectious pediatric uveitis: An update on immunomodulatory management. *Pediatr Drugs* 2009;**11**:229-241
20. Doycheva D, Deuter C, Stuebiger N, Biester S, Zierhut M. Mycophenolate mofetil in the treatment of uveitis in children. *Br J Ophthalmol* 2007;**91**:180-4
21. Kilmartin DJ, Forrester JV, Dick AD. Cyclosporin A therapy in refractory non-infectious childhood uveitis. *Br J Ophthalmol* 1998;**82**:737-42
22. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). *Prog Retin Eye Res* 2004;**23**:617-37
23. Imrie FR, Dick AD. Biologics in the treatment of uveitis. *Curr Opin Ophthalmol* 2007;**18**:481-486
24. Smith JR, Hart PH, Coster DJ, Williams KA. Mice deficient in tumor necrosis factor receptors p55 and p75, interleukin-4, or inducible nitric oxide synthase are susceptible to endotoxin-induced uveitis. *Invest Ophthalmol Vis Sci* 1998;**39**:658-61
25. Koizumi K, Poulaki V, Doehmen S, Welsandt G, Radetzky S, Lappas A, Kociok N, Kirchhof B, Joussen AM. Contribution of TNF-alpha to leukocyte adhesion, vascular leakage, and apoptotic cell death in endotoxin-induced uveitis in vivo. *Invest Ophthalmol Vis Sci* 2003;**44**:2184-91

26. Diaz-Llopis M, Garcia-Delpech S, Salom D, Udaondo P, Bosch-Morell F, Quijada A, Romero FJ, Amselem L. High-dose infliximab prophylaxis in endotoxin-induced uveitis. *J Ocul Pharmacol Ther* 2007;**23**:343-50
27. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, Zierhut M. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007;**91**:319-24
28. Foeldvari I, Nielsen S, Kummerle-Deschner J, Espada G, Horneff G, Bica B, Olivieri AN, Wierk A, Saurenmann RK. Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. *J Rheumatol* 2007;**34**:1146-50
29. Gallagher M, Quinones K, Cervantes-Castaneda RA, Yilmaz T, Foster CS. Biological response modifier therapy for refractory childhood uveitis. *Br J Ophthalmol* 2007;**91**:1341-4
30. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T, Tyrrell PN, Feldman BM, Laxer RM, Schneider R, Silverman ED. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006;**45**:982-9
31. Sharma SM, Ramanan AV, Riley P, Dick AD. Use of infliximab in juvenile onset rheumatological disease-associated refractory uveitis: efficacy in joint and ocular disease. *Ann Rheum Dis* 2007;**66**:840-1
32. Tynjala P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, Lahdenne P. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. *Rheumatology (Oxford)* 2008;**47**:339-344
33. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2005;**44**:1008-11
34. Smith JA, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, Robinson M, Kim J, Barron KS. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;**53**:18-23
35. Hale S, Lightman S. Anti-TNF therapies in the management of acute and chronic uveitis. *Cytokine* 2006;**33**:231-7
36. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. *J Pediatr* 2006;**149**:833-6
37. Taban M, Dupps WJ, Mandell B, Perez VL. Etanercept (enbrel)-associated inflammatory eye disease: case report and review of the literature. *Ocul Immunol Inflamm* 2006;**14**:145-50
38. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. *Arthritis Rheum* 2007;**56**:3248-52
39. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA, Chartash EK. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;**50**:1400-11
40. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe RK, Weiner LW, Horneff G, Huppertz HI, Olson NY, Medich JR, Carcereri-De-Prati R, McIlraith MJ, Giannini EH, Martini A. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;**359**:810-20
41. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. *J Pediatr* 2006;**149**:572-575
42. Thornton J, Lunt M, Ashcroft DM, Baildam E, Foster H, Davidson J, Gardner-Medwin J, Beresford MW, Symmons D, Thomson W, Elliott RA. Costing juvenile idiopathic arthritis: examining patient-based costs during the first year after diagnosis. *Rheumatology (Oxford)* 2008;**47**:985-990
43. BSPAR. http://www.bspar.org.uk/downloads/clinical_guidelines/BSPAR_guidelines_eye_screening_2006.pdf . 2009
44. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* 1985;**92**:467-471
45. Chylack LT, Jr., Wolfe JK, Singer DM, Leske MC, Bullimore MA, Bailey IL, Friend J, McCarthy D, Wu SY. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. *Arch Ophthalmol* 1993;**111**:831-836
46. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;**40**:1202-1209

47. Nugent J, Ruperto N, Grainger J, Machado C, Sawhney S, Baildam E, Davidson J. The British version of the childhood health questionnaire (CHAQ) and the child health questionnaire (CHQ). *Clin Exp Rheumatol* 2001;**19 (Suppl 23)**:S163-S167
48. FDA. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174474.htm. 2009
49. Caspersen S, Elkjaer M, Riis L, Pedersen N, Mortensen C, Jess T, Sarto P, Hansen TS, Wewer V, Bendtsen F, Moesgaard F, Munkholm P. Infliximab for inflammatory bowel disease in Denmark 1999-2005: clinical outcome and follow-up evaluation of malignancy and mortality. *Clin Gastroenterol Hepatol* 2008;**6**:1212-7
50. de Vries HS, van Oijen MG, de Jong DJ. Serious events with infliximab in patients with inflammatory bowel disease: a 9-year cohort study in the Netherlands. *Drug Saf* 2008;**31**:1135-44
51. Kempen JH, Daniel E, Dunn JP, Foster CS, Gangaputra S, Hanish A, Helzlsouer KJ, Jabs DA, Kacmaz RO, Levy-Clarke GA, Liesegang TL, Newcomb CW, Nussenblatt RB, Pujari SS, Rosenbaum JT, Suhler EB, Thorne JE. Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. *BMJ* 2009;**339**:b2480
52. Ilowite NT. Update on biologics in juvenile idiopathic arthritis. *Curr Opin Rheumatol* 2008;**20**:613-618
53. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, Apaz MT, Baildam E, Fasth A, Gerloni V, Lahdenne P, Prieur AM, Ravelli A, Saurenmann RK, Gamir ML, Wulffraat N, Marodi L, Petty RE, Joos R, Zulian F, McCurdy D, Myones BL, Nagy K, Reuman P, Szer I, Travers S, Beutler A, Keenan G, Clark J, Visvanathan S, Fasanmade A, Raychaudhuri A, Mendelsohn A, Martini A, Giannini EH. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007;**56**:3096-3106
54. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;**31**:2290-2294
55. Magni-Manzoni S, Ruperto N, Pistorio A, Sala E, Solari N, Palmisani E, Cugno C, Bozzola E, Martini A, Ravelli A. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2008;**59**:1120-1127
56. Beecham J, Knapp M. Costing psychiatric interventions. In: Thornicroft, Graham, (ed.) Measuring mental health needs. Gaskell, London, UK, pp. 200-224. ISBN 9781901242607. 2001
57. Department of Health. NHS reference costs 2007-08. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945. 2007
58. Curtis L. Costs of Health and Social Care 2007. Personal Social Services Research Unit, University of Kent. 2007
59. Sung L, Petrou S, Ungar W. Measuring health utilities in children and their parents. In: Ungar W, ed. Economic Evaluation in Child Health. Oxford University Press. 2009
60. National Institute for Health and Clinical Excellence (NICE). Guide to the Methods of Technology Appraisal. www.nice.org.uk. 2008
61. McCabe CJ, Stevens KJ, Brazier JE. Utility scores for the Health Utilities Index Mark 2: an empirical assessment of alternative mapping functions. *Med Care* 2005;**43**:627-635
62. Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA, Brand CS, Brazier JE. The impact of age-related macular degeneration on health status utility values. *Invest Ophthalmol Vis Sci* 2005;**46**:4016-4023
63. Glick H, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. Oxford: Oxford University Press. 2007
64. Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation. pp. 256 Oxford: Oxford University Press. 2006
65. Kotaniemi K, rkela-Kautiainen M, Haapasaari J, Leirisalo-Repo M. Uveitis in young adults with juvenile idiopathic arthritis: a clinical evaluation of 123 patients. *Ann Rheum Dis* 2005;**64**:871-874
66. Carvounis PE, Herman DC, Cha S, Burke JP. Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. *Graefes Arch Clin Exp Ophthalmol* 2006;**244**:281-90
67. ICH. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. http://private.ich.org/LOB/media/MEDIA436.pdf. 1994

68. Murphy CC, Greiner K, Plskova J, Frost NA, Forrester JV, Dick AD. Validity of using vision-related quality of life as a treatment end point in intermediate and posterior uveitis. *Br J Ophthalmol* 2007;**91**:154-156
69. Murphy CC, Hughes EH, Frost NA, Dick AD. Quality of life and visual function in patients with intermediate uveitis. *Br J Ophthalmol* 2005;**89**:1161-1165
70. Lee RW, Creed TJ, Schewitz LP, Newcomb PV, Nicholson LB, Dick AD, Dayan CM. CD4+CD25(int) T cells in inflammatory diseases refractory to treatment with glucocorticoids. *J Immunol* 2007;**179**:7941-7948
71. Lee RW, Schewitz LP, Nicholson LB, Dayan CM, Dick AD. Steroid refractory CD4+ T cells in patients with sight-threatening uveitis. *Invest Ophthalmol Vis Sci* 2009;**50**:4273-4278
72. Schewitz LP, Lee RW, Dayan CM, Dick AD. Glucocorticoids and the emerging importance of T cell subsets in steroid refractory diseases. *Immunopharmacol Immunotoxicol* 2009;**31**:1-22
73. Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. *Immunity* 1999;**10**:387-398
74. V. Kalinina Ayuso, Evelyne Leonce van de Winkel, Aniki Rothova, Joke Helena de Boer. Relapse Rate of Uveitis Post-Methotrexate Treatment in Juvenile Idiopathic Arthritis. American Journal of Opthamology; DOI: 10.1016/j.ajo.2010.08.021
75. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol 2002; 29(5):1058-1064.
76. Consolaro A, Ruperto N, Bazso A et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009; 61(5):658-666.
77. Tanner Score: Blondell, Roster and dave, 1999. Disorders of Puberty. Am Fam Physician; 60(1): 209-18, 223 - 4
78. Oliveira S, Ravelli A, Pistorio A, Castell E, Malattia C, Prieur AM et al. Proxy-reported health related quality of life of patients with juvenile idiopathic arthritis: the Paediatric Rheumatology International Trials Organisation multinational quality of life cohort study. Arthritis Rheum 2007; (1): 35-43

22 APPENDICES

Appendix A: Trial Management Group Composition

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* Non-independent members of Trial Steering Committee

Appendix B: LOCS III grading adapted from Chylack et al[45]