

STUDY PROTOCOL v3.3

The Long-term Safety and Efficacy of Biologic Therapies in
Children with Rheumatic Diseases

(BCRD Study)

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INTRODUCTION

Importance of Safety and Efficacy data of Biologic Therapies

The management of rheumatic disease has been revolutionised with the recent advent of biologic therapies such as monoclonal antibodies and fusion proteins (1). However initial hopes that a few doses of these drugs may affect a cure have not been realized. There are few patients who can stop treatment without subsequent disease flare. These are therefore potent new drugs which require long-term use, with long-term immune modulation making long-term efficacy and safety monitoring vital. Health economic implications of expensive long-term drugs also need careful assessment against the lower disease activity scores on biologic treatment and therefore likely less long-term damage. Despite more specific therapeutic targeting, these agents can be associated with rare but severe adverse events that underline the importance of determining their efficacy, toxicity and pharmacodynamics (2). This is particularly so in children where significant differences to adults have already been noted. Appropriate length of follow up in children is not easy to define and 10, 15, 20 or even 30 year follow-up may be necessary to fully evaluate long-term malignancy risk.

Limited safety and efficacy in the biologic era – example of Etanercept

Following a randomised clinical trial which supported its efficacy and short safety (3), etanercept was licensed as the first biologic for use in active polyarticular JIA (ages 4-17). The drug was approved by The National Institute for Health and Clinical Excellence (NICE) in March 2002 for children who have had an inadequate response to MTX. Long-term follow-up out to 8 years of this original cohort has continued and to date there have been no reports of tuberculosis, opportunistic infections, malignancies, lymphomas, lupus, demyelinating disorders, or deaths (4). Although there have been increasing reports of the use of these agents in adults, the use of these agents in a person with a maturing immune system and a fundamentally different disease may result in a different safety profile from that seen in adults. In addition to specific issues around safety, there are the additional challenges of understanding the effects of cytokine blockade in children as they grow, develop and mature into adults. There is thus a need for ongoing formalised study of children receiving new therapies beyond that of the short term clinical trial, such that this risk can be fully quantified.

To date, there has been very little published on the “real-world” safety and effectiveness of etanercept or other biologics in children with JIA. A recent meta-analysis concluded that in general, data on serious adverse events in children was missing (5). However, information emerging to date has suggested that etanercept may not be as effective in children with systemic arthritis (6). There is also evidence that infliximab may be the preferred anti-TNF for children with uveitis (7). Data on adverse events and serious adverse events is also conflicting. An early report from a French study of 61 children reported a 20% discontinuation rate for severe adverse events (6). This compares to a German study which had followed 322 children reported 69 adverse events (20 infections) (?serious/severe) over a median of 12 months of follow-up (8), although only 3.4% of children withdrew following an adverse event. More recently, further follow-up of this cohort has reported that the combination of etanercept (ETA) with background methotrexate (MTX) does not appear to result in a higher rate of adverse events compared to ETA monotherapy (0.16/pyr versus 0.15/pyr respectively) (9). These results appear to contrast with data from a UK JIA Biologics Register (10). Most concerning is the report of a non-Hodgkin’s lymphoma in a German patient, although there was documented previous exposure to MTX and azathioprine (9). Possible malignancy risk is likely to be over a much longer time frame than any currently reported safety follow up studies. It is not known whether there is an increased malignancy risk in JIA per se, as there is in adult onset rheumatoid disease or the long-term follow-up data on the safety of methotrexate in rheumatic diseases in childhood.

The need for post-marketing safety assessment of etanercept in the UK has resulted in the establishment of the British Society for Paediatric and Adolescent Rheumatology (BSPAR) Etanercept Study. This study was established in January 2004 and aims to compare an exposed group of children with JIA whose first exposure to a biologic is etanercept to a comparison cohort of children

with JIA with similar disease characteristics receiving methotrexate therapy. The main source of funding for this study comes from BSPAR, who have worked with Pfizer to establish this study and forms an integral part Pfizer's required post-marketing pharmacovigilance. However, the set-up of this project does not allow expansion to collect safety data on biologic drugs other than etanercept.

Paucity of evidence base for use of other biologics in JIA

Despite there now being 9 biologic therapies approved for adults with inflammatory arthritis: five anti-TNF agents (etanercept, infliximab, adalimumab, golimumab and certolizumab pegol), the Interleukin-1 receptor antagonist, anakinra, the B-cell depleting therapy, rituximab, the costimulation molecule abatacept and the IL-6 inhibitor, tocilizumab, few are licensed for use in JIA. However, the environment of biologics for JIA has evolved significantly over the past 5 years. Until recently, the anti-TNF therapy, etanercept (ETN), remained the only biologic approved for JIA. Adalimumab has now been licensed for children aged 4 years and older. More recently, abatacept received a European license for polyarticular JIA, and even more significant, tocilizumab became the first bDMARD approved specifically for systemic JIA. Canakinumab has recently followed with a European license granted in 2013. Other biologics licensed for use in adults are also being prescribed increasingly in the paediatric population (eg. infliximab, anakinra, rituximab). Thus, the repertoire of available (licensed and unlicensed) agents has expanded, as have the number of children who have been exposed to multiple biologics in childhood. The experience with many of these agents has been limited to those enrolled in clinical trials, i.e. low numbers of children receiving the agents under controlled conditions. There remains an extreme paucity of "real-world" outcome data of biologic use in children with JIA. Despite their limited use, there is increasing evidence that there may be certain occasions where an alternative to etanercept as first line biologic following failure of MTX may be warranted. These include the use of tocilizumab as first line therapy for children with systemic arthritis (6;15) or the use of infliximab for children with concurrent uveitis (7). Increasing off-label use of biologic therapies in paediatric rheumatological diseases has recently been outlined by a systematic review of their use in the treatment of JIA (5). They highlighted major gaps in the evidence for other biological therapy in JIA and significant methodological issues with published series. Despite this lack of evidence, there are no current trials of biologic therapies in other paediatric rheumatic diseases other than JIA despite their increasing off-label use (2). Further trials are underway and newer biologic agents are continually being developed. Establishing a mechanism for the prospective collection of safety and efficacy data will ensure all biologics, licensed and unlicensed, are carefully monitored for safety signals.

Priority area - MCRN/ARUK Paediatric Rheumatology CSG

The Medicines for Children Research Network/Arthritis Research UK Paediatric Rheumatology Clinical Studies Group (CSG) is a multi-disciplinary group of experts that has the role of setting a UK strategic prioritisation for clinical trials and related studies for the whole spectrum of paediatric rheumatology. It is advisory to the MCRN, Arthritis Research UK, and the Pharmaceutical Panel of the NIHR Health Technology Assessment programme. It has identified, of highest priority, the safety and efficacy of biological therapies in all relevant diseases, both pre- and post-marketing, as a key major area to support and develop in its proactive and reactive activities. This is illustrated recently by the recommendation by both the CSG and the MCRN Industry Study Adoption Committee that approval of the Industry sponsored Tocilizumab Trial was dependent upon assuring their ongoing safety and efficacy monitoring of this new biological therapy.

A key goal of the CSG is that all paediatric rheumatology patients in the UK being treated with a new biologic therapy will have an opportunity to participate in a randomised trial of that agent. While such trials are being developed, through the support of the CSG and in collaboration with

international collaborators (e.g. PRINTO, CARRA), the CSG recommend strongly that every effort should be made to ensure robust, consented, prospective safety and efficacy data of off-label use is collected. While ensuring a minimum of invaluable uncontrolled observational data, this will inform and facilitate formal trial design.

NICE, EMEA and MHRA recommendations for prospective safety and efficacy of biologic therapies

NICE recommendations of their approval of etanercept (<http://www.nice.org.uk/nicemedia/pdf/JIA-PDF.pdf>) underlined the obligation to clinicians (and industry) to carry out ongoing study of dosage, outcome and toxicity as well as ongoing monitoring of disease activity and clinical effectiveness in individual cases. In its recommendations for future research NICE stated that "studies are required to determine long-term clinical outcomes, in particular joint damage, unexpected adverse events, and whether or when the drug can be withdrawn if remission is achieved" and that such data on biologic therapy data "will be essential to establish the longer-term clinical effectiveness" ... "as well as the potential for adverse effects."

Such recommendations for long term safety and efficacy monitoring of etanercept and other biologicals in paediatrics have been made clearly by the EMEA (<http://www.emea.europa.eu/pdfs/human/ewp/042204.pdf>). Both etanercept and other biologic therapies are also included under MHRA Drugs under Intensive Surveillance (<http://www.mhra.gov.uk/index.htm>). Indeed, the importance of ongoing pharmacovigilance was stressed in a recent publication in JAMA, which found that up to a quarter of all new biologics on the market had further "Dear healthcare professional communications" or new "black box warnings" issued after marketing authorization was granted, again stressing the limited ability of clinical trials to detect less common or latent adverse events (16).

It is of note that long term safety and efficacy of biologics across paediatric rheumatic diseases have been identified as of highest priority in the current ERANET consultation process (www.mcrn.org.uk).

Importance of Long-term Safety and Efficacy of Biologic Therapies in Children with Juvenile Idiopathic Arthritis

Robust, prospective observation of children receiving all biologic agents is crucial and justified, based on the number of important questions surrounding their use during routine care and where they are currently being used off-label, to inform the development of clinical trials. These include:

1. What proportion of children responds to these drugs in routine use?
2. Who responds to these drugs in routine use?
3. How long do children remain on these agents and are there any identifiable characteristics of those who discontinue therapy prematurely?
4. What types and rates of adverse events are observed?
5. Do the types of adverse events observed change with duration of therapy?
6. What is the risk of malignancy, and in particular lymphoma?
7. Which children are at risk of adverse events?
8. Is the safety profile different in different JIA subtypes?
9. Is the safety profile/efficacy of these agents different in adolescents/young people versus young children?
10. What effects do these drugs have on growth and development, including puberty?

Pharmacogenetics of Biologic Response

Prescribing medications in children has historically been largely empirical but it is now essential that we move away from this era and begin to generate information that will allow paediatricians to determine early in disease which patients are best suited for a particular therapeutic agent and

which patients may be at risk for serious potentially life-threatening complications from standard treatment regimens. It has been shown in adults, that response is not random but associated with specific clinical, genetic, and psychological factors and the use of pharmacogenetic tests are becoming increasingly important within the clinic. Children, as well as adults, should benefit from the discoveries of the genomic era. Given that diseases that originate during childhood, including arthritis, often persist into adulthood it is important that attempts to understand the genetic basis of age-specific disease processes also take account of the fact that the period of human development encompasses the prenatal period through adolescence, and is a rapidly changing, dynamic process. Pharmacologic modulation of developing gene networks may have unintended and unanticipated consequences that do not become apparent or relevant until later in life. With this in mind it is important that as well as describing the safety and efficacy of biologics, this study aims to collect the appropriate data and material that will, in the future, allow us to begin to identify early predictors of response. Setting up a Biobank of DNA (from either blood or saliva) alongside the clinical data collection will make this a very real possibility in the near future.

OBJECTIVES

The main objectives of this study are:

1. To document the off-label use of biologics, biosimilars and other new treatments for JIA in the UK
2. To test the hypothesis that use of these therapies in children with JIA increase the risk of serious* infection, malignancy, other important co-morbidity and death compared to children receiving MTX.
3. To test the following subsidiary hypothesis
 - a. any increased risk is related to dose or duration of therapy,
 - b. There are specifically identifiable disease characteristics that act synergistically to increase the risk,
4. To assess the benefits of therapy, defined using normal clinical indicators (e.g. JIA30/50/70 response) and compare these to any increases in the adverse outcomes listed above.
5. To establish a BioBank of children receiving biologic therapy in the UK.

** A serious adverse event is defined according to the ICH as any event resulting in death, is life-threatening at the time of the event (i.e. not an event which could theoretically have been life threatening if it had been more severe), requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect(17). Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for acute bronchospasm, blood dyscrasias, or seizures which do not result in hospitalisation". This could also include certain infections, including infections treated with home IV antibiotics or other certain infections which might not normally result in hospitalisation (i.e. Varicella).*

DESIGN

The study proposed is a prospective cohort study comparing the risk of development of the endpoints between:

1. an exposed group of children with JIA with their first exposure to a biologic, biosimilar or other new drug (other than etanercept),

And

2. a comparison cohort of children with JIA with similar disease characteristics receiving methotrexate therapy.

Recruitment to the study will continue until the study end date; this is now 31/12/2031 but may be extended beyond this time if additional funding is secured.

STUDY LOCATION

The main infrastructure of the study will be located at the University of Manchester and will join the Biologic Studies Group portfolio. This has many advantages including the simplification and avoidance of duplication of all organisational and logistical aspects for the coordinating centre.

SUBJECTS

Consent

Informed written consent will be obtained from all parents and assent from patients as appropriate. This can be via the usual face-to-face consent in a routine clinic appointment, or via 'remote consent' as outlined below. This is to allow for the changes in the way that patients are seen in clinics due to the COVID-19 pandemic, with some appointments being held over telephone / video call rather than in person, or some appointment falling outside of the 6 month recruitment window.

These methods will be available to consent new participants on to the study, as well as obtaining re-consents for reasons including: participants who have reached their 16th birthday and should now consent for themselves; for those who have changed treatment groups and are being asked to re-register, and for those who have moved to be seen at another hospital (including transition to adult services).

Obtaining and recording consent remotely for patients new to the study

Once a potential participant is identified as eligible and noted that they may not return to clinic within the 6 month recruitment window, efforts to obtain consent remotely should be made so that the recruitment is not missed.

To obtain consent remotely, it is important to ensure that the potential participant / parent is fully aware of what is involved; the participant information sheet/s will be sent to the participant/parent via post or email, and a time arranged to discuss the study via telephone call or video call. The potential participant/parent should ideally be given at least 24 hours to consider the information provided before contact is made. Any questions can be answered and it will be made clear that participation in the study is not mandatory, with the option to withdraw at any time which will not affect the care or treatment they receive.

The below process should be followed to obtain consent remotely:

- Send the *BCRD Remote Recruitment* document to the potential participant (or parent/guardian if under 16 years old), along with the participant information sheet, transparency information sheet and three blank copies of the consent form. The text can be pasted in to the body of an email if this is being sent via email (with the other documents included as attachments).
- Nurse/delegated health care professional telephones the participant/parent (ideally allowing at least 24 hours for them to consider the information) to discuss the study and answer any questions
- If participant/parent is happy to be involved, they sign three copies of the consent form and post them back to the hospital.

Note: E-consent (i.e., providing an electronic signature by means such as a scan of a signed consent form to return via secure email) can be used if preferred, as per the HRA and MHRA 'Joint statement

on seeking consent by electronic methods' guidance in September 2018 (<https://www.hra.nhs.uk/about-us/news-updates/hra-and-mhra-publish-joint-statement-seeking-and-documenting-consent-using-electronic-methods-econsent/>). A site file note should be written to document this, which should be stored with the consent form at site for audit purposes (or a short note can be made on the consent form to record this, if preferred).

- The rheumatology/research team countersigns the consent forms, posts one fully signed form back to the participant/parent, sends one to the study team and keeps the other in the site file. If the participant/parent has provided e-consent (rather than consent via ink signature), a copy of the site file note (if this has been used, detailed above) should also be sent to the participant/parent as a record of this.
- The participant can now be registered with the study in the usual way. A copy of the consent form (and site file note if applicable) should also be sent to the study team at the University of Manchester at registration.

Obtaining re-consent for participants already registered with the study

- Post the *BCRD Remote Reconsent* document to the participant (or parent/guardian if under 16 years old), along with the participant information sheet, transparency information sheet and three blank copies of the consent form. The text can be pasted in to the body of an email if this is being sent via email (with the other documents included as attachments)
- Nurse/delegated health care professional is available to answer any questions via email/telephone (contact details provided on letter/email).
- If participant/parent is happy to re-consent, they sign three copies of the consent form and post them back to the hospital.
Note: E-consent (i.e., providing an electronic signature by means such as a scan of a signed consent form to return via secure email) can be used if preferred, as per the HRA and MHRA 'Joint statement on seeking consent by electronic methods' guidance in September 2018 (<https://www.hra.nhs.uk/about-us/news-updates/hra-and-mhra-publish-joint-statement-seeking-and-documenting-consent-using-electronic-methods-econsent/>). A site file note should be written to document this, which should be stored with the consent form at site for audit purposes (or a short note can be made on the consent form to record this, if preferred).

The rheumatology/research team countersigns the consent forms, posts one fully signed form back to the participant/parent, sends one to the study team and keeps the other in the site file. If the participant/parent has provided e-consent (rather than consent via ink signature), a copy of the site file note (if this has been used, detailed above) should also be sent to the participant/parent as a record of this.

- If the participant does not want to provide a reconsent, please inform the study team at the University of Manchester, and the participant will no longer be under follow-up.

Where possible, all participants should be reconsented at the age of 16 years old.

Biologic Exposed cohort

The biologic exposed cohort will be children with JIA, starting therapy with a biologic, biosimilar or other new therapy. In patients exposed to a number of biologic therapies, on-going inclusion of data collection will continue. Inclusion criteria for such subjects are:

1. children should either satisfy the revised ILAR classification criteria for JIA at the time of registration or be classified as having been diagnosed with JIA by the consultant rheumatologist,
2. age < 18 years
3. willingness to give informed consent for long term follow-up including access to all medical records.
4. minimum of one treatment with a biologic/biosimilar/other new therapy
5. time from start of biologic therapy to enrolment < 6 months.

External validity will be maximised by attempting to ascertain all children, newly treated with biologic/biosimilar/other new therapies. Recruitment will be co-ordinated at a national level. The study will be based in the United Kingdom.

Non-exposed cohort

The safety outcomes of the children recruited to this study will be compared to a cohort of children who are receiving MTX for JIA and have never been prescribed a biologic therapy. Recruitment to this cohort ceased in December 2014.

Notification of cases

It will be the responsibility of the treating rheumatologist or designate to obtain parent/patient consent prior to registration. Patient information sheets, consent forms and a copy of this protocol will be made available on the study website and via the study coordinator directly. Receipt of registration and baseline forms would then act as the initiating event for the collection of all necessary follow up.

Core baseline data

The following information will be collected, using a standardised form on both the exposed and unexposed controls:

1. ILAR JIA subtype (including the presence or absence of those features listed in ILAR criteria for JIA),
2. age, gender, height, weight, month/year recalled symptom onset, month/year first consulted paediatric rheumatology
3. previous drug history of disease modifying agents including duration of therapy, reason for discontinuation and prior adverse events,
4. significant co-morbidity (from a list),
5. all current therapy,
6. Core outcome variables (COVs, namely: Active and limited joint count, ESR, Physician and parent global assessment, CHAQ and pain score) as well as baseline haemoglobin level and mean corpuscular volume (MCV) levels (recorded from the case notes where available – no additional blood tests will be requested).

Biobank

In addition to the collection of core clinical data, a blood sample or saliva sample will be collected from all children for genetic analysis (with informed consent). This will be collected at a time when blood is being taken as part of routine clinical care, which may be at the local hospital or GP surgery if not at the usual paediatric rheumatology centre. If blood is not likely to be obtained, then a saliva sample collection kit may be requested. Copies of the signed consent form will be retained for as long as the samples are stored for use in research.

The costs of specific gene / pharmacogenetic investigations will be carried out by separate funding.

Follow-up

The follow up of all children will be organised by the national coordinating centre and undertaken to assess:

1. Any change in therapy,
2. Core outcome variables (COV) including active and limited joint count, ESR, CHAQ score, parent general evaluation and physician global assessment - During the first year of therapy on each biologic drug, data on all COV's will also be collected. At later time points, disease severity will be obtained using the CHAQ. Haemoglobin level and MCV (recorded from the case notes where measured – no additional blood tests will be measured) will also be collected over the first year of therapy as a potential novel marker of treatment response.
3. Development of any endpoint of interest (serious adverse event), with date of onset, and in particular serious infection, mortality, malignancy, development of new co-morbidities requiring referral to hospital or any event otherwise felt to be medically significant or important.

Change in therapy

The recruiting clinician will be contacted at 6 months, 12 months and then yearly and asked to provide data concerning any change in anti-rheumatic treatment over the preceding year. This includes continuation on drug and commencement of any new co-therapy. Additional data on disease activity at the time new drugs are started will also be collected, which will be collected again six months after the change.

Ascertainment of endpoints

This will be achieved using a number of complementary approaches:

1. All exposed and control individuals will be “flagged” with NHS England (previously known as NHS Digital and, prior to that, the Health and Social Care Information Centre) for continuous surveillance, linkage with NHS datasets (including but not limited to hospital episode statistics, maternity services dataset, mental health services dataset), and notification of mortality and the development of any malignancy. A copy of the death certificate will be obtained for those who die and a copy of the histology requested for those who develop a malignancy;
2. The referring physician will also be contacted at 6 months, 12 months and then yearly to determine the occurrence of any significant adverse event.
3. The Child Health Utility 9D (CHU-9D) will be collected at baseline and at each follow up point to measure disease burden. It is suitable for completion by the participant themselves whilst in clinic, or with the help of the participant's parent if the participant is between 5-7 years old. The information would be entered on to the study database alongside the usual follow up forms. We would not collect this from participants who are under 5 years of age.

Where a serious or suspected serious adverse event is reported, a series of further validation steps will follow to confirm the diagnosis and the therapy at the time of the event. A system will be developed to collect specified information on certain events of interest (i.e. serious infections, malignancy, uveitis, demyelination, macrophage activating syndrome). Copies of hospital discharge summaries or consultant letters will also be requested for any hospital admissions. A copy of the death certificate will be obtained from the Health and Social Care Information Centre for any death occurring within the UK. As the use of these drugs is evolving, other events of special interest may emerge and therefore, it is important to collect as much information as possible on all serious adverse events. This thorough system of collecting adverse event information ensures that new signals will be captured by the study.

Length of Follow-up

All children will be followed for a minimum of 5 years and will continue for the duration of the study;

however, an important outcome of this study will be the transition of children from childhood through to adolescence and into adulthood, in terms of growth and development, and therefore, ideally all children should be followed at least until adulthood (aged 21 years). However, for some children this could include > 15 years of follow-up and the current funding structure does not allow for such extended follow-up. However, follow-up of all children will continue until at least the age of 21 as far as the length of the study allows. A "Transition Questionnaire" has been developed to collect details on schooling, higher education, employment prospects, reproduction and social life and will be collected from the participant at the time of transition to adult services (usually occurring between 16 – 18 years of age) and again at around the time of their 21st birthday. The questionnaire will be handed to the participant at the approximately the right times by the study nurse, along with a pre-paid envelope for their return to the coordination centre offices in Manchester. If the participant would prefer to complete the form online, there is an option for them to provide the nurse or healthcare professional with their email address. This will then be sent to the study coordinator who will email the participant a unique link to complete the survey securely online. In addition, linkage with NHS datasets ensures long-term follow-up of patients. It will help answer important long-term outcome questions that are being asked daily in the clinical setting.

One of the challenges in paediatric research is maintaining contact with children as they move from paediatric to adult services. For some children, this will not be an issue (i.e. children receiving all care through an adult rheumatology service or children receiving care from a paediatric rheumatologist who continues to follow-up children until adulthood). However, if patients switch doctors through a transition process (or transfer directly to adult services) this will require a new physician assuming involvement with the study. If this is the case, a number of scenarios are envisioned:

1. If the patient sees an adult rheumatologist within the same Trust, then no additional ethical/R&D approval will be required. However, contact will be made with the adult rheumatologist and arrangements put in place to coordinate the continued collection of data.
2. If the child moves to a different hospital who does not already have patients enrolled in the study, then additional local ethics and R&D may need to be obtained. The study coordinator will contact the new physician and if they are agreeable, liaise with them to make the process as seamless as possible. Arrangements will then be put in place to coordinate continued collection of data.

UK CRN Portfolio adoption

The study has been adopted on to the UK Clinical Research Network, ID 7725.

Sample size and recruitment

The recruitment of the biologic-treated subjects to the study will be determined by a number of external factors. These include:

1. The licensing of new biologic, biosimilar and other new agents for use in children with JIA,
2. The approval of licensed agents by the National Institute for Health and Clinical Excellence (NICE),
3. The recommendation by NICE all subjects with JIA treated with these agents within a specified approval period should be enrolled in such a study,
4. The use of these agents by rheumatologists.

Sample size estimates should ideally be based on estimates of the risk of the outcome of interest in an untreated population. However, there is limited information available on how frequently serious adverse events occur with either methotrexate or new biologic agents. It is expected that use of these agents and therefore, recruitment to the study will continue to increase over time. As recruitment increases the number of risk hypotheses that can be investigated will also increase. The other issue that will influence statistical power is the duration of follow-up. Under a model that

proposes that the increased risk of a long term hazard is constant over the duration of follow-up, then the number of person-years at risk increases in direct proportion to the length of follow up. If we assume a recruitment rate of 50 children per year over 5 years of study and each child is treated for a median of 3 years, this would lead to a total treated person years of 750 years at the end of the study. Assuming a similar recruitment to the MTX arm of the study, this would allow us to detect a doubling of risk in serious adverse events occurring at a rate of 3/100 treated pyrs in an untreated cohort ($\alpha = 0.05$, $\beta = 0.80$). In reality, many of the events of interest are likely to be rarer than this and thus, it thus seems prudent to ensure the sample sizes discussed above are the minimum target recruitment. Indeed, with the extension of the study to 31/12/2031, a target sample size of 2000 participants is suggested. As recruitment increases, the number of risk hypotheses that can be investigated will increase. In addition, continued follow-up of these children will allow exploration of issues related to long-term use of these agents with respect to the developing immune system.

Loss to follow up will not be an issue for the outcomes of mortality or malignancy – or other hospital visits that may be recorded in the hospital episode statistics, maternity services dataset, or mental health services dataset – as all subjects will be flagged with the NHS England, although risk attribution will not be fully possible without corresponding follow-up data from the hospital, which will provide details on drug changes and therapies received.

Section 251 will be applied to the linkage of all recruited patients with national datasets where consent is deemed insufficient.

Comparability of exposed and non-exposed cohorts

The greatest concern with this study is the risk of confounding by indication. In general, treated and untreated subjects in an observational study will differ in a number of variables which are related to the outcome under study. This may be particularly true in observational treatment studies in JIA, where, due to the current treatment paradigm, after failure with MTX, most children will move on to a biologic agent rather than another traditional DMARD. Therefore, by definition, the treated cohort will have more severe disease. The recruitment process outlined above will be monitored on a 6 monthly basis and comparisons undertaken between the distributions of covariates between the cohorts recruited to both groups to take into account any substantive shift from non-exposed to exposed status. Residual differences will be adjusted for in the analysis.

Collection of data

Core baseline and follow-up data will be generally be collected by a web-based system, which in most cases will be completed by a nurse affiliated with the local centre, though there is the opportunity for the nurse to post/fax the forms to the coordinating centre for entry if this is preferred. The study database details any follow ups that are outstanding as well as giving a list of follow ups that are due in the coming month for each centre.. The nature of NHS England linkage is such as to ensure near complete follow-up for two events of malignancy and mortality, although it would be preferable to have similar complete follow-up from the patient's local centre to ascertain the risk of other rare or unusual adverse events.

ANALYSIS

The primary objective of this study will be to study the occurrence and risk of serious adverse events in children receiving biologic/biosimilar/other new therapy compared to children receiving MTX to study what, if any, additional risk is being placed on children by the use of biologic therapy. The initial analyses will consist of comparisons in baseline status between the individuals in the different cohorts. The final analysis of endpoints will be based on comparing the risks of events over time using regression models appropriate to the outcome of interest, taking into account differences between groups in potential confounders and effect modifiers.

Interim analyses

A template for monitoring of crude rates of serious and other selected adverse events of interest in the exposed and unexposed cohorts will be developed and monitored on a 6-monthly basis. Such analyses will be a guide to the ultimate levels of recruitment and length of follow up required. Such analysis will include an on-drug model as well as an ever-treated model, regardless of subsequent biologic or non-biologic therapy.

A Data Monitoring Committee (DMC) has been convened. The DMC will be independent of the principal investigators and will have the power to request interim analyses and advise on the timing and nature of any publications. The DMC should include at least one paediatrician and one statistician/epidemiologist.

Specific analysis will include:

1. Treatment effectiveness
 - a. With a paucity of clinical trials and other observational studies, it remains unknown how effective new biologic agents will be in children with JIA. Available clinical trials of anti-TNF agents have demonstrated that these agents are very effective in a proportion of children with JIA. However, less is known about who is responding. The risk of ongoing uncontrolled disease includes worsening disability, growth retardation and potentially more severe adverse events. Therefore, ongoing analysis will be undertaken to identify factors associated with response, including JIA subtype, disease specific features common across all JIA subtypes and the benefits of co-therapy. Initially analysis will look specifically at clinical and demographic features but future analyses will also include pharmacogenetic studies.
 - b. Treatment continuation with detailed analysis of reasons for discontinuation and predictors of drug persistence.
 - c. Recently it has been postulated that a rise in MCV may be a surrogate of treatment response in adult patients receiving DMARDs (18). This has not been explored in children with JIA. Therefore, we will conduct an analysis of change in red blood cell MCV over the first year of treatment and correlate this with standard measures of treatment response.
2. Safety
 - a. A detailed analysis of the rates of serious adverse events will be undertaken including event rate and risk compared with the MTX group. Given the likely differences between these two groups, propensity models and treatment weighting will need to be considered. A crude analysis will be repeated on a six-monthly basis to monitor for safety signals (see above).
 - b. An analysis of safety outcomes in different subgroups will also be undertaken. Subgroups may be defined by disease subgroup, co-therapy or other features of disease (e.g. uveitis).
 - c. A specific analysis of the most frequent adverse events will be done. This will likely include serious infections but can look at others in time. Included in this analysis will be a study of risk factors for serious infection in children receiving anti-TNF therapy as well as a study of risk over time.
 - d. Collaborations will be made with other international registers to explore combined analysis of rarer outcomes, including but not limited to, demyelination and malignancy

End of Study

Recruitment to the study will continue until the study end date; this is now 31/12/2031 but may be extended beyond this time if additional funding is secured. Continued analysis of data in this study will continue until this date, but may be extended beyond this time if additional funding is secured.

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