Global: Interventional Investigator Initiated Study (IIS) Post-Authorisation Safety Study (PASS) Protocol Finalization Signature Page

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Signature: _____ **Date:** _____

Name:

Approver's Name	Title	Date and Time (UTC)
[redacted]	Deputy QPPV	15-Feb-2019 13:58:33

Proposal for establishment of a UK post-marketing surveillance registry to study the effectiveness, safety and prescribing habits of tocilizumab for the treatment of giant cell arteritis in the UK National Health Service, nested within the existing structure of the UK GCA Consortium and UKIVAS studies

Short title: TARGET GCAT Registry

Ethics reference	UK GCA Consortium 05/Q1108/28 Yorkshire and the Humber – Leeds West Research Ethics Committee An ethical amendment to the UK GCA Consortium for a tocilizumab Registry sub-study was granted on 03 July 2018
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EXECUTIVE SUMMARY

Tocilizumab is now licensed in the US and EU for the prevention of relapses in giant cell arteritis (GCA) following the successful clinical trial GiACTA. However, because this is the first introduction of IL-6 pathway inhibition into clinical care of GCA, there remain important clinical questions regarding the effectiveness and safety of this therapy in routine clinical practice. Post-marketing surveillance is essential in order to provide precise and generalizable estimates of risks and benefits of this treatment. In particular, it is not known if tocilizumab affects the incidence of long-term complications of GCA, such as visual loss, large-vessel aneurysm or stenosis.

In the UK, a commissioning decision by the National Institute of Health and Care Excellence (NICE) has been announced, allowing the use of tocilizumab in GCA. This decision will be reviewed after a specified time-period (anticipated to be three years) and is likely to be dependent on real-life clinical outcome data, including data relevant to health economic analyses such as resource use and health-related quality of life. Unique to the UK, is the stipulation that tocilizumab can be prescribed for no more than one year and only once for each patient. It is important to capture post-treatment relapses and compare these data with European cases where no such stipulations for use apply.

The UK GCA Consortium (UK GCA) research study was established in 2005 and currently recruits from 44 NHS sites across the UK. In addition to clinical data elicited by patient interview and medical notes review, patients are asked to provide explicit consent for genetic (whole-genome) analysis of blood samples, review of their archived temporal artery biopsy tissue, and for linkage to NHS databases such as Hospital Episode Statistics.

The UKIVAS (UK and Ireland Vasculitis Rare Disease Group) Registry is a collaboration between patients, clinicians and scientists to create the first comprehensive database of vasculitis patients in the UK and Ireland. It contains information on patients with systemic vasculitis (including GCA) attending centres across the UK and Ireland. It has been in operation for over five years, currently hosts over 70 active data collection sites, and is continually expanding. UKIVAS has established a unique database for the collection of data relevant to vasculitis, and this would provide an ideal model on which to base data collection for the proposed Registry. UKIVAS is currently being used successfully in a research collaboration with Roche to provide post-marketing data on the long term effects of rituximab in anti-neutrophil cytoplasm associated vasculitis in a single centre cohort of patients in Cambridge, UK.

To date, over 1,900 patients diagnosed with GCA have been recruited to UK GCA, and recruitment rates exceed 350 per annum. There are 4,900 patients in UKIVAS (of which over 500 have GCA) with approximately 100 more patients with GCA being recruited each year.

A particular issue for tocilizumab in GCA is that patients with GCA are typically elderly and this population has a significant comorbidity burden. Standard therapy for GCA is long-term glucocorticoid ("steroid") therapy, with or without methotrexate. Many of the likely adverse effects of tocilizumab (predicted from experience of other indications, such as infection and diverticulitis) are also more frequent with all three of these other risk factors (age, comorbidity and steroid toxicity). In order to interpret correctly safety data on the use of tocilizumab in this patient group, any comparison of adverse event rates between patients with GCA who either receive, or do not receive tocilizumab, will need to control for prescribing decisions using methods such as propensity score matching or adjustment.

Nesting a post-marketing surveillance registry within the UK GCA Consortium using the UKIVAS data capture system will provide added value in the following ways:

1. It will allow access to rich clinical, histological and genomic data that would not be otherwise collected in routine clinical care.

2. It will allow us to identify and recruit controls (who are not prescribed tocilizumab) to determine if putative safety signals relate to tocilizumab, concomitant medications (methotrexate, glucocorticoids) age, and comorbidity. It will also allow us to estimate the relative effectiveness of tocilizumab compared to glucocorticoids in real world settings (e.g. in terms of prevention of relapse).

3. It will provide us with the ability to link to relevant NHS databases (such as HES) to allow collection of data relevant to long-term safety and health economic analyses in future add on studies.

STUDY SYNOPSIS

Study title	TARGET Giant Cell Arteritis Tocilizumab Registry (GCAT)
Study aim	To assess the effectiveness and safety of tocilizumab in controlling refractory or relapsing GCA in patients who require escalation of therapy to reach sustained remission defined by the absence of active disease features
Study design	Nested longitudinal observational (cohort) study
Registry study (longitudinal sub-study)	Patients with refractory and relapsing GCA who fulfil NHSE criteria for tocilizumab prescription as part of their routine clinical care
Nested within and recruited from	UK GCA Consortium study (already established) UKIVAS (already established)
Planned sample size	Patients prescribed tocilizumab for GCA within the NHS (500 within three-year study period) and 500 age-, sex- and centre-matched controls.
Planned study period	• Total study duration: 3 years (36 months) • Anticipated start date: March 2019 • Patient recruitment: 16 months • Data collection: we will collect data from recruited participants (patients prescribed tocilizumab and controls not prescribed tocilizumab) at four time points over a study period of 33 months: 1. baseline (before treatment commences) 2. after 6 months of treatment, or 6 months from baseline for controls 3. at the end of treatment (usually 12 months), or 12 months from baseline for controls 4. 6 months after treatment with tocilizumab has ceased, or 18 months after baseline for controls. This timeline accounts for the last date a patient can be recruited to obtain a full 18 months follow up. • Data analysis: the quality of data will be monitored to ensure completeness and accuracy throughout the study. Analysis will be performed on a rolling basis until all data has been collected, and for three months after the final date of data collection. • Reports: will be provided to Roche on a rolling basis every six months during the period of data collection. The first report will be available six months after data collection commences. A final report will be delivered once all data has been collected and analysed.

1. BACKGROUND AND RATIONALE

1.1. Giant cell arteritis

Giant cell arteritis (GCA) is the most common form of primary systemic vasculitis, with up to 75,000 cases a year identified in the EU and US. It occurs almost exclusively in people over the age of 50 years and is considered to be a medical emergency. It can lead to significant morbidity across a variety of systems, due to both the disease, and complications of treatment. About 40% of patients experience serious visual manifestations. Irreversible ischaemic complications, including blindness, may occur despite immediate use of high-dose glucocorticoids.

The aetiology of GCA is unknown, and current therapies are non-specific and associated with major side effects. Current UK management guidelines recommend an initial prednisolone dose of 40mg daily, or 60mg in the presence of ischaemic features. Patients with acute/threatened visual loss often receive intravenous methylprednisolone to reduce the risk of permanent visual loss. There is weak evidence for the use of concurrent immunosuppressants in GCA, and most UK patients commence glucocorticoid monotherapy. This contrasts with other inflammatory disorders and vasculitides where early immunosuppressive therapy improves patient outcomes. GCA has a high relapse rate (30–78%) and 50% remain glucocorticoid dependent two- to three-years post diagnosis. Patients therefore have substantial and costly morbidity and mortality from glucocorticoid toxicity (58–86%) including cardiovascular disease, hypertension, diabetes, fractures, severe infections, myopathy and cataracts.

Outcome data for GCA patients comprise small cohort studies from single centres. There is significant reporting bias when novel therapies are first introduced into clinical practice, which underestimates their real benefit. In addition, the outcome of patients treated with standard therapies in routine care may not reflect the outcomes reported during clinical trials. Moreover, there are differences in the severity of the disease and in the way individuals respond to treatment. These are not well understood but influence the way patient cohorts are managed. Understanding factors that influence disease outcomes, and the impact of different therapies in routine care, can only be achieved using a larger number of patients from multiple sites.

1.2. The UK GCA Consortium and UKIVAS

The UK GCA Consortium (UK GCA) for patients with suspected and diagnosed GCA was established in 2005 (REC 05/Q1108/28) and is led by the main applicant of this proposal (Prof Morgan). The original purpose of this observational study was to find genetic determinants of GCA susceptibility in order to yield novel insights into disease pathogenesis. To date, over 1,900 patients with suspected or clinically diagnosed GCA have been recruited from 44 primary and secondary care centres in England and Wales. All centres are actively recruiting patients, and we are still adding new sites. Patients have a single study visit and data are recorded, usually by a research nurse, by patient interview supplemented by review of medical notes. The clinical data

currently collected covers diagnosis (features and manifestations, diagnostic tests), co-morbidities, smoking and alcohol history, steroid treatment, flares, drug history, adverse events and family history. We also collect data related to race and the English Indices of Deprivation (derived from home post codes). We have access to blood test results (including markers of inflammation such as C-reactive protein [CRP], Erythrocyte sedimentation rate [ESR], and plasma viscosity [PV]) and temporal artery biopsy blocks and slides if taken as part of diagnosis. Data is compiled in a central database, and samples are collected from all sites and stored in HTA licenced premises in the School of Medicine (University of Leeds, UK). Samples collected from this study have already been used to perform tests such as proteomics, genetics, metabolomics and biomarker profiling to generate novel insights into the disease pathogenesis.

The UKIVAS Registry (REC 10/H1102/77) is a data repository for adults and children who have been diagnosed with any form of primary systemic vasculitis and followed in secondary care. It was established in 2011 and comprises core clinical data from 4,900 patients attending over 70 centres across the UK and Ireland. New centres continue to join the study. The long-term vision is to collect outcome data from patients' medical records at the time of routine clinical visits. Data are entered directly by site teams to a secure web-based database held at the University of Oxford (the chief investigator of UKIVAS, Prof Luqmani, is a co-applicant on this proposal). This allows analysis in variations in disease susceptibility and outcomes, and enhances the evidence base for the diagnosis and treatment of patients with vasculitis. It also provides rapid recruitment of potential patients for inclusion in other studies and therapeutic trials in vasculitis.

We propose that a tocilizumab post-marketing surveillance registry is set up as a sub-study of the UK GCA Consortium study. The main UK GCA Consortium study has a one-time study visit in which detailed clinical data are collected by a member of the research team; patients optionally consent to genetic and pathology studies, data linkage, and/or being contacted for future research studies. We propose that, additional to this, longitudinal data are collected as part of routine clinical care in a sub-study of patients: cases (prescribed tocilizumab for GCA) and controls (eligible for, but not prescribed tocilizumab for GCA).

1.3. The role of the MRC TARGET Partnership

The TARGET Partnership was established in August 2017 following the award of a Partnership Grant from the Medical Research Council. The Principal Investigator is Professor Ann Morgan (University of Leeds), and there are further co-applicants and partners from academia, the NHS and industry. Roche Products Ltd are already a partner and Dr [redacted] ([redacted] – [redacted]) is the Industry Representative on the Partnership Management Board.

The aim of TARGET is to build a multi-speciality partnership between clinicians, scientists, industry and patients who have a common interest in improving outcomes for patients with GCA and reducing glucocorticoid toxicity. TARGET Partners will

provide necessary expertise and links to academia and the NHS, ensure engagement from the outset, and build a Registry that will provide Roche with the data required to make a comprehensive assessment of the effectiveness, safety and prescribing habits associated with the use of tocilizumab in the treatment of GCA.

1.4. Registry data collection

Patients already recruited to UK GCA who are prescribed tocilizumab from March 2019 will be invited to participate in the Registry sub-study and contribute longitudinal data at their clinical care visits.

Patients not already recruited to UK GCA will be invited to consent to the main UK GCA Consortium study and commence the longitudinal part of the study (the Registry sub-study) simultaneously. These would also be eligible for UKIVAS, and would be invited to separately consent to participate in the UKIVAS registry.

Electronic data capture systems, based on existing UKIVAS data collection systems, will be set up to facilitate rapid data entry at the time of enrolment and at routine follow up visits from NHS computers. Core data will include demographics, diagnosis and diagnostic tests, and co-morbidities. Longitudinal data will include disease activity (Birmingham Vasculitis Activity Score [BVAS]), patient reported outcome measures, tests and observations, medications, and adverse events. Data will be validated at the point of data entry to minimise data entry errors and missing data. Training, where necessary, will be provided for investigators using these measures to ensure data quality.

The database will be GCP compliant and full specification details documented. It will be hosted on a secure server and maintained at the University of Leeds. Direct access will be granted to local research teams at participating NHS sites who will submit data directly to the on-line study database. User activity, data return, completeness and accuracy will be audited centrally. A standard operating procedure for security procedures, user access, data back-up and audit will be maintained for the duration of the study.

The database will include an interface to record details of participant consent for the Registry and related sub-studies, ensuring datasets are compiled and shared appropriately with external researchers and commercial companies. Participants' NHS numbers will be entered into the database by local teams, but will be encrypted centrally to ensure confidentiality. Storage of health service unique identifiers, such as the NHS numbers (England and Wales) or the Community Health Index (Scotland) prevents duplicate registrations and enables local teams to readily identify and track patient visits and data. Participation in other research studies, and death and enrolment status will also be maintained to ensure appropriate follow up.

2. AIM AND OBJECTIVES

Aim: to assess the effectiveness and safety of tocilizumab in controlling refractory or relapsing GCA in patients who require escalation therapy* to reach sustained remission.

Primary objective: to determine the proportion of eligible patients who achieve sustained partial or complete remission 6 months after the start of tocilizumab.

Secondary objectives

1. To determine the proportion of eligible patients who achieve sustained complete remission 6 months after the start of tocilizumab

2. To assess the safety and effectiveness of tocilizumab (in comparison to other strategies for refractory/relapsing disease) in patients with GCA who require escalation therapy as a result of refractory or relapsing disease

3. To compare characteristics of real-world patients prescribed tocilizumab (demographics, disease severity, risk factors for steroid toxicity, relative contra-indications to tocilizumab therapy, concomitant medications) to characteristics of tocilizumab clinical trial populations

4. To describe relapse** rates in patients with GCA treated with tocilizumab at treatment completion (usually 12 months in the UK) and 6 months following discontinuation of tocilizumab

5. To describe disease activity, ischaemic complications and drug related toxicity during the first 6 and 12 months following the start of tocilizumab, compared to other treatment strategies for refractory/relapsing disease

6. To describe patterns of glucocorticoid dosing, including estimated cumulative dose and time to discontinuation of glucocorticoids, in patients with GCA who are treated with tocilizumab, compared to other treatment strategies for refractory/relapsing disease

7. To describe reasons for premature discontinuation of tocilizumab

8. To estimate the prevalence of glucocorticoid toxicity (e.g. weight gain, fracture, diabetes, infection, or new psychiatric diagnosis) in patients with GCA who are treated with tocilizumab, compared to other strategies for refractory/relapsing disease

9. To invite patients who agree to take part in the current study to consent to being approached to participate in future related studies of their condition, including randomised controlled trials

**Escalation therapy is defined as an increase in drug therapy for GCA, including an increase in prednisolone daily dose (by at least 10mg per day or above a threshold of 20mg per day) and/or addition of further immunosuppressant therapy (such as methotrexate or tocilizumab). **Relapse is defined as relevant signs, symptoms or laboratory evidence of disease activity of GCA verified in secondary care and requiring escalation therapy.*

3. STUDY DESIGN

This will be a matched observational cohort study, nested within the UK GCA Consortium cohort, using the established UKIVAS data collection systems. Participants will be invited to consent to the collection of clinical data on diagnosis, investigations, treatment and outcomes.

Patients will be recruited to the study if they have been diagnosed with GCA and are either experiencing a relapse of disease or have refractory disease, and have either started, or are about to commence, escalation therapy as part of standard care. Patients must fulfil the NHS England criteria for refractory or relapsing disease as follows:

1. NHS England Refractory disease definition: inability to induce remission in a patient with GCA who has either i) a definitive diagnosis of GCA (on biopsy or imaging e.g. USS/CT/MRA/PET-CT), or ii) definite ischaemic signs or symptoms with a significant risk of end organ damage or vascular damage, despite optimal standard care for which no other cause has been identified.

2. NHS England Relapsing disease definition: a patient with GCA who has previously responded to treatment with one of the following a) biopsy or imaging (e.g. USS/CT/MRA/PET-CT) evidence of currently active or progressive GCA, or b) evidence of definite ischaemic complications, such as acute ischaemic optic neuropathy, scalp necrosis, limb claudication, stroke or any other ischaemic or vascular complication due to GCA, or c) previous evidence of GCA (on biopsy or imaging e.g. USS/CT/MRA/PET-CT), AND clear recurrence of previous symptoms and/or increased inflammatory markers (e.g. CRP, ESR, PV) for which no other cause for increased inflammatory markers has been identified (e.g. active infection or other cause).

Patients will be informed about the study by their routine clinical care team when they are identified as having refractory or relapsing disease and referred to a regional Specialist Commissioning Rheumatology or Ophthalmology MDT for consideration of treatment escalation as part of standard clinical care. If they agree to participate, a member of the research team will contact them by letter of invitation or by telephone. After they have provided written informed consent, study specific data will be taken at the same time as the collection of clinical data and any routine blood tests.

4. PARTICIPANT IDENTIFICATION

Patients taking part in the Registry sub-study must be eligible for the UK GCA Consortium study (in short, they must have a diagnosis of GCA and be willing and able to consent; for formal criteria see the UK GCA protocols). For inclusion in the Registry sub-study, they must have refractory or relapsing GCA as defined by NHS England's commissioning statement for tocilizumab and require treatment escalation.

5. REGISTRY PROCEDURES

5.1. Recruitment

The policy currently adopted by UK GCA will be followed when recruiting patients into the Registry. Patients will be identified and approached by their clinical teams in outpatient clinics and wards to invite them to discuss the study with the Principal Investigator or other member of the research team in the outpatient clinics/wards or by letter of invitation or telephone call. Patients will be invited to participate having their anonymised clinical data entered into a national dataset.

Patient information sheets, consent forms and a copy of this protocol will, with permission, be made available on the TARGET website or directly from TARGET.

5.2. Informed consent

The Participant Information Sheet will be presented to the patient detailing the nature of the Registry, what it will involve for the participant, and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the Registry at any time, for any reason, and without prejudice to future care. The patient will be allowed as much time as they wish to consider the information, ask the research team questions, or consult with their GP or other independent parties to decide whether or not they will participate.

It will be the responsibility of the referring clinician or nurse to obtain patient consent. Written consent will be obtained by means of participant dated signature and the dated signature of the person who presented and obtained the informed consent. The person who obtains consent will be suitably qualified and experienced, and will have been authorised to do so by the Principal Investigator. The participant must personally sign and date the consent form before data are collected. If a participant has visual impairment, such that they are not able to read the document or provide written consent, they may ask for verbal details of the study and allow someone to provide a proxy signature. A copy of the signed consent form will be given to the participant and the original signed form will be retained at the study site (copies will be sent to the University of Leeds). Provision will be made for participants to be consented by mail or by telephone. Patients returning the consent form by post will be asked to personally sign and date the consent form and return it to the local investigator for countersigning before any study specific procedures are performed. This will optimise recruitment of patients who have an established diagnosis of GCA, but who may not be due to attend a routine clinic appointment for some months. In addition, sites may consult local patient research registries and their local UK GCA database to identify patients who have consented to be contacted to consider participation in related research studies.

5.2.1. Consent for use of data

Provision will be made in the consent form for non-identifiable clinical information to be shared with academic and commercial collaborators in the UK and internationally for use in ethically approved research. Participants may also agree to the storage of their personal information by the local research team so they can be contacted in the future to be invited to participate in related research. The version of the consent form, and any restrictions to use of data, will be entered on the central database by the local study team to ensure specific consent is recorded alongside the patient's clinical data.

5.3. Data collected for the Registry

Detailed data regarding diagnosis and clinical features of GCA will already have been collected at a research visit on entry to the UK GCA/UKIVAS main studies. It is recognised that the patient may be recruited to the Registry sub-study substantially later than original recruitment into the UK GCA/UKIVAS main studies. For this reason, a standardised minimal core dataset relevant to clinical practice will be collected on recruitment to the Registry sub-study.

Demographic and core clinical data at the time of enrolment into the Registry will be recorded directly to an on-line database by the investigator or designated member of the research team. This type of data is already captured in UKIVAS, and we have developed a comprehensive data dictionary for the capture of longitudinal data including laboratory tests and observations, medication, accident and emergency data, comorbidities and disease activity. We are therefore ideally placed to apply our tested methodology to the proposed Registry.

We will liaise with EU collaborators who are also creating National Registries to assess the effectiveness and safety of tocilizumab for the treatment of GCA (Professor [redacted], [redacted], France; Professor [redacted], [redacted], Germany) to ensure standardisation in relation to data collection, and to ensure thorough consideration of all measures required to support the aim and objectives of the Registry. At baseline (after consent has been provided but before treatment with tocilizumab has commenced where applicable) the following information may be collected by the recruiting clinician, using a standardised data collection form:

1. Diagnosis and supporting investigations with dates (laboratory, biopsy, imaging)
2. Age, sex and ethnicity
3. Current and previous drug history, including glucocorticoid therapy and disease modifying agents, start and stop dates, and dose adjustments
4. Concomitant medications
5. History of adverse events with dates relevant to glucocorticoids; attribution to disease, medication, or other cause; disease severity; history of any toxicity to be evaluated during follow-up (including weight gain, fractures, psychiatric diagnosis, diabetes)
6. Co-morbidities (especially relative contra-indications to glucocorticoid or tocilizumab therapy)

7. Height, weight, and blood pressure in each arm
8. Smoking status
9. Patient and physician global scores of GCA activity
10. Structured assessment of disease activity and damage
11. Core laboratory data: haemoglobin concentration, neutrophil count, platelet count, erythrocyte sedimentation rate, C-reactive protein, lipids
12. Reason for starting tocilizumab (or other strategy): refractory or relapsing disease, coded with options for different diagnostic grounds to help with the assessment of the differences between cases and controls at baseline

Follow-up visits for the Registry, conducted every 6 months (+/- 4 weeks) at the time of the patients' routine clinic visits, will collect repeated information as appropriate (items 3 to 11). Outcome data will also be collected as relevant to the Objectives of the Registry listed above, such as relapse, remission, and disease- and treatment-related adverse effects. In addition, all data relevant to fulfilment of NICE guidance for NHS England tocilizumab prescribing will be recorded.

Each site investigator will be contacted every 6 months during the data collection period and asked to complete a standard data form covering any change in treatment and occurrence of outcomes over the preceding 6 months. This includes continuation on drug or reasons for stoppage, details of any change in glucocorticoid dose, and commencement of any new co-therapy. Clinical data will be collected on all new serious co-morbidities occurring in the previous period.

Diligent attempts will be made to follow up non-responders (unless further follow-up is refused). We will attempt to contact non-responders by telephone, mail and email on at least three occasions. A date of withdrawal will be recorded for patients who refuse further follow-up as well as the reason for withdrawal (if known).

5.4. Drug contra-indications

Absolute and relative contraindications for prednisolone and tocilizumab and will be recorded where relevant for use in statistical analyses. We will document any cases where patients are given tocilizumab despite meeting an exclusion criteria and provide outcome summaries of such cases.

5.5. Reporting Non-serious Adverse Events, Adverse Events of Special Interest, Serious Adverse Events and Special Situations

Safety assessments will consist of monitoring and recording Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs) and non-serious Adverse Events (nsAE), performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the treatment as per standard medical practice.

5.5.1. Non-serious adverse events

For the purposes of this Registry, a nsAE is defined as something new to the patient that has occurred since exposure to the Roche product/enrolment on the study. Pre-existing conditions do not need to be reported as AEs: they should only be reported if the condition has worsened since patient enrolment into the Registry and exposure to tocilizumab. The new medical diagnosis only should be reported, and not all the individual signs and symptoms associated with that diagnosis. The Research Nurse will review patients' medical notes prior to each six monthly Registry visit and enter any new medical diagnoses that have been documented by the clinician as part of the standard care patient review that may have occurred during the period between Registry visits.

5.5.2. Adverse events of special interest

In this Registry, the AESIs are:

1. Anaphylaxis
2. Bleeding events
3. Demyelination
4. Gastrointestinal perforations
5. Hepatic events
6. All infections
7. Malignancies
8. Myocardial infarction
9. Stroke

With the exception of some infections which may be reported as AESIs, the AESIs in this Registry may be considered to be serious adverse events (SAEs) and therefore the protocol for reporting SAEs will be followed. Any AESI not considered to be an SAE will be captured at routine visits by the clinician. Rolling monthly reports will be provided to Roche.

5.5.3. Serious Adverse Events

A Serious Adverse Event (SAE) is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All serious morbidities will be coded by a trained nurse and reported (within 24 working hours of becoming aware of them) to the Registry Manager. The Registry Manager is responsible for alerting the Clinical Advisory Team and Roche within 24 working hours of such events and will provide a full follow-up report of each event in the succeeding six-monthly report. Following the report of any SAEs either by subject or clinician, the referring research nurse will be contacted by TARGET (within 24 working hours) and asked to provide further details (event type, date, severity, seriousness, causality and outcome).

5.5.4. Special Situations

The following reports (collectively termed 'Special Situations' [SS]) will be collected even in the absence of an AE:

- Abuse: this corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Drug Interaction: this refers to the action of one drug upon the efficacy or toxicity of one or more other drugs. Drug interaction also includes drug/food, drug/device and drug/alcohol interactions.
- Intercepted Medication Error: this refers to situations where a medication error occurred, and an intervention caused a break in the chain of events in the treatment process before reaching the patient. The intervention has prevented actual harm being caused to the patient.
- Pregnancy Exposure: this refers to situations where the embryo or foetus may have been exposed to a medicinal product(s), either through maternal exposure or transmission of a medicinal product via semen following paternal exposure. This includes "Breastfeeding", a situation following exposure to a medicinal product from breast milk in infants.
- Lack of Therapeutic Efficacy: this refers to a situation of lack of therapeutic efficacy of a medicinal product.
- Medication Error: a medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (including potential medication errors or intercepted medication errors).
- Misuse: this refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.
- Occupational Exposure: this refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation.
- Off Label Use: this relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization.
- Overdose: this refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum

recommended dose according to the authorized product information. Clinical judgment should always be applied.

- Potential Medication Error: this refers to the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. It refers to all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product by all persons who are involved in the medication process.
- Suspected Transmission of an Infectious Agent: transmission of an infectious agent via a medicinal product.

SS will be captured at routine visits by the clinician and will be documented and reported in line with the protocol for reporting nsAEs. Line listings for nsAEs and SS will include the following information:

- Protocol number (WA40984)
- Patient number
- Date of birth
- Patient initials, as applicable
- Primary reporter country (and country of occurrence of event if different to that of primary reporter)
- Adverse Event term / MedDRA term
- Seriousness of event
- Onset date of event
- Death date (if applicable)
- Study drugs received
- Date of first dose
- Cause(s) of event related to Roche Medicinal Product
- Adverse Event description
- Adverse Event outcome

5.6. Discontinuation/withdrawal of participants from the Registry

Participants have the right to withdraw from the study at any time. They may have the option of withdrawing from the Registry sub-study but remaining in the UK GCA /UKIVAS main studies. In addition, the Investigator may discontinue a participant from the study at any time if they consider it necessary for any reason including ineligibility (arising during the study or retrospectively having been overlooked at screening) or loss to follow up. The date of, and reason for, withdrawal will be recorded and coded. If a patient elects to subsequently alter any component of their preferential consent, this will be recorded by the local investigator in the central study database. Any clinical data already collected or shared will continue to be used in the study as outlined in the patient consent form. As in the UKIVAS database model, our database will monitor participant status and withdrawal from the Registry or any sub-study.

5.7. Use of the Registry for future trial-within-cohort studies

We plan to develop the Registry as a basis for a "trials within cohorts" (TwiCS) study. The cohort will be used to identify patients potentially eligible for one or more randomised controlled trials (RCT) evaluating treatment strategies for GCA, such as: the efficacy and safety of continuing tocilizumab therapy beyond one year (i.e. beyond what is currently funded by NHS England) compared to limiting therapy to one year (randomising patients to receive placebo or active drug after one year of open label therapy); switching patients to alternative disease-modifying drugs compared to placebo at the end of one year of tocilizumab therapy; randomising patients to different dose regimens of glucocorticoid monotherapy following completion of one year of tocilizumab therapy). We will seek separate funding for these RCTs and all stakeholders in the Registry will have the opportunity to contribute to trial design.

The TwiCS study design will provide added value by ensuring (a) efficient identification of potentially eligible patients at an appropriate point in their disease course, (b) patients give prospective consent for data collected prior to RCT enrolment which can be used to inform trial design and analyses, (c) common sets of outcomes can be collected across the Registry and RCT in identical ways, enabling pre-planned comparisons of RCT versus non-RCT participants (again with consent gained prospectively at enrolment, without additional burden to the non-RCT participants) and (d) research capacity is already in place at potential trial recruitment sites, expediting study setup and local approvals.

6. DATA MANAGEMENT

6.1. Data capture

Data will be entered by the local study team directly to a web-based database. A unique anonymised study ID assigned to each patient will be created in the Registry database. Only the local study team will have access to patient identifiable information, which will be recorded and maintained in the local study screening log against the unique study ID. The data items will include: demographics (including the postcode in order to determine the area-based socio-economic status); comorbidity; diagnosis, clinical, pathology and radiological results; disease assessment scores; general health measures; prescribed medication; validated patient reported outcome measures.

Every effort will be made to ensure the database is created in time for the start of the study. If this is not achieved, all centres will use paper-based questionnaires. These will be sent to the University of Leeds and stored until the database is ready for data entry. Data entry will be completed by the Project Management team at Leeds. This contingency plan will allow us to capture data from all consenting patients who receive tocilizumab for their GCA as soon as it becomes available to them.

6.2. Data linkage and data protection

The patient's NHS number will be entered in the database as a central identifier. This will be used to link participant records in other data sources. The NHS number will be viewable at the site, but encrypted centrally and researchers will only have access to pseudonymised data. We will search all sites to ensure patients have not previously registered with UK GCA, UKIVAS or the Registry in order to prevent duplicate enrolment.

6.3. Data security and quality assurance

All data related to the project will be held at the Leeds Institute of Data Analytics at the University of Leeds. This Centre provides a secure data handling through the Integrated Research Campus (IRC). IRC processes are based on international standards and legal requirements for the confidentiality, availability and integrity of data. Processes are determined by the IRC's Information Security Management System (ISMS) for which the IRC has ISO 27001 and HSCIC IGT Level 2 accreditation.

Direct access will be granted to authorised representatives from the Sponsor and host institutions for monitoring and/or audit of the study to ensure compliance with regulations. Data will be submitted directly from local research teams to the on-line database. Only the local research team will be able to link the study ID to patient identifiable information. User activity, data return, completeness and accuracy will be audited centrally. Sites will receive quarterly data reports listing any outstanding data or data queries. Standard operating procedures for security procedures, user access, data back-up and audit will be maintained. We request funding for the Registry database to be maintained for the duration of the study data collection and analysis

period (3 years) but we will retain participant data in line with University standards for data management (a period of at least ten years post study closure).

There is potential for patients to enter into both UK GCA and UKIVAS because many sites are recruiting patients into both studies. We will ensure each patient entered into the GCAT Registry is unique by providing an anonymised GCAT reference number which will be used in UK GCA and UKIVAS as appropriate.

A Data Monitoring and Ethics Committee (DMEC) will be established through the TARGET Partnership Management Board (analogous to a Data Safety and Monitoring Board established for major clinical trials). If needed, the DMEC will be independent of the principal investigators and Roche, and will have the power to request interim analyses and advise on the timing and nature of any publications. The DMEC will include at least one epidemiologist and one statistician.

7. ANALYSES AND STATISTICAL METHODS

7.1. Sample size

The UK GCA Consortium is an ongoing study and we expect further sites to join. Based on previous recruitment rates (and on patients already recruited to UK GCA), the study sample for the Registry would be expected to reach approximately 3,000 by 2021. We also have at least 550 patients with diagnosed GCA registered within UKIVAS, and this number of recruits will continue to rise. We therefore anticipate recruiting up to 1,000 participants to the proposed Registry.

Using data from the Clinical Practice Research Database and The Health Improvement Network we estimate there will be 4,500 new cases of GCA per year in England. There are no good prevalence studies, but using data from Sweden and Italy we estimate there are 22,000 prevalent cases in the UK.

We have analysed data from one site ([redacted]) to show 168 out of 327 patients with a diagnosis of GCA have been started on a disease modifying agent in the past 2 years, indicating that around 50% of patients are likely to require escalation of therapy in real world data. We estimate 20–50% of these patients would be offered tocilizumab. If a conservative estimate was given on willingness to be recruited to the GCAT Registry of 70%, the end result would be 45–114 patients recruited from this centre into the study over an 18 month period.

If we use data on recruitment of patients into the UK GCA Consortium and the UKIVAS study to date, and assume a conservative 1,500 prevalent cases with 10–30% having refractory/relapsing forms of the disease, this would equate to 105–315 cases eligible for tocilizumab. We anticipate a higher uptake of tocilizumab use in patients with recently diagnosed disease and estimate approximately 30% of newly recruited patients will be eligible for tocilizumab in the recruitment period. Recruitment is currently 450 patients per year across both studies, which would equate to 95 patients per year.

We anticipate recruitment to these studies will increase substantially with the establishment of a national MDT framework. The framework will promote the GCAT Registry and there is already significant national interest. In order to recruit 1,000 participants into the GCAT Registry we will need to enrol additional centres, with an initial focus on several high recruiting sites to the UKIVAS registry, who are not already participating in the UK GCA Consortium study (such as [redacted]).

Apart from UKIVAS sites 9 and 15, which are in the Republic of Ireland, we will approach all 13 investigators of sites not already contributing to UK GCA to invite them to participate in the GCAT Registry (total of 1,858 potential recruits). We will work with the NIHR Clinical Research Network (CRN), which is made up of 15 Local CRNs, to promote the Registry to potential new sites. Their clinical research infrastructure can help identify sites with the capacity and expertise to participate in the Registry.

7.2. Statistical methods

Statistical analyses will be conducted in line with the study objectives according to a pre-specified Data Analysis Plan to be agreed. In particular, we will track cumulative steroid prescription and document post-tocilizumab flares and relapse. Data from controls will allow us to compare rates of relapse and toxicity, and glucocorticoid discontinuation between the two groups using appropriate multivariate survival models in order to explore the potential steroid-sparing effects of tocilizumab.

In future studies, we would like to compare the effects of withdrawal of tocilizumab after 1 year of treatment (UK cases), with the effects of longer-term treatment with tocilizumab (European cases) and discussions with European Registry coordinators are ongoing.

8. REGISTRY STEERING COMMITTEE AND MANAGEMENT

The Registry Steering Committee will comprise a number of different specialists from the UK, including rheumatologists and other specialists involved in the management of these patients, such as ophthalmologists and neurologists. The Committee will include a patient representative and the Chair of the TARGET Partnership. The remit of the Committee will be to: review and approve the protocol; oversee recruitment to the Registry; provide data management support; oversee data analysis. The Committee will meet twice yearly and interim meetings by teleconference may be held as appropriate. The Primary Investigator will be responsible for the day-to-day monitoring and management of the study.

9. PUBLICATION POLICY

The lead investigators – Ann Morgan (AM), Raashid Luqmani (RL), Mar Pujades Rodriguez (MPR) – will be involved in reviewing drafts of manuscripts, abstracts and any other publications arising from the Registry. Authors will acknowledge the Registry funder in all publications. Authorship will be determined in accordance with the ICMJE guidelines and all contributors will be acknowledged. With permission, any results arising from the analysis of data obtained through the Registry will be made available on the Registry website, at seminars and meetings with GCA patient support networks, and at academic, clinical or industry events.

The primary remit of the GCAT Registry is to produce post-marketing surveillance data on the use of tocilizumab for the treatment of GCA. We will also welcome the development of additional projects that may take advantage of the opportunities offered by the GCAT Registry. We suggest two separate policies to address the issues of authorship: one for primary papers and one for associated papers.

9.1. Principles for authorship

These principles are based on consideration of:

1) Compliance with the most current version of the International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to Biomedical Journals: Writing and Editing for Biomedical Journals requires named authors to meet all three of the following 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, 2) involvement with drafting of the article or revising it critically for important intellectual content, and 3) final approval of version to be published.
2) Being as inclusive as feasible, we recognise that complying with authorship guidelines, drafting the article, or revising it critically for important intellectual content becomes increasingly impractical with large numbers.

9.2. Primary papers

Primary papers are considered to be all those which describe the outcomes of taking tocilizumab for GCA. These projects will be largely driven by the efforts of the lead investigators and we therefore propose they will take senior authorship role, in rotation, for all papers. For each paper, the other investigators will take joint second or penultimate places in the authorship list, unless there is no readily identifiable primary author amongst the group, in which case one of the lead investigators will take primary authorship for the work. In some instances, joint first or joint second authorship may be considered more appropriate and the final decision rests with the lead investigators.

We will encourage all papers to include a junior primary author in order to recognise their contribution to the project. This is coupled with the expectation that they will undertake the main task of preparing the first draft and oversee the editing changes. If the primary author cannot undertake this task, or there is no suitable primary author, one of the other lead investigators can propose themselves to this role.

Members of the core GCAT Registry team will be listed as authors, with the proviso that they fulfil the role of an author in being involved in reviewing and revising the manuscript in a timely fashion. The core team is defined as AM, RL and MPR in addition to the Registry Manager, the Registry Database Manager, the Registry Coordinator, the Registry Statistician, and the Registry Database Designer. Members of the Scientific Advisory Board may also be listed as authors with the proviso outlined above.

All investigators will be listed as collaborators. In addition, we will include an appendix for each paper (if allowed by the publishing journal) of all staff involved in the study at each site who were not defined as either authors or collaborators. We aim to ensure that all individuals who have been involved in supporting the Registry will be acknowledged as fairly as possible.

We will encourage open access publication where possible, but do not have unlimited funds to support publication costs.

9.3. Associated papers

The authorship guidelines for associated projects will reflect the nature of the work completed. The lead investigators retain the right to be authors on all associated projects. However, they will decide whether or not to enforce this for each paper on a case-by-case basis. It is likely that all associated papers will be based on projects for which the lead investigators have provided substantial input because all sub-projects will be brought before them (as members of the TARGET Partnership Management Board) for discussion and approval. Furthermore, all associated projects will take advantage of the GCAT Registry infrastructure and database.

We will ask the lead investigator of each sub-project to liaise with the lead investigators over publication of the paper/s and for them to take the lead in deciding on eligibility for authorship and order of authors. The lead investigators would not expect to be either first or senior author on any of these papers unless they are primarily responsible for that sub-project. All associated papers would be expected to include investigators and core team members who have made substantial contributions to that project as authors for that particular paper. The final decision regarding authorship on all associated papers will rest with the lead investigators.

All abstracts arising from associated projects should be submitted to the lead investigators as part of the regular communication process, but at least 10 working days before any deadline, in order to ensure sufficient time for review and revisions if needed. Each associated project will have an allocated point of contact (AM, RL or MPR) who will be responsible for liaising regularly with the associated study members and who will therefore be aware of planned submissions as they emerge. The allocated point of contact will be responsible for ensuring the quality of associated studies and providing feedback on the progress of these studies to the wider TARGET

Partnership Management Board. It is the expectation that authorship on abstracts will follow the same rules as for the full papers; exceptions to full lists of authors on abstracts may be made in cases where author names and affiliations substantially count toward word/character limits for the abstract text. The final decision regarding authorship on all abstracts will rest with the lead investigators.

We will encourage the use of contributorship with an appendix to acknowledge those involved less directly in the study, but would not expect the full list to necessarily apply to each associated paper. However, we require that all those significantly involved in each GCAT Registry paper should be acknowledged. The TARGET Partnership Management Board will take responsibility for providing a full list of personnel who could be named as authors, contributors or appear in the appendix. This list will be available on the TARGET website. It will be the responsibility of the senior author and the allocated member of the GCAT Registry for that particular paper to edit the list.

10. STUDY GOVERNANCE

10.1. Regulatory and ethical considerations

The UK GCA Consortium is conducted in accordance with all applicable regulatory requirements and Sponsor policy, and in accordance with ICH Good Clinical Practice and the General Data Protection Regulation. This includes, but is not limited to: REC/HRA review and favourable opinion/approval of the study protocol and amendments as applicable; obtaining signed informed consent; investigator reporting requirements.

10.2. Site setup

NHS organisations interested in participating can contact the study coordinator directly requesting the local information pack. The study team may also liaise with the local clinical research networks (CRNs) to identify potential sites.

10.3. Expression of interest

When an expression of interest is made, the study coordinator will forward the local information pack for the study. This pack contains:

- NHS REC Application Form (study pre-dates IRAS)
- MREC Study Approval letter
- Letter of HRA Approval for a study processed under HRA Approval
- Complete and current document set
- Study Schedule of Events
- Study Statement of Activities
- Model Agreement for Non-Commercial Research in the Health Service (mNCA)
- Tissue Transfer Agreement (TTA: applies to the main study arms (retrospective and prospective) of UK GCA only, not the GCAT Registry)

10.4. Assessment phase

In accordance with the HRA's guidance on NHS site setup in England, the study coordinator will enter preliminary discussions with the interested site before initiating setup. In addition to the local information pack, sites will be asked to consider: In which study arm (e.g. retrospective, prospective) and sub-studies they will participate; who the study personnel will be (i.e. PI, research nurse, CTA, etc.); number of eligible patients, and how they will be approached.

10.5. Formal setup and training

If sites proceed with setup they will complete the mNCA and TTA and send to the study coordinator for approval. Once approved, signatures will be obtained at the NHS organisation, followed by final sign-off by Sponsor. At this stage, the study coordinator will notify the HRA of the addition a new site and schedule a site initiation teleconference (SIV). All non-controlled documents, such as the CRF and laboratory documents, will be distributed before the teleconference for local study team review. The following will be covered during the site initiation teleconference:

- Brief study background and rationale
- Inclusion and exclusion criteria
- Identifying and contacting eligible patients

- Conducting study visits
- Completing the CRF from patient interview and notes review
- Electronic data entry (if applicable)
- Sending study documents to Sponsor
- Data management (queries, missing data, data linkage)
- Reporting study recruitment to the Central Portfolio Management System (CPMS)

10.6. Commencement of recruitment

Following the SIV, the study coordinator and the study team will liaise on practical matters such as setting up the Investigator Site File to ensure everything is ready for recruitment to commence. When the SIV has been conducted, the HRA has approved the addition of a new site, and the NHS organisation has issued confirmation of Capacity and Capability (C&C), the study coordinator will issue a 'green light' notification on behalf of the Sponsor and recruitment can commence.

10.7. Study monitoring

Monitoring will ensure study procedures, laboratory and data collection processes are of high quality and meet Sponsor and regulatory requirements. It will also ensure protection of patients participating in the study. For each site, a monitoring plan detailing the level and frequency of monitoring will be developed based on the study arms and sub-studies they participate in.

10.8. Source data and documents

According to ICH GCP E6, 1.51, this includes 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 (which can be original records or certified copies). According to ICH GCP E6, 1.52, original documents, data and records include: hospital records; clinical and office charts; laboratory notes; memoranda; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; subject files; records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

10.9. Record keeping and archiving

The investigator at each site will make arrangements to store the essential study documents (defined in ICH GCP E6, Section 8) until Sponsor informs the investigator that the documents are no longer to be retained. The investigator is responsible for archiving and continued storage of all relevant source documents. It is the responsibility of Sponsor to inform the investigator/site as to when the essential study documents no longer need to be retained.

10.10. *Reporting serious GPP non-compliance*

The International Society for Good Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (GPP) will be followed if non-compliance should occur.

11. REGISTRY DEVELOPMENT

GCA is a rare disease, and collaboration with academics, clinicians and industry is essential to advance our understanding of this disease and to improve treatment and outcomes in vulnerable adults. Future development of the Registry provides an opportunity to combine data with ongoing projects in GCA to further research into the disease.

11.1. Research database

An ethically-approved research database will be established to provide the infrastructure for the longer term storage and maintenance of Registry data. The database will store Registry data from patients who consent to the use of their anonymised data in future related research. Separate consent to the research database will be sought from participants for the continued collection of outcome data from patient medical records. The database could link data from this study with other academic or commercial ethically approved related studies in GCA, including the UK GCA Consortium (REC 05/Q1108/28) and UKIVAS (REC 10/H1102/77). This resource would be overseen by a Data Access Committee that would function through the TARGET Partnership Management Board.

The Partnership Management Board meet every month to discuss TARGET activity including any request for data. Access will be granted on an application only basis. There will be a seven step application process for access to data. This process will remain the same for all parties regardless of their relationship to TARGET.

1) Search for data. Interested parties will use an online search engine to find data that match their criteria. The search engine will be hosted through the TARGET Informatics Platform.
2) Register an account. Anyone wishing to apply for data will need to create an on-line account. Details we require from account holders will include name, job title, business name and address, email and telephone number. This will expedite multiple applications, and deter speculative approaches. Once the appropriate data have been identified, applicants will be asked to complete a standardised application form. We will produce a guidance document to help researchers with their applications.
3) Review and submit. If co-applicants are listed, they must have reviewed all the information in the application before submission.
4) TARGET check. Applications will be checked for missing information by a member of the TARGET team. We will decide on the level of review required by asking the following: is the project already peer-reviewed by an external funder or equivalent? Has similar work been completed already?
5) Review Committee of request. A light-touch review will be conducted by the Executive Committee and if a more detailed review is needed then a Specialist Group Review will be convened.
6) Decision. We aim to provide an outcome within four weeks of submission.

7) Data released. Data will once an appropriate data exchanged agreement has been established.

11.2. NHS audit

The Registry would potentially provide surrogate information about the caseload of GCA clinical activity at each contributing site, thus supporting NHS England's Statement of Intent that specialised centres must be research active and have sufficient caseload to build recognised expertise. It could provide reliable data to support commissioner oversight of the compliance with NHS England Commissioning Policies for the use of high cost treatments.

12. PATIENT AND PUBLIC INVOLVEMENT IN RESEARCH

The concept of a post-marketing surveillance Registry of this kind would be strongly welcomed by members of the public and patient support groups. Many patients with a rare disease regret the lack of progress in understanding their disorder because of its rarity. We will ask for opinion from members of the public and patient support groups about our patient documentation (invitation letter and consent forms) and would consult them in the development of the database. All protocols will be reviewed by PMR GCA UK and by Vasculitis UK. The TARGET Partnership Management Board already includes a patient representative from Vasculitis UK (Mr John Mills), and two patient representatives from PMR GCA UK ([redacted] and [redacted]).

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Participant confidentiality

The study staff will ensure participants' privacy and confidentiality are maintained. Participants will be identified only by a unique participant ID number on the central electronic database. The patient's NHS number will be entered to the database by the patient's clinical team. The NHS number will be viewable at the local site only and encrypted centrally. Researchers will only have access to pseudonymised data. Identifiable data, such as consent forms and associated study documents, will be stored securely and will only be accessible by the local study team and authorised personnel for audit purposes. The study will comply with all relevant legislature and regulation including the UK Policy Framework for Health and Social Care Research and the EU General Data Protection Regulation.

13.2. Expenses and benefits

The majority of study visits will take place at the same time as routine clinic appointments. Reasonable travel expenses (up to the value of [redacted]) for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

14. FINANCE AND INSURANCE

14.1. Funding

We are seeking funding from Roche to establish the Registry and to maintain it for a period of three years in the first instance. Future support for the Registry, with permission from Roche, may be sought from a number of NHS, academic and commercial projects which would utilise the data and/or identify cohorts from the Registry.

We will collect data during the period of three years in which tocilizumab is conditionally available to patients through the NHS. In line with University standards for data management, all data will be maintained for a period of at least ten years after the study has ended.

We request funding to support: patient recruitment; data collection; data management; data analysis; six-monthly reports; training, monitoring and coordination of all participating sites, including initiation of new sites (see **TABLE 1** for a detailed breakdown of responsibilities and **FIGURE 1** for the Registry Gantt chart).

Anonymised, amalgamated reports will be provided to Roche on a rolling six-monthly basis throughout the data collection period and a final report will be provided once all data has been collected and analysed. These reports will comment on the performance of tocilizumab in the treatment of GCA in comparison to control groups in terms of the key parameters of interest (as outlined in the aim and objectives). Further reports may be requested by Roche at any time but by agreement outside this proposal and at a cost related to the complexity of information requested.

14.2. Insurance

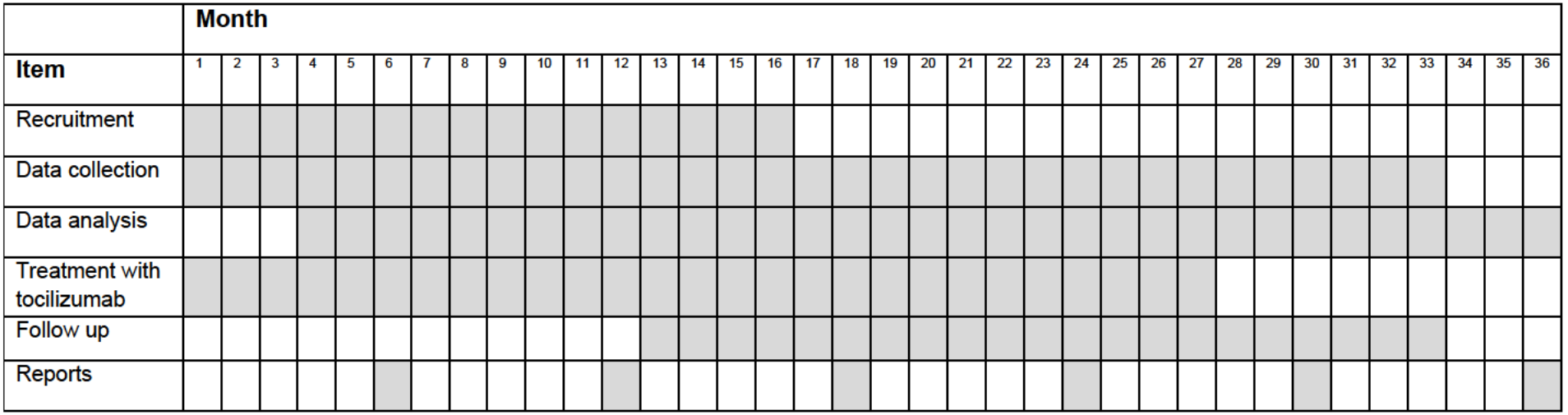
The University of Leeds has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment that is provided.

TABLE 1: breakdown of responsibilities of the Registry Team

Staff	Responsibilities
Clinical Advisory Team	
Professor Ann Morgan (PI) Chair of TARGET	Study leadership; clinical expertise in relation to data analysis, reports and publications; monthly internal meetings with the Leeds and Oxford research teams; bi-annual meetings with Roche
Professor Raashid Luqmani (Co-I) Vice-chair of TARGET	Study leadership; clinical expertise in relation to data analysis, reports and publications; monthly internal meetings with the Leeds and Oxford research teams; bi-annual meetings with Roche.
Statistics and Epidemiology Team	
Dr Mar Pujades Rodriguez (Co-I) TARGET Partnership Board: Academic-Industry Liaison	Epidemiological and statistical leadership in relation to study design, data analysis, reports production and publication strategy.
Registry Statistician (Grade 7, staff member TBC)	The Statistician will work with the team to ensure all data recorded matches the project requirements, and that all reports map directly to the reporting structure defined in the protocol. They will ensure data quality and analyse data provided by the Registry. They will finalise all reports submitted to the Registry team for approval prior to submission to Roche.
Project Management	
Registry Manager (Grade 7, staff member TBC)	The Registry Manager will be responsible for: study set-up and implementation (including obtaining regulatory and ethical approvals); site set up, initiation and staff training (including liaising with R&D and each individual site-based research team, negotiating contracts, site visits); continued monitoring and evaluation of sites; protocol amendments; site updates. They will be responsible for delivering the six-monthly reports to Roche (with support from the Clinical Advisory and Statistics and Epidemiology Teams) and answering any questions that may arise from these reports.
Registry Coordinator (Grade 4, staff member TBC)	The Registry Coordinator will be responsible for: continual supply of study materials and consumables, and receiving and checking documents. They may be asked to conduct data cleaning tasks provided by the Registry Analyst.
Database Management	
Dr Anthea Craven – Registry Database Manager (Grade 8)	The Registry Database Manager will supervise the creation and establishment of an electronic web-based data capture system to facilitate longitudinal recording of medical status in routine clinical care. Once this is established, they will be responsible for quality assurance (including checking data entry from external sites), data quality, raising queries with sites and the timely response to those queries, and providing technical assistance. They will work closely with the Registry Manager to ensure the delivery of data updates, data analysis and reports (including reports of SAEs).

Registry Database Designer (Grade 7, staff member TBC)	The Registry Database Designer will customise the existing UKIVAS database for the needs of the GCAT Registry. They will test and implement the Registry database across all sites, taking into account variation in IT provision at different NHS trusts. They will work with the team to ensure the database design matches the requirements of the project exactly and that the user interface is effective and intuitive. They will ensure report design and outputs from the database are in appropriate formats for statistical analysis. They will be responsible for system security, and will liaise with the LIDA group to ensure the server is adequately backed up and maintained.

FIGURE 1: Registry Gantt chart



15. THE ROLE OF ROCHE

The goals of Roche and the rheumatological community are similar in seeking accurate estimates of any benefits and any increased risk of adverse events. It may be a prerequisite for continued drug licence approval, that a Registry such as the one proposed is established.

Professor Ann Morgan (University of Leeds) and Professor Raashid Luqmani (University of Oxford) will be jointly responsible for the proposed Registry through their roles as Chair and Co-Chair (respectively) of the TARGET Partnership: the University of Leeds will act as Study Sponsor. We invite Roche representatives to form part of the oversight committee for the Registry, and request that they promote the aims of and objectives of the Registry and use their network to maximise recruitment of patients.

Roche will have a crucial role in raising awareness of the Registry and contributing their experience into the nature and type of data collected. Any final decisions related to the analyses, interpretation and publication of data will be agreed through the TARGET Partnership Management Board who will arrive at decision by consensus wherever possible. If this is not possible a vote will be held. The threshold for a vote to pass is 50% of those present and entitled to vote (with the Chair having casting vote in the case of a tie).

Aggregated data will be shared in confidence with Roche, but individual identifiable patient data will not be released. Roche will be shown drafts of any publications, reports, abstracts or other material prior to submission for presentation or publication. Roche can ask for clarifications or amendments to such material. Roche has the option of requesting additional specific analyses, via the TARGET Partnership Board (costs will be provided on request and will depend on the complexity of the work required). All investigators will complete an annual ‘Declaration of conflict of interests’, which will be added to all publications.

16. THE ROLE OF TARGET

TARGET will be the owner of the data that emerges from the Registry. The Registry Manager will report on an annual basis to such committees or sub-committees that TARGET deems appropriate.