# NETSCC, HTA

# 20th October 2010

# COmparison of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: a Trial (CONSTRUCT)

# Protocol

| | |
|---|---|
| **Funder's reference number:** | National Institute for Health Research Health Technology Assessment Programme (HTA) 06/78/03 |
| **Sponsor's protocol number:** | 06/78/03 – Version 3-2 20Aug2010 |
| **Sponsor's reference:** | RIO 031-08 |
| **EudraCT number:** | 2008-001968-36 |
| **REC reference:** | 08/MRE09/42 |
| **ISRCTN:** | ISRCTN22663589 |
| **Sponsor's name:** | Swansea University (SU) |
| **Sponsor's address:** | Department of Research & Innovation, Swansea University, Singleton Park, Swansea, SA2 8PP. Tel. 01792 285412 |

**NB In this trial:**

- **infliximab will be administered as Remicade®**
- **ciclosporin will be administered as Sandimmun/Neoral®**

**CONSTRUCT Trial Office**
School of Medicine, Swansea University, Singleton Park, Swansea, SA2 8PP
Tel: 01792 606600 Fax: 01792 606599
Email: CONSTRUCTHelpdesk@swansea.ac.uk

**RANDOMISATION WEBSITE DETAILS**

www.bangor.ac.uk/imscar/nworthtrials/

| Role | Name | Affiliation | Address | Telephone No. |
|---|---|---|---|---|
| Chief Investigator (CI) | Professor John G Williams* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513401 |
| Principal Investigator (Methodology) | Professor Ian Russell* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 602939 |
| Principal Investigator (Health Economics) | Professor David Cohen* | University of Glamorgan | Faculty of Health Sport and Science<br>Pontypridd<br>CF37 1DL | 01443 483827 |
| Principal Investigator (Qualitative) | Professor Frances Rapport* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513497 |
| Outcomes Methodologist & Statistician | Dr Wai Yee Cheung* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513410 |
| Principal Investigator (Routine Data) | Dr Stephen Roberts* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513433 |
| Principal Investigator (Information Science) | Jayne Morgan* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513402 |
| Clinical Specialist / Consultant Gastroenterologist | Dr Linzi Thomas* | Abertawe Bro Morgannwg University NHS Trust | Singleton Hospital<br>Sketty Lane<br>Swansea<br>SA2 8QA | 01792 285033 |
| Methodologist & Statistician | Dr Daphne Russell* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513411 |
| Health Economics Researcher | Dr Fasih Alam | University of Glamorgan | Faculty of Health Sport and Science<br>Pontypridd<br>CF37 1DL | 01443 483882 |
| Trial Manager | Dr Anne Seagrove* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513411 |
| Trial Information and Quality Manager | Dr Kym Thorne* | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 602062 |
| Trial Administrator | Emma Riordan | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513405 |
| Trial Clerical Assistant | Judy Williams | Swansea University | School of Medicine<br>Swansea University<br>Singleton Park<br>Swansea SA2 8PP | 01792 513426 |
| **CONSTRUCT Helpdesk** | | | | **01792 606600** |

* Protocol authors

**Study sites:** see Appendix 1

**Signatures**

Professor John G Williams, Chief Investigator

Signature _____ Date _____

Professor Ian T Russell, Principal Investigator (Methodology)

Signature _____ Date _____

Professor David Cohen, Principal Investigator (Health Economics)

Signature _____ Date _____

Professor Frances Rapport, Principal Investigator (Qualitative)

Signature _____ Date _____

Dr Wai Yee Cheung, Outcomes Methodologist & Statistician

Signature _____ Date _____

Dr Stephen Roberts, Principal Investigator (Routine Data)

Signature _____ Date _____

Jayne Morgan, Principal Investigator (Information Science)

Signature _____ Date _____

Dr Linzi Thomas, Clinical Specialist / Consultant Gastroenterologist

Signature _____ Date _____

Dr Daphne Russell, Methodologist & Statistician

Signature _____ Date _____

Dr Anne Seagrove, Trial Manager

Signature _____ Date _____

Dr Kym Thorne, Trial Information and Quality Manager

Signature _____ Date _____

**Principal Investigator:**

Signature _____ Date _____

# CONTENTS

# 1. BRIEF SUMMARY

Ulcerative colitis (UC) is a chronic debilitating disease that affects approximately 150,000 people in the UK.[1 2] There are many unanswered questions regarding causes, course, treatment and outcome of UC; this is against a background of rapidly developing new therapies. In about 10% of cases, UC presents as acute severe colitis requiring inpatient admission. Treatment includes intravenous steroids but about 40% of UC patients are steroid resistant. In the past when no other treatments were available, emergency colectomy was the only other option. Although mortality following emergency colectomy has fallen over time, it is still as high as 10% at three months.[3] Infliximab and ciclosporin are two immunosuppressive agents that offer hope for the treatment of steroid resistant UC. There is evidence that infliximab and ciclosporin are both effective at least in the short term. However, since most studies of infliximab and ciclosporin are small single centre studies with relatively few numbers of cases, evidence about their effects is limited and there is a lack of evidence in the longer term about their clinical and cost effectiveness.

The overall aim of this trial is to compare the clinical and cost effectiveness of infliximab and ciclosporin for patients with steroid resistant UC. A further objective is to establish comprehensive long term data collection using a web-based clinical information system to enable further research questions to be answered regarding clinical progress and outcome following treatment for acute severe UC.

This study comprises a cohort of patients admitted with suspected or known colitis, within which we will identify patients with acute severe ulcerative colitis (UC) who are steroid resistant and recruit them to a two-arm, multicentre, pragmatic randomised controlled trial (RCT) involving 40 centres in the UK. It is our hope that we will be able to follow all these patients for at least 10 years using routinely collected data to gain further knowledge about long term progress and outcome after medical and surgical treatment for acute severe UC. Thus, inpatients with suspected or known colitis will be recruited to the cohort until recruitment to the trial is complete (approximately 1400 patients). Cohort participants who fail to respond to treatment using two to five days intravenous steroids but do not, at the time of entry to the RCT, require surgery, will be recruited to the RCT until recruitment to the trial is complete. RCT patients will be randomised to either infliximab or ciclosporin, with 240 patients in each of the two arms.

To compare the clinical and cost effectiveness of infliximab and ciclosporin and gain new knowledge about acute severe UC following treatment, the primary outcome measure will be Quality of Life (QoL) as measured by UKIBDQ[4]. Two other QoL measures, EQ-5D[5] and SF12[6] will be secondary outcomes. Other secondary outcome measures will be emergency and planned colectomy, mortality, quality adjusted survival, readmissions, incidence of malignancies, incidence of serious infections, incidence of renal disorders, incidence of new symptoms, incidence of adverse events, disease activity, total NHS costs and patient borne costs. Patient interviews will be undertaken to investigate the views of RCT patients regarding therapies for acute severe UC.

Data on all patients (cohort and RCT) will be collected using a centralised, securely hosted clinical information system, supplemented by record linkage of electronically held routine data. Designed research data collection will continue for two years on RCT patients. Collection of routine data will be carried out at 12 and 24 months for all patients.

## 2. BACKGROUND INFORMATION

The investigational products for this trial are infliximab and ciclosporin, both immunosuppressive agents.

UC is a chronic debilitating disease that affects approximately 150,000 people in the UK.[1 2] In about 10% of cases, UC presents as acute severe colitis requiring inpatient admission. Treatment includes intravenous steroids but about 40% are steroid resistant. In the past when no other treatments were available, emergency colectomy was the only other option. Although mortality following emergency colectomy has fallen over time, it is still as high as 10% at three months.[3]

Infliximab and ciclosporin are two immunosuppressive agents that offer hope for the treatment of steroid resistant UC. There is evidence that infliximab and ciclosporin are both effective at least in the short term, particularly among people who respond partially to steroid treatment, although there are concerns about high rates of later relapses. However, since most studies of infliximab and ciclosporin are small single centre studies with relatively few numbers of cases, evidence about their effects is still limited.

Several studies have advocated the use of infliximab in patients with moderate or severe UC,[7-10] especially steroid resistant UC patients who do not tolerate or prefer ciclosporin A.[9] A recent systematic review of infliximab, using a meta analysis of 34 studies, found an average (2.3 weeks) short term response and remission of 68% and 40% respectively, and an average long term (8.9 months) response and remission of 53% and 39% respectively.[10] Two large scale RCTs also found significant differences in the improvement of the total IBDQ score and the SF-36 physical and mental component summaries for infliximab patients at eight weeks when compared with placebo (all $p<0.001$).[11]

Many studies support the use of ciclosporin as a safe and effective treatment for steroid resistant UC,[12-14] although it has been associated with side effects including dose-related toxicity risks,[13 15 16] as well as long-term failure rates.[13-15 17] A recent systematic review reported a mean response rate of 73% but poor long-term response rates, with one study reporting that 65% of patients relapsed after one year and 90% after three years.[17] Another review of 32 studies reported a 51% short term success rate.[18]

A recent Cochrane review concluded that there was limited evidence that ciclosporin was more effective than standard treatment for severe UC and that long term benefits were unclear.[19] Importantly, it also advocated the need for research on the long term impact on quality of life and cost effectiveness of ciclosporin.

To summarise, while recent studies have reported that infliximab and ciclosporin are often effective in the short term, there is a lack of evidence in the longer term about their clinical and cost effectiveness. Rigorous longer term investigation is now required for both therapies.

There is also a lack of knowledge and understanding about the clinical progress and outcome following admission with acute severe UC and our approach gives us the potential to collect long term routine data.

**NB In this trial:**

- **infliximab will be administered as Remicade®**
- **ciclosporin will be administered as Sandimmun®/Neoral®**

**Terminology**

We use a number of terms in this document, which we define as follows:

- *Operational data* are the administrative, demographic and clinical data that is recorded in patient records, in structured, analysable form in the course of the delivery of care.
- *Routine data* are the administrative, demographic and clinical data that are extracted from hospital records (and where appropriate, coded in ICD-10 and OPCS-4) for the purpose of central returns to the secondary uses service (SUS), where it is made available as hospital episode statistics (HES).
- *Designed data* are the data specifically collected for the purposes of a research study.

- A *cohort* is a well defined group of patients that is followed-up longitudinally and on which data are collected over time but which does not receive any intervention.
- A *data repository* is an operational data store that holds and manages operational data from service encounters.
- A *data warehouse* is a data store accessed by a single data management system, containing linked data that may come from diverse sources, and held for analysis in anonymised form.

## 3. TRIAL OBJECTIVES

The overall aim of this trial is to compare the clinical and cost effectiveness of Remicade and Sandimmun/Neoral for patients with steroid resistant UC.

Specific objectives are to:

i). Compare QoL across the two treatment groups (Remicade and Sandimmun/Neoral)
ii). Compare mortality, disease activity and morbidity across the two treatment groups
iii). Compare emergency colectomy rates across the two treatment groups
iv). Investigate the views of patients regarding treatments
v) Compare cost effectiveness of the two treatments in terms of cost per quality-adjusted life-year, using primary data from the two years of the trial and to extend this comparison by modelling lifetime costs and effects.

## 4. TRIAL DESIGN

The project will comprise a cohort and a two arm, pragmatic, RCT involving at least 40 centres in the UK.

Subjects will be recruited to the cohort as inpatients with suspected or known colitis until recruitment to the trial is complete. It is anticipated that this will involve approximately 1400 patients. All patients who meet the cohort inclusion and exclusion criteria will be invited to consent to the cohort element of the study after full oral and written explanation, as soon as possible after admission. Baseline data will be collected as soon as possible after consent has been given.

Cohort participants diagnosed with UC who fail to respond to two to five days intravenous steroids will be recruited to the RCT until recruitment to the trial is complete. The option to recruit into the RCT can be discussed with the patient after 48 hours of intravenous steroids, although the RCT may be discussed with the patient on day 1 of their admission. Patients who meet the RCT inclusion and exclusion criteria will be invited to consent, after full oral and written explanation, to be randomised to either Remicade or Sandimmun/Neoral. This will involve 240 patients in each of the two treatment arms. There is no placebo control as patients will be severely ill and will need treatment. See Appendix 2 CONSTRUCT Flow Chart.

Data on all patients (cohort and RCT) will be collected and held on a centralised clinical information system accessed over a virtual private network via the secure NHS N3 network. All patients will be asked to consent to data capture using this system. This will be supplemented by record linkage of electronically held routine data.

Designed research data collection within the RCT will continue for two years. The designed baseline data already collected for cohort participants will be supplemented by routine data. For RCT patients, designed research data will be supplemented by operational clinical data extracted from patients' records, and by routine data on NHS resource use in HES, and mortality from the ONS.

The study will incorporate an economic evaluation of the cost effectiveness of treatment with Remicade and Sandimmun/Neoral, and will also use telephone interviews to investigate the views of patients regarding therapies for acute severe UC.

### 4.1. Outcome measures

a) The primary outcome measure will be **QoL** using the disease specific UK-IBDQ[4] questionnaire.
b) The generic SF-12[6] and EQ-5D[5] QoL questionnaires will be secondary outcome measures. All three questionnaires will be administered at baseline and at three, six, 12, 24 months.

Other secondary outcome measures will be:

c) **Emergency and planned colectomy**; colectomy may be undertaken based on clinical judgement and patient agreement. The separate incidences of emergency and elective colectomy will be measured up to two years post-admission.
d) **Mortality** at 24 months.
e) **Re-admissions**; including for non-UC specific causes.
f) **Incidence of malignancies**; colorectal malignancies, other GI malignancies, other malignancies.
g) **Incidence of serious infections during treatment;** bacterial infections, pneumonia, abscess, other serious infections.
h) **Incidence of renal disorders during treatment.**
i) **Incidence of new symptoms during or attributable to treatment;** from among those listed as potential side effects in Summary of Product Characteristics for the drugs.
j) **Incidence of adverse events:** grouped according to their classification as SUSARs, SARs, SAEs, ARs or AEs (see page 18). These will include those described in c – i above.
k) **Disease activity**; measured by Truelove and Witts criteria. Full blood count, inflammatory markers and albumin will be measured at baseline and at three, six, 12 and 24 months.
l) **Quality adjusted survival**; to combine the effects of QoL and mortality, will be measured up to two years follow-up and then modelled for lifetime Quality Adjusted Life Years.
m) **Total NHS costs**; measured by an economic health resource use questionnaire and hospital activity data, up to two years follow-up. These will be combined with quality adjusted survival in the economic analysis.
n) **Patient borne costs**; including number of days off work per year and travel costs for health care, up to two years follow-up. These will be reported separately from the NHS costs and will not be included in the cost utility estimates.
o) **Patient views**; elicited through telephone interviews following discharge from hospital at approximately three months and then six to eight months into follow-up. These will be conducted for 24 patients, 12 (5%) in each of the two treatment arms.

### 4.2. Baseline Data Collection

Baseline data for all patients will be collected at recruitment and will include:

**Socio-demographic details:**

i) Including age, sex, ethnic group and truncated post-codes, which will be used to generate measures of social deprivation (Indices of Multiple Deprivation for England, Welsh Indices of Multiple Deprivation for Wales, Carstairs' Deprivation scores for Scotland, Northern Ireland Multiple Deprivation Measure and Townsend scores for all four countries).

**Administrative details:**

ii) **Admission details**

**Clinical details:**

iii) **Disease history**; including presenting complaint, duration of disease since first diagnosis, previous medical and surgical treatments received, together with details of any previous biologic, concomitant or steroid therapies.
iv) **Co-morbidities**; in particular, cardio-respiratory, liver, and renal disease, diabetes and hypertension.
v) **UC symptoms and signs**; including duration of symptoms in current episode, stool frequency, blood pressure, pulse, and temperature.
vi) **Treatment details**; including type, dose and duration of steroid therapy.
vii) **Pathology results**; including full blood count**,** ESR, CRP, GGT, GFR, albumin, liver function tests, urea, creatinine, electrolytes, total cholesterol, total bilirubin,
viii) **Extent of disease** and colonic area involved (Montreal classification of IBD[20]).
ix) **Histopathology results;** including stool culture results and histological diagnosis**.**
x) Family history of IBD
xi) **General**; height, weight and smoking status.

**Quality of life:**

xii) **QoL measures**. Three QoL questionnaires will be administered as one questionnaire as soon as practicable following consent; if not already completed for the cohort, completion of these questionnaires by RCT patients must precede randomisation to Remicade or Sandimmun/Neoral.

QoL questionnaires, health resource use questionnaires and some pathology results will be repeated at various intervals during follow-up, as detailed below.

### 4.3. Data Collection

A securely hosted, centralised clinical information system will support data capture at each of the 40 study centres enabling both the designed research data collection over two years, and the potential operational clinical data capture over the subsequent eight years. The data repository will be an existing generic clinical information system (GeneCIS), designed and supported by Swansea University, first implemented in the gastroenterology department at Neath Port Talbot Hospital, and since extended to four other gastroenterology departments in England and Wales. Both cohort and RCT patients will be asked to consent to data capture using this system which will be used to record administrative, socio-demographic, and clinical data from hospitals visits, and QoL data at designated time points. Research staff at study centres will enter data directly onto the system over a virtual private network via the NHS N3 network. Other data sources will include patient notes during admission, pathology systems and routine data from HES, ONS mortality data and primary care systems. Where there are discrepancies in data obtained from more than one source, the medical records will be scrutinised. Overall data collection is summarised in the table below which shows the data types, sources and methods of collection. This table also shows longer term follow-up in a planned extension to the study; this extension does not form part of the present project.

**Table: Summary of data to be collected and source of data**

| **Type of data** | **Initial inpatient stay** | **Two-year designed research data collection & record linkage** | | | | | | **Potential annual follow-up (yrs 3-10)** | |
|---|---|---|---|---|---|---|---|---|---|
| | **RCT and cohort** | **RCT** | | | | **Cohort** | | **RCT** | **Cohort** |
| **Time (months)** | **0+** | **3** | **6** | **12** | **24** | **12** | **24** | **yearly** | **yearly** |
| **Demographic** | **O** | | | | | | | | |
| **Administrative** | **O** | | | | | | | | |
| **Clinical** | **O** | **O / R** | **O / R** | **O / R** | **O / R** | **R** | **R** | **R** | **R** |
| **Pathology Results** | **O** | **O** | **O** | **O** | **O** | **R** | **R** | | |
| **Outcomes - QoL** | **P** | **P** | **P** | **P** | **P** | **R** | **R** | **P** | |
| **Outcomes - Mortality** | | **O / R** | **O / R** | **O / R** | **O / R** | **R** | **R** | **R** | **R** |
| **Outcomes - Readmissions** | | **O / R** | **O / R** | **O / R** | **O / R** | **R** | **R** | **R** | **R** |
| **Outcomes - Colectomy** | | **O / R** | **O / R** | **O / R** | **O / R** | **R** | **R** | **R** | **R** |
| **Hospital Costs – exc. Drugs*** | **O** | **O** | **O** | **O** | **O** | | | **R** | |
| **Other NHS Costs** | | **P** | **P** | **P** | **P** | | | **P** | |
| **Patient reported AEs** | | **P** | **P** | **P** | **P** | | | | |
| **Patient borne costs** | **P** | **P** | **P** | **P** | **P** | | | **P** | |
| **Patient views** | | **P** | **P** | | | | | | |

Key:

| | |
|---|---|
| P - Data collected by research professionals direct from patient | * - all drugs included under 'Other NHS Costs' even if dispensed in hospital |
| O - Operational clinical data extracted from hospital records | **P**atient data collected at specified time points |
| R - Routinely collected data (HES, ONS, EDW, SMR) | **O**perational and **R**outine data collected at specific time points indicated but cover period since last data collection. |

The trial data repository uses a clinical record system that can potentially be used to collect operational data at health service contacts, informing the management of patients. Rigorous operational data capture is particularly important for a chronic disorder such as UC, which requires long term monitoring because of the unpredictable relapsing nature of the disease. Data for aggregation and analysis by the CONSTRUCT research team will be pseudonymised and held separately from operational data in a secure data warehouse. The CONSTRUCT statisticians will not have access to patient identifiable data and wherever possible will be blinded to the treatment received. The CONSTRUCT qualitative researchers will have access to patient-identifiable data but not the clinical data linked to patients. See Data Handling and Record Keeping, p27, for more detail.

All patients admitted with suspected or known colitis will be asked to consent to be part of the cohort. The progress of all patients will be monitored through HES, using record linkage to monitor readmissions, surgery and mortality.

Research data collection will continue for two years. The first baseline operational clinical data measures will be entered by research staff directly onto GeneCIS and the first patient reported QoL baseline questionnaire (UKIBDQ, SF-12, EQ-5D) will be completed as an inpatient administered by a specialist IBD or research nurse as soon as practicable after consent and entered onto GeneCIS. Subsequent questionnaires at three, six, 12 and 24 months and potentially annually thereafter will preferably be completed at outpatient hospital visits, again administered by a specialist IBD or research nurse, when the patient visits for follow-up appointments. When this is not possible, participants will be contacted by phone by the research staff and asked to complete the questionnaire verbally at a convenient time.

For RCT patients, information about hospital and primary care contacts, investigations, treatment and surgery will also be recorded at each hospital follow-up visit at three, six, 12 and 24 months. The results of clinical investigations including blood tests will be captured at the same follow-up points. It is anticipated that these tests will be performed as part of a patient's normal clinical care so additional tests and visits will not be required.

**Economic data**

An economic evaluation will be undertaken. A cost utility analysis will use the EQ-5D to estimate QALYs and costs will be determined from an NHS perspective. Patient-level data on resource use in hospital over the initial two years of the study will be monitored using GeneCIS and routinely collected data, if necessary supplemented by scrutiny of hospital medical records. These will include drugs, drug related complications, surgery, inpatient length of stay (ICU/HDU/ward) and outpatient clinic attendances. NHS resource use outside hospital will be monitored by questions added to the QoL questionnaires completed at three, six, 12 and 24 months and potentially annually thereafter. These will include all contacts with health professionals in primary care and the community. Patient recall has been shown to be a valid method to estimate health service resource use[21]. Costs will be calculated using current UK national prices where available and from published sources.[22] Where these are not available, local cost data from Finance Departments of participating sites will be used. Patient borne costs will be monitored via additional questions in the questionnaires completed at baseline, three, six, 12 and 24 months and potentially annually thereafter.

**Qualitative interviews**

Patient telephone interviews will be used to determine and understand patients' experiences and perceptions of treatment with Remicade, Sandimmun/Neoral or other therapies for acute severe UC. Patients will be given the opportunity to indicate their willingness to be interviewed by initialling a statement on the RCT Consent Form.

Five per cent of randomised patients will be interviewed using purposive quota sampling to identify 12 recruited patients who agree to be interviewed drawn from the two arms of the RCT. This will give a total of 24 participants enabling a wide representation of therapy, age and sex of patients from a range of centres. Their experiences will be captured at two stages during the study to explore their views at approximately three months and six to eight months after they receive treatment.

The first interviews will follow a structured format to ensure consistency of data collection. The main emphasis of the interviews will be to investigate patient views in terms of their priorities for their health and wellbeing, ease of taking the drugs, side effects and response to treatment. The follow up interviews will be important to explore patients' experiences since the treatment. They will adhere to a similar schedule but will include some additional questions to explore what has happened to patients

following treatment; for example, changes over time in people's opinions of the treatment, changes to their health, approaches to treatment and personal interaction with healthcare professionals.

Telephone interviews are the most appropriate method for obtaining patients' views in this trial, although they have advantages and disadvantages. Advantages include reduced interviewer effects, better uniformity in delivery, greater standardisation of questions, researcher safety, greater cost-efficiency and faster results.[23] Disadvantages include difficulties in contacting people as a result of call screening, answer phones and ex-directory numbers.[24] However, it is not anticipated that these will be an issue in this trial as the researchers will have access to the majority of patient telephone numbers or will send a letter to potential interviewees asking them to make the initial contact. As the sample of patients to be interviewed is geographically dispersed, telephone interviews are the most feasible method in this trial. They can take place at a time convenient to the patient, will not involve additional travel for the patient and will also save researcher travel time and will help ensure a wide population view.

The interviews will be recorded and transcribed and then analysed using standard thematic analysis that relates to the schedule and the way the questions are asked.

### 4.4. Feasibility, Pre-pilot and Pilot Studies

We will undertake feasibility and pre-pilot studies to test and streamline the pathway for identifying and recruiting eligible patients up to and including randomisation, but without implementing treatment, and to refine and validate the main patient-completed questionnaire. To permit this we submitted a Substantial Amendment building on the approval already in place to approach patients on the first day of their admission with acute diarrhoea (and thus suspected UC) and a small number of patients who have existing colectomies.

In the first half of 2009 we wish to study in four NHS Trusts – Abertawe Bro Morgannwg University Health Board (ABM), Cardiff & Vale University Health Board, Oxford Radcliffe Hospitals Trust and the Newcastle upon Tyne Hospitals NHS Foundation Trust – to determine whether the patient pathway we have developed in consultation with potential participating centres across the UK reflects the reality of clinical practice and will thus enable us to recruit patients to the definitive trial. Early in this period we will refine the economic health resource use questionnaire, the UK-IBDQ and the Case Report Forms (CRFs) to be used for clinical data capture. The economic health resource use questionnaire is an instrument that usually needs calibrating to the condition under study. Though members of the CONSTRUCT team developed and validated the UK-IBDQ for use in outpatient settings[4] it must be refined and revalidated for inpatients to reflect both the wider range and frequency of symptoms in hospital and the potential for future colectomy. This requires both several extra questions and a wider range of responses to all questions. To ensure that the resulting questionnaire is clear to patients, as well as psychometrically sound, we shall approach relevant patients in these hospitals, give them Information Leaflets, seek informed consent, and ask them to complete questionnaires as soon as possible after their admission. Research Professionals (RPs) from the Clinical Research Collaboration Cymru will interview patients and collect their 'Truelove and Witts[25] scores' to provide the yardstick for the revised questionnaire. The RP will also ask patients the following four questions:

1. Are any of these questions difficult to understand?
2. Were there any questions you did not want to answer?
3. Are there any aspects of your bowel condition not covered by the questionnaire?
4. Are there any questions that did not relate to your bowel condition?

The RP will use a separate assessment form to record patients' responses to these questions, designed to investigate the acceptability and content validity of the modified UK-IBDQ.

Consenting patients will then be followed through the recruitment pathway to check for potential problems, e.g. availability of pre-eligibility data, difficulty tracking patients – but not approached for consent to either cohort or RCT.

Having refined the pathway, and the modified UK-IBDQ and economic health resource use questionnaire in the light of this feasibility study, we shall conduct a pre-pilot study in the Trusts/Health Boards. This will test the recruitment process up to but not including randomisation, to ensure that all the initial components of this study work together. Although the clinical and research process will be very similar to that in the feasibility study (akin to early rehearsals of a dramatic production), the role of pre-pilot is closer to that of dress rehearsal. Thereafter we shall use the resulting cohort of between

20 and 40 patients to test aspects of study design beyond initial recruitment before the centres undergo formal piloting according to the protocol already approved.

**Pilot Studies**
Following the pre-pilot, the use of GeneCIS (the online data collection system), the patient recruitment, randomisation and primary data collection processes will be piloted. Each centre will be asked to recruit and successfully randomise one RCT patient. This will be followed by a meeting with investigators to establish any lessons to be learnt from the pilot. Unless there are major problems that threaten the integrity of the trial, RCT and cohort patients recruited during the pilot period will be included in the main study.

### 4.5. Long-term follow-up

We hope to continue follow-up for a further eight years using record linkage of routine inpatient, mortality and primary care data and annual questionnaires. Record linkage would use the facilities already in place in the Health Informatics Research Unit (HIRU), School of Medicine, Swansea. Routine data would include:

- **Inpatient and daycases**; (HES in England, Patient Episode Database Wales (PEDW) in Wales and the Scottish Morbidity Record (SMR) in Scotland). These will broadly include socio-demographic data (age, sex, ethnic group, truncated post-codes for post-code based social deprivation measures, etc), admission and discharge administrative data, co-morbidity data from secondary and subsidiary diagnoses, clinical data on case severity, and data on colectomy as emergency or elective surgery.
- **Mortality**; details of all deaths that occur among the trial participants and the electronic comprehensive cohort in England and Wales will be identified from systematic record linkage of the inpatient data to ONS mortality data. This has been in operation on a national basis in England since 1998 and is currently being set up in Wales, with completion due well before the start of this component of the trial.
- **Primary care**; more detailed information on co-morbidities among the trial participants both after and before their participation in the trial will be obtained, where possible, from the increasing coverage of linked inpatient and GP data.

Using these information sources, follow up on all patients will be extended for eight years for key long term outcome measures, including mortality, emergency colectomy, elective colectomy and major morbidity measures involving hospitalisation and surgery, and most of the NHS costs measures. This is a major bonus in providing long term follow-up for the trial patients, as well as creating the potential for a larger electronic comprehensive cohort of patients with inflammatory bowel disease.

## 5. SELECTION AND WITHDRAWAL OF SUBJECTS

### 5.1. Recruitment

The target population for the cohort are all inpatients, aged 16 and above, with suspected or known colitis. The cohort will involve approximately 1400 patients from at least 40 hospitals.

The target population for the RCT are inpatients, aged 18 and above, with acute severe UC (defined using Truelove and Witts criteria, see Appendix 3, or clinical judgement and endoscopic appearances, see Appendix 4) who have failed to respond to intravenous steroid medication, but do not, at the time of entry to the RCT, require emergency surgery. Patients may be approached for entry into the RCT over a 72-hour period, starting 48 hours after the commencement of intravenous hydrocortisone but will not be randomised until steroid resistance has been confirmed by the clinical team (usually after 2 – 5 days of treatment). The RCT will recruit a total of 480 patients from at least 40 hospitals (240 patients to Remicade and 240 patients to Sandimmun/Neoral, an average 12 patients from each hospital). Completion of the QoL questionnaires by RCT patients must precede randomisation to Remicade or Sandimmun/Neoral.

The treatment of patients who do not consent to the cohort / RCT, will not change in any way.

### 5.2. Inclusion and exclusion criteria

***Cohort inclusion criteria***

Patient admitted acutely (ie not planned) with symptoms of colitis (defined as frequent loose stool), who ***also*** have either

a. A history of ulcerative colitis (previously confirmed histologically)
   **OR**
b. The endoscopic appearance of colitis (on current episode)

***Cohort exclusion criteria***

1. Patient aged under 16 years of age on admission
2. Patient from a vulnerable group (see Appendix 5)
3. Patient with no previous history of UC, who have a histopathological diagnosis inconsistent with Inflammatory Bowel Disease (ie has infective colitis)
4. Patient unable to consent for themselves

These patients will then continue with treatment as part of their normal clinical care.

Patients who fail to respond to intravenous steroids and meet the following RCT inclusion and exclusion criteria will be invited to consent, after full oral and written explanation of the study, to randomisation to Remicade or Sandimmun/Neoral. Patients who have consented to the cohort but decline randomisation will continue as part of the cohort and their treatment will not be changed in any way.

***RCT inclusion criteria***

Patients admitted acutely (ie an emergency admission) with severe colitis (as evidenced by a Mayo score of ≥2 on endoscopic finding, see Appendix 4) who fail to respond to 2-5 days of intravenous hydrocortisone therapy, who ***also*** have either:

a. A histological diagnosis of ulcerative colitis in this episode
**OR**
b. A histological diagnosis of indeterminate colitis in this episode, where clinical judgement (based on macroscopic appearance/disease distribution/previous history) suggests a diagnosis of ulcerative colitis rather than Crohn's disease
**OR**
c. Typical symptoms of ulcerative colitis but histology awaited
**OR**
d. A history of ulcerative colitis (previously confirmed histologically)

***RCT exclusion criteria***

1. Patient aged under 18 years of age on admission
2. Patient with histological diagnosis inconsistent with ulcerative colitis (indeterminate colitis is not necessarily "inconsistent with ulcerative"-see inclusion criteria b)
3. Patient with enteric infection confirmed on stool microscopy/culture or histology (includes salmonella, shigella, clostridium difficile, campylobacter and CMV)
4. Patient from a vulnerable group (as defined in Appendix 5)
5. Patient unable to consent for themselves
6. Patient who are pregnant (as evidenced by +ve pregnancy test) or currently lactating
7. Women of child-bearing potential who are not prepared to use adequate contraception during treatment with Remicade (infliximab) and for 6 months afterwards in line with the Summary of Product Characteristics
8. Patient with current malignancy, excluding basal cell carcinoma
9. Patient with serious co-morbidities, including:
   a. Immunodeficiency
   b. Myocardial infarction (within last month)
   c. Moderate or severe heart failure (NYHA class III/IV)
   d. Acute stroke (within last month)
   e. Respiratory failure
   f. Renal failure
   g. Hepatic failure

h. Active, or suspected active tuberculosis
i. Other severe infections (as determined by the investigator) such as sepsis, abscesses and opportunistic infections

10. Patient with a history of hypersensitivity to
    a. Infliximab (Remicade)
    b. Ciclosporin (Sandimmun/Neoral)
    c. Polyethoxylated oils (Sandimmun Concentrate for IV Infusion)
11. Concomitant use of tacrolimus or rosuvastatin
12. Patients who do not speak English well enough to take part in the study, and for whom local translation services cannot be provided
13. Where clinical need determines the patient should undergo emergency colectomy without further medical treatment
14. Patients currently taking part in other clinical trials
15. Patients who have received treatment with either infliximab (Remicade) or ciclosporin (Sandimmun/Neoral) in the three months before admission

### 5.3. Consent

Patients will give written informed consent by signing and dating either a cohort or RCT-specific consent form. The person taking consent must countersign and date the form and record that consent has been given in a patient's medical records.

A nurse or research professional can take consent to the cohort if they are authorised to do so on the Delegation Log and have undergone consent and GCP training. They can also explain the RCT to the participant but consent must be signed by the PI (or doctor with delegated authority on the Delegation Log) who must recheck eligibility and confirm that the participant understands the RCT.

### 5.4. Withdrawal

Patients can withdraw from the cohort or RCT whenever they wish, and do not have to give a reason. However, any reasons given must be documented. Their subsequent treatment will not be affected in any way. Patients may also withdraw from the questionnaire element of the study, but be retained for other follow-up. Any patients lost to follow-up must be traced and the reasons for their loss documented whenever possible.

For RCT patients, a clinical judgement of failure to respond to treatment with either Remicade or Sandimmun/Neoral will normally prompt surgical referral. These patients will remain in the trial and be followed up as they continue their normal clinical care. At any time between randomisation and the end of treatment, the patient or clinical staff may discontinue or change the allocated treatment. This does not constitute withdrawal from the trial.

### 5.5. Randomisation and stratification

An RCT is the most appropriate method for comparing two drugs to understand their clinical and cost effectiveness.

Following baseline observations, patients who meet the RCT inclusion criteria and give consent will be randomised to Remicade or Sandimmun/Neoral. Remote web randomisation to CONSTRUCT will be managed from a randomisation centre in Bangor using a secure password-protected site. The randomisation will be performed by dynamic allocation to protect against subversion while ensuring that each arm of the RCT is balanced for stratification by centre.

For validation purposes, additional information will be requested including the participant's study number, month and year of birth, and the name of the person requesting the randomisation (each centre will have a list of one or more research staff who have been trained and are authorised to use the randomisation website). The following questions (with yes/no alternatives) will be asked during the randomisation process:

1. Has consent been given?
2. Does the patient meet the inclusion criteria on page 14/15?
3. Does the patient have **none** of the exclusion criteria on page 14/15?
4. Has the baseline questionnaire been completed?

If the responses are 'Yes' to all four questions the patient can be randomised.

The research staff requesting randomisation will be told the name of the drug to be allocated to the patient and told that there will be immediate confirmation of the participant's study number and drug by email.

The outcomes of randomisation will be recorded on the randomisation database, a trial register at Swansea University, at the study site in patients' records, and in the remotely hosted data repository.

The drugs will be held in the hospital pharmacies at the study sites. When a patient is randomised, the research staff will fax the relevant pharmacy a copy of the confirmation of patient study number and drug. The drug will be over-labelled with the EudraCT number, sponsor, patient's study number, name and address of supplier, 'For Clinical Trial Use Only', as well as the dose directions.

As this is an open trial there is no requirement for codes or procedures for the study sites to be able to break them.

### 5.6. End of the trial

Patients will be recruited until recruitment to the trial is complete and followed-up for two years. The trial will end and be analysed after the last two year follow-up contact with any patient in the trial. However, consenting patients may continue to be followed-up annually for a further eight years to obtain long term outcome data.

In the event of the trial being prematurely terminated the sponsor will notify the Medicines and Healthcare products Regulatory Agency (MHRA) immediately and at least within 15 days from the trial being halted using a Declaration of End of Trial form and will clearly explain the reasons and outline procedures for storing/archiving data collected.

## 6. TREATMENT OF SUBJECTS

There will be no interventions that are not part of normal clinical care for cohort patients. Both the drugs under investigation are already in use for this indication.

Patients consenting to the RCT will be randomised to either Remicade or Sandimmun/Neoral. Both these drugs will be used as detailed below. Deviations from this protocol will be recorded, with reasons, but any such patients remain in the trial. Relapse or failure (determined by clinical judgement) to respond at any stage will usually prompt surgical referral.

**Infliximab (Remicade)** is indicated for the treatment of moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or Azathioprine, or who are intolerant to or have medical contraindications for such therapies. It is indicated for intravenous use in adults (≥ 18 years) with UC.

**Ciclosporin (Sandimmun/Neoral)** (intravenous or oral, unlicensed therapy for UC has a rapid onset of action and is effective in the short term management of severe UC. Intravenous Sandimmun is rapidly effective as a salvage therapy for patients with refractory colitis, who would otherwise face colectomy, but its use is controversial because of toxicity and long term failure rate.

**Trial intervention:**

***Infliximab***

Those randomised to infliximab will receive it as Remicade as 5mg/kg intravenous infusion over a 2 hour period, at baseline and at 2 and 6 weeks after the first infusion, in accordance with local prescribing guidelines and policies.

***Ciclosporin***

Those randomised to ciclosporin will be given it as Sandimmun as 2 mg/kg/day by continuous infusion. The infusion should be changed 6 hourly. It is recommended that non-PVC bags and administration sets are used. Intravenous treatment will continue for up to seven days according to response or trial failure (colectomy, withdrawal etc). Patients responding to ciclosporin will be switched to oral ciclosporin 5.5 mg/kg/day in two divided doses as Neoral, with dose adjusted to achieve a trough ciclosporin concentration of 100 – 200 ng/ml. Whole blood ciclosporin levels should be measured according to local practice ideally 48 hours after oral therapy and then approximately

every two weeks. Patients will continue on ciclosporin to 12 weeks.

***For both treatments***
Azathioprine or 6-mercaptopurine should be started at therapeutically appropriate doses in **both groups** at week 4, at the discretion of the supervising consultant.

Steroids must be tapered to zero by week 12 in **both groups** in patients that remain well but should be re-escalated in patients that become symptomatic.

Septrin should be given as prophylaxis against Pneumocystis jiroveci (carinii) pneumonia in **both groups**, at the discretion of the supervising consultant.

After 12 weeks, treatment is at the discretion of the supervising consultant.

It is recommended that the Summary of Product Characteristics for Remicade and Sandimmun/Neoral (available in the Trial Site File) is consulted at the time of first prescription.

Storage accountability and dispensing will be made from the hospital pharmacy department in accordance with GCP Guidelines. Hospital pharmacies will be provided with a CONSTRUCT Pharmacy Trial File.

At the end of the trial patients will continue to be followed up by the gastroenterology team as part of their normal clinical care.

# 7. ASSESSMENT OF SAFETY

## 7.1. Known and potential risks and benefits to human subjects

Prior to recent innovations in biological therapies such as infliximab (Remicade) and ciclosporin (Sandimmun/Neoral), patients with acute severe steroid resistant UC had little other option than emergency colectomy. Even today, this still carries a mortality rate of 10% at three months.[3] The potential benefits to trial participants are considerable as many small scale studies have shown that both infliximab and ciclosporin lead to short term remission for most patients with steroid resistant UC.[8 15] The trial will provide evidence in the longer term about both the clinical and cost effectiveness of infliximab and ciclosporin.

UC affects about 150,000 people in the UK and, together with Crohn's disease, is one of the three most important disorders seen by gastroenterologists. It often leads to severe morbidity, grossly impaired quality of life, frequent and long inpatient stays and emergency colectomy. It is a major burden for many thousands of people and a major drain on health care resources. The trial therefore has great potential benefits for both patients and society.

Regarding risks to patients, there is some evidence from small scale studies of dose specific toxicity risks for ciclosporin.[13 15 16] However, in the event of these occurrences, treatment would be stopped although the patients will remain in the trial and will continue to be followed up unless they actively withdraw. There is also a small potential for possible distress among the trial participants when completing QoL questionnaires. The questionnaires will be administered by a specialist IBD/research nurse, who would be able to provide or access counselling for the patients in the event of any distress. Importantly, the patients will also be offered the opportunity to withdraw from this or future questionnaires, or from the whole study follow-up, at any stage.

As sponsor, Swansea University will delegate the responsibility for GCP and pharmacovigilance to the Principal Investigator at each trial site, formalised by a Clinical Trial Agreement.

## 7.2. Informing trial participants of possible benefits and known risks of the trial

Patients will be given full oral and written explanation of the trial. Information sheets will be given to patients to keep which will explain in detail all the benefits and risks of participating in the trial. Research staff will be available to answer any questions and respond to any difficulty experienced during the trial. Patients will be given the opportunity to nominate an advocate (e.g. family member) if they wish. Relapse or failure to respond to either Remicade or Sandimmun/Neoral at any stage will usually prompt surgical referral. These patients will be followed up as intention to treat.

Contact details for CONSTRUCT will be in the Patient Information Leaflet given to patients so that they have a contact point if they have any queries relating to the study. Patients with clinical queries will be referred back to the PI or other appropriately qualified person.

# 8. ADVERSE EVENTS (AEs)

UC is characterised by relapse and remission. In relapse, patients will experience diarrhoea with or without blood, abdominal discomfort, urgency, at times incontinence, ill health, anaemia and tiredness. Ten per cent of patients whose disease is serious enough to warrant admission die in the three years following admission.[3]

## 8.1. Events that will not be identified as AEs in this study

- ***Progression or exacerbation of the patient's underlying disease being treated by the study drug.*** However, clinical sequelae that result from disease progression, such as pleural effusion or small bowel obstruction, are reportable as AEs.
- ***Medical or surgical procedures*** as such (e.g., surgery, endoscopy, tooth extraction, etc); however the condition (the "triggering event") that leads to the procedure may be an AE.
- ***Pre-existing conditions or symptoms*** present or detected prior to the first dose that do not worsen (must be recorded as such in the source documents)
- ***Recognised undesirable effects from the study medications*** noted in previous clinical studies and post-marketing surveillance (see below). These effects will be captured as part of data collection for the study.

The recognised undesirable effects will be found in the most recent versions of the Summary of Product Characteristics for Remicade, Sandimmun and Neoral. These are available online at http://emc.medicines.org.uk/ (specific links are available below) or in the Trial Site File.

---

For the recognised undesirable effects of Remicade® please refer to the most recent version of the Summary of Product Characteristics at:

**http://emc.medicines.org.uk/medicine/3236/SPC/Remicade+100mg+powder+for+concentrate+for+solution+for+infusion/**

---

For the recognised undesirable effects of Sandimmun® please refer to the most recent version of the Summary of Product Characteristics at:

**http://emc.medicines.org.uk/medicine/1317/SPC/SANDIMMUN+Concentrate+for+Solution+for+Infusion+50mg+ml/**

---

For the recognised undesirable effects of Neoral® please refer to the most recent version of the Summary of Product Characteristics at:

**http://emc.medicines.org.uk/document.aspx?documentid=1307**

---

## 8.2. Safety monitoring and reporting

Responsibility for ensuring GCP adherence, reporting adverse events in accordance with the Clinical Trial Regulations, etc, is the delegated responsibility of the Principal Investigator (PI) and the research team for each site. A Clinical Trial Agreement will be put in place once the trial has regulatory approval from the MHRA and ethics approval.

The procedures which follow for monitoring and reporting safety must be adhered to by collaborating sites.

The following definitions identify the different types of AE and their associated reporting requirements (adapted from the EU Directive)[26]. All AEs should be assessed for causality, seriousness and expectedness. That is whether the AE is related to the intervention; whether the AE is serious; and

whether the AE was unexpected. The table shows how these three features apply to the main types of AEs.

### 8.3. Types of adverse events

| | Adverse Events (AE) | Adverse Reactions (AR) | Serious Adverse Events (SAE) | Serious Adverse Reactions (SAR) | Suspected Unexpected Serious Adverse Reactions (SUSAR) |
|---|---|---|---|---|---|
| Is the medical occurrence considered to be related to trial intervention? | N | Y | N | Y | Y |
| Is the medical occurrence serious? | N | N | Y | Y | Y |
| Is the medical occurrence unexpected? | N | N | N | N | Y |

***Causality***

Causality is the degree to which an untoward medical occurrence can be attributed to the trial intervention and can be classed as either *unrelated, unlikely to be related, possibly related, probably related or definitely related*. Only untoward medical occurrences that are considered to be either *possibly, probably or definitely related* to the intervention will be reported as having a causal relationship.

If the untoward medical occurrence is not considered to have a causal relationship with the intervention at the time of the event (i.e. it is not believed to be a consequence of the intervention) this will be classified as an AE. However, if it is considered to have a causal relationship with the intervention at the time of the event it will be classified as an Adverse Reaction (AR). Some events are caused by the UC condition or the initial steroid-resistance; these are not classed as ARs.

***Seriousness***

Any untoward medical occurrence will be deemed serious if it:

- results in death
- is life-threatening (whereby the subject was at risk of death at the time of the event; it does not refer to an event that may hypothetically have caused death if it were more severe)
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- results in a congenital anomaly or birth defect
- is defined by the trial.

All serious events not considered to have a causal relationship with the intervention will be classified and reported as a Serious Adverse Event (SAE). All serious events that are considered to have a causal relationship with the intervention will be classified as a Serious Adverse Reaction (SAR).

***Expectedness***

An untoward medical occurrence will be considered to be 'unexpected' if its nature and severity are not consistent with the information available for that intervention. Known undesirable effects for the intervention are considered to be expected. If an AE is considered 1) to be related to intervention 2) is serious and 3) unexpected then it will be classed as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

### 8.4. Responsibility for reporting

Responsibility for reporting is the delegated responsibility of the PI and the research team for each site. The reporting requirements differ depending on the causality, seriousness and expectedness of the medical occurrence as summarised in the flow diagram of safety reporting (Appendix 6).

All AEs must be (1) recorded (Appendix 7, AE Screening Form), (2) evaluated by the PI or other designated person responsible for the clinical aspect of the trial in each site, and (3) included in the annual safety report to the MREC/LREC and MHRA, and in regular reports to the DMEC and funding body.

The AE Screening Form (Appendix 7) will be used by the PI or authorised person to determine the expectedness, causality and seriousness of the event. If a decision cannot be made, the PI will refer the decision to the CI.

SUSARs and only SUSARs will be reported as soon as possible and at the latest within 24 hours of knowledge of the event to the CI via the CONSTRUCT Trial Office using the SUSAR Report Form (Appendix 8 SUSAR Report Form). Please ensure that all relevant sections have been completed.

Other AEs should be recorded but do not require expedited reporting.

The SUSAR Report Form (Appendix 8) will be used to send follow-up information to the CI as soon as possible and at the latest within 5 days of the SUSAR. This form will also be used to send further follow up information collected later than 5 days post SUSAR (using a copy of the last page of the form) until the SUSAR has resolved or a decision for no further follow up has been taken.

All follow up information will be forwarded to MHRA/REC according to reporting requirements.

For fatal or life-threatening SUSARs the MHRA and MREC must be notified as soon as possible but no later than seven calendar days after the sponsor has first knowledge of the event. Non-fatal and non life-threatening SUSARs must be reported to the MHRA and the MREC as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the event. Further relevant follow-up information will be given as soon as possible.

The CI (or WWORTH Clinical Trials Unit Manager) will report the SUSAR to the MHRA using the eSUSAR reporting system using the information provided on the SUSAR Report Form. The reports produced will also be used to inform the MREC.

The Fieldwork Handbook provides detailed instructions.

To help identify adverse events, RCT patients will be given a Membership Card showing their study ID. They will be asked to show this whenever they are seen by a doctor who is not part of the team treating them for UC. It will state that the patient is taking part in a clinical trial and give a contact number for the PI and/or research professional.

# 9. STATISTICS

## 9.1. Sample size and recruitment rate

To detect an effect size of 0.3 (i.e. a difference in UK-IBDQ mean score between infliximab (Remicade) and ciclosporin (Sandimmun/Neoral) groups of at least 0.3 of the population standard deviation) with 80% power when using a 5% significance level requires at least 180 patients to complete data collection in each group. Data from potential collaborating sites indicate that most expect to care for more than 10 steroid resistant patients per annum. We will aim to recruit 480 patients from at least 40 hospitals. Experience suggests that about 25% may drop out over the two-year follow-up period. We therefore expect to follow 180 (75%) patients in each group over two years.

## 9.2. Data analysis

**Statistical analysis**

The primary data analysis will be on an intention to treat basis, reflecting the pragmatic nature of the trial design. The primary outcome measure will be QoL as measured by the UKIBDQ. The main trial analysis will use an area under curve approach to obtain each patient's average quality of life over 24 months. Important predictors that may affect QoL during follow-up, including QoL measures at baseline, study site, disease severity, co-morbidities and age group, will be considered for inclusion as covariates. Multi-level modelling may be used to differentiate the effect of the covariates from the effect of the intervention on patients' QoL during follow-up.

**Economic evaluation**
Mean differential costs between the two drug groups will be estimated. As cost data are often highly skewed non-parametric bootstrapping methods will be used to test for differences in costs between groups.[27] Unless one treatment is dominant (lower cost greater effect), results will be reported in the form of an incremental cost utility ratio (cost/QALY). A cost effectiveness acceptability curve will show the probability of the more costly intervention having an incremental cost utility ratio below a range of acceptability thresholds.[28]

Data collected in years 3 – 10 will identify the long term pattern of costs and effects following the treatment received within the trial. At regular intervals the model will be replicated using the most recent data from patients who participated in the RCT. This will provide evidence of the validity of modelling using within trial data.

**Qualitative analysis**
The patient interviews will be recorded and transcribed and then analysed using standard thematic analysis that relates to the schedule and the way the questions are asked.

## 10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Trial-related monitoring, audits, Research Ethics Committee reviews and regulatory inspections will be permitted, allowing access to data and documents where required by appropriately qualified personnel and in accordance with the Data Protection Act 1998 (located at http://www.opsi.gov.uk/Acts1998/ukpga 19980029 en 1).

## 11. QUALITY CONTROL AND QUALITY ASSURANCE

The CONSTRUCT Trial Information and Quality manager is responsible for all aspects of quality and will conduct this trial in accordance with the principles of GCP outlined by the ICH-GCP to ensure that it will comply with the EU directive 2001/20/EC[26] and the Medicines for Human Use (Clinical Trials) Regulations 2004[29]. The research is guided by the MRC Guidelines for Good Clinical Practice in Clinical Trials[30] and the Research Governance Frameworks for England[31], Scotland[32], Northern Ireland[33] and Wales (2001 version is currently being updated).

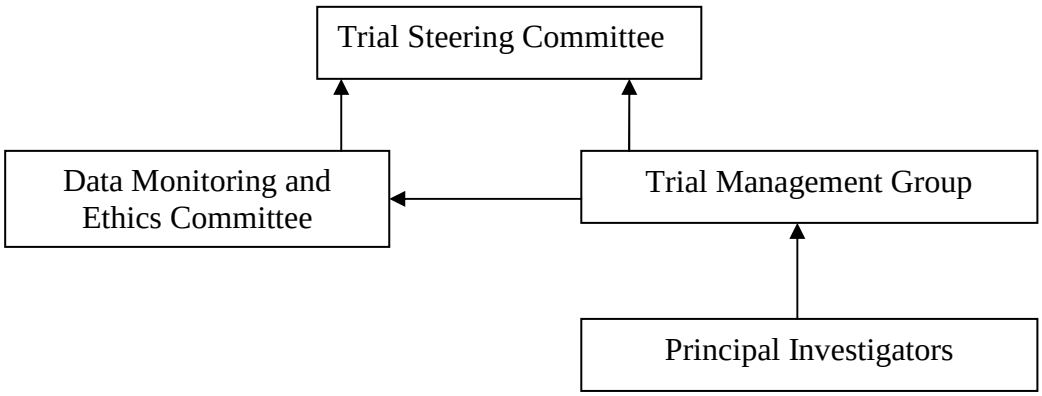
A **Trial Steering Committee** (TSC) will provide overall supervision of the trial, and will meet at six-monthly intervals. It will oversee the general conduct and progress of the trial and adherence to the protocol, patient safety and the consideration of new information of relevance to the trial.

A **Trial Management Group** (TMG) will manage the project and report to the TSC at appropriate intervals. The Chief Investigator will chair the TMG which will meet every month. PIs in each study site will report to the TSC through the TMG.

A **Data Monitoring and Ethics Committee** (DMEC) will monitor study data at interim periods provided by the Trial Information and Quality Manager and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. They have access to comparative data and interim analyses and may request the unblinding of such data at any time. The DMEC will also consider requests for the release of data. The DMEC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies. If new evidence becomes available during the course of the trial, it is the responsibility of the Trial Information and Quality Manager to provide that information to the DMEC to allow them to consider such issues and make recommendations on the continuation of the trial to the TSC.

If two or more SUSARs occur in either of the Remicade or Sandimmun/Neoral groups, or there is an apparent imbalance in SAEs between the groups, the TMG will report this to the chair of the DMEC. The DMEC will examine the evidence, and if there is evidence of imbalance in SARs or SAEs between the treatment groups that requires further action, they will report this to the TSC.

**Trial management structure**




A summary of reporting procedures is attached as Appendix 9.

## 12. ETHICS

The clinical and cost effectiveness of Remicade and Sandimmun/Neoral in the long term are not known. The only ethical means of determining these are therefore through an RCT.

All trial documentation, including patient information leaflets and consent forms, proforma GP letters, have been submitted for approval. To conform to the data protection and freedom of information acts, all data will be anonymised and stored securely. No published material will contain patient identifying information.

Full ethical approval has been secured from the Wales Research Ethics Committee and local NHS permissions will be in place at each trial site. We have obtained a EudraCT Number (2008-001968-36) and have clinical trial authorisation (CTA) from the MHRA. We have ensured that there is appropriate insurance/indemnity to cover the liability of the investigator. In addition, all patients entering into the trial will be asked for written informed consent and any SUSARS will be monitored, recorded and reported to the TSC and DMEC, the sponsor, MHRA and ethics committee as appropriate. An annual safety report will be provided.

Patients can withdraw from the trial at any time with no impact on their treatment.

As sponsor Swansea University is responsible for the initiation and management of CONSTRUCT. Responsibility for GCP and pharmacovigilance will be delegated to the PI at each trial site, formalised by a Clinical Trial Agreement.

### 12.1. Obtaining informed consent from participants whenever possible

Patients will give written informed consent. Only patients aged 18 or over and giving informed consent will participate in the RCT. Patients aged 16 or over and giving informed consent will participate in the cohort. Informed consent will be obtained when potential participants are being advised as inpatients, both orally and in writing, by their consultant gastroenterologist and/or research professional/nurse to ensure that the patient fully understands the nature of the trial and can ask any questions (see page 15 for details). Patients will also be informed that they can withdraw from the trial at any point and that doing so will not affect the care they receive. Patients will be given a copy of their consent to keep.

## 13. DATA HANDLING AND RECORD KEEPING

All data acquisition, storage and transmission will comply with the Data Protection Act.

We will use our own generic clinical information system (GeneCIS) to support data handling and record keeping and to automate the administrative processes of the trial (eg tracking follow up and sending reminders). The system will also manage data validation and facilitate quality assurance.

The IT infrastructure is summarised in the diagram overleaf. Data will be captured, stored and analysed using our securely hosted, generic clinical information system, GeneCIS. Data will be held

in a remote, professionally managed repository and accessed over a virtual private network via the secure NHS N3 network. Participating sites will only have access to identifiable data for those patients under their care, and will not be able to view any other records.

Data for analysis will be extracted in pseudonymised form for data linkage and analysis. The data will be stored in a securely hosted data warehouse.

The Trial Information and Quality Manager (TIQM) will be responsible for ensuring an appropriate standard of data quality is maintained and may be required to provide the Data Monitoring and Ethics Committee (DMEC), with unblinded data in relation to adverse events. Consequently, the TIQM will require access to all data including patient identifiable data, and will not be involved in outcome analysis.

During the provision of training and end user (helpdesk) support in the operational environment, and with permission from the local authorised user, it may be necessary for study support staff to have temporary and confidential sight of patient identifiable data, even though they will not have independent access to it. This is because it may be unavoidable for study support staff to see data on an individual patient being recorded or otherwise in use by local staff in the course of providing site support.

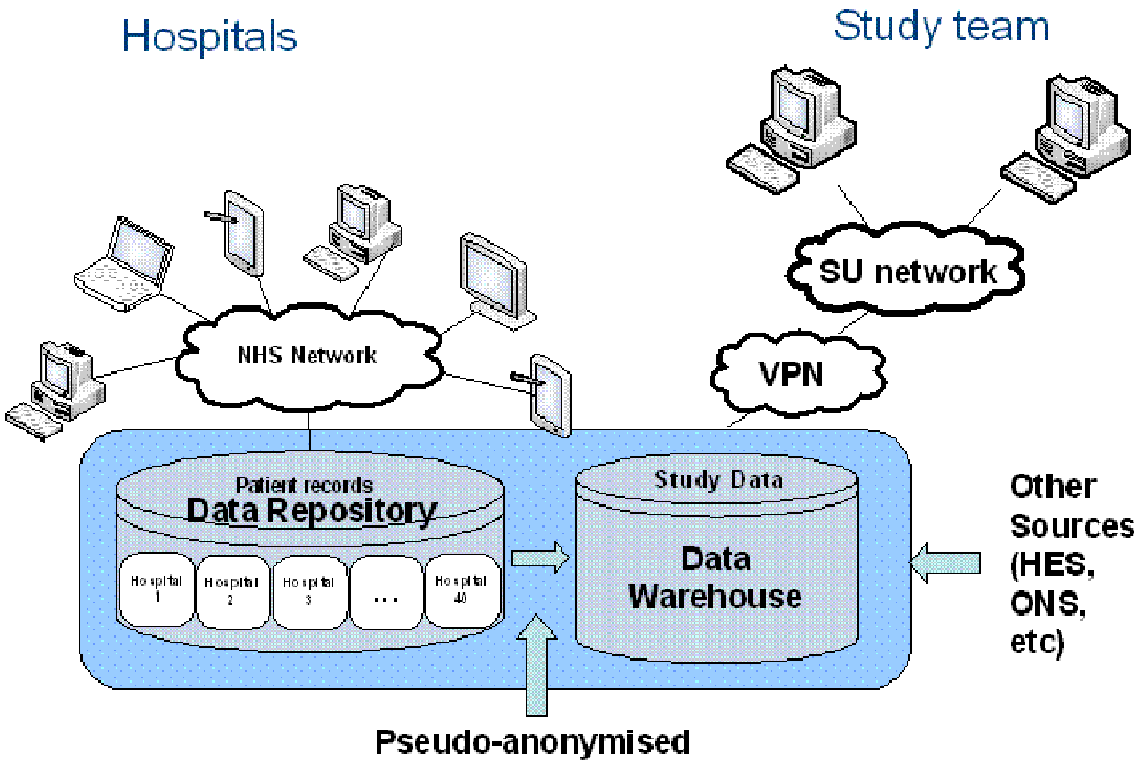
The database administrator is required to have access to all areas of the system for the purposes of technical system support and maintenance, but is not involved in the conduct of the study. The study has relevant standard operating procedures on staff confidentiality responsibilities and all staff are trained in their responsibilities.

The system will incorporate administrative scheduling and automated outputs to support scheduling interviews and follow-up appointments, communications with participants, and the trial management processes. It will also log all communications and track the progress of each participant in relation to the trial pathway, alerting research staff to discrepancies as appropriate.

Study staff responsible for analysis will have access to the original data, with each participant identified only by a unique pseudonymous identifier. They will not have access to participants' personal details.

All data will be backed up comprehensively on a daily basis as part of the fully managed service according to an agreed protocol.

GeneCIS will validate data on entry for content and format wherever possible. Data design will include the definition of data entry questions and allowable answers, which will be displayed to the user as pick lists. Free text comments will be permitted to allow additional clarification detail or comments to be added as necessary. A comprehensive set of quality assurance reports will facilitate data validation. Records will be continuously monitored for completeness and quality. Ambiguous or inconsistent entries will be queried with research staff at the relevant site. Triangulation of data from different sources will also be used to check for inconsistencies, and investigated where appropriate.




Qualitative interviews will be conducted by an experienced qualitative researcher. Qualitative data will be recorded and transcribed and stored securely, with restricted access, with each participant's record identified only by the unique study identifier.

In accordance with the MRC/Wellcome Trust data sharing policy, data arising from the project will be made available to the scientific community, with as few restrictions as possible. We will expect exclusive use of study data throughout the funded duration of the project. We will store data arising from the project throughout its duration and will release data to others with appropriate high quality meta data. We appreciate that this is our responsibility as data custodians. Following completion of the project, arrangements will be made for extensive anonymised data collected from this project to be deposited at the University of Essex data archive. Data sharing will be encouraged, especially through the Essex data archive.

## 14. FINANCING AND INSURANCE

### 14.1. Finance

CONSTRUCT is funded by a grant from the National Institute for Health Research Health Technology Assessment Programme to Swansea University. No drug manufacturing company is sponsoring the trial. Manufacturers of Remicade or Sandimmun/Neoral have had no involvement with the design nor will they be involved with the management or reporting of the trial. This ensures adequate objectivity with regard to the study findings.

### 14.2. Cost implications

CONSTRUCT has been designed to minimise costs for participating hospitals. Patients will be receiving either Remicade or Sandimmun/Neoral as part of their normal medical treatment and patient follow-ups scheduled for the trial are timed to fit in with the standard follow up for these patients.

### 14.3. Indemnity

NHS indemnity liability arrangements will apply for negligence on the part of any health care professional involved in the study.

Additional no fault and legal liability arrangements have been made through the sponsor's insurers.

## 15. REPORTING AND DISSEMINATION

A detailed publication policy will be devised once the trial has started. We are committed to publishing as widely as possible in peer reviewed journals and to ensuring that appropriate recognition is given to everyone who has worked on the trial.

## 16. APPENDICES

1. Potential study sites
2. CONSTRUCT Flow Chart
3. Truelove and Witts criteria
4. Scoring based on endoscopic appearance (part of Mayo clinical/Disease activity index)
5. Vulnerable groups
6. Flow Chart of Safety Reporting
7. AE Screening Form
8. SUSAR Report Form
9. Summary of reporting procedures

## 17. REFERENCES


1. Rubin GP, Hungin AP, Kelly PJ, Ling J. Inflammatory bowel disease: epidemiology and management in an English general practice population. *Aliment Pharmacol Ther* 2000;14(12):1553-9.
2. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53 Suppl 5:V1-16.
3. Roberts SE, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ* 2007;335(7628):1033-6.
4. Cheung WY, Garratt AM, Russell IT, Williams JG. The UK IBDQ-a British version of the inflammatory bowel disease questionnaire. development and validation. *J Clin Epidemiol* 2000;53(3):297-306.
5. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37(1):53-72.
6. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and vaidity. *Medical Care* 1996;34(3):220-33.
7. Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not steroid-refractory ulcerative colitis: a randomized pilot study. *Eur J Gastroenterol Hepatol* 2004;16(11):1167-71.
8. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353(23):2462-76.
9. Aberra FN, Lichtenstein GR. Infliximab in ulcerative colitis. *Gastroenterol Clin North Am* 2006;35(4):821-36.
10. Gisbert JP, Gonzalez-Lama Y, Mate J. Systematic review: Infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007;25(1):19-37.
11. Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. *Am J Gastroenterol* 2007;102(4):794-802.
12. Naftali T, Novis B, Pomeranz I, Leichtman G, Maor Y, Shapiro R, et al. Cyclosporin for severe ulcerative colitis. *Isr Med Assoc J* 2000;2(8):588-91.
13. Hawthorne AB. Ciclosporin and refractory colitis. *Eur J Gastroenterol Hepatol* 2003;15(3):239-44.
14. Message L, Bourreille A, Laharie D, Quinton A, Galmiche JP, Lamouliatte H, et al. Efficacy of intravenous cyclosporin in moderately severe ulcerative colitis refractory to steroids. *Gastroenterol Clin Biol* 2005;29(3):231-5.
15. Haslam N, Hearing SD, Probert CS. Audit of cyclosporin use in inflammatory bowel disease: limited benefits, numerous side-effects. *Eur J Gastroenterol Hepatol* 2000;12(6):657-60.
16. Van Assche G, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003;125(4):1025-31.
17. Creed TJ, Probert CS. Review article: steroid resistance in inflammatory bowel disease - mechanisms and therapeutic strategies. *Aliment Pharmacol Ther* 2007;25(2):111-22.
18. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007;5(1):103-10.
19. Shibolet O, Regushevskaya E, Brezis M, Soares-Weiser K. Cyclosporine A for induction of remission in severe ulcerative colitis. *Cochrane Database Syst Rev* 2005(1):CD004277.
20. Satsangi J, Silververg MS, Vermiere S, Colombel J F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *GUT* 2006;55:749-753.
21. Brown JB, Adams ME. Patients as reliable reporters of medical care process: recall of ambulatory encounter events. *Medical Care* 1992;30:400-11.
22. Curtis L, Netten A. *Unit Costs of Health and Social Care*. Canterbury: University of Kent, 2006.
23. Shuy RW. *In-Person versus Telephone Interviewing. Handbook of Interview Research. Gubrium J F and Holstein J A.* California: Sage, 2002.
24. Bryman A. *Social Research Methods*. Oxford: Oxford University Press, 2004.
25. Truelove S, Witts L. Cortisone in ulcerative colitis: final report on a therapeutic trial. *BMJ* 1955;2:1041-8.
26. The European Parliament and the Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. *Official Journal of European Union 2001*, 2001.
27. Efron B, Tibshirani R. *An Introduction to the Bootstrap*. NewYork: Chapman and Hall, 1993.
28. Drummond MF, Sculpher MJ, Torance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic evaluation of Health Care Programmes (3rd ed)*. Oxford: Oxford University Press, 2005.
29. The Medicines for Human Use (Clinical Trials) Regulations 2004. *Statutory Instrument No 1031*: HMSO, 2004.

30. MRC. Guidelines for Good Clinical Practice in Clinical Trials. *MRC Clinical Trials Series*. London: MRC, 1998.
31. Department of Health. Research Governance Framework for health and social care. Second ed. London, 2005.
32. Scottish Executive Health Department. Research Governance Framework for Health and Community Care, 2006.
33. Department of Health Social Services and Public Safety. Research Governance Framework for Health and Social Care. Northern Ireland, 2002.

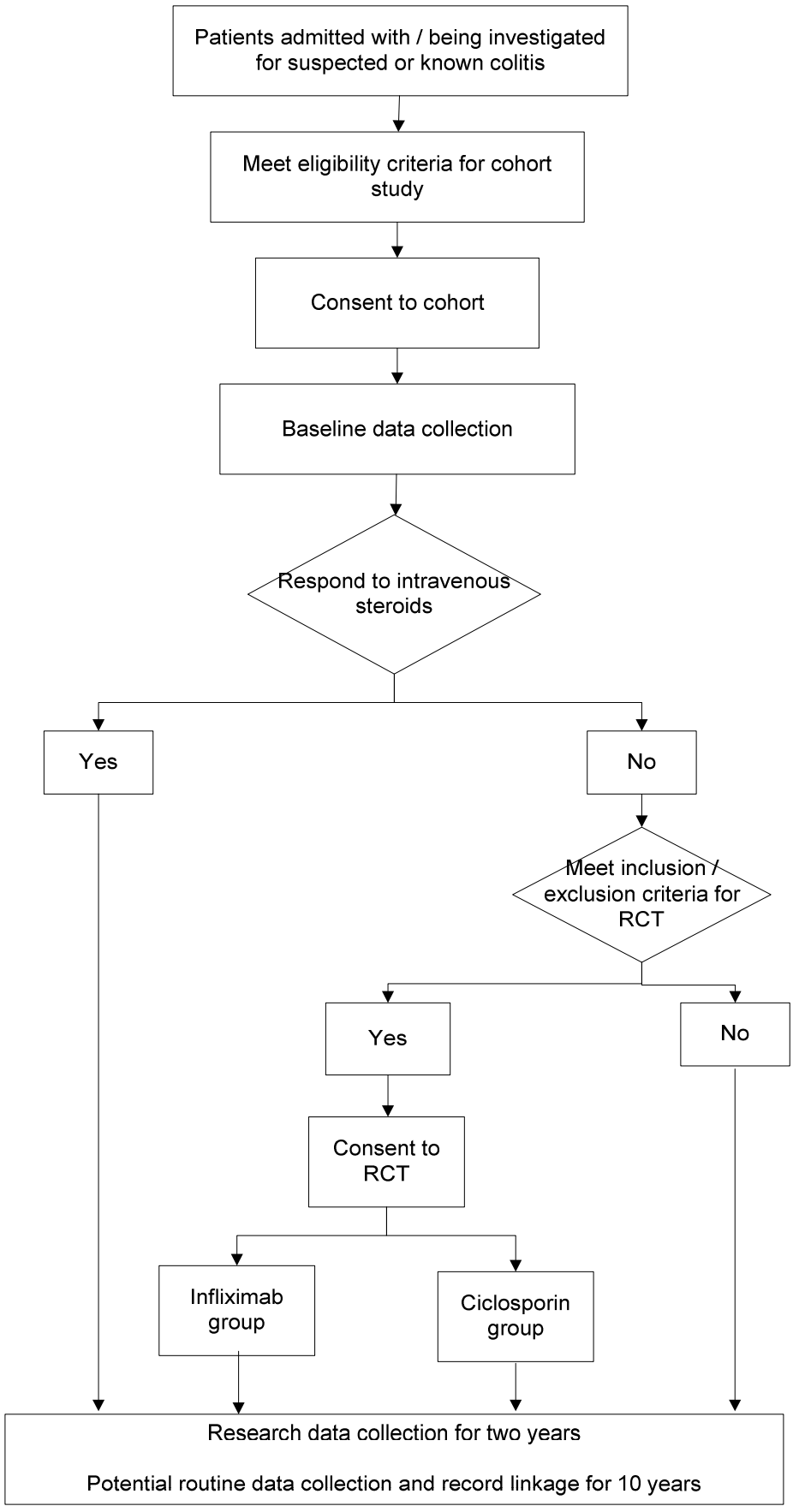
**APPENDIX 1**

## Potential study sites

| |
|---|
| Abertawe Bro Morgannwg University Health Board (Singleton, Morriston, Neath Port Talbot, Princess of Wales Hospitals) |
| Addenbrooke's Hospital, Cambridge |
| Barking, Havering and Redbridge Hospitals NHS Trust (King George Hospital/Queen's Hospital) |
| Barnet & Chase Farm Hospitals NHS Trust |
| Barts and The London NHS Trust |
| Belfast Health & Social Care Trust, Northern Ireland |
| Chelsea & Westminster NHS Foundation Trust |
| Bradford Teaching Hospitals NHS Foundation Trust |
| Lancashire Teaching Hospitals |
| Conquest Hospital |
| Countess of Chester Hospital |
| Derby City General Hospital |
| Dewsbury District Hospital , Dewsbury |
| Dudley Group of Hospitals |
| Frenchay Hospital, North Bristol NHS Trust |
| Frimley Park Hospital, Frimley, Surrey |
| Gartnavel General Hospital, Glasgow |
| Gateshead Health NHS Foundation Trust |
| Gloucestershire Royal Hospital, Gloucestershire Hospitals NHS Foundation Trust |
| Harrogate & District Foundation NHS Trust |
| Heart of England NHS Trust (Good Hope/Heartlands/Solihull) |
| Hinchingbrooke Hospital, Huntingdonshire |
| Homerton University Hospital NHS Foundation Trust |
| Hull Royal Infirmary |
| James Paget University Hospital NHS Foundation Trust |
| John Radcliffe Hospital, Oxford |
| King's Mill Hospital, Nottingham |
| Kings College Hospital, London |
| Leeds General Infirmary |
| Leighton Hospital, Crewe, Cheshire |
| Llandough Hospital |
| Manchester Royal Infirmary |
| Mayday Hospital, Croydon |
| Musgrove Park Hospital, Taunton and Somerset NHS Trust |
| New Cross Hospital, Wolverhampton |
| Newcastle upon Tyne Teaching Hospitals Foundation Trust (Royal Victoria Infirmary/Freeman Hospital) |
| Ninewells Hospital, Dundee |
| Norfolk and Norwich University Hospital |
| North Cumbria University Hospitals NHS Trust |
| Northumbria Healthcare Trust |
| QEII Hospital, Welwyn Garden City |
| Queen Elizabeth Hospital, Birmingham |
| Queen Mary's Sidcup NHS Trust |
| Rotherham Foundation Trust, South Yorkshire |
| Royal Berkshire Hospital, Reading |
| Royal Bournemouth Hospital |
| Royal Devon & Exeter NHS Foundation Trust |
| Royal Glamorgan Hospital, Pontypridd |
| Royal Gwent Hospital, Newport |

| |
|---|
| Royal Hallamshire Hospital, Sheffield |
| Royal Liverpool University Hospital |
| Royal Shrewsbury Hospital |
| Royal Sussex County Hospital, Brighton |
| Salford Royal NHS Foundation Trust |
| Southampton General Hospital |
| Southport & Ormskirk Hospitals NHS Trust |
| Stirling Royal Infirmary |
| St George's Healthcare Trust, London |
| St Mark's Hospital, Harrow |
| St Mary's Hospital, London |
| The Lewisham Hospital NHS Trust, London |
| Torbay Hospital, Torquay |
| University College Hospital, London |
| University Hosp of Wales Cardiff |
| University Hospital of North Tees |
| University Hospital Coventry |
| University Hospital Nottingham |
| University Hospitals Bristol NHS Foundation Trust |
| University Hospitals of Leicester NHS Trust (Leicester Royal Infirmary/Leicester General Hospital) |
| West Middlesex University Hospital |
| Western General Hospital, Edinburgh |
| Winchester and Eastleigh Healthcare NHS Trust |
| Wishaw General Hospital, Lanarkshire |
| Wythenshawe Hospital, University Hospital of South Manchester |
| York Hospitals NHS Foundation Trust |

CONSTRUCT Flowchart



**APPENDIX 3**

**Definition of acute severe colitis according to Truelove and Witts, modified 2009:**

bloody stool frequency of 6 or more daily

and any one of the following additional criteria:

pulse >90 bpm

temperature >37.8$^{o}$C

haemoglobin <10.5 g/dL

ESR >30 mm/hr OR CRP > 30 mgs/L

**The definition used for intravenous steroid resistant colitis is:**

stool frequency >8 stools a day

or stool frequency of between 3 – 8 stools/day with a CRP >45 mgs/L

A clinical judgement of intravenous steroid resistant colitis in patients not meeting these criteria will be accepted provided the reason is documented.

**APPENDIX 4**

**Scoring based on endoscopic appearance**
**(part of Mayo clinic score / Disease activity index)**

0 = Normal or inactive disease

1 = Mild: erythema, decreased vascular pattern, mild friability

2 = Moderate: marked erythema, absent vascular pattern, friability, erosions

3 = Severe: spontaneous bleeding, ulceration

**APPENDIX 5**

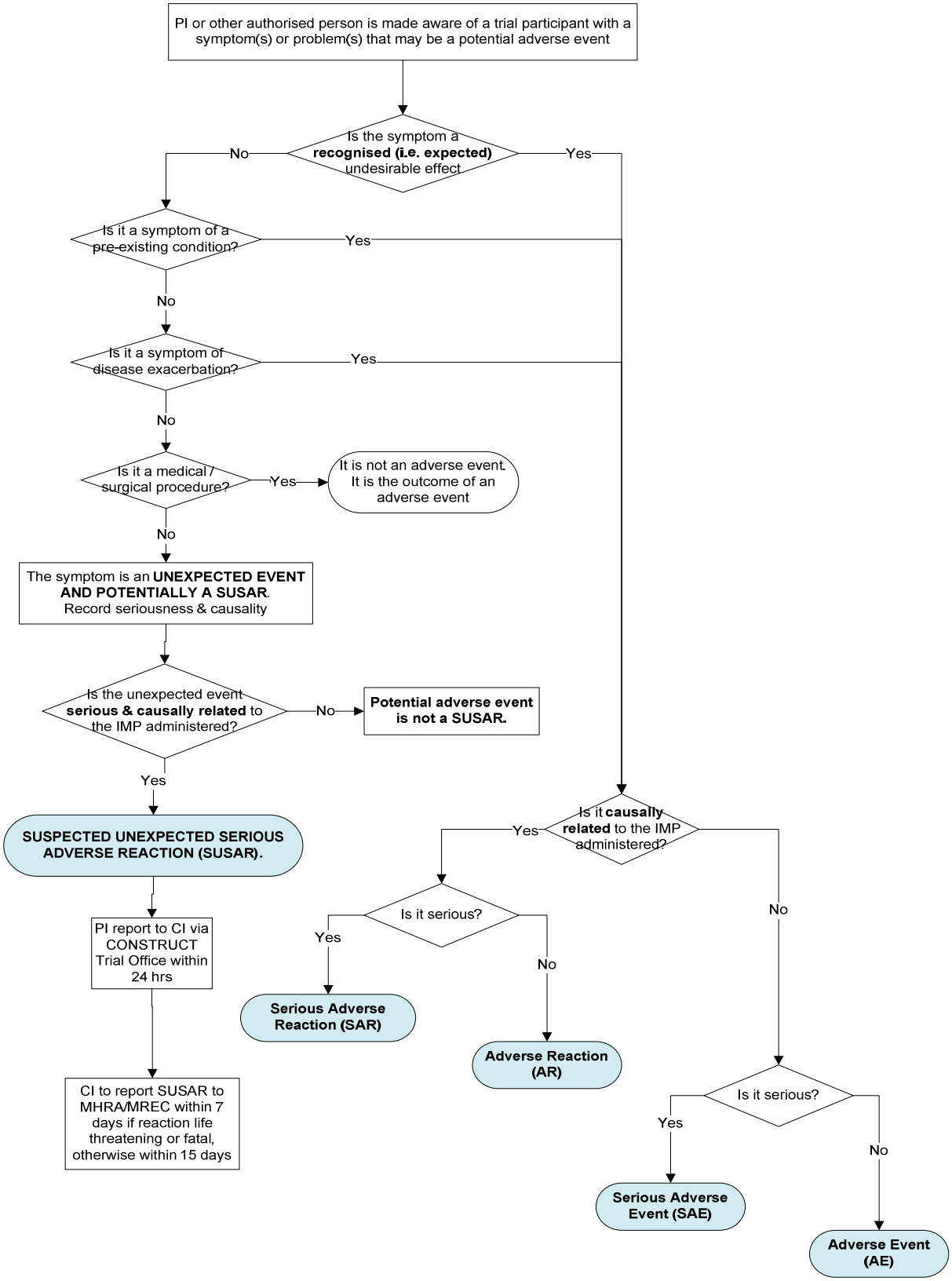
# Vulnerable Groups

Children under 16
Adults with learning disabilities
Adults who are unconscious
Adults who have a terminal illness
Adults in emergency situations
Adults with severe mental illness (particularly if detained under Mental Health Legislation)
Adults with severe cognitive impairment
Prisoners
Young offenders

This has been adapted from guidance from the National Research Ethics Service to meet the needs of a trial which is treating patients with a severe illness.

We have not included patients with severe illness: this trial will include such patients as this will be the reason for their acute admission and treatment.

# Flow Chart Of Safety Reporting



construct
building the evidence

# Adverse Event (AE) Screening Form

CONSTRUCT Helpdesk - Tel: 01792 606600 Fax: 01792 606599 Email: CONSTRUCTHelpdesk@swansea.ac.uk

Participant study ID: | | | | | | | |

**Please complete this form if the participant has any new signs or symptoms and fax it to the Trial Office on 01792 606599 as soon as possible.**

| **Start date:** | *d* | *d* | *m* | *m* | *y* | *y* | **Start time:** | *h* | *h* | *m* | *m* | ***Duration:*** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Event description:** | | | | | | | | | | | | | |

| **Severity:** | | Mild | | Moderate | | Severe | **Trial drug:** | | Remicade® | | Sandimmun® |
|---|---|---|---|---|---|---|---|---|---|---|---|

**QUESTION 1 - Is the symptom/problem a known, undesirable effect of the trial drug (see protocol or SPC), in terms of its nature and severity?**

☐ **Yes (Only complete Question 1a, 1b and 1c)** ☐ **No (Go to Question 2)**

1a) Please state which one(s) _____

_____

**1b) Relation to trial drug (causality)**

- ☐ Not related
- ☐ Unlikely to be related
- ☐ Possibly related
- ☐ Probably related
- ☐ Definitely related

**1c) Seriousness of event**

- ☐ Resulted in death
- ☐ Is/was life threatening
- ☐ Resulted in disability/incapacity
- ☐ Required hospitalisation/prolonged hospital stay
- ☐ Resulted in congenital abnormality/birth defect
- ☐ Not serious (none of the above)

**QUESTION 2 - Is the symptom/problem a stable symptom of a pre-existing condition?**

This question only concerns symptoms of medical conditions (other than UC) that were identified prior to the first treatment dose, and that have NOT significantly worsened since treatment commenced. If symptoms of a pre-existing symptom have worsened following trial treatment, this question should be answered "No"

☐ **Yes (Only complete Question 2a, 2b and 2c)** ☐ **No (Go to Question 3)**

2a) Please state which one(s) _____

_____

**2b) Relation to trial drug (causality)**

- ☐ Not related
- ☐ Unlikely to be related
- ☐ Possibly related
- ☐ Probably related
- ☐ Definitely related

**2c) Seriousness of event**

- ☐ Resulted in death
- ☐ Is/was life threatening
- ☐ Resulted in disability/incapacity
- ☐ Required hospitalisation/prolonged hospital stay
- ☐ Resulted in congenital abnormality/birth defect
- ☐ Not serious (none of the above)

# Adverse Event (AE) Screening Form

**CONSTRUCT Helpdesk - Tel: 01792 606600** **Fax: 01792 606599** **Email: CONSTRUCTHelpdesk@swansea.ac.uk**

Participant study ID: | | | | | | | |

**QUESTION 3 - Is the symptom/problem in keeping with an exacerbation or progression of the underlying disease (ulcerative colitis)?** NOTE: This does NOT include the clinical sequelae resulting from disease progression. In such cases, the answer should be "No".

☐ **Yes (Only complete Question 3a, 3b and 3c)** ☐ **No (Go to Question 4)**

3a) Please state which one(s) _____

_____

**3b) Relation to trial drug (causality)**

☐ Not related
☐ Unlikely to be related
☐ Possibly related
☐ Probably related
☐ Definitely related

**3c) Seriousness of event**

☐ Resulted in death
☐ Is/was life threatening
☐ Resulted in disability/incapacity
☐ Required hospitalisation/prolonged hospital stay
☐ Resulted in congenital abnormality/birth defect
☐ Not serious (none of the above)

**QUESTION 4 - Is the event an admission for a medical or surgical procedure?** NOTE: This does NOT include the "triggering event" that leads to the procedure (which should be considered under its own merit)

☐ **Yes (Only complete Question 4a, 4b and 4c)** ☐ **No (Go to Question 5)**

4a) Please state which one(s) _____

_____

**4b) Relation to trial drug (causality)**

☐ Not related
☐ Unlikely to be related
☐ Possibly related
☐ Probably related
☐ Definitely related

**4c) Seriousness of event**

☐ Resulted in death
☐ Is/was life threatening
☐ Resulted in disability/incapacity
☐ Required hospitalisation/prolonged hospital stay
☐ Resulted in congenital abnormality/birth defect
☐ Not serious (none of the above)

**QUESTION 5 - AT THIS POINT THE EVENT HAS BEEN CATEGORISED AS AN UNEXPECTED EVENT. Please indicate the causality and seriousness of the event below**

**Relation to trial drug (causality)**

☐ 1. Not related
☐ 2. Unlikely to be related
☐ **3. Possibly related**
☐ **4. Probably related**
☐ **5. Definitely related**

**Seriousness of event**

☐ **1. Resulted in death**
☐ **2. Is/was life threatening**
☐ **3. Resulted in disability/incapacity**
☐ **4. Required hospitalisation/prolonged hospital stay**
☐ **5. Resulted in congenital abnormality/birth defect**
☐ 6. Not serious (none of the above)

**NOTE: If causality = 3, 4 or 5 AND seriousness = 1, 2, 3, 4 or 5, the event is a Suspected Unexpected Serious Adverse Reaction. Proceed to complete a SUSAR Report Form and send both forms to the Trial Office preferably within 24 hours of becoming aware of the event.**

| Initials of person completing this form: | Signature: | Date form completed: |
|---|---|---|

construct
building the evidence

**SUSAR Report Form**

**CONSTRUCT Helpdesk - Tel: 01792 606600 Fax: 01792 606599 Email: CONSTRUCTHelpdesk@swansea.ac.uk**

| Participant study ID: | | | | | | | | SUSAR ID: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

# Research Related SUSAR Report Form

Once a SUSAR has been identified, please complete **Sections 1-6** on this form with as much information as possible before sending to the CONSTRUCT Trial Office, by fax: 01792 606599 or email: CONSTRUCTHelpdesk@swansea.ac.uk within 24 hours of knowledge of the event. Please update all sections as information becomes available and complete **Sections 7-9** before resending the form within **5 days of sending the initial or previous report** until the SUSAR has resolved or a decision for no further follow up has been taken. (If further follow up reporting is required please copy and use the last page of this form.)

## 1. Details of study

| | |
|---|---|
| **Full title of study:** | |
| **Study centre (Trust):** | |
| **Study site (hospital):** | |
| **R&D No:** | |
| **Ethics No:** | |
| **EudraCT No:** | |

## 2. Details of participant affected by SUSAR

| **Study ID number:** | **Initials:** | **DOB (dd/mm/yyyy):** | **Gender:** | **Height:** | **Weight:** |
|---|---|---|---|---|---|
| | | | | | |

**Disease history – prior diseases suffered by the participant not being treated by the study medication**

| **Disease name:** | **Start date** | **End date** | **Continuing** *(Yes / No / Unknown)* |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

**Drug history - non-study medication taken outside of the last 3 months** *(medication within 3m is classed as concomitant)*

| **Drug name** | **Start date** | **End date** |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |

CONSTRUCT Helpdesk - Tel: 01792 606600 Fax: 01792 606599 Email: CONSTRUCTHelpdesk@swansea.ac.uk

Participant study ID: | | | | | | SUSAR ID: | | | | | | | | |

## 3. Reaction details

| Country of origin: | |
|---|---|

| Reaction | Reaction outcome *(Recovered / Recovering / Not recovered / Recovered with sequelae / Fatal / Unknown)* | Start date | End date |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

**Narrative - Detailed description of SUSAR**

| **Setting** *(e.g. hospital, out-patient clinic, home, nursing home):* | |
|---|---|
| **Body site(s):** | |
| | |
| **Diagnosis** (if available): | |

**Other information:**

**Seriousness**

☐ Death ☐ Life threatening ☐ Hospitalisation ☐ Disabling ☐ Congenital anomaly ☐ Other

**Details of medical tests undertaken relevant to SUSAR**

| Test | Result | Unit | Test date |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

CONSTRUCT Helpdesk - Tel: 01792 606600 Fax: 01792 606599 Email: CONSTRUCTHelpdesk@swansea.ac.uk

Participant study ID: | | | | | | SUSAR ID: | | | | | | | | |

| 4. **Details of IMP(s)** *(all study medication taken in the last 3 months)* | | | |
|---|---|---|---|
| | **IMP #1** | **IMP #2** | **IMP #3** |
| **Drug name** *(use Remicade, Sandimmun or Neoral as appropriate)* | | | |
| **Drug characterisation** *(suspect / concomitant)* | | | |
| **Drug dosage** | | | |
| **Drug dose interval** | | | |
| **Form** *(e.g. capsule, cream, IV infusion)* | | | |
| **Route of administration** | | | |
| **Indication the drug is being used to treat** | | | |
| **Start date** | | | |
| **End date** | | | |
| **Action taken** *(drug withdrawn / dose reduced / dose increased / dose not changed, unknown / not applicable)* | | | |

| | **IMP #4** | **IMP #5** | **IMP #6** |
|---|---|---|---|
| **Drug name** | | | |
| **Drug characterisation** | | | |
| **Drug dosage** | | | |
| **Drug dose interval** | | | |
| **Form** | | | |
| **Route of administration** | | | |
| **Indication … used to treat** | | | |
| **Start date** | | | |
| **End date** | | | |
| **Action taken** | | | |

CONSTRUCT Helpdesk - Tel: 01792 606600 Fax: 01792 606599 Email: CONSTRUCTHelpdesk@swansea.ac.uk

| Participant study ID: | | | | | | SUSAR ID: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

## 5. Action taken at 24h (initial reporting interval)

| |
|---|
| |
| |
| |
| |
| |
| |
| |

## 6. Details of Principal Investigator, or delegated physician (at this site) writing the initial report details (at 24h)

| | | |
|---|---|---|
| Name: | | |
| Job title/role in the study: | | |
| Contact address: | | |
| Email address: | | |
| Telephone No: | | |
| Signature: | | Date: |

## Additional information *(refer to section number)*

| Section number | Further information |
|---|---|
| | |
| | |
| | |
| | |

**CONSTRUCT Helpdesk - Tel: 01792 606600** **Fax: 01792 606599** **Email: CONSTRUCTHelpdesk@swansea.ac.uk**

| Participant study ID: | | | | | | SUSAR ID: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

Please complete the following sections as part of the **follow up** reporting process for this SUSAR (within 5 days of the initial or previous report being sent to the CONSTRUCT Trial Office until the SUSAR has resolved or a decision for no further follow up has been taken).

| **7. Update on outcome assessed at follow-up reporting interval (within 5 days of initial or previous report)** |
|---|
| ☐ Resolved*<br>☐ Ongoing*<br>☐ Died* |
| * Give details of outcome indicated (including, for death, cause and post mortem details if available) |
| |
| |
| |
| |
| |

| **8. Details of any further action taken since first report** |
|---|
| |
| |
| |
| |
| |
| |

| **9. Details of Principal Investigator, or delegated physician (at this site) making the follow up report** (if different from the person in Section 6) | | |
|---|---|---|
| Name: | | |
| Job title/role in the study: | | |
| Contact address: | | |
| Email address: | | |
| Telephone No: | | |
| Signature: | | Date: |

SUSAR Report Form V3-0 19Aug 2010

**APPENDIX 9**

# Summary of Reporting Procedures

**Safety & Progress Reports**

**Reports required**

| | **Annual safety Reports** | **Annual Progress Reports** | **End of study reports** |
|---|---|---|---|
| **Required** | **Yes** | **Yes** | **Yes** |
| | Sent to –<br>MHRA<br>REC* | Each year submitted to main REC** | End of the study, the CI will send report*** to<br>Sponsor<br>MHRA<br>REC |
| | Reports all SUSARs both expected & unexpected | To include information on safety of participants | |

* Annual Safety reports submitted to the main REC must be accompanied by the Safety report cover sheet. Reports and cover sheet, available at –
http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports/safety-reports-for-ctimps/#submissionofreports

** Annual progress reports for IMPs and non-IMP studies – Forms available at, -
http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/progress-reports/#Annualprogress

*** End of study report forms for IMP studies, available at –
http://eudract.emea.europa.eu/docs/Declarationoftheendoftrialform170805withfields.doc