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Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: a Trial (CONSTRUCT)

Protocol

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In this trial:

- **infliximab is administered as Remicade®**
- **ciclosporin is administered as Sandimmun® followed by Neoral®**

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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 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 monitor clinical progress and outcome following treatment for acute severe UC.

This study includes a cohort of patients admitted with suspected or known colitis, within which we identify patients with acute severe colitis who are steroid resistant and recruit them to a two-arm, multicentre, pragmatic randomised trial in some 70 centres in the UK. We hope to follow all these patients for at least 10 years using routinely collected data to monitor long term progress and outcome after medical and surgical treatment for acute severe colitis. We are recruiting inpatients with acute severe colitis (defined using the criteria of Truelove and Witts[25] – Appendix 3; or clinical judgement and sigmoidoscopic appearances, where appropriate – Appendix 4) to the cohort between the summer of 2010 and the end of 2012 (about 2.5 years, yielding about 1400 patients). We recruit to the trial, cohort participants who fail to respond to approximately two to five days intravenous steroids but do not at that time require surgery. We randomise trial participants to either infliximab or ciclosporin, with a target of at least 125 patients in each of the two arms.

To compare the clinical and cost effectiveness of infliximab and ciclosporin, the primary outcome measure is quality-adjusted survival as weighted by participants' scores on the Crohn's and Colitis Questionnaire (CCQ), our extension of the validated UK IBDQ[4] to cover acute severe colitis. Two other QoL measures, EQ-5D[5] and SF12[6], are secondary outcomes. Other secondary outcome measures are: emergency and planned colectomies; readmissions; incidence of malignancies, serious infections, renal disorders, adverse events; disease activity, NHS costs and patient-borne costs. Interviews will investigate the views of trial participants on therapies for acute severe UC and the views of healthcare professionals on the two drugs and their administration.

We use a centralised, securely hosted clinical information system, and linkage of electronically held routine data, to collect data on all participants in cohort and trial. Designed research data collection will continue until the end of 2013 from trial participants (who thus contribute data for between one and 3.5 years). We shall collect and analyse routine data on all trial participants at the end of 2013.

Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID), the European gastro-intestinal trials group, has completed recruitment, analysis and reporting of a similar trial called CYcloSporine versus InFliximab (CYSIF). The main differences are that CYSIF recruited only 110 patients, followed them for only one year, and collected no data on quality of life or costs. To get the best from both trials CONSTRUCT and GETAID investigators have formally agreed that, after analysing and seeking to publish both trials separately, they will pool data and undertake a joint definitive patient-level meta-analysis. The CYSIF team will follow participants for two years in all; and the CONSTRUCT team will extend the measurement of quality of life and costs in three ways:

- by adding generic questionnaires at 18, 30 and 36 months;
- by adding 4 focused questionnaires following colectomy and any ensuing corrective surgery; and
- by extending data collection for all trial participants, whenever recruited, until the end of 2013,

The joint analysis will use the enhanced CONSTRUCT dataset and the techniques of survival analysis, statistical missing value imputation and economic modelling to impute costs and quality of life for all CYSIF participants and all CONSTRUCT participants who generate data on survival, colectomy or quality of life after randomisation.

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 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 improvements in total IBDQ score and 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 research on the long term effects of ciclosporin on quality of life and cost effectiveness.

Finally, la Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID) recently reported that the trial 'CYcloSporine versus InFliximab (CYSIF)', the first head-to-head comparison of these two drugs, found no significant differences in 'treatment failure' within 98 days, defined as any of: (i) no clinical response after seven days (ii) no remission without steroids after 98 days (iii) relapse between 7 and 98 days (iv) serious adverse event leading to treatment interruption (v) colectomy or (vi) death. However CYSIF recruited only 110 patients, followed them for only 98 days and collected no data on quality of life or costs.

Thus, while infliximab and ciclosporin are often effective in the short term, there is little long-term evidence and very little about comparative clinical and cost effectiveness. Rigorous long-term comparison of these costly therapies is therefore essential. To minimise the cost of this long-term comparison to the UK, we have formally agreed to pool data with CYSIF and undertake a joint patient-level meta-analysis.

The CYSIF team will follow participants for two years in all; and the CONSTRUCT team will extend the measurement of quality of life and costs in three ways:

- by adding generic questionnaires at 18, 30 and 36 months;
- by adding 4 focused questionnaires following colectomy and any ensuing corrective surgery; and
- by extending data collection for all trial participants, whenever recruited, until the end of 2013,

The joint analysis will use the enhanced CONSTRUCT dataset and the techniques of survival analysis, statistical missing value imputation and economic modelling to impute costs and quality of

life for all CYSIF participants and all CONSTRUCT participants who generate data on survival, colectomy or quality of life after randomisation.

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In this trial:

- **infliximab is administered as Remicade®**
- **ciclosporin is administered as Sandimmun followed by 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 CONSTRUCT.

A *cohort* is a 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 aim of this trial is to compare the clinical and cost effectiveness of Remicade or Sandimmun followed by Neoral for patients with steroid resistant UC over 3.5 years.

Specific objectives are to:

i) Compare QoL across the two treatment groups (Remicade or Sandimmun followed byNeoral).
ii) Compare mortality, disease activity and morbidity across the two treatment groups.
iii) Compare emergency colectomy rates across the two treatment groups.
iv) Compare cost effectiveness of the two treatments in terms of cost per quality-adjusted life-year, using primary data from the 3.5 years of the trial.
v) Extend this comparison by modelling lifetime costs and effects.
v) Investigate the views of patients about these treatments.
vi) Investigate the views of healthcare professionals about the drugs and their administration

4. TRIAL DESIGN

The project comprises a cohort and a two-arm, pragmatic randomised trial, both in some 70 centres in the UK. We recruit participants to the cohort as inpatients with suspected or known colitis. We predict that, by the end of 2012, this will include about 1400 patients. All patients who fulfil the cohort eligibility criteria are invited to consent to join the cohort study as soon as possible after admission and full oral and written explanation. We collect baseline data from them as soon as possible after they give consent.

Until the end of 2012 we are recruiting to the trial cohort participants diagnosed with UC who fail to respond to approximately two to five days of intravenous steroids but do not at that time require surgery. We encourage participating centres to mention the trial to cohort participants soon after admission, and to discuss the option of joining the trial with them as soon as appropriate. After full oral and written explanation we invite patients who fulfil the trial inclusion and exclusion criteria to consent to randomisation to either Remicade or Sandimmun followed by Neoral. There is no placebo control as patients are severely ill and need treatment (Appendix 2 CONSTRUCT Flow Chart). We are confident of recruiting 250 patients to the trial by the end of 2012.

We hold data on all patients (cohort and RCT) on a centralised clinical information system accessed over a virtual private network via the secure NHS N3 network. We ask all patients to consent to data capture using this system, and to linkage of their electronically held routine data.

Designed research data collection will continue until the end of 2013. The designed baseline data collected from cohort participants will be supplemented by routine data. The designed research data collected from trial participants will be supplemented by operational clinical data extracted from their records, routine data on NHS resource use from HES, and mortality from ONS.

The study will incorporate an economic evaluation of the cost effectiveness of treatment with Remicade or Sandimmun followed by Neoral. It will also use telephone interviews to investigate the views of patients regarding therapies for acute severe UC and telephone or face-to-face interviews with healthcare professionals to understand their views about the two drugs and their administration.

4.1. Outcome measures

a) The primary outcome measure is quality-adjusted survival, weighted by scores on the disease-specific CCQ. (We have renamed the UKIBDQ the Crohn's and Colitis Questionnaire to reflect an increased scope.)

b) The generic SF-12[6] and EQ-5D[5] QoL questionnaires are secondary outcome measures. We ask all trial participants to complete all three questionnaires at baseline and three, six and 12 months; and to complete them at 18, 24, 30 and 36 months if they reach these timepoints of the trial. We also ask all trial participants who undergo a colectomy or subsequent corrective surgery to complete the post-colectomy version of CCQ on discharge following surgery, and at 4, 8 and 12 weeks after discharge; we have elaborated the original trial design in these ways, both for consistency with CYSIF and to strengthen our estimation of quality-adjusted survival,which is now the primary outcome measure for CONSTRUCT.

Other secondary outcome measures, all measured till the end of 2013, that is up to 3.5 years from randomisation to the trial:

c) **Emergency and planned colectomy**; centres report all colectomies undertaken based on clinical judgement and patient agreement, both emergency and elective.

d) **Mortality**.

e) **Re-admissions,** including those for non-UC-specific causes.

f) **Incidence of malignancies**, subdivided between colorectal, other GI and other malignancies.

g) **Incidence of serious infections during treatment**, including bacterial infections, pneumonia, abscesses, and other serious infections.

h) **Incidence of renal disorders during treatment.**

i) **Incidence of new symptoms during or attributable to treatment.**

j) **Incidence of adverse events**, grouped as SUSARs, SARs, SAEs, ARs or AEs and including all relevant events described in c) – i) above.

k) **Disease activity**, measured by the criteria proposed by Truelove and Witts[25]: to this end we seek to measure full blood count, inflammatory markers and albumin at baseline and three, six, 12, 18, 24, 30 and 36 months.

l) **Quality of life**, measured by the CCQ.

m) **NHS costs**, measured by a healthcare resource use questionnaire and hospital activity data; the economic analysis will combine these with quality adjusted survival.

n) **Patient borne costs**, including number of days off work and travel costs to healthcare; we shall report these separately from NHS costs because the main economic analysis takes the perspective of the NHS.

o) **Patient views**, of the alternative drugs elicited through 12 (10%) telephone interviews in each arm following discharge from hospital about three months and 12 months after randomisation.

p) Healthcare professional views about the drugs and their administration; a minimum of 8 clinicians and 4 nurses will be interviewed.

We have extended the maximum trial period to 3.5 years in this way to strengthen both our general design and estimation specifically of quality-adjusted survival, now the primary outcome measure.

4.2. Baseline Data Collection

We shall collect baseline data for all patients at recruitment, including:

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 are administered as one questionnaire as soon as practicable following consent; if not already completed for the cohort, completion of these questionnaires by trial participants must precede randomisation to Remicade or Sandimmun followed by Neoral.

QoL questionnaires, health resource use questionnaires and some pathology results are repeated at various intervals during follow-up, as detailed in 4.1b) above and 4.3 below.

4.3. Data Collection

A securely hosted, centralised clinical information system supports data capture at each of the 70 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 is 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 six other gastroenterology departments in England and Wales. Both cohort and RCT patients are asked to consent to data capture using this system which is used to cord administrative, socio-demographic, and clinical data from hospitals visits, and QoL data at designated time points. Research staff at study centres enter data directly onto the system over a virtual private network via the NHS N3 network. Other data sources 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 in-patient stay	3.5 year designed research data collection & record linkage									Potential annual follow-up (yrs 3.5-10)	
	RCT & cohort	RCT							Cohort		RCT	Cohort
Time (months)	0+	3	6	12	18	24	30	36	12	24	yearly	yearly
Demographic	O											
Administrative	O											
Clinical	O	O / R	O / R	O / R	O / R	O / R	O / R	O / R	R	R	R	R
Pathology Results	O	O	O	O	O	O	O	O	R	R		
Outcomes - QoL	P	P	P	P	P	P	P	P	R	R	P	
Outcomes - Mortality		O / R	O / R	O / R	O / R	O / R	O / R	O / R	R	R	R	R
Outcomes - Readmissions		O / R	O / R	O / R	O / R	O / R	O / R	O / R	R	R	R	R
Outcomes - Colectomy		O / R	O / R	O / R	O / R	O / R	O / R	O / R	R	R	R	R
		Additional data collection for colectomy patients										
Hospital Costs – exc. Drugs*	O	O	O	O	O	O	O	O			R	
Other NHS Costs		P	P	P	P	P	P	P			P	
Patient reported AEs		P	P	P	P	P	P	P				
Patient borne costs	P	P	P	P	P	P	P	P			P	
Patient views		P		P								
Professional views		Interviews conducted										

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 is pseudonymised and held separately from operational data in a secure data warehouse. The CONSTRUCT statisticians do not have access to patient identifiable data and wherever possible are blinded to the treatment received. The CONSTRUCT qualitative researchers have access to patient-identifiable data but not the clinical data linked to patients. See Data Handling and Record Keeping, p22, for more detail.

All patients admitted with suspected or known colitis are 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 up to 3.5 years. The first baseline operational clinical data measures are entered by research staff directly onto GeneCIS and the first patient reported QoL baseline questionnaire (CCQ, SF-12, EQ-5D) is completed as an inpatient administered by a specialist IBD or research nurse as soon as practicable after consent and entered onto GeneCIS. Subsequent

questionnaires are completed at three, six and 12 months and potentially at 18, 24, 30 and 36 months, and potentially annually thereafter. Questionnaires are posted to patients in advance of their follow up appointment with a request to complete it either the day before their appointment or bring the blank copy and complete it at the follow-up appointment. When this is not possible, participants are contacted by phone by the research staff and asked to complete the questionnaire verbally at a convenient time or be sent the questionnaire by post.

For RCT patients, information about hospital and primary care contacts, investigations, treatment and surgery are also recorded at each hospital follow-up visit at three, six and 12 and potentially at 18, 24, 30 and 36 months. The results of clinical investigations including blood tests are captured at the same follow-up points. It is anticipated that these tests are performed as part of a patient's normal clinical care so additional tests and visits are not 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 3.5 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 (in ICU, HDU or ward) and outpatient clinic attendances. NHS resource use outside hospital will be monitored by questions added to the QoL questionnaires completed at three, six and 12 months and potentially at 18, 24, 30 and 36 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 and 12 and potentially at 18, 24, 30 and 36 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 or Sandimmun followed by Neoral or other therapies for acute severe UC. Patients are given the opportunity to indicate their willingness to be interviewed on the RCT consent form.

Ten 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 and 12 months after they receive treatment.

The first interviews follow a structured format to ensure consistency of data collection. The main aim of the interviews is to investigate patients' priorities for their health and wellbeing, ease of taking the drugs, side effects and response to treatment. The follow up interviews will 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 in 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 are recorded and transcribed and will be analysed using standard thematic analysis that relates to the schedule and the way the questions are asked.

Interviews with healthcare professionals will be conducted to understand their views about the two drugs and issues surrounding their administration. A minimum of 8 doctors and 4 nurses will be interviewed by a researcher either by telephone or face to face. Health professional interviews will address the ease of handling a range of drugs for UC, aspects of drug provision that might influence professional preference for one drug over another, and impressions of other groups' contribution to treatment and care. For example, it might be the case that nurses will wish to describe consultant practices and vice-versa, thus providing a response to professional interaction, professional mindset development, different groups' ways of working and differences surrounding the treatment of UC, as well as the administration of drugs for UC.

Interviews with professionals will take place on an individual basis to enable professionals to voice their opinions freely, irrespective of other group views. Working on a one-to-one basis will also separate nurse from consultant interviews providing richer understanding of nuances in the provision of care and ensuring a richer dataset than might be obtained through, for example, focus groups with mixed professional groups.[25]

4.4. Feasibility, Pre-pilot and Pilot Studies

We undertook a feasibility study 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 test the main patient-completed questionnaire. To permit this we built on the approval already in place to approach patients on the first day of their admission with acute diarrhoea (and thus suspected UC) and several patients with existing colectomies.

Over the winter of 2009-10 we ran a feasibility study in a local Health Board – Abertawe Bro Morgannwg University Health Board (ABM), – to test whether the resulting pathway reflected the reality of clinical practice and enabled us to recruit patients to the definitive trial. We also refined the healthcare resource use questionnaire, the CCQ and the Case Report Forms (CRFs) for clinical data collection. In particular the healthcare resource use questionnaire is an instrument that needed calibrating to the condition under study. Though members of the CONSTRUCT team had previously developed and validated the UK-IBDQ for use in outpatient settings[4], we used the feasibility and pilot studies to refine and revalidate it for inpatients to reflect both the wider range and frequency of symptoms in hospital and the likelihood of future colectomy. We also renamed it as the Crohn's and Colitis Questionnaire (CCQ) to reflect its increased scope. To this end we added several extra questions and a wider range of responses to all questions. To ensure that the resulting questionnaire was clear to patients, as well as psychometrically sound, we approached relevant patients in these hospitals, gave them Information Leaflets, sought informed consent, and asked them to complete questionnaires as soon as possible after their admission.

Research Professionals (RPs) from the National Institute for Social Care and Health Research (NISCHR) Clinical Research Centre interviewed patients and collected their 'Truelove and Witts[26] scores' to provide the yardstick for the revised questionnaire. The RPs also asked patients 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 RPs used a separate assessment form to record patients' responses to these questions, designed to investigate the acceptability and content validity of the CCQ.

Consenting patients in the feasibility study were then 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 both the pathway, and the CCQ and economic health resource use questionnaire in the light of this feasibility study, we conducted a pre-pilot study. This tested 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 were 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 used 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 were piloted. Each centre was asked to recruit and successfully randomise one RCT patient. This was followed by a meeting with investigators to establish any lessons to be learnt from the pilot. As there were no major problems threatening the integrity of the trial, we have included trial and cohort patients recruited during the pilot period in the main study.

4.5. Long-term follow-up

We hope to continue follow-up for up to 10 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 up to 10 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 70 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 where appropriate, see Appendix 4) who have failed to respond to intravenous steroid medication, but do not at that time require surgery. Patients may be approached for entry into the RCT as soon as appropriate but will not be randomised until steroid resistance has been confirmed by the clinical team (after approximately 2 – 5 days of IV steroid treatment). The RCT will recruit a total of 250 patients from at least 65 hospitals (125 patients to Remicade and 125 patients to Sandimmun followed by Neoral, an average 4 patients from each hospital). Completion of the QoL questionnaires by RCT patients must precede randomisation to Remicade or Sandimmun followed by Neoral.

The treatment of patients who do not consent to the cohort or 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 stools), 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 (eg has infective colitis only)
4. Patient unable to consent for themselves

These patients 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 are invited to consent, after full oral and written explanation of the study, to randomisation to Remicade or Sandimmun followed by Neoral. Patients who have consented to the cohort but decline randomisation continue as part of the cohort and their treatment does not change in any way.

Trial inclusion criteria

Patients admitted acutely (ie an emergency admission) with severe colitis (as evidenced by eg a Mayo score of at least 2 on endoscopic finding, see Appendix 4) who fail to respond to approximately 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 or 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)

Trial 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 or 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 or 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 and 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 followed by Neoral) in the three months before admission
16. Patient with contraindication(s) to treatment with Infliximab (Remicade®) or Ciclosporin (Sandimmun®/Neoral®)

5.3. Consent

Patients 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 check 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 should 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 should 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 followed by Neoral normally prompts surgical referral. These patients remain in the trial and are 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 arerandomised to Remicade or Sandimmun followed by Neoral. Remote web randomisation to CONSTRUCT ismanaged from a randomisation centre in Bangor using a secure password-protected site. The randomisation is 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 is requested including the participant's study number, month and year of birth, and the name of the person requesting the randomisation (each centre has a list of one or more research staff who have been trained and are authorised to use the randomisation website). The following questions are asked during the randomisation process:

1. Has consent been given?
2. Does the patient meet the inclusion criteria on page 14 or 15?
3. Does the patient have **none** of the exclusion criteria on page 14 or 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 are given the name of the drug to be allocated to the patient and there will be immediate confirmation of the participant's study number and drug by email. The outcomes of randomisation are 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 are held in the hospital pharmacies at the study sites. When a patient is randomised, the research staff fax the relevant pharmacy a copy of the confirmation of patient study number and drug. The drug is 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 over a 2.5 year period and followed-up for up to 3.5 years. The trial will end and be analysed after the last follow-up contact with any patient in the trial. However, consenting patients may continue to be followed-up annually for up to 10 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 and archiving data collected.

6. TREATMENT OF SUBJECTS

There are 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 are randomised to either Remicade or Sandimmun followed by Neoral. Both these drugs are used as detailed below. Deviations from this protocol are 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 Aziathioprine, 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 and 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 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 are 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 continues for up to seven days according to response or trial failure (colectomy, withdrawal etc). Patients responding to ciclosporin are 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 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 or Sandimmun and Neoral (available online, see page 18 for website addresses, or in the Trial Site File) is consulted at the time of first prescription.

Storage accountability and dispensing is from the hospital pharmacy department in accordance with GCP Guidelines. Hospital pharmacies are 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 and 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 or 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 delegates 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 are given full oral and written explanation of the trial. Information sheets are given to patients to keep which explain in detail all the benefits and risks of participating in the trial. Research staff are available to answer any questions and respond to any difficulty experienced during the trial. Patients are given the opportunity to nominate an advocate (e.g. family member) if they wish. Relapse or failure to respond to either Remicade or Sandimmun followed by Neoral at any stage usually prompts surgical referral. These patients are followed up as treatment allocated .

Contact details for CONSTRUCT are 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 are 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. Adverse Events that are identified as expected events in this study include:

- ***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, should be considered for expectedness separately.
- ***Medical or surgical procedures*** as such (e.g., surgery, endoscopy, tooth extraction, etc); however the condition (the "triggering event") that leads to the procedure should be considered for expectedness separately.

- ***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).

The recognised undesirable effects can 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 in the box below) or the Trial Site File. These are updated frequently so we advise that the online versions of the SPCs are consulted.

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 is put in place with each site.

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)[27]. 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 and reported 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 will 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 regular reports to the DMEC and funding body.The PI or authorised person will use the AE Screening Form (Appendix 7) to judge the expectedness, causality and seriousness of the event. If a decision cannot be made, the PI will refer the decision to the CI.

The PI or authorised person must report all SUSARs 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). All other AEs, including SAEs and SARs 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. The last page of this form will also be used to send follow up information collected more than 5 days after the SUSAR until it has resolved or a decision not to follow up further.

For fatal or life-threatening SUSARs the CI or authorised person (which includes the WWORTH Clinical Trials Unit Manager) must use the eSUSAR reporting system to notify MHRA of the information on the SUSAR Report Form 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 as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the event. Relevant follow-up information will be forwarded to MHRA as soon as possible. The CI (or authorised person) will use the MHRA report to inform the REC about the SUSAR.

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

We have strengthened the original plan for monitoring serious adverse events, both for consistency with CYSIF and to strengthen our estimation of the effects of the two drugs under evaluation.

9. STATISTICS

9.1. Sample size and recruitment rate

For CONSTRUCT to detect an effect size of 0.35 in quality-adjusted survival (i.e. a difference between infliximab (Remicade) and ciclosporin (Sandimmun followed by Neoral) groups of at least 0.35 of the population standard deviation) with 80% power when using a 5% significance level requires at least 125 patients to provide data on survival, colectomy or quality of life in each group. Randomisation data from the start of recruitment in the summer of 2010 till the end of September 2011 provide convincing evidence that we shall easily exceed this target by the end of 2012.

The resulting total of 360 patients in CONSTRUCT or CySIF will yield 80% power at 5% significance of detecting an effect size of 0.30 in survival adjusted by quality of life, imputed when necessary. Though 25% of CONSTRUCT participants may drop out over the follow-up period of at least 12 months, all analyses will exploit the techniques of statistical imputation used successfully by the COGNATE [28] and FolATED [29] trials to maintain effective sample sizes at 250 for CONSTRUCT and 360 for the joint analysis.

9.2. Data analysis

Statistical analysis

The primary data analysis will be by treatment allocated, reflecting the pragmatic nature of the trial design. The primary outcome measure will be quality-adjusted survival, as weighted by the CCQ. The main trial analysis will use analysis of covariance to estimate the difference in areas under quality-adjusted survival curves and estimate all participants' total quality-adjusted survival over their period in the trial. We shall test predictors that may affect this criterion, including QoL at baseline, study site, disease severity, co-morbidities and age group, for inclusion as covariates. Both the definitive analysis of CONSTRUCT and the joint analysis of CONSTRUCT and CYSIF will use the enhanced CONSTRUCT dataset and the techniques of survival analysis, statistical imputation of censored and missing data, and economic modelling to impute costs and quality of life for all participants who generate data on survival, colectomy or quality of life after randomisation.

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.[30] 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.[31]

Data collected in years 3.5 up to year 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 trial. This will provide evidence of the validity of modelling using within trial data.

Qualitative analysis

The patient and healthcare professional interviews are recorded and transcribed and will be analysed by standard thematic analysis based on the schedule and the way the questions are asked.

10. DIRECT ACCESS TO SOURCE DATA AND 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 conducts this trial in accordance with the principles of GCP outlined by the ICH-GCP to ensure that it complies with the EU directive 2001/20/EC[27] and the Medicines for Human Use (Clinical Trials) Regulations 2004[32]. The research is guided by the MRC Guidelines for Good Clinical Practice in Clinical Trials[33] and the Research Governance Frameworks for England[34], Scotland[35], Northern Ireland[36] and Wales (2001 version is currently being updated).

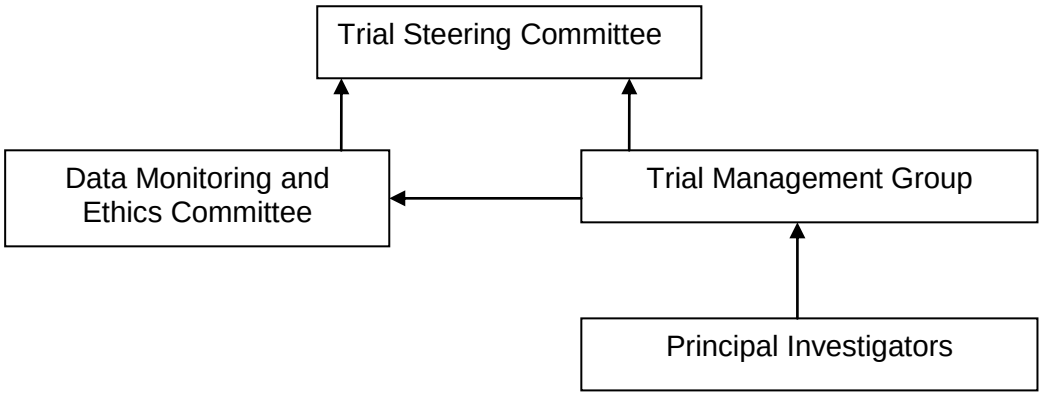
A **Trial Steering Committee** (TSC) provides overall supervision of the trial, and meets at six-monthly intervals. It oversees the general conduct and progress of the trial and adherence to the protocol, patient safety and the consideration of new information of relevance to the trial.

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

A **Data Monitoring and Ethics Committee** (DMEC) monitors study data at interim periods provided by the Trial Information and Quality Manager and makes 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 the Remicade group or Sandimmun followed by Neoral group, 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 or Sandimmun followed by 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 Research Ethics Committee for Wales 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 or indemnity to cover the liability of the investigator. In addition, all patients entering into the trial are 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 is 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 give written informed consent. Only patients aged 18 or over and giving informed consent participate in the RCT. Patients aged 16 or over and giving informed consent participate in the cohort. Informed consent is obtained when potential participants are being advised as inpatients, both orally and in writing, by their consultant gastroenterologist, or research professional or nurse to ensure that the patient fully understands the nature of the trial and can ask any questions (see page 15 for details). Patients are also informed that they can withdraw from the trial at any point and that doing so will not affect the care they receive. Patients are 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.

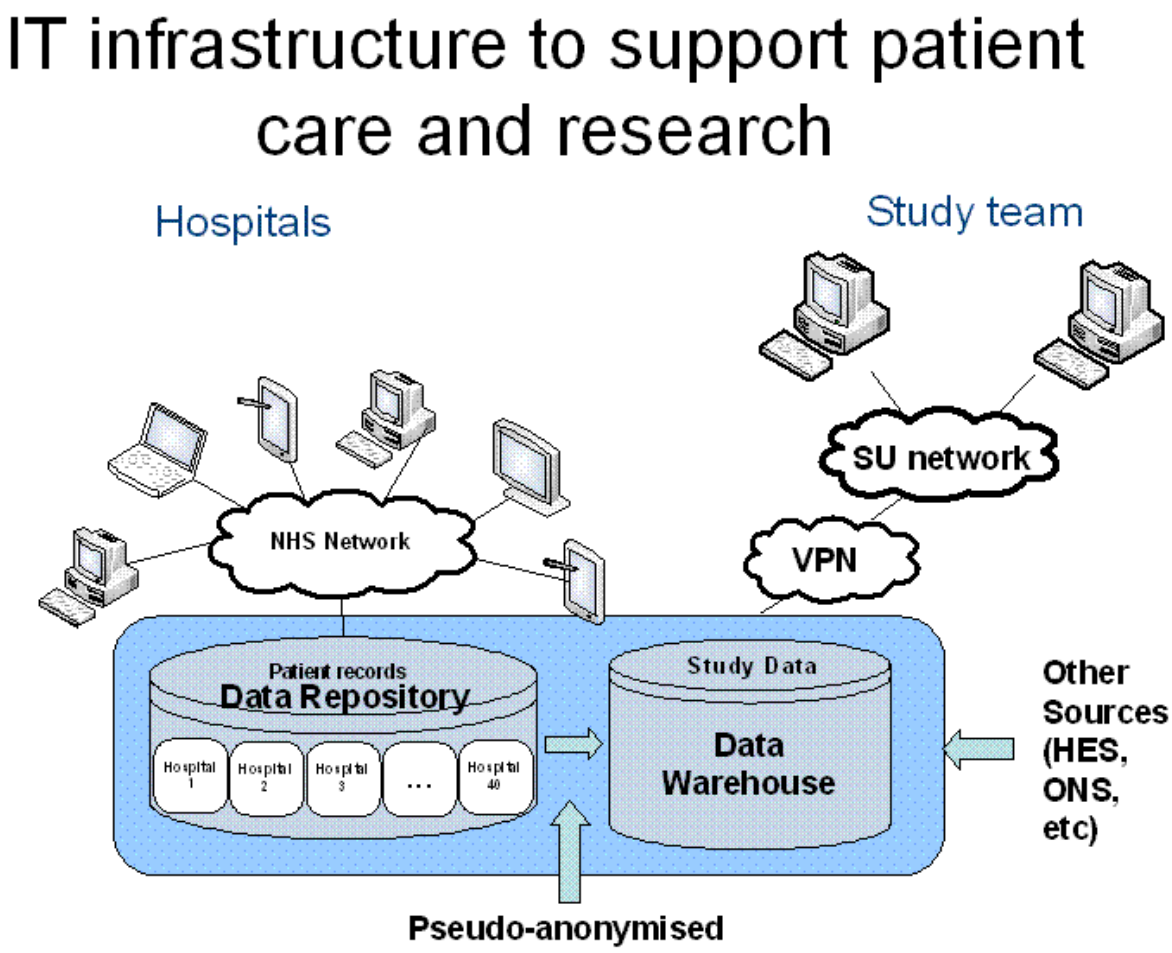
The database administrator is required to have access to all areas of the system for the purposes of technical system support and maintenance, but is not involved in the conduct of the study. The study has relevant standard operating procedures on staff confidentiality responsibilities and all staff 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 are conducted by an experienced qualitative researcher. Qualitative data is 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, Sandimmun and 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 receive either Remicade or Sandimmun followed by 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

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 and 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;55:749-53.
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. *Unit Costs of Health and Social Care*. Canterbury: University of Kent, 2010.
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. Williams R, Rapport F, Tudor Hart J, Elwyn G, Lloyd B, Rance J, et al. The prevention of type 2 diabetes:general practitioner and practice nurse options. *British Journal of General Pratice* 2004;54:531-35.
26. Truelove S, Witts L. Cortisone in ulcerative colitis: final report on a therapeutic trial. *BMJ* 1955;2:1041-8.
27. 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.
28. Park K. Cancer of the oesophagous or gastricus: new assessment of the technology of endosonography (COGNATE) NIHR HTA 01/01/03, 2011-in editorial review.

29. Russell I. Folate Augmentation of Treatment - Evaluation of Depression: a randomised controlled trial, NIHR HTA 04/35/08, 2011-in editorial review.
30. Efron B, Tibshirani R. *An Introduction to the Bootstrap*. NewYork: Chapman and Hall, 1993.
31. 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.
32. The Medicines for Human Use (Clinical Trials) Regulations 2004. *Statutory Instrument No 1031*: HMSO, 2004.
33. MRC. Guidelines for Good Clinical Practice in Clinical Trials. *MRC Clinical Trials Series*. London: MRC, 1998.
34. Department of Health. Research Governance Framework for health and social care. Second ed. London, 2005.
35. Scottish Executive Health Department. Research Governance Framework for Health and Community Care, 2006.
36. Department of Health Social Services and Public Safety. Research Governance Framework for Health and Social Care. Northern Ireland, 2002.

APPENDIX 1

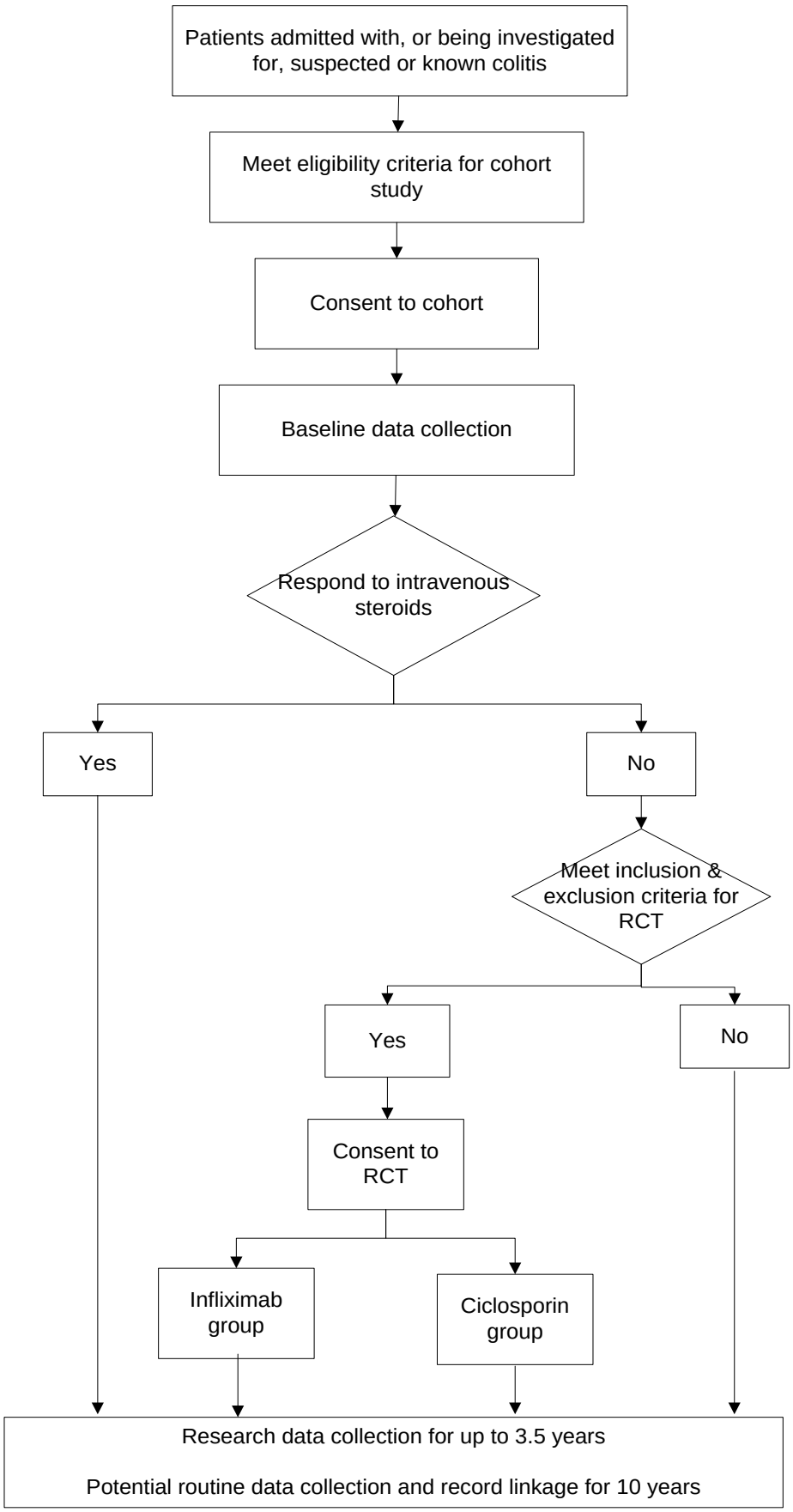
Potential study sites

Abertawe Bro Morgannwg University Health Board (Singleton, Morriston, Neath Port Talbot)
Addenbrooke's Hospital, Cambridge
Aneurin Bevan Health Board (Royal Gwent Hospital)
Barking, Havering and Redbridge Hospitals NHS Trust (King George and Queen's Hospitals)
Barnet & Chase Farm Hospitals NHS Trust
Barts and The London NHS Trust
Basildon and Thurrock University NHS Foundation Trust
Belfast Health & Social Care Trust, Northern Ireland
Blackpool Teaching Hospitals NHS Foundation Trust
Bradford Teaching Hospitals NHS Foundation Trust
Central Manchester University Hospitals NHS Foundation Trust (Manchester Royal Infirmary)
Chelsea & Westminster NHS Foundation Trust
Chesterfield Royal Hospital NHS Foundation Trust
City Hospitals Sunderland NHS Foundation Trust
Colchester Hospital University NHS Foundation Trust
Countess of Chester Hospital NHS Foundation Trust
Croydon Health Services NHS Trust (Mayday Hospital)
Derby Hospitals NHS Foundation Trust
Dewsbury District Hospital , Dewsbury
Doncaster & Bassetlaw Hospitals NHS Foundation Trust
Dorset County Hospitals NHS Foundation Trust
Dudley Group of Hospitals
East Sussex Healthcare NHS Trust (Conquest Hospital)
Frimley Park Hospital NHS Foundation Trust
Gateshead Health NHS Foundation Trust (Queen Elizabeth Hospital)
Gloucestershire Hospitals NHS Foundation Trust
Harrogate & District Foundation NHS Trust
Heart of England NHS Trust
Hinchingbrooke Healthcare NHS Trust
Hull & East Yorkshire Hospitals NHS Trust
Imperial College Healthcare NHS Trust (St Mary's Hospital)
James Paget University Hospital NHS Foundation Trust
Kings College Hospital, London
Kingston Hospital NHS Foundation Trust
Lancashire Teaching Hospitals
Leeds Teaching Hospitals NHS Trust (Leeds General Infirmary)
Leighton Hospital, Crewe, Cheshire
Lewisham Hospital NHS Trust
Llandough Hospital
Luton & Dunstable Hospitals NHS Foundation Trust
Maidstone & Tunbridge Wells NHS Trust
Newcastle upon Tyne Teaching Hospitals NHS Foundation Trust (Royal Victoria Infirmary and Freeman Hospital)
NHS Greater Glasgow & Clyde (Glasgow Royal Infirmary)
NHS Forth Valley (Stirling Royal Infirmary)
NHS Highland (Raigmore Hospital)
NHS Lanarkshire (Wishaw Hospital)
NHS Lothian (Western General Hospital)
Norfolk and Norwich University Hospitals NHS Foundation Trust
North Bristol NHS Trust

North Cumbria University Hospitals NHS Trust
North Tees and Hartlepool NHS Foundation Trust (University Hospital of North Tees)
North West London Hospitals NHS Foundation Trust (St Mark's Harrow)
Nottingham University Hospitals NHS Trust
Oxford Radcliffe Hospitals NHS Trust
Northumbria Healthcare Trust
Pennine Acute Hospitals NHS Trust
University Hospitals Birmingham NHS Foundation Trust (Queen Elizabeth Hospital)
Rotherham NHS Foundation Trust
Royal Berkshire Hospital NHS Foundation Trust
Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust
Royal Devon & Exeter NHS Foundation Trust
Hampshire Hospital NHS Foundation Trust (Royal Hampshire County Hospital)
Royal Liverpool & Broadgreen University Hospitals NHS Trust
Shrewsbury and Telford Hospital NHS Trust (Royal Shrewsbury Hospital)
Brighton and Sussex University Hospitals NHS Trust (Royal Sussex County Hospital)
Salford Royal NHS Foundation Trust
Sandwell and West Birmingham Hospitals NHS Trust
Scarborough and North East Yorkshire NHS Trust (Scarborough Hospital)
Sheffield Teaching Hospitals NHS Foundation Trust (Royal Hallamshire Hospital)
Sherwood Hospitals NHS Foundation Trust (King's Mill Hospital)
South Devon Healthcare NHS Foundation Trust (Torbay Hospital)
South London Healthcare NHS Trust (Princess Royal & Queen Elizabeth Hospitals)
South Tees Hospitals NHS Foundation Trust (James Cook University Hospital)
South Tyneside NHS Foundation Trust
Southport & Ormskirk Hospitals NHS Trust
Stockport NHS Foundation Trust (Stepping Hill Hospital)
St George's Healthcare Trust, London
Tameside Hospital NHS Foundation Trust
Taunton and Somerset NHS Trust (Musgrove Park Hospital)
The Lewisham Hospital NHS Trust, London
The Royal Wolverhampton Hospitals NHS Trust (New Cross Hospital)
University College London Hospitals NHS Foundation Trust
University Hospitals Coventry and Warwickshire NHS Trust
University Hospital of North Durham
University Hospital of North Staffordshire NHS Trust
University Hospital of South Manchester (Wythenshawe Hospital)
University Hosp of Wales Cardiff
University Hospitals Bristol NHS Foundation Trust
University Hospitals of Leicester NHS Trust (Leicester Royal Infirmary and Leicester General Hospital)
Universith Hospital of South Manchester
University Hospital Southampton NHS Foundation Trust
Warrington & Halton Hospitals NHS Foundation Trust
West Middlesex University Hospital NHS Trust
Western Sussex Hospitals NHS Trust (Worthing Hospital)
Weston Area Health NHS Trust (Weston General Hospital
Wrightington, Wigan and Leigh NHS Foundatin Trust (Royal Albert Edward Infirmary)
Wye Valley NHS Trust
Yorkshire Hospitals NHS Foundation Trust

APPENDIX 2

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.

Scoring based on endoscopic appearance
(part of Mayo clinic score and 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

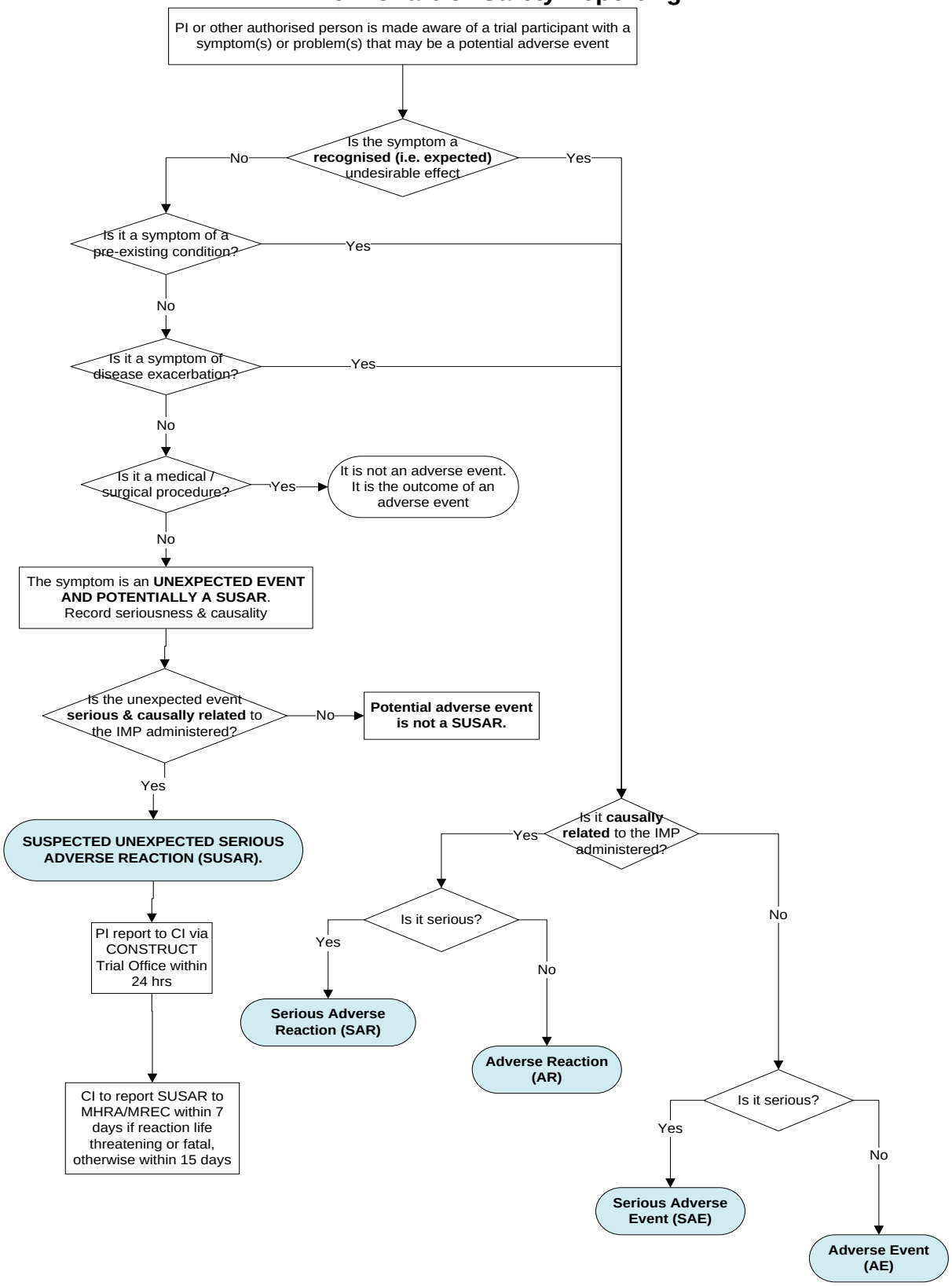
Vulnerable Groups

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



AE reporting flowchart V1-3 080310

construct
building the evidence

Adverse Event (AE) Screening Form

www.construct.swansea.ac.uk

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

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

PLEASE COMPLETE THIS FORM IF THE PARTICIPANT HAS ANY NEW SIGNS OR SYMPTOMS OR A COLECTOMY

Start date:	*d*	*d*	*m*	*m*	*y*	*y*	**Start time:**	*h*	*h*	*m*	*m*	***(or Duration):***	
End date:	*d*	*d*	*m*	*m*	*y*	*y*	**End time:**	*h*	*h*	*m*	*m*		

Event description *(please give as much detail as possible):*

Severity:			**Outcome:**		
	Mild			Complete resolution	
	Moderate			Persisting problem	
	Severe			Irreversible consequences:	Surgery required
Trial drug:				*(please state which one)*	Death
	Remicade®				Other *(please specify)*
	Sandimmun®			Unknown	
	Neoral®			Other *(please specify)*	

QUESTIONS TO DETERMINE THE "EXPECTEDNESS" OF THE ADVERSE EVENT:

*"Yes" should only be ticked for **ONE** of the four questions below. As soon as a "Yes" has been ticked, complete the seriousness and causality categories overleaf.*

1) Is the symptom/problem a known, undesirable effect of the trial drug, *please check the Summary of Product Characteristics (SPC)*, in terms of its nature and severity?

☐ **Yes**
☐ **No**

If Yes, please turn over, if No go to Question 2

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

NOTE: 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, select "No"

☐ **Yes**
☐ **No**

If Yes, please turn over, if No go to Question 3

3) Is the symptom/problem in keeping with an exacerbation or progression of the underlying disease (ulcerative colitis)?

NOTE: If the problem resulted in surgery/colectomy, please answer "No" and go to Question 4.

☐ **Yes**
☐ **No**

If Yes, please turn over, if No go to Question 4

4) Is the event a medical or surgical procedure e.g colectomy/colonoscopy?

☐ **Yes**
☐ **No**

Whether Yes or No, please turn over

Please turn over for further instructions

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

****

If you have selected "Yes" for any of the earlier questions (1 – 4) *the adverse event is expected and, by definition, cannot be a SUSAR. Please complete the seriousness and causality categories below for the "expected" event, sign the form and fax to the CONSTRUCT Trial Office:*

Relation to trial drug (causality)

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

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)

If you have selected "No" for all of the earlier questions (1 – 4) *the adverse event is unexpected and could be a SUSAR. Please complete the seriousness and causality categories below for the "unexpected" event:*

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)

If causality = 3, 4 OR 5 AND seriousness = 1, 2, 3, 4 OR 5, the event is a **Suspected Unexpected Serious Adverse Reaction (SUSAR).**

You MUST now complete a SUSAR Report Form and send both the AE Screening and SUSAR Forms to the CONSTRUCT Trial Office within 24 hours of becoming aware of the event. Please refer to the Fieldwork Handbook for further instructions.

If the unexpected event is either not serious, not related or both, only fax the completed AE Screening Form as the event is not a SUSAR.

Name of person completing this form:		Signature:		Date form completed:	
Name of counter signatory:		Signature:		Date of countersignature:	

Once completed, please fax this form to the CONSTRUCT Trial Office on 01792 606599 as soon as possible.

CONP12 AE Screening Form v3-1 16May2012

SUSAR Report Form

Email: CONSTRUCTHelpdesk@swansea.ac.uk **Fax: 01792 606599**

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: CONSTRUCTSUSAR@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 at the follow up reporting period 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:	COmparison of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: a Trial
Study centre (Trust):	
Study site (hospital):	
R&D No:	
Ethics No:	08/MRE09/42
EudraCT No:	2008-001968-36

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 <u>outside</u> of the last 3 months *(medication within 3m is classed as concomitant)*

Drug name	**Start date**	**End date**

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 (including severity):

Seriousness

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

Details of medical tests undertaken relevant to SUSAR

Test	**Result**	**Unit**	**Test date**

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 same format as CTA application)*			
Drug characterisation *(suspect / concomitant)*			
Drug dosage			
Drug dose interval			
Form *(e.g. capsule, 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			

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

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 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 the initial or previous report)	
☐ Resolved ☐ Ongoing ☐ 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 to the person in Section 6)		
Name:		
Job title/role in the study:		
Contact address:		
Email address:		
Telephone No:		
Signature:		Date:

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 – MHRA REC*	Each year submitted to main REC**	End of the study, the CI will send report*** to Sponsor MHRA 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