CONSTRUCT DMEC charter

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Revision History

Date	Summary of changes	Author	Version
19/12/08	Creation of DMEC charter	KT	1-0
22/12/08	Amendment of DMEC charter following TMG 19/12/08	KT	1-1
03/01/09	Addition of Chris Probert as DMEC member	KT	1-2
26/01/09	Amendment of charter following DR amendments of v1-2	KT	1-3
26/08/09	Amendment of charter in line with DMEC action points	KT	1-4
16/09/09	Addition of revised draft tables as Annex 4	KT & DR	2
11/08/10	Addition of patient representative detail, removal of DR as statistician and amendments to Introduction to clarify patients in cohort.	KT	2-1
22/10/12	Amendment of Section 3. Introduction, to reflect updated protocol v3.3; Amendment of Section 4. DMEC Composition, to include statistician. Removal of WYC as Construct Outcomes Measures Specialist, and inclusion of HH. Removal of KT as Trial Information and Quality Data Manager, and Inclusion of MG. Inclusion of AW as Trial Statistician.	MG	3-0

Distribution details

Date	Version circulated	Distribution list
26/01/09	V1-3	DMEC members as listed in V1-3
27/08/09	V1-4	DMEC members, DR and WYC
16/09/09	V2-0	DMEC members, DR & WYC
	V2-1	DMEC members, DR & WYC
24/10/12	V3-0	DMEC members and AW

CONTENTS

1. Document history

This document has been drafted using the DAMOCLES template located on the University of Aberdeen Health Services Research Unit website (http://www.abdn.ac.uk/hsru/documents/damocles-charter.doc). It has been modified to suit the requirements of the CONSTRUCT trial.

2. Abbreviations used

Abbreviation	Full text
CI	Chief Investigator
DMEC	Data Monitoring and Ethics Committee
PI	Principal Investigator
RCT	Randomised Controlled Trial
T&W	Truelove & Witts
TMG	Trial Management Group
TSC	Trial Steering committee
UC	Ulcerative Colitis

3. Introduction

The purpose of this document is to describe the roles and responsibilities of the independent Data Monitoring and Ethics Committee (DMEC) for the CONSTRUCT trial, including the timing, frequency and format of meetings, methods of providing information to and from the DMEC, statistical issues and relationships with other committees.

The CONSTRUCT study

- Comparison of iNfliximab and ciclosporin in Steroid Resistant Ulcerative Colitis: a Trial (CONSTRUCT)
- Sponsor's name & number – Swansea University, RIO 031-08
- EudraCT number – 2008-001968-36
- ISRCTN – ISRCTN22663589

The CONSTRUCT study comprises a cohort and an embedded two-arm, multicentre, pragmatic randomised controlled trial (RCT) involving 67 centres in the UK. Inpatients admitted with suspected or known colitis will be recruited to the cohort, over a one year period (to include 1400 participants by the end of 2012). Cohort participants with acute severe ulcerative colitis (UC) who fail to respond to treatment using two to five days intravenous steroids but do not, at the time of entry to the trial, require surgery, will be recruited to the RCT. Consenting RCT patients will be randomised to either infliximab (prescribed as Remicade®) or ciclosporin (prescribed as Sandimmun® and Neoral®), with 125 patients in each of the two arms.

Data on all patients (cohort and RCT) will be collected using a centralised securely hosted clinical information system, supplemented by record linkage of electronically held routine data. Designed research data collection will continue for two years on all patients. Operational clinical data collection, routinely collected data and record linkage will then continue for the following eight years on all patients.

The overall aim of this trial is to compare the clinical and cost effectiveness of Remicade (Infliximab) and Sandimmun/Neoral (Ciclosporin) for patients with steroid resistant UC. Specific objectives are to:

- Compare QoL across the two treatment groups (Remicade and Sandimmun/Neoral)
- Compare mortality, disease activity and morbidity across the two treatment groups
- Compare emergency colectomy rates across the two treatment groups
- Investigate the views of patients regarding treatments
- Compare cost effectiveness of the two treatments in terms of lifetime cost per quality-adjusted life-year, initially using primary data from the two years of trial and eventually using 10 year follow up data from the cohort

A further objective of the CONSTRUCT cohort study is to establish comprehensive long-term data collection using a web-based clinical information system to enable further research questions to be answered regarding clinical progress and outcome following treatment with acute severe UC.

However the DMEC will not have responsibility for the cohort study, and cohort data will only be reported as it affects recruitment to the trial.

4. DMEC Composition

The DMEC will consist of at least three members, including a statistician and a clinician. The members should be independent of the trial (e.g. should not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, should be declared. A short competing interest form (see Annex 1) should be completed and returned by the DMEC members to Mrs Michelle Grey (details overleaf) as soon as possible.

The members of the DMEC for the CONSTRUCT trial are:

NAME	Title	Email	Tel. number
Prof Tim Peters (chair)	Professor of Primary Care Health Services Research	tim.peters@bristol.ac.uk	0117 331 3834
Prof Stirling Bryan	Associate Director, Centre for Clinical Epidemiology and Evaluation	stirling.bryan@ubc.ca	604 875 4776
Prof Phil Routledge	Professor of Clinical Pharmacology	routledgepa@cardiff.ac.uk	029 2074 2051
Prof Chris Probert	Professor of Gastroenterology at Bristol Royal Infirmary	Chris.Probert@liverpool.ac.uk	01517 954010
Peter Canham	Crohn's & Colitis UK Patient Involvement Adviser	petercanham@pca.org.uk	01697 352689
Reporting to the DMEC on behalf of the CONSTRUCT trial team:			
Dr Alan Watkins	CONSTRUCT Trial Statistician	A.Watkins@swansea.ac.uk	01792 295853
Mrs Michelle Grey	CONSTRUCT Trial Information and Quality Manager	M.K.Grey@swansea.ac.uk	01792 602062
Dr Hayley Hutchings	CONSTRUCT Outcome Measures Specialist	H.A.Hutchings@swansea.ac.uk	01792 513412
plus any other members of the trial team requested by the DMEC			

The DMEC members were approved and invited by the CONSTRUCT Trial Management Group (TMG). The Chair, Prof. Peters, has previous experience of serving on DMECs and experience of chairing meetings, and will be required to facilitate and summarise discussions. Prof. Peters, will also act as the DMEC statistician.

The CONSTRUCT trial statistician, Dr Watkins, will produce or oversee the production of the report to the DMEC. He will also participate in DMEC meetings, guiding the DMEC through the report, participating in DMEC discussions as requested by the DMEC and, on some occasions, taking notes. The Trial Outcome Specialist, Dr Hutchings, may assist or replace Dr Watkins for a particular meeting if the DMEC agrees.

Mrs Grey, the Trial Information and Quality Manager, will attend all DMEC meetings to observe discussions and take notes where appropriate. Where the DMEC require unblinded data, Mrs Grey will be the only person allowed to unblind the data so as not to compromise the analysis of the final dataset by the statistician. She will also contribute to the production of the non-confidential sections of the DMEC report and will disseminate reports from the DMEC to the TMG where necessary.

At any time during the meeting, the DMEC may require Dr Watkins, Mrs Grey or both to leave. If neither is present, the DMEC chair is responsible for any internal note-taking or minutes they consider necessary.

All electronic / written correspondence between the DMEC and the CONSTRUCT trial should be directed in the first instance to Mrs Grey using the following contact details:

Tel: 01792 602062; Fax 01792 606599; email: m.k.grey@swansea.ac.uk;
Postal address: Biobank Suite, Room 244, Grove Building, School of Medicine, Swansea University, Singleton Park, Swansea SA2 8PP.

The Chief Investigator, Prof John Williams, may be asked, and should be available, to attend open sessions of the DMEC meeting. Other specialists within the team (e.g. health economist) may also be asked to attend or give written responses to particular queries.

5. Roles and responsibilities

The aim of the committee is to safeguard the interests of CONSTRUCT trial participants, assess the safety and effectiveness of the interventions during the trial, to advise the trial team so as to protect the validity and credibility of the trial, and to monitor the overall conduct of the trial.

5.1. Terms of reference

The DMEC will receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).

The DMEC should inform the Chair of the TSC if, in their view, the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there is a reasonable expectation that this new evidence would materially influence patient management

The DMEC's interim reviews of the trial's progress will include updated figures on recruitment, data quality, and main outcomes and safety data. More specifically, they will:

- assess data quality, including completeness (and by so doing encourage collection of high quality data)
- monitor recruitment figures and losses to follow-up
- monitor compliance with the protocol by participants and investigators
- monitor evidence for treatment differences in the main outcome measures
- monitor evidence for treatment harm (e.g. serious adverse events)
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some participant subgroups
- suggest additional data analyses
- advise on protocol modifications suggested by investigators or sponsors (e.g. to inclusion criteria, trial endpoints, or sample size)
- monitor planned sample size assumptions
- monitor continuing appropriateness of patient information
- monitor compliance with previous DMEC recommendations
- consider the ethical implications of any recommendations made by the DMEC
- assess the impact and relevance of external evidence assembled by members of the trial team

6. Before or early in the trial

All potential DMEC members will have sight of the protocol and the DMEC charter before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor, scrutiny by other trial committees and a research ethics committee. Therefore, if a potential DMEC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the trial office and may decide not to accept the invitation to join. DMEC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

The DMEC will meet before the trial starts to discuss the protocol, the trial, analysis plan and future meetings, and to have the opportunity to clarify any aspects with the trial team. The DMEC should meet again within one year of recruitment commencing.

7. Issues specific to the trial or treatments

UC is a chronic debilitating disease that affects approximately 150,000 people in the UK. 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. Thus the condition being treated is acute and life threatening.

Infliximab and ciclosporin are two immunosuppressive agents that offer hope for the treatment of steroid resistant UC. There is evidence that both are 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. Nevertheless some deaths and a substantial number of adverse reactions to both drugs will be expected. This is a pragmatic trial, and analysis will be by intention-to-treat. This is particularly important when, as here, treatment may be withdrawn or changed for a substantial minority of participants.

The primary outcome is patient quality of life. Details of all secondary outcomes are listed in Annex 4 (taken from the CONSTRUCT Protocol v3-3). This annex supersedes Annex 3 which was described in charter V2-0, although Annex 3 has been retained in this charter for information.

In this trial:

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

Infliximab is licensed for the treatment of patients with steroid resistant UC in patients receiving oral steroids. Ciclosporin is not licensed for the treatment of steroid resistant UC but is used for the treatment of that condition.

The trial includes health economic outcomes, including cost effectiveness. Thus even if no difference in effectiveness is found between the two treatments, the trial may still result in a clear distinction between treatments.

8. Relationships with other bodies

The DMEC is completely independent of the CONSTRUCT TSC, sponsor, study PIs and other regulatory bodies such as ethics committees and the MHRA. It does not make decisions about the trial, but rather makes recommendations to the chair of the TSC (and TMG in some cases).

Members will be reimbursed for travel and accommodation. Queries about expenses claims should be directed to Mrs Grey in the first instance.

Competing interests should be disclosed using the proforma contained in Annex 1. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility.

DMEC members should not use interim results to inform trading in pharmaceutical shares, and should not trade in stock of companies affected by the trial until the results are published knowledge.

9. Organisation of DMEC meetings

The DMEC will meet before the trial starts, and again within six months of starting recruitment. The exact frequency of subsequent meetings will be determined by the DMEC, but will normally be at least once a

year. The wishes of the DMEC and needs of the trial office will be considered when planning each meeting. DMEC meetings will in general be scheduled a few weeks before meetings of the Trial Steering Committee, to which the DMEC will submit its report and recommendations.

All meetings should be face-to-face if possible, with teleconference as a second option. Since one of the CONSTRUCT DMEC members is located in Canada, he will be allowed access to all meetings via teleconference to make his contributions.

Anyone attending the meeting remotely by teleconference is required to email any relevant documents to the DMEC chair and Mrs Grey **one week** before the meeting.

Meetings may consist of a mixture of open and closed sessions. There will be three levels of categorisation of sessions as follows:

> **Level 1** – **Open session.** Open to all invited CONSTRUCT TMG personnel.
> **Level 2** – **Semi-closed session.** Open only to AW, MG and HH (or other appropriate TMG members depending on the topic being discussed).
> **Level 3** – **Closed session.** Only DMEC committee members to attend. This excludes AW, MG and HH unless they are specifically invited to closed sessions.

Any TMG members present will treat DMEC meetings as strictly confidential and not discuss them with any other TMG member not invited. Information about recruitment, data quality and aggregated outcomes and safety data will usually be discussed in open sessions.

10. Trial documentation and procedures to ensure confidentiality and proper communication

Accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented. Safety data based on pooled data will be presented and overall outcome data (numbers of events, or averages of scale measures) may also be presented, at the discretion of the DMEC.

In addition to all the material available in the open and semi-closed sessions, the closed session material will include safety data and limited outcome data by treatment group. DMEC members will view blinded data produced by the trial statistician. Where they require the codes facilitating the blinding to be "broken", Mrs Grey will produce the codes to allow unblinded access in a closed session in the absence of the trial statistician.

Only the DMEC members will see the full range of accumulating data and interim analysis.

DMEC members do **not** have the right to share confidential information with anyone outside the DMEC, including the CI.

Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the DMEC members. Mrs Grey will be required to do this.

The DMEC will receive the report at least two weeks before any meetings. The report and all other relevant documentation will be circulated by Mrs Grey.

The DMEC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMEC members should destroy all interim reports.

11. Decision making

Possible recommendations could include:-

- No action needed, trial continues as planned

- Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence
- Stopping recruitment within a subgroup
- Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up
- Sanctioning or proposing protocol changes

The DMEC should review and agree any interim analysis plans. The approved draft tables will be saved within the charter as Annex 4.

11.1. The role of formal statistical methods

As the trial outcomes include survival, some interim comparative analysis will be needed to inform DMEC decisions, but in the first instance this will not be as complex as that planned for the final trial results. The analyses to be used will be specified at the first DMEC meeting, but are likely to include cumulative comparisons of mortality and colectomy rates.

If the initial comparisons indicate that more information is needed, the DMEC may ask for further interim analyses. These, like the initial comparisons, will use dummy allocation codes to preserve blindness of both DMEC and analysts. If the DMEC requires unblinding before making a decision, Mrs Grey will reveal the unblinding codes.

Formal statistical methods are more generally used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Thus **no specific stopping guideline** for the trial has been laid down in advance. However, in general, recommendations should be consistent with the statistical evidence (e.g. if based on an imbalance in outcome, that outcome should be unlikely to have arisen by chance).

11.2. How decisions will be reached

The role of the Chair should be to summarise discussions and encourage consensus; thus in each area of discussion the Chair should usually give their own opinion last.

Every effort should be made for the DMEC to reach a unanimous decision. If the DMEC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data.

It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made.

Effort should be made for all members to attend. The trials office team will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference.

If, at short notice, any DMEC members cannot attend at all then the DMEC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. There should be at least three attendees present for the DMEC to proceed to decision-making.

If the DMEC is considering recommending major action after such a meeting the DMEC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMEC.

If the report is circulated before the meeting, DMEC members who will not be able to attend the meeting may pass comments to the DMEC Chair for consideration during the discussions.

If a member does not attend a meeting, they should be available for the next meeting. If that member does not attend a second meeting, they will be asked if they wish to remain part of the DMEC. If they do not attend a third meeting, they will be replaced.

12. Reporting

The DMEC will report its recommendations in writing to the TSC chair within two weeks. Where appropriate, this should be copied to Mrs Grey, who will disseminate the findings at the next CONSTRUCT TMG.

The minutes will be taken by Mrs Grey for open sessions and by a nominated member of the DMEC for closed sessions. Separate records will be held for open and closed sessions. Minutes from closed sessions will not be disseminated outside the DMEC unless there are exceptional circumstances. The DMEC Chair should sign off any minutes or notes.

If the DMEC has serious problems or concerns with a TSC decision, a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMEC's concerns. Depending on the reason for the disagreement, confidential data may have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial.

13. After the trial

At the end of the trial there may be a meeting to allow the DMEC to discuss the final data with principal trial investigators/sponsors and give advice about data interpretation and publication. The DMEC may wish to see a statement that the trial results will be published in a correct and timely manner.

DMEC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMEC meetings should be included in the body of this paper.

The DMEC may wish to be given the opportunity to read and comment on any publications before submission.

Members of the DMEC may only discuss issues from their involvement in the trial 12 months after the primary trial results have been published, or when permission is agreed with the overseeing committee.

12. Appendices

Annex 1: Competing interest form

Potential competing interests of Data Monitoring and Ethics Committee members for the *CONSTRUCT Trial (RIO 031-08)*

The avoidance of any perception that members of a DMEC may be biased in some fashion is important for the credibility of the decisions made by the DMEC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMEC member should remove the conflict or stop participating in the DMEC. Table 1 lists potential competing interests.

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Frequent speaking engagements on behalf of either of the interventions
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in either of the trial arms
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following section and return to the trials office.

☐ **No,** I have no competing interests to declare
☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests: _____

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Annex 2: Summary of suggested DMEC report contents

1. Recruitment

By centre and overall:

- Cumulative recruitment and recruitment in the most recent time period
- Reasons for exclusion
- Withdrawals split according to treatment group (full – all aspects of data collection or partial – QoL questionnaire data collection only). Reports will refer to both the treatment phase and at follow-up.
- A CONSORT diagram will be used to illustrate recruitment for the trial by centre and overall.

2. Randomisation

To include details of how randomisation is proceeding.

3. Data Quality

Questionnaires:

- Interviews scheduled, completed, missed at each time point
- Individual measures within interviews – missing answers (quality of life and health economic separately)

Clinical (GeneCIS) records:

- Identification process
- Treatment phase (including compliance with treatment protocol)
- Main outcomes
- Trial endpoints

4. Outcomes

Overall (open, by centre) and by treatment (closed – dummy group allocations):

- number (%) of deaths; emergency colectomies; other trial endpoints

QoL overall (open) and by treatment (closed – dummy group allocations):

- SF-12v2, EQ-5D, UK-IBDQ scores, (mean, SD, n) at baseline and follow-ups. All data to be used in calculating the QoL scores for patients will also be reported.

5. Adverse events (some of these will overlap with outcomes)

Overall (open, by centre) and by treatment (closed – dummy group allocations; also by centre if overall shows a difference):

- Reported Suspected Unexpected Serious Adverse Events (SUSARs) in detail
- Other reported adverse reactions, by category (number, %)
- number (%) of documented adverse events during treatment, adverse reactions (including separately those that result in treatment withdrawn)

Basic statistical tests will be done, and any significant imbalances reported.
All tests will have estimates, confidence intervals and p-values accompanying them in the reports.

Annex 3: List of primary and secondary outcome measures to be reported by CONSTRUCT (as recorded in the CONSTRUCT Protocol v21)

Outcome measures

a) The primary outcome measure will be **QoL** measured at 24 months using the disease-specific UK-IBDQ questionnaire.

b) The generic SF-12 and EQ-5D QoL questionnaires will be secondary outcome measures. All three questionnaires will be administered at baseline and at three, six, 12, 24 months.

Other secondary outcome measures will be:

c) **Emergency and planned colectomy**; colectomy may be undertaken based on clinical judgement and patient agreement. The separate incidences of emergency and elective colectomy will be measured up to two years post-admission.

d) **Mortality** at 24 months.

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

f) **Incidence of malignancies**; colorectal malignancies, other GI malignancies, other malignancies.

g) **Incidence of serious infections during treatment;** bacterial infections, pneumonia, abscess, other serious infections.

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

i) **Incidence of new symptoms during or attributable to treatment;** from among those listed as potential side effects in Summary of Product Characteristics for the drugs.

j) **Overall incidence of adverse events:** grouped according to their classification as SUSARs, SARs, SAEs, ARs or AEs. These will include those described in c – i above.

k) **Disease activity**; measured by Truelove and Witts criteria. Full blood count, inflammatory markers and albumin will be measured at baseline and at three, six, 12 and 24 months.

l) **Quality-adjusted survival**; to combine the effects of QoL and mortality, will be measured up to two years follow-up and then modelled for lifetime Quality-Adjusted Life Years.

m) **Total NHS costs**; measured up to two years follow-up. These will be combined with quality-adjusted survival in the economic analysis.

n) **Patient borne costs**; including number of days off work per year and travel costs for health care, up to two years follow-up. These will be reported separately from the NHS costs and will not be included in the cost utility estimates.

o) **Patient views**; elicited through telephone interviews, following discharge from hospital at approximately two to three and six to eight months into follow-up. These will be conducted for 24 patients, 12 (5%) in each of the two treatment arms.

Annex 4: Dummy tables (v1.2 - revised following DMEC meeting 090909)

RECRUITMENT

Table 1 Recruitment and progress of centres

Number of centres that have reached:	**Date1 (last reported)**	**Date2 (now)**
Full trial		
Pilot phase		
Set-up (approval obtained)		
Seeking ethical approval		
Considering/negotiating participation		
Total		

Table 2 Recruitment of participants

Centre	**Date**		**Number randomised**		**Rate per month**		**Projected at end trial**
	Start pilot	**Start full trial**	**Recent** (past 3mth)	**Total**	**Recent** (past 3mth)	**Since started**	
1. XXXXXXXX 2. YYYYYYYY etc							
All live centres	**---**	**---**					

Figure 1: Recruitment graph (all centres combined: cumulative number of participants randomised by time since start of trial; reference line of number required to reach target if recruit at constant rate)

Table 3 Exclusions, withdrawals and deaths

	Number (%) by Date1	**Number (%) by Date2**
Identified as potential participants: steroids started	a	a
Status interim: still potentially eligible	b	b
Identified (status resolved)	**c=a-b**	**c=a-b**
Responded to IV steroids	d (% of c)	d (% of c)
Emergency colectomy	e (% of c)	e (% of c)
Failed other eligibility (inclusion/exclusion) criteria	f (% of c)	f (% of c)
Refused consent	g (% of c)	g (% of c)
Randomised	**h (% of c)**	**h (% of c)**
Withdrawn (full)	i (% of h)	i (% of h)
Withdrawn (partial)[#]	j (% of h)	j (% of h)
Died (not withdrawn)	k (% of h)	k (% of h)
Alive and not withdrawn	l (% of h)	l (% of h)

NB: d-g are not eligible, d+e+f+g+h=c; i+j+k+l=h. i and j may include patients who subsequently died.
#: Partial withdrawal is from patient-assessed QoL/resource use only (continue collection of other data).

Figure 2: Current CONSORT Diagram (includes extra path for interim status. Final full CONSORT Diagram will include withdrawals and deaths during each of the 5 follow-up periods)

DATA QUALITY

Table 4 QoL/resource use questionnaires possible to date, and those which took place.

	Withdrawn therefore missed	Died or q're prior to death missed	Number missed for other reasons	Still pending	Number complete	Total possible *(excluding pending)*	% complete
Baseline							
Three month							
Six month							
One year							
18 months							
2 years							
Total							

Table 5 QoL/resource use questionnaires possible, and those which took place, by centre.

Centre *(Any time point)*	Number complete	Total possible	% complete
1. XXXXXXXX...			
2. etc			
Total			

Table 6 QoL/resource use questionnaires: missing items.

	Number of questionnaires	Number (mean) UK-IBDQ items missing	Number (%) with at least one UK-IBDQ item missing	Number (%) with at least one EQ-5D item missing	Number (mean) resource use items missing	Number (%) with at least one resource use item missing
Baseline						
Three month						
Six month						
One year						
2 years						
Total						

DEMOGRAPHIC AND BASELINE COMPARISONS

Table 7 Demographic and baseline characteristics by treatment group (coded).

Number (%) unless stated	**Group A**	**Group B**	**Whole sample**
Male			
Baseline QoL measures:			
Mean (sd) min, max			
UK-IBDQ (range 0-100, 0 good):			
Dimension 1			
Dimension 2			
Dimension 3			
Dimension 4			
Dimension 5			
Global (average)			
EQ-5D			
Euroqol VAS			
SF-12: physical			
SF-12: mental			
Total			

NOTE: UK-IBDQ dimensions and global measure (if any) may change after pre-pilot and development work

OUTCOMES

Table 8 Survival by treatment group (coded).

Number (%)	**Status**		**Total**		**Survival analysis**
	Alive	**Dead**		**Significance**	**Hazard ratio (95% CI)**
Group A					
Group B					
Total					

Note: the trial has no formal stopping rule, but significance levels are included to inform DMEC judgement

Figure 3: Survival by allocation group (two survival curves on one graph, all centres combined)

Table 9 Emergency colectomy and other incidences by treatment group (coded).

Number (%)	**Group A**	**Group B**	**Total**	**Relative risk (95% CI)**	**Significance level**
Emergency colectomy					
Elective colectomy					
Malignancy					
Readmission					
During treatment:					
Serious Infections					
Renal disorders					
New symptoms					
Treatment stopped/changed					
Total					

Note: the trial has no formal stopping rule, but significance levels are included to inform DMEC judgement

Table 10 UK-IBDQ (primary outcome measure) at baseline and follow-up by treatment group (coded): responses by survivors.

	Number A, B	A: mean (sd)	B: mean (sd)	Difference (95% CI)
Baseline				
3 month				
6 month				
12 month				
24 month				
Total				

Notes:

(1) primary outcome measure to be finalised after pre-pilot & development work: global or dimension
(2) this table does not include imputed values from missing interviews or death
(3) these comparisons, unlike Table 11, are subject to survival bias

Table 11 UK-IBDQ (primary outcome measure) at baseline and follow-up by treatment group (coded). If dead, value is minimum observed UK-IBDQ.

	Number A, B	A: mean (sd)	B: mean (sd)	Difference (95% CI)
Baseline				
3 month				
6 month				
12 month				
24 month				
Total				

Notes:

(1) primary outcome measure to be finalised after pre-pilot & development work: global or dimension
(2) this table does not include imputed values from missing interviews

ADVERSE EVENTS

Table 12 Adverse events.

Number (% rate per participant)	Events			Rate ratio (95% CI)	People with at least one event			Relative risk (95% CI)
Type of event	**Group A**	**Group B**	**Total**		**Group A**	**Group B**	**Total**	
SUSAR (individual details in text)								
Serious Adverse Reaction:								
- leading to treatment withdrawal								
- all SARs								
Serious Adverse Event (unrelated to Ciclo/Inflix)								
Non-trivial adverse reaction listed as known side-effect of infliximab								
Non-trivial adverse reaction listed as known side-effect of ciclosporin								
Total								

Note: The DMEC are notified of all SUSARs as they occur. The DMEC report will summarise these individually in text following this table.

Tables 13 and 14, and Figure 4 - only made available at the final DMEC meeting.

If other comparisons show a large imbalance between groups earlier in the trial, the UK-IBDQ (primary outcome) will be compared in the same way at the latest time point for which adequate participant numbers are available.

For the final analysis report, parameter estimates and confidence intervals for covariates and interactions (if any) in the final model will be included in the Table.

Table 13 Primary outcome, and UK-IBDQ, EQ-5D, SF-12 at 24 months by treatment group (coded): imputed[#].

	Number A, B	A: mean (sd)	B: mean (sd)	Difference	Adjusted Difference (95% CI)
UK-IBDQ (primary outcome)					
UK-IBDQ dimensions at 24m					
.....etc.					
EQ-5D					
Euroqol VAS					
SF-12: physical					
SF-12: mental					
Total					

#: Deaths before 24 months replaced by 0.0 for EQ-5D, or by minimum observed value at that time in either group for UK-IBDQ or SF-12; other missing values for those who have already had 24 months follow-up imputed if information available.

Table 14 Quality-adjusted survival by treatment group (coded).

Number (%)	Survival (QALY)		Survival analysis	
	Mean	Median	Significance	Hazard ratio (95% CI)
Group A				
Group B				
Total				

Figure 4: Quality-adjusted survival by allocation group (two survival curves on one graph, all centres combined. Time axis measured in QALY's – quality-adjusted life years)