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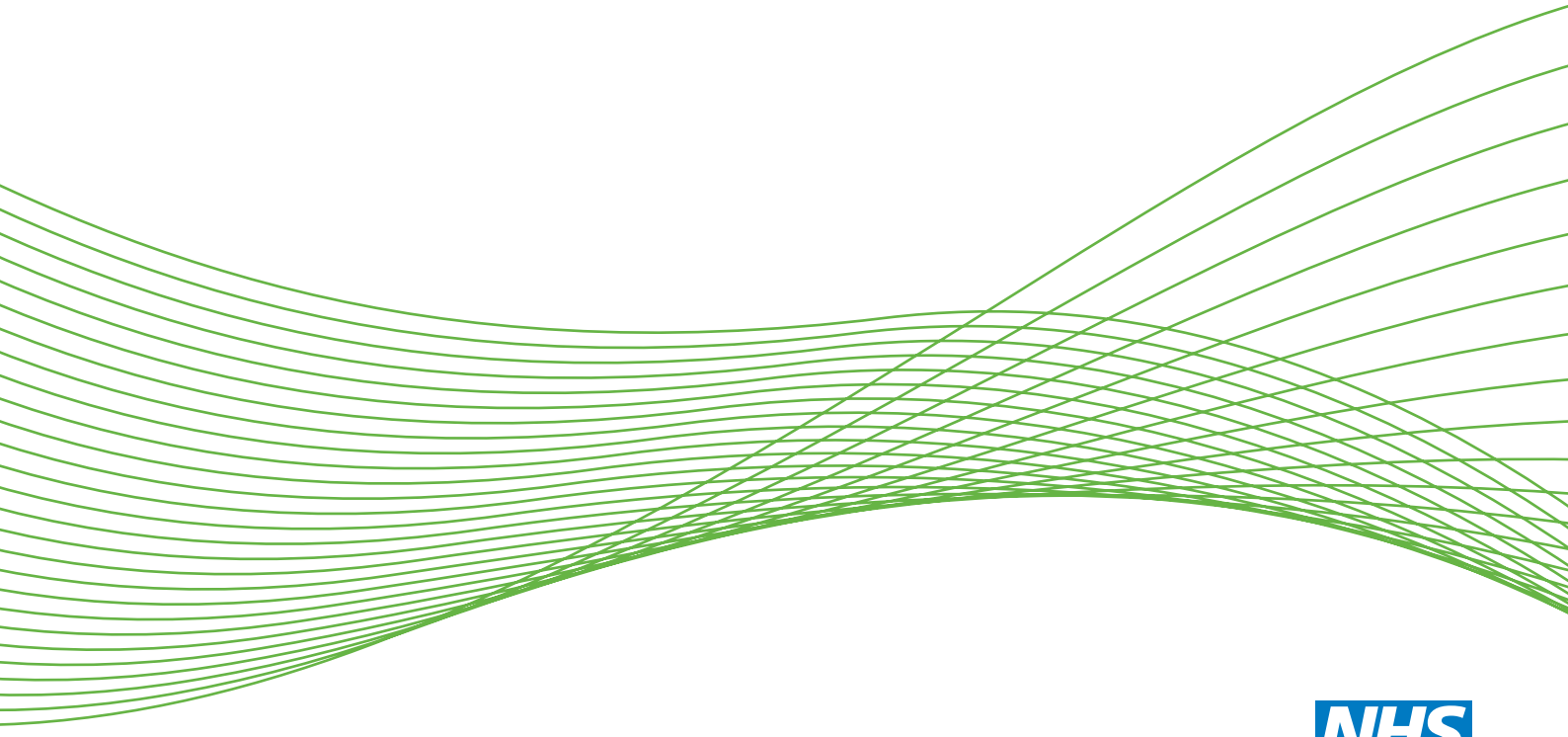

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Abstract

Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT)

John G Williams,[1]* M Fasihul Alam,[2] Laith Alrubaiy,[1] Clare Clement,[1] David Cohen,[3] Michelle Grey,[1] Mike Hilton,[4] Hayley A Hutchings,[1] Mirella Longo,[2] Jayne M Morgan,[1] Frances L Rapport,[1] Anne C Seagrove[1] and Alan Watkins[1]

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Background: The efficacy of infliximab and ciclosporin in treating severe ulcerative colitis (UC) is proven, but there has been no comparative evaluation of effectiveness.

Objective: To compare the clinical effectiveness and cost-effectiveness of infliximab and ciclosporin in treating steroid-resistant acute severe UC.

Method: Between May 2010 and February 2013 we recruited 270 participants from 52 hospitals in England, Scotland and Wales to an open-label parallel-group, pragmatic randomised trial. Consented patients admitted with severe colitis completed baseline quality-of-life questionnaires before receiving intravenous hydrocortisone. If they failed to respond within about 5 days, and met other inclusion criteria, we invited them to participate and used a web-based adaptive randomisation algorithm to allocate them in equal proportions between 5 mg/kg of intravenous infliximab at 0, 2 and 6 weeks or 2 mg/kg/day of intravenous ciclosporin for 7 days followed by 5.5 mg/kg/day of oral ciclosporin until 12 weeks from randomisation. Further treatment was at the discretion of physicians responsible for clinical management. The primary outcome was quality-adjusted survival (QAS): the area under the curve (AUC) of scores derived from Crohn's and Ulcerative Colitis Questionnaires completed by participants at 3 and 6 months, and then 6-monthly over 1–3 years, more frequently after surgery. Secondary outcomes collected simultaneously included European Quality of Life-5 Dimensions (EQ-5D) scores and NHS resource use to estimate cost-effectiveness. Blinding was possible only for data analysts. We interviewed 20 trial participants and 23 participating professionals. Funded data collection finished in March 2014. Most participants consented to complete annual questionnaires and for us to analyse their routinely collected health data over 10 years.

Results: The 135 participants in each group were well matched at baseline. In 121 participants analysed in each group, we found no significant difference between infliximab and ciclosporin in QAS [mean difference in AUC/day 0.0297 favouring ciclosporin, 95% confidence interval (CI) –0.0088 to 0.0682; $p = 0.129$]; EQ-5D scores (quality-adjusted life-year mean difference 0.021 favouring ciclosporin, 95% CI –0.032 to 0.096; $p = 0.350$); Short Form questionnaire-6 Dimensions scores (mean difference 0.0051 favouring ciclosporin, 95% CI –0.0250 to 0.0353; $p = 0.737$). There was no statistically significant difference in colectomy rates [odds ratio (OR) 1.350 favouring infliximab, 95% CI 0.832 to 2.188;

$p = 0.223$]; numbers of serious adverse reactions (event ratio = 0.938 favouring ciclosporin, 95% CI 0.590 to 1.493; $p = 0.788$); participants with serious adverse reactions (OR 0.660 favouring ciclosporin, 95% CI 0.282 to 1.546; $p = 0.338$); numbers of serious adverse events (event ratio 1.075 favouring infliximab, 95% CI 0.603 to 1.917; $p = 0.807$); participants with serious adverse events (OR 0.999 favouring infliximab, 95% CI 0.473 to 2.114; $p = 0.998$); deaths (all three who died received infliximab; $p = 0.247$) or concomitant use of immunosuppressants. The lower cost of ciclosporin led to lower total NHS costs (mean difference –£5632, 95% CI –£8305 to –£2773; $p < 0.001$). Interviews highlighted the debilitating effect of UC; participants were more positive about infliximab than ciclosporin. Professionals reported advantages and disadvantages with both drugs, but nurses disliked the intravenous ciclosporin.

Conclusions: Total cost to the NHS was considerably higher for infliximab than ciclosporin. Nevertheless, there was no significant difference between the two drugs in clinical effectiveness, colectomy rates, incidence of SAEs or reactions, or mortality, when measured 1–3 years post treatment. To assess long-term outcome participants will be followed up for 10 years post randomisation, using questionnaires and routinely collected data. Further studies will be needed to evaluate the efficacy and effectiveness of new anti-tumour necrosis factor drugs and formulations of ciclosporin.

Trial registration: Current Controlled Trials ISRCTN22663589.

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List of abbreviations

AE	adverse event
AESF	adverse event screening form
AR	adverse drug reaction
ASC	acute severe ulcerative colitis
AUC	area under the curve
CC	complications and comorbidity
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CONSTRUCT	Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation
CRF	case report form
CUCQ	Crohn's and Ulcerative Colitis Questionnaire
CUCQ+	Crohn's and Ulcerative Colitis Questionnaire with post-colectomy extension
CySIF	CycloSporine versus InFliximab
DMEC	Data Monitoring and Ethics Committee
EQ-5D	European Quality of Life-5 Dimensions
EURECA	Electronic records underpinning REsearch and CAre
GCP	good clinical practice
GeneCIS	Generic Clinical Information System
GETAID	la Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives
GP	general practitioner
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IMP	Investigational Medicinal Product
MATRICS	Method for Aggregating The Reporting of Interventions in Complex Studies
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OR	odds ratio
PCQ	Post-Colectomy Questionnaire
PFQ	Participant Follow-up Questionnaire
PI	principal investigator
PROM	patient-reported outcome measure
QALY	quality-adjusted life-year
QAS	quality-adjusted survival
QoL	quality of life
R&D	research and development
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SAR	serious adverse reaction
SD	standard deviation
SF-12	Short Form-12 items
SF-6D	Short Form questionnaire-6 Dimensions
SPC	Summary of Product Characteristics

SUSAR	suspected unexpected serious adverse reaction	UC	ulcerative colitis
TMG	Trial Management Group	UK-IBDQ	United Kingdom Inflammatory Bowel Disease Questionnaire
TSC	Trial Steering Committee		

Plain English summary

Ulcerative colitis can present rapidly with severe symptoms. Infliximab and ciclosporin, the trial drugs, can improve severe colitis, but their relative effectiveness in acute attacks is not known.

We recruited 270 patients admitted to 52 hospitals in the UK who had failed to respond to steroids given into a vein, and allocated them at random between the trial drugs. They completed quality-of-life (QoL) questionnaires on admission, 3 and 6 months after treatment, and then 6-monthly for 1–3 years. We compared QoL scores between the trial drugs over patients' time in the study. Both improved QoL, but there was no real difference between them.

We also compared length of hospital stay following recruitment, number of colectomies (removal of the colon) despite treatment with a trial drug, side effects and mortality. There was no real difference between the two drugs in any of these measures. The much lower cost of ciclosporin meant that total NHS costs over 30 months were also much lower with ciclosporin.

We conducted 35 interviews with 20 patients. Those who had received infliximab were generally more positive about treatment than those on ciclosporin. We interviewed 23 doctors and nurses, who reported advantages and disadvantages with both trial drugs. However, nurses particularly disliked the prolonged intravenous ciclosporin regimen.

We concluded that ciclosporin is much cheaper than infliximab. Nevertheless, there is no difference in the performance of these two trial drugs.

Scientific summary

Introduction

Ulcerative colitis (UC) is a chronic debilitating disease that affects about 150,000 people in the UK. Acute severe ulcerative colitis (ASC) affects 25% of patients, and requires hospital admission and treatment with intravenous steroids. About 40% of these patients do not respond to steroid therapy and until 10 years ago colectomy was the only available treatment.

The efficacy of ciclosporin and infliximab in treating steroid-resistant UC is proven, but their relative clinical effectiveness and cost-effectiveness is not known.

Objectives

Our objectives were to compare quality of life (QoL), mortality, colectomy rates, adverse events (AEs) and resource use for up to 3 years after treatment with infliximab or ciclosporin to estimate the clinical effectiveness and cost-effectiveness of these two drugs in managing ASC that had failed to respond to intravenous steroids. We also sought to explore the views of patients and professionals about the two treatments.

Methods

We conducted an open-label parallel-group, pragmatic randomised trial using mixed quantitative and qualitative methods. We recruited participants from a cohort of patients admitted with ASC to hospitals across Great Britain.

We assessed QoL through patient-completed questionnaires at baseline, 3 and 6 months after treatment and then 6-monthly for 1–3 years. Data on colectomy rates, mortality, AEs and resources were collected on case report forms (CRFs) completed by research staff at the same intervals.

We assessed the relative cost-effectiveness of the trial drugs through cost–utility analysis, which estimated differences between groups in NHS costs and quality-adjusted life-years (QALYs).

Our qualitative studies explored participants' experiences of their disease and the trial drugs, and the preferences of health-care professionals between the trial drugs and their use.

We used the Method for Aggregating The Reporting of Interventions in Complex Studies, which we had previously developed in another complex study, to integrate and compare findings from the mixed methods used in Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT). We classified our outcomes into effects on participants; effects on gastroenterological services and professionals; and effects on the rest of the NHS and society.

In due course we shall supplement our designed research data with routinely collected data. We have consent from trial participants to access their routine data and send them annual questionnaires for 10 years from recruitment.

Participants

We created a comprehensive cohort of admitted patients because we expected difficulty in identifying acutely ill patients who needed urgent treatment and in obtaining baseline data from them. We invited patients with known or suspected UC to join this cohort soon after admission and collected their baseline data as soon as possible after they gave consent.

We recruited from the cohort to the trial those patients who failed to respond to intravenous steroids, fulfilled the trial inclusion and exclusion criteria and gave informed consent. The treatment of patients who did not give consent did not change in any way.

Trial inclusion criteria

We included patients who had been admitted unscheduled with colitis judged as severe (by the criteria of Truelove and Witts, a Mayo score of at least 2 on endoscopic finding, or clinical judgement); who then failed to respond to about 2–5 days of intravenous hydrocortisone; and also had a proven histological diagnosis of UC, indeterminate colitis where clinical judgement suggested a diagnosis of UC rather than Crohn's disease, or symptoms typical of UC awaiting histology.

Trial exclusion criteria

We excluded patients aged < 18 years; from vulnerable groups or unable to consent; with an enteric infection or histological diagnosis inconsistent with UC; who were pregnant, lactating, or fertile but unwilling to use contraception for 6 months after randomisation; suffering current malignancy, except for basal cell carcinoma; with serious comorbidity, including immunodeficiency, recent myocardial infarction, heart failure, acute stroke, respiratory failure, renal failure, hepatic failure, or severe infection; with known hypersensitivity to infliximab, ciclosporin or polyethoxylated oils; using tacrolimus or rosuvastatin; whose English was poor in the absence of local translator services; needing emergency colectomy without further medical treatment; currently participating in another clinical trial; treated with either infliximab or ciclosporin within 3 months of admission; or showing any other contraindication to treatment with infliximab or ciclosporin.

Qualitative studies

We used purposive quota sampling to identify 12 representative consenting participants from each arm of the trial for two interviews. We used purposive sampling to interview 15 consultants from three strata: sites that recruited well to cohort and trial; sites that recruited well to cohort but less well to trial; and sites that recruited poorly. We also interviewed eight nurses from good recruiting sites.

Interventions

Participants randomised to infliximab received Remicade® (Merck Sharp & Dohme Ltd) in 5-mg/kg intravenous infusions over 2 hours – forthwith, and at 2 and 6 weeks after the first infusion – in accordance with local prescribing guidelines.

Participants randomised to ciclosporin received Sandimmun® (Novartis Pharmaceuticals UK Ltd) by continuous infusion of 2 mg/kg/day, continued for up to 7 days if successful, when it was switched to twice-daily Neoral® tablets (Novartis Pharmaceuticals UK Ltd) delivering 5.5 mg/kg/day, with the dose adjusted to achieve trough ciclosporin concentration of 100–200 ng/ml. After 12 weeks, treatment was at the discretion of the participant's consultant.

For both treatments we gave centres discretion to start azathioprine or 6-mercaptopurine at therapeutic doses in week 4 and use was similar in both groups. We asked them to discontinue steroids by week 12 in participants who remained well but to reinstate them if symptoms returned. We also asked centres to give co-trimoxazole as prophylaxis against *Pneumocystis jiroveci* (formerly *carinii*) pneumonia in both groups.

Outcomes

The primary outcome was the area under the curve (AUC) of scores derived from the Crohn's and Ulcerative Colitis Questionnaire (CUCQ), a disease-specific patient-reported outcome measure which extends the validated United Kingdom Inflammatory Bowel Disease Questionnaire to cover acute illness and colectomy, and which we validated concurrently.

Secondary outcomes included change in Short Form-12 items and European Quality of Life-5 Dimensions (EQ-5D) scores; mortality; colectomies, both emergency and planned; serious adverse events (SAEs) and serious adverse reactions (SARs); and length of stay.

Economic outcomes included NHS costs and health-related quality of life (HRQoL), measured by EQ-5D.

Qualitative outcomes covered participant and professional views of the drugs and their consequences.

Sample size

Our original target analysable sample size was 360 participants, based on a primary outcome of a change in HRQoL over 2 years. However, in 2012 slower recruitment than predicted led us to revise the primary outcome and reduce the target analysable sample size to 250.

The changes required statistical imputation to exploit the resulting data set and we estimated that data from 250 participants would be sufficient to detect an effect size of 0.35 in CUCQ scores with 80% power at a 5% significance level.

Randomisation

We allocated participants at random between infliximab and ciclosporin, using a web-based password-protected adaptive algorithm to protect against subversion while ensuring that each trial arm was balanced by centre.

Blinding

As this was an open trial, there was no need for procedures to inform sites about allocated treatments. However, the chief investigator, trial methodologist, outcomes specialist, health economists and statisticians remained blind to them until the Trial Steering Committee and Data Monitoring and Ethics Committee had reviewed and approved the analysis of the primary outcome.

Statistical methods

Clinical effectiveness

Primary analysis was by treatment allocated, reflecting the pragmatic nature of the trial design. We used a general linear model to estimate differences in quality-adjusted survival (QAS) between groups, adjusting for covariates including trial site; age; gender; ethnic group; QoL at baseline; disease severity at baseline;

immunosuppressant therapy at baseline (using a binary indicator set equal to 1 for participants then taking azathioprine, 6-mercaptopurine or methotrexate); and time in follow-up.

Secondary analyses adjusted for the same covariates as primary analysis and compared between groups: QAS per day (again using general linear models); QoL scores (using methods for repeated measures); proportion of participants undergoing colectomy (using binary logistic regression); time to colectomy (censored at the end of follow-up and analysed by Cox regression); proportion of participants suffering one or more AEs (using binary logistic regression); and mortality.

We examined residual diagnostics in analyses that assume normality, with the options of data transformation and bootstrapping when residual distributions were markedly non-normal. We excluded identified outliers and reanalysed the revised data sets. We reported analyses in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines, including estimated differences with 95% confidence intervals (CIs), representing two-tailed tests at the 5% significance level.

Imputation of missing data

We used statistical imputation of censored and missing data, to impute QoL and costs for all participants who generated data on survival, colectomy or QoL after randomisation.

Cost-effectiveness

We collected data on NHS resource use from CRFs and Participant Follow-up Questionnaires (PFQs) completed at each follow-up time point. To minimise recall bias, PFQs reported resource use over the previous 3 months, leaving gaps in the data which we imputed. We estimated all costs in 2012–13 prices inflated when necessary using the NHS Pay and Prices Index and applied a discount rate of 3.5% per annum.

Our primary economic analysis assessed cost-effectiveness over 30 months by aggregating costs and QALYs for participants for whom we had EQ-5D data. We fitted statistical models for NHS costs and QALYs using allocated drug days since randomisation and the logarithm of those days as independent variables. We used the resulting coefficients to adjust NHS costs and QALYs to a period of 730 days. Costs and QALYs were further adjusted for baseline covariates. We used non-parametric bootstrapping to generate scatterplots on the cost-effectiveness plane and produced cost-effectiveness acceptability curves (CEACs) to show the probability of treatments being cost-effective against thresholds of willingness to pay.

Results

Participant flow

We know of 2065 potentially eligible patients admitted between May 2010 and March 2013 to 62 participating hospitals in England, Scotland and Wales. Of those, 1614 were consented into the CONSTRUCT cohort. From these, 52 hospitals recruited 270 participants into the trial and followed them for 1–3 years. Each arm comprised 135 participants, of whom 121 (90%) contributed to definitive analysis of the primary outcome. Funded data collection finished in March 2014.

Baseline characteristics

At baseline, there were no statistically significant differences between arms in demographic or disease characteristics, or QoL scores.

Primary outcomes

There was no significant difference in QAS between infliximab and ciclosporin; the mean adjusted difference in total area under the CUCQ curve was 7.9 favouring ciclosporin (95% CI –22.0 to 37.8; $p = 0.603$); and mean adjusted difference in AUC per day was 0.0297 favouring ciclosporin (95% CI –0.0088 to 0.0682; $p = 0.129$).

Secondary outcomes

At no time point after randomisation was there any significant difference between groups in CUCQ scores (mean adjusted difference in AUC/day of survivors 0.0195 favouring ciclosporin, 95% CI –0.0191 to 0.0581; $p = 0.319$), Short Form questionnaire-6 Dimensions scores (mean adjusted difference 0.0051 favouring ciclosporin, 95% CI –0.0250 to 0.0353; $p = 0.737$); EQ-5D scores (QALY mean adjusted difference 0.021 favouring ciclosporin, 95% CI –0.032 to 0.096; $p = 0.350$). There was also no significant difference between groups in: mortality (all three who died had taken infliximab; $p = 0.25$); colectomy rates [odds ratio (OR) 1.350 favouring infliximab, 95% CI 0.832 to 2.188; $p = 0.223$]; or time to colectomy (hazard ratio 1.234 favouring infliximab, 95% CI 0.862 to 1.768; $p = 0.251$). Although length of hospital stay after randomisation ostensibly did not differ between groups (mean adjusted difference 1.542 days more for ciclosporin, 95% CI –1.297 to 4.381 days assuming normal distribution of residuals in general linear model; $p = 0.286$), that distribution was so skewed as to invalidate the assumption of normality; hence, we transformed these stays by taking logarithms and estimated that the geometrical mean of adjusted stays after ciclosporin was a factor of 1.527 times longer than that after infliximab (95% CI 1.278 to 1.817; $p < 0.001$).

Adverse events

There was no statistically significant difference between the two drugs in SARs or SAEs. Fourteen infliximab participants reported 16 SARs and nine ciclosporin participants reported 10 SARs (event ratio 0.938 favouring ciclosporin, 95% CI 0.590 to 1.493; $p = 0.788$; OR 0.660 favouring ciclosporin, 95% CI 0.282 to 1.546; $p = 0.338$). Sixteen infliximab participants reported 21 SAEs and 17 ciclosporin participants reported 25 SAEs not related to disease progression or colectomy (event ratio 1.075 favouring infliximab, 95% CI 0.603 to 1.917; $p = 0.807$; OR 0.999 favouring infliximab, 95% CI 0.473 to 2.114; $p = 0.998$). There were two malignancies on infliximab (basal cell carcinoma and colorectal cancer) and one on ciclosporin (endometrial cancer). Three participants died, all following infliximab ($p = 0.247$). The cause of death was disseminated malignancy from colorectal cancer in one and perioperative pneumonia with sepsis, in the presence of multiple comorbidities, in two.

Cost-effectiveness

In the primary analysis at 30 months, total health service costs for ciclosporin (£14,609) were significantly lower than for infliximab (£20,241) (mean adjusted difference –£5632, 95% CI –£8305 to –£2773; $p < 0.001$): despite the average difference of nearly 2 days in length of hospital stay after recruitment needed to complete ciclosporin treatment, the difference in cost was because of the much higher cost of acquiring infliximab. QALY gains were similar in both groups: the mean adjusted difference of 0.021 QALYs favours ciclosporin, but is not statistically significant (95% CI –0.032 to 0.096 QALYs; $p = 0.350$). The CEAC shows ciclosporin to have 85% probability of being cost-effective over a wide range of thresholds of willingness to pay. Sensitivity analysis showed similar results at 12 and 24 months. Technically, therefore, ciclosporin dominates infliximab.

Qualitative results

Interviews with participants revealed the substantial impact of UC on their QoL, and the potential benefits from these medical treatments and from surgery. Participants treated with infliximab generally spoke more positively about the treatment than those treated with ciclosporin. Interviews with nurses showed preference for infliximab, largely because of the resource-intensive infusion protocol for ciclosporin. Although some consultants favoured infliximab, most were indifferent, perceiving both drugs as effective, with a more predictable speed of benefit with ciclosporin balancing a perceived higher rate of side effects.

Discussion

We have shown that ciclosporin costs the NHS much less than infliximab but is clinically no less effective. Even so, 120 participants (45%) needed a colectomy. Our findings are consistent with those of the study Comparing Cyclosporine with Infliximab in steroid-refractory severe attacks of ulcerative colitis (CySIF), the

only other randomised trial of these two drugs for acute severe UC. However, CySIF was much smaller and did not collect data on costs, QoL or the views of participants or professionals.

Our interviews highlighted the debilitating effect of UC; participants liked infliximab better than ciclosporin, but doctors were more equivocal, whereas nurses disliked the more resource-intensive infusion requirements of ciclosporin. By following participants over the next 10 years, through both questionnaires and routine data, we plan to extend our quantitative findings, especially on colectomies and other readmissions.

Trial registration

This trial is registered as ISRCTN22663589.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background and literature review

Background

Ulcerative colitis (UC) is a chronic debilitating disease that affects about 150,000 people in the UK.[1,2] Some 25% of patients with UC present either for the first time or later, with acute severe ulcerative colitis (ASC) requiring hospital admission.[3] In patients with ASC, intravenous steroids are the first-line treatment.[4] However, about 30–40% of these patients are resistant to intensive steroid therapy.[5,6] Previously, colectomy was the only available option for these patients.[5] Although mortality following emergency colectomy has fallen over time, 10% of patients die within 3 months of surgery.[7]

The use of intravenous or oral ciclosporin (Sandimmun® or Neoral®, Novartis Pharmaceuticals UK Ltd),[8,9] a calcineurin inhibitor that selectively inhibits T-cell function, and infliximab (Remicade®, Merck Sharp & Dohme Ltd),[10,11] a monoclonal antibody that targets tumour necrosis factor α, then offered hope for the treatment of steroid-resistant UC.

Several studies support the use of infliximab in patients with moderate or severe UC,[12–15] especially steroid-resistant UC patients who do not tolerate ciclosporin.[12] A recent systematic review and meta-analysis of 34 infliximab studies found an average short-term response and remission of 68% and 40%, respectively, and an average long-term response and remission of 53% and 39%, respectively.[15] However, there are concerns about high rates of later relapses.[16,17] Two large randomised controlled trials (RCTs) also found highly significant improvements in total Inflammatory Bowel Disease Questionnaire (IBDQ)[18] score and Short Form questionnaire-36 items physical and mental component scores[19] for infliximab patients at 8 weeks when compared with placebo.[20] The current UK National Institute for Health and Care Excellence (NICE) guidelines allow the use of infliximab only when ciclosporin is contraindicated or as part of a research study.[21]

Several studies support the use of ciclosporin as a safe and effective treatment for steroid-resistant UC,[22–24] although it has been associated with side effects including dose-related toxicity[23,25,26] and long-term failure.[23–25,27] A systematic review and meta-analysis of 31 ciclosporin studies reported a mean short-term response rate of 71%;[28] one study reported that 65% of patients relapsed after 1 year and 90% after 3 years.[27] Another review of 32 studies reported a 51% short-term success rate.[29] However, the relevant 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.[30] It also advocated research into the long-term effects of ciclosporin on quality of life (QoL) and its cost-effectiveness.

Review of literature

We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials, original studies, systematic reviews and meta-analyses that compare ciclosporin and infliximab in the management of acute UC resistant to steroid therapy up to the 31 July 2014. We used the search terms: 'ciclosporin', 'infliximab', 'ulcerative colitis', 'acute severe ulcerative colitis' and 'steroid resistant ulcerative colitis'. We included synonyms, different spellings and drug brand names in our search to identify all relevant articles. We used the electronic search strategies checklist of the Cochrane Collaboration.[31]

We identified nine observational studies and one RCT[32–41] that compared the efficacy and safety of ciclosporin with those of infliximab (*Table 1*). Although both ciclosporin and infliximab were effective in steroid-resistant UC, results did not agree which drug was better.[32–35] One small retrospective study[34] of 38 patients with acute UC resistant to steroids showed a higher rate of colectomy in patients who received ciclosporin (63% and 68% at 3 and 12 months, respectively) than in those who received infliximab

TABLE 1 Results of the systematic review: studies that compare infliximab and ciclosporin use in steroid-resistant acute UC

Study	Number of patients	Main outcomes reported	Follow-up period
Laharie *et al.*, 2012[41]	• 58 patients had ciclosporin • 57 patients had infliximab	Treatment failure: 60% with ciclosporin and 54% with infliximab ($p = 0.52$) SAEs: 16% with ciclosporin and 25% with infliximab Mucosal healing: 47% with ciclosporin and 45% with infliximab ($p = 0.85$) UK-IBDQ scores improved by 78 points with ciclosporin and 100 points with infliximab ($p = 0.19$) Colectomies: 17% in the ciclosporin and 21% in the infliximab group	98 days
Leblanc *et al.*, 2011[38]	• 65 patients had infliximab after ciclosporin failure • 21 patients had ciclosporin after infliximab failure	Colectomy rate: 54% in infliximab group and 67% in ciclosporin group Clinical remission: 25% in infliximab group and 14% in ciclosporin group AEs: 23% in infliximab group and 24% in ciclosporin group	22 months
Mañosa *et al.*, 2009[40]	• 16 patients had infliximab after failure of ciclosporin	Six patients (37.5%) required colectomy and 19% of patients had SAEs	195 days
Maser *et al.*, 2008[37]	• 10 patients had infliximab after ciclosporin failure • 9 patients had ciclosporin after infliximab failure	Clinical remission: 40% in the infliximab-salvage group and 33% in the ciclosporin-salvage group The median duration of remission: 13.6 months in the infliximab-salvage group and 21.0 months in the ciclosporin-salvage group Colectomy rate: 40% in the infliximab group and 44% in the ciclosporin group SAEs: one in the infliximab group and two in the ciclosporin group	Average duration of follow-up was 7.8 months for infliximab and 17.7 months for ciclosporin
Dean *et al.*, 2012[34]	• 19 patients had infliximab • 19 patients had ciclosporin	Colectomy rate: 63% for ciclosporin and 21% for infliximab ($p = 0.0094$) at 3 months. By 12 months the rates were 68% and 37% for ciclosporin and infliximab, respectively ($p = 0.06$) Steroid dependence at 12 months was 50% for ciclosporin and 25% for infliximab ($p = 0.36$) There was no statistical difference in AEs between the two groups ($p = 0.17$)	12 months

TABLE 1 Results of the systematic review: studies that compare infliximab and ciclosporin use in steroid-resistant acute UC (*continued*)

Study	Number of patients	Main outcomes reported	Follow-up period
Chaparro *et al.*, 2012[39]	• 47 patients had infliximab after failure of ciclosporin	Colectomy rate was 30% SAE rate was 23%	58 weeks
Croft *et al.*, 2013[36]	• 45 patients had ciclosporin • 38 patients had infliximab	Colectomy rate: 44% for ciclosporin and 16% for infliximab at discharge ($p = 0.006$). At 3 months the colectomy rates were 47% vs. 24% ($p = 0.04$), and at 12 months colectomy rates were 58% vs. 35% ($p = 0.04$) for ciclosporin and infliximab, respectively	12 months
Sjoberg *et al.*, 2012[32]	• 49 patients had infliximab • 43 patients had ciclosporin	Colectomy rates: 5% vs. 27% at 15 days, 7% vs. 23% at 3 months and 23% vs. 43% at 12 months for ciclosporin and infliximab, respectively ($p < 0.05$)	12 months
Mocciaro *et al.*, 2012[33]	• 30 patients had infliximab • 35 patients had ciclosporin	Colectomy rates: 28.5% vs.17% ($p = 0.25$) at 3 months and 48% vs. 17% at 12 months ($p = 0.007$) for ciclosporin and infliximab, respectively The 1–2–3 year cumulative colectomy rates were 48%, 54%, 57% in the ciclosporin group and 17%, 23%, 27% in the infliximab group ($p < 0.05$)	The mean follow-up was 74.7 months for ciclosporin and 33.6 months for infliximab
Daperno *et al.*, 2004[35]	• 15 patients had ciclosporin • 6 patients had infliximab	Clinical remission: 53% in the ciclosporin group vs. 67% in the infliximab group Colectomy rates: 47% in the ciclosporin group vs. 33% in the infliximab group	49 months

AE, adverse event; SAE, serious adverse event.

(21% and 37% at 3 and 12 months, respectively); there was no significant difference between groups in adverse events (AEs) or steroid dependence. A prospective study[36] found the colectomy-free rate at discharge, and at 3 and 12 months from admission, was significantly higher in patients who had infliximab as a rescue therapy ($n = 45$) compared with those who had ciclosporin ($n = 38$). A minute retrospective study[35] of two cohorts of patients (15 on ciclosporin and six on infliximab) showed a higher rate of colectomy and opportunistic infection in patients who received ciclosporin compared with those who received infliximab. A retrospective study of 49 patients on infliximab and 43 patients on ciclosporin showed that colectomy frequencies were significantly lower after rescue with ciclosporin than with infliximab, with no death or opportunistic infection.[32] Mocciaro *et al.*[33] retrospectively examined the outcomes of 30 patients who received ciclosporin and 30 patients who received infliximab for steroid-resistant acute UC and reported that the rate of colectomy at 12 months was 48% in the ciclosporin group compared with 17% in the infliximab group ($p = 0.01$); both drugs were equally safe without severe AEs. A recent UK inflammatory bowel disease (IBD) audit reported increased use of infliximab compared with ciclosporin in managing ASC; the clinical response rate was higher in patients who received infliximab.[42]

Four studies[37–40] explored the use of infliximab and ciclosporin as a second-line rescue therapy by crossing them over after failure of these agents as a first-line therapy. The studies concluded that the use of ciclosporin or infliximab as second-line rescue therapy induced remission in up to two-thirds of patients.[38] However, this remission was of limited duration, the rate of colectomy was around 40%, and the rate of serious adverse events (SAEs) ranged from 16% to 23%.[37–40]

A recent meta-analysis of 321 patients in six retrospective cohort studies[32–35,37,38] concluded that infliximab and ciclosporin are comparable when used as rescue therapy in acute severe steroid-refractory UC. However, the outcome measures were limited to colectomy rates, adverse drug reactions (ARs) and postoperative complications over 12 months.[43]

Against this background of observational studies that compared these two drugs only indirectly, la Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID) recently reported on the trial CycloSporine versus InFliximab (CySIF),[41] the first head-to-head comparison of these two drugs. CySIF found no significant differences in 'treatment failure' within 98 days, defined as any of the following: (i) no clinical response after 7 days; (ii) no remission without steroids after 98 days; (iii) relapse between 7 and 98 days; (iv) SAE leading to treatment interruption; (v) colectomy; or (vi) death. However, CySIF recruited only 110 patients, followed them for only 98 days, reported no data on QoL and collected no data on costs or from participants.

The qualitative research reported in the literature on infliximab focuses on its role in treating rheumatoid arthritis.[44] There is no qualitative study that explores the use of ciclosporin in the treatment of acute UC. One qualitative study exploring patient and parent experiences of infliximab in paediatric gastroenterology, found favourable views of the drug when used in a hospital environment.[45] To our knowledge, no studies, qualitative or otherwise, have explored health professionals' views of drug administration for treating steroid-resistant UC. This is disappointing as qualitative methods are well suited to investigate personal experience, individual perception and belief and meaning systems,[46,47] enabling triallists to clarify patients' and clinicians' understandings of clinical practice and drug regimes.[48,49] Therefore, there is a need for a trial that also seeks the experiences and views of patients with acute UC about treatments and changes in health over time and of health-care professionals about ease of drug handling and drug preference.

Patients with UC incur substantial health-care costs over many years. As well as the direct costs of treatment by drug or surgery, UC patients consume a wide range of health-care resources including spells in hospital, attendances at emergency departments, outpatient visits, endoscopies and other investigations. Nevertheless, no study has assessed the cost-effectiveness of infliximab and ciclosporin in a head-to-head clinical trial. Instead, Markovian economic models have created hypothetical cohorts of patients with acute UC resistant to steroids to assess the cost-effectiveness of infliximab compared with ciclosporin and surgery.[50,51] These models used published evidence[6,8,10,52] to extrapolate the costs and effects in quality-adjusted life-years (QALYs) gained by each drug. Although these models conclude that infliximab is a cost-effective treatment in comparison with ciclosporin and surgery, we need to interpret this claim with caution. Theoretical models cannot capture all aspects of disease progression and their costs; and require assumptions to replace unavailable primary data. Furthermore, they excluded patient mortality and side effects while assuming that infliximab had a better side effect profile and mortality rate than both ciclosporin and surgery. Therefore, direct comparison of the clinical effectiveness and cost-effectiveness of infliximab and ciclosporin in patients with acute UC is essential.

In summary, infliximab and ciclosporin are often effective in the short term, but there is little long-term evidence about their relative clinical effectiveness and cost-effectiveness. The Evidence Review Group report commissioned by NICE concluded: 'The results consistently indicate that the move from standard care to ciclosporin is highly cost-effective'.[53] Thus the policy issue is clear: should the NHS make a further move from ciclosporin to infliximab?

Hence we designed Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT) to achieve a rigorous, comprehensive, long-term comparison of these drugs. In particular, during the trial we enhanced measurement of QoL and costs in four ways:

1. extending data collection for all trial participants, whenever recruited, until 28 February 2014
2. adding questionnaires at 18, 30 and 36 months to those at 3, 6, 12 and 24 months
3. adding four questionnaires following colectomy and any ensuing corrective surgery
4. planning to use the techniques of survival analysis and statistical imputation of missing values to impute costs and QoL for all CONSTRUCT participants who generate data on survival, colectomy or QoL after randomisation.

Aim and objectives

The aim of this trial was to compare the clinical effectiveness and cost-effectiveness of infliximab and ciclosporin for patients with steroid-resistant UC over a period of up to 3 years.

Specific objectives were to:

1. compare health-related quality of life (HRQoL) after these two treatments
2. compare mortality, morbidity and disease activity between treatments
3. compare colectomy rates between treatments
4. compare cost-effectiveness of treatments in cost per QALY
5. investigate the views of patients about their health and treatments
6. investigate the views of health-care professionals about the treatments and their ease of administration.

Chapter 2 Methods

Trial design

We conducted an open-label parallel-group, pragmatic randomised trial using mixed methods: quantitative (including health economics and routinely collected data) and qualitative.[54]

Our primary outcome measure was quality-adjusted survival (QAS)[55] weighted by participants' scores on the Crohn's and Ulcerative Colitis Questionnaire (CUCQ), our extension of the validated UK-IBDQ to include severe colitis and post-colectomy states. Secondary outcomes included two generic measures of QoL [European Quality of Life-5 Dimensions (EQ-5D) and Short Form questionnaire-12 items (SF-12)], emergency and planned colectomy rates, AEs and mortality.

We assessed the relative cost-effectiveness of the trial drugs through cost–utility analysis from the perspective of the NHS and Personal Social Services, as recommended by NICE.[56] These analyses assessed differences between groups in total costs and QALYs.

Our qualitative studies aimed to enrich our quantitative results by exploring participants' experiences of UC and the trial drugs, and their priorities for health and well-being. We also explored health-care professionals' preferences between the trial drugs and their administration.

We used the Method for Aggregating The Reporting of Interventions in Complex Studies (MATRICS), which we had previously developed in another complex study, to integrate and compare the findings from the mixed methods used in CONSTRUCT.[57] We classified our outcomes into effects on participants; effects on gastroenterological services and professionals; and effects on the rest of the NHS and society. Using the MATRICS template, we combined all comparable findings into summary statements and highlighted where different methods resulted in inconsistent statements.

As we expected difficulty in recruiting acutely ill patients in hospital and completing their baseline data, we created a comprehensive cohort. We invited patients with known or suspected UC to join this cohort soon after admission. We explained that, if they had UC and did not respond to intravenous steroids, they might need other drug treatment; so, if they were suitable, we would invite them to further treatment as part of a clinical trial. To increase the chance of recruiting them, we collected their baseline data as soon as possible after they had consented.

From May 2010 until the end of February 2013 we recruited from the cohort to the trial those participants with UC who failed to respond to intravenous steroids over about 2–5 days, but did not then need surgery. After full written and oral explanation we invited participants who fulfilled the trial inclusion and exclusion criteria to consent to randomisation between infliximab and ciclosporin. Placebo controls would have been unethical, as these severely ill patients need treatment, as the NICE Evidence Review Group recognised.[53]

We shall supplement our designed research data with routinely collected data held by the Health & Social Care Information Centre in England, the Secure Anonymised Information Linkage database in Wales, or the Health Informatics Centre in Scotland. As these data are not yet available for the full period of the trial, we shall analyse and report them in due course. We have consent from participants in both cohort and trial to access their routine data for 10 years from recruitment, and from trial participants to send them questionnaires over that period.

Recruitment

Trial sites

Via the British Society of Gastroenterology we asked consultant gastroenterologists to express interest in taking part in the study and to complete a questionnaire. We considered sites that had treated four or more patients with steroid-resistant UC in the previous 12 months to be eligible and invited them to seek local approval. As a result we initiated the trial in 67 NHS trusts or health boards, covering both teaching and district general hospitals in England, Scotland and Wales. We phased the initiation of these sites, reflecting the time needed to gain local research and development (R&D) approval.

Participants in cohort and trial

The target population for the cohort were inpatients with ASC, known or suspected, who were potentially eligible for the trial. The target population for the trial were cohort members who failed to respond to a course of about 2–5 days of intravenous steroid medication, but did not then need surgery. We invited eligible patients into the cohort as soon as feasible and into the trial once the clinical team had confirmed steroid resistance. The treatment of patients who did not consent to cohort or trial did not change in any way.

Participants in qualitative study

We used purposive quota sampling to identify 12 representative consenting participants from each arm of the trial for interview on two occasions (see *Appendix 1*). To include participants from sites starting later in the trial pro rata, we maintained a list of eligible participants.

We also interviewed principal investigators (PIs) and nurses responsible for administering and monitoring the drugs across the trial sites. We included both professions to explore drug administration, physical effects of both drugs on patients, personal preferences and their participation in CONSTRUCT. We used purposive sampling to recruit 12 PIs from three strata: sites that recruited well to cohort and trial; sites that recruited well to cohort but less well to trial; and sites that recruited poorly to both cohort and trial. However, we recruited all eight nurses from good recruiting sites as others would have little relevant experience of the trial drugs.

Informed consent

Patients eligible for the cohort received cohort participant information sheets (see *Appendix 2*) and oral explanation from consultant gastroenterologists or research professionals (usually research nurses); in response, patients gave written consent by signing and dating a cohort consent form (see *Appendix 3*). Cohort participants who became eligible for the trial received the patient information sheet (RCT) (see *Appendix 4*), and gave written consent by signing and dating a trial consent form (see *Appendix 5*). For both cohort and trial, those taking consent countersigned and dated the form to confirm that the participant had fully understood the nature of the study and had an opportunity to ask questions; they also put a copy of that consent in the participant's medical record and gave another copy to the participant.

Research professionals could take consent to the cohort if authorised to do so on the site delegation log following appropriate training, including in good clinical practice (GCP). Although they could also explain the trial to cohort patients, responsibility for countersigning lay with the site PI or another doctor with delegated authority on the site delegation log. The trial consent form included consent to take part in qualitative interviews.

Withdrawal

The procedure for consenting participants stressed that they could withdraw from the cohort or trial whenever they wished without giving a reason and without affecting their care in any way. However, we documented any reasons given. Participants could stipulate the level of withdrawal: from the allocated treatment, from completion of further participant questionnaires, from consent to the use of any of their routine, or from any combination of these. We also encouraged site staff to trace participants lost to follow-up and document reasons when possible.

Between randomisation and the end of the trial, there were decisions to change allocated treatments, but these did not require withdrawal from this pragmatic trial. These included failure to respond to treatment with infliximab or ciclosporin, usually leading to surgical intervention.

Trial inclusion criteria

Patients admitted as emergency admissions with severe colitis (according to Truelove and Witts,[4] a Mayo score of at least 2 on endoscopic finding or clinical judgement) who fail to respond to about 2–5 days of intravenous hydrocortisone therapy, who *also* had either:

- histological diagnosis of UC in this episode
- histological diagnosis of indeterminate colitis in this episode when clinical judgement (based on macroscopic appearance, disease distribution or previous history) suggested a diagnosis of UC rather than Crohn's disease
- symptoms typical of UC awaiting histology; or
- history of UC confirmed histologically.

Trial exclusion criteria

- Aged < 18 years of age on admission.
- Histological diagnosis before randomisation inconsistent with UC.
- Enteric infection confirmed before randomisation by stool microscopy, culture or histology (including *Salmonella*, *Shigella*, *Clostridium difficile*, *Campylobacter* and cytomegalovirus).
- Vulnerable patient.
- Unable to consent.
- Positive pregnancy test or current lactation.
- Woman of childbearing potential unwilling to use contraception during and for 6 months after treatment with infliximab in accordance with the Summary of Product Characteristics (SPC).
- Current malignancy, except basal cell carcinoma.
- Serious comorbidity, including immunodeficiency, myocardial infarction within last month, moderate or severe heart failure (New York Heart Association class III or IV), acute stroke within last month, respiratory failure, renal failure, hepatic failure and active or suspected tuberculosis.
- Other severe infections including sepsis, abscesses and opportunistic infections.
- History of hypersensitivity to infliximab, ciclosporin or polyethoxylated oils (notably Sandimmun Concentrate for Solution for Infusion).
- Current use of tacrolimus or rosuvastatin.
- English not good in absence of local translator.
- Need for emergency colectomy without further medical treatment.
- Currently taking part in another clinical trial.
- Treatment with either infliximab or ciclosporin in the 3 months before admission.
- Any other contraindication to treatment with infliximab or ciclosporin.

Sample size and power

Our original target analysable sample size was 360 participants, based on a primary outcome of a change in HRQoL over 2 years.[54] However, in 2012 slower recruitment than predicted led us to seek agreement from the Trial Steering Committee (TSC), Data Monitoring and Ethics Committee (DMEC) and Health Technology Assessment (HTA) programme to revise the primary outcome and reduce the analysable sample size to 250. We also proposed to analyse the area under the curve (AUC) of scores on the CUCQ collected every 6 months up to 3 years from randomisation; and to include participants who had undergone colectomy by developing and validating a post-colectomy extension to the CUCQ, which we termed the Crohn's and Ulcerative Colitis Questionnaire with post-colectomy extension (CUCQ+).

The changes required statistical imputation to exploit the resulting data set. As these techniques are difficult to incorporate into power calculations, we used a simpler calculation based on *t*-tests of mean CUCQ scores at 12 months. To detect an effect size of 0.35 in these scores with 80% power when using a

5% significance level, required that we analyse at least 250 trial participants. We used the techniques of statistical imputation applied successfully by the Cancer of the Oesophagous or Gastricus: New Assessment of the Technology of Endosonography[58] and Folate Augmentation of Treatment – Evaluation of Depression (FolATED)[59] trials to achieve an effective sample size of 250 for CONSTRUCT.

Randomisation

We allocated at random between infliximab or ciclosporin all participants who completed baseline assessment, met the trial inclusion criteria and gave informed consent. We used a password-protected website that accessed an adaptive algorithm to protect against subversion while ensuring that each trial arm was balanced by centre.[60] To validate each request for randomisation, the website asked:

- for the participant's trial number, and month and year of birth
- for the name of person requesting randomisation (limited to those trained and authorised)
- if consent had been given
- if the participant had met the inclusion criteria
- if the participant had *none* of the exclusion criteria
- if the baseline questionnaire been completed.

If the responses to all four questions were 'yes', the website gave the name of the drug allocated to the participant and immediately confirmed the trial number and drug by e-mail, and recorded those on the randomisation database.

Hospital pharmacies at trial sites held the trial drugs. After each randomisation, the research staff confirmed study number and drug by fax to the relevant pharmacy who labelled the drug with the European Union Drug Regulating Authorities Clinical Trials number, sponsor, participant's trial number, name and address of supplier, dose and 'For Clinical Trial Use Only'.

Blinding

As this was an open trial, there was no need for procedures to inform sites about allocated treatments. However, the chief investigator, trial methodologist, outcomes specialist, health economists and statisticians remained blind to them until the TSC and DMEC had reviewed and approved the analysis of the primary outcome.

Interventions

Participants randomised to infliximab received it as Remicade in 5-mg/kg intravenous infusions over 2 hours – forthwith, and at 2 and 6 weeks after the first infusion – in accordance with local prescribing guidelines.

Participants randomised to ciclosporin received it as Sandimmun by continuous infusion of 2 mg/kg/day. We asked sites to change the infusion every 6 hours, using non-polyvinyl chloride (PVC) bags and administration sets. Intravenous treatment continued for up to 7 days if successful. They switched participants responding to ciclosporin to twice-daily oral doses delivering 5.5 mg/kg/day, and adjusted doses to achieve trough ciclosporin concentration of 100–200 ng/ml. They measured whole-blood ciclosporin levels according to local practice, ideally 48 hours after oral therapy and then every 2 weeks. After 12 weeks, treatment was at the discretion of the participant's consultant.

We asked centres to consult the SPC for Remicade or Sandimmun and oral ciclosporin (all available online) at the time of first prescription.

For both treatments we gave centres discretion to start azathioprine or 6-mercaptopurine at therapeutic doses in week 4. We asked them to eliminate steroids by week 12 in participants who remained well, but to reinstate them in participants who became symptomatic. We also asked centres to give co-trimoxazole as prophylaxis against *Pneumocystis jiroveci* (formerly *carinii*) pneumonia in both groups.

Outcome measures

Primary outcome

The primary outcome was the AUC of CUCQ scores. This is equivalent to QAS weighted by scores on the disease-specific CUCQ. We concurrently validated the CUCQ, which extends the validated UK-IBDQ[61] to cover acute illness and colectomy.

Secondary outcomes

(a) Disease-specific QoL, measured by the CUCQ.
(b) and (c) Generic QoL, measured by the SF-12.[62]
(d) Mortality.
(e) Colectomies, both emergency and planned.
(f) AEs.
(g) Readmissions, including those for causes other than UC.
(h) Malignancies.
(i) Serious infections.
(j) Renal disorders.
(k) Disease activity, using the criteria proposed by Truelove and Witts.[4]

Economic outcomes

(l) NHS costs.
(m) HRQoL, measured by EQ-5D.[63]
(n) Participants' time off work.

Qualitative outcomes

(o) Participants' views of their drugs and their consequences.
(p) Professional views of both drugs and their consequences.

Adverse events

Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031 describe thus:[64]

- AE: any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by, or related to, that product.
- AR: any untoward and unintended response to a medicinal product which is related to any dose administered to the subject.
- Unexpected adverse reaction: an adverse reaction, the nature and severity of which is not consistent with the information in the SPC for the medicinal product.
- SAE or serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR): any AE, adverse reaction or unexpected adverse reaction, respectively, that:

  i. results in death
  ii. is life-threatening
  iii. requires hospitalisation or prolongation of existing hospitalisation
  iv. results in persistent or significant disability or incapacity; or
  v. is a congenital anomaly or birth defect.

Causality

Causality is the degree to which an untoward medical occurrence can be attributed to the trial intervention rather than the underlying UC. We used the subjective scale: unrelated, unlikely to be related, possibly related, probably related or definitely related. We classed only the last three as ARs or SARs having a causal relationship. However, we did not class events caused by UC, notably worsening colitis or initial steroid resistance, as ARs. We reported SARs to the Medicines and Healthcare products Regulatory Agency (MHRA) annually.

Expectedness

We considered AEs, ARs, SAEs and SARs as 'unexpected' if their nature and severity was not consistent with the relevant SPC. Expected events included:

- progression or exacerbation of the participant's underlying UC, including clinical sequelae of progression, such as worsening diarrhoea or abdominal pain
- medical or surgical procedures including surgery and endoscopy; however, we considered events that led to procedures and surgical sequelae, such as pleural effusion or small bowel obstruction, separately
- conditions or symptoms present or detected before the first dose that did not worsen
- recognised undesirable effects found in the current SPCs for Remicade, Sandimmun or Neoral; as SPCs updated regularly during the trial, we recommended that PIs consult the versions online.

Monitoring adverse events

In view of the extensive side effects of both trial drugs documented in their SPCs, and the many sequelae of disease progression, the protocol stipulated that we did not require expedited reporting of serious events from sites, unless they were unexpected, in which case we asked for notification within 24 hours.

We designed adverse event screening forms (AESFs) to enable local PIs to assess seriousness, causality and expectedness in a logical sequence (see *Appendix 6*). Sites sent AESFs, once countersigned by local PI or authorised person, securely via FaxPress to the trial office. The CONSTRUCT data manager was responsible for initial screening of AESFs, paying particular attention to completeness, raising queries with the local team and immediately notifying the chief investigator of events that might be classified as SUSARs. If uncertain, the chief investigator discussed them with the local PI before the final decision. We entered screened AESFs onto our Generic Clinical Information System (GeneCIS; version 10i, Swansea University, Swansea) and regularly checked that they were consistent with data on colectomies reported through case report forms (CRFs). Clinicians within the trial team reviewed the accumulating data on AEs, and commented on GeneCIS, if necessary after discussion with the local team.

At the end of the study, two clinicians in the trial team reviewed all SAEs to ensure consistency of interpretation in the final report, informed by data from sites on the duration of use of the drugs beyond the 3-month intervention period specified in the protocol. Once that period was complete, clinical management varied from participant to participant according to their progress and the clinical judgement of the local team. The reviewers also took the different pharmacokinetic profiles of the trial drugs into account because the bio-availability of ciclosporin is short-lived, whereas bio-availability of infliximab can persist until 6 months after the last infusion. With the exception of malignancy, therefore, we judged relatedness unlikely if the event occurred more than 1 month after ciclosporin, or more than 6 months after infliximab.

Problems caused by UC and the trial drugs may coincide in a single event. When an AESF documented a serious event, usually admission, and included more than one problem (e.g. abnormal liver and renal function tests), we used clinical judgement to decide which related to the drug and which was the prime cause of admission, and classified SAEs and reactions by body system.

Data collection

Baseline and follow-up data

At recruitment to cohort, we collected:

i. sociodemographic details: age, sex, ethnic group and truncated post codes, used to generate measures of social deprivation (Indices of Multiple Deprivation for England, Welsh Index of Multiple Deprivation, Carstairs Deprivation Scores for Scotland and Townsend scores for all three countries)
ii. details of admission
iii. disease history, including presenting complaint, time since first diagnosis and previous treatment, including any previous surgery, or biologic or steroid therapies
iv. comorbidities, in particular cardiorespiratory, liver or renal disease, diabetes mellitus or hypertension
v. UC signs and symptoms, including duration of symptoms in current episode, stool frequency, blood pressure, pulse and temperature
vi. current treatment, including type, dose and duration of steroid therapy
vii. pathology results, including full blood count, inflammatory markers, liver and renal function tests, and total cholesterol
viii. site and extent of disease according to Montreal classification of IBD[65]
ix. histopathology results, including stool culture and histological diagnosis
x. family history of IBD
xi. height, weight and smoking status.

At 3 and 6 months after randomisation, and at 6-monthly intervals until 36 months, we collected clinical and resource-use data from participants' records (see *Appendix 7*).

Process of data collection

Research staff at trial sites asked all trial participants to complete the Participant Baseline Questionnaire including the CUCQ, SF-12, EQ-5D and questions on primary care resource use (see *Appendix 8*); and the similar Participant Follow-up Questionnaire (PFQ) which also included questions about intercurrent events at 3, 6 and 12 months, and at 18, 24, 30 and 36 months if they reached these time points before March 2014 (see *Appendix 9*). Following admission a baseline CRF was completed by research staff to document demographic and clinical details (see *Appendix 10*).

We asked trial sites to arrange outpatient appointments to coincide with these times whenever compatible with routine clinical management. Local research staff posted PFQs to participants and asked them to bring completed questionnaires to clinics. Participants could either complete and return them by post or seek help at the clinic. We also asked sites to complete CRFs recording intercurrent events, secondary care resource use and drug treatment at these times, preferably at the outpatient appointments, or else from medical records (see *Appendix 11*).

The trial office sent Post-Colectomy Questionnaires (PCQs) and business reply envelopes to trial participants who underwent colectomy on discharge following surgery and at 4, 8 and 12 weeks thereafter (see *Appendix 12*). This PCQ included the CUCQ+, the post-colectomy version of the CUCQ and the EQ-5D.

Electronic data capture

We captured designed data on our existing GeneCIS, based on the Oracle(R) object-relational database management system (RDBMS version 10g, Oracle Corporation UK Ltd, Reading). The system is implemented in a three-tier architecture and remotely hosted in a professionally managed, secure environment. With support from local information technology departments, we provided access to hospital sites over the NHS N3 network.

We customised GeneCIS to support the trial following a detailed evaluation of requirements, including process mapping. The resulting electronic data capture structure reflected trial data requirements organised in a clinically logical manner. GeneCIS includes data validity controls, including predefined pick lists, and format and range constraints. We provided contextual guidance as help text and used system alerts to warn users when specific combinations of entered data affected eligibility, the potential for AEs or other important items.

Sites could choose either to enter data collection forms into GeneCIS locally or send completed forms by secure FaxPress to the trial office. Sixteen sites used local data entry; the rest faxed paper forms. The basic system and user interface were identical at sites and the trial office.

Data management and record keeping

All data acquisition, storage, transmission and use complied with the Data Protection Act.[66] The trial office recorded forms received on a bespoke Microsoft Access® 2007 database (Microsoft Corporation, Redmond, WA, USA) for tracking paperwork, and stored all forms in locked cabinets within a secure office with controlled access. We backed up GeneCIS and Access databases every day.

All GeneCIS users had role-based access to the system, including trial staff engaged in system configuration, data entry, helpdesk support or quality assurance. Those with authorised access to identifiable data did not contribute to analysis. Qualitative researchers had access to identifiable data to contact participants, but not to their clinical data. Trial sites had access only to identifiable data for their participants and could not view any other records.

We extracted data for analysis in pseudonymised form identified by participants' trial numbers.

Data quality and information governance

We asked PIs to maintain site delegation logs authorising staff to perform defined tasks, to sign off any changes and to send them to the trial manager. When we updated trial documents including CRFs, we circulated new versions to sites with appropriate instructions. Sites replaced previous versions but retained them in trial site files.

We asked those making essential changes to data collected on paper to strike the original entry only once, insert the new data, and record the date and initials of the person responsible. GeneCIS maintained an electronic audit trail by annotating all data with the user, date and time of entry. It also checked data at entry, notably for correct format and within specified ranges. We subjected the resulting data to rigorous quality assurance, compared all anomalies with the paper source documents and consulted local staff when necessary.

We transcribed and reviewed interview data as soon as possible. We analysed the final transcripts without identifying patient, professional or hospital.

Routine data

Funded research data collection continued until March 2014. We plan to supplement the designed baseline data collected from cohort and trial participants with routinely collected data, including Hospital Episode Statistics (and the equivalent in Wales and Scotland), and mortality from the Office for National Statistics. We plan to continue follow-up for up to 10 years by linking routine mortality, inpatient and primary care data. Record linkage will use the existing facilities of the Farr Institute at Swansea University Medical School. Using these information sources, we plan to monitor all participants' long-term outcomes, notably mortality, colectomies both emergency and elective, and major morbidity including hospitalisation and surgery, and thus most of their NHS costs. Hence we aim to achieve long-term follow-up of both trial participants and a large comprehensive cohort of patients with UC.

Qualitative methods

Trial participant interviews

To understand trial participants' experiences and perceptions of treatment by infliximab, ciclosporin and surgery, we conducted telephone interviews at about 3 and 12 months after recruitment. We aimed to investigate their priorities for their health and well-being, and their perceptions of taking the drugs, side effects and response to treatment.

We first sought consent to interview when recruiting participants to the CONSTRUCT cohort. We sampled interviewees from those subsequently recruited to the trial. Hence they had all been admitted with ASC and received either infliximab or ciclosporin. We contacted those sampled following their first outpatient appointment after discharge, invited them to take part and arranged convenient 1-hour slots to enable them to talk freely without feeling rushed. As more than 50 trial sites across the UK contributed participants, interviews by telephone to participants' homes enabled us to cover the trial population, minimise cost and ensure confidentiality.

Trained qualitative researchers used a semistructured approach to guide participants through the interview questions and give them the opportunity to develop their responses and raise issues that were important to them. The opening questions of the first interview schedule encouraged participants to think and talk about their health, what was important about it, and what good and bad health meant to them (see *Appendix 13*). More specific questions followed about their experiences of treatment, drug regimes and health care, and about their outcomes. We soon recognised that some participants had already required surgery for their colitis. We therefore adapted the interview schedule to capture the views of these participants (see *Appendix 14*).

At the end of each of these initial interviews, we asked participants to take part in a second interview about 12 months later to explore their subsequent experiences. For those, we used similar interview schedules but added questions, notably to explore changes in their health, in their opinions of treatment and in their interactions with health-care professionals (see *Appendix 15*). Again, we arranged convenient 1-hour slots for telephone interviews.

Health-care professional interviews

These aimed to gain insight into professional preferences between the two drugs and their personal contribution to the trial. Our specific objectives were to explore their views about:

- administration of the two drugs, including ease of handling
- effects of the drugs on health-care provision
- personal preferences between the drugs
- drug regulation and current policy
- surgery for UC
- equipoise in recruiting to the trial.

We therefore planned semistructured interviews lasting 30–40 minutes with flexibility for interviewees to expand on important issues and access their broad knowledge base. Our schedule covered interviewees' beliefs and ways of working; aspects of drug provision that may affect preferences; their interaction with patients and others; and their contribution to the trial (see *Appendices 16* and *17*). We offered interviews face to face or over the telephone. We conducted separate interviews with consultants and nurses to provide a richer understanding of differences between professional groups. With participants' consent we recorded and transcribed interviews for analysis.

Definition and validation of outcome measures

Background

We are entirely committed to the philosophy, expounded by NICE and implemented by the National Institute for Health Research (NIHR), that the ultimate criteria for interventions in health care are clinical effectiveness and cost-effectiveness in improving the survival and QoL of patients over extended periods. Although we admire how the GETAID investigators implemented the CySIF trial with little funding, they recruited only 110 patients, followed them for only 98 days and reported only on 'treatment failures'. This is not a good basis for NHS investment decisions worth hundreds of millions of pounds. Instead we chose QAS as our primary outcome and recruited enough participants to yield the power to discriminate between two contrasting drugs. That still left us with the task of developing and validating a comprehensive patient-reported outcome measure (PROM) applicable across the broad spectrum of disease severity within UC.

There are several disease-specific QoL measures for patients with IBD.[18,67–71] The most widely used is the McMaster Inflammatory Bowel Disease Questionnaire.[18,67,68,72,73] As it had not been validated for the UK, we previously conducted a development and validation study to anglicise it as the UK-IBDQ.[61] As this was a community study, however, we recognised in designing CONSTRUCT within acute care that, to avoid ceiling effects, we had to modify the UK-IBDQ by extending the range of responses for all items to include more severe replies; the number of items to include more questions addressing severe symptoms; and the frequency of administration in participants undergoing surgery. Furthermore, the UK-IBDQ has no questions about the impact on QoL of colectomy, which reportedly happens to 9–21% of those with UC.[74–76] We therefore derived from the UK-IBDQ a PROM for patients suffering from moderate to severe symptoms of Crohn's or UC with or without stoma. We called this the CUCQ in its basic form, and the CUCQ plus stoma extension (CUCQ+) in its extended form. Preliminary validation of the CUCQ confirmed that it met essential psychometric criteria,[77] with the result that the national IBD registry adopted it. Although we developed the CUCQ as a tool for both conditions, we validated it only on UC patients. As the development and concurrent validation of CUCQ and CUCQ+ underpin the primary analysis of CONSTRUCT, we now describe that validation.

Methods

We used the standard psychometric approach outlined by Streiner and Norman[78] to develop and validate the CUCQ and CUCQ+ in three stages:

- item generation
- initial development in the CONSTRUCT cohort
- definitive validation in the CONSTRUCT trial sample.

We used the 32 UK-IBDQ items [see *Appendix 8, Section A: Crohn's and Colitis Questionnaire (CCQ)*], as the basis for developing the CUCQ and CUCQ+. We also reviewed the literature on PROMs in gastroenterology to identify additional items. After drafting the CUCQ and CUCQ+, we recruited an expert panel of gastroenterologists, outcome specialists, statisticians and patients to review the resulting questions and response options, and ensure they were appropriate for UC patients.

We piloted the draft questionnaires on a sample of 20 UC patients with or without stoma from Neath Port Talbot Hospital, Port Talbot, who were not participating in CONSTRUCT. We asked them to complete CUCQ or CUCQ+ as appropriate and added four supplementary questions:

- Did you find any of the questions difficult to understand?
- Was there any question you did not want to answer?
- Was there any aspect of your bowel condition not covered by these questions?
- Did you find any of these questions not applicable to you?

For our initial validation, we used patients recruited to the CONSTRUCT cohort but not the trial, who had therefore completed the CUCQ at baseline. Of the 32 CUCQ questions (see *Appendix 18*), six were not relevant to post-colectomy participants:

- Q1: On how many days over the last 2 weeks have you had loose or runny bowel movements?
- Q2: On how many days in the last 2 weeks have you noticed blood in your stools?
- Q6: On how many days over the last 2 weeks have you opened your bowels more than three times a day?
- Q9: On how many days over the last 2 weeks have your bowels opened accidentally?
- Q24: On how many days over the last 2 weeks have you wanted to go back to the toilet after you thought you had emptied your bowels?
- Q26: On how many days over the last 2 weeks have you had to rush to the toilet?

We therefore designed the CUCQ+ (see *Appendix 9, For patients with stoma*), with 10 stoma-specific questions replacing these six questions, making a total of 36 questions.

- S1: On how many days over the last 2 weeks have you been afraid that other people might hear your stoma?
- S2: On how many days over the last 2 weeks have you been worried that other people might smell your stools?
- S3: On how many days over the last 2 weeks have you been worried about possible leakage from your stoma bag?
- S4: On how many days over the last 2 weeks have you had problems with care for your stoma?
- S5: On how many days over the last 2 weeks have you found the skin around your stoma irritated?
- S6: In the last 2 weeks have you felt embarrassed because of your stoma?
- S7: In the last 2 weeks have you felt less complete because of your stoma?
- S8: In the last 2 weeks have you felt less attractive as a result of your stoma?
- S9: In the last 2 weeks have you felt less feminine/masculine as a result of your stoma?
- S10: In the last 2 weeks have you been dissatisfied with your body as a result of your stoma?

To calculate scores for participants who had not undergone surgery, we used the 32 CUCQ questions. For post-colectomy participants, we used the 10 stoma-specific questions and the 26 stoma-relevant CUCQ questions to calculate CUCQ+ scores. In analysing and validating both CUCQ and CUCQ+, we calculated scores as follows:

1. We scored questions with four responses as 0, 1, 2 or 3 in ascending severity.
2. We scored questions with responses between 0 and 14 days as the actual value.
3. We reversed the scoring of questions with wording in the reverse direction (Q7, Q22 and Q32) to code all questions in the same direction.
4. We rescaled questions between 0 and 1 by dividing actual responses by their maximum score (3 or 14).
5. We calculated CUCQ scores for non-colectomy participants, and CUCQ+ scores for post-colectomy participants, by summing all valid responses and dividing by the number of completed questions.
6. So the lower the CUCQ+ (or CUCQ score), the better the respondent's health. In analysing the AUC, however, it is necessary to subtract the total CUCQ+ (or CUCQ) score from 1, so that higher scores show better health, consistent with both EQ-5D and SF-12.

However, we calculated CUCQ and CUCQ+ scores only when participants had responded to at least 75% of the questions – 24 out of 32 or 27 out of 36, respectively. If participants had completed fewer than 75% of questions, we treated the total CUCQ or CUCQ+ score as missing. To give equal weight to each question answered, our analysis plan used the original 32 CUCQ questions for non-colectomy participants and the 36 CUCQ+ questions for post-colectomy participants. To test the sensitivity of our findings to this simple approach, we repeated the analysis in two ways. First, we gave equal weight to core scores and stoma-specific scores, thus giving more weight to the latter. Second, we gave the stoma-specific scores 6 out of 26 of the weight given to core scores, as the original UK-IBDQ comprised 26 questions relevant to stomas and 6 questions inapplicable to stomas, thus giving less weight to stoma-specific scores.

Still following Streiner and Norman,[78] we conducted initial psychometric development of the CUCQ on CONSTRUCT cohort patients (who had not had a colectomy):

1. We examined the 32 sets of response frequencies for floor or ceiling effects.
2. We calculated the Kaiser–Meyer–Olkin measure of sampling adequacy and Bartlett's test to judge whether or not principal component analysis was appropriate.
3. We calculated Cronbach's alpha (which should exceed 0.7 for good internal consistency).
4. We calculated item-total correlations for each question (which should exceed 0.2 for good homogeneity).
5. We undertook principal component analysis to assess the underlying structure; we considered factors important if their eigenvalues were clearly > 1, and individual questions as useful if their factor loadings exceeded 0.4.
6. We assessed the construct validity of the scale by examining the correlation between the CUCQ and two generic QoL questionnaires (EQ-5D and SF-12).

Then we undertook definitive validation of the CUCQ and CUCQ+ on the CONSTRUCT trial sample. First, we compared demographic characteristics of that sample with the cohort to ensure that they were similar. Then we analysed the trial sample in essentially the same psychometric way as the cohort, and tested whether or not the principal components arising from these two analyses were consistent. Finally, we repeated the principal component analysis of the trial sample after 12 months and tested whether or not principal components arising from the CUCQ for non-colectomy patients and those arising from the CUCQ+ for post-colectomy patients were consistent.

We also analysed reliability and responsiveness for the trial sample, initially combining CUCQ and CUCQ+ and then comparing them. We assessed test–retest reliability of the scales on participants who reported no change in their condition at successive assessments; we considered scales reproducible if intraclass correlation exceeded 0.75. We assessed responsiveness of the scales to change on participants who reported a change in their condition; we considered scales responsive if the responsiveness ratio exceeded 0.5.

Analysis

Clinical effectiveness

Primary analysis was by treatment allocated, reflecting the pragmatic nature of the trial design. *Figure 1* illustrates the primary outcome measure – the AUC defined by CUCQ scores at baseline and all available time points before 31 March 2014 – also known as 'QAS'. Within research into PROMs, there is a general convention that for generic PROMs 'higher is better' whereas for condition-specific PROMs 'lower is better'. However, in order to be consistent with both EQ-5D and SF-12 we have subtracted calculated CUCQ scores from 1, so that higher is better.

We calculated this area by summing the areas of the component trapezia, thus assuming linearity between successive CUCQ scores, and setting the score at the end of follow-up equal to the last recorded score (last one carried forward). This method accommodates both missing values and extra values like those arising from PCQs.

The main analysis used a general linear model to estimate differences in QAS between groups, adjusting for covariates that may affect this measure, including trial site; data collected while assessing eligibility for cohort and trial, notably the sociodemographic variables age, gender, ethnic group, QoL, disease severity; current immunosuppressant therapy (using a binary indicator set equal to 1 for participants taking azathioprine, 6-mercaptopurine or methotrexate); and time in follow-up. We combined rare categories in factors like ethnic group, taking account only of observed numbers in each category and the coherence of new groupings.

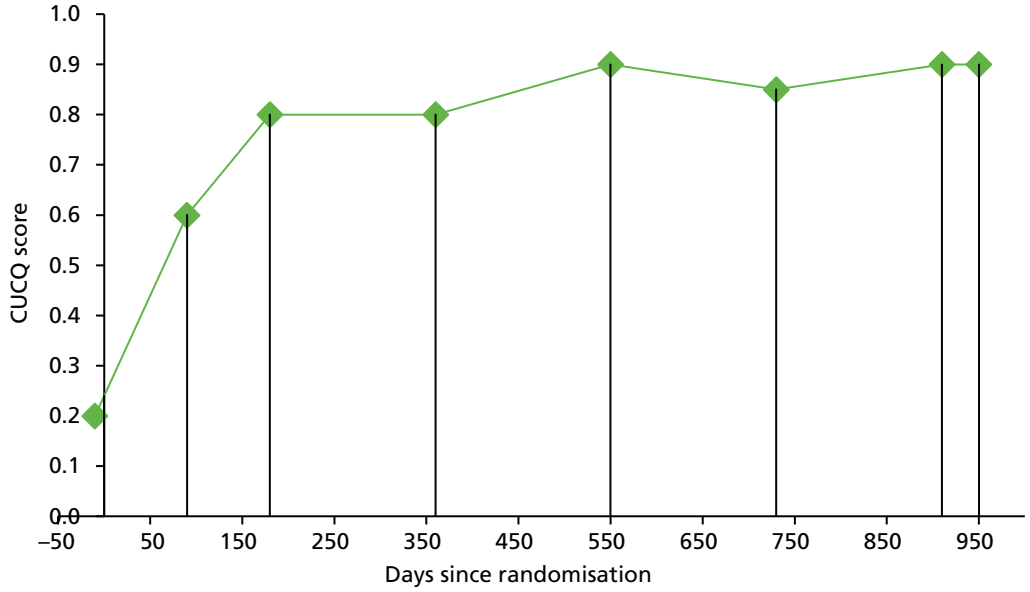

FIGURE 1 Primary outcome measure: area under the CUCQ curve.

Secondary analyses adjusted for the same covariates as primary analysis and compared between groups: QAS per day (again using general linear models); QoL scores (using methods for repeated measures); proportion of participants undergoing colectomy (using binary logistic regression); time to colectomy (censored at the end of follow-up, and analysed by Cox regression); proportion of participants suffering one or more AEs (using binary logistic regression); and mortality.

We examined residual diagnostics in analyses that assume normality, with the options of data transformation and bootstrapping when residual distributions were markedly non-normal. We excluded identified outliers and reanalysed the revised data sets. We supplemented analyses by descriptive comparisons between groups in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines, including estimates with 95% confidence intervals (CIs), representing two-tailed tests at the 5% significance level.

Imputation of missing data

We used statistical imputation of censored and missing data to impute costs and QoL for all participants who generate data on survival, colectomy or QoL after randomisation. Thus we excluded participants without follow-up data, as calculation of QAS requires one or more CUCQ scores in follow-up.

None of the questionnaires has an official algorithm for imputing missing answers. So we imputed missing values within participant interviews using the Expectation Maximisation option in the Missing Value Analysis module within Statistical Package for the Social Sciences version 22 (SPSS Inc., Chicago, IL, USA), and calculated scores according to the instructions for the measure in question. When necessary we imputed missing scale and subscale scores by regression using the available values of that score at other times and the allocated treatment group. To avoid introducing outliers, we restricted imputed scores to the range observed for that measure in that group.

Cost-effectiveness

We collected data on NHS resource use from CRFs and PFQs completed at each follow-up time point, supplemented by data from other sources, notably, PCQs completed by patients undergoing colectomy, SAE forms and any relevant information provided by sites. Together CRFs covered resource use over the whole period during which participants were in the trial because each CRF recorded resource use since the previous CRF. To minimise recall bias, however, PFQs reported resource use over the previous 3 months.[79] This left gaps in the data, which we imputed. We estimated all costs in 2012–13 prices inflated when necessary using the NHS Pay and Prices Index. We applied a discount rate of 3.5% per annum to costs occurring beyond 12 months. We applied the same annual discount rate of 3.5% for QALYs beyond 12 months.

Participant Baseline Questionnaires recorded data on resource use in the 3 months before their consent for use as a covariate to account for any existing imbalances in resource use. As this resource use preceded randomisation, we did not include it in the costs analysed.

We based the cost of infusing ciclosporin (Sandimmun) on reported dose and duration in whole vials; and oral ciclosporin on reported dose and duration in whole dispensing packs (*Table 2*). We also added the cost of monitoring ciclosporin levels. We based the cost of infliximab (Remicade) on the reported dose in whole vials and, for infusions after the initial episode in hospital, we added the cost of admitting participants as day cases (£311).

We also estimated the cost of preparing and delivering drug infusions from a questionnaire completed by 42 trial sites (81% of the 52 recruiting sites). For typical infusions they reported who mixes the infusion (nurse or pharmacist); the time taken to prepare the infusion; and the frequency of bag changes for ciclosporin participants. We multiplied by relevant unit costs:[81] nurse £41 per hour; pharmacist £47 per hour; and £1.50 per infusion or bag change. For centres that did not respond to the questionnaire we imputed preparation and delivery costs by mean substitution.

Case report forms recorded data on hospital episodes, including the episode leading to recruitment. PFQs reported data on admissions to hospitals other than the trial site. To these we applied unit costs from either the 2012–13 Healthcare Resource Group (HRG) code FZ37 (non-elective episodes of inflamatory bowel disease without interventions, 19 years and over) or the HRG code FZ74 (non-elective episodes complex large intestine procedure, 19 years and over) and 'complications and comorbidity' (CC) codes based on participants' length of stay in hospital (see *Table 3*). We costed days in hospital beyond the average for that HRG-CC at the published rate. For subsequent surgical procedures we used expert clinical opinion to identify the 2012–13 HRG code most appropriate to the information recorded as free text on the CRF, which often detailed specific procedures undertaken during each operation. *Table 3* shows selected secondary procedures and their HRG codes, but not the many CC codes per HRG. Again, we used CC codes based on participants' lengths of stay and costed excess days at published rates.

TABLE 2 Trial drugs: published unit costs (£)

Drug	Dose	Unit cost (£)
Ciclosporin (Sandimmun)	50 mg/ml, 1-ml ampoules	£1.94
Oral ciclosporin	100 mg, 30-capsule pack	
Neoral		£72.57
Deximune® (Dexcel Pharma Ltd)		£51.30
Capimune® (Mylan)		£51.30
Infliximab (Remicade)	100-mg vial	£419.62

Source of costs: *British National Formulary*.[80]

TABLE 3 Published unit costs for hospital admission (£)

HRG code		National average unit cost (£)	Average length of stay (days)	Cost per day (£)	Excess bed-day rate (£)
Without surgery[a]					
Non-elective: IBD without interventions, 19 years and over (FZ37)	CC 0	1546	3.78	409	243
	CC 1–2	1692	4.39	385	237
	CC 3–4	2218	5.62	395	230
	CC 5+	12,630	7.82	336	229
With surgery (primary procedure)[a]					
Non-elective: complex large intestine procedure, 19 years and over (FZ74)	CC 0–2	5822	8.92	653	196
	CC 3–5	7573	12.60	601	162
	CC 6–8	8623	17.21	501	390
	CC 9+	10,136	19.93	509	229
With surgery (selected subsequent procedures)[b]					
Closure of stoma	FZ13		Costs dependent on CC code		
Ileoanal pouch	FZ69				
Reversal of ileostomy	FZ83				
Proctecomy, ileoanal pouch, loop ileostomy	FZ73				
Completion proctectomy	FZ77				

a NHS reference costs 2012–13.[82]
b Expert clinical opinion.

Case report forms also recorded data on non-trial drugs administered to participants as inpatients. When the CRF did not record dose, we assumed that the participant had received the lowest dose recommended in the *British National Formulary*.[80] When the CRF did not record duration, we assumed that participants took any prescribed gastroenterology drugs throughout their hospital stay; we extended this rule to seven other drugs – alendronic acid, amlodipine, bisoprolol fumarate, clopidogrel, gliclazide, losartan potassium and rampiril. For all other inpatient drugs without specified duration we costed a single day's dose. As we costed over 1800 drugs and formulations, we do not report them all here.

Participant Follow-up Questionnaires also reported data on non-trial drugs prescribed while participants were in the community. We costed these according to the dose and duration of treatment recommended by the *British National Formulary* in whole packs. Where duration was not recorded we assumed that the participant received a single pack.

Finally, PFQs reported on participants' other encounters with the NHS, including general practitioners (GPs), nurses and other professionals at surgery, at home, in the community or by telephone; NHS Direct or NHS24; hospital emergency departments; and outpatient clinics (*Table 4*). Our main source of unit costs was Curtis,[81] who included salaries and expenses, costs of training and qualifications, and capital and overhead costs.

TABLE 4 NHS resource use unit costs (£)

Resource	Details	Source	Unit cost (£)
NHS contacts			
A&E visits	Treatments leading to admitted (not admitted) £146 (£112)	Curtis 2012[83]	112.00
Admitted nights	NIHR Clinical Research Network industry costing template	NIHR 2014[84]	386.37
Clinic visit	As outpatient appointment. Weighted average £135 (p. 107)	Curtis 2013[81]	135.00
Consultant: medical (p. 245) – per contract hour £139			
Clinic visit	Length of contact assumed same as GP (11.7 minutes) at £27.11	Curtis 2013[81]	27.11
Telephone call	Length of telephone call assumed same as GP (7.1 minutes) at £16.45	Curtis 2013[81]	16.45
Consultant: psychiatric (p. 246) – per contract hour £140			
Clinic visit	Length of contact assumed same as GP (11.7 minutes) at £27.29	Curtis 2013[81]	27.29
Telephone call	Length of telephone call assumed same as GP (7.1 minutes) at £16.57	Curtis 2013[81]	16.57
Consultant: surgical (p. 246) – per contract hour £140			
Clinic visit	Length of contact assumed same as GP (11.7 minutes) at £27.30	Curtis 2013[81]	27.30
Dietitian	(p. 226) Hourly rate £35. Assumed session length same as GP practice nurse – 15.5 minutes	Curtis 2013[81]	9.04
GP (including travel, direct staff and qualification costs) (p. 191)			
At practice	Per patient contact lasting 11.7 minutes	Curtis 2013[81]	45.00
Home visit	Per out of surgery visit lasting 23.4 minutes	Curtis 2013[81]	114.00
Telephone call	Per telephone consultation lasting 7.1 minutes	Curtis 2013[81]	27.00
Health visitor			
Home visit	(p. 185) Per hour of home visiting – £71. Assumed length of visit same as GP home visit – 23.4 minutes	Curtis 2013[81]	27.69
Telephone call	(p. 185) Per hour of patient-related work – £59. Assumed length of telephone call same as GP practice nurse (6 minutes)	Curtis 2013[81]	5.90
Hospital (telephone call)	Assumed contact with clinical nurse specialist (p. 189) per hour of client contact – £90. Rate per 6 minutes' telephone contact – £9	Curtis 2013[81]	9.00
Midwife	(p. 186) Costed as nurse specialist (community) band 6 – £49 per hour. Length of contact assumed same as GP practice nurse – 15.5 minutes	Curtis 2013[81]	12.66
NHS Direct (telephone call)		Digitalhealth.net 2013[85]	20.00
Nurse (GP practice)	GP practice nurse (p. 188) per hour of face-to-face contact rate – £52. Per average contact lasting 15.5 minutes – £13.43	Curtis 2013[81]	13.43
Nurse (home visit)	Community nurse (including district nursing sister, district nurse) (p. 183) per hour of home visiting (including travel) – £70. Assumed length of home visit same as GP (23.4 minutes) – £27.30	Curtis 2013[81]	27.30

TABLE 4 NHS resource use unit costs (£) (*continued*)

Resource	Details	Source	Unit cost (£)
Nurse specialist (p. 186) hourly rate £49			
Clinic visit	Assumed length of visit same as GP practice nurse – 15.5 minutes	Curtis 2013[81]	12.66
Home visit	Assumed length of visit same as GP home visit – 23.4 minutes	Curtis 2013[81]	19.11
Telephone call	Length of telephone call assumed as calls to hospital (6 minutes) at £4.90	Curtis 2013[81]	4.90
Outpatient visit: gastroenterology	Service code 301	Department of Health 2015[82]	137.00
Outpatient visit: general	Weighted average £135 (p. 107)	Curtis 2013[81]	135.00
Paramedic visit	Ambulance services – see, treat and refer (p. 107)	Curtis 2013[81]	177.00
Pharmacist	(p. 228) Per hour of direct clinical patient time – £94. Assumed length of session same as GP visit – 11.7 minutes	Curtis 2013[81]	18.33
Phlebotomist:	NHS Jobs (www.jobs.nhs.uk) specify that phlebotomists are clinical support workers with a salary between £14,000 and £22,000 p.a.	Curtis 2013[81]	4.10
Clinic visit	Clinical support worker (p. 237) hourly rate £21. Assumed length of contact same as GP visit – 11.7 minutes	Curtis 2013[81]	4.10
Home visit	Clinical support worker (community) (see p. 187) hourly rate – £30. Assumed length of contact same as GP home visit 23.4 minutes	Curtis 2013[81]	11.70
Physiotherapist	(p. 223) Hourly rate – £36. Assumed session length – 30 minutes	Curtis 2013[81]	18.00
Psychologist	(p. 179) Clinical psychologist – £134 per hour of client contact. Length of contact assumed same as GP practice nurse – 15.5 minutes	Curtis 2013[81]	34.62
Ultrasound	Less than 20 minutes	Department of Health 2015[82]	51.00
Walk-in centre	(p. 109) Walk-in services leading to not admitted	Digitalhealth.net 2013[85]	41.00
Tests and investigations			
Ciclosporin levels		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	22.00
Abdominal X-ray		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	65.00
Barium enema		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	215.00

continued

TABLE 4 NHS resource use unit costs (£) (*continued*)

Resource	Details	Source	Unit cost (£)
Barium follow through		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	350.00
Barium meal		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	175.00
Calcium and phosphate		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	4.10
Chest X-ray		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	50.00
Clotting profile		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	3.28
Colonoscopy with biopsy		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	827.00
Colonoscopy without biopsy		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	767.00
C-reactive protein		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	3.00
CT scan		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	475.24
Erythrocyte sedimentation rate		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	3.28
Flexible sigmoidoscopy		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	344.00

TABLE 4 NHS resource use unit costs (£) (*continued*)

Resource	Details	Source	Unit cost (£)
Full blood count		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	3.95
Liver function tests		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	4.45
MRI scan		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	574.91
Oesophagogastroduodenoscopy		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	610.00
Rigid sigmoidoscopy		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	210.11
Stool culture/testing		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	2.70
Thiopurine methyltransferase testing		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	31.70
Urea and electrolytes		Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards	3.65

A&E, accident and emergency; CT, computerised tomography; MRI, magnetic resonance imaging; p.a., per annum.

Case report forms also recorded data on the number and type of investigations undertaken. We estimated unit costs for these from two local but dissimilar trial sites – in Cardiff and Swansea (see *Table 4*). When participants died or withdrew further access to medical records, sites completed the next CRF from data available up to that time.

The primary outcome for economic analysis was QALYs estimated from the EQ-5D questionnaire within the PFQ administered at baseline and subsequent assessments. Participants who underwent colectomy also completed the EQ-5D within the PCQ at discharge from surgery and 4, 8 and 12 weeks thereafter. EQ-5D assesses HRQoL on five dimensions – mobility, self-care, usual activities, pain or discomfort, and anxiety or depression – using three levels for each dimension. We converted these to a single utility using the UK tariff.[86]

We used the methods described above to impute missing data, which can happen in three ways:

1. CRF or PFQ received missing individual resource items
2. CRF or PFQ received but not covering the entire period since previous CRF; or
3. CRF or PFQ due but not received.

In these three scenarios we imputed thus:

1. We used age, gender, weight, ethnic group, smoking status and hospital data to impute missing items. If more than two were missing, we used mean regression imputation; as regression assumes normally distributed errors, we used log-transformation when the data broke this assumption.
2. We assumed that resource use varied linearly and therefore replaced missing data by the mean of the data available before and after, weighted if necessary.
3. After checking whether or not non-responders differed from responders in sociodemographic characteristics, we using the method described in (2).
4. Censoring data occurred because of the change to protocol which meant that not every participant could be followed up for the same length of time. We studied the mechanism of censoring[87] on a range of variables including study arm. As these showed all censoring to be missing completely at random, no adjustments were made to resource data to account for any censoring effects.

We estimated total costs by aggregating participants' resource use. Although data collection for early participants could extend for 36 months, there were very few of these. Our primary analysis therefore compared costs and assessed cost-effectiveness over 30 months.

The calculation of the cost-effectiveness point estimate included all participants for whom we had EQ-5D data. In principle we aggregated their costs and QALYs over their (variable) periods in the study. To ensure that costs and QALYs covered the same periods, we compared the number of days covered by CRFs and PFQs. We fitted statistical models for NHS costs and QALYs using allocated drug, days since randomisation and the logarithm of those days as independent variables. We used the result coefficients to adjust NHS costs and QALYs to a period of 730 days.

We undertook two contrasting sensitivity analyses: the first restricted analysis to 12 months, and thus analysed all 270 participants but none of their data beyond 12 months; the second restricted analysis to 24 months and those participants who took part for at least that duration.

To account for uncertainty in the costs and QALYs used to estimate incremental cost-effectiveness in these analyses, we used non-parametric bootstrapping to generate 5000 replicates, shown in the scatterplots of the cost-effectiveness planes. The resulting cost-effectiveness acceptability curves (CEAC) show the proportion of replicates considered cost-effective at each threshold of willingness to pay for an additional QALY (including the £20,000 and £30,000 thresholds currently used by NICE).[56]

We are developing a Markov model to predict costs and QALYs beyond the follow-up period of the study. As the long-term effectiveness of both trial drugs in UC is unknown, the model will explore uncertainty in outcomes over 20 years. It will estimate the long-term probability of colectomy effects on costs and QALYs.[88]

Data to be collected for 5 years after the end of recruitment will monitor costs and effects of both trial drugs on trial patients. At regular intervals we or our successors will update the Markov model, and thus our conclusions, using the most recent data from trial participants. Any discrepancies between costs and effects modelled beyond the trial period and those actually demonstrated by the long-term follow-up will help to validate the use of economic modelling in economic evaluation for this condition.

Qualitative analysis of trial participant interviews

We analysed the 3-month interviews using both thematic and schematic methods. Thematic analysis is a structured approach that uses coding to conceptualise research data and classify them into meaningful and relevant categories.[89] Schema analysis identifies patterns and themes within data in line with study aims and interview topics; it thus combines elements of the linguistic and sociological traditions. It posits that people use cognitive simplifications to help make sense of the complex information they receive. Analysis starts with careful reading of the texts to identify linked themes paying attention to patterns of speech and the repetition of key words and phrases, noting metaphors and commonalities in their reasoning.[90]

We began thematic analysis of the initial interviews after completing four interviews. Three qualitative researchers (ACS, SW, FLR) read the transcripts and met to discuss emerging findings. They developed an analysis framework and iterative process for subsequent transcripts to refine and clarify themes and their linked categories.

A subset of the CONSTRUCT trial team then undertook the schema analysis as a group. We chose this sequence for three reasons: to validate the thematic framework by verifying that all elements were cogent and comprehensible; to engage a range of contributing disciplines; and to give those analysing other trial data sets insight into the lives of participants. We asked each subgroup member to read transcripts from three participants; one treated with infliximab, another with ciclosporin and the last with ciclosporin followed by surgery; and to write one-page schematic overviews of the main features of each transcript about participants' stories relating to QoL and treatment regimes. We circulated these overviews to all group members for discussion and synthesis; and the thematic analysis framework for refinement and validation.

We began the thematic analysis of the 12-month interviews after completing the analysis of the 3-month interviews. The same three qualitative researchers read the transcripts of the first four interviews and again met to discuss their findings. Another iterative process followed to identify themes that had not emerged at 3 months.

Qualitative analysis of health-care professional interviews

These transcripts underwent a thematic analysis technique known as 'framework analysis' to develop a template linking data to study aims and objectives (see *Appendix 19*). Framework analysis is a semistructured approach that, like generic thematic analysis, uses coding to conceptualise and classify research data.[89] Three qualitative researchers (FLR, CC, ACS) individually coded transcripts as they were completed. Then they met to derive a unified coding structure including essential and incidental themes and their linked categories. Continuing group work enabled them to refine the developing framework as interviews progressed, with major themes retaining both nuance and ambiguity.

Using MATRICS to synthesise results

We used the MATRICS from our previous study[57] to synthesise CONSTRUCT's findings in five steps. The MATRICS proforma comprises three 'layers' (see *Appendix 20*):

1. potential effects of the intervention(s) under evaluation (derived from the aims and objectives of the study)
2. methods used in that evaluation
3. research findings.

Step 1: identify, categorise and code effects

We derived the potential effects of CONSTRUCT from its aims and added effects that emerged over the course of the trial; we grouped them in three columns:

1. on participants
2. on gastroenterology services and professionals
3. on the rest of NHS and society.

We populated layer 1 with these effects using one cell per effect under the three defined columns, and numbered each effect.

Step 2: code methods used by CONSTRUCT

We listed each method or instrument used (e.g. CRFs, questionnaires, interviews and routine data) in layer 2 and gave each method a unique letter.

Step 3: create joint alphanumeric codes

We assigned letters to each effect in layer 1 showing how we had investigated them. For example, if disease-specific QoL was effect 2 investigated by the CUCQ questionnaire labelled B, we recorded B alongside effect 2 in layer 1. Similarly, we assigned numbers to each method in layer 2 showing all the effects they had investigated. For example, we recorded effect 2 alongside method B in layer 2. Effects investigated by more than one method have extra letters in layer 1; methods investigating more than one effect have extra numbers in layer 2.

Step 4: identify and code all research findings

We listed the individual findings from each component of CONSTRUCT in layer 3 of the MATRICS proforma. We illustrated them textually or by summary statistics, and labelled them with codes derived from layers 1 and 2 to identify the corresponding effects and methods.

Step 5: synthesise complementary findings and reorder contrasting findings

We merged comparable findings into composite statements, irrespective of which effects were investigated or methods used and listed all codes associated with each. This enabled us to show that more than one effect or method had reported the same outcome. When findings were not comparable, even opposing, we kept them as separate rows in layer 3, but put them together.

Governance and management

Ethics and research governance

The Research Ethics Committee (REC) for Wales gave ethical approval (Ref 08/MRE09/42) and each participating trust or health board gave NHS R&D approval. The trial has European Union Drug Regulating Authorities Clinical Trials number (2008-001968-36) and clinical trial authorisation from the MHRA. We have sought to conform with the Research Governance Frameworks for England,[91] Scotland[92] and Wales;[93] the principles of GCP outlined by the International Conference on Harmonisation (www.ich.org/), the European Union Directive 2001/20/EC[94] and *The Medicines for Human Use (Clinical Trials) Regulations 2004*.[64]

Trial management

We established:

- a TSC which oversaw the trial by meeting twice per year
- a DMEC which monitored trial data in accordance with an agreed charter (see *Appendix 21*) and reported to the TSC
- a Trial Management Group (TMG) comprising academics, health professionals, researchers and a representative of service users which undertook general management of the trial, met every month and reported to the TSC and funders through reports every 6 months.

The available members of the research team also met every week.

Service users

In accordance with the relevant West Wales Organisation for Rigorous Trials in Health standard operating procedure,[95] we included service users as active contributors at all stages of this trial. They provided separate members of TSC, DMEC and TMG, contributed to the research process and provided valuable insights into UC. In particular they contributed to the development of the CUCQ+, the primary outcome measure; helped to maximise recruitment rates; attended the series of report writing days; and gave much valuable help and advice outside these meetings. *Appendix 22* summarises the personal experience of one service user.

Feasibility and piloting

Before the trial began, we undertook a feasibility study to refine our understanding of the patient pathway, the CUCQ and the economic resource-use questionnaires. We then conducted a pre-pilot study to test the recruitment process up to but not including randomisation. Thereafter we used the resulting cohort of between 20 and 40 patients to test aspects of trial design beyond initial recruitment. Following the pre-pilot study, we piloted GeneCIS (our online trial data management system), participant recruitment and randomisation, and data collection processes. We asked each active centre to recruit and randomise one trial participant. We then met site PIs to learn from the pilot. As we encountered no major problems we incorporated cohort and trial participants recruited during the pilot in the main study.

Safety monitoring and reporting

Clinical trial agreements were in place at each site. Thus we delegated responsibility for adhering to GCP and reporting AEs in accordance with clinical trial regulations to site PIs and their research teams. These PIs, or others authorised by the site delegation log, recorded all AEs on AESFs and assessed the seriousness, causality and expectedness of each. If sites could not make these decisions, they referred them to the chief investigator. In view of the established and extensive side effect profile of both drugs, the protocol required expedited reporting of SUSARs, but not AEs, ARs, SAEs or SARs. We reported the number of notified SAEs and SARs to each meeting of the DMEC; and of SARs in annual safety reports to MHRA and the REC for Wales.

To help identify AEs, we gave trial participants membership cards showing their trial numbers and asked them to show this whenever they saw doctors outwith the team treating them for UC.

Quality assurance

We sought to comply with the principles of quality assurance described by the Medical Research Council (MRC) *Guidelines for Good Clinical Practice in Clinical Trials*[96] the European Union Directive 2001/20/EC,[94] *The Medicines for Human Use (Clinical Trials) Regulations 2004*,[64] and the Research Governance Frameworks for England,[91] Scotland[92] and Wales.[93]

We anonymised all research data and stored them securely. All research team members attended GCP training every 2 years and undertook trial-specific training in the protocol, recruiting participants, completing CRFs and reporting AEs. The TMG developed and reviewed a quality plan describing the quality assurance and quality control processes implemented within the trial to ensure a high level of quality. We developed fieldwork, data collection and GeneCIS handbooks to maintain consistency across trial sites.

Dissemination

We seek to comply with the CONSORT guidelines.[97] We seek to publish widely in high-impact peer-reviewed journals and disseminate trial findings at national and international conferences. We are committed to give appropriate recognition to all who have worked on the trial. We have registered CONSTRUCT in the public registry (www.controlled-trials.com/isrctn) with ISRCTN22663589.

Data sharing

In accordance with the MRC–Wellcome Trust data sharing policy, we shall make data from CONSTRUCT available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs. In particular we shall deposit anonymised data in the University of Essex data archive and thereby encourage wider use.

Summary of protocol changes

Changes to the protocol were approved by the DMEC, TSC, MHRA, REC and the NIHR HTA programme.

Before protocol publication

Number of sites

We had initially planned to work with 40 sites, but it became clear that a smaller number of patients were being recruited per site than we had anticipated so we increased the number of sites.

Power calculation

In June 2012 we obtained approval to increase the target effect size from 0.3 to 0.35, still in the range of small 'effect' sizes; this needed at least 250 patients to provide data on survival, colectomy or QoL in each group.

The design of CONSTRUCT required a combination of survival analysis and statistical imputation to get full value from the resulting data set. As these techniques were difficult to incorporate into power calculations, we presented a simpler calculation based on *t*-tests of mean CUCQ scores at 12 months. For CONSTRUCT to detect an effect size of 0.35 in these scores (i.e. a difference between infliximab and ciclosporin groups of at least 0.35 of the population standard error), with 80% power when using a 5% significance level, required that we analysed at least 250 of the 270 participants recruited to the trial. Although more than 10% of CONSTRUCT participants were likely to drop out over the follow-up period of at least 12 months, all analyses exploited the techniques of statistical imputation used successfully by the Cancer of the Oesophagus or Gastricus: New Assessment of the Technology of Endosonography[58] and Folate Augmentation of Treatment – Evaluation of Depression[59] trials to maintain the effective sample size at 250. Our initial, more conservative, power calculation had proposed to recruit 480 participants (to yield an analysable sample of 360); not to impute missing data statistically, therefore to allow for 25% loss to follow-up; and thus to yield 80% power to detect a slightly smaller effect size of 0.30 in CUCQ scores. We amended our target to 270 participants once the difficulty of identifying patients with acute steroid-resistant UC became clear early in recruitment.

Trial intervention

Our original protocol stated that ciclosporin should be given for up to 5 days, but it was felt that stopping at 5 days might deprive patients of a response. On 21 January 2010 approval was given to increase this to 7 days and included approval for a recommendation that sites should use non-PVC bags and administration sets for ciclosporin.

Analysis

On 21 January 2010, following a suggestion by our DMEC to change the analysis, we obtained approval to change from 'quality of life at 24 months' to 'analysis using an area under the curve approach to obtain each patient's quality of life over 24 months'.

On 6 June 2012 approval was given for the primary analysis of CONSTRUCT to use full statistical imputation.

Trial inclusion/exclusion criteria

Without changing the basic content of our inclusion/exclusion criteria, we rewrote them to make them clearer to follow and approval was given on 21 January 2010.

To ensure that cohort patients were not missed, on 22 September 2010 we gained approval to:

- amend the protocol to clarify that potential patients for the cohort were those admitted with 'suspected or known colitis' rather than 'acute severe colitis'
- remove 'with blood apparent' from the cohort inclusion criteria as it may not always be apparent in patients with colitis.

To ensure that trial participants were not missed approval was given to:

- change the Mayo score (colitis severity score) in the RCT inclusion criteria from 3 to ≥ 2 as it was felt eligible patients would be excluded because of the higher score.

In June 2012 we gained approval to relax the requirement for sigmoidoscopy to assess eligibility, as feedback from sites indicated that in a patient with a previous history of UC, further sigmoidoscopy might not be done.

We were also permitted to clarify that 2–5 days of intravenous steroid treatment before a decision was made whether or not a patient had responded, was an approximate length of time as this reflected what happens in normal clinical practice.

Recruitment of participants

We had initially planned to complete recruitment over a 1-year period. However, following unforeseen delays in R&D approval and a smaller number of patients recruited per site than we had anticipated, we realised this would not be possible. Approval to lengthen the recruitment period until recruitment to the trial was complete was given on 22 September 2010. Subsequently, the NIHR HTA programme granted us a 24 month-funded extension to complete the trial.

In December 2010 we gained approval to make payments to sites to cover investigator costs at £50 per cohort and £100 per trial participant recruited.

Data collection

We took the opportunity of the 24-month extension to enhance our data collection to capture more data about QoL post colectomy and to collect this more frequently. We did this by:

- extending data collection for all trial participants, whenever recruited, until early 2014
- adding questionnaires at 18, 30 and 36 months; participant reconsent was sought where necessary
- adding four questionnaires following colectomy and any ensuing corrective surgery; participant reconsent was sought where necessary
- planning to use survival analysis, statistical missing value imputation and economic modelling to impute QoL and costs for all participants who generate data after randomisation.

We also sought approval to:

- conduct interviews with health-care professionals to elicit their views about the two drugs and their different modes of administration in response to emerging evidence of potential hidden costs in the administration of ciclosporin in particular
- conduct the second participant interview at 12 months rather than at 6 months.

Outcome measures

With agreement of the TSC and DMEC we changed the primary outcome measure to QAS weighted by scores on CUCQ and approval was given on 6 June 2012.

Since protocol publication

Economic analysis

- The economic analysis covered a 30-month period.
- The comparison of NHS resource use between the two groups did not adjust for inpatient stay in intensive care unit and high-dependency unit.
- Patient-borne costs were limited to time off work.
- The proposed long-term economic modelling has not yet been completed.

Chapter 3 Results

Recruitment

A total of 68 sites agreed to take part in the study: 62 in England, three in Scotland and three in Wales. The sites ranged from large teaching hospitals to large and small district general hospitals. One site was deactivated because of a protocol deviation.

Sixty-four sites recruited patients to the cohort and 52 of these recruited participants to the trial. The first site was activated in March 2010 with the first cohort patient recruited in May 2010 and the first trial participant randomised in June 2010. We randomised the last trial participant in February 2013 and completed follow-up in February 2014.

Over the course of the study, two sites that had recruited a total of eight cohort patients, withdrew citing the following reasons:

- one replacement PI with a treatment preference
- one site not recruiting and felt unlikely to recruit in the near future.

In addition, two sites that had not recruited to the cohort withdrew citing the following reasons:

- one PI leaving and no replacement
- one site lack of research support.

Figure 2 shows that 2065 patients were screened for the cohort and 1614 consented to join it. Of these, 276 were eligible for the trial and were randomised. Six participants were randomised in error: five randomised to ciclosporin were found to have raised cholesterol levels between randomisation and treatment and one randomised to infliximab was found to have cytomegalovirus after randomisation and one dose of infliximab. These six were therefore judged to have been randomised in error and were removed from analysis.

Centre differences in recruitment patterns

Eight sites recruited 11 or more trial participants, 17 sites recruited four to eight participants, 18 recruited two or three participants, nine recruited one participant, with 12 sites recruiting to the cohort only, whereas three sites did not recruit at all (see *Appendix 23*).

Participant flow

Figure 2 presents the CONSORT flow diagram and summarises patient throughput from recruitment of the first participant in May 2010 to randomisation of the final participant in February 2013.

Figure 3 summarises participant follow-up over the 3-, 6-, 12-, 18-, 24-, 30- and 36-month time points to the end of follow-up on 28 February 2014; 90% of participants contributed to definitive analysis.

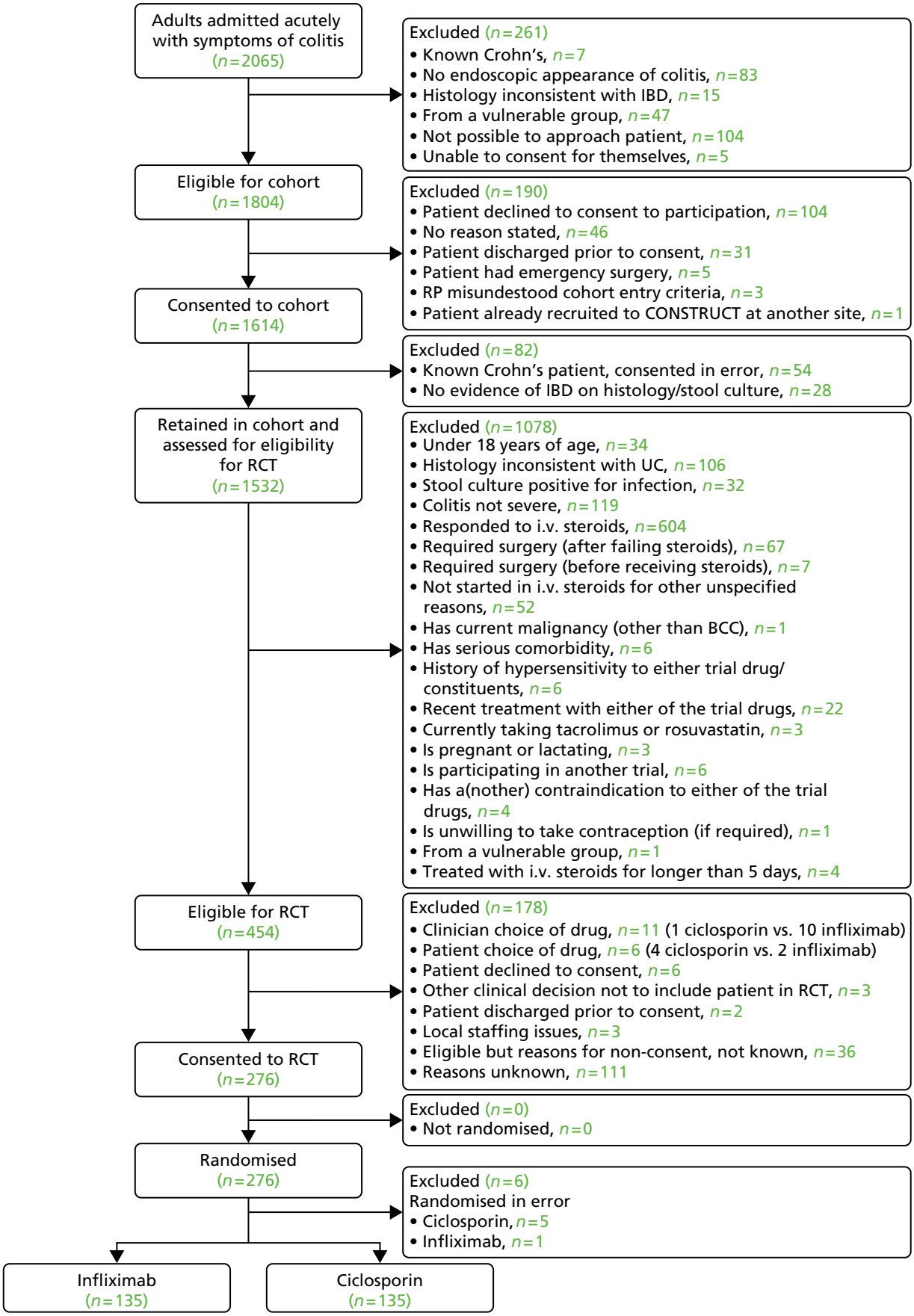

FIGURE 2 Participant recruitment. BCC, basal cell carcinoma; i.v., intravenous; RP, research professional.

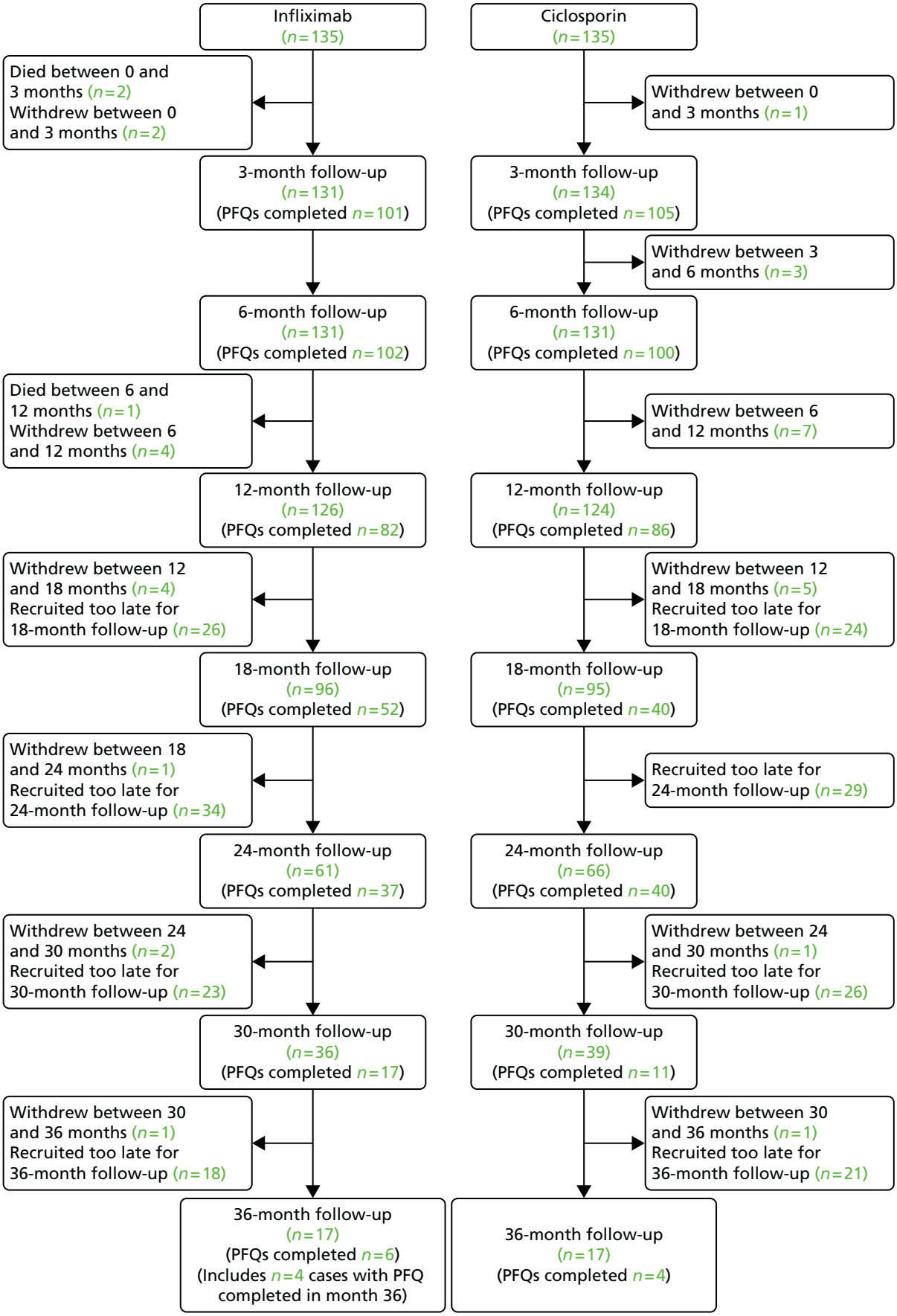

FIGURE 3 Participant follow-up.

Table 5 shows the data that were obtained as the trial progressed.

Table 6 lists the secondary data available for analysis at each time point. The patients who withdrew from further access to medical records are included in the data available when there were enough data to impute the rest of the secondary care resources. For example, if the patient withdrew soon after the surgery at baseline, the data on hospital costs and trial drugs was used to impute the remainder of resource use to 3 months.

Feasibility and pilot study

Because of the complexity of CONSTRUCT, we conducted a feasibility study at our local health board to test our patient identification and recruitment processes up to randomisation, pilot a modified version of the UK-IBDQ and health resource-use questionnaire, and construct a list of frequently used drugs. The feasibility study ran from March 2009 to June 2009 when 20 patients had been recruited. A report from the local research professional provided helpful insights about points of admission for patients with colitis and how best to identify them; demonstrated that the consent process worked; and showed how to capture a discharge to ensure appropriate study follow-up. It allowed us to refine some of our study documentation and test the drugs list and health resource-use questionnaire. The data from the 20 patients were used to validate the modified UK-IBDQ (see *Appendix 8*).

TABLE 5 CONSTRUCT data flow

Follow-up period (months)	In trial at period start	Data obtained	Died	Withdrew further access to medical records	Yielded no further data after period end
Infliximab					
0–3	135	135	2	2	0
3–6	131	130	0	0	0
6–12	129	124	1	1	21
12–18	105	76	0	0	38
18–24	67	63	0	0	28
24–30	38	32	0	0	23
30–36	15	8	0	0	–
Ciclosporin					
0–3	135	135	0	2	0
3–6	133	132	0	0	0
6–12	133	129	0	1	28
12–18	104	70	0	0	32
18–24	72	67	0	1	30
24–30	41	28	0	0	23
30–36	18	10	0	0	–

Note
The number of participants in the trial at the end of each period is equal to the number in the trial at the start of that period minus those who died during that period, minus those who withdrew access to medical records and minus those who left the study on 28 February 2014.

TABLE 6 Secondary data available for analysis at each time point

Follow-up period (months)	In trial at period start	Data obtained	Died	Withdrew further access to medical records	Yielded no further data after period end
Infliximab					
0–3	135	135	2	2	0
3–6	131	131	0	1	0
6–12	131	131	1	3	21
12–18	106	84	0	1	38
18–24	67	65	0	0	28
24–30	39	27	0	1	23
30–36	15	8	0	0	–
Ciclosporin					
0–3	135	135	0	2	0
3–6	133	133	0	0	0
6–12	133	133	0	2	28
12–18	103	85	0	1	32
18–24	72	71	0	1	30
24–30	49	30	0	0	23
30–36	26	9	0	0	–

We planned a pre-pilot study, including pseudo-randomisation, in five sites and, during the training for this, queries and suggestions from PIs and research professionals led us to make some amendments; where appropriate approval was sought from REC for Wales and the MHRA for these amendments.

The pre-pilot study started in September 2009 in our local health board, but did not commence at the other four sites because of delays caused by R&D approval, staff on leave and staff requiring consent training. By January 2010 several other sites had obtained R&D approval for the full study and to avoid further delay a decision was made at the TMG that our local health board had fulfilled the pre-pilot requirements and we should start the main study. A decision was reached by the TMG that as sites gained R&D approval they would start the study using paper documentation prior to GeneCIS implementation. The documentation would have a 'pilot' watermark to distinguish the documents used pre GeneCIS and sites were encouraged to feed back so that amendments could be made before GeneCIS was finalised. When GeneCIS implementation began, sites were sent a revised set of documents with the 'pilot' watermark removed.

The first trial participant recruited at each site was considered to be a pilot. After the first trial participant was recruited, we checked the documentation and processes and sought feedback from the PI or research professional about any issues that had occurred.

Validation of outcome measures

Item generation: devising the items for the CUCQ and CUCQ+

Following exploration of the UK-IBDQ and the gastrointestinal literature related to PROMs, we developed the CUCQ and CUCQ+. *Appendix 18* shows the major differences between the UK-IBDQ and the CUCQ and CUCQ+. Question 7 from the original UK-IBDQ (related to admission to hospital) was removed from the CUCQ and CUCQ+. A new question was added to the CUCQ/CUCQ+ (Q15, related to getting up to use the toilet after going to bed). In addition, where the original UK-IBDQ had four fixed-response options relating to questions 'in the past 2 weeks, how often . . .?', the CUCQ/CUCQ+ used open-response options to take account of any potential floor and ceiling effects.

As the UK-IBDQ did not have any questions for post-colectomy patients, we developed 10 specific stoma-related questions for the CUCQ+ (S1–S10).

Piloting the CUCQ and CUCQ+

We did not modify the CUCQ or CUCQ+ following piloting as none of the patients regarded any of the questions difficult to answer or that there were any specific aspects that were not covered by the questionnaire. The patients with a stoma did not answer the six questions that we had previously identified as not being relevant and instead completed the additional 10 stoma questions.

Baseline demographics of the development and validation samples

We had data from a total of 1240 patients in our cohort development sample and 270 patients in our RCT validation sample (total 1510). We compared the baseline demographic characteristics of the two samples. *Table 7* gives details of the characteristics of the two samples.

Psychometric validation of the CUCQ in the validation sample (CONSTRUCT cohort sample)

We examined the data prior to undertaking principal component analysis. The Kaiser–Meyer–Olkin measure of sampling adequacy was 0.924 and the Barlett's test of sphericity was 0.000, indicating that the data were suitable principal component analysis.

All 32 CUCQ questions had a response rate of at least 93% in the cohort development sample (*Table 8*). Based on our set criteria of responding to at least 24 out of the 32 (75%) total questions, there were 1226 (99%) patients for whom we were able to calculate a CUCQ score.

The internal consistency of the CUCQ was excellent with a Cronbach's alpha of 0.900. Correlations of all 32 questions with the total score exceeded 0.2 (*Table 9*). None of the questions had a response frequency > 80%. The data therefore did not exhibit any floor or ceiling effects.

TABLE 7 Clinical and demographic characteristics of cohort and RCT participants (maximum $N = 1510$)

Patient characteristic	Cohort sample (maximum $n = 1240$)	RCT sample (maximum $n = 270$)	p-value
Gender			
Male	656	170	0.003*
Female	584	100	
Mean age at recruitment, years (SD)	41.42 (17.66)	40.06 (15.31)	0.240
Ethnicity			
White	1133	250	0.377
Asian or Asian British	65	12	
Black or black British	8	3	
Other ethnic groups	18	2	
Mixed	11	0	
Missing	5	3	
Smoking status			
Never smoked	514	112	0.829
Non-smoker (history unknown)	95	19	
Current smoker	102	27	
Ex-smoker	481	105	
Mean weight, kg (SD)	73.05 (17.63)	74.14 (15.09)	0.353
Mean height, m (SD)	1.70 (0.11)	1.71 (0.09)	0.160
Truelove and Witt classification[4]			
Severe	1033	251	0.000*
Not severe	174	16	
Mayo score			
0	35	4	0.000*
1	103	4	
2	391	68	
3	483	183	
Family history			
Yes	147	46	0.023*
No	1072	221	
Comorbidity: IHD			
Yes	49	6	0.165
No	1179	263	
Comorbidity: CVD			
Yes	16	2	0.446
No	1213	267	

continued

TABLE 7 Clinical and demographic characteristics of cohort and RCT participants (maximum $N = 1510$) (*continued*)

Patient characteristic	Cohort sample (maximum $n = 1240$)	RCT sample (maximum $n = 270$)	*p*-value
Comorbidity: resp			
Yes	70	15	0.934
No	1157	254	
Comorbidity: liver			
Yes	7	3	0.320
No	1221	266	
Comorbidity: BP			
Yes	102	18	0.376
No	1112	248	
Mean duration of symptoms (SD)	32.71 (43.64)	39.60 (51.95)	0.025*
Mean EQ-5D (SD)	0.57 (0.31)	0.51 (0.30)	0.040*
Mean CUCQ (SD)	0.40 (0.16)	0.36 (0.13)	0.001*
Mean SF-6D (SD)	0.57 (0.11)	0.56 (0.11)	0.090
Mean blood: Hb (SD)	12.30 (2.10)	12.82 (2.16)	0.918
Mean blood: ESR (SD)	39.63 (28.52)	41.50 (27.24)	0.607
Mean blood: CRP (SD)	61.30 (70.62)	83.30 (81.13)	0.000*
Mean blood: Alb (SD)	36.71 (6.88)	33.18 (6.57)	0.000*
Mean blood: Cr (SD)	77.02 (26.33)	77.20 (19.44)	0.915
Mean blood: Chol (SD)	4.09 (1.37)	3.81 (1.03)	0.147
Mean TW-CCRF-SF (SD)	11.15 (6.77)	12.63 (6.76)	0.021*
Mean TW-CCRF-BSF (SD)	10.48 (6.71)	11.75 (6.95)	0.007*
Mean TW-CCRF-HR (SD)	88.79 (17.79)	89.55 (16.76)	0.526
Mean TW-CCRF-Temp (SD)	36.80 (0.69)	36.91 (0.69)	0.021*

Alb, albumin; BP, blood pressure; Chol, cholesterol; Cr, creatinine; CRP, C-reactive protein; CVD, cerebrovascular disease; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; IHD, ischaemic heart disease; resp, respiratory disease; SD, standard deviation; SF-6D, Short Form Questionniare-6 items; TW-CCRF-BSF, Truelove and Witts cohort case report form bloody stool frequency; TW-CCRF-HR, Truelove and Witts cohort case report form heart rate; TW-CCRF-SF, Truelove and Witts cohort case report form stool frequency; TW-CRF-Temp, Truelove and Witts cohort case report form temperature.

TABLE 8 Frequency of missing values for each of the 32 CUCQ questions within the cohort development sample ($N = 1235$)

Question	Number of missing responses, *n* (%)
1	9 (0.73)
2	14 (1.13)
3	12 (0.97)
4	12 (0.97)
5	13 (1.05)
6	15 (1.21)
7	14 (1.13)
8	19 (1.54)
9	19 (1.54)
10	13 (1.05)
11	10 (0.81)
12	15 (1.21)
13	14 (1.13)
14	15 (1.21)
15	11 (0.89)
16	18 (1.46)
17	26 (2.11)
18	14 (1.13)
19	17 (1.38)
20	11 (0.89)
21	17 (1.38)
22	10 (0.81)
23	13 (1.05)
24	12 (0.97)
25	14 (1.13)
26	15 (1.21)
27	11 (0.89)
28	86 (6.96)
29	17 (1.38)
30	16 (1.30)
31	18 (1.46)
32	18 (1.46)

TABLE 9 The 32 CUCQ questions, their item-total correlations and their maximum response rate

Question	Item-total correlation	Maximum response rate (%)
On how many days over the last 2 weeks have you had loose or runny bowel movements?	0.344	76.2
On how many days in the last 2 weeks have you noticed blood in your stools?	0.257	49.3
On how many days over the last 2 weeks have you felt tired?	0.530	66.8
In the last 2 weeks have you felt frustrated?	0.532	38.7
In the last 2 weeks has your bowel condition prevented you from carrying out your work or other normal activities?	0.513	33.5
On how many days over the last 2 weeks have you opened your bowels more than three times a day?	0.425	72.2
On how many days over the last 2 weeks have you felt full of energy?	0.347	73.3
In the last 2 weeks did your bowel condition prevent you from going out socially?	0.539	36.4
On how many days over the last 2 weeks have your bowels opened accidentally?	0.261	42.9
On how many days over the last 2 weeks have you felt generally unwell?	0.554	58.6
In the last 2 weeks have you felt the need to keep close to a toilet?	0.586	47.1
In the last 2 weeks has your bowel condition affected your leisure or sports activities?	0.549	50.2
On how many days over the last 2 weeks have you felt pain in your abdomen?	0.441	47.5
On how many nights over the last 2 weeks have you been unable to sleep well (days if you are a shift worker)?	0.516	46.9
On how many nights in the last 2 weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed?	0.466	50.1
In the last 2 weeks have you felt depressed?	0.539	49.7
In the last 2 weeks have you had to avoid attending events where there was no toilet close at hand?	0.524	35.8
On how many days over the last 2 weeks have you had a problem with large amounts of wind?	0.207	32.5
On how many days over the last 2 weeks have you felt off your food?	0.423	24.5
Many patients with bowel problems have worries about their illness. How often during the last 2 weeks have you felt worried?	0.540	33.7
On how many days over the last 2 weeks has your abdomen felt bloated?	0.415	33.1
In the last 2 weeks have you felt relaxed?	0.460	46.9
In the last 2 weeks have you been embarrassed by your bowel problem?	0.480	37.1
On how many days over the last 2 weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?	0.501	27.9
In the last 2 weeks have you felt upset?	0.586	57.6
On how many days over the last 2 weeks have you had to rush to the toilet?	0.561	48.2
In the last 2 weeks have you felt angry as a result of your bowel problem?	0.444	45.0
In the last 2 weeks, has your sex life been affected by your bowel problem?	0.361	41.0
On how many days over the last 2 weeks have you felt sick?	0.419	27.2
In the last 2 weeks have you felt irritable?	0.505	53.7
In the last 2 weeks have you felt lack of sympathy from others?	0.314	61.5
In the last 2 weeks have you felt happy?	0.398	55.1

The principal component analysis indicated that there were seven factors with an eigenvalue of > 1 and which explained approximately 57% of the variance in the data. The scree plot indicated that there was an elbow in the scree plot between the fourth and fifth factors. We rotated the solution based on four factors using direct oblimin principal component analysis (*Table 10*). The principal component analysis identified that the first factor covered emotional symptoms; the second bowel symptoms; the third social activities; and the fourth general symptoms.

TABLE 10 Principal component analysis of the CONSTRUCT CUCQ questions from the development sample based on a four-factor solution

	Factor			
	1	2	3	4
Percentage of factor's contribution	26.716	8.408	6.162	5.452
Eigenvalue	8.549	2.691	1.972	1.745
CUCQ16	0.760			
CUCQ25	0.744			
CUCQ27	0.740			
CUCQ30	0.708			
CUCQ4	0.610			
CUCQ20	0.607			
CUCQ23	0.558			
CUCQ31	0.530			
CUCQ22				
CUCQ32				
CUCQ1		0.754		
CUCQ6		0.751		
CUCQ26		0.642		
CUCQ2		0.615		
CUCQ24		0.563		
CUCQ15		0.535		
CUCQ14				
CUCQ18				
CUCQ8			–0.837	
CUCQ12			–0.790	
CUCQ5			–0.768	
CUCQ17			–0.723	
CUCQ11			–0.623	
CUCQ28				
CUCQ10				0.629
CUCQ3				0.611
CUCQ13				0.578
CUCQ7				0.554
CUCQ19				0.497
CUCQ29				0.433
CUCQ9				–0.403
CUCQ21				

Notes
Extraction method: principal component analysis.
Rotation method: oblimin with kaiser normalisation (rotation converged in 11 iterations).

The CUCQ scores achieved significant correlations with the two generic HRQoL scales (SF-12 mental and physical component scores and the EQ-5D) scores demonstrating good construct validity (*Table 11*).

Table 12 illustrates the percentage variance that each of the 32 questions contributed to the total CUCQ score in the CONSTRUCT cohort development sample. Ten of the 32 questions contributed over 90% of the variance in the total score. These 10 questions could be future candidates for a shortened version of the CUCQ. We will undertake further work to test the validity of a shortened version of the CUCQ.

Psychometric validation of the CUCQ in the validation sample (CONSTRUCT randomised controlled trial sample)

For the purposes of this report, we calculated CUCQ+ scores for stoma extension patients on the basis of equal weighting for each score. Further analysis will be carried out to explore weighting of the stoma-specific questions.

The internal consistency of the CUCQ in the RCT sample was excellent, with a Cronbach's alpha of 0.845. *Table 13* illustrates the percentage variance that each of the 32 questions contributed to the total CUCQ score in the RCT validation sample.

Table 14 indicates the number of patients for whom we collected a CUCQ/CUCQ+ score at each time period within the RCT validation sample.

The CUCQ scores achieved significant correlations at baseline with the two generic HRQoL scales (SF-12 mental and physical component scores and the EQ-5D) in the RCT validation sample scores demonstrating good construct validity (*Table 15*).

Testing reliability and responsiveness of the CUCQ

We assessed the reproducibility or test–retest reliability of the CUCQ on those patients who reported no change in their condition between completion of follow-up questionnaires. We included those patients who had indicated no change in their bowel condition on the transition question between the 3- and 6-month periods (How has your QoL changed since the last time you filled in a questionnaire?).

There were 34 patients who reported no change in their condition at 3–6 months. The Cronbach's alpha was 0.582, indicating moderate agreement between the CUCQ scores. Further exploration of the test–retest scores is needed to determine any differences in the reliability of the CUCQ scale between stoma and non-stoma patients. The judgement of 'stability' was based on subjective assessment by the patient. The clinical assessment of stability and how this affects the test–retest reliability will also be explored. In addition, the correlation between the CUCQ test–retest reliability and the generic EQ-5D and SF-12 reliability requires further analysis.

TABLE 11 Correlations between the CUCQ score and the SF-12 mental and physical component scores and EQ-5D in the CONSTRUCT development sample

Scale	CUCQ
SF-12 MCS	0.588[a]
SF-12 PCS	0.444[a]
EQ-5D	0.429[a]

MCS, mental component score; PCS, physical component score.
a $p < 0.001$ Pearson's correlation.

TABLE 12 Model summary of the CUCQ questions within the CONSTRUCT cohort development sample

Question	Cumulative % of variance
Q25: In the last 2 weeks have you felt upset?	38.6
Q11: In the last 2 weeks have you felt the need to keep close to a toilet?	59.5
Q3: On how many days over the last 2 weeks have you felt tired?	70.6
Q14: On how many nights over the last 2 weeks have you been unable to sleep well (days if you are a shift worker)?	76.3
Q21: On how many days over the last 2 weeks has your abdomen felt bloated?	79.9
Q17: In the last 2 weeks have you had to avoid attending events where there was no toilet close at hand?	82.9
Q4: In the last 2 weeks have you felt frustrated?	85.4
Q26: On how many days over the last 2 weeks have you had to rush to the toilet?	87.4
Q19: On how many days over the last 2 weeks have you felt off your food?	89.2
Q23: In the last 2 weeks have you been embarrassed by your bowel problem?	90.4
Q12: In the last 2 weeks has your bowel condition affected your leisure or sports activities?	91.5
Q6: On how many days over the last 2 weeks have you opened your bowels more than three times a day?	92.5
Q30: In the last 2 weeks have you felt irritable?	93.3
Q13: On how many days over the last 2 weeks have you felt pain in your abdomen?	94.2
Q28: In the last 2 weeks has your sex life been affected by your bowel problem?	94.9
Q16: In the last 2 weeks have you felt depressed?	95.6
Q18: On how many days over the last 2 weeks have you had a problem with large amounts of wind?	96.2
Q29: On how many days over the last 2 weeks have you felt sick?	96.7
Q5: In the last 2 weeks has your bowel condition prevented you from carrying out your work or other normal activities?	97.1
Q24: On how many days over the last 2 weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?	97.4
Q20: Many patients with bowel problems have worries about their illness. How often during the last 2 weeks have you felt worried?	97.8
Q15: On how many nights in the last 2 weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed?	98.1
Q2: On how many days in the last 2 weeks have you noticed blood in your stools?	98.3
Q32: In the last 2 weeks have you felt happy?	98.7
Q31: In the last 2 weeks have you felt lack of sympathy from others?	98.9
Q10: On how many days over the last 2 weeks have you felt generally unwell?	99.1
Q9: On how many days over the last 2 weeks have your bowels opened accidentally?	99.3
Q27: In the last 2 weeks have you felt angry as a result of your bowel problem?	99.5
Q8: In the last 2 weeks did your bowel condition prevent you from going out socially?	99.6
Q22: In the last 2 weeks have you felt relaxed?	99.8
Q7: On how many days over the last 2 weeks have you felt full of energy?	99.9
Q1: On how many days over the last 2 weeks have you had loose or runny bowel movements?	100

TABLE 13 Model summary of the CUCQ questions within the CONSTRUCT RCT validation sample

Questions	Cumulative % of variance
Q10: On how many days over the last 2 weeks have you felt generally unwell?	34.5
Q30: In the last 2 weeks have you felt irritable?	58.8
Q12: In the last 2 weeks has your bowel condition affected your leisure or sports activities?	67.4
Q3: On how many days over the last 2 weeks have you felt tired?	74.0
Q23: In the last 2 weeks have you been embarrassed by your bowel problem?	79.1
Q24: On how many days over the last 2 weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?	81.8
Q16: In the last 2 weeks have you felt depressed?	84.0
Q29: On how many days over the last 2 weeks have you felt sick?	86.2
Q5: In the last 2 weeks has your bowel condition prevented you from carrying out your work or other normal activities?	87.8
Q18: On how many days over the last 2 weeks: have you had a problem with large amounts of wind?	89.5
Q32: In the last 2 weeks have you felt happy?	90.8
Q28: In the last 2 weeks has your sex life been affected by your bowel problem?	91.7
Q14: On how many nights over the last 2 weeks have you been unable to sleep well (days if you are a shift worker)?	92.7
Q20: Many patients with bowel problems have worries about their illness. How often during the last 2 weeks have you felt worried?	93.7
Q17: In the last 2 weeks have you had to avoid attending events where there was no toilet close at hand?	94.5
Q2: On how many days in the last 2 weeks have you noticed blood in your stools?	95.2
Q26: On how many days over the last 2 weeks have you had to rush to the toilet?	95.8
Q31: In the last 2 weeks have you felt lack of sympathy from others?	96.3
Q21: On how many days over the last 2 weeks has your abdomen felt bloated?	96.7
Q27: In the last 2 weeks have you felt angry as a result of your bowel problem?	97.1
Q22: In the last 2 weeks have you felt relaxed?	97.5
Q19: On how many days over the last 2 weeks have you felt off your food?	97.8
Q13: On how many days over the last 2 weeks have you felt pain in your abdomen?	98.1
Q11: In the last 2 weeks have you felt the need to keep close to a toilet?	98.4
Q9: On how many days over the last 2 weeks have your bowels opened accidentally?	98.7
Q4: In the last 2 weeks have you felt frustrated?	98.9
Q15: On how many nights in the last 2 weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed?	99.2
Q7: On how many days over the last 2 weeks have you felt full of energy?	99.4
Q8: In the last 2 weeks did your bowel condition prevent you from going out socially?	99.6
Q25: In the last 2 weeks have you felt upset?	99.7
Q1: On how many days over the last 2 weeks have you had loose or runny bowel movements?	99.9
Q6: On how many days over the last 2 weeks have you opened your bowels more than three times a day?	100

TABLE 14 Response rate to baseline and follow-up questionnaires in the RCT validation sample

Time point	Scale (total sample, $N = 270$) CUCQ/CUCQ+, *n* (%)
Baseline	267 (98.9)
3 months	202 (74.8)
6 months	200 (74.1)
12 months	168 (62.2)
18 months	91 (33.7)
24 months	77 (28.5)
30 months	27 (10)
36 months	10 (3.7)

TABLE 15 Correlations between the CONSTRUCT total score and the SF-12 mental and physical component scores and EQ-5D in the CONSTRUCT validation sample

Scale	CUCQ
SF-12 MCS	0.588[a]
SF-12 PCS	0.452[a]
EQ-5D	0.459[a]

MCS, mental component score; PCS, physical component score.
a $p < 0.001$ Pearson's correlation.

We assessed the responsiveness of the CUCQ on those patients who had reported an improvement or a deterioration in their condition on the transition question between the 3- and 6-month period. There were 146 patients who reported a change in their condition in this period. The responsiveness ratio (mean change in scores for those patients who reported a change divided by the standard deviation (SD) of the scores of the stable patients) was 0.200. This indicated moderate responsiveness. Further analysis is required to explore differences in the responsiveness of the scale between the stoma and non-stoma patients.

Principal component analysis of the CUCQ showed that there were four underlying dimensions that made clinical sense. Internal consistency of the total CUCQ score was demonstrated by an excellent Cronbach's alpha. The construct validity of the CUCQ was demonstrated by significant correlations with the SF-12 mental and physical component scores and with the EQ-5D. Moderate intraclass correlations between the test and retest scores demonstrated the reproducibility of the instrument. In addition, the scale was found to be responsive to change.

We will undertake further work to explore whether or not there are any differences in the validity of the scale between the stoma and non-stoma patients. In addition, we will carry out additional analysis to explore the CUCQ clinical subscales and the potential for developing a shortened version of the CUCQ.

Clinical effectiveness

Baseline characteristics

We compared the trial participants in the two groups in terms of various characteristics (*Table 16*); there are no statistically significant differences between the groups.

TABLE 16 Baseline demographic and clinical characteristics for each group

Variables	Infliximab ($n = 135$)	Ciclosporin ($n = 135$)
Age at randomisation (years), mean (SD) [*n*]	39.3 (15.5) [135]	39.8 (15.0) [135]
Gender: proportion, *n*/*N* (%)		
Female	46/135 (34.1)	54/135 (40.0)
Male	89/135 (65.9)	81/135 (60.0)
Ethnicity: proportion, *n*/*N* (%)		
White	126/134 (94.0)	124/133 (93.2)
Asian or Asian British	5/134 (3.7)	7/133 (5.3)
Black or black British	2/134 (1.5)	1/133 (0.8)
Other ethnic groups	1/134 (0.7)	1/133 (0.8)
Weight (kg), mean (SD) [*n*]	74.3 (15.0) [135]	73.9 (15.3) [134]
Smoking: proportion, *n*/*N* (%)		
Never smoked/non-smoker	58/130 (44.6)	75/134 (56.0)
Current/ex-smoker	72/130 (55.4)	59/134 (44.0)
Family history: proportion, *n*/*N* (%)		
Yes (any one of mother, father, sibling, child)	28/132 (21.2)	19/135 (14.1)
No	104/132 (78.8)	116/135 (85.%)
Condition severity (using Truelove and Witt's criteria[4]): proportion, *n*/*N* (%)		
Severe	97/133 (72.9)	95/131 (72.5)
Not severe	36/133 (27.1)	36/131 (27.5)
Montreal Score: proportion, *n*/*N* (%)		
E1	7/124 (5.6)	10/126 (7.9)
E2	64/124 (51.6)	54/126 (42.8)
E3	53/124 (42.7)	62/127 (49.2)
Mayo score: proportion, *n*/*N* (%)		
0	2/131 (1.5)	1/128 (0.8)
1	2/131 (1.5)	2/128 (1.6)
2	35/131 (26.7)	35/128 (27.3)
3	92/131 (70.2)	90/128 (70.3)
Receiving any of azathioprine, 6-mercaptopurine or methotrexate at baseline, *n*/*N* (%)		
At least one	16/135 (11.9)	26/135 (19.3)
None	119/135 (88.1)	109/135 (80.7)
Duration of symptoms for current episode (days), mean (SD) [*n*]	37.6 (46.0) [135]	41.4 (57.5) [131]
EQ-5D, mean (SD) [*n*]	0.5185 (0.2961) [132]	0.4958 (0.3142) [133]
CUCQ score, mean (SD) [*n*]	0.3664 (0.1334) [134]	0.3574 (0.1325) [133]

Data analysed

Recruitment to the RCT started when participant UCL0001 was randomised on 24 June 2010 and continued until participant ABH0016 was randomised on 26 February 2013; the CONSORT diagram (see *Figure 2*) summarises recruitment between these dates and the number of PFQs (see *Figure 3*) actually completed at each stage. Our primary outcome, the QAS,[55] can be computed for $n = 242$ cases with at least one post-randomisation value of the CUCQ or CUCQ+.

Analysis

Outcomes were analysed using an appropriate model. Specifically, we used linear models for measurement outcomes (assuming normality, also assessed via residual diagnostics) in which trial site appeared as a random factor; logistic regression for binary (yes/no) outcomes; Cox survival regression models for times to events; we also analysed the three profiles of QoL scores for each participant using a repeated-measures linear model. Analyses, in which a group effect was always included, considered the following covariates and factors: gender; weight; age at randomisation; ethnicity; smoking status; family history; duration of symptoms; disease severity (as assessed by the criteria proposed by Truelove and Witt[4]); immunosuppressant therapy (using binary indicator set equal to 1 for participants taking azathioprine, 6-mercaptopurine or methotrexate at baseline); EQ-5D and CUCQ scores at baseline; and time in follow-up. We progressed by eliminating, in turn, and starting with the least significant, all covariates and factors found to be not statistically significant at the 5% level, and concluded when all remaining covariates and factors were statistically significant.

Tables 17–20 provide raw and adjusted comparisons between groups, some indication of the extent of the intracluster correlation in variables between participants at the same site and details of statistically significant factors and covariates. The adjusted comparison reflects the nature of the variable under consideration: we present an odds ratio (OR) for logistic regression models for binary variables; a hazard ratio for survival analyses and an additive group effect (Δ, in same units as dependent variable) for linear models for continuous variables.

Quality-adjusted survival and quality-adjusted survival per day

Figures 4 and *5* show the mean QAS and QAS per day for the two groups, together with 95% CIs for the means. For both variables, the mean for the ciclosporin group is higher than its infliximab counterpart, although the clear overlap in the 95% CIs indicate that observed differences are not statistically significant, as is confirmed in our analysis. There are relatively high values for the intracluster correlations in these variables, albeit with wide CIs (reflecting the relatively small – in statistical terms – sample sizes).

Proportions undergoing colectomy: time to colectomy

Table 17 shows that the observed difference in the proportions of participants subsequently undergoing colectomy in the two groups is not statistically significant; nor is the difference in time to colectomy. *Figure 6*, the Kaplan–Meier curves of the time to colectomy in the two groups, illustrates the higher proportion of colectomies in the ciclosporin group.

TABLE 17 Primary and safety outcomes, analysed by treatment allocated

Outcome	Raw data		Adjusted comparison	95% CI	Intracluster correlation	
	Infliximab	Ciclosporin			Estimate	95% CI
QAS[a]						
Mean	564.0	587.0	$\Delta = 7.90$ ($p = 0.60$)	–21.97 to 37.77	0.065	0.015 to 0.147
SD	241.9	226.2				
n	121	121				

continued

TABLE 17 Primary and safety outcomes, analysed by treatment allocated (*continued*)

Outcome	Raw data		Adjusted comparison	95% CI	Intracluster correlation	
	Infliximab	Ciclosporin			Estimate	95% CI
QAS per day[b]						
Mean	0.7052	0.7331	Δ = 0.0297 (p = 0.129)	–0.0088 to 0.0682	0.094	0.028 to 0.189
SD	0.1811	0.1580				
n	121	121				
Participants subsequently undergoing colectomy: proportion, *n*/*N* (%)	55/135 (40.7)	65/135 (48.1)	OR = 1.350 (p = 0.223)	0.832 to 2.188	0	n/a
Time to colectomy (days)[c]						
Mean	810.8	744.1	HR = 1.234 (p = 0.251)	0.862 to 1.768	0	n/a
n	135	135				
Total number of SARs	16	10	ER = 0.938 (p = 0.788)	0.590 to 1.493	0	n/a
One SAR per participant	12	8				
Two SARs per participant	2	1				
Participants with one or more SARs proportion, *n*/*N* (%)[d]	14/135 (10.4)	9/135 (6.7)	OR = 0.660 (p = 0.338)	0.282 to 1.546	0.050	0.008 to 0.132
Total number of SAEs	21	25	ER = 1.075 (p = 0.807)	0.603 to 1.917	0	n/a
One SAE per participant	12	13				
Two SAEs per participant	3	2				
Three SAEs per participant	1	0				
Four SAEs per participant	0	2				
Participants with one or more SAEs proportion, *n*/*N* (%)[e]	16/135 (11.9)	17/135 (12.6)	OR = 0.999 (p = 0.998)	0.473 to 2.114	0	n/a
Post-randomisation LOS (days)[f]						
Mean	10.32	12.21	Δ = 1.542 (p = 0.28	–1.297 to 4.38	0.025	0.002 to 0.089
SD	13.55	10.18				
n	135	135				
Logarithm of post-randomisation LOS[g]						
Mean	1.878	2.289	Δ = 0.421 (p < 0.001)	0.245 to 0.597	0.024	(0.001 to 0.085)
SD	0.887	0.626				
n	135	135				
Mortality: proportion, *n*/*N* (%)	3/135 (2.2)	0/135 (0)				

ER, event ratio; HR, hazard ratio; LOS, length of stay; n/a, not applicable.
Figures; significant covariates and factors:
a *Figure 4*; days in follow-up (p < 0.001); CUCQ at baseline (p < 0.001); EQ-5D at baseline (p = 0.015).
b *Figure 5*; CUCQ at baseline (p < 0.001); weight (p = 0.011).
c *Figure 6*; intracluster correlation assessed using time to event.
d Age at randomisation (p = 0.006).
e Age at randomisation (p = 0.031); symptoms duration (p = 0.049).
f *Figure 7a*; age at randomisation (p < 0.001); gender (p = 0.034); smoking (p = 0.032).
g *Figure 7b*; age at randomisation (p < 0.001); gender (p = 0.013); EQ-5D at baseline (p = 0.007).

TABLE 18 Quality-of-life measures, analysed by treatment allocated

Outcome	Raw data, mean (SD) [*n*]		Adjusted comparison	95% CI
	Infliximab	Ciclosporin		
CUCQ[a]				
Month 0	0.3664 (0.1334) [134]	0.3574 (0.1325) [133]	$\Delta = 0.0195$ ($p = 0.319$)	–0.0191 to 0.0581
Month 3	0.7455 (0.1830) [99]	0.7187 (0.1855) [103]		
Month 6	0.7497 (0.1952) [101]	0.7505 (0.2083) [99]		
Month 12	0.7284 (0.2110) [82]	0.7927 (0.1738) [86]		
Month 18	0.7837 (0.1769) [52]	0.8179 (0.1321) [39]		
Month 24	0.8102 (0.1702) [36]	0.8264 (0.1256) [40]		
Month 30	0.8099 (0.1644) [17]	0.8502 (0.1140) [10]		
Month 36	0.7611 (0.0966) [6]	0.8380 (0.1390) [4]		
SF-6D[b]				
Month 0	0.5632 (0.1066) [128]	0.5517 (0.1047) [127]	$\Delta = 0.0051$ ($p = 0.737$)	–0.0250 to 0.0353
Month 3	0.7194 (0.1357) [96]	0.7066 (0.1383) [100]		
Month 6	0.7401 (0.1439) [99]	0.7384 (0.1513) [95]		
Month 12	0.7610 (0.1479) [78]	0.7624 (0.1551) [85]		
Month 18	0.7449 (0.1459) [50]	0.7954 (0.1323) [39]		
Month 24	0.7782 (0.1485) [37]	0.7867 (0.1197) [37]		
Month 30	0.7947 (0.1190) [17]	0.8095 (0.1065) [11]		
Month 36	0.7413 (0.1159) [6]	0.7603 (0.1334) [4]		
EQ-5D[c]				
Month 0	0.5185 (0.2961) [132]	0.4958 (0.3142) [133]	$\Delta = 0.0144$ ($p = 0.527$)	–0.0304 to 0.0592
Month 3	0.8000 (0.2090) [99]	0.7791 (0.2409) [103]		
Month 6	0.7957 (0.2387) [102]	0.8107 (0.2111) [100]		
Month 12	0.8021 (0.2235) [81]	0.8327 (0.2336) [86]		
Month 18	0.8238 (0.2179) [51]	0.8821 (0.1290) [40]		
Month 24	0.8634 (0.1835) [37]	0.8678 (0.1871) [38]		
Month 30	0.8815 (0.1229) [17]	0.9225 (0.1193) [11]		
Month 36	0.8430 (0.1361) [6]	0.8203 (0.1300) [4]		

SF-6D, Short Form Questinnaire-6 items.
a *Figure 8*; significant covariates, weight ($p = 0.010$), gender ($p = 0.026$).
b *Figure 9*; no significant covariates.
c *Figure 10*; significant covariates, weight ($p = 0.001$), age at randomisation ($p = 0.029$), smoking ($p = 0.037$), gender ($p = 0.039$).

TABLE 19 Post-randomisation CUCQ QoL measure for all participants, analysed by treatment allocated, adjusting for colectomy status

Outcome	Raw data:[a] outcome, mean (SD) [*n*]		Adjusted comparison[b,c]	95% CI
	Infliximab	Ciclosporin		
Interval 1[d]			$\Delta_{Group} = 0.0130$ ($p = 0.511$)	–0.0259 to 0.0519
All	0.6877 (0.2128) [145]	0.6926 (0.1951) [157]	$\Delta_{Colectomy} = -0.0476$ ($p = 0.004$)	–0.0800 to –0.0152
BC	0.7658 (0.1822) [75]	0.7216 (0.1941) [76]		
PC	0.6041 (0.2125) [70]	0.6653 (0.1932) [81]		
Interval 2				
All	0.7425 (0.2076) [112]	0.7398 (0.2008) [118]		
BC	0.7750 (0.1856) [72]	0.7881 (0.1918) [68]		
PC	0.6841 (0.2338) [40]	0.6743 (0.1957) [50]		
Interval 3				
All	0.7313 (0.2134) [87]	0.7700 (0.1783) [100]		
BC	0.7648 (0.1983) [55]	0.8168 (0.1530) [50]		
PC	0.6737 (0.2289) [32]	0.7231 (0.1906) [50]		
Interval 4				
All	0.7577 (0.1903) [58]	0.8099 (0.1352) [45]		
BC	0.7782 (0.1779) [38]	0.8358 (0.1403) [27]		
PC	0.7190 (0.2112) [20]	0.7710 (0.1206) [18]		
Interval 5				
All	0.7999 (0.1742) [38]	0.8226 (0.1267) [39]		
BC	0.8054 (0.1812) [27]	0.8407 (0.1168) [28]		
PC	0.7861 (0.1633) [11]	0.7763 (0.1446) [11]		
Interval 6				
All	0.8140 (0.1684) [17]	0.7190 (0.2588) [16]		
BC	0.8770 (0.1006) [11]	0.8446 (0.1284) [8]		
PC	0.6983 (0.2137) [6]	0.5934 (0.3016) [8]		
Interval 7				
All	0.7611 (0.0966) [6]	0.8380 (0.1390) [4]		
BC	0.7398 (0.1158) [4]	0.8948 (0.0978) [3]		
PC	0.8039 (0.0313) [2]	0.6673 (n/a) [1]		

BC, denotes scores from questionnaires completed by participants before a colectomy; n/a, not applicable; PC, denotes scores from questionnaires completed by participants following a colectomy.

a The study design, enabling participants to complete questionnaires relatively soon after a post-randomisation colectomy, makes it rather difficult to reconcile numbers in *Tables 18* and *19*; in *Table 18*, each participant contributes no more than one value per stage, but, in *Table 19*, it is possible that one participant completes several questionnaires in an interval, and, furthermore, that an earlier questionnaire contributes to the BC subgroup while one (or more) later questionnaires contribute to the PC subgroup.

b Significant covariates: weight ($p = 0.019$).

c Omitting the group variable makes only minor differences to the estimate of the effect of a colectomy on CUCQ scores.

d Post-randomisation follow-up is divided into seven intervals, as follows: interval 1, up to (and including) 135 days post randomisation; interval 2, from 136 to (and including) 274 days post randomisation; interval 3, from 275 to (and including) 456 days post randomisation; interval 4, from 457 to (and including) 639 days post randomisation; interval 5: from 640 to (and including) 821 days post randomisation; interval 6, from 822 to (and including) 1004 days post randomisation; interval 7: ≥ 1005 days post randomisation.

TABLE 20 Post-randomisation CUCQ QoL measure for participants undergoing a colectomy, analysed by treatment allocated, adjusting for colectomy status

	Raw data, mean (SD) [*n*]			
Outcome	Infliximab	Ciclosporin	Adjusted comparison[a]	95% CI
Interval 1[b]			$\Delta_{Group} = 0.0266$ ($p = 0.367$)	–0.0317 to 0.0848
All	0.6119 (0.214) [84]	0.6649 (0.1979) [104]	$\Delta_{Colectomy} = 0.0271$ ($p = 0.244$)	–0.0185 to –0.0726
BC	0.6510 (0.2091) [14]	0.6631 (0.2184) [23]		
PC	0.6041 (0.2125) [70]	0.6653 (0.1932) [81]		
Interval 2				
All	0.6842 (0.2254) [53]	0.6903 (0.1980) [61]		
BC	0.6847 (0.2077) [13]	0.7630 (0.2008) [11]		
PC	0.6841 (0.2338) [40]	0.6743 (0.1957) [50]		
Interval 3				
All	0.6701 (0.2248) [39]	0.7207 (0.1928) [52]		
BC	0.6537 (0.2209) [7]	0.6596 (0.3299) [2]		
PC	0.6737 (0.2289) [32]	0.7231 (0.1906) [50]		
Interval 4				
All	0.7001 (0.2159) [23]	0.7752 (0.1186) [19]		
BC	0.5740 (0.2481) [3]	0.8512 (n/a) [1]		
PC	0.7190 (0.2112) [20]	0.7710 (0.1206) [18]		
Interval 5				
All	0.7673 (0.1689) [123]	0.7763 (0.1446) [11]		
BC	0.5595 (n/a) [1]	(n/a)		
PC	0.7861 (0.1633) [11]	0.7763 (0.1446) [11]		
Interval 6				
All	0.6983 (0.2137) [6]	0.5934 (0.3016) [8]		
BC	(n/a)	(n/a)		
PC	0.6983 (0.2137) [6]	0.5934 (0.3016) [8]		
Interval 7				
All	0.8039 (0.0313) [6]	0.6673 (n/a) [1]		
BC	(n/a)	(n/a)		
PC	0.8039 (0.0313) [2]	0.6673 (n/a) [1]		

BC, denotes scores from questionnaires completed by participants before a colectomy; n/a, not applicable; PC, denotes scores from questionnaires completed by participants following a colectomy.

a Significant covariates: none.

b Post-randomisation follow-up is divided into seven intervals, as follows: interval 1, up to (and including) 135 days post randomisation; interval 2, from 136 to (and including) 274 days post randomisation; interval 3, from 275 to (and including) 456 days post randomisation; interval 4, from 457 to (and including) 639 days post randomisation; interval 5: from 640 to (and including) 821 days post randomisation; interval 6, from 822 to (and including) 1004 days post randomisation; interval 7: ≥ 1005 days post randomisation.

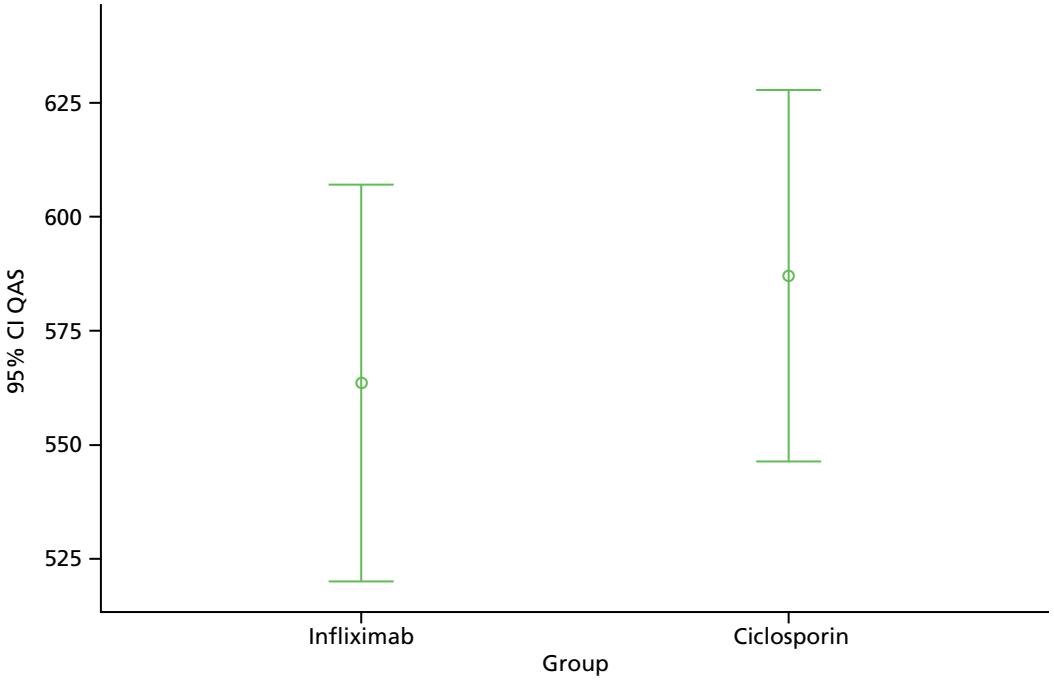

FIGURE 4 Means and 95% CI for QAS (the QAS or area under the CUCQ curve from randomisation until end of follow-up on 28 February 2014) for the two groups.

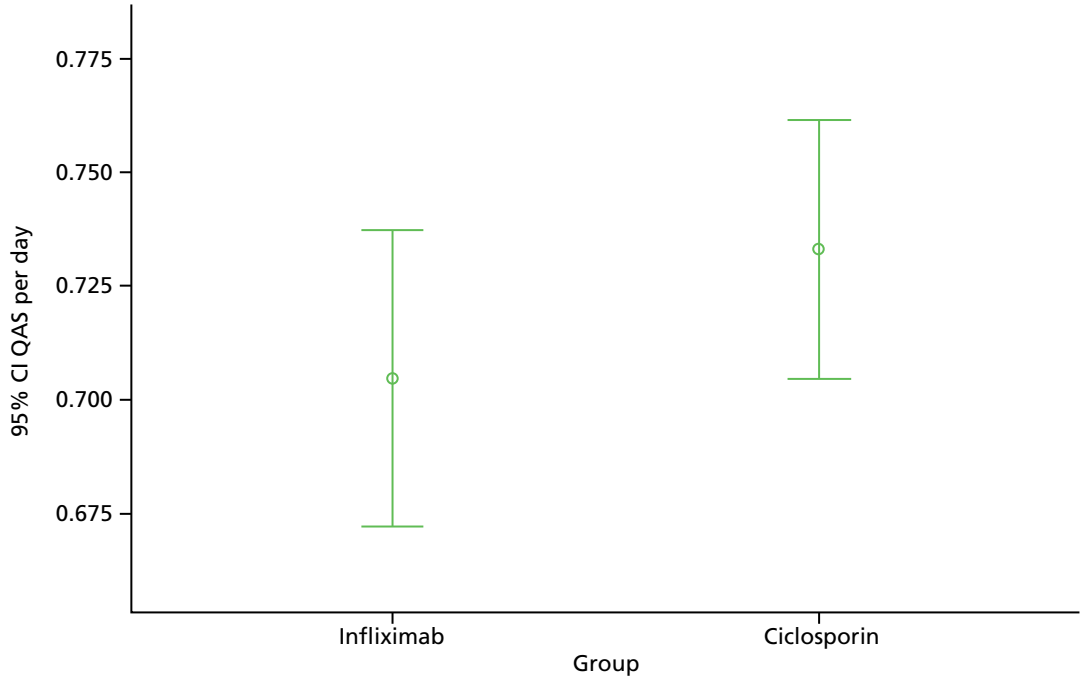

FIGURE 5 Means and 95% CI for QAS per day [defined as QAS divided by the time (in days) from randomisation until the end of follow-up] for the two groups.

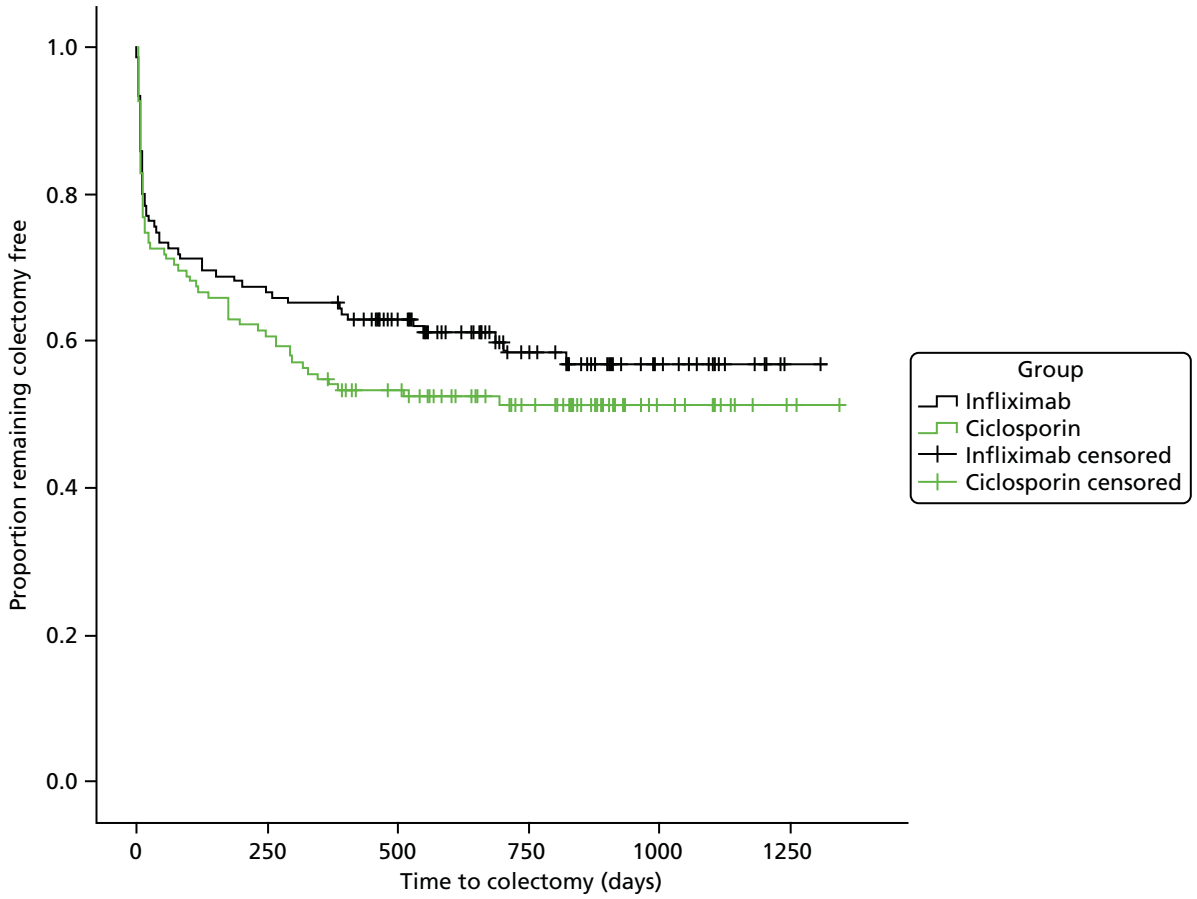

FIGURE 6 Kaplan–Meier plots showing the proportion remaining colectomy-free in the two groups over time (in days) in follow-up, censored at the end of follow-up on 28 February 2014.

Proportions with serious adverse reactions and serious adverse events

Table 17 shows that the observed difference in the proportions of participants reporting a SAR in the two groups is not statistically significant; the same is also true for the proportions of participants reporting a SAE.

Post-randomisation length of stay

Figure 7a displays box plots of the post-randomisation length of stay data for the two groups, and, together with the numerical summaries in *Table 17*, illustrates the skewed nature of these values. Transformed values (based on taking natural logarithms) are shown in *Figure 7b*, which shows that the transformation has considerably reduced the original skewness. Formal analysis shows that, although differences in the raw data are deemed to be not statistically significant, the corresponding analysis of the transformed data leads to the contrary conclusion that differences on the logarithmic scale are statistically different. As assumptions underpinning statistical models are more appropriate to the analysis of the transformed data, we should not readily accept conclusions based on the analysis of the raw data: the evidence on the equality of post-randomisation lengths of stay is thus rather more nuanced than an initial examination indicates.

Quality-of-life profiles

Table 18 presents numerical summaries of the three QoL measures [namely CUCQ, Short Form Questinnaire-6 dimensions (SF-6D), EQ-5D] at the various stages in follow-up. As discussed elsewhere, these summaries include, for the CUCQ, values obtained from the CUCQ+ when the extended version of the questionnaire was administered to patients post colectomy, and treats these as pari passu with other CUCQ scores; however, the summaries do not include values generated via specific PCQs, as such questionnaires are not always readily associated with a specific time in follow-up. (For the avoidance of doubt, it may again here be emphasised that CUCQ+ scores obtained from PCQs are included in participants' CUCQ profiles, and hence contribute to QAS and QAS per day.)

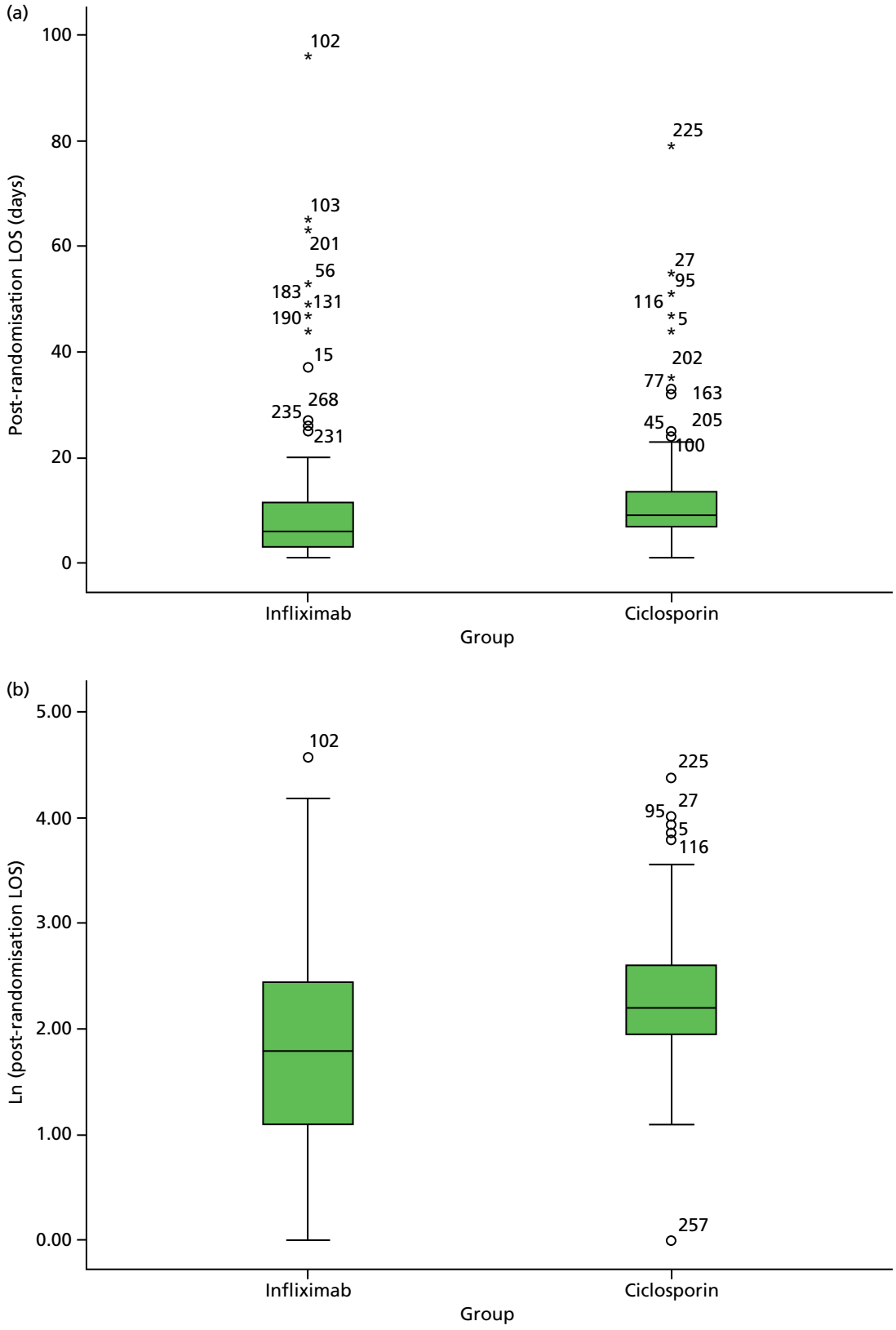

FIGURE 7 Box plots of post-randomisation LOS for the two groups. (a) Post-randomisation LOS in days; and (b) natural logarithms (Ln) of post-randomisation LOS. LOS, length of stay.

The profiles of the three QoL measures, shown in *Figures 8* (CUCQ), *9* (SF-6D) and *10* (EQ-5D) are broadly very similar. They show an initial rise over 1 year from values at baseline followed by a levelling off; the profile for the two groups are also very similar to each other. Formal analysis, summarised in *Table 18*, confirms that the observed differences are not statistically significant.

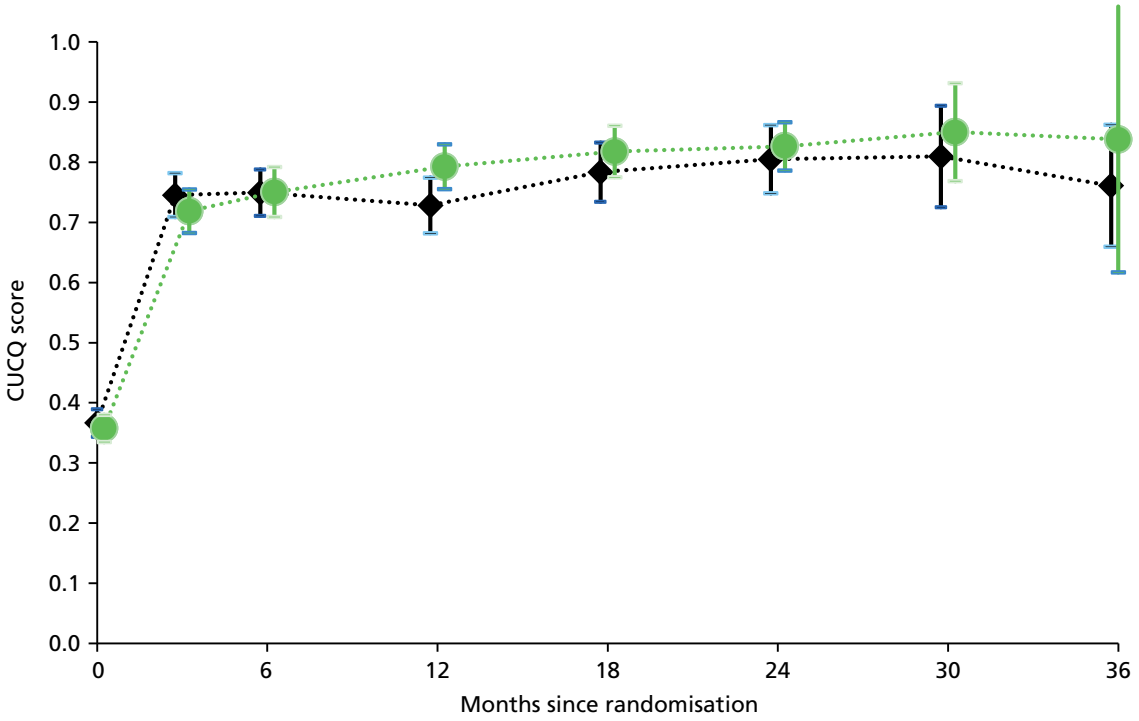

FIGURE 8 Mean CUCQ scores and 95% CI for the two groups at specific points in follow-up.

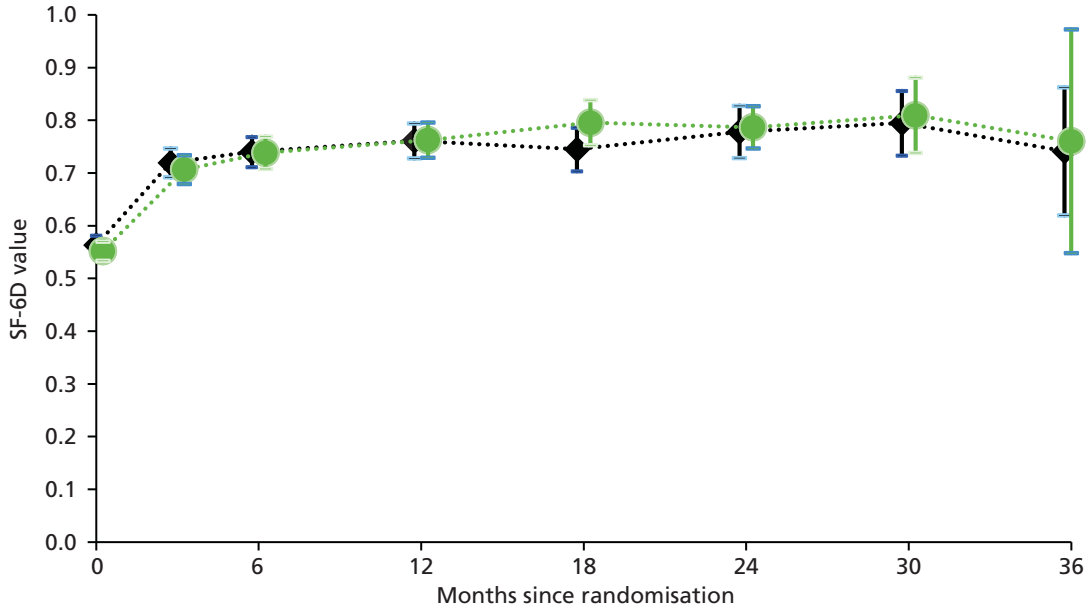

FIGURE 9 Mean SF-6D values and 95% CI for the two groups at specific time points in follow-up.

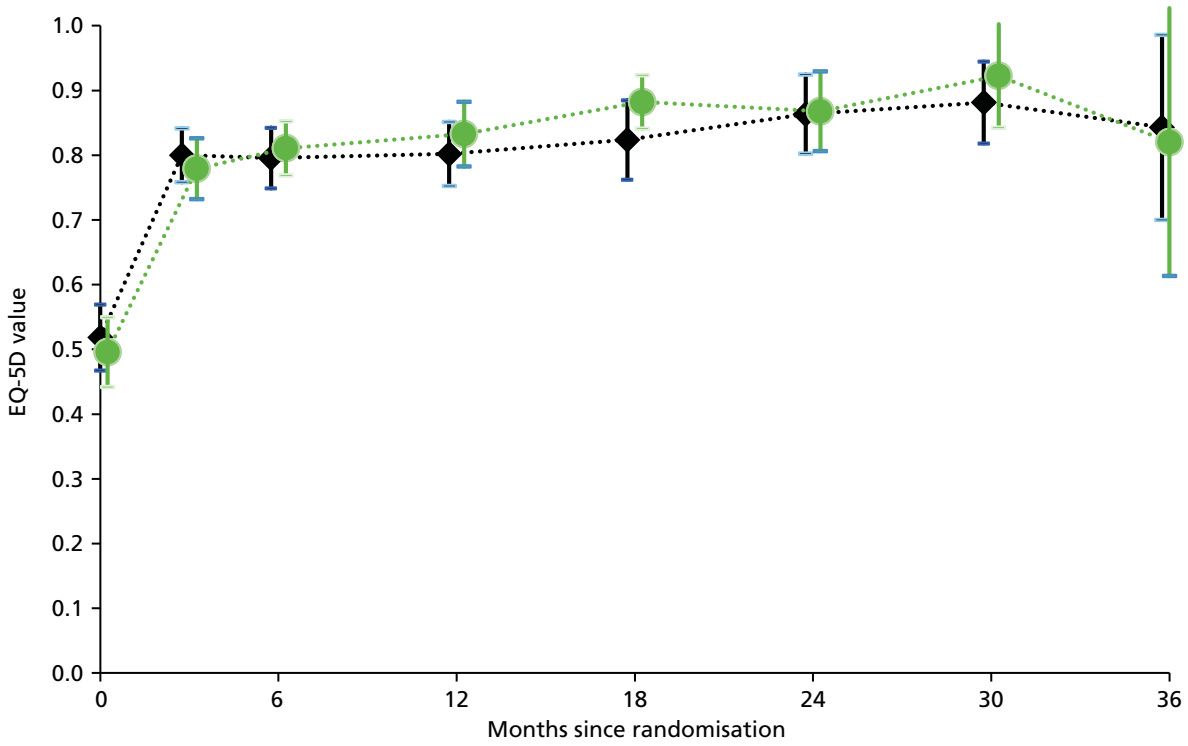

FIGURE 10 Mean EQ-5D values and 95% CI for the two groups at specific time points in follow-up.

Adverse events

Tables 21–23 summarise the categories of AEs reported on each drug and the clinical system affected.

Overall, 16 patients who had infliximab and 17 patients who had ciclosporin reported 21 and 25 (respectively) SAEs that were not related to disease progression or surgery. Fourteen patients who had infliximab and nine patients who had ciclosporin had 16 and 10 (respectively) SARs. There was no statistical significant difference between the two drugs in relation to the total SAEs ($p = 0.807$) and SARs ($p = 0.788$).

Three participants died, all following infliximab. In two cases this was due to sepsis in the presence of multiple comorbidities (including diabetes mellitus), at 20 days (preoperative) and 65 days (postoperative) following randomisation. One participant died from disseminated colorectal cancer at 278 days. This case was unusual in that signet ring cells were identified on histology of the resected specimen, raising the possibility of a lung primary but the multidisciplinary team concluded that primary was colorectal.

TABLE 21 Summary of all AEs reported

Event	Infliximab	Ciclosporin
SUSAR	0	0
SAR	16	10
SAE total	145	178
SAE IBD related	36	47
SAE surgery related	88	106
SAE other	21	25
AR	48	75

TABLE 22 Summary of the clinical system affected in SAEs

SAE	Infliximab	Ciclosporin
Infection	8	16
Gastrointestinal	1	1
Chest infection	1	4
Skin infection	1	2
Post surgical	4	4
UTI	0	2
Non-specific	1	3
Neurological	1	0
Gastrointestinal	5	2
Renal	0	0
Respiratory	2	0
Cardiovascular	0	3
Haematological	0	0
Psychiatric	1	1
Musculoskeletal	1	1
Venous thromboembolism	1	1
Other	2	1

UTI, urinary tract infection.

TABLE 23 Summary of the clinical system affected in SARs

SAR	Infliximab	Ciclosporin
Infection	8	1
C. diff	1	0
Chest infection	3	0
Skin infection	0	1
Post surgical	1	0
Others	3	0
Neurological	2	3
Gastrointestinal	1	2
Renal	0	2
Malignancy[a]	1 (colorectal cancer)	1 (endometrial cancer)
Allergy/infusion reaction	2	0
Psychiatric	1	0
Respiratory	1	0
Hepatic	0	1
Others	0	0

a One participant on infliximab developed a cutaneous basal cell carcinoma, but was not admitted for treatment, and the event was therefore classified as an AR. There were therefore two malignancies on infliximab and one on ciclosporin. The colorectal cancer was unusual in that it had some histological features suggestive of a lung primary. The local multidisciplinary team considered the case carefully and concluded that this was a single colorectal primary.

Continuation of treatment

As this was a pragmatic trial, local PIs were able to continue treatment with the trial Investigational Medicinal Products (IMPs) at their discretion and to add immunosuppressive drugs. *Figure 11* displays the continuation of infliximab and ciclosporin.

Tables 24–30 show the numbers of individual patients on immunosuppressants at baseline and following randomisation. *Table 24* summarises the number of patients receiving immunosuppressants prescribed (azathiporine, 6-mercaptopurine, methotrexate) and *Tables 25–30* break the figures down by individual drugs and those given in combination. No patient received more than two immunosuppressants at any one time. No significant differences have been identified. These data are derived from the patient-completed questionnaires at each time point.

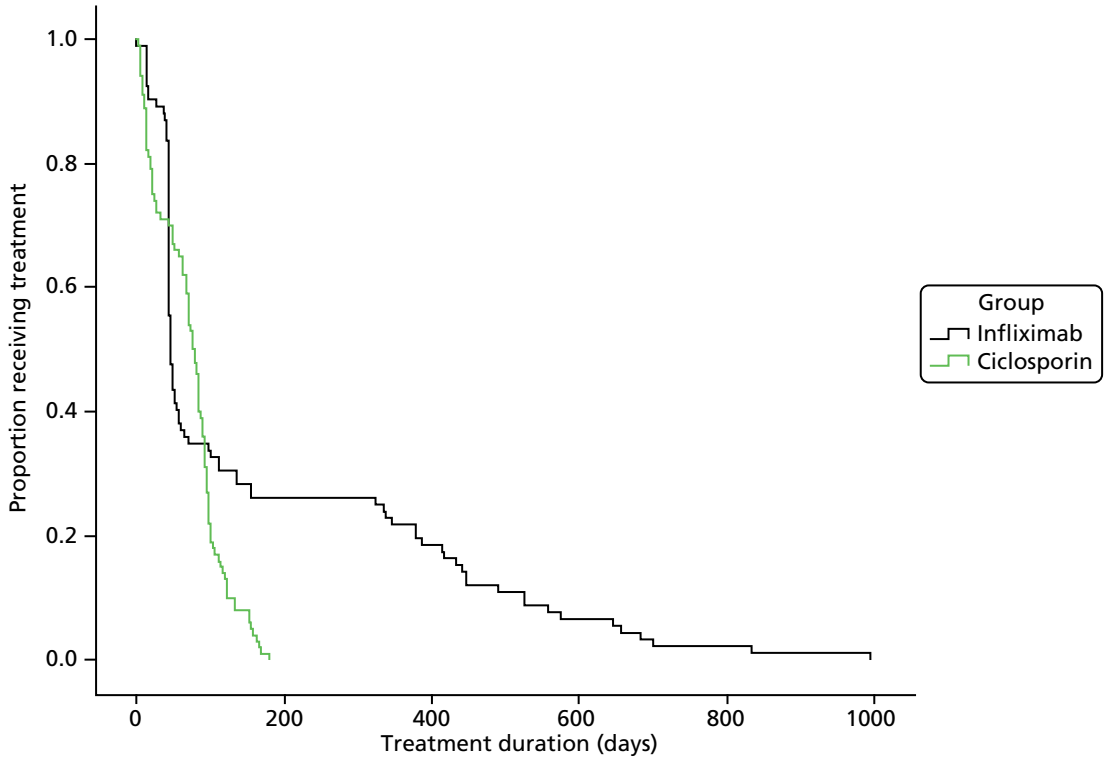

FIGURE 11 Kaplan–Meier plot of the treatment duration (in days) for the two groups; there is no attempt to distinguish further subgroups with different reasons for discontinuation of treatment, nor is there any censoring for cases when the end of treatment is not recorded.

TABLE 24 Total number of patients on immunosuppressants at each time period

Period	Total	Infliximab, *n* (% within arm)	Ciclosporin, *n* (% within arm)
Pre baseline	42	16 (11.9)	26 (19.3)
3 months	122	56 (42.7)	66 (49.3)
6 months	113	56 (42.7)	57 (43.5)
12 months	84	39 (31.0)	45 (36.3)
18 months	42	23 (24.0)	19 (20.5)
24 months	38	18 29.5)	20 (30.3)
30 months	19	10 (27.8)	9 (23.1)
36 months	7	4 (23.5)	3 (17.6)

TABLE 25 Occurrence of azathioprine (alone) prescribing in each trial period

Period	Total	Infliximab, *n* (% within arm)	Ciclosporin, *n* (% within arm)
Pre baseline	28	14 (10.4)	14 (10.4)
3 months	100	50 (38.2)	50 (37.3)
6 months	80	40 (30.5)	40 (30.5)
12 months	62	28 (22.2)	34 (27.4)
18 months	31	16 (16.7)	15 (15.8)
24 months	25	12 (19.7)	13 (19.7)
30 months	14	8 (22.2)	6 (15.4)
36 months	6	3 (17.6)	3 (17.6)

TABLE 26 Occurrence of 6-mercaptopurine (alone) prescribing in each trial period

Period	Total	Infliximab, *n* (% within arm)	Ciclosporin, *n* (% within arm)
Pre baseline	8	2 (1.5)	6 (4.4)
3 months	13	3 (2.3)	10 (7.5)
6 months	24	15 (11.5)	9 (6.9)
12 months	19	11 (8.7)	8 (6.5)
18 months	9	6 (6.3)	3 (3.2)
24 months	13	6 (9.8)	7 (10.6)
30 months	5	2 (5.6)	3 (7.7)
36 months	1	1 (5.9)	0

TABLE 27 Occurrence of methotrexate (alone) prescribing in trial period

Period	Total	Infliximab, *n* (% within arm)	Ciclosporin, *n* (% within arm)
Pre baseline	2	0	2 (1.5)
3 months	3	0	3 (2.2)
6 months	5	1 (0.8)	4 (3.1)
12 months	3	0	3 (2.4)
18 months	1	0	1 (1.1)
24 months	0	0	0
30 months	0	0	0
36 months	0	0	0

TABLE 28 Occurrence of azathiporine + 6-mercaptopurine in combination in trial period

Period	Total	Infliximab	Ciclosporin
Pre baseline	0	0	0
3 months	2	1	1
6 months	2	0	2
12 months	0	0	0
18 months	0	0	0
24 months	0	0	0
30 months	0	0	0
36 months	0	0	0

TABLE 29 Occurrence of azathiporine + methotrexate in combination in trial period

Period	Total	Infliximab	Ciclosporin
Pre baseline	4	0	4
3 months	1	0	1
6 months	1	0	1
12 months	0	0	0
18 months	1	1	0
24 months	0	0	0
30 months	0	0	0
36 months	0	0	0

TABLE 30 Occurrence of 6-mercaptopurine + methotrexate in combination in trial period

Period	Total	Infliximab	Ciclosporin
Pre baseline	0	0	0
3 months	3	2	1
6 months	0	0	0
12 months	0	0	0
18 months	0	0	0
24 months	0	0	0
30 months	0	0	0
36 months	0	0	0

Cost-effectiveness

Analysis of missing data

Table 31 reports the number of observations missing at each data collection time between the two arms of the trial.

The amount of missing data was greater for items reported on the PFQ which was completed by the participant as compared with the CRF which was completed by the research nurse. Participants who withdrew from the study were more likely to withdraw only from responding to further questionnaires (PFQ) than from accessing their medical records (CRF) leading to more missing data from the PFQ.

Data on trial drug administration costs were missing for 41 infliximab and 24 ciclosporin participants. Data on oral ciclosporin were missing for two participants who had completed the protocol single infusion.

We used age, gender, study arm, ethnicity, smoking, weight, and baseline SF-6D, EQ-5D and CUCQ scores to assess randomness of missing data.

For CRF data, the pattern of missing data on tests and investigations and drugs delivered to inpatients was studied at 18, 24 and 30 months and no significance was shown.

At 3 months, the pattern of missing PFQ data showed statistical significance for gender, with 41 males (25%) and 12 females (12%) not providing responses ($p = 0.017$). At 12 months, younger people (mean age 36.35 years, SD 14.59 years) were less likely to provide responses than the rest of the cohort (mean age 40.44 years, SD 15.85 years) ($p = 0.045$). This was also the case at 24 months, younger people (mean age 36.89 years, SD 14.10 years) versus the rest of the cohort (mean age 43.52 years, SD 14.56 years) ($p = 0.012$).

At each follow-up point, however, missing data were evenly distributed between study arms, suggesting that the imputation process adopted should not have led to any estimation bias.

Comparison of costs

For cost comparisons, we analysed data on all participants for whom we had cost data for each follow-up period. In these comparisons, we performed tests for statistical significance independently for each period, owing to the different sample sizes at each time point. For the incremental cost-effectiveness analysis we analysed cost data for those participants for whom we had effectiveness data and summed total costs over the whole of the follow-up period.

Trial drug costs

A total of 42 of 52 of sites that recruited participants to the RCT responded to our survey regarding preparation and delivery of trial drugs. Pharmacists prepared infliximab infusions at 11 sites and prepared ciclosporin infusions at seven sites. All other infusions were prepared by nurses. For infliximab, the mean administration costs were £17.66 (SD £25.05) per infusion. For ciclosporin they were £35.41 (SD £28.48) per day during which the infusion was received.

Eighty-eight infliximab participants received the three infusions specified in the protocol; 98 received two infusions and 134 received a single infusion. Thirty-four participants received additional infusions (minimum = 1, maximum = 13) with a mean of 1.20 (SD 2.71) additional infusions.

One hundred and thirty-two ciclosporin participants received the single infusion specified in the protocol with a mean (SD) infusion duration of 5.0 (SD 1.8) days. Of these, 100 were switched to oral following their single infusion with a mean duration on oral ciclosporin of 52.0 (SD 48.8) days.

Table 32 shows the mean costs of treatment with the two trial drugs. As most participants on oral ciclosporin completed their treatment within 3 months, all oral ciclosporin costs have been attributed to

TABLE 31 Number of missing observations (% if more than 5%) at each data point

	Baseline to 3 months		6 months		12 months		18 months		24 months		30 months	
Resource item	Infliximab	Ciclosporin	Infliximab	Ciclosporin	Infliximab	Ciclosporin	Infliximab	Ciclosporin	Infliximab	Ciclosporin	Infliximab	Ciclosporin
Trial drug administration	41 (30)	24 (18)	–	–	–	–	–	–	–	–	–	–
Number of subsequent infusions of infliximab	0	n/a	–	–	–	–	–	–	–	–	–	–
Number of patients on oral ciclosporin	n/a	2	–	–	–	–	–	–	–	–	–	–
Tests/ investigations/ drugs in hospital CRF	2	1	1	6	7	6	16 (12)	18 (13)	5	2	5	12 (9)
NHS resource-use PFQ	26 (20)	27 (20)	27 (21)	29 (22)	43 (34)	36 (30)	30 (37)	30 (43)	25 (41)	28 (43)	8 (30)	17 (60)

n/a, not applicable.

TABLE 32 Mean (SD) costs of infliximab and ciclosporin (£)

	Ciclosporin			Infliximab		
Follow-up period (months)	*n*	Mean (SD) cost (£)	95% CI (£)[a]	*n*	Mean (SD) cost (£)	95% CI (£)[a]
0–3[b]	135	880 (649)	569 to 734	135	4823 (2199)	4464 to 5181
4–6	–	–	–	131	638 (1474)	399 to 902
7–12	–	–	–	131	837 (2179)	486 to 1232
13–18	–	–	–	84	773 (1942)	385 to 1211
19–24	–	–	–	65	337 (1450)	37 to 693
25–30	–	–	–	27	175 (907)	0 to 510
Total (£)	118,800			935,837		

a Bias-corrected 10,000 bootstrap replications.
b Cost of oral ciclosporin attributed to 3 months.

the first 3 months. Infliximab is clearly the more costly treatment with a mean cost in the first 3 months of £4823 (SD £2199) compared with £880 (SD £649) for ciclosporin and with costs for additional infliximab infusions continuing beyond this period.

Baseline spell in hospital: length of stay

All participants were recruited and randomised while inpatients. Mean length of stay of this baseline spell in hospital (i.e. from randomisation to discharge) was slightly higher for ciclosporin participants but the difference was not statistically significant: ciclosporin 12.21 (SD 10.18) days, infliximab 10.32 (SD 13.55) days (95% CI –1.06 to 4.69 days; $p = 0.20$) as shown in *Table 33*.

Twenty-eight participants in the infliximab arm (20.7%) had surgery during the baseline spell compared with 34 in the ciclosporin arm (25.2%). The mean length of stay for those who had surgery was similar between groups: infliximab 22.89 (SD 14.90) days versus ciclosporin 21.38 (SD 14.65) days (95% CI –9.03 to 5.91 days; $p = 0.68$).

A total of 107 participants in the infliximab arm (79.2%) were discharged from their baseline spell in hospital without having surgery compared with 101 in the ciclosporin arm (74.8%). For those who did not have surgery, the mean length of stay was higher for ciclosporin participants at 9.13 (SD 5.45) days versus 7.02 (SD 11.07) days for infliximab, although the difference was not statistically significant (95% CI –9.03 to 5.91 days; $p = 0.08$).

Cost of hospitalisation without surgery

The cost of the baseline spell in hospital for participants who did not have surgery is shown in *Table 34*, which also shows costs for all subsequent non-surgical hospital admissions. The mean differences were not statistically significant in any period.

TABLE 33 Mean (SD) length of baseline spell in hospital (days)

	Ciclosporin		Infliximab			95% CI[a] (days)		
Participants	*n*	Mean (SD) (days)	*n*	Mean (SD) (days)	Mean difference (ciclosporin – infliximab) (days)	Lower	Upper	*p*-value
All	135	12.21 (10.18)	135	10.32 (13.55)	1.90	–1.06	4.69	0.20
No surgery	101	9.13 (5.45)	107	7.02 (11.07)	2.11	–0.34	4.17	0.08
Surgery	34	21.38 (14.65)	28	22.89 (14.90)	–1.55	–9.03	5.91	0.68

a Bias-corrected 10,000 bootstrap replications.

TABLE 34 Non-surgical hospital admissions and mean (SD) costs (£)

Follow-up period	Ciclosporin				Infliximab				Mean difference (ciclosporin – infliximab) (£)	95% CI[a]		*p*-value
	Admitted, *n*	Sample, *n*	Mean (£)	SD (£)	Admitted, *n*	Sample, *n*	Mean (£)	SD (£)		Lower (£)	Upper (£)	
Baseline spell, no surgery	101	135	2124	1691	107	135	1796	2590	328	–201	793	0.220
End of baseline spell to 3 months	24	135	890	2413	30	135	941	2729	–52	–662	538	0.870
4–6 months	23	133	604	1677	14	131	365	1330	238	–126	614	0.201
7–12 months	32	133	927	2377	30	131	1094	2761	–167	–778	425	0.598
13–18 months	13	85	464	1326	13	84	589	1708	–125	–592	312	0.596
19–24 months	10	71	740	2508	14	65	571	1299	169	–463	910	0.618
25–30 months	1	30	129	705	3	27	315	1061	186	–688[b]	266[b,c]	0.445
Total (£)		706,303				655,851						

a Bias-corrected 10,000 bootstrap replications.
b Based on 9807 samples.
c CI computed by percentile method rather than bias-corrected and accelerated method.

Cost of hospitalisation with surgery

Table 35 shows the number of participants who had colectomies or other surgical procedures by follow-up period. None of the differences was statistically significant (chi-squared test).

Table 36 shows the costs of surgical admissions at each follow-up point. There were no statistically significant differences between groups at any point.

NHS resource use

The costs of NHS resource use in the 3 months prior to baseline are shown in *Table 37*. There were no statistically significant differences across individual resource items apart from prescription drugs in which the mean cost for ciclosporin participants was significantly higher: £224 (SD £223) versus £166 (SD £185), mean difference £58 (95% CI £9 to £107; $p = 0.020$). Total costs were not significantly different with a mean cost for ciclosporin participants of £1115 (SD £1291) versus with £1034 (SD £1047), mean difference £80 (95% CI –£194 to £352; $p = 0.573$).

The total costs of all NHS contacts (as itemised above) are shown in *Table 38*. *Table 38* also shows the costs of prescribed drugs other than the trial drugs given to participants as inpatients and by prescription in the community, and the costs of tests and investigations. There were no statistically significant differences between arms for any items during any period.

Incremental cost-effectiveness

Results relate to a 'within-trial' cost-effectiveness analysis using primary data collected within the period of study and without lifetime extrapolation. Base-case costs and QALYs to be reported below cover 30 months adjusted by the number of days over which each participant contributed data. *Table 39* shows that the mean number of days that ciclosporin participants contributed CRF data was slightly higher than for infliximab participants: 645.9 (SD 204.8) days versus 623.7 (SD 224.0) days, but the mean difference of 22.2 days was not statistically significant (95% CI –32.2 to 77.4 days; $p = 0.433$). A similar pattern was shown for PFQ data: 673.0 (SD 226.0) days versus 653.2 (SD 224.8) days, mean difference 19.7 days (95% CI –36.8 to 76.5 days; $p = 0.509$).

Base-case costs and QALYs are shown in *Table 40*. The mean difference in QALYs was 0.023 in favour of ciclosporin, but this is not statistically significant (95% CI –0.053 to 0.101; $p = 0.563$). The mean difference in costs was –£5632 in favour of ciclosporin and is statistically significant (95% CI –8348 to –2880; $p < 0.001$).

TABLE 35 Colectomy and other surgical procedures

	Ciclosporin ($n = 135$)		Infliximab ($n = 135$)		
Follow-up period	Colectomy, *n*	Other procedures, *n*	Colectomy, *n*	Other procedure, *n*	*p*-value[a]
Baseline spell	34	–	28	–	0.235
Discharge to 3 months	8	1	10	1	0.533
4–6 months	9	3	4	4	0.356
7–12 months	11	13	5	13	0.239
13–18 months	2	11	5	7	0.169
19–24 months	1	67	2	5	0.279
25–30 months	0	1	1	3	0.460

a Chi-squared test.

TABLE 36 Mean (SD) costs of colectomy and other surgical procedures (£)

	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab) (£)	95% CI[a]		
Follow-up period	*n*	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)		Lower (£)	Upper (£)	*p*-value
Baseline spell										
Colectomy	135	2432	4640	135	2074	4451	358	–749	1466	0.519
Discharge to 3 months										
Colectomy	135	354	1535	135	525	2195	–170	–642	253	0.461
Other	135	18	205	135	5	53	13	–13[b,c]	58[c]	0.474
4–6 months										
Colectomy	133	348	1446	131	170	1005	178	–123	494	0.247
Other	133	0	0	131	8	88	–8	–29[b,d]	7[d]	0.319
7–12 months										
Colectomy	133	439	1542	131	214	1105	226	–95	562	0.172
Other	133	589	2415	131	656	2665	–67	–694	546	0.830
13–18 months										
Colectomy	85	46	425	84	204	967	–158	–402[b,e]	47[e]	0.173
Other	85	435	1332	84	526	2329	–91	–700	420	0.757
19–24 months										
Colectomy	71	204	1721	65	110	648	94	–246[b,f]	604[f]	0.670
Other	71	590	2555	65	281	1037	309	–278	1059	0.350

Follow-up period	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab) (£)	95% CI[a]		*p*-value
	n	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)		Lower (£)	Upper (£)	
25–30 months										
Colectomy	30	0	0	27	289	1501	–289	–1076[b,g]	217[g]	0.327
Other	30	192	1051	27	234	677	–42	–444[b,h]	457[h]	0.856
Total (£)										
Colectomy	499,175			433,258						
Other	165,392			156,426						

a Bias-corrected 10,000 bootstrap replications.
b CI computed by percentile rather than bias-corrected and accelerated method.
c Based on 9529 samples.
d Based on 9837 samples.
e Based on 9915 samples.
f Based on 9457 samples.
g Based on 6346 samples.
h Based on 9817 samples.

TABLE 37 Mean (SD) cost of NHS resource use 3 months prior to randomisation (£)

	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab) (£)	95% CI[a]		
NHS service	*n*	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)		Lower (£)	Upper (£)	*p*-value
GP surgery visits	135	119	119	134	124	120	–5	–34	25	0.761
Home visits	135	14	56	134	20	61	–6	–20	8	0.378
Phone calls	135	46	89	134	34	46	12	–5	31	0.166
A&E attendances	135	41	82	135	50	99	–8	–30	13	0.453
Clinic visits	135	210	256	135	168	313	42	–24	104	0.229
Hospitalisation	135	380	882	135	554	1128	–174	–411	55	0.159
Prescription drugs	135	224	223	135	166	185	58	9	107	0.020
Total	135	1115	1291	135	1034	1047	80	–194	352	0.573

A&E, accident and emergency.
a Bias-corrected 10,000 bootstrap replications.

TABLE 38 Mean (SD) costs of NHS resource use post randomisation (£)[a]

Follow-up period (months)	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab) (£)	95% CI[b]		*p*-value
	n	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)		Lower (£)	Upper (£)	
Cost of all NHS contacts										
0–3	105	204	397	105	165	363	40	–62	137	0.455
4–6	99	86	98	104	93	116	–8	–36	21	0.609
7–12	85	80	110	82	77	110	3	–30	35	0.871
13–18	40	69	96	50	72	89	–3	–41	36	0.871
19–24	37	55	75	36	64	81	–9	–46	28	0.627
25–30	11	26	44	18	29	42	–4	–35	32	0.826
Total (£)	41,815			39,737						
Cost of prescribed drugs (hospital inpatient)										
0–3	133	66	157	131	61	141	6	–30	43	0.757
4–6	127	11	43	130	7	32	4	–5	14	0.392
7–12	127	19	99	124	10	37	9	–8	33	0.350
13–18	67	9	39	68	18	100	–9	–34	10	0.509
19–24	69	35	193	60	9	29	26	–11	84	0.278
25–30	18	< 1	< 1	22	9	29	–9	–23[c]	< 1[c]	0.166
Total (£)	15,606			12,103						

continued

TABLE 38 Mean (SD) costs of NHS resource use post randomisation (£)[a] (*continued*)

Follow-up period (months)	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab) (£)	95% CI[b]		*p*-value
	n	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)		Lower (£)	Upper (£)	
Cost of prescribed drugs (community)										
0–3	105	215	223	105	168	168	47	–6	100	0.086
4–6	100	186	221	104	165	187	21	–34	78	0.459
7–12	85	150	188	82	164	190	14	–69	43	0.628
13–18	40	138	128	50	194	203	–57	–125	10	0.110
19–24	37	136	188	36	196	184	–60	–146	26	0.170
25–30	11	155	158	18	134	175	20	–102	142	0.745
Total (£)	66,182			67,416						
Costs of clinical tests and investigations										
0–3	134	676	705	133	684	744	–8	–179	164	0.927
4–6	127	255	434	130	193	357	63	–33	161	0.209
7–12	127	388	653	124	346	550	42	–106	194	0.581
13–18	67	170	296	68	286	485	–117	–254	12	0.093
19–24	69	312	715	60	223	466	89	–111	311	0.399
25–30	18	140	259	22	236	425	–96	–323	109	0.384
Total (£)	207,683			196,986						
Costs of clinic visits										
0–3	134	408	351	134	416	274	–8	–82	66	0.834
4–6	130	285	279	131	259	238	26	–39	92	0.422
7–12	125	387	400	123	378	386	10	–84	102	0.856

Follow-up period (months)	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab) (£)	95% CI[b]		
	n	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)		Lower (£)	Upper (£)	*p*-value
13–18	67	371	421	68	334	300	38	–86	165	0.556
19–24	67	355	417	60	286	363	69	–65	204	0.322
25–30	18	240	194	22	319	316	–79	–244	66	0.338
Total (£)	193,059			183,057						
Costs of A&E attendances										
0–3	134	29	82	134	30	77	1	–20	19	0.932
4–6	130	25	90	131	25	76	0	–20	21	0.985
7–12	125	38	108	123	36	108	2	–24	28	0.877
13–18	67	12	48	68	21	76	–10	–32	9	0.375
19–24	67	22	62	60	21	70	1	–22	23	0.919
25–30	18	6	26	22	15	72	–9	–48[d]	17	0.588
Total (£)	14,272			14,741						

A&E, accident and emergency.
a Costs shown are for comparison between groups. Beyond 6 months, PFQ data only reflect costs in 3 months prior to each follow-up point and not the total cost for the period.
b Bias-corrected 10,000 bootstrap replications.
c Based on 9870 samples.
d Based on 9839 samples.

TABLE 39 Mean (SD) days in study by data collection method

Data collection method: recruitment to 30 months	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab) (days)	95% CI		
	n	Mean (days)	SD (days)	*n*	Mean (days)	SD (days)		Lower (days)	Upper (days)	*p*-value
CRF	113	645.92	204.80	117	623.70	223.95	22.22	–32.23	77.36	0.433
PFQ	113	672.89	226.03	117	653.21	224.84	19.67	–36.83	76.54	0.509

TABLE 40 Mean (SD) QALYs and costs over 30 months and mean difference (ciclosporin – infliximab) weighted by participants' time in study

QALYs and costs	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab)	95% CI[a]		
	n	Mean	SD	*n*	Mean	SD		Lower	Upper	*p*-value
QALYs	113	1.921	0.29	117	1.898	0.31	0.023	–0.053	0.101	0.563
Costs (£)	113	14,609	10,838	117	20,241	10,433	–5632	–8348	–2880	0.000

a Bias-corrected 10,000 bootstrap replications.

The cost-effectiveness plane representing 5000 bootstrap replications is shown in *Figure 12*. Most observations are in the south-east quadrant suggesting that ciclosporin dominates infliximab.

The CEAC shown in *Figure 13* shows ciclosporin to have a 73–74% probability of being cost-effective over virtually all willingness-to-pay thresholds. The almost horizontal curve is due to the difference in effects being close to zero.[59,98]

Table 41 shows base-case costs and QALYs over 30 months further adjusted using baseline EQ-5D and CUCQ scores and participants' weight as covariates for QALYs and baseline cost as a covariate for costs. The mean difference in QALYs remains in favour of ciclosporin but is slightly reduced by 0.002 to 0.021 QALYs, which is not statistically significant (95% CI – 0.032 to 0.096; $p = 0.35$). The mean difference in costs (–£5632) is unchanged and is statistically significant (95% CI –£8305 to –2773; $p < 0.001$).

The cost-effectiveness plane is shown in *Figure 14*. The decrease in spread is due to reduced standard errors. Ciclosporin continues to dominate infliximab with the CEAC (*Figure 15*) showing ciclosporin to have an 85% chance of being cost-effective over all willingness-to-pay thresholds.

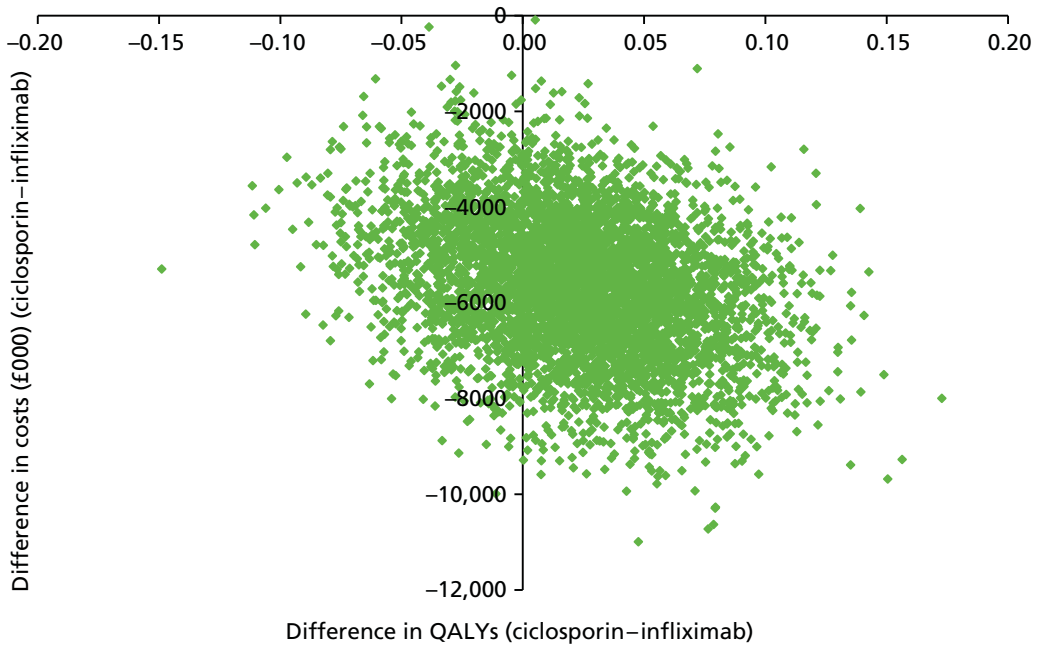

FIGURE 12 Base-case (30-month) cost-effectiveness plane adjusted for by participants' length of time in study.

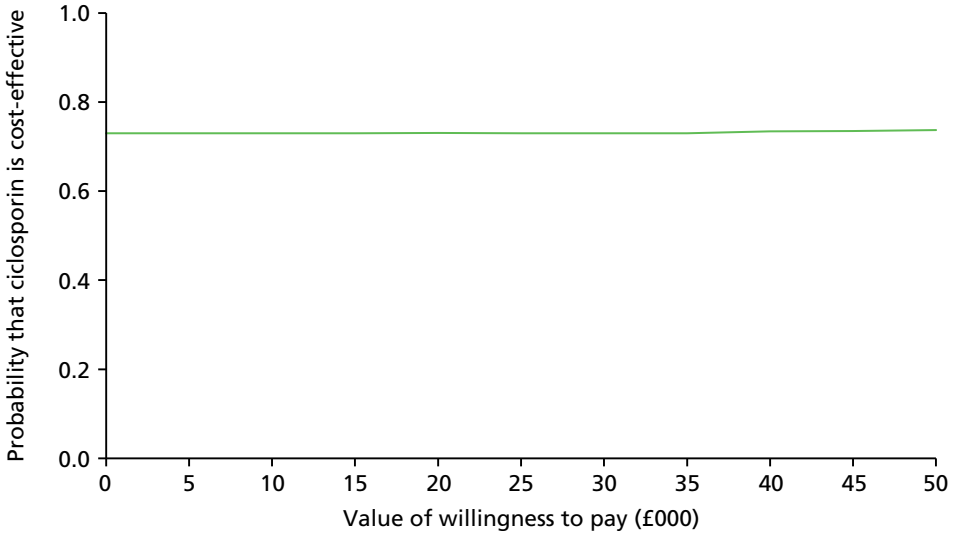

FIGURE 13 Base-case (30-month) CEAC adjusted by participants' length of time in study.

TABLE 41 Mean (SD) QALYs and costs over 30 months and mean difference (ciclosporin – infliximab) adjusted for baseline covariates

	Ciclosporin			Infliximab			Mean difference (ciclosporin – infliximab)	95% CI[a]		
QALYs and costs	*n*	Mean	SD	*n*	Mean	SD		Lower	Upper	*p*-value
QALYs	113	1.921	0.18	117	1.900	0.16	0.021	–0.032	0.096	0.350
Costs (£)	113	14,609	593	117	20,241	695	–5632	–8305	–2773	0.000

a Bias-corrected 10,000 bootstrap replications.

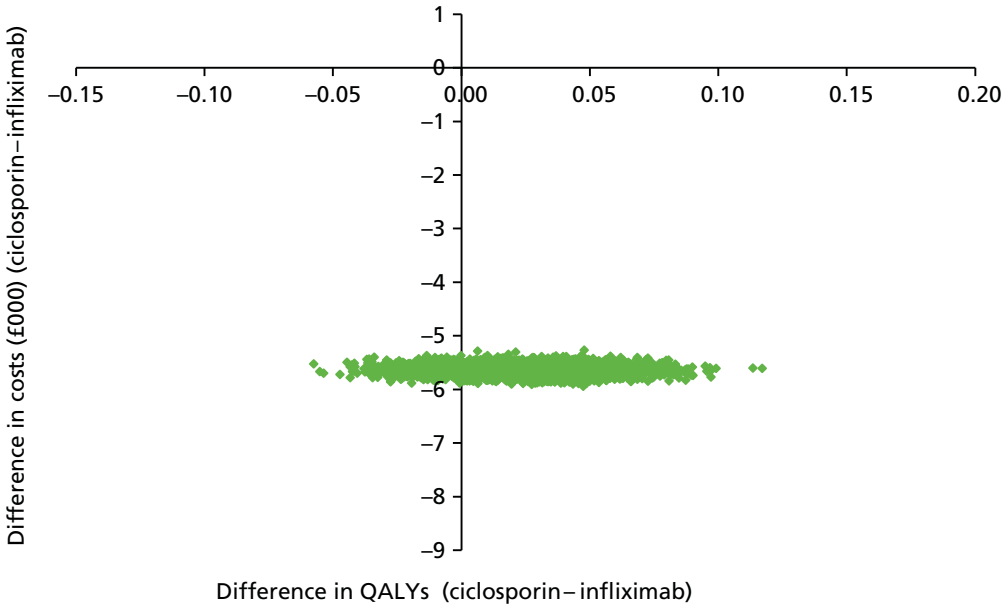

FIGURE 14 Base-case (30-month) cost-effectiveness plane weighted for participants' time in study and adjusted for baseline covariates.

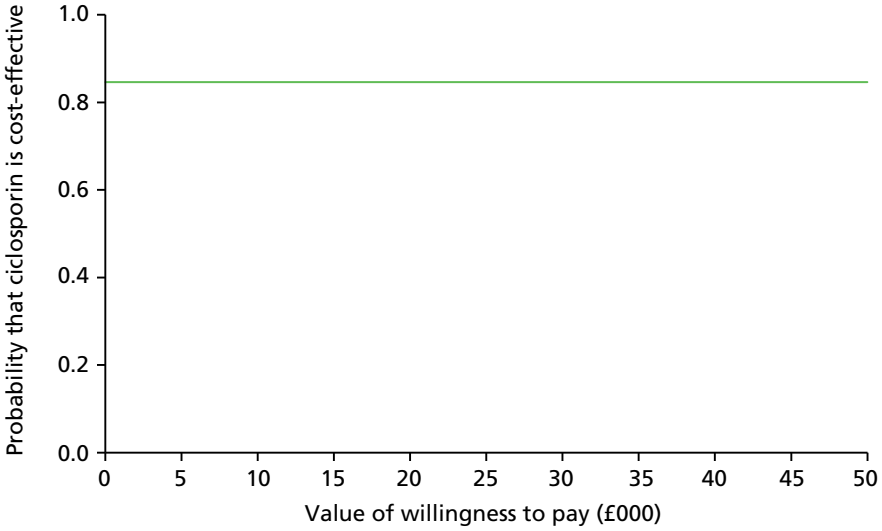

FIGURE 15 Base-case (30-month) CEAC weighted for participants' time in study and adjusted for baseline covariates.

Sensitivity analyses

Table 42 below shows results at 12 and 24 months which are similar to the base case, in that the differences in QALYs at both time points are in favour of ciclosporin and are small (0.027 and 0.022 QALYs at 12 and 24 months, respectively). The mean difference at 12 months is marginally statistically significant ($p = 0.049$), but not at 24 months ($p = 0.479$). Mean differences in costs in both cases are again in favour of ciclosporin (–£4568 and –£4498 and are statistically significant; 12 months ($p < 0.001$), 24 months ($p < 0.001$). These two sensitivity analyses are consistent with the base case showing ciclosporin to dominate infliximab.

Participants' time off work

Mean participants' time off work in the 3 months prior to baseline was similar at 7.70 (SD 15.62) days and 8.27 (SD 14.32) days for infliximab and ciclosporin participants, respectively. There were very few differences between groups at other follow-up points suggesting that treatment had no differential impact on participants' time off work as shown in *Table 43*.

TABLE 42 Mean (SD) QALYs and NHS costs and mean difference (ciclosporin – infliximab) at 12 and 24 months: complete-case analyses

	Ciclosporin		Infliximab		Mean difference (ciclosporin – infliximab)		
QALYs and costs	*n*	Mean (SD)	*n*	Mean (SD)		95% CI[a]	*p*-value
QALYs: 12 months	109	0.802 (0.106)	115	0.775 (0.079)	0.027	–0.001 to 0.054	0.049
Total NHS costs (£): 12 months	109	10,796 (138)	115	15,364 (169)	–4568	–4609 to –4528	0.000
QALYs: 24 months	62	1.650 (0.166)	58	1.628 (0.169)	0.022	–0.039 to 0.082	0.479
Total NHS costs (£): 24 months	62	14,773 (1607)	58	19,271 (2181)	–4498	–5231 to –3799	0.000

a Bias-corrected 10,000 bootstrap replications.

TABLE 43 Mean (SD) participants' time off work (days) and mean difference

	Ciclosporin		Infliximab		Mean difference (ciclosporin – infliximab)	
Period	*n*	Mean (SD)	*n*	Mean (SD)		*p*-value (95% CI)
Baseline	133	8.27 (14.32)	131	7.70 (15.62)	0.57	0.76 (–3.06 to 4.20)
3 months	103	16.19 (29.45)	101	15.64 (27.39)	0.55	0.89 (–7.30 to 8.40)
6 months	96	6.48 (15.97)	102	3.92 (15.75)	2.56	0.26 (–1.89 to 7.01)
12 months	85	4.31 (16.67)	81	4.30 (14.34	0.01	1.00 (–4.77 to 4.79)
18 months	40	5.68 (18.03)	52	1.71 (3.62)	3.96	0.18 (–1.88 to 9.81)
24 months	40	2.74 (10.52)	40	2.99 (13.56)	–0.25	0.93 (–5.65 to 5.15)
30 months	13	1.15 (3.87)	18	1.58 (5.62)	–0.43	0.80 (–3.92 to 3.06)

Participant interviews

Number of interviews completed

The qualitative section in *Chapter 2* explained that we planned to conduct a total of 24 interviews at 3- and 12-month intervals with participants after randomisation and treatment. However, after 20 3-month interviews had been analysed, data saturation was reached and the TMG confirmed that no further interviews were needed.

The number of 3-month interviews completed was split evenly between those randomised to infliximab and those to ciclosporin, with 10 participants in each group, of which three in each group had also had a colectomy. There were three females and seven males in each treatment group and their ages ranged from 21 to 75 years, as shown in *Table 44*.

To assess the representativeness or otherwise of the 20 participants selected for interview, we compared the primary outcome, QAS per day, in terms of group and interview status. The numerical summaries of means and SDs in *Table 45* are consistent with the box plots in *Figure 16*, and show that, in both groups, those interviewed are reasonably similar to those not interviewed.

It is worth noting the wide age range of the interviewees, but that their views and experiences were similar and the only differences seemed to relate to views about reversal procedures for those who had had surgery to treat their UC. This is explained below.

The length of time since the participants had been diagnosed with UC varied from just a few weeks to as long as 30 years. However, those who had only recently been diagnosed had generally been experiencing symptoms for several months.

TABLE 44 Details of interview participants

	Infliximab		Ciclosporin	
Participants	Males	Females	Males	Females
Number interviewed	7	3	7	3
Age range (years)	23–64	21–44	27–75	31–59
Mean age (years)	44	32	51	43

TABLE 45 Numerical summaries of QAS per day

Group	Infliximab, mean (SD) [*n*]	Ciclosporin, mean (SD) [*n*]
Interview status		
Interviewed	0.6863 (0.2227) [9]	0.7754 (0.0778) [10]
Not interviewed	0.7062 (0.1786) [112]	0.7293 (0.1630) [111]

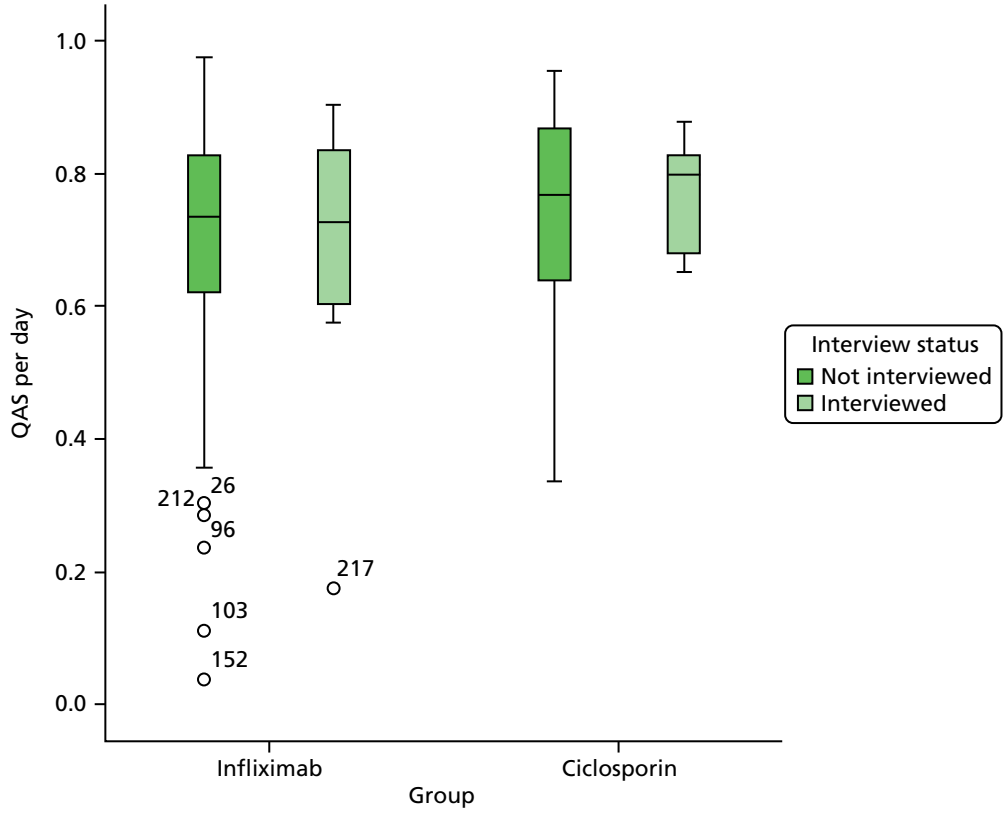

FIGURE 16 Graphical summaries of QAS per day.

With many participants working, the interviews often took place when people returned home from work. The interviews lasted between 15 minutes (unusually short) and 45 minutes in length (more common), and all participants agreed that the interviews could be recorded.

As soon as possible after an interview had taken place, recordings were transcribed and then reviewed by the interviewer. The interview transcripts were anonymised and any names or geographical details were removed from the transcripts.

At 12 months, 15 of the interviewees agreed to a second interview (eight infliximab, seven ciclosporin); one participant had died, two did not want to take part in the second interview and two could not be contacted. One participant in each treatment group, one male and one female, had undergone colectomy since their first interview and one male participant who had undergone a colectomy before the first interview had since had two further operations, pouch surgery followed by ileostomy closure. In total, 35 interviews were conducted with 20 participants.

Analysis of data

Thematic analysis

When the three qualitative study researchers met (including the interviewer and qualitative study lead), they concurred on the themes that were emerging from the four completed 3-month interviews and developed a first draft of an analysis framework. An iterative process followed as more interviews were completed and the analysis framework continued to develop (see *Appendix 24*).

When 20 interviews had been completed, the three researchers met to discuss whether or not any new themes were emerging and considered that data saturation had been reached. A proposal was put to the TMG that sufficient interviews had been undertaken and it was agreed that no more 3-month interviews were required.

Once the 3-month interview analysis was complete, analysis of the 12-month interviews commenced. The same iterative process followed as more 12-month interviews were completed and the analysis framework extended.

Group analysis

Seven members of the study team (in addition to the three qualitative researchers) agreed to take part in group analysis of the 3-month interviews and were sent three transcripts each (one from a participant who had taken infliximab, one who had taken ciclosporin and one who had taken ciclosporin followed by a colectomy). Following clear instructions (see *Chapter 2*), each person wrote three one-page schematic overviews, which were circulated to all those taking part together with the draft analysis framework. Group members looked through the various documents ahead of a full group meeting.

During the meeting, each one-page overview was reviewed and it was clear that each member of the group had created something that covered the main emergent themes derived from the analysis framework.

Findings

Main issues arising

The main issues that emerge from the findings are presented ahead of a more detailed presentation of the qualitative findings for ease of access by the reader and to ensure the main points are not lost:

- Participants express a liking for infliximab because of its positive outcome, relatively simple method of administration and lack of side effects.
- The dramatically debilitating symptoms of UC that impact on participants' QoL and, consequently, on family and friends, is particularly noticeable in this disease type.
- Participants have to live with the ongoing unpredictability of symptoms and treatment and it is this unpredictability of the disease that makes it particularly difficult for patients and health-care professionals to manage their health.
- Unlike other chronic diseases, UC is considered an embarrassing disease making it an isolating and awkward experience for patients because of its impact on managing their life and work.
- The lack of apparency and visibility of either symptoms or outcome also impacts on patients' sharing knowledge of the disease with others.
- Surgery is feared, but following it most participants at 3 months experience relief and recognise the health benefits.
- At 12 months the difficulties for some of living with a stoma were coming to the fore.
- Participants would like to understand what causes UC and its links with stress and diet and would welcome greater information provision.
- Ready access to an IBD nurse was suggested as particularly important for members of this patient group.

Introduction

In spite of the variation in the duration of the disease among participants, similar stories were revealed about living and coping with UC; the physical, mental and emotional impact of the condition; the treatments; and people's concerns and hopes for the future.

The findings that follow are presented as a story so the 13 themes derived from the analysis framework (see *Appendix 24*), are presented as a narrative rather than under thematic headings. This enables data to be understood in accordance with participants' presentations of their own illness story, according to a progressive journey from their realisation of the problem, receipt of treatment and management of the condition, to their views of the future. Presenting the findings in this way indicates how UC becomes present and understandable in people's lives as time passes, whereas presenting the findings thematically would have provided a much more disjointed picture of an illness which is, in effect, often a very long-term chronic condition.

As one of the main aims of CONSTRUCT is the comparison of the two drugs in the treatment of steroid-resistant ASC, after a brief section about interviewees' views on their general health, we will present their views on the drugs themselves. During their admission all the participants had received one of the drugs and their views illuminate strength of opinion around both.

Following the comparison of participants' views of the drugs, is a presentation of how the disease impacts on participants' lives and the effect of symptoms on participants' health; the impact on wider family members and friends and their understanding of the disease; participants' experiences of treatment and sharing in the decision-making process with health-care professionals; views on surgery and experiences of undergoing a colectomy; and finally, hopes and expectations for the future.

As there were similarities in participant dialogue at 3 and 12 months, any similarities will not be reiterated. Rather, the report concentrates on new views and experiences in relation to the original 13 themes.

By presenting outcomes in this way, we have aimed to identify both personal experiences of health and illness, and care and treatment options from an individualistic perspective over a period of a year.

All the quotes in this section are from trial participants; they are shown in italics and include an anonymised code and the line number of the quote in the transcript.

Participants' views on their general health

For many of the participants their UC was the only significant illness they had experienced, and even for those with longer term UC, their recent inpatient stay was often their first admission with the disease. Thus, it soon became apparent that many participants had not given much thought to their health, up to that point, considering themselves fit and healthy. It is against this background that participants reflected on more general questions about their health.

A basic desire to lead a 'normal' life, to have sufficient energy and to be fit and healthy to do everyday things was a strong element of the response to general health questions. Participants considered 'normal life' and 'everyday things' as including the ability to be able to socialise, work and travel, and spoke in terms of wanting to have the freedom and be without constraints, to allow them to pursue these activities. They considered good health as having plenty of energy, not being reliant on medication, not having symptoms or pain and not having to go to the toilet every few minutes. In contrast, participants related bad health to being 'imprisoned' by their illness symptoms, by which they meant being housebound, unable to socialise, as well as being physically constrained to having pain and discomfort, lacking energy and being dependent on others.

These issues were raised again when people were asked how their UC had affected their QoL and it was here that the intensity of the suffering caused by UC became strongly apparent. This was particularly the case for those who had experienced symptoms for a only a few weeks or months before becoming so ill that they had to be admitted to hospital, it was a shock that they had reached this state so quickly: '*a bit of a bolt out of the blue*' (GHI0028.164), it had been a frightening experience and at only 3 months after their treatment they were still trying to adjust to this life-changing event.

At 12 months, while the course of the disease for the participants had differed, their basic desire to live a normal life, to be able to socialise, work and travel, had not changed.

Treatment in the trial: participants' views of infliximab and ciclosporin

When participants discussed their views of either ciclosporin or infliximab, for some recall about the earliest days of their treatment was hazy as they were so ill that they just could not remember: *'For the first few days I wasn't sure what they were giving me*' (PQR0053.216). However, most were able to recall details later on, and their views are presented below.

Ciclosporin

Intravenous infusion and tablets Participants who were randomised to ciclosporin recalled having this while in hospital as an intravenous infusion or drip. There was a sense of relief that treatment was being provided and that this just 'happened'. However, some found being hooked up to a drip continuously, and for several days, a nuisance. It was also restrictive, because either the drip stand had to be taken everywhere: '*me and my mate*' (RST0021.271) or the participant had to ask a nurse to disconnect them: '*loss of freedom, I found that quite irritating, personally found that frustrating*' (BCD0012.218).

Some found the fact that the intravenous ciclosporin bag needed changing frequently was also inconvenient as it meant being woken at night, and for one participant it meant not being able to relax, knowing that the bag needed changing. No one criticised nursing staff and there was praise for the care received. However, a participant at a site with no previous experience of ciclosporin, suggested that more training was required as the participant found himself '*telling them but they couldn't do it until someone else came so could be waiting for bag to be changed*' (RHS0021.348).

Some found the intravenous ciclosporin easier than the oral form of ciclosporin because once they started the tablets they had to have tests to monitor the levels in their blood which meant going back to hospital for the test and then returning for the results and further treatment. The oral ciclosporin was noted as having a distinctive smell, a 'different', 'strange' smell like beer. While none of the participants said it was unpleasant, one said there were others in hospital who disliked it. The tablets were also noted for their large size: *'they're like horse pills*' (SHT0001.109), although no one said this made taking them difficult. The advantage of the tablets was that there were 'no needles' involved and they could be taken at home.

Side effects of ciclosporin Participants described the following side effects from ciclosporin: mood swings; tingling in the fingers and toes; a head rush; increased facial and body hair; tiredness; a rash on the arms; hand tremors; and cramping in hands and feet. Women were particularly concerned about an increase in facial hair, but found that it fell out or decreased once they stopped the ciclosporin.

Short-term outcomes with ciclosporin Two participants did not respond to intravenous ciclosporin and required emergency surgery. The others did respond and started oral ciclosporin and made comments such as: '*It worked so we love ciclo. It saved my bowel*' (TUV0001.310); '*unbelievably, not unbelievably better but miles better than what I had been*' (RST0021.319); '*feel myself getting progressively better*' (BCD0012.403); '*got the condition under control*' (CDE0010.190).

One participant who initially responded to ciclosporin had a relapse and the tablets were restarted, but there was no improvement and she was switched to infliximab. After the switch the participant reported that she realised she had not been feeling that good on ciclosporin: '*You sort of think yeah I'm sort of finally cured, I'm managing well but now I think, uh, uh, I wasn't*' (PQR0053.344).

Longer-term outcome with ciclosporin It was difficult for participants to comment on whether or not they felt the ciclosporin was still having an effect and working for them, as most were no longer taking it, or were on other medications so found it difficult to attribute their current health to a specific medication.

Infliximab

Intravenous infusions Participants who were randomised to infliximab recalled having their first infusion as an inpatient in hospital. There was a sense that being hooked up to a drip for a few hours was not an issue, you were in hospital anyway: '*I was just lying in a hospital bed so I could doze off, read a book*' (KLM0010.153) and: '*it was fantastic, machine did it all, just pumped into me*' (FGH0011.87). A couple of participants felt that having treatment given as an intravenous infusion meant that it was more 'direct' and reached 'your system' more quickly.

After discharge participants returned every 6–8 weeks for a further infusion and this was viewed as a good way of having treatment as they did not have to take tablets: '*there is not any managing of it because it's a 2-hour infusion and then you're not due back in for another 6–8 weeks so in that way it's fantastic, I'm not having to get up every morning and take about 20 different tablets*' (OPQ0005.395).

Side effects of infliximab The side effects reported from infliximab tend to be fairly immediate with separate participants commenting on a weird sensation in the legs; feeling a bit strange – vague, sort of dopey; becoming 'roasting hot' during the first infusion; feeling a little hot and cold after the second infusion; getting hot and sweaty in bed for a week, some 2–3 weeks following infusion.

Short-term outcome with infliximab Three participants did not respond to infliximab and required surgery. The participant mentioned above who switched from ciclosporin to infliximab, noticed the difference with her condition improving within a day. Others who responded used comments such as: '*straightaway noticed a difference. All benefits and no negatives. Saved me from surgery*' (JKL0033.347); '*It was my saviour . . . real amazing cure . . . miracle drug for me*' (MNO0034.331); '*It does work, it definitely does work*' (OPQ0005.213); '*Really worked on me so they might not have to operate*' (IJK0014.170); '*Colon saver*' (FGH0011.167).

Longer-term outcome with infliximab As with ciclosporin, it was difficult for participants to comment on whether or not they felt infliximab was still having an effect and working for them, as most were taking other medications so it was difficult to attribute their current health to a specific medication: '*whether it is still the infliximab having an effect, it's possible kind of thing . . .* ' (MNO0034.368). A couple of participants felt that the effects were still lasting, but two participants did comment that as they neared the time of their next infusion, they felt that the effects were beginning to wear off.

Reflections on ciclosporin and infliximab at 12 months

By the time of the second interview none of the participants was receiving ciclosporin or infliximab. One infliximab participant had been concerned about stopping after just three doses but was relieved that he had experienced no problems since. Four of those randomised to infliximab and two to ciclosporin had experienced no flare-up of their UC since they completed their treatment with the trial drugs. Flare-ups had occurred for two participants, one from each group, but at the time of the interview both were improving.

The majority of participants spoke more about the treatments they had received since the trial treatment (see *Treatment for ulcerative colitis*), but thinking back, one ciclosporin participant recalled that she developed '*terrible facial, arm and leg hair*' which took 3 months to settle, but she reiterated '*we love ciclosporin, apart from the smell*' (TUV0001.348). Another stated that ciclosporin 'kept him going' but that he could not stay on it because '*it was quite toxic*' (ABC0010.82). One interviewee, randomised to infliximab but who did not respond and had surgery during the same admission, had been treated with ciclosporin several years ago and considered it one of the most successful of all treatments he had received. In contrast, one participant was relieved not to be on ciclosporin and steroids because of side effects and '*autoimmune issues*' (BCD0012.597)

Three participants commented on infliximab as '*convenient*' (LMN0009.87), '*easy in comparison with just having ordinary pills*' (QRS0028.336), and that they '*would have it again*' (FGH0011.283) and that it meant '*not taking medication daily*' (PQR0053.509). A participant who initially had infliximab followed quickly by surgery, thought that having treatment with infliximab '*every so often would have been easy-peasy*' (QRS0028.342) in comparison with the living with a '*bag*'.

One participant had responded well to three doses of infliximab and wanted to continue it as she wanted to start a family. Because of funding restrictions, a case was put to the local primary care trust to allow her to continue but this was refused which she described as '*quite a blow*' (MNO0034.352). At the time of the second interview she was 3 months pregnant and having a flare-up: '*colitis and the pregnancy don't seem to get along*' (MNO0034.170). She felt that infliximab would have kept her well and her '*quality of life would be much better now if I was able to continue it*' (MNO0034.780).

To reiterate, the presentation of participant views and experiences has begun with their views about the two drugs, ciclosporin and infliximab, at 3 and 12 months, in line with the study's main aim of comparing clinical effectiveness and the objectives of comparing QoL and investigating participant views of the two treatments. From here on we discuss outcomes of the qualitative interviews in terms of the participants' journey through their experiences of symptoms, diagnosis, treatment and the impact of UC on their lives.

Onset and diagnosis

It was clear from the interviews that the onset of UC varies from person to person. There were some people who were diagnosed many years ago, some in the last year and some who were diagnosed when they were admitted with severe symptoms that had only been present for a few weeks.

A picture has emerged of a convoluted and sometimes frustrating treatment story from early onset to misdiagnosis. If often begins with mild symptoms such as going to the toilet more frequently and having some bleeding, to an eventual GP visit with a misdiagnosis of haemorrhoids:

> *I went to the doctor a couple of times but he told me I'd got piles. So I wasted about a month going to see the doctor and he just gave me stuff for piles.*
>
> *LMN0009.111*

Some participants visited their GP several times but it was only when their symptoms did not settle and indeed became worse, particularly if participants reported weight loss, that they were referred for an endoscopy:

> *I kept going back and saying something is not right. It wasn't until I went to the doctors and said, I know I'm overweight . . . 100K [kg] and a week, 8, 9, 10 days after I had lost 10K [kg] in that short time and they thought there is something seriously wrong and then they decided to 'let's get you in and get a scope done'.*
>
> *NOP0004.349*

At endoscopy some participants were given a clear diagnosis of UC and some were told that they had some 'inflammation of the bowel' and the word 'colitis' may have been used.

There were some examples of people who knew that they had UC but soldiered on nevertheless with their symptoms: '*you just put up with it because you just think well I'm just getting old or just, you know, that's how life is, I can't afford time off*' (RST0021.90), but this particular participant explained that '*it shook me to the core*' (RST0021.86) when his consultant would not let him go home and he realised just how ill he was.

An interesting observation from a couple of participants was their attitude to being in hospital as they felt like 'frauds' among some of the seriously ill people in beds nearby: '*I'm looking around going I feel like a fraud really . . . there are a lot of sick people in there that you know, weren't probably coming out of the place*' (RST0021.289).

Unpredictability of ulcerative colitis

The unpredictability of the course of the disease was a problem for many people who had no idea when their next flare-up might occur. Some commented that between flare-ups, having UC does not impact on one's QoL, but that when a flare-up occurs, experiences are of pain and discomfort. These are exacerbated by an increase in bowel movements, often with urgency and bloody diarrhoea, which necessitates frequent, very rushed visits to the toilet. Participants described this loss of bodily function as being unable to rely on their body, leading to a sense of giving up control over their bodies. Some people, with longer-term disease, used the term 'rumbling along' to describe the way in which their UC was generally controlled by medication, but with occasional flare-ups that required an adjustment to their medication. These participants were used to planning their lives around toilets because of the urgency and frequency their UC caused and would often have a change of clothing with them; some spoke about the worry of what would happen if they were on a train and had an 'accident' when they could not reach a toilet in time:

> *Get used to the fact that you are going to have to change your clothes once maybe twice a day . . . even though you are prepared for it because you know it's going to happen but actually you are fighting it every minute of the day.*
>
> *QRS0028.109*

> *I was quite impressed by my planning – it feels like a military procedure at times.*
>
> *RST0021.223*

However, participants jokingly commented on their knowledge of all the toilet stops on a regular car journey, for example to and from work, or the distances between motorway service stations and explained that their first action in a new venue or location was to locate the toilets as soon as they arrived; thus, planning outings around toilets just became a part of their lives.

Participants described how, if a flare-up was not controlled adequately with medication, within a matter of weeks their symptoms began to have a massive impact on their life, and how normal life ceased and many everyday activities were curtailed. On a practical side, there was a need to be near a toilet, as participants had increased bowel movements and for some the increasing symptoms eventually meant not being able to leave the home:

> *When I'm ill, you're a bit stuck, especially with UC, when you're having a flare-up you're on the edge, you can be a bit worried about going out if you've got to think about going to the loo and things like that.*
>
> *KLM0010.22*

> *Colitis can make you a prisoner that you don't venture far away from a toilet . . . have to memorise where all the toilets are and things like that. It makes you a prisoner to the disease.*
>
> *DEF0016.60&67*

At 12 months the disease had caused no further problems for four infliximab and two ciclosporin participants; one had been so well that at times she felt as though she did not have UC. One ciclosporin and two infliximab participants had experienced flare-ups; one of the latter associated the flare-up with pregnancy. All were on medication and continued to be followed up and were clear that if symptoms developed they would quickly make contact with their IBD nurse or GP for advice because they '*would want to catch it earlier*' (BCD0012.214). They understood that a prompt change in medication could prevent them becoming as ill as they had been before.

This section has highlighted some of the practicalities of living with UC, but, as described, when the symptoms are not adequately controlled they can have a massive impact on the life of someone with UC. Impact of symptoms on life is described in more detail below.

Impact of symptoms on life

The impact of symptoms like diarrhoea and disturbed nights resulted in people's health deteriorating, often within only a few weeks, reducing them from leading an active life – socialising, going to work and exercising – to being housebound. They often suffered from a lack of energy, weight loss and exhaustion, the latter being an issue that many emphasised and referred to several times during their interview:

> *Basically tiredness was one of the things that was really difficult.*
>
> *NOP0004.91*

Participants spoke frequently about how an important part of their life was being able to go out and socialise with friends and family. However, for many participants life had to be put on hold and they spoke about this as being hard to cope with and a significant change:

> *Flare-up – it was dictating to me what I was able to do, not me dictating it.*
>
> *RST0021.25*

The condition made attending sporting events, such as football and cricket, particularly difficult because of the travel involved and the busy toilets during break times. One participant explained that before his diagnosis he had followed his football team across the country but had been unable to do so as he could not risk needing the toilet urgently while travelling on coaches for hours:

> *I used to do a lot of football and travel to football all over the country, that's what I love doing, but the last year I haven't been able to do that . . . have to sit on a bus . . . don't feel comfortable doing that . . . used to travel every weekend but haven't done it for the last, oh since I got diagnosed. I don't feel comfortable doing it.*
>
> *NOP0004.27*

A cricket goer explained that he could not eat with everyone else but had to wait until after the lunch break:

> *Go and watch the cricket . . . take some lunch but I was conscious that you know getting close to lunch, . . . I'm thinking to myself well I can't have anything to eat at lunch because the moment I have something to eat within minutes I have got to go to the loo and I know there are 20,000 people coming out of the ground going into the toilet and I can't queue for the toilet.*
>
> *RST0021.204*

Those in employment explained that they had tried to continue working for as long as possible, coping with frequent visits to the toilet, until they reached a point at which it was simply physically impossible for them to carry on. This could depend on the type of employment people were in; for instance, people working as teachers or nurses could not simply drop what they were doing to dash to the toilet: '*you can't just walk off at any given moment because you are responsible for patients and you may well be the only*

nurse in a certain area so it was very difficult' (MNO0034.85). One participant commented on how difficult it was at work when speaking to somebody and suddenly knowing that there was a need to urgently go to the toilet, meaning that they were no longer able to pay attention. An issue for some younger UC participants was the potential impact on careers which could be affected by ongoing flare-ups requiring time off work. The condition can cause huge changes in lifestyle, impacting on not only the participant but close others as well:

> *I couldn't be around my kid when I was feeling pretty low.*
>
> *QRS0028.101*

There appears to be a trajectory for participants of any age in that they go from being someone with an active life, to the disease having an increasingly detrimental physical impact, when they are tied to home and too unwell to do anything more than sit or lie down, which often leads to mental and emotional stress as life narrows:

> *I was spending all day in a chair or in bed barely able to eat and my life just consisted of going to the toilet and sitting still trying to occupy my mind and not go crazy.*
>
> *GHI0028.119*

It is clear that for some participants, UC had taken them entirely by surprise, changing from someone with good health to someone with a chronic condition that is difficult to control. For many, life had taken a different and unexpected path:

> *Holidays were a nightmare because like just going to an airport or flying became a major chore.*
>
> *QRS0028.100*

For those wishing to travel there was the added difficulty of obtaining travel insurance following an admission with their UC.

During the second-round interviews, with their symptoms under control, the QoL for participants had improved; the football fan was pleased to report that he had returned to watching games and following surgery and the cricket goer was able to plan his days more easily. Several people commented on the fact that they had been on holiday and could plan events with more confidence.

Participants reflected on the last 12 months of their lives according to changes at work following extreme illness and being diagnosed with a chronic disease. One participant had 'grabbed' the opportunity to take a job which involved travelling all over the country, saying: '*I can't not do it, you just never know what could happen but I'm not going to say no, just in case*' (NOP0004.36). The period off work made a participant realise that she could get by and as a result she moved house and starting working for herself. Another explained that the experience had made her and her husband rethink and plan their lives a bit more; they got paperwork organised, went on holiday and had long weekends away (TUV0001.414). A surgery participant who had moved from manual to office work reversed the situation as he could wear more comfortable clothes which made managing his stoma easier.

It is clear that the symptoms of UC and being diagnosed with a chronic illness can have a massive impact on participants' lives but it is the nature of the symptoms of UC that can make it difficult for sufferers to talk about their disease with others, as shown in the next section.

Embarrassment about sharing knowledge with others

In contrast to some other chronic conditions, many UC sufferers consider it an embarrassing illness because of its association with 'bottoms', 'bleeding from your bottom', diarrhoea and going to the toilet. Because of the embarrassing connotations, participants explained how they select who they share knowledge with, often discussing it only with close family members and friends:

> *. . . three men wouldn't stand around a bar and one say to the other two 'I've been for a camera today', you know, it's not the sort of thing . . . I sort of relate it a bit to probably to ladies, to breast cancer a few years ago and I think men with the prostate cancer, 'cos that's a bit of a taboo subject but it is starting to come out there now.*
>
> *RST0021.127*

It was often in the context of work that participants started to describe the embarrassment that they felt about their condition, as it is an illness that is difficult to talk about with colleagues: '*it's hardly a glamorous disease that you wish to chit chat about*' (MNO0034.88). However, participants found that when they did explain their disease to their employers and colleagues, those people were understanding and supportive; several participants emphasised just how supportive they found their place of work to be:

> *Work have been absolutely brilliant, I couldn't ask for any more to be perfectly honest with you.*
>
> *NOP0004.150*

Some participants felt that their UC made going out as part of a larger group more difficult. On occasion the group needed to be made aware that a very urgent toilet stop was required but this was difficult to communicate to a group and caused embarrassment for the person needing the toilet.

> *We go on motorcycle trips and they'll just think, oh we'll go from A to B and that will take us two and a half hours without having to go to the loo. Me and my partner we can just stop but it's difficult if you're in a group of, might be 10 people on bikes, it's difficult to . . . it's that kind of . . . that's where you think we won't go on this trip or something, we'll just go by ourselves.*
>
> *KLM0010.97*

It is a disease that for the most part does not manifest itself openly and, thus, others are unaware of UC patients' suffering; several participants raised the issue about the lack of a broader awareness of UC as a chronic condition. They felt that it had a low media profile in comparison with some other chronic conditions (such as asthma), and participants wished that more famous people with the condition might come forward to champion their disease and raise awareness. Those coping with the outcomes of bowel surgery for UC raised the same issues. In general, the low profile was attributed to the embarrassing nature of the disease, which was seen to set it apart from other chronic conditions.

At 12 months similar issues arose, but a participant reflected that '*you need to be able to speak to people and share what's happened to you*' (TUV0001.584), whereas two surgery participants were keen to share their experiences with other sufferers to help them to understand the impact of surgery and coping with a stoma.

Impact of ulcerative colitis on family and friends

The life-changing nature of UC clearly impacts on families and friends, particularly during periods of a flare-up. Those with young children described how their UC left them unable to look after and play with their children, increasing the need for others to help. Others acknowledged that it affected aspects of their partner's social life and, for some, the limitations on travel impacted on family travel plans:

> *I'm retired and one of the things I would like to do is to go around the world with my wife and we can afford to do it now but I simply, at the moment haven't really got the energy for it.*
>
> *ABC0010.86*

However, the predominant observation made by participants was about the support provided by their families and friends. The different types of support included hospital visits, the understanding shown by relatives to participants' needs and their support in practical aspects of a participant's life, such as helping to plan a journey. This support also helped participants emotionally as the condition became more difficult to cope with when a flare-up occurred:

> *My mum . . . ended up working a bit less and my dad . . . having to go into hospital . . . at the end of the day he was working. And my older brother . . . he was having to visit me, so he had to forego a few things he would usually do. . . so mainly in hospital that it had the biggest impact on my family.*
>
> *GHI0028.69*

At 12 months, the impact of UC on family and friends was spoken about in particular by those who had had surgery, either before the first interview or since (see *Surgery*). However, one participant felt that friends and family got bored with the disease: '*so talking to an absolute, vague stranger, there's something quite soothing about it . . . just go through it from start to finish*' (MNO0034.729).

One participant explained that he had visited his workplace to discuss returning to work and was aware that word had got out that he had a stoma. He said that some individuals did not look at his face but were '*constantly staring to see if they could see this thing*' (DEF0016.860). He felt that this was rude and said that his wife was so annoyed that she had to walk away.

Acquiring knowledge about ulcerative colitis

Participants appeared to be well informed about their condition. For those diagnosed many years ago their experiences and interactions with doctors and nurses had informed them about the condition and its treatment, while many UC sufferers have used the internet to find out more information. One participant, diagnosed 30 years ago, regretted not using the internet to look for developments in treatment over the years, as he felt that he may have missed out on a treatment that might have helped, instead of putting up with his symptoms all those years.

Those newly diagnosed with UC can be provided with information about 'Crohn's and Colitis UK' a national organisation dedicated to 'Inform, Support and Research' or be put in touch with an IBD nurse specialist at their local hospital. Crohn's and Colitis UK (previously National Association for Crohn's and Colitis) provides a lot of information about UC, living with and managing the condition and about its treatment. It provides information on a website, or paper information can be provided, and has local support groups in many parts of the country.

Some spoke about their IBD nurse, explaining that they had direct access and could contact the nurse at any time for information and help when their symptoms increased:

> *I do come up with questions from time to time but I must admit the IBD nurse is brilliant, you just pick the phone up to him and he is more than happy to speak to you about anything so definitely the support I have received is excellent.*
>
> *NOP0004.423*

However, IBD nurses are not necessarily available in all hospitals and a couple of participants expressed strong opinions about the need for their presence and the very valuable role they play in helping to manage UC.

In spite of the information that was available, participants had a number of unanswered questions about the cause of their disease and mentioned the need for more research in this area in order to ensure that other family members could be supported if they did get UC. Participants were also unsure about what triggered a flare-up and wanted more information on this particular aspect of their disease, including information about the links between UC, stress and diet:

> *Colitis is very difficult, it's very difficult to manage and certain foods can set it off, etc. and stress is another thing so trying to identify the foods that set it off and stay away from stress is key.*
>
> *OPQ0005.370*

With regard to diet it was acknowledged that there may be some misinformation on the internet, and several people commented on contradictory advice about whether or not there is a link between diet and UC.

Ultimately, participants wanted to see a cure for the condition; although they recognised that it might be too late for them, they wished to prevent others from having to suffer with the condition:

> *I would love somebody to come up with a cure for it even though the stable door has . . . been bolted for me.*
>
> *DEF0016.767*

Participants appeared to be less questioning about UC at 12 months, as only a few comments arose about a cure for UC and the relationship between stress, diet and disease. The fact that they knew they had easy access to care appeared to be more important for the stage they were in and the course of the disease.

Treatment for ulcerative colitis

The cacophony of drugs

If diagnosed with UC, participants were started on medication; they spoke about this 'controlling' their symptoms, some for many years without any problems, and how, when experiencing a flare-up, an adjustment to existing medication or a change in therapeutic pathway brought their symptoms back under control. However, some participants had experienced greater difficulties in keeping their UC under control and spoke about various medications – azathioprine, mesalazine (Pentasa®, Ferring Pharmaceuticals Ltd; Asacol®, Warner Chilcott Ltd), 6-mercaptopurine, methotrexate, steroids and foam enemas – effectively a cacophony of drugs, that they had tried, but against a background of the unpredictability of not knowing what might work and for how long and when a different treatment might be required:

> *Other things like Salazopyrin [Pfizer Ltd], you're having 2, 4 times a day, imagine that during the day if you're based at the office or something, it's quite hard work.*
>
> *QRS0028.161*

All of the participants had been admitted to hospital approximately 3 months earlier because their UC symptoms were uncontrolled and they needed treatment with intravenous steroids. Those who knew that they had UC before admission appeared to have had a good understanding of their situation and knew that if they failed to respond to intravenous steroids their treatment options were narrowing to a more powerful drug or surgery; they recognised this as a last chance before surgery:

> *I'm in the last chance saloon I suspect.*
>
> *ABC0010.281*

However, although many were very familiar with the drugs, some were less familiar with infliximab and ciclosporin; they knew of them but perhaps not in as much detail. One participant said that had she been at home when she knew one of these drugs was going to be used, she would have looked it up on the internet, as she would have liked a bit more information, particularly about the long-term effects.

Those who were newly diagnosed had to assimilate the information about their condition and treatment options quickly, at a time when they were extremely ill. It was clear from all participants' comments that they were so ill at the time that decisions about their treatment almost passed them by:

> *I was having so many injections and blood tests at the time in hospital that I didn't even notice it.*
>
> *QRS0028.134*

> *You could have put a blank cheque in front of me and I would have signed it.*
>
> *STU008.216*

Once discharged, participants had to continue taking medication and more often than not they were on more than one drug. For those who had previously been well, there was a period of adjustment, not only coming to terms with their diagnosis but also getting used to taking medication: '*just remembering to always have them with me and going on holiday . . . suddenly settle into a routine . . . I mean now it's so much part of my life but that just seems normal but to begin with seemed quite alien*' (BCD0012.375).

On the whole, people were fairly philosophical about having to take medication and were prepared to take anything that would work: '*whatever is going to help me to get better or at least help me fight towards getting better*' (OPQ0005.414).

There were mixed experiences for those who had remained on medical therapy over the 12-month period, and these participants spoke about how it had been trial and error to find treatments they could tolerate that would keep their disease under control. Some participants explained that taking medication had become part of their normal life, whereas for one it was a '*challenge fitting taking medication into routine*' (MNO0034.452).

The unpredictability of treatment was still clear, with participants understanding that some treatments, such as 6-mercaptopurine, could be taken for a limited time only. The uncertainty as to what would happen after that was highlighted by the view that medical treatments were not always successful.

Shared treatment decisions

As mentioned earlier, participants were well informed about their UC; they knew the signs and symptoms that indicated a flare-up and the various treatments available and, armed with this knowledge, they took part in shared decision-making with clinicians about their treatment. This was particularly evident when participants spoke about surgery as a treatment option:

> *Been hospitalised more in last 5 years than previous 30 and spoke long and hard to the surgeon and medical doctors and we all agreed that my QoL would be improved if the bowel was gone basically.*
>
> *DEF0016.362*

> *Discussed surgery quite strongly really but again the consultant is quite happy to try and get it treated first, you know, try and get it under control with some medication.*
>
> *RST0021.677*

However, participants clearly understood that if they failed to respond to the various treatments, there may be a time when their 'body' made the treatment decision for them:

> *If you are so bad and it gets to the point where it could put your life at risk then obviously you have to have it done.*
>
> *JKL0033.521*

Several participants commented on their reasons for taking part in the trial. They felt that it was a positive step as they received more attention and had ready access to the research nurse if they had any queries. One participant was relieved to enter the trial because it removed the responsibility of making a decision between ciclosporin and infliximab: '*there could never be any comeback on what decision I made*'. (MNO0034). However, several participants said that they just wanted to help others and to prevent others suffering in the same way.

The participants all continued to attend hospital for follow-up at 12 months and commented on positive relationships with their doctors and IBD nurses. Some also highlighted how helpful their GPs had been. However, one participant had become frustrated by seeing different doctors at each appointment and having to explain his history and treatment on each occasion.

Those on medical treatment understood that they had to take responsibility and seek out help when they experienced symptoms that could indicate a flare-up of their UC and, over the course of 12 months, became familiar with the medical therapies and side effects. Although it was apparent that they discussed their treatment with their doctors and nurses, there was also a sense that shared treatment decisions were limited, as decisions had to be based on whether a treatment worked or caused side effects.

Surgery

The majority of participants spoke about surgery as being absolutely the last treatment they wanted to have. It was certainly a shock to the newly diagnosed that they could be facing surgery. Terms such as 'saving' or 'losing' colons were used, and participants did not want to have to wear a bag:

> *It was worthwhile because I walked out of there without a bag [laughs] . . . that's what meant the most to me. It's just the fear of the unknown, the effect it can have on your life I suppose, life changes.*
>
> *TUV0001.242*

> *So realistically if it wasn't, didn't try this, it was going to be down the route of surgery which I didn't want to go down that route at this moment . . . it's quite a high probability at some point . . . but I'm 28 and I'd rather try and leave it for as long as I possibly could.*
>
> *NOP0004.266*

However, most were philosophical about the possibility of future surgery and realised that they would have very little choice if it became necessary:

> *If it presents me, if Dr X said to me, I won't have choice, my body will make it for me.*
>
> *TUV0001.262*

> *If it's something I have to have done, I can't say no I don't want it, I have to anyway and to be fair they've explained the operation and it's not so bad, come on, they're trying to fix me you know, there will be no need for any pills, no need for running to the hospital and all the NHS spending money on me if they can just cut it out. I know I would have to have the bag for a few months but then they stitch me back so it's not permanent, it's temporary again. That would annoy me if I were to end up with a bag really, just the idea . . . if I know it is for 3 months, fine.*
>
> *PQR0053.533*

> *. . . rather have it now when I've still got some energy left than in my 70s when I'm too old to do anything.*
>
> *ABC0010.354*

Those who had undergone surgery actually appeared to reach a point during their hospital admission at which they became resigned to the fact that it was going to happen; they knew that the infliximab or ciclosporin was not working and that an operation was inevitable, and there was an acceptance of what was to come:

> *I felt really fed up so I was actually quite happy, to be honest to have the operation by the time it came round. . . it wasn't really a difficult decision to make in the end.*
>
> *GHI0028.207*

> *I've had it for 30 years, mentally I was prepared for the surgery so to a degree maybe we could have carried on with the drug but I had had enough by then. So it was frustrating really, the drug had improved it but it hadn't improved enough, they were prepared to maybe stick it out more but I mentally wasn't prepared for much more.*
>
> *QRS0028.214*

Those who had undergone surgery acknowledged that had the drug treatment worked they would have been happy to continue with that, as they would not have known any different, but after the surgery they were actually relieved that it had been done, as it meant an end to their UC:

> *Once I'd had the operation there was a sort of a bit of a peace in my body, it was like there was a fight going on forever, even when I think it's under control, there's still this sort of underlying . . . that's what I think of it as a fight, because it's not settled . . . my body shouting at me and that's not there anymore.*
>
> *KLM0010.262*

> *I **wish** [patient emphasis] I'd had this operation the day I was diagnosed to tell you the truth. It was the moment I woke up after the operation I thought, cor this is fantastic, . . . the fog had cleared and when you are living with it you just deal with it, you just get on with life, you don't realise how much it did effect me over those 10 years. So yeah, quite honestly, if I could have had the operation then I would have had it done and now I would have been 10 years down the line . . . it's like hindsight isn't it.*
>
> *STU008.188*

However, the relief was not felt by all. One man who had fought against surgery when diagnosed 55 years before said '*I'm so glad I did because I now know the pitfalls of surgery now I've had it and I wouldn't have liked to have thought that I had that as a young man*' (DEF0016.99). He had felt suicidal after his surgery, saying that he '*felt like jumping off a roof*' but '*my wife and family have been instrumental in making me shake myself and realise that basically it's either that or end up in a graveyard and when you look at it in that respect it's not so bad*' (DEF0016.580).

Although most felt that surgery had been a good thing, it did create issues for some in relation to the practicalities of managing the stoma and the bag, restrictions with regard to clothing and concerns about how others would react to seeing the bag, which for some led to a change in attitude to being able to go swimming:

> *Go down to the beach . . . I've got to keep my T-shirt on which is something I wouldn't look forward to because I like to jump in the sea . . . I don't want people staring all the time.*
>
> *STU008.155*

> *it's cumbersome and it's a pain but what price is being healthy really, . . . I'm happy to have it but in a way I'm not happy to have it, because of the inconvenience, but no I'm just happy I'm well.*
>
> *STU008.256*

Participants conveyed that being older made it a little easier to cope mentally with the outcomes of surgery and suggested that they would have been less tolerant when they were younger:

> *Old enough now that it's a bit of a laugh and joke. If I was younger I'm sure I wouldn't have taken to it. It is quite intrusive but I think when you're a bit older it is a lot easier to deal with, mentally really.*
>
> *QRS0028.307*

In the same way that participants were selective about whom they told about the condition, they were selective about who knew about their surgery, in part because they felt that people would not understand and in part '*because some people can be cruel*' (DEF0016.613). Participants tended to tell family and close friends, and would inform colleagues where necessary:

> *. . . with friends and family I haven't found it difficult talking about the illness and having the stoma and what needs to happen with it. Not had too much of an impact on my relationship with my girlfriend . . . she's been very understanding about it.*
>
> *GHI0028.268 & 281*

In spite of the support and understanding, some participants were clearly very conscious of the physical changes to their body and referred to how this impacted on personal relationships: '*my love life is not what it was*' (DEF0016.496). They empathised with their partners having to see the bag but would then comment on how understanding and supportive their partners were.

As with UC, there was a feeling that there was a low media profile about living with a stoma because of the stigma associated with it: '*there is nobody famous with a colostomy that will admit to having one*' (DEF0016.779).

Several participants spoke about the possibility of having reversal surgery and, again, age was shown to influence attitudes, with younger participants keen to get on with the process of getting life back to normal and older participants appearing more likely to accept life with the stoma:

> *If I was, don't know, 20 years younger, I'd probably go for reversal and take my chance because I wouldn't want to live with the bag but at 50 I'm hardly likely to head down the beach and stuff like that.*
>
> *QRS0028.289*

The surgery participants were aware that the outcome of reversal surgery was more successful if it was completed sooner rather than later and were well informed of the risks involved in further surgery. They were also aware that they would still need to use the toilet more frequently than most people but, having suffered from UC, that was not a concern:

> *They say I'm always going to be a little bit more regular than a normal human being [laughs], if you see what I mean, but it's something you live with anyway with colitis, don't you, because you're always going to the loo a lot more times than people without it so that's something I can live with because I've already got used to that bit.*
>
> *STU008.146*

One participant felt that the consultant treating him was quite keen that he should have surgery, but as a self-employed person he expressed concern about needing extra time off work for the initial surgery and reversal operations, saying that '*financially I can't afford to have this time off work at the moment*' (RST0021.652).

Reflections on surgery after 12 months

The views and experiences of the participants who had had a colectomy were markedly different. Just one participant, a young man diagnosed with UC followed by infliximab and then surgery within the same admission, had gone on to have two further operations to achieve reversal. He said it had been a 'long haul' and that surgery was '*not a magic wand that could make me as healthy and normal as I was before*' (GHI0028.189), but that his QoL improved by not having a stoma. He had no regrets and was happy not to have to medically manage UC.

Two men had found that intimate relationships had suffered, one from the outset because he '*does not like to look at the bag*', a '*constant reminder*' (QRS0028.452), and the other when he had experienced a significant deterioration in his sex life:

> *My personal and sex life has absolutely plummeted because . . . well, it's not a very nice thing to have flapping about and you wear shirts and things like that but it's not the same, my wife is very frustrated about it and we try to deal with it but . . .*
>
> *STU0008.250*

In contrast, a young woman reported that her relationship with her partner had not been affected by the stoma and was so pleased with the outcome of laparoscopic colectomy and the control having a stoma gave her that she did not think she would have the procedure reversed. An older man had a similar view; he was not convinced by what he had heard of the success of reversal surgery but did state that had he been younger, with an active sex life, '*reconnection*' would have been important.

The 12-month interviews highlighted that although some considered surgery as a cure, two participants spoke about still having colitis, as the rectal stump was affected by UC which meant they continued on medical treatment as well as managing their stoma. Although one was coping with this, the other said that he '*still felt like a prisoner*' as he was waiting for surgery to remove the remaining bowel. In addition, the practicalities of emptying the bags were mentioned, which required an ongoing awareness of the location of public toilets.

A couple of participants commented on the conflict of provision of stoma bags and equipment by stoma nurses funded by manufacturers. This resulted in being offered a limited choice when there may be more suitable styles; these other styles were available to patients, but the onus was on the patient to know what to ask for.

The two participants who had surgery since the first interview felt that there could be better information provision before and after surgery, particularly with regard to the stoma, with one commenting that they would have liked to have spoken to someone who actually had a stoma.

Concerns, hopes and aspirations for the future

The most significant concern for participants who had not had surgery was the unpredictable nature of the course of UC and, as a consequence, the uncertainty surrounding their future treatment. For those concerned with what the future would bring, surgery was often at the back of their mind:

> *If you can ward off the surgery for a decade it's worth, I think it's worth doing. It may come to it, I may have to have it one day and it is always at the back of my mind but I would rather have it later than sooner.*
>
> *JKL0033.533*

Some of those who were only recently diagnosed were finding it hard to adjust to the fact that they had a chronic disease that would require ongoing care. They reflected on others they knew learning to cope with long-term chronic conditions such as asthma, but although they had responded to treatment and were reasonably physically fit, they were mentally vulnerable:

> *My symptoms have been non-existent since the infliximab pretty much but all of my emotions and everything else is still kind of, almost seems way out of proportion to the bowel symptoms.*
>
> *MNO0034.286*

> *A lot of the stuff that I like to do that I couldn't do and even now I probably could do it but I'm wary about doing anything. So it's still in the back of my mind all the time.*
>
> *NOP0004.119*

Participants were interviewed only a few months after they had been hospitalised and many were going through a transition period with their medication. They spoke about the drugs they were on and what was planned, but did so in the context of uncertainty about what would work and for how long: '*where we need to go, where do we go from here, stay on the ciclosporin or what really*' (RST0021.474). Some were aware about the funding issues with infliximab and were concerned about whether or not they would be allowed to continue on it in spite of the fact that it was working for them.

Many participants spoke about what had become their 'normal for me' health and were happy to accept an increased need to use the toilet only three or four times per day in comparison with 20–30 times per day, understanding that this could be achieved only by using medication. However, for those whose symptoms had completely resolved, taking medication was a constant reminder: '*I could almost sort of forget that I have been ill . . . it's a shame that I always have to take them because that's a constant reminder actually that you know, I've been ill and it might come back*' (BCD0012.520&600).

Some younger participants expressed concerns about the impact of the various drugs on their future plans of having a family and were worried about the effects on their fertility: '*only got married last year and we haven't had a family yet and with most of these drugs there are issues with getting pregnant*' (MNO0034.513).

Some of those who had surgery said that they hoped to have the reversal procedures and looked forward to a time when it was all over and they could get their life back on track. Others, who tended to be the older participants, were less interested in having a reversal; they accepted the stage they had reached, were relieved that their UC had been dealt with and were prepared to live with a stoma and with the practicalities and restrictions it presented.

The future 12 months later

Life had changed for the participants by the time of the second interview. Seven of the eight who had not required surgery appeared to have come to terms with having a chronic illness that required ongoing treatment and living with the uncertainties of that treatment, but seemed more confident about being able to control the disease. They appeared to be reassured by the ready access to advice from IBD nurses; in particular, those who had a flare-up commented on the speed of the response when it was needed.

The eighth stated that that she had '*not adjusted to it from the point of view of . . . just feeling angry or sorry for yourself . . . I feel I should feel happier*' (MNO0034.240). However, this participant was coping with a flare-up that she associated with being pregnant, the pregnancy being classed as high risk because of her disease and the fact that she had not been allowed to stay on infliximab. She said that it '*. . . is not how I ever pictured being pregnant*' (MNO0034.220).

At the time of the second interviews it was some of the surgery participants who were unsure of what the future held as they were thinking about whether or not to have reversal surgery and the ongoing impact of the stoma on their personal relationships, and two expressed concerns about managing the stoma as they got older and the thought of someone else having to deal with it for them.

Conclusion

The findings from these interviews confirm the liking that patients have for infliximab, because of the treatment regime described, fewer side effects and ease of handling the drug. Ciclosporin was less favourably described, with more side effects, greater problems of drug handing and a more onerous treatment regime.

The physical symptoms that UC sufferers described, particularly when experiencing a flare-up, are dramatic and debilitating clearly indicated by these data in terms of the effects of symptoms on patients' lives, leading to social isolation as their health deteriorates. Efforts should be made to ensure prompt diagnosis, to encourage known UC patients to report changes in their symptoms as soon as possible and to offer appropriate treatment that patients favour, which should be administered as quickly as possible.

A significant issue that emerged was the need for better support and greater information to enable patients to manage the impact of unpredictable symptoms and ongoing treatment regimes.

More research needs to be conducted to explore the views of UC patients post surgery, and to provide more information that could support the decision-making process of those facing surgery. As the views of participants following surgery were generally positive, there should be further research into the surgical treatment of UC as a real alternative to medical treatment.

An awareness raising campaign about UC (and Crohn's disease) including details about surgery would encourage people to seek help earlier and help to destigmatise UC, thereby reducing the embarrassment felt by sufferers and those living with the outcomes of surgery.

Professional interviews

Main issues arising

The main issues that emerge from the findings above are:

- Professional interviews indicate a clear preference for infliximab among nurses.
- Most doctors are more equivocal and prepared to wait for evidence of effectiveness and safety before making up their minds.
- Some doctors are strongly in favour of infliximab, wishing to see it as the drug of choice in view of its ability to deal with the many complex symptoms this disease group displays; its ease of administration; fewer adverse side effects; greater familiarity; convenience; greater perceived effectiveness; and ease of handling.
- Ciclosporin is more cumbersome to administer and requires additional monitoring, which puts pressure on an already overstretched workforce.
- Professionals view nurse colleagues as more familiar with the administration of infliximab and note the fewer demands it puts on nurses' time.
- Ciclosporin is more restrictive on patients' movements, leaving them frustrated and in need of more intensive support from nurses who must be present to manage complications.
- Professionals question current NICE guidelines and government regulations around drug use and the restrictions that this places on their professional autonomy.
- Professionals want to gain a clearer understanding of how the drugs affect patients' lives.
- Professionals complement the trial for shining a light on this area of study which they see as seriously under-researched.

Introduction

Data saturation was achieved following the completion of 23 interviews. Fifteen consultants and eight nurses formed the interview cohort. The consultant stratification was as follows: eight from high trial and cohort recruiting sites; four from high cohort/no or low trial sites; and three from poor cohort and trial sites. The nurses were all from high trial recruiting sites (the same sites as the eight consultants) and nurses from nil or low trial sites, or poor overall trial and cohort sites were not included (see *Chapter 2*). The analysis framework (see *Appendix 19*), led to a rich data set comprising (a) descriptions of the practicalities of administering and monitoring the two drugs and (b) contextual factors influencing professionals' views of the effects of infliximab and ciclosporin on the alleviation of symptoms or QoL. In addition, analysis led to (c) greater understanding of professional personal preference for one or other drug or other therapies; (d) clarification of professional experience and entry into the trial; and (e) perspectives on current government policy regarding the regulation of drugs and of NICE guidelines. Underpinning views and preferences from both nurses and consultants was an ongoing concern for patient welfare, informed patient choice and joint decision-making.

The main themes and categories derived from interviews are displayed in *Box 1* and described in detail below alongside verbatim quotations. All quotations are coded to indicate whether a consultant or nurse was speaking and the transcription line numbers.

Drug administration and management

Consultants and nurses, when asked about the administration of infliximab and ciclosporin, were keen to point out that consideration must not only be given to the administration process but also to the lead-up procedure ('*work up to treatment*', consultant, HP7.45). Patient work-up was seen as a vitally important step in administering the drugs. However, work-up was said to be something that was neither given enough consideration within the drug guidelines, nor discussed in terms of positive and negative consequences and its effect on the rest of the administration process, such as its effect on drug handling. Interviewees described the work-up necessary for the provision of infliximab and ciclosporin in similar terms; however, following initial work-up administration, infliximab was much easier to handle than the administration activities necessary for the provision of ciclosporin. First, there was less to be concerned about during that period of time, and, second, the process had less impact on workload, especially for nurses, while both drugs demanded due care and attention. Attention to detail was described according to the careful mixing of drugs and other preparations necessary for treatment, prescreening of patients and patient preparedness for the intravenous infusions. In this respect ciclosporin was consistently described as the more complicated of the two, with a longer administration time (continuous as opposed to 2 hours for infliximab), and with the need for frequent changes of intravenous bags (infliximab is a one-off infusion). This had a knock-on effect on health-care professionals' work schedules:

> *It [ciclosporin] goes on over a longer period of time obviously, so the need [for nurses] to continually make up bags and things over a longer period of time rather than just the one off infusion.*
>
> *Consultant, HP13.25*

> *It's [ciclosporin] time consuming for the nurses and slightly messy. You know it's complicated and it's work for the nursing staff.*
>
> *Consultant, HP15.19*

BOX 1 Thematic framework: main themes and categories

Drug administration and management

Lead-up to treatment.

Drug administration and effectiveness.

Adverse effects.

Drug management.

Longer-term effects and drug maintenance.

Personal preference and involvement in the trial

Personal preference of consultants and nurses.

Views on other health-care professionals' preferences.

Being part of a trial.

Surgery.

Equipoise.

Negotiated care and shared decision-making.

Costs

Costs of the two drugs.

Comparative costs.

Evidence and guidelines

Evidence related to NICE guidelines.

The regulation of drugs and drug policy.

Nurses' views accorded with consultant opinion on this matter. In addition, nurses were keen to emphasise the complexities resulting from contextual and geographical factors that had to be contended within a busy hospital setting, such as managing patients on different wards requiring an infusion and, as a consequence, the greater number of nurses with advanced prescribing capabilities necessary on the wards at any one time:

> *Having to make it up [ciclosporin] every 6 hours is time consuming, changing lines, always having two nurses to check it because the way the GI [gastrointestinal] unit is split is there's a corridor up between the two wards so obviously bed cover etc. but only to have one trained [nurse] each side is a bit difficult . . . geography of the wards . . . we've no one else to check the drugs.*
>
> *Nurse, HPN19.21/28/29*

> *You have to be mindful that the continuous infusion [ciclosporin] has to be prescribed to cover the weekend until Monday.*
>
> *Nurse, HPN18.27*

The practicalities of a lengthier ciclosporin infusion had implications for patients' well-being too, with health professionals having to spend more extensive periods of time in hospital dealing with patients who were '*frustrated*' (nurse, HPN21.98) with highly restricted movement:

> *[Ciclosporin] fairly cumbersome for both the staff and equally importantly for patients because once you are tied to the drip and associated drip stand, it sort of restricts patients moving around.*
>
> *Consultant, HP12.10*

> *Patients don't particularly like being hooked up to it for such a long period . . . it's [ciclosporin] restrictive.*
>
> *Nurse, HPN25b.52/57*

Views on the ease of administering individual drugs were clearly influenced by an individual's familiarity with the drug in question. Thus, those with more experience of ciclosporin tended to be more positive about that drug, and there were suggestions that nurses should be trained in both drugs as they faced a steep '*learning curve*' (consultant, HP13.123) particularly in relation to ciclosporin. Nevertheless, support for the administration of infliximab was stronger and it was repeatedly described as the '*easier*' (consultant HP5.18 and nurse HPN18.169) and more '*convenient*' (consultant, HP12.78) drug:

> *Infliximab has an advantage (over ciclosporin) in that it's just a 2 hour infusion and then it's done . . . there's no problem with infliximab, I think it's a good drug to administer, I think it's an easy drug to administer . . . I like infliximab because once you've done it, you've done it for two weeks.*
>
> *Consultant, HP14.26/30/33*

Although both drugs were perceived to be effective, ciclosporin was faster acting and the slower response time with infliximab presented a challenge in terms of whether to continue with infliximab or look towards a different treatment. Ciclosporin was more '*clear-cut*' (consultant, HP11.81) and consultants felt more confident in their decision-making and timings with regard to this drug. In addition, consultants worried about the ambiguous information available for ciclosporin response rates, as these did not appear to match patients' actual responsiveness, made all the more complex by the need for an extended administration period:

> *Tend to use ciclosporin as acting more quickly.*
>
> *Consultant, HP4.171*

This is the one thing I don't like about infliximab, because there is no data to give us a clear timescale or timeline for decision-making.

Consultant, HP11.94

Sometimes it's a bit challenging that you have given them infliximab if they are going to take sort of a week to 10 days time would you hold your nerve?

Consultant, HP12.47

In addition to response times, adverse effects were of major importance in treating patients with one or other drug. Ciclosporin in particular was seen to have a range of associated adverse effects, which included drug toxicity, renal failure, neurological impairment, seizures, tremors and hypertension. Consultants were '*uneasy*' (consultant, HP9.56) about the drug, seeing it as '*dangerous*' (consultant, HP6.72). Even those advocating its use tended to be apprehensive about the adverse effects in the longer term, thus viewing it as more of a bridging therapy. These views were reinforced by a perceived lack of evidence of ciclosporin's longer-term benefits.

Don't want to use it [ciclosporin] in the longer term because of side effects, so switch to azathioprine as soon as possible.

Consultant, HP6.99

I'm always a little bit more nervous with it [ciclosporin] . . . and I think that's from the side effects of renal impairment . . . I think the side effects profile of ciclosporin, although maybe it has not come out in studies, still concerns us more.

Consultant, HP16.278/281

. . . potentially quite significant side effects that can happen . . . slightly uncomfortable feeling about it [ciclosporin].

Consultant, HP9.60

It's [ciclosporin] a bit debatable although I use it, I worry about toxicity and the liver, use it half-heartedly, when no choice.

Consultant, HP3.29/32/33

An adverse risk profile for ciclosporin, we were told, results in increased patient monitoring and checking of drug and blood levels, which, in addition to a more resource-intensive process, impacts on nurses' time. This is particularly noticeable on a busy ward where there are difficulties with nurse-to-patient ratios, and nurses had the sense that their profession was struggling with workload increases, impacting on their ability to give equal time to all patients under their care. They reported occasionally '*forgetting*' (nurse, HPN24.255) to monitor ciclosporin patients fully. Infliximab, on the other hand, did not warrant any additional monitoring and no issues associated with monitoring were raised:

It's [ciclosporin] time consuming with regards to observation, particularly on a busy ward when you've got one nurse to 10 patients, it can take quite a huge part of your workload.

Nurse, HPN21.16

We have to monitor this patient closely for any side effects . . . it [ciclosporin] takes 3 hours because you've got to do obs [observations] for a couple of hours, but then sometimes we tend to forget because we get busy with other patients . . . so ideally it should be one to one.

Nurse, HPN24.249/255

Although infliximab also carried a risk profile that included adverse reactions, causing particular hesitancy in prescribing it for the older patient, it was favoured for its fewer side effects and longer-term efficacy:

> *Most of the time it [infliximab] goes without incident.*
>
> *Nurse, HPN19.83*

> *Have only ever seen minor reactions to the infliximab.*
>
> *Nurse, HPN21.82*

However, consultants pointed out that they felt frustrated about policy restrictions and government guidelines that prevented them from using infliximab in the way in which they wished to, including the need to justify its use in the longer term:

> *We now have to request the funding for patients with UC on long-term infliximab so that's a bit of a challenge and it means that decisions are made differently to whether a patient is going into maintenance infliximab.*
>
> *Nurse, HPN19.154/156*

> *It's already an issue because we can't really treat as maintenance with infliximab so obviously if a patient responds well we've had to get exceptional funding and things like that so there is a case for it I think.*
>
> *Nurse, HPN22.103*

Personal preference and trial involvement

Consultants clearly recognised the effect that their own experience of using one or other drug had on their personal preference. Some consultants, as indicated in *Drug administration and management*, have a preference for infliximab, based on its ease of preparation; easier administration; lower negative impact on nurse care provision, staffing and workloads; longer-term benefits; and reduced adverse effects. In addition, both consultants and nurses pointed to greater patient tolerance and enhanced patient convenience. Further reasons for stated preferences included familiarity with the drug, drug effectiveness, greater clinical expertise and knowledge and general sense of '*unease*' (consultant, HP9.58) with the use of ciclosporin:

> *My personal view is that they probably have equal efficacy, I think infliximab has less side effects so if I was given a free choice, if I was asking it for me or for my loved ones, I would opt for infliximab.*
>
> *Consultant, HP5.65*

> *When a patient was given infliximab I was rather pleased and when they were given ciclosporin I was less enthusiastic . . . we wondered about the tolerance for the patient and convenience for the patient.*
>
> *Consultant, HP15.380/394*

Nurses' views mimicked those of their consultant counterparts, expressing a preference for infliximab based on its ease of administration, perceived patient benefits and personal experience and familiarity with the drug. They highlighted the restrictions of patients being hooked up to a ciclosporin infusion for longer periods of time while suffering from bowel disturbances, and noted patients' preference for infliximab in this respect. Ciclosporin was described as '*high maintenance*' (nurse, HPN25a, 174):

> *I prefer it when they have infliximab . . . I think it's easier for the patients because it's just one infusion . . . it's a couple of hours, instead of being hooked up. I mean keep in mind they have profuse diarrhoea . . . I think it's easier to administer as a nurse and it's easier for the patient to receive.*
>
> *Nurse, HPN18.165/169/173/178/189*

> *Personally I feel that the infliximab is better but that's only because of the experiences we've had with the infliximab rather than the ciclosporin . . . seen patients do very well on it, particularly when before perhaps there wouldn't have been any other outcome than surgery.*
>
> *Nurse, HPN21.209/217*

This personal preference was not, however, across the whole interview cohort, with two consultants describing their preference for ciclosporin, based on personal familiarity with the drug, its quicker-acting properties and its ability to disappear from the system once the drug administration had been halted. However, even these two interviewees stressed the need to retain a level of vigilance and to *'be more wary'*:

> *Rather more relaxed about it [ciclosporin], paradoxically, simply because I know when the IV [intravenous] infusion is stopped then the drug disappears.*
>
> *Consultant, HP10.75*

> *I've used it [ciclosporin] for a very long time and I'm comfortable with it.*
>
> *Consultant, HP11.160*

In spite of these personal preferences, there remained a genuine sense of uncertainty as to which drug was the more beneficial at the time of the trial, particularly in relation to people's views of trial entry, trial management and patient recruitment. Most health-care professionals commented that effectiveness was equivocal across the two drugs, genuinely wanting answers from the trial team as to the '*better*' of the two. This desire was described as patient-driven, based on which of the two was more effective and well received by patients.

> *If the result was that ciclosporin was a lot better we'd use it and if the results were that infliximab was a lot better we'd use it.*
>
> *Consultant, HP16.622*

> *The difference (between drugs) is not sufficiently dramatic that I would say it was unethical to put them into a randomised study.*
>
> *Consultant, HP15.460*

Professionals welcomed the CONSTRUCT trial and congratulated the trial team for moving this body of work forward so successfully, in spite of what was described as a somewhat '*ambiguous*' area of research. They discussed the fact that they had attempted to actively recruit patients into the trial, despite, in the lower recruiting sites, a lack of success, which was put down to busy workloads and lack of joined-up working patterns.

Surgery

Health professionals had mixed views about using alternative therapies, such as surgery, for acute UC. Colectomy, for example, was generally seen as a '*last resort*' (nurse, HPN21.247) when all other therapies had failed, with some health-care professionals describing feeling '*disappointed*' (consultant, HP9.210) with colectomy being needed. Consultants argued that although surgery was an option, other medical avenues should be exhausted first before reaching that point:

> *It's [colectomy] always a last resort . . . It's not something I'm comfortable sending them off to have surgery.*
>
> *Nurse, HPN21.247*

Having a colectomy was also seen as a difficult decision to get patients to agree to, and discussions around surgery had to be highly individualised and dealt with on a patient-by-patient basis. Most professionals described colectomy as an option that needed discussion first, to provide both counselling for patients and

an assessment of patients' views: '*once it comes out you cannot put it back*' (consultant, HP13.338). Patients were seen to be often '*nervous*' (consultant, HP13.330) of surgery and wanted to put it off for as long as possible, and for this reason alone it was important to have medical options available to prolong the time before surgery. However, at times surgery was seen as being put off for '*too long*' (consultant, HP20.192), resulting in more difficult decision-making and complications for patients:

> *I think it comes down to a personal decision, I think it's very important to have lots of discussions about the options, medical or surgical . . . it's very difficult if they're newly diagnosed and they come in with their first presentation . . . some people can come with obvious pre-conceived ideas about things anyway and I think it's important to explore those feelings.*
>
> *Nurse, HPN19.254/267*

Colectomy was recognised as a '*lifesaving*' procedure for some patients to which patients responded positively once surgery was over and symptoms were alleviated:

> *My personal thoughts are that you know that's their last resort and I think the majority of patients feel the same that they would try any form of medical management.*
>
> *Nurse, HPN25b.137*

Policy development and drug regulation

Health-care professionals were clearly aware of the cost of infliximab and saw the implications of the high cost to be driving policy development and guidelines for practice. Guidelines around the use of the drug ultimately affected clinical decision-making:

> *There is an issue of cost of course, we're pushed all the time to stop it for cost reasons.*
>
> *Consultant, HP15.120*

Although health-care professionals understood the need for rigorous guidelines around the use of the drugs, many also linked guidelines to an enforced restriction of the use of infliximab, emphatically arguing that the NICE guidelines were outdated, outmoded and out of step with more recent evidence. This left them feeling frustrated and constrained in their ability to provide the best and most appropriate care for their patients. They described the situation as one in which they had '*their hands tied*' (consultant, HP6, 127.131), indicating that the more recent clinical evidence and their own personal experience showed infliximab as the drug that needed to be used more widely. As a consequence, they urged that guidelines became more flexible in order to accommodate patients' needs more appropriately:

> *It's very hard to find anyone who supports the NICE guidance in its present format.*
>
> *Consultant, HP16.516*

> *I sort of treat it with a bit of contempt.*
>
> *Consultant, HP9.239*

The point was repeatedly reinforced that, although the guidelines were there to be adhered to, there was a clear sense of rebellion within the profession, with clinicians '*ignoring*' (consultant, HP9.236) guidelines when they could find ways around them in order to best meet patient needs. Thus, health-care professionals welcomed a much-needed change to the NICE guidelines that allowed for the greater flexibility of drug use, led primarily from an assessment of patient need:

> *You can usually find a reason why ciclosporin would be contraindicated . . . I don't think it's a particularly sensible NICE guidance based on the lack of evidence that they have to make their decision and therefore in all honesty because we can, we slightly ignore it.*
>
> *Consultant, HP9.232/236*

I think it's unduly restrictive and I think it will eventually change. I think it's actually quite hard to adhere to as well. I mean you've got a patient who you want to give treatment to, you're duty bound to give the best treatment and in some cases that's going to be infliximab.

Consultant, HP14.208

Patient benefit and negotiated care

Throughout the discussions around the administration of the drugs, treatment of patients, personal preference, the value of surgery, and adherence to guidelines and regulations, was a professional focus on patient benefit and need. Nurses and consultants gave many examples of the decisions that were being made that took into account what was best for the patient, especially when it came to a consideration of a patient's personal circumstances:

I like to tailor the treatment to the patient.

Consultant, HP10.144

The drug we choose ultimately depends on the patient.

Consultant, HP5.75

Nurses were more influenced by the patient experience than the consultants were, perhaps as a result of their extended contact with the patients, and nurses discussed their preference in the context of patient convenience and QoL:

It worked really well on that patient . . . there's a quicker response time with infliximab . . . patients pass comments and they always tell me I feel much better after this one.

Nurse, HPN24.33/118

It's whatever is best for the patient . . . I think it's different for each patient and I think that they need to be given the choice and have all the information because for some patients it can be a very good treatment [colectomy] and give them back their quality of life.

Nurse, HPN22.139/157

As evident in the last quote, the notion of negotiated care was central to the consultation as far as consultants were concerned, and ongoing patient care and decision-making was perceived as being shared across and within multidisciplinary teams. This led to a shared professional responsibility, with the patient–clinician interaction the ultimate example of this:

Our surgeons are very active in decision-making, and multidisciplinary team meetings twice a week.

Consultant, HP5.121

Care is negotiated with the patient, patient input is important, but predefined pathways are according to previous discussions.

Consultant, HP4.113

Patient views are as important as anything else, combined with weighing up risks and benefits, we involve them hugely.

Consultant, HP7.103

The results of this interview study indicate that doctors would make a judgement between the two drugs largely on effectiveness but that there is a clear preference among nurses for infliximab. Ciclosporin is more complex and cumbersome to administer, requiring additional monitoring which tends to be particularly problematic on busy wards with extensive demands on an already overstretched health-care professional workforce. The longer administrative process restricts patient's movements and leaves them feeling frustrated. It is also excessively demanding on the time of specialist nurses and other health-care

professionals, who need to be present to manage any complications, and there is more intensive patient monitoring due to the drug's adverse risk profile. Consequently, professionals question current NICE guidelines and government regulations around drug use and suggest a sense of rebellion about the restrictions placed on their autonomy and their practice.

Not only are professionals keen to change regulations surrounding current prescribing and drug administration, they also want changes to longer-term patient maintenance and monitoring, preferring infliximab as the longer-term drug of choice in view of its success in dealing with the many complex symptoms that the disease group displays, as well as it being the more familiar, convenient, effective and easy to handle of the two.

Chapter 4 Results synthesis MATRICS

Table 46 illustrates the effects that we investigated in the CONSTRUCT trial, in relation to effects on patients; effects on gastroenterology services and professionals; and effects on the rest of NHS and society. Some effects related to more than one category. We decided that patient views about the drugs and side effects and patient views about their illness including family involvement were effects related to both the patient and the rest of NHS and society. We also decided that professional views about the drugs, preferences, guidelines and equipoise were an effect related to both gastroenterology services, and the NHS and the rest of society.

Table 46 illustrates layer 1 and *Table 47* illustrates layer 2 of the MATRICS and the specific methods that we used to investigate the effects.

Table 48 illustrates layer 3 of the MATRICS with the synthesised findings from CONSTRUCT.

TABLE 46 Layer 1 illustrating the effects being investigated and the methods used to do so

Layer 1: effects		
Effects on patients	**Effects on gastroenterology services and professionals**	**Effects on the rest of NHS and society**
1. Quality-adjusted patient survival [A]		
2. Patient disease-specific QoL [B]		
3. Patient generic QoL [C, D]		
4. Health gain [C]		
5. Mortality [E]		
6. Colectomies – planned and emergency [E][H][I]		
7. Readmissions [E]		
8. AEs [E]		
9. Malignancies [E]		
10. Serious infections [E]		
11. Renal disorders [E]		
12. Other new symptoms [E]		
13. Disease activity [F]		
14. Patient time off work [G]		
15. Patient views about the drugs and side effects [H]		15. Patient views about the drugs and side effects [H]
16. Patient views about their illness including family involvement [H]		16. Patient views about their illness including family involvement [H]
	17. Professional views about the drugs, preferences, guidelines and equipoise [I]	17. Professional views about the drugs, preferences, guidelines and equipoise [I]
		18. NHS costs [J, K]
		19. Patient time off work [G]

Note
Each number denotes the effects being investigated and the letters identify the specific method used in the study.

TABLE 47 Layer 2 illustrating the methods used and the effects that they were investigating

Layer 2: methods	
Code	**Method**
A [1]	Analysis of AUC using the CUCQ
B [2]	Analysis of CUCQ scores (patient questionnaire)
C [3, 4]	Analysis of EQ-5D scores (patient questionnaire)
D [3]	Analysis of SF-12 scores (patient questionnaire)
E [5, 6, 7, 8, 9, 10, 11, 12]	Hospital administrative data patient questionnaires
F [13]	Calculation of TrueLove and Witts score,[4] full blood count, inflammatory markers and albumin
G [14, 18]	Patient time off work (patient questionnaire)
H [15, 16]	Semistructured patient interviews
I [17]	Semistructured interviews with health professionals
J [18]	NHS costs (patient questionnaire)
K [18]	Hospital activity data

Note
Each number denotes the effects being investigated and the letters identify the specific method used in the study.

TABLE 48 Layer 3 illustrating the summarised findings of the study

Layer 3: findings	
Code	**Finding(s)**
Effects on patients	
1A, 2B, 3C, 3D, 5E, 6E, 7E, 8E, 9E, 10E, 11E, 12E, 13F	There was no significant difference between ciclosporin and infliximab in QAS; disease-specific and generic QoL; mortality and colectomy rates; readmissions; AEs; malignancies; serious infections; renal disorders; other new symptoms
17I	Nursing preference for infliximab because of resource-intensive intravenous administration of ciclosporin. Some doctors perceive fewer side effects, greater patient benefits and easier management of long-term care
4C: health gain EQ-5D	There was no significant difference in generic health gain
14G: patient time off work	There was no significant difference in patients' time off work
15H: patient views about the drugs and side effects	Patients participants want to normalise their lives, go back to work, feel well again and be less drug dependent From experience, patients who received infliximab reported fewer side effects and more manageable treatment regime when compared with patients who received ciclosporin However, they would favour whichever drug will enable this to happen as easily and quickly as possible
16H: patient views about their illness including family involvement	Patients emphasised extensive impact of the disease on their QoL Patients would welcome early diagnosis and reduction to the effect of lengthy illness and the cacophony of drugs on their lives and the lives of their families Family understanding and support is crucial

TABLE 48 Layer 3 illustrating the summarised findings of the study (*continued*)

Layer 3: findings	
Code	**Finding(s)**
	Patients have to live with unpredictability of symptoms and treatment
	This is, unlike other chronic conditions, considered an embarrassing disease, making it isolating and awkward
	Lack of visibility of symptoms makes it hard to share experiences with others
	Patients and family members seek better and more readily available information and more IBD specialist nurses to support their specific needs
	Patients fear and avoid surgery for stoma, but many who undergo surgery report on its positive effects on QoL
	Patients want to understand what causes the disease and possible links to diet and stress
Effects on gastroenterology services and professionals	
17I: professional views about the drugs, preference, guidelines and equipoise	Clinician preference for infliximab over ciclosporin as regards treatment and ongoing management: easier administration, fewer side effects, greater patient benefits, easier management of long-term care
	Views that NICE guidelines need to be brought in line with professional preference suggesting current practice and regulations around drug use should be reconsidered. Maintenance and monitoring easier with infliximab
	Lack of equipoise among those interviewed
	Benefits of trial for seeking answers to which drug is more efficacious and supporting regulatory change
	Consultants' views that nurses are less familiar with administering ciclosporin and increased nurse workload for ciclosporin patients
Effects on the rest of NHS and society	
18J, 18K: NHS costs	Total health-care costs were higher for infliximab patients due solely to the higher drug acquisition cost
19G: patient time off work	Treatment given had no effect on patients' time off work

Chapter 5 Discussion

Summary of findings

The CONSTRUCT trial recruited 270 participants from 52 hospitals in England, Scotland and Wales between May 2010 and February 2013 and followed them up until March 2014, that is, for between 1 and 3 years following treatment with either infliximab or ciclosporin, allocated at random. Rigorous analysis of 242 (90%) patients, excluding 28 who provided no analysable data, showed no significant difference between the two drugs in the primary outcome of QAS, equivalent to the AUC of QoL scores from the CUCQ (mean difference in AUC/day 0.0297 favouring ciclosporin, 95% CI –0.0088 to 0.0682; $p = 0.129$). There was also no significant difference in EQ-5D scores (QALY mean difference 0.021 favouring ciclosporin, 95% CI –0.032 to 0.096; $p = 0.350$); SF-6D scores (mean difference 0.0051 favouring ciclosporin, 95% CI –0.0250 to 0.0353; $p = 0.737$); colectomy rates (OR 1.350 favouring infliximab, 95% CI 0.832 to 2.188; $p = 0.223$); time to colectomy (hazard ratio 1.234 favouring infliximab, 95% CI 0.862 to 1.768; $p = 0.251$), the incidence of SARs (14 participants on infliximab vs. 9 on ciclosporin, OR 0.660 favouring ciclosporin, 95% CI 0.282 to 1.546; $p = 0.338$) or the incidence of SAEs (16 participants on infliximab vs. 17 on ciclosporin, OR 0.999 favouring infliximab, 95% CI 0.473 to 2.114; $p = 0.998$). Three patients died, all of whom had received infliximab ($p = 0.25$).

Although length of hospital stay after randomisation ostensibly did not differ between drugs (mean adjusted difference 1.542 days more for ciclosporin, 95% CI –1.297 to 4.381 days, assuming normal distribution of residuals in general linear model; $p = 0.286$), that distribution was so skewed as to invalidate the assumption of normality; hence, we transformed these stays by taking logarithms and estimated that the geometrical mean of adjusted stays after ciclosporin was a factor of 1.523 times longer than that after infliximab (95% CI 1.278 to 1.817; $p < 0.001$). Although infliximab thus used fewer hospital resources, its much higher acquisition cost resulted in a much lower total NHS cost for ciclosporin (mean difference –£5632, 95% CI –£8305 to –£2773; $p < 0.001$).

Interviews with patients revealed the substantial impact of UC on their QoL and the potential benefits from these medical treatments and from surgery. Participants treated with infliximab generally spoke more positively about the treatment than did those treated with ciclosporin. Interviews with nurses showed a preference for infliximab, largely because of the resource-intensive infusion protocol for ciclosporin and the resulting restrictions on patients. Although some consultants favoured infliximab, most were indifferent, perceiving both drugs as effective, with the more predictable speed of benefit with ciclosporin balancing its perceived higher rate of side effects.

Trial progress and conduct

This trial took nearly 7 years to complete from the first notification of intention to fund in November 2007. Recruitment started in 2010. Our initial plan was to recruit 480 patients and follow them all for 2 years, measuring change in disease-specific QoL as our primary outcome. Research governance delays[99] and slow recruitment led us to seek approval from the DMEC, TSC and HTA for a change in the primary outcome in 2010 and a funded trial extension in 2011. The essential changes were:

- Change in the primary outcome from change in disease-specific QoL scores at 2 years to QAS.[55] QAS is derived from the AUC described by scores from disease-specific QoL questionnaires completed by participants 6-monthly for 1–3 years after randomisation.
- Reduction in target analysable sample size from 360 to 250.
- Follow-up to last for 1–3 years depending on recruitment date.

The implementation of these changes required additional follow-up visits and patient-completed questionnaires.

Sixty-seven hospitals from England, Scotland and Wales collaborated with us on this study, of which 62 recruited patients to the cohort and 52 recruited participants to the trial. This large number of sites was necessary because of the relative infrequency of admission with ASC, which is a life-threatening condition and patients are very sick when admitted to hospital. To facilitate recruitment to the trial the opportunity was explained to patients on admission and baseline data collected at that time. This generated a cohort of 1532 patients with ASC, from which the trial participants were recruited when they failed to respond adequately to treatment with intravenous hydrocortisone. The patients in this cohort have given consent for their progress to be monitored for 10 years using routinely collected data. Fifty per cent of the patients in the cohort ($n = 775$) settled without steroids or responded to initial treatment with intravenous hydrocortisone and 74 were so ill they went for colectomy before randomisation was possible. We eventually recruited 270 patients to the trial and followed them up for 1–3 years.

We measured disease-specific QoL using the CUCQ and used the scores to compare QAS. The CUCQ is derived from the UK-IBDQ, an anglicised version of the Inflammatory Bowel Disease Questionnaire that we validated 14 years prior to this study.[61] Modification was required because the UK-IBDQ has only been validated for stable or moderately active IBD and we needed an instrument that would be appropriate to use when the disease was severe as well as mild or in remission. We validated the CUCQ concurrently with the trial, using data from participants and other sources.[100]

The validated 32-question CUCQ that we used is different from the McMaster Inflammatory Bowel Disease Questionnaire[18] in several aspects (see *Appendix 18*). The wording of the questions in the CUCQ are modified and anglicised to use in the UK. The response options of the CUCQ were simplified using a combination of close-ended and a four-level Likert scale answers instead of the seven-level Likert answers used in the IBDQ. In order to avoid acquiescence bias (yes-set),[101,102] three questions about happiness, being relaxed and having energy were phrased in a way that the higher the number, the higher level of QoL for that attribute. Their scores were then reversely coded before adding them to the total score. The items covered by the 32 questions in both the CUCQ and IBDQ are relatively the same. Therefore, we did not use the IBDQ in the construct validity testing of the CUCQ and used the SF-12, EQ-5D and disease severity indices instead. However, the CUCQ includes a question about urgency and rushing to toilet, which does not exist in the IBDQ. The IBDQ asks about the need to get up at night to go to toilet and the lack of good sleep in one question, whereas the CUCQ asks about these two items in two separate questions. The advantages of using the CUCQ are its simplicity, wider coverage of the symptoms of acute IBD, and that it is free to use by health-care professionals.

To be able to continue to measure QoL after surgery we developed and validated an extension to the CUCQ which asked questions more relevant to patients with a stoma (CUCQ+). This was sent to participants post colectomy by the trial office, on discharge and 4, 8 and 12 weeks post discharge.

Deaths and withdrawals meant that QoL questionnaire scores were available from 121 participants in each group up to the end of their participation in the trial, a retention rate for the primary outcome of 90%. Secondary outcomes were measured using data extracted from patient records by research professionals and recorded in CRFs (with completion rates as shown in *Table 6*). The retention rate to 2 years is excellent but falls off at 30 and 36 months, reflecting mainly non-attendance of participants as their condition has improved. The completion rate at 18 months is low because the 18-month data collection point was added after the protocol was modified and required reconsent, meaning that some participants were missed.

The 121 participants in each group with evaluable primary outcome data were sufficient to demonstrate clearly that there is no significant difference between the two treatments in clinical effectiveness over the first 3 years after treatment. This does, however, also reflect the QoL after surgery, a high colectomy rate in both arms of the study (41% following infliximab; 48% after ciclosporin) and continuation of treatment with infliximab or ciclosporin beyond the prescribed intervention period at the discretion of the attending physician. Ciclosporin was discontinued by all participants by 180 days, whereas infliximab was continued for 1 year in one-quarter of participants and up to 3 years in a few.

In 2009 we applied to the HTA programme and the MRC to use the CONSTRUCT trial to explore the possibility and validity of using data collected at the point of care to support a pragmatic trial that was embedded in clinical care. This Electronic records Underpinning REsearch and CAre (EURECA) proposal was not funded but we nevertheless took the opportunity to explore the feasibility and acceptability of using GeneCIS, a non-commercial clinical management system that has been successfully deployed for many years in a small number of disciplines in six hospitals, to support the trial, while also giving participating sites the opportunity to use this system to support clinical care. The system required customisation to underpin some aspects of the trial and enabled extensive quality control to be applied to the data, especially where it was possible to triangulate data received from different sources (CRFs, AE reports and patient questionnaires). Intensive efforts were made to verify or clarify data that was ambiguous or in conflict (e.g. the dates and nature of an operation). Sixteen sites took up the opportunity to enter data directly into the system, the rest returning their CRFs and patient questionnaires to the trial office for data entry. Although our experience with CONSTRUCT has shown that an operational clinical information system can support a pragmatic RCT and it is likely that the concept of integrated data collection for clinical care and research will take some time to take root. In spite of the failure of the EURECA proposal to secure funding to evaluate this in detail, we believe the principle of using high-quality point-of-care clinical data to support prospective pragmatic trials remains valid, particularly if national standards are applied to the structure and content of electronic patient records.[103]

The management and co-ordination of the CONSTRUCT trial was based on PRojects IN Controlled Environments Version 2 principles. We held weekly meetings of the core team in the trial manager's office, at which we reviewed recruitment and retention, SAEs that needed discussion and any other issues raised, such as progress with the concurrent validation of the CUCQ. All of the research team attended monthly TMG meetings and we used these meetings more formally to review trial progress, including action, risk and issue logs. When specific issues needed to be addressed we set up one-off TMG 'operational group meetings' to resolve the issues or make plans. The TSC and DMEC met to review progress and give valuable advice at key milestones in the project. The chief investigator and trial manager liaised with sites mainly through e-mail, or by telephone if the issue was complex or urgent.

We were fortunate in this study to have benefited from enthusiastic, expert and thoughtful input from representatives of the patient community. Mike Hilton was a regular and wise contributor to our monthly TMG meetings, providing particularly useful advice when we were developing a post-colectomy extension to the primary outcome QoL instrument. He was also instrumental in improving recruitment by jointly authoring a letter to sites with the chief investigator. Laura Hawes and Peter Canham regularly attended the TSC and DMEC meetings, respectively, and provided feedback and useful advice over the course of the study. Clare Baggridge also gave us very useful insights from the perspective of a health professional who has undergone colectomy for UC. They have all given us permission to recognise their input in this way. Mike Hilton's thoughts on his engagement with the study are included at *Appendix 22*. The input of lay members throughout has been invaluable and we believe it adds weight to the external validity of our findings.

Strengths and weaknesses of the study

The CONSTRUCT trial has been a complex trial to run for many reasons. The severity of the illness, nature of the symptoms and relative rarity of the presentation of ASC meant that case ascertainment, recruitment, retention and data collection have all been challenging. Methodologically we took a pragmatic approach, allowing local investigators flexibility in the clinical situation. For example, we allowed local clinical judgement to over-ride the results of objective tests when assessing the response to intravenous steroids. This was important, as it is well known that high doses of steroids can suppress markers of disease severity, giving a false and dangerous impression of recovery. We also allowed local flexibility in the duration of treatment with steroids and clinicians were allowed to exercise clinical judgement regarding the continuation or change in treatment once the per-protocol intervention was complete. As a result many participants continued on the allocated treatment for some time, more continuing for longer on infliximab than ciclosporin. The use of concomitant immunosuppressive therapy with azathioprine or 6-mercaptopurine after the intervention period was similar in both groups. We believe that this pragmatic acceptance of clinical judgement means that the results of the trial genuinely reflect current clinical practice.

Because of the severe and incapacitating nature of the symptoms suffered by patients with ASC we informed them about the trial at the earliest opportunity after admission and sought their consent for baseline data collection at that time. This meant that disease-specific QoL (the primary outcome measure) was completed by potential participants before treatment with steroids and some days before they were randomised into the trial. In spite of this, the two groups were well matched at baseline in terms of demographic characteristics and baseline CUCQ scores. There was, however, an unexpected preponderance of males in the trial in both groups. There are a number of possible explanations for this, which we are investigating.

The transition from cohort to trial varied from site to site, and the CONSORT diagram identifies 178 paticipants who were not randomised, although they were potentially eligible. For some of these potential participants, we have not been able to ascertain the reasons why they did not take part in the trial, but we suspect that patient or professional preference for a treatment may have inhibited consent and randomisation in some cases. The participants interviewed had experience of only one treatment, but there appeared to be more enthusiasm and satisfaction for infliximab than for ciclosporin. For both participants and professionals this was largely because of the cumbersome and constraining requirements for intravenous infusion of ciclosporin and it is possible that oral treatment may be more popular. We chose intravenous ciclosporin, before a transfer to the oral version, as we feared that tablets might be poorly tolerated and absorbed in very sick patients; however, given the effectiveness of ciclosporin, we feel that first-line oral therapy should be explored further, particularly as colonic release preparations become available.[104]

The primary outcome (QAS) was compared using data from QoL questionnaires (PFQs) completed at baseline, 3 months and 6 months and then 6-monthly until February 2014. All participants were, therefore, eligible for follow-up for 1 year, but only 34 (17 in each arm) were recruited early enough to be followed up for 3 years. The number of PFQs completed at each time point, and the reasons for shortfall, are shown in the CONSORT diagram. Some participants failed to return a PFQ at one or more time points but, overall, primary outcome data were available for 121 participants in each arm. There were three deaths and 31 withdrawals (14 infliximab and 17 ciclosporin) over the course of the study, which account for some gaps, but in some cases, and despite reminders, expected questionnaires were not returned. This is understandable: UC is a debilitating and depressing condition for the sufferer and, when well, patients do not like being reminded of their illness.

The incidence of SARs was similar in both arms of the trial. As the known side effect profile of both drugs is very extensive, we specified in the protocol that we did not require expedited reporting of serious events unless they were thought to be unexpected. Assessment of expectedness included featuring in the specification of product characteristics or being attributable to disease progression or surgical intervention.

At the start of the trial we stressed in the Fieldwork Handbook that AESFs have dual purpose. The first is to aid the decision process that will define whether or not the event is unexpected and, through this, enable us to detect any trend towards SUSARs to the treatment which might indicate a threat to patient safety. We detected no SUSARs, which is not surprising given the very extensive clinical experience with drugs that have both been in use for the treatment of IBD for over 20 years. The second purpose of the reporting system was to give us the data to be able to compare the incidence of events which are known side effects of the two drugs as a secondary outcome measure. This was a complex process that we addressed as rigorously as possible. Although all events had been monitored during the course of the study, two clinicians in the research team reviewed all SAEs again at the end of the study in order to ensure the consistency of our interpretation of their relatedness to the IMPs. When considering the relatedness of each event to the IMP, decisions were informed by data from sites on the duration of use of treatment with the IMP beyond the 3-month intervention period specified in the protocol. It was important that we did this because once the intervention period was complete, clinical management was no longer per protocol and therefore varied from subject to subject according to their progress and the clinical judgement of the local team. We also took into account the different pharmacokinetic profiles of the two IMPs. It is known that the bio-availability of ciclosporin is short-lived after cessation of treatment, whereas bio-availability of infliximab, although varying from subject to subject, can persist up to 6 months after the last infusion.[105] Therefore, with the exception of malignancy, we considered that relatedness would be unlikely if the event occurred more than 1 month after cessation of treatment with ciclosporin, but could be related up to 6 months after infliximab. These principles were agreed with the Clinical Trials Unit and the DMEC before we undertook the review.

Both UC and the drugs being evaluated are known to cause many clinical problems, some of which may be manifest together in a single event. When an AE report documented a serious event (usually admission) but included more than one problem (e.g. abnormal liver and renal function test results), we used our clinical judgement to decide which (if any) could be related to the IMP and which was the prime cause for admission. In addition, and in order to capture all problems reported, we analysed the events by both the total number of events, and the total number of problems, which we categorised by affected body system. The results of this re-evaluation of serious events led to few changes in category (which were all agreed with local PIs) and overall there was no difference between the two drugs in their toxicity profile in the study.

There were three malignancies: a case of endometrial cancer on ciclosporin, and a basal cell skin cancer and a colorectal cancer on infliximab. The last of these was unusual in that, although it was detected in the colonic specimen removed at colectomy, the histology identified signet ring cells, suggestive of a lung primary. Although dual primaries were considered, this was thought to be unlikely on review by the local multidisciplinary team.

Three participants died, all following treatment with infliximab, a difference from ciclosporin that is not statistically significant. Two deaths were due to sepsis (one pre operative and one post operative). In both cases this was associated with multiple comorbidities, including diabetes mellitus. One was from disemminated malignancy from colorectal cancer.

We took a rigorous approach to data quality. We maintained close contact with sites by e-mail and repeatedly stressed the importance of data completeness. We reviewed all the primary outcome data entered onto GeneCIS before analysis. The overall item omission or transcription error rate was $< 1\%$ and those identified were corrected. Many secondary outcome data were derived from a variety of sources, giving us the opportunity to triangulate many items. We undertook monitoring visits to eight sites, including six of the highest recruiting hospitals. These did not identify any data issues except for a few AEs that had not been reported. None of these was a SUSAR but two were SARs.

An evidence review commissioned by NICE in 2008[53] expressed concerns over the uncertainty in estimates of effectiveness, particularly with regard to colectomy rates, which had been used to model the cost-effectiveness of infliximab versus ciclosporin. This was because of the very small number of RCTs, which themselves were small, and to criticism of the use of evidence from mixed-treatment comparisons. The CONSTRUCT trial provided the opportunity to gain trial-based data from a sufficiently powered head-to-head comparison.

The economic evaluation showed very little difference in effectiveness at 30 months using all available data and adjusting for the number of days each patient had been in the study (0.021 QALYs in favour of ciclosporin). Very similar results were shown using more conventional complete-case analyses at 12 and 24 months where the mean difference in QALYs were 0.027 and 0.022 QALYs, respectively, in favour of ciclosporin. Infliximab, however, is considerably more costly in terms of direct treatment costs, whereas the two treatments did not differ significantly in terms of other NHS resources. Given the similar clinical effectiveness this means that infliximab is dominated by ciclosporin. The probabilistic sensitivity analysis, which takes into account the joint uncertainty in costs and effects, shows ciclosporin to have an 85% chance of being cost-effective when considered against a range of willingness-to-pay thresholds, including the £20,000–30,000 per extra QALY currently used by NICE.

These results differ from a modelling exercise by Punekar and Hawkins,[51] which showed infliximab to be more costly but also more effective than ciclosporin. The base-case incremental cost per additional QALY gained was £19,545, which, being below the current NICE threshold, was judged to be cost-effective. A more recent application of the same model to the Netherlands[50] produced an incremental cost-effectiveness ratio of €24,277. Modelling, however, requires assumptions which may not be borne out in clinical practice. For example, both studies assumed that infliximab patients receive three infusions as per protocol, whereas in our pragmatic study the number of infliximab infusions was at the discretion of clinicians who delivered more than three infusions to 34 of 135 infliximab patients and up to 13 infusions in one case, and not all participants received the initial three infusions. Similarly, cost-effectiveness results of the models were shown to be sensitive to assumptions about body weight which the UK base case assumed was 80 kg per patient and the Netherlands base case assumed was 70 kg. We were able to use each participant's treatment using their actual weights: mean 74.0 kg for ciclosporin participants and 74.4 kg for infliximab participants.

The mixed-methods approach we adopted for the study shows the importance of considering a wider range of information. Given the lack of any significant difference between the two drugs in quantitative comparison of their clinical effectiveness, the results of our qualitative research assume greater importance and the validity of our findings requires detailed scrutiny. The views we obtained from participants about infliximab, ciclosporin and surgery are important, unique, detailed, from a broad age range and UK wide. The interviewees were chosen at random, but stratified by age, treatment and surgery, and the demographic and baseline characteristics of the 20 participants who were interviewed were no different from the rest of the participants in the study. Applying the criteria of credibility, transferability, dependability and confirmability set out by Guba,[106] we believe we used a rigorous qualitative approach which we have described and reference in detail (see *Appendix 19*).[107–111]

Our approach and conduct of interviews with professionals were similarly rigorous. Many doctors volunteered a treatment preference and those who preferred infliximab tended to hold strong views, although most stressed that clinical effectiveness and safety were their prime concerns, hence their support for the trial and willingness to adopt a position of equipoise. Nurses were more strongly critical of ciclosporin, in particular the cumbersome and constraining intravenous regimen. We were alert to a potential lack of equipoise at some sites and monitored this. We believe that the final distribution of participants from across the UK, and the close matching of baseline data from the two groups, demonstrates that there was no bias relating to this.

The establishment of a cohort of 1532 subjects who were admitted to hospital with ASC, and have given their consent for us to monitor their clinical progress over 10 years, is a considerable strength of the study, particularly as we also have consent to monitor the progress of the trial participants by questionnaires over this time.

As a trial to explore effectiveness rather than efficacy our outcome measures were subjectively patient focused, rather than objective measures of disease activity, but the value of both drugs in terms of efficacy has already been established by the CySIF trial[41] and our results are concordant with their findings.

Owing to the small number of participants who contributed cost data at 36 months, we conducted the economic evaluation to 30 months rather than 36 as in the effectiveness evaluation. The number of missing data varied between resource items. However, this was low for the main cost drivers and all missing data were randomly distributed according to patients' clinical and sociodemographic variables and study arm.

We are aware that our attempt to capture all costs may have led to some double counting. For example, although the CRF would capture all accident and emergency attendances at the centre in which the participants was receiving their treatment (case notes), it would miss any that may have occurred at other hospitals (e.g. while the participant was on holiday). A question about accident and emergency attendances at other hospitals was therefore included in the PFQ but despite the clarity of the instruction it is possible that some participants reported study centre accident and emergency attendances which were already recorded on the CRF.

Our qualitative data from participants were obtained by telephone interview. We confirmed that the demographic characteristics matched those of the overall study participation and saturation was reached with professional interviews as with patient interviews.

External validity

Participants were recruited from a good mix of large and small district general and teaching hospitals, distributed throughout Great Britain, and we believe our study population is representative of severe UC in the UK. The participants were predominantly Caucasian and further analysis is needed to explore the extent to which ethnicity and age reflect the UK distribution of ASC.

Our findings are concordant with the results of the GETAID CySIF study,[41] an efficacy trial in 116 subjects that found no difference in patient response rates, colectomy rates or AEs 3 months after treatment (*Table 49*).

TABLE 49 GETAID CySIF study

Outcome	Infliximab (%)	Ciclosporin (%)
Treatment failure	54	60
Response at day 7	86	84
Colectomy rate at 3 months	23	18
SAEs	29	18

The methodologies and the findings of the two studies are complementary. CySIF used evidence from hospitals in Western Europe to establish that both drugs are equally effective, whereas we used a UK-wide study to show that this also applies to their clinical effectiveness.

The CySIF and CONSTRUCT trials are the only two fully reported randomised trials of these two drugs in this condition, and provide compelling evidence that there is no difference between ciclosporin and infliximab in efficacy or clinical effectiveness. Although, overall, ciclosporin is cheaper than infliximab, the single infusion is more resource intensive to administer and is less well liked by both patients and nurses who administer the infusions. The side effect profile is similar and, given orally, it would be much cheaper to administer. We were concerned that oral administration would not be feasible in very sick patients, but this would undoubtedly be possible in some patients, and we believe that the use of oral ciclosporin to pre-empt admission is worth evaluating. A very small trial comparing oral ciclosporin with intravenous infliximab in 30 participants has been reported in abstract form only and found no difference in efficacy 2–3 years after treatment.[112]

The study started to recruit in 2010 and, now that Remicade is off patent, biosimilar biologic treatments have started to appear,[113] but this study will provide a benchmark for their effectiveness. The cost of infliximab is likely to reduce with this competition. Newer biologic treatments are also appearing, some of which can be given orally.

The pragmatic approach taken in CONSTRUCT reflects the real world of clinical practice. In particular, we believe that the clinical judgement allowed in determining how ill potential participants were, the flexibility permitted in assessing their response to intravenous steroids and the clinical freedom encouraged in deciding how long to continue treatment after the intervention period was complete all contribute to the external validity of our results.

Similarly, our primary outcome includes the impact of continuing medical treatment and of colectomy undertaken when treatment fails. Although the impact of surgery on the participant tends to be positive, this is seen equally in both arms of the study. Although this may distort the apparent beneficial effect of the primary intervention, both in terms of clinical outcome and cost, it will not impact on the comparative results. As would be expected, we have shown that there is a dip in QoL after surgery, but this recovers.

Our data so far do suggest that colectomy is not a bad outcome. This conclusion reflects our previous analysis of routinely collected data about IBD from the whole of England, which demonstrated a continuing mortality after admission with UC without colectomy.[7]

Patients fear colectomy, largely because of the threat of an ileostomy, but surgical techniques and expertise mean that a stoma is not necessarily a long-term outcome. The patients we interviewed who had undergone surgery were pleased with the result, particularly those who had suffered long-term ill health before their final exacerbation. Given the epidemiological evidence that mortality after admission with UC without surgery is as high 3 years later as mortality from emergency colectomy,[7] there are reasons to consider surgery earlier rather than later. Whether or not this requires a large-scale randomised trial to compare medical and surgical treatment should be debated, particularly as observational studies have shown that treatment with both drugs is associated with a rising colectomy rate as time goes on – as high as 80% at 7 years after treatment with ciclosporin (*Table 50*) – although the rate appears to be lower, and declining, after infliximab.[122] Long-term follow-up of our trial and cohort patients will be very important to corroborate or refute these findings. We will analyse routinely collected data about readmission, colectomy and mortality over 10 years to look at this.

TABLE 50 Colectomy rates after treatment in observational cohorts since 2000

Study	Drug	2 weeks	Late	Details
Teisner *et al.*, Denmark[114]	Infliximab		37%	Median follow-up 22 months; range 4–57 months
Mortensen *et al.*, Denmark[115]	Infliximab	18%	39%	Median follow-up 17 days; range 2–651 days
Jarnerot, Sweden[116]	Infliximab		46%	At 2 years
Jakobovits *et al.*, Oxford[117]	Infliximab	15%	57%	At 3 months
Waters *et al.*, Exeter[118]	Infliximab	16%	64%	At 4 years
Campbell *et al.*, Oxford[119]	Ciclosporin		58%	At 7 years
Molnar *et al.*, Hungary[120]	Ciclosporin	22%	63%	Mean follow-up 2.9 years
Actis *et al.*, Italy[9]	Ciclosporin		65%	At 7 years
Moskovitz *et al.*, Belgium[121]	Ciclosporin		88%	At 7 years

Implications

The comprehensive design of CONSTRUCT has greatly strengthened the conclusions of CySIF, a small European trial that studied few clinical outcomes. There is no difference between infliximab and ciclosporin in the effectiveness with which they treat steroid-resistant ASC, not only in the incidence of 'treatment failure' but also in HRQoL, both generic and specific to UC. Nevertheless, nurses generally disliked the greater resource demands of intravenous ciclosporin, which led to participants on that drug spending a mean of 2 extra days as inpatients. Although 20 representative trial participants generally spoke more favourably about infliximab, gastroenterologists were more equivocal. Given current NHS budgetary constraints the dominant finding of our rigorous evaluation is that, even after subtracting the difference in hospital costs because of longer hospital stays, the net mean cost of ciclosporin to the NHS per participant was still £5632 lower than that of infliximab.

As NICE is currently consulting on the use of infliximab in severe colitis, these findings are timely. The clear conclusion from our quantitative data is that, despite the substantial difference in cost, the two drugs are similar in effectiveness and toxicity. Nevertheless, nurses prefer to administer infliximab and patients who received it seem to be more satisfied than those who were given ciclosporin. In designing CONSTRUCT we chose to start with ciclosporin given intravenously before switching to oral administration, as we believed that most patients would be too sick for immediate oral treatment. However, it is clear from our qualitative findings that intravenous ciclosporin is inconvenient and disliked by many patients and professionals and hence we wonder whether or not oral ciclosporin would have been effective from the start, and could even pre-empt admission in patients who are developing severe symptoms. These are important questions for research, especially as colonic release formulations are already in development.

Future research

We hope to follow both trial and cohort patients for up to 10 years, thus yielding important conclusions on long-term outcomes, notably on further colectomies and hospital admissions. Before then, CONSTRUCT has generated several questions which we plan to address through further analysis including:

1. How representative are our participants of UK patients with ASC?
2. Do females respond to steroids better than males?
3. How well do our baseline data predict subsequent need for colectomy?
4. How quickly does QoL improve after colectomy?
5. Can CONSTRUCT help to address whether or not colectomy is more clinically effective and cost-effective than medical treatment?
6. Do the characteristics of investigators influence their attitude to treatments?

We suggest that there is a strong case for new trials to evaluate:

1. the relative clinical effectiveness and cost-effectiveness of medical and surgical treatment for ASC
2. the relative clinical effectiveness and cost-effectiveness of intravenous versus oral ciclosporin for acute UC especially if colonic release ciclosporin becomes available
3. the relative clinical effectiveness and cost-effectiveness of using oral ciclosporin to pre-empt admission in severe but pre-acute colitis
4. the relative clinical effectiveness and cost-effectiveness of new anti-tumour necrosis factor drugs, currently the subject of a NICE appraisal and intravenous or oral ciclosporin.[123]

Conclusions

The total cost to the NHS was much higher for infliximab than ciclosporin. Nevertheless, there was no significant difference between the two drugs in clinical effectiveness, colectomy rates, incidence of SAEs or reactions, or mortality.

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Contributions of authors

All 13 authors contributed to design and data collection or analysis and interpretation, commented on successive drafts and approved the version to be published. More specifically:

John G Williams (Professor of Health Services Research and Consultant Gastroenterologist) was principal applicant and chief investigator of the trial. He wrote the first draft and co-ordinated the editing of the final report.

M Fasihul Alam (Health Economist and Modeller) contributed to analysing and interpreting the economic data and drafting this report, and led designing the cost-effectiveness modelling.

Laith Alrubaiy (Clinical Academic Trainee in Gastroenterology) contributed to the validation of the CUCQ and CUCQ+, screening and analysing AEs and drafting this report, in which he contributed in particular the first draft of the background and literature review.

Clare Clement (Qualitative Research Officer) collected and analysed qualitative data; she led the writing of the professional views.

David Cohen (Professor of Health Economics) was coapplicant and PI for health economics.

Michelle Grey (Data Manager) co-ordinated data collection.

Mike Hilton (service user) contributed to the design of the trial and drafting this report.

Hayley A Hutchings (Associate Professor) developed and validated the CUCQ and CUCQ+ analysis, led the MATRICS results and contributed to interpreting data and drafting this report.

Mirella Longo (Health Economist) contributed to analysing and interpreting the economic data, and drafting this report.

Jayne M Morgan (Information Scientist) was co-applicant and led the development and operational use of the data management system, GeneCIS.

Frances L Rapport (Professor of Qualitative Health Research) was coapplicant and the PI for the qualitative research.

Anne C Seagrove (Trial Manager/Research Officer) was co-applicant and trial manager; she contributed to developing and implementing the design and management of the trial. She also collected and analysed qualitative data, led the writing of the participant views and contributed to drafting and co-ordinating this report.

Alan Watkins (Senior Trials Statistician) was the trial statistician; he undertook primary statistical analysis and contributed to interpreting data and drafting this report.

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Publications and presentations

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Data sharing statement

All available data can be obtained from the corresponding author via e-mail to construct@swansea.ac.uk.

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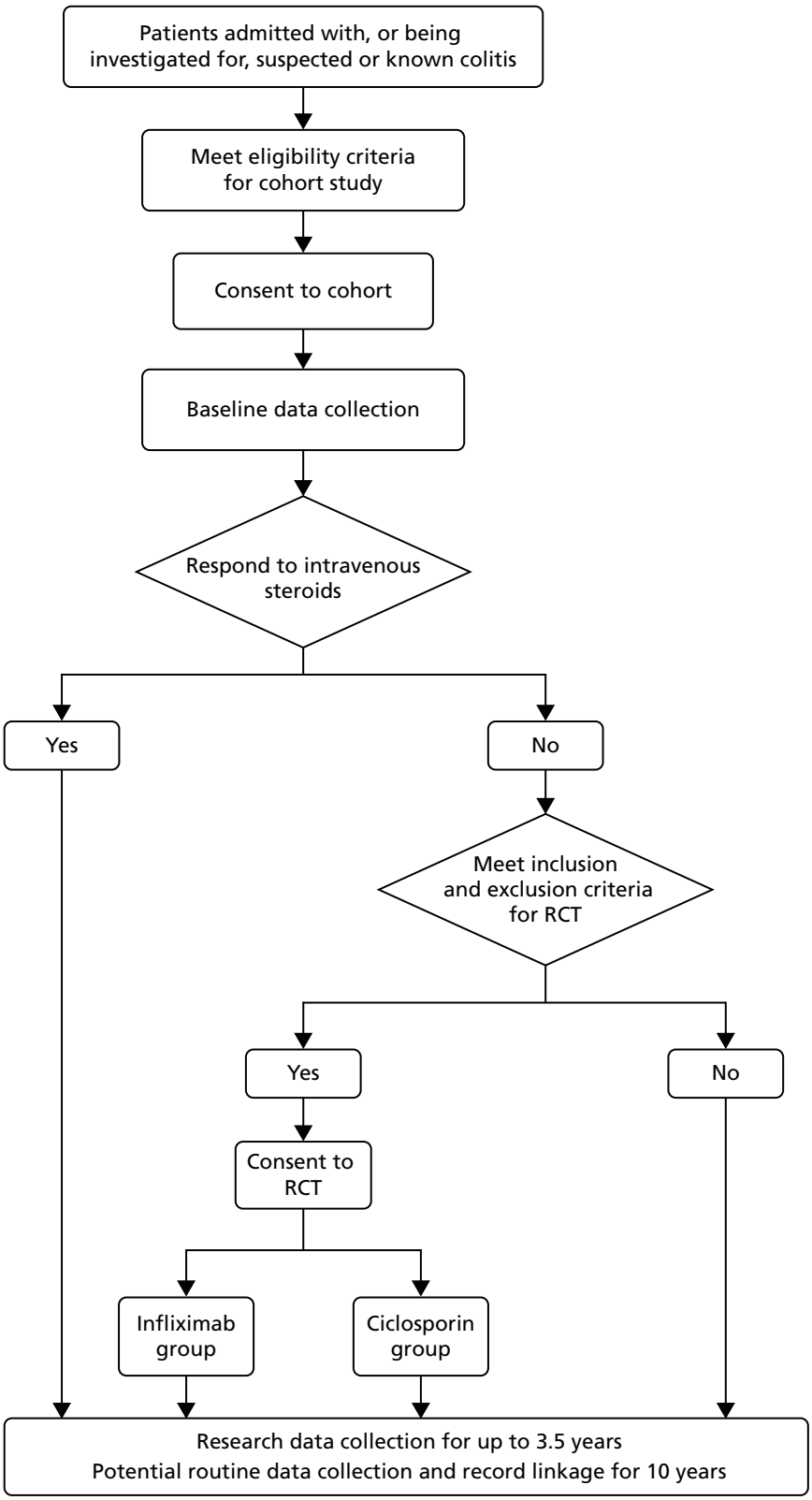
Appendix 1 CONSTRUCT flow chart



Appendix 2 Patient information sheet (cohort)

PATIENT INFORMATION SHEET (COHORT)

(Pt Info Cohort V13 10Oct2011.doc)

You have been admitted to hospital because you have bowel problems. This might be a new problem and you will have tests to find out what is causing this or it may be a flare-up of a disease that you already know about.

This information leaflet is about an important study that is doing research into inflammatory bowel diseases called ulcerative colitis and Crohn's disease. Specifically, it is looking into the long term effects ulcerative colitis has on people's quality of life. About 150,000 people in the UK have ulcerative colitis and it is one of the most important diseases seen by gastroenterologists.

We would like to invite you to take part in this research study. This leaflet gives you information about the study - please take time to read it carefully to decide whether or not you wish to take part. Your consultant or specialist nurse will talk to you about the study. Please talk to others, such as your family about it if you wish. Please ask if there is anything that is not clear or if you would like more information.

What is the purpose of the study?
We want to find out more about the progress of these conditions and the outcomes following treatment for the diseases. By taking part in this study, you will be helping us to learn more about ulcerative colitis and Crohn's disease and their treatment.

Why have I been invited?
We are inviting all patients admitted to hospital who might have ulcerative colitis or Crohn's disease, to take part.

Do I have to take part?
No. Your participation in this study is entirely voluntary. It is up to you to decide whether to take part or not. Even if you do decide to take part, you are free to leave the study at any time and without giving a reason. This will not affect your future medical care in any way. If you do decide to participate you will be given this information sheet to keep and be asked to sign a consent form.

What will happen to me if I take part?
If you agree to take part, we will first ask you to:

- Sign the consent form which is your indication that you understand the study and agree to take part.
- Complete a questionnaire that will include questions about your health, feelings and quality of life and use of health services. The questionnaires take around 30 minutes to complete.
- If you are found to have inflammatory bowel disease you will stay in the study. If not, then you are not able to take part.
- In addition, we will follow your progress over 10 years, using hospital information about any investigations, treatment or surgery you may have.

If you are found to have ulcerative colitis rather than Crohn's disease, you will be treated over the next few days with drugs known as steroids (although both illnesses may be treated with steroids). Steroids work in the majority of cases of ulcerative colitis but not in all. If they do not make you better, surgery may be needed. There are also two powerful drug treatments that some hospitals use to try to treat the attack and avoid the need for surgery. We are comparing these two treatments in a clinical trial to see which is best. If steroids are not sufficiently effective in treating you, we will tell you more about this clinical trial to see if it would be suitable for you. Taking part in the first section of the study would not oblige you to take part in the treatment trial.

What will I have to do?
At the moment all we are asking you to do is to be part of the group of patients who will complete one questionnaire and whose progress will be followed over the next ten years.

Will my taking part in this study be kept confidential?
Yes. All information which is collected about you during the course of the research will be kept strictly confidential in accordance with ethical and legal practice and the Data Protection Act.

You will be given a unique study number and any data will be collected and stored with this number. Any personal identification will be stored separately from the data. The clinical team looking after you and the research team are the only people who will know specific personally identifiable information that would allow someone to identify you and contact you. Your personal information (name, date of birth, home postcode and NHS number) will not be revealed in any audit, study report or publication, at any time.

If you agree to take part your GP will be informed.
What will happen to the results of the research study?
The results of the study will be used to help doctors understand the progress and outcomes following treatment of inflammatory bowel disease.

Who is organising and funding research?
The study is being run by the College of Medicine at Swansea University in collaboration with the University of Glamorgan and Bangor University. The study is funded by the National Institute for Health Research Health Technology Assessment Programme.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by Wales Research Ethics Committee.

What happens when the research study stops?
As a patient with ulcerative colitis or Crohn's disease you will continue to be reviewed in the gastroenterology clinic so your follow up will be as normal.

What will happen if I don't want to carry on with the study?
You may withdraw your consent and discontinue your participation in this study at any time without the need to give us a reason. This would not in any way affect the normal standard of care you receive.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the Trial Manager, Anne Seagrove, XXXX or the Trial Administrator, Emma Riordan, XXXX, who will do their best to answer your questions.

For information regarding your treatment, you should speak to [PI details].

Appendix 3 Consent form (cohort)

CONSENT FORM (COHORT)
(Patient Consent Form Cohort V2-0 10Oct2011)

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

Title of Project: CONSTRUCT

Name of person taking consent:

	Please initial each box
1. I confirm that I have read and understand the information sheet dated 10 October 2011 Version 13 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes may be looked at by a research nurse, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to the research team holding personally identifiable information	
5. I agree that a copy of this Consent Form is sent to the CONSTRUCT Trial Office	
6. I agree to data being collected through the research computer	
7. I agree to the completion of a questionnaire	
8. I give my permission for my progress to be followed for up to ten years using information taken from my NHS records	
9. I agree to my GP being informed of my participation in the study	
10. I agree to aspects of my anonymised data being used for reports about the research	
11. I agree to take part in the above study	

Your name in capitals	Date	Signature

Name of person taking consent in capitals	Date	Signature

When completed, the original should be kept in the Trial Site File, a copy should be kept in the medical notes, a copy be given to the patient and one sent to the CONSTRUCT Trial Office.

Appendix 4 Patient information sheet (randomised controlled trial)

PATIENT INFORMATION SHEET (RCT)
(Patient Info RCT V18 10Oct2011)

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

About 150,000 people in the UK have ulcerative colitis and it is one of the most important diseases seen by gastroenterologists. CONSTRUCT is an important study set up to improve the treatment of ulcerative colitis.

We would like to invite you to take part in this research study. We appreciate that you are not feeling well at the moment but before you decide you need to understand why the research is being done and what your involvement would be. This leaflet gives you information about the study - please take time to read it carefully to decide whether or not you wish to take part. Your consultant or specialist nurse will talk to you about the study. Please talk to others, such as your family about it if you wish. Please ask if there is anything that is not clear or if you would like more information.

What is the purpose of the study?
Patients with ulcerative colitis that is resistant to steroid treatment may need to change to a different treatment or require surgery. Two treatments are available for treatment in these circumstances infliximab (which would be prescribed as Remicade) and ciclosporin (which would be prescribed as Sandimmun/Neoral). These drugs are often an effective treatment in the short term but we don't know which is best and there is little information about their longer term effects on health and quality of life.

To help doctors recommend the best drug treatment for patients we want to find out how effective these drugs are for patients in the long term and understand if one drug is more effective than the other. By taking part in this study, you will be helping doctors to decide which drug they should recommend.

Why have I been invited?
You have been diagnosed with ulcerative colitis and are being treated as an inpatient in a hospital that is taking part in this study of people with your condition. Your ulcerative colitis has not responded adequately to steroids and you now need additional treatment.

Do I have to take part?
No. Your participation in this study is entirely voluntary. It is up to you to decide whether to take part. If you decide to take part, you are free to leave the study at any time and without giving a reason. This will not affect your medical care in any way. If you decide to participate you will be given this information sheet to keep and be asked to sign a consent form.

What will happen to me if I take part?

- If you agree to take part, we will first ask you to sign a consent form which is your indication that you understand the study and agree to take part.
- You will be treated with either infliximab or ciclosporin. The treatment will be chosen randomly (by chance) by a computer
- You will have an equal chance of receiving either infliximab or ciclosporin. You will know which drug you are being given. Whichever drug is chosen for you, it will be given to you in the same way that it would be given if you were not taking part in the study.
- If you are given infliximab this will be given into a vein via a drip. If you are given ciclosporin, the initial treatment is given into a vein, with further doses given in capsule form.
- Infliximab will be given at 0, 2 and 6 weeks, unless there is any problem. Because it is an antibody it normally stays in the body for 6-8 weeks. Ciclosporin will be given for 12 weeks, unless there is any problem. Because it is not long-lasting in the body, it is given every day.
- No normal treatment will be withheld whilst you take part in the study.

- It is important that you realise that treatment is not always effective. If the trial treatment doesn't make you better, you are likely to need surgery. There are no other medical treatments that have been shown to be effective in this situation.
- If you agree to take part we will ask you to complete a questionnaire, if you have not already done so. This needs to be done before you receive the trial drug treatment. The questionnaires will include questions about your health, feelings and quality of life and use of health services and take around 30 minutes to complete.
- We will ask you to complete further questionnaires at three, six, 12. 18 and 24 months after your treatment followed by one questionnaire a year over the next eight years. The questionnaires take around 30 minutes to complete. These questionnaires may be completed on a computer with the help of a nurse when you attend for follow up appointments so you will not be required to make additional visits to the hospital.
- If a questionnaire cannot be completed at the hospital, we will telephone you to make arrangements to complete it, possibly over the phone.
- If you agree to take part and then require an operation on your bowel, we will also ask you to complete questionnaires when you are discharged from hospital after your operation and then monthly for 3 months.
- In addition, we will follow your progress over 10 years, using hospital information about any investigations, treatment or surgery you may have.
- You will also be giving permission for us to have copies of the results of the blood tests you will have done as part of your normal care. This includes the tests done while you are an inpatient and the tests that will be done after you have been discharged from hospital at three, six, 12, 18 and 24 months after your treatment. These tests should be done at your routine follow up appointments so we will not be asking you to make additional hospital visits or have additional blood tests. The blood tests over the two years will show us how inactive or active your ulcerative colitis is and the questionnaires will allow us to see how your quality of life and general health changes following the drug treatment
- A sample of patients will be asked to take part in a telephone interview with a researcher three months and twelve months after treatment to find out their views about the treatment and progress. These interviews will be recorded and typed up but will be stored under a number so it will not be possible to identify you. You will be given the opportunity to indicate whether you agree to this when you complete the consent form.

What will I have to do?
You will be expected to take the medication as directed by your doctors and they will advise you on whether you can continue to take other medication or other prescribed or over-the-counter drugs and whether you will need to make any changes to your diet.

You might already be or have recently been involved in another drug study. If this is the case, you cannot participate in this study.

When you are discharged from hospital, you will be attending for outpatient appointments as part of your normal clinical care and we are not asking you to make additional visits but would urge you to keep your scheduled hospital appointments.

An important part of this study is the information we gain from the questionnaires that you complete so we do ask that you complete all the questionnaires so that we have a complete set of data for you.

What is the drug that is being tested?
The two drugs that are being studied are infliximab and ciclosporin. These are not new drugs. The drugs are already used to treat patients with your condition but we do not yet know which is better, or the long term effects of either drug.

The drugs will be given to you in the same way as they would if you were not taking part in the study. Both drugs will initially be given via a drip into one of your veins. Sometimes further doses of the drugs will be given.

What are the alternatives for treatment?
For patients with ulcerative colitis who have become resistant to treatment with steroids, advanced medical therapies are required and the two drugs that we are studying are available for the treatment of this condition. The only other treatment available is surgery and this is usually only undertaken if patients fail to respond to the advanced medical therapies.

What are the possible disadvantages and risks of taking part?
There are no additional risks associated with taking part in this trial as you would be prescribed one of the two drugs whether or not you take part in the trial.

What are the side effects of any treatment received when taking part?
Like all medicines infliximab and ciclosporin sometimes cause side effects in some people. Please remember that when you first receive the treatment you will be an inpatient and will be monitored closely by the specialist team looking after you.

You should be aware that the following side effects have been reported:

Infliximab
Most side effects are mild to moderate. However some may be serious and may require treatment. Side effects may appear up to six months after the last treatment.

Up to 10% (one in 10) people have experienced: Headache, dizziness, nausea, abdominal symptoms, allergic reactions, rash, urticaria, viral infections (for example herpes), respiratory infections (cold, sinus infections, bronchitis, pneumonia).

Up to 1% (one in 100) people have experienced: Depression, agitation, sleep disturbances, impaired wound heeling, bacterial infections, (for example tuberculosis, urinary tract infections, deep skin infections, sepsis), fungal infections, asthma, abnormal liver function, low blood cell counts including anemia, worsening of demyelinating nerve disease, autoimmune disease activation (SLE, lupus), worsening of heart failure, hair loss, bleedings, allergic anaphylactic reactions, injection site reactions.

Less than 0.1% (one in 1000) people have experienced: Gastrointestinal bleedings or perforation, circulatory failure, multiple sclerosis, lymphoma.

Ciclosporin
Most side effects are mild to moderate. However some may be serious and may require treatment.

More than 10% of people have experienced: Kidney problems, high blood pressure, headache, tremor and increased levels of lipids (for example cholesterol) in the blood.

Up to 10% of (one in 10) people have experienced: Numbness or tingling, loss of appetite, feeling or being sick, stomach pain, diarrhoea, swollen gums, liver problems, high level of uric acid or potassium in the blood, low levels of magnesium in the blood, muscle pain or cramp, increased hair growth on the body and tiredness.

Up to 1% of people (one in 100) have experienced: Seizures, confusion, disorientation, decreased responsiveness, agitation, sleeplessness, visual disturbances, blindness, coma, partial paralysis, loss of co-ordination, changes in blood (for example anaemia), allergic rash, water retention which may cause swelling and weight increase.

Up to 0.1% of people (one in 1000) have experienced: Problems with the nerves that control muscles, inflammation of the pancreas, high levels of glucose in the blood, muscle weakness, wasting of muscles, destruction of red blood cells which may be associated with kidney problems, changes in the menstrual cycle in women and slight enlarging of the breasts in men.

Up to 1 in 10,000 people have experienced: Swelling at the back of the eye which may be associated with an increase in pressure inside the head (benign intracranial hypertension) and visual disturbances.

Like other medicines that dampen down the immune system ciclosporin may cause tumours or other malignancies, particularly of the skin. It may also make you more likely to get infections which may be serious.

What are the possible benefits of taking part?
You will be receiving one of the two drugs as part of your treatment and by taking part in the trial you will be helping to identify which of the two drugs is the most effective treatment for people with your condition. This means that if you need this type of treatment in the future, your doctors will be better informed about which of the two drugs to give you.

What happens when the research study stops?
As a patient with ulcerative colitis you will continue to be reviewed in the gastroenterology clinic so your follow up will be as normal.

What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You may withdraw your consent and discontinue your participation in this study at any time without the need to give us a reason. This would not in any way affect the normal standard of care you receive.

What if there is a problem?

Complaints
If you have a concern about any aspect of this study, you should ask to speak to the local research team who will do their best to answer your questions. Alternatively you may wish to contact the coordination team in Swansea (Trial Manager Anne Seagrove, XXXX or Professor John G Williams, XXXX Trial Secretary, Emma Riordan, XXXX).

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from [details]

Harm

Non-negligent harm: As sponsor of this trial, Swansea University have insurance should you suffer non-negligent harm.
Negligent harm: As sponsor of this trial, Swansea University have insurance should you suffer negligent harm.

NHS based research
In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?
Yes. All information which is collected about you during the course of the research will be kept strictly confidential in accordance with ethical and legal practice and the Data Protection Act.

You will have a unique trial number and any data will be collected and stored with this number. Any personal identification will be stored separately from the data. The clinical team looking after you and the research team are the only people who will know specific personally identifiable information that would allow someone to identify you and contact you.

If you agree to take part your GP will be informed. If you do not want your GP to be informed you can indicate this on the consent form.

What will happen to any samples I give?
Any samples you give will be part of your routine clinical care and will therefore be dealt with as normal in the hospital. We will be given copies of the results by your hospital doctor.

Will any genetic tests be done?
No genetic tests will be done as part of this study.

What will happen to the results of the research study?
The results of the study will be used to help doctors choose the best treatment for patients with steroid resistant ulcerative colitis. Your personal information (name, date of birth, home postcode and NHS number) will not be revealed in any audit, study report or publication, at any time.

You will be asked if you would like to receive a summary of the results of the research.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed approved by Wales Research Ethics Committee.

The study has also been given Clinical Trial Authorisation by the Medicine and Healthcare Products Regulatory Agency (MHRA) and permission from the hospital's Local Research Ethics Committee and Research and Development Office.

Who is organising and funding research?
The study is being run by the College of Medicine at Swansea University in collaboration with the University of Glamorgan and Bangor University. The study is funded by the National Institute for Health Research Health Technology Assessment Programme.

What happens when the research study stops?
As a patient with ulcerative colitis you will continue to be reviewed in the gastroenterology clinic so your follow up will be as normal.

What will happen if I don't want to carry on with the study?
You may withdraw your consent and discontinue your participation in this study at any time without the need to give us a reason. This would not in any way affect the normal standard of care you receive.

Appendix 5 Consent form (randomised controlled trial)

CONSENT FORM (RCT)
(Patient Consent RCT V2-0 10Oct2011)

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

Title of Project: CONSTRUCT

Name of person taking consent:

	Please initial each box
1. I confirm that I have read and understand the information sheet dated 10 October 2011 Version 18 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes may be looked at by a research nurse, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to the research team holding personally identifiable information	
5. I agree that a copy of this Consent Form is sent to the CONSTRUCT Trial Office	
6. I agree to the random selection of my drug treatment	
7. If I am a woman of child-bearing potential, I agree to use adequate contraception during treatment and for 6 months afterwards if given Remicade.	
8. I agree to data being collected through the research computer	
9. I agree to the completion of questionnaires for two years	
10. I agree to complete an annual questionnaire and my progress being followed for a further eight years using information taken from my NHS records	
11. I agree to my GP being informed of my participation in the study	
12. I agree to aspects of my anonymised data being used for reports about the research	
13. I agree to take part in the above study	
14. I agree, if requested, to take part in two telephone interviews (optional)	
15. I agree to the telephone interviews being audio recorded (optional)	

Your name in capitals	Date	Signature

Name of person taking consent in capitals	Date	Signature

When completed, the original should be kept in the Trial Site File, a copy should be given to the patient, one kept in the medical notes and one sent to the CONSTRUCT Trial Office.

Appendix 6 Adverse event screening form

construct
building the evidence

EudraCT Number: 2008-001968-36 **FAX : 01792 606599 Email: CONSTRUCTHelpdesk@swansea.ac.uk**

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	***PTO 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)		Seriousness of event	
☐	Not related	☐	Resulted in death
☐	Unlikely to be related	☐	Is/was life threatening
☐	Possibly related	☐	Resulted in disability / incapacity
☐	Probably related	☐	Required hospitalisation / prolonged hospital stay
☐	Definitely related	☐	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)		Seriousness of event	
☐	1) Not related	☐	**1) Resulted in death**
☐	2) Unlikely to be related	☐	**2) Is/was life threatening**
☐	**3) Possibly related**	☐	**3) Resulted in disability / incapacity**
☐	**4) Probably related**	☐	**4) Required hospitalisation / prolonged hospital stay**
☐	**5) Definitely related**	☐	**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.

Appendix 7 Summary of data to be collected and source

Summary of data to be collected and source of data

	Initial inpatient stay	3.5-year designed research data collection and record linkage									Potential annual follow-up (years 3.5–10)	
Type of data	RCT and 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	
Mortality		O/R	O/R	O/R	O/R	O/R	O/R	O/R	R	R	R	R
Readmissions		O/R	O/R	O/R	O/R	O/R	O/R	O/R	R	R	R	R
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 (excluding drugs[a])	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										

O, operational clinical data extracted from hospital records; P, data collected by research professionals direct from patient (patient data collected at specified time points); R, routinely collected data (Hospital Episode Statistics, Office for National Statistics, Patient Episode Database Wales, standardised mortality ratio), operational and routine data collected at specific time points indicated but cover period since last data collection.

a All drugs included under 'other NHS costs' even if dispensed in hospital.

Source: CONSTRUCT Protocol V3–3 31 March 2012.

Appendix 8 Participant Baseline Questionnaire

Participant Baseline Questionnaire

(v9-0 22Mar2012)

CONSTRUCT

Swansea University College of Medicine, Singleton Park, Swansea SA2 8PP

Phone: +44(0)1792 513411/513405 **Fax: +44 (0)1792 606599**

Email: construct@swansea.ac.uk

Thank you for agreeing to participate in this study. The answers you give for this questionnaire will help us to find out whether the treatments you receive are helpful for your condition.

The information you provide will be completely confidential and will not be accessible by any third parties.

Please answer all the questions. Although it may seem that some questions are asked more than once, it is still important that you answer every one.

If you find it difficult to answer a question, please do the best you can. If you are unsure what the question is asking, please ask the research nurse to explain it.

Please follow the instructions for each section of the questionnaire carefully as the sections ask you to think back about different periods of time.

Date questionnaire started:	*d*	*d*	*m*	*m*	*y*	*y*	*y*	*y*
Time questionnaire started:	*h*	*h*	*m*	*m*	*(using 24h clock)*			
Date questionnaire completed:	*d*	*d*	*m*	*m*	*y*	*y*	*y*	*y*
Time questionnaire completed:	*h*	*h*	*m*	*m*	*(using 24h clock)*			
Patient initials:								

For completion by the researcher only

Name of researcher completing this questionnaire: _____

Has the patient completed the questionnaire without you being present?

- ☐ Yes in full
- ☐ Yes in part
- ☐ No

Section A: Crohn's and Colitis Questionnaire (CCQ)

The following questions ask for your views about your bowel problem and how it has affected your life over the **last two weeks**.

Please answer **all the questions**. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

If you **do not wish to answer a question,** please leave it blank and complete **page 9** with details of the question and reason(s) why it was not answered.

---

1. On how many days over the last **two weeks** have you had loose or runny bowel movements?

   ☐ days

2. On how many days in the last **two weeks** have you noticed blood in your stools?

   ☐ days

3. On how many days over the last **two weeks** have you felt tired?

   ☐ days

4. In the last **two weeks** have you felt frustrated?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

5. In the last **two weeks**, has your bowel condition prevented you from carrying out your work or other normal activities?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

6. On how many days over the last **two weeks** have you opened your bowels more than three times a day?

   ☐ days

7. On how many days over the last **two weeks** have you felt full of energy?

   ☐ days

8. In the last **two weeks** did your bowel condition prevent you from going out socially?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

9. On how many days over the last **two weeks** have your bowels opened accidentally?

   ☐ days

10. On how many days over the last **two weeks** have you felt generally unwell?

    ☐ days

11. In the last **two weeks** have you felt the need to keep close to a toilet?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

12. In the last **two weeks**, has your bowel condition affected your leisure or sports activities?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

13. On how many days over the last **two weeks** have you felt pain in your abdomen?

[ ] days

14. On how many nights over the last **two weeks** have you been unable to sleep well (days if you are a shift worker)?

[ ] nights (or days)

15. On how many nights in the last **two weeks** have you had to get up to use the toilet because of your bowel condition after you have gone to bed?

[ ] nights

16. In the last **two weeks** have you felt depressed?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

17. In the last **two weeks** have you had to avoid attending events where there was no toilet close at hand?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

18. On how many days over the last **two weeks**, have you had a problem with large amounts of wind?

[ ] days

19. On how many days over the last **two weeks** have you felt off your food?

[ ] days

20. Many patients with bowel problems have worries about their illness. How often during the last **two weeks** have you felt worried?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

21. On how many days over the last **two weeks** has your abdomen felt bloated?

    ☐ days

22. In the last **two weeks** have you felt relaxed?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

23. In the last **two weeks** have you been embarrassed by your bowel problem?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

24. On how many days over the last **two weeks** have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?

    ☐ days

25. In the last **two weeks** have you felt upset?

    a) No, not at all
    b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

26. On how many days over the last **two weeks** have you had to rush to the toilet?

☐ days

27. In the last **two weeks** have you felt angry as a result of your bowel problem?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

28. In the last **two weeks**, has your sex life been affected by your bowel problem?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

29. On how many days over the last **two weeks** have you felt sick?

☐ days

30. In the last **two weeks** have you felt irritable?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

31. In the last **two weeks** have you felt lack of sympathy from others?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

32. In the last **two weeks** have you felt happy?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

If you did not complete any of these questions, please record the question number(s) below and, if possible, give a reason why it was not completed.

Question N°	Reason for non-completion

Section B: 3 month Health Status

Please circle which one of the five statements below best describes the effect of your bowel condition over the last **three months**?

1	2	3	4	5
Unwell all of the time	Unwell most of the time	Unwell about half of the time	Well most of the time	Well all of the time

Section C: SF-12

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please tick the **one box** that best describes your answer.

1. **In general**, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Moderate activities, such as moving a table, pushing a vacuum cleaner, or playing golf	☐	☐	☐
b) Climbing several flights of stairs	☐	☐	☐

3. During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	☐	☐	☐	☐	☐
b) Were limited in the kind of work or other Activities	☐	☐	☐	☐	☐

4. During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	☐	☐	☐	☐	☐
b) Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

5. During the past **4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

6. These questions are about how you feel and how things have been with you during the past **4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past **4 weeks**…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
b) Did you have lots of energy?	☐	☐	☐	☐	☐
c) Have you felt downhearted and low?	☐	☐	☐	☐	☐

7. During the past **4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Section D: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today**.

Mobility

I have no problems in walking about	❑ A
I have some problems in walking about	❑ B
I am confined to bed	❑ C

Self-Care

I have no problems with self-care	❑ A
I have some problems washing or dressing myself	❑ B
I am unable to wash or dress myself	❑ C

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	❑ A
I have some problems with performing my usual activities	❑ B
I am unable to perform my usual activities	❑ C

Pain/Discomfort

I have no pain or discomfort	❑ A
I have moderate pain or discomfort	❑ B
I have extreme pain or discomfort	❑ C

Anxiety/Depression

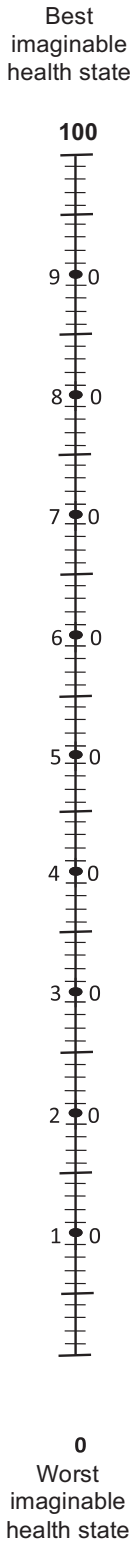
I am not anxious or depressed	❑ A
I am moderately anxious or depressed	❑ B
I am extremely anxious or depressed	❑ C

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Office use only:

Health state indicated *(whole number between 0 and 100).*

Section E: Resource use questionnaire

This section is about the health care you have received – **apart from any services at the hospital where you were recruited.**

All questions refer to the **three months before your admission for this episode**.

We would like to know about contacts you have had with health professionals in the last three months **for any reason - not just with regard to your bowel condition**.

Please ensure that if you tick "Yes", that you also enter the number of times alongside the corresponding healthcare professional. Where there is no number written in a box, we will assume that the answer is zero.

---

1. In the last **3 months**, have you been seen for any reason by any of the following **at your GP surgery?**

   - *Your own or another GP*
   - *Nurse*
   - *Any other health professional (e.g. dietician, physiotherapist, health visitor)*

   No ☐ ***Please go to Question 2***

   Yes ☐ Please enter the number of times for…

   - Your own or another GP ☐
   - Nurse ☐
   - Other (please specify) ☐

   _____

2. In the last **3 months**, have you been seen for any reason by any of the following **at home?**

   - *Your own or another GP*
   - *Nurse*
   - *Any other health professional (e.g. dietician, physiotherapist, health visitor)*

   No ☐ ***Please go to Question 3***

   Yes ☐ Please enter the number of times for…

   - Your own or another GP ☐
   - Nurse ☐
   - Other (please specify) ☐

   _____

3. In the last **3 months,** have you had a **telephone** discussion with any of the following **about any health issue** (NOT just to make or change appointments)?

   - *With anyone at your GP surgery*
   - *With anyone at any hospital*
   - *With NHS Direct (NHS 24 if in Scotland)*
   - *With a health professional at another location*

No ☐ ***Please go to Question 4***

Yes ☐ Please enter the number of times….

- *With anyone at your GP surgery* ☐
- *With anyone at any hospital* ☐
- *With NHS Direct / NHS 24* ☐
- *With a health professional at another location* ☐

(Please specify) _____

4. In the last **3 months**, have you visited an accident and emergency (A&E) department **other than** at the hospital where you were recruited to the study?

No ☐ ***Please go to Question 5***

Yes ☐ Please enter the number of times you visited another A&E ☐

5. In the last **3 months**, have you been admitted as an in-patient (i.e. stayed overnight in hospital) for any reason at a hospital **other than** at the hospital where you were recruited to the study?

No ☐ ***Please go to Question 6***

Yes ☐ Please enter the number of **nights** you spent in hospital ☐

6. If **you are in work**, did you take any time off work *either* due to illness *or* in order to see any health professional, for any reason, in the last **3 months**? *If you do not work, select "No".*

No ☐ ***Please go to Section F***

Yes ☐ Please enter the number of day (to the nearest **half day**) ☐

Section F: Drugs use questionnaire

Section F concerns **ONLY prescribed drugs taken regularly in the three months prior to the admission.**

Please do NOT include any of the following

1) drugs purchased without a prescription,

2) drugs given as an inpatient at the study centre during the admission

3) drugs which were prescribed to be taken on an "as required" basis.

Please give details of how each drug was **INTENDED** to be taken (i.e. the prescription details), rather than how it **WAS** taken.

Have you been given a **prescription** for any of the following drugs in the last **three months**? *If so, please record the strength of each tablet, the number to be taken per dose and the dose frequency. If the course was less than 3 months, please record the number of days it was prescribed for.*

Drugs for colitis *(listed in alphabetical order)*

Name of Drug	Strength of each tablet	Number taken per dose	Dose frequency	Duration (days) if short course
Asacol MR				
Azathioprine				
Budenofalk				
Codeine phosphate				
Colazide				
Dipentum				
Entocort				

Continued overleaf

Name of Drug	Strength of each tablet	Number taken per dose	Dose frequency	Duration (days) if short course
Imodium				
Lomotil				
Mercaptopurine				
Mesavant XL				
Methotrexate				
Pentasa				
Prednisolone by mouth*				
Salazopyrin				
Salofalk				
Tacrolimus				

*For oral prednisolone with reducing dose, please provide details below.

Suppositories for colitis

Have you been given a prescription for any of the following suppositories in the last **three months**? *If so, please record the strength of each tablet, the number to be taken per dose and the dose frequency. If the course was less than 3 months, please record the number of days it was prescribed for.*

Name of Suppository	Strength	Number taken per dose	Dose frequency	Duration (days) if short course
Asacol				
Pentasa				
Salofalk				
Predsol				

Enemas for colitis

Have you been given a prescription for any of the following **prescribed** enemas in the last **three months**? *If so, please state how many you were prescribed.*

Asacol _____

Colifoam _____

Pentasa _____

Predenema _____

Predfoam _____

Predsol _____

Salofalk _____

Medication for general GI disorders

Have you been given a prescription for any of the following **prescribed** drugs in the last **three months**?

If so, please record the strength of each tablet, the number to be taken per dose and the dose frequency. If the course was less than 3 months, please record the number of days it was prescribed for.

Name of Drug	Strength of each tablet	Number to be taken per dose	Dose frequency	Duration (days) if short course
Axid (Nizatidine)				
Buscopan (Hyoscine)				
Colofac (Mebeverine)				
Colpermin (Peppermint oil)				
Fybogel (Ispaghula husk)				
Maxolon (Metoclopramide)				
Merbentyl (Dicycloverine)				
Motilium (Domperidone)				
Nexium (Esomeprazole)				
Losec (Omeprazole)				
Pariet (Rabeprazole)				
Pepcid (Famotodine)				
Protium (Pantoprazole)				
Questran (Colestyramine)				
Spasmonal (Alverine)				
Tagamet (Cimetidine)				
Zantac (Ranitidine)				
Zoton (Lansoprazole)				

Medication not listed

Have you been **given a prescription** for any other drugs in the **three months** prior to your admission that have not been listed here such as antibiotics or drugs for any health condition, not just your bowel condition.

If so, please enter the details of the drug(s) in the table below.

REMEMBER - do not include:

1) any drugs purchased without prescription
2) drugs which were prescribed to be taken on an "as required" basis.

Please give details of how each drug was **INTENDED** to be taken (i.e. the prescription details), rather than how it WAS taken.

Drug Name	Strength of each tablet	N° taken per dose	Dose frequency	Duration (days) if short course
e.g. amoxicillin	*500mg*	*1*	*3 times a day*	*7 days*

Please record any additional drugs or comments on the blank page overleaf.

Appendix 9 Participant Follow-Up Questionnaire

construct

building the evidence

Participant Follow up Questionnaire

(v3-0 22Mar2012)

Follow up interval (please tick one):	
3 month	
6 month	
12 month	
18 month	
24 month	
30 month	
36 month	

CONSTRUCT

Swansea University College of Medicine, Singleton Park, Swansea SA2 8PP

Phone: +44(0)1792 513411/513405 Fax: +44 (0)1792 606599

Email: construct@swansea.ac.uk

Thank you for agreeing to continue participating in this study. The answers you give for this questionnaire will help us to find out whether the treatments you receive are helpful for your condition. The information you provide will be completely confidential and will not be accessible by any third parties.

You may wish to complete this questionnaire prior to your appointment with the CONSTRUCT Research Professional. If you do, please do not complete it until **the day before your appointment**. If you cannot complete some of the questions, please ask the Research Professional for advice when you meet. They will help you with any queries you have. Alternatively, you may wish to bring the blank questionnaire with you to your appointment with the Research Professional and complete it with them.

Please answer all the questions. Although it may seem that some questions are asked more than once, it is still important that you answer every one. If you find it difficult to answer a question, please do the best you can. If you are unsure what the question is asking, please ask the research professional to explain it when you meet.

Please follow the instructions for each section of the questionnaire carefully as the sections ask you to think back about different periods of time.

If you have any queries about the questionnaire, please contact us on XXXX or email XXXX.

Date questionnaire started:	*d*	*d*	*m*	*m*	*y*	*y*	*y*	*y*	
Time questionnaire started:	*h*	*h*	*m*	*m*	*(using 24h clock)*				
Date questionnaire completed:	*d*	*d*	*m*	*m*	*y*	*y*	*y*	*y*	
Time questionnaire completed:	*h*	*h*	*m*	*m*	*(using 24h clock)*				
Patient initials:									

For completion by the research professional only

Name of researcher helping to complete this questionnaire: _____

Has the participant completed the questionnaire without you being present?

☐ Yes in full ☐ Yes in part ☐ No

Section A: Crohn's and Colitis Questionnaire (CCQ)

The following questions ask for your views about your bowel problem and how it has affected your life over the **last two weeks**.

The terms bowel problem or bowel condition refer to all aspects of your bowel illness and its related treatments. If you do not have a bowel, please answer using the "not applicable" response for questions 1, 2, 6, 9, 24 and 26.

Please answer **all the questions**. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

1. On how many days over the last **two weeks** have you had loose or runny bowel movements?

   ☐ days ☐ *Not Applicable*

2. On how many days in the last **two weeks** have you noticed blood in your stools?

   ☐ days ☐ *Not Applicable*

3. On how many days over the last **two weeks** have you felt tired?

   ☐ days

4. In the last **two weeks** have you felt frustrated?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

5. In the last **two weeks**, has your bowel condition prevented you from carrying out your work or other normal activities?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

6. On how many days over the last **two weeks** have you opened your bowels more than three times a day?

   ☐ days ☐ *Not Applicable*

7. On how many days over the last **two weeks** have you felt full of energy?

   ☐ days

8. In the last **two weeks** did your bowel condition prevent you from going out socially?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

9. On how many days over the last **two weeks** have your bowels opened accidentally?

   ☐ days ☐ *Not Applicable*

10. On how many days over the last **two weeks** have you felt generally unwell?

    ☐ days

11. In the last **two weeks** have you felt the need to keep close to a toilet?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

12. In the last **two weeks**, has your bowel condition affected your leisure or sports activities?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

13. On how many days over the last **two weeks** have you felt pain in your abdomen?

    ☐ days

14. On how many nights over the last **two weeks** have you been unable to sleep well (days if you are a shift worker)?

    ☐ nights (or days)

15. On how many nights in the last **two weeks** have you had to get up to use the toilet because of your bowel condition after you have gone to bed?

☐ nights

16. In the last **two weeks** have you felt depressed?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

17. In the last **two weeks** have you had to avoid attending events where there was no toilet close at hand?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

18. On how many days over the last **two weeks**, have you had a problem with large amounts of wind?

☐ days

19. On how many days over the last **two weeks** have you felt off your food?

☐ days

20. Many patients with bowel problems have worries about their illness. How often during the last **two weeks** have you felt worried?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

21. On how many days over the last **two weeks** has your abdomen felt bloated?

☐ days

22. In the last **two weeks** have you felt relaxed?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

23. In the last **two weeks** have you been embarrassed by your bowel problem?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

24. On how many days over the last **two weeks** have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?

    ☐ days ☐ *Not Applicable*

25. In the last **two weeks** have you felt upset?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

26. On how many days over the last **two weeks** have you had to rush to the toilet?

    ☐ days ☐ *Not Applicable*

27. In the last **two weeks** have you felt angry as a result of your bowel problem?

    a) No, not at all
    b) Yes, some of the time
    c) Yes, most of the time
    d) Yes, all of the time

28. In the last **two weeks**, has your sex life been affected by your bowel problem?

    a) No, not at all
    b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

29. On how many days over the last **two weeks** have you felt sick?

[ ] days

30. In the last **two weeks** have you felt irritable?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

31. In the last **two weeks** have you felt lack of sympathy from others?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

32. In the last **two weeks** have you felt happy?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

33. How has your quality of life changed since the last time you filled in a questionnaire? Please circle one of the five statements below:

1	**2**	**3**	**4**	**5**
Much better now	Somewhat better	About the same	Somewhat worse	Much worse

What date did you complete the last questionnaire?

d	*d*	*m*	*m*	*y*	*y*	*y*	*y*

Supplementary question

Do you have a stoma?

Yes Please continue with the questions below

No Please go straight to **Section B** on page 13

For patients with stoma

The following questions ask for your views about your **stoma** and how it has affected your life over the **last two weeks**.

Please choose only **one** answer for each of the questions. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

1 On how many days over the last **two weeks** have you been afraid that other people might hear your stoma?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

2 On how may days over the last **two weeks** have you been worried that other people might smell your stools?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

3 On how many days over the last **two weeks** have you been worried about possible leakage from your stoma bag?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

4 On how many days over the last **two weeks** have you had problems with care for your stoma?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

5 On how many days over the last **two weeks** have you found the skin around your stoma irritated?

a) None
b) On one or two days only

c) On three to seven days

d) On eight to fourteen days (i.e. more than every other day)

6 In the last **two weeks** have you felt embarrassed because of your stoma?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

7 In the last **two weeks** have you felt less complete because of your stoma?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

8 In the last **two weeks** have you felt less attractive as a result of your stoma?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

9 In the last **two weeks** have you felt less feminine / masculine as a result of your stoma?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

10 In the last **two weeks** have you been dissatisfied with your body as a result of your stoma?

a) No, not at all

b) Yes, some of the time

c) Yes, most of the time

d) Yes, all of the time

If you did not complete any of the questions asked so far, please record the question number(s) below and, if possible, give a reason why it was not completed.

Question N°	Reason for non-completion

Section B: 3 month Health Status

Please circle which one of the five statements below best describes the effect of your bowel condition over the last **three months**?

1	2	3	4	5
Unwell all of the time	Unwell most of the time	Unwell about half of the time	Well most of the time	Well all of the time

Section C: SF-12

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please tick the **one box** that best describes your answer.

8. **In general**, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

9. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Moderate activities, such as moving a table, pushing a vacuum cleaner, or playing golf	☐	☐	☐
b) Climbing several flights of stairs	☐	☐	☐

10. During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	☐	☐	☐	☐	☐
b) Were limited in the kind of work or other activities	☐	☐	☐	☐	☐

11. During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	☐	☐	☐	☐	☐
b) Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

12. During the past **4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

13. These questions are about how you feel and how things have been with you during the past **4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past **4 weeks**…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
b) Did you have lots of energy?	☐	☐	☐	☐	☐
c) Have you felt downhearted and low?	☐	☐	☐	☐	☐

14. During the past **4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Section D: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today**.

Mobility

I have no problems in walking about	❑ A
I have some problems in walking about	❑ B
I am confined to bed	❑ C

Self-Care

I have no problems with self-care	❑ A
I have some problems washing or dressing myself	❑ B
I am unable to wash or dress myself	❑ C

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	❑ A
I have some problems with performing my usual activities	❑ B
I am unable to perform my usual activities	❑ C

Pain/Discomfort

I have no pain or discomfort	❑ A
I have moderate pain or discomfort	❑ B
I have extreme pain or discomfort	❑ C

Anxiety/Depression

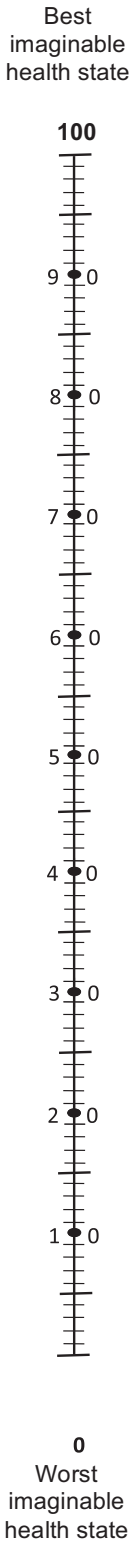
I am not anxious or depressed	❑ A
I am moderately anxious or depressed	❑ B
I am extremely anxious or depressed	❑ C

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Office use only:

Health state indicated *(whole number between 0 and 100).*

Section E: Resource use questionnaire

This section is about the health care you have received – **apart from any services at the hospital where you were recruited.**

All questions refer to the **three months before your follow up appointment.**

We would like to know about contacts you have had with health professionals in the **last three months for any reason - not just with regard to your bowel condition**.

Please ensure that if you tick "Yes", that you also enter the number of times alongside the corresponding healthcare professional. Where there is no number written in a box, we will assume that the answer is zero.

---

1. In the last **3 months**, have you been seen for any reason by any of the following **at your GP surgery?**

   - *Your own or another GP*
   - *Nurse*
   - *Any other health professional (e.g. dietician, physiotherapist, health visitor)*

   No ☐ ***Please go to Question 2***

   Yes ☐ Please enter the number of times for…

   - Your own or another GP ☐
   - Nurse ☐
   - Other (please specify) ☐

   _____

2. In the last **3 months**, have you been seen for any reason by any of the following **at home?**

   - *Your own or another GP*
   - *Nurse*
   - *Any other health professional (e.g. dietician, physiotherapist, health visitor)*

   No ☐ ***Please go to Question 3***

   Yes ☐ Please enter the number of times for…

   - Your own or another GP ☐
   - Nurse ☐
   - Other (please specify) ☐

   _____

4. In the last **3 months,** have you had a **telephone** discussion with any of the following **about any health issue** (NOT just to make or change appointments)?

   - *With anyone at your GP surgery*
   - *With anyone at any hospital*
   - *With NHS Direct (NHS 24 if in Scotland)*
   - *With a health professional at another location*

No ☐ ***Please go to Question 4***

Yes ☐ Please enter the number of times….

- *With anyone at your GP surgery* ☐
- *With anyone at any hospital* ☐
- *With NHS Direct / NHS 24* ☐
- *With a health professional at another location* ☐

(Please specify) _____

4. In the last **3 months**, have you visited an accident and emergency (A&E) department **other than** at the hospital where you were recruited to the study?

No ☐ ***Please go to Question 5***

Yes ☐ Please enter the number of times you visited another A&E ☐

5. In the last **3 months**, have you been admitted as an in-patient (i.e. stayed overnight in hospital) for any reason at a hospital **other than** at the hospital where you were recruited to the study?

No ☐ ***Please go to Question 6***

Yes ☐ Please enter the number of **nights** you spent in hospital ☐

6. If **you are in work**, did you take any time off work *either* due to illness *or* in order to see any health professional, for any reason, in the last **3 months**? *If you do not work, select "No".*

No ☐ ***Please go to Section F***

Yes ☐ Please enter the number of day (to the nearest **half day**) ☐

Section F: Drugs use questionnaire

Section F concerns **ONLY prescribed drugs taken regularly in the last three months.**

Please do NOT include any of the following

1) drugs purchased without a prescription,

2) drugs given as an inpatient at the study centre during an inpatient admission

3) drugs which were prescribed to be taken on an "as required" basis.

Please give details of how each drug was **INTENDED** to be taken (i.e. the prescription details), rather than how it **WAS** taken.

If you are unsure about how to answer this section, please leave it blank and complete it with the Research Professional during your study-related appointment. Please bring your drugs or prescriptions with you to help complete the tables.

Have you been given a **prescription** for any of the following drugs in the last **three months**? *If so, please record the strength of each tablet, the number to be taken per dose and the dose frequency. If the course was less than 3 months, please record the number of days it was prescribed for.*

Drugs for colitis *(listed in alphabetical order)*

Name of Drug	Strength of each tablet	Number taken per dose	Dose frequency	Duration (days) if short course
Asacol MR				
Azathioprine				
Budenofalk				
Codeine phosphate				
Colazide				
Dipentum				

Continued overleaf

Name of Drug	Strength of each tablet	Number taken per dose	Dose frequency	Duration (days) if short course
Entocort				
Imodium				
Lomotil				
Mercaptopurine				
Mesavant XL				
Methotrexate				
Pentasa				
Prednisolone by mouth*				
Salazopyrin				
Salofalk				
Tacrolimus				

*For oral prednisolone with reducing dose, please provide details below.

Suppositories for colitis

Have you been given a prescription for any of the following suppositories in the last **three months**? *If so, please record the strength of each tablet, the number to be taken per dose and the dose frequency. If the course was less than 3 months, please record the number of days it was prescribed for.*

Name of Suppository	Strength	Number taken per dose	Dose frequency	Duration (days) if short course
Asacol				
Pentasa				
Salofalk				
Predsol				

Enemas for colitis

Have you been given a prescription for any of the following **prescribed** enemas in the last **three months**? *If so, please state how many you were prescribed.*

Asacol _____

Colifoam _____

Pentasa _____

Predenema _____

Predfoam _____

Predsol _____

Salofalk _____

Medication for general GI disorders

Have you been given a prescription for any of the following **prescribed** drugs in the last **three months**?

If so, please record the strength of each tablet, the number to be taken per dose and the dose frequency. If the course was less than 3 months, please record the number of days it was prescribed for.

Name of Drug	Strength of each tablet	Number to be taken per dose	Dose frequency	Duration (days) if short course
Axid (Nizatidine)				
Buscopan (Hyoscine)				
Colofac (Mebeverine)				
Colpermin (Peppermint oil)				
Fybogel (Ispaghula husk)				
Maxolon (Metoclopramide)				
Merbentyl (Dicycloverine)				
Motilium (Domperidone)				
Nexium (Esomeprazole)				
Losec (Omeprazole)				
Pariet (Rabeprazole)				
Pepcid (Famotodine)				
Protium (Pantoprazole)				
Questran (Colestyramine)				
Spasmonal (Alverine)				
Tagamet (Cimetidine)				
Zantac (Ranitidine)				
Zoton (Lansoprazole)				

Medication not listed

Have you been **given a prescription** for any other drugs in the **three months** prior to your admission that have not been listed here such as antibiotics or drugs for any health condition, not just your bowel condition.

If so, please enter the details of the drug(s) in the table below.

REMEMBER - do not include:

1) any drugs purchased without prescription
2) drugs which were prescribed to be taken on an "as required" basis.

Please give details of how each drug was **INTENDED** to be taken (i.e. the prescription details), rather than how it WAS taken.

Drug Name	Strength of each tablet	N° taken per dose	Dose frequency	Duration (days) if short course
e.g. amoxicillin	*500mg*	*1*	*3 times a day*	*7 days*

Please record any additional drugs or comments on a blank page and attach it.

Section G: Participant-reported adverse events

a) Have you had any of the following diagnoses **since you were last seen by the Research Professional for your CONSTRUCT-related appointment**?

- If "Yes" is ticked, record the site(s) of the condition and the date(s) of the diagnosis.

- Please note that further information will be required to complete an Adverse Event (AE) Screening Form for that diagnosis. You will be asked for a brief description during your follow up appointment with the Research Professional.

Incidence of ….	No	Yes	Site(s) of condition (on the body)	Date of diagnosis
Colorectal malignancies				*d d m m y y y y*
				d d m m y y y y
Other gastrointestinal malignancies				*d d m m y y y y*
				d d m m y y y y
Non-gastrointestinal malignancies				*d d m m y y y y*
				d d m m y y y y
Pneumonia				*d d m m y y y y*
				d d m m y y y y
Abscesses				*d d m m y y y y*
				d d m m y y y y
Other serious bacterial infections				*d d m m y y y y*
				d d m m y y y y
Renal disorders				*d d m m y y y y*
				d d m m y y y y

Continued overleaf…

b) Have you experienced any **NEW** problems or symptoms **since you were last seen by the Research Professional** for your CONSTRUCT study-related appointment which was not listed on p25?

- **No** **The questionnaire is now complete.** Please record the date and time of completion on p3.
- **Yes** Please provide details of the new problem(s) / symptom(s) separately below

Start date *(dd/mm/yyyy)*	**End date (if appropriate)** [1] *(dd/mm/yyyy)*	**Brief description of the problem / symptom**

1 If condition is still present, please record “unresolved” in this column

Appendix 10 Cohort case report form

construct
building the evidence
www.construct.swansea.ac.uk

EudraCT Number: 2008-001968-36CONSTRUCTHelpdesk@swansea.ac.uk

Centre / Hospital Name

Participant study ID						

Please begin to complete this Case Report Form (CRF) once the participant has consented to the CONSTRUCT cohort study.

- The CRF should be completed using black ink and BLOCK CAPITALS.
- **Once Section 1 has been completed, it should be detached from the rest of the CRF, faxed separately from the rest of the CRF and stored in a secure location for data protection purposes.**
- **RCT eligibility criteria questions are written in bold. Those responses that make the participant ineligible for the RCT are in bold and have a [X].**
- Once each page has been completed, the person completing it should initial and sign their name and record the date of completion at the bottom of that page.
- Any amendments to the CRF should be done by crossing out the error **once**, initialling and dating that action. The new entry should be written in alongside as clearly as possible.
- If you have any queries relating to the completion of this CRF, please contact the CONSTRUCT Helpdesk by email on CONSTRUCTHelpdesk@swansea.ac.uk
- Please fax all pages in accordance with the instructions written on the relevant pages of this CRF to the CONSTRUCT Trial Office on 01792 606599.

Participant study ID							

Section 1a: Participant demographics

Title: ☐ Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Dr Other *(specify)*

Surname: _____

Forename(s): _____

Date of birth: d d m m y y y y ***NOT eligible for the RCT if <18y [X]***

Gender: ☐ Male ☐ Female

NHS N°: | | | | | | | | | | |

Hospital N°: | | | | | | | | | | |

Home address: _____

_____

Postcode: | | | | | | | | |

Tel. No: | 0 | | | | | | | | | | |

Ethnic group: ☐ White ☐ Mixed ☐ Black ☐ Any other ethnic group *(specify)* ☐ Asian _____

Section 1b: Participant's GP details

GP full name: _____ GP ID code: _____

Practice name: _____ GP Practice code: _____

Practice address: _____

_____

Practice postcode: | | | | | | | | |

Once Section 1 has been completed, detach it, fax it to the CONSTRUCT Trial Office on 01792 606599 and then store it in a secure location away from the rest of the CRF.

Section 2: Details of presenting complaint(s)

What are the relevant presenting complaints for this episode?

(Tick all appropriate responses)

☐	No relevant symptoms			
☐	Diarrhoea……	*If so, record stool frequency*	☐	*(per day)*
☐	Bloody diarrhoea……	*If so, record bloody stool frequency*	☐	*(per day)*
☐	Abdominal pain			
☐	Tiredness			
☐	Malaise (feeling unwell)			
☐	Weight loss			
☐	Other(s) *(specify)*			

_____

_____

_____

Duration of current symptoms for this episode? ☐ *(days)*

Section 3: Past medical & surgical history

3a – Inflammatory Bowel Disease (IBD) history

Has the participant been previously diagnosed with IBD?

☐ No **If No, go straight to Section 3b**

☐ Yes If Yes, please indicate which IBD was diagnosed and complete the sub-questions

☐ **Ulcerative colitis (UC)** (please answer sub-question a)

a) Extent of disease

- ☐ *E1 – Ulcerative proctitis (limited to rectum)*
- ☐ *E2 – Left sided UC (distal to splenic flexure)*
- ☐ *E3 – Extensive UC (extends proximal to splenic flexure)*
- ☐ *Unknown disease extent*

☐ **Crohn's disease** (please answer sub-questions a-e)

a) Age at diagnosis

- ☐ *Below 16 years old*
- ☐ *Between 17 and 40 years old*
- ☐ *Above 40 years old*
- ☐ *Unknown age at diagnosis*

b) Location of disease

- ☐ *Ileal Crohn's*
- ☐ *Colonic Crohn's*
- ☐ *Ileocolonic Crohn's*
- ☐ *Isolated upper GI disease*
- ☐ *Disease location unknown*

c) Is there a concomitant upper GI disease? ☐ *Yes* ☐ *No* ☐ *Unknown*

d) Disease behaviour

- ☐ *Non-stricturing, non-penetrating*
- ☐ *Stricturing*
- ☐ *Penetrating*

e) Is there a concomitant perianal disease? ☐ *Yes* ☐ *No* ☐ *Unknown*

☐ **Indeterminate colitis** (please answer sub-question a)

a) Extent of disease

- ☐ *Proctitis (limited to rectum)*
- ☐ *Left sided colitis (distal to splenic flexure)*
- ☐ *Extensive colitis (extends proximal to splenic flexure)*
- ☐ *Unknown disease extent*

☐ **Microscopic colitis**

☐ **Unknown type of IBD**

Date of diagnosis (*nearest month and year*):

m	m	y	y	y	y

3b – Drug history

Please tick to indicate which drug(s) the participant has been prescribed and how long ago it was last taken. Then record the month and year the drug was first prescribed.

*NOTE: PARTICIPANT IS **INELIGIBLE** FOR RCT IF ANY BOXES MARKED WITH **[X]** ARE TICKED*

Drugs list	***When drugs last taken***				***Date first prescribed***					
	Never prescribed	**In the past (but not last 3m)**	**In last 3m (but not currently)**	**Taken for current episode**						
Oral steroid therapy e.g. prednisolone				*	*m*	*m*	*y*	*y*	*y*	*y*
* Duration of current steroid treatment (*days*):										
Biological therapies e.g. Infliximab			*[X]*	*[X]*	*m*	*m*	*y*	*y*	*y*	*y*
Rosuvastatin (Crestor®)			*[X]*	*[X]*	*m*	*m*	*y*	*y*	*y*	*y*
Ciclosporin (Sandimmun®, Neoral®)			*[X]*	*[X]*	*m*	*m*	*y*	*y*	*y*	*y*
Tacrolimus (Prograf® / Fujimycin)			*[X]*	*[X]*	*m*	*m*	*y*	*y*	*y*	*y*
Azathioprine					*m*	*m*	*y*	*y*	*y*	*y*
Methotrexate					*m*	*m*	*y*	*y*	*y*	*y*
Mercaptopurine (6-MP / Puri-Nethol®)					*m*	*m*	*y*	*y*	*y*	*y*
Sulfazalazine					*m*	*m*	*y*	*y*	*y*	*y*
Mesalazine					*m*	*m*	*y*	*y*	*y*	*y*
Other aminosalicylate					*m*	*m*	*y*	*y*	*y*	*y*

(please specify) _____

3c – Drug allergies

Does the participant have a history of hypersensitivity to any of the following:

*NOTE: PARTICIPANT IS **INELIGIBLE** FOR RCT IF ANY BOXES MARKED WITH **[X]** ARE TICKED*

	Yes	No
Infliximab (Remicade®)	[X]	
Ciclosporin (Sandimmun® / Neoral® / Deximune®)	[X]	
Polyethoxylated oils	[X]	

3d – Co-morbidities

Please indicate which statement is correct by ticking the relevant box.

*NOTE: PARTICIPANT IS **INELIGIBLE** FOR RCT IF ANY BOXES MARKED WITH **[X]** ARE TICKED*

Ischaemic heart disease (IHD)		No history
		IHD but no recent MI
	[X]	**Acute MI in last month**
Heart failure		No history
	[X]	**Moderate / severe heart failure**
Cerebrovascular disease (CVD) & stroke		No history
		CVD but no acute stroke
	[X]	**Acute stroke within last month**
Respiratory disease		No history
		Chronic respiratory disease
	[X]	**Respiratory failure**
Renal disease		No history
		Chronic renal disease
	[X]	**Renal failure**
Hepatic (liver) disease		No history
		Chronic liver disease
	[X]	**Hepatic failure**
Immunodeficiency		No current diagnosis of immunodeficiency
	[X]	**Current diagnosis of immunodeficiency**
Active tuberculosis		No active / suspected active tuberculosis
	[X]	**Active / suspected active tuberculosis**
Severe infection		No severe infection

	[X]	**Severe infection present**
Malignancy		No current malignancy (excl. BCC)
	[X]	**Current malignancy diagnosed (not including BCC)**
Severe cognitive impairment		No
	[X]	**Severe cognitive impairment diagnosed**
Diabetes mellitus		No diagnosis of diabetes mellitus
		Type 1 diabetes mellitus
		Type 2 diabetes mellitus
		Other diabetes type e.g. LADA
		Diabetes type unknown
		Unknown whether participant has diabetes mellitus
Hypertension		No hypertension
		Participant has hypertension
		Unknown whether participant has hypertension
Hypercholesterolaemia requiring treatment		No hypercholesterolaemia requiring treatment
		Participant has hypercholesterolaemia requiring treatment
		Unknown whether participant has hypercholesterolaemia

3e – Previous surgical procedures

Please tick to indicate whether the participant has had any of the following **surgical** procedures? If they have, please record the year of surgery.

Procedures	**Unknown**	**No**	**Yes**	**If Yes, year of surgery**			
Colonic surgery				y	y	y	y
Small bowel surgery				y	y	y	y
Gastric surgery				y	y	y	y
Appendicectomy				y	y	y	y
Cholecystectomy				y	y	y	y
Open urological surgery				y	y	y	y
Open gynaecological surgery *				y	y	y	y

**Tick "No" if participant is male*

Section 4: Family & social history

4a – Family history

Does the participant have a **first degree relative** previously diagnosed with an IBD?

☐	No	***(If No, go to Section 4b)***
☐	Yes	If Yes, please complete below

Please indicate which diagnosis the parent(s) had by **ticking** in the relevant column.

Relationship	Ulcerative Colitis	Crohn's disease	Indeterminate colitis	Microscopic colitis	Unknown
Mother					
Father					

Please enter the **number** of siblings and children with a diagnosis of each IBD in the relevant column

Relationship	Ulcerative Colitis	Crohn's disease	Indeterminate colitis	Microscopic colitis	Unknown
Sibling(s)					
Child(ren)					

4b – Social history

For each question, please indicate which **ONE** statement is correct:

4b.i Participant's smoking status:

- ☐ Current smoker
- ☐ Ex-smoker
- ☐ Non-smoker (history unknown)
- ☐ Never smoked
- ☐ Unknown

4b.ii Pregnancy / lactation status:

Date of pregnancy test:	d	d	m	m	y	y	y	y

	Not applicable *(participant is female and menstruating / participant is female and post-menopausal / participant is male)*
	Participant not currently pregnant or lactating *(**MUST** be confirmed by negative pregnancy test if of child bearing age and to be considered for RCT)*
[X]	**Participant is currently pregnant** *(**MUST** be confirmed by pregnancy test wherever appropriate)*
[X]	**Participant is currently lactating and breastfeeding**

4b.iii Participant's participation in other clinical trials:

	Participant not in any other clinical trials
[X]	**Participant in another clinical trial(s)**

(If so, please specify which one(s))

_____

_____

_____

Section 5: Baseline clinical data

Please record test results that correspond closest to the **date of admission** for this episode.

Place a **cross** in the final column if the test was not done (routinely / on this occasion).

5a – Clinical measurements on admission

Measurement	Result		Test NOT done X
Weight	_____	*(Kg)*	
Height	_____	*(m)*	
Pulse	_____	*(bpm)*	
Temperature	_____	*(ºC)*	
Systolic blood pressure	_____	*(mm Hg)*	
Diastolic blood pressure	_____	*(mm Hg)*	

5b – blood results on admission

Haemoglobin	_____	(*g/dL*)	
Urea	_____	(*mmol/L*)	
Creatinine	_____	(*mmol/L*)	
Sodium	_____	(*mmol/L*)	
Potassium	_____	(*mmol/L*)	
Chloride	_____	(mmol/L)	
Bicarbonate	_____	(*mmol/L*)	
C-Reactive protein (CRP)	_____	(mg/L)	
Erythrocyte Sedimentation Rate (ESR)	_____	(mm/hr)	
Alanine transaminase (ALT)	_____	(*U/L*)	
Aspartate transaminase (AST)	_____	(*U/L*)	
Alkaline phosphatase (ALP)	_____	(*U/L*)	
Total bilirubin	_____	(*µmol/L*)	
Gamma glutamyl transpeptidase (GGT)	_____	(*U/L*)	
Albumin	_____	(*g/L*)	
Total cholesterol	_____	(*mmol/L*)	
Truelove & Witts score *(see overleaf)*	_____	**(range 0-4)**	
Glomerular Filtration Rate (GFR)	_____	*(mL/min/m^2)*	

Calculating the Truelove & Witts score - *1st stage T&W score to be calculated by determining if the patient had bloody stool frequency of 6 or more daily and any one of the following additional criteria:*

- *pulse >90 bpm;*
- *haemoglobin <10.5 g/dL;*

- *temperature >37.8°C;*
- *ESR >30 mm/hr **or** CRP > 30 mg/L.*

- *Count the number of additional criteria met by the patient (up to 4) and insert this number as their T&W score.*
- *If the patient **only** has a bloody stool frequency of more than 6 per day, **enter "0".***
- *If the patient does **not** have a bloody stool frequency of more than 6 per day, **enter "0".***

5c – Endoscopy performed

Was an endoscopy performed?

	Yes
	No If No, clinical judgement of disease severity:

	Severe colitis
[X]	**Not severe colitis**

Date of endoscopy:

d	d	m	m	y	y	y	y

Endoscopic findings:

[X]	**NORMAL or inactive disease (score = 0)**
[X]	**MILD: erythema, decreased vascularity, mild friability (score = 1)**
	MODERATE: marked erythema, absent vascularity, friability, erosions (score = 2)
	SEVERE: Spontaneous bleeding, ulceration (score = 3)

5d – Stool culture results

Please indicate which of the following statements is correct:

☐ Stool culture normal (negative for infection)

☐ Growth on stool *(see notes below)*

Date of stool culture results: | d | d | m | m | y | y | y | y |

Growth identified as:

- [X] **Campylobacter on stool culture**
- [X] **Salmonella on stool culture**
- [X] **Shigella on stool culture**
- ☐ C difficile
  - [X] **C difficile on stool culture**
  - ☐ C difficile on toxin ELISA *(see note #3 below)*
    - Number of positive toxin ELISA tests ☐
- [X] **Cytomegalovirus (CMV) on stool culture**
- [X] **Amoebiasis on stool culture**
- [X] **Unclassified / other infection (please specify)**

☐ Equivocal stool test result (please give details)

_____

_____

NOTES:

1) If the participant is proven to have infective colitis with NO evidence of any other IBD, they must be excluded from the cohort study by completing the **Cohort Exclusion Form**.

2) If the participant has infective colitis alongside another IBD, they may remain in the cohort.

3) A positive *C difficile* result on ELISA can be overridden by a clinical decision if the test is considered unreliable (see Section 5f). *C difficile* on stool culture excludes the patient from the RCT.

5e – Histology results

Please indicate which of the three following statements is correct:

	Histology not done – participant known to have ulcerative colitis (go to Section 5f)
[X]	**Histology reported as normal**
	Abnormalities reported on histology

Date of histology results:

d	d	m	m	y	y	y	y

Abnormality reported as:

	Ulcerative colitis
[X]	**Crohn's disease**
	Indeterminate colitis which is…

	Clinically ulcerative colitis
[X]	**Clinically Crohn's disease**

[X]	**Cytomegalovirus (CMV) colitis**
[X]	**Microscopic colitis**
[X]	**Other histology results (please specify)**

_____

5f – Clinical conclusion after all test results received

Conclusion:

	UC only – no other abnormal test results
	UC + results that do not exclude from RCT (e.g. C diff on ELISA)
[X]	**UC + <u>infection</u> that excludes from RCT**
[X]	**UC + <u>other cause of exclusion</u> from RCT (e.g. age <18y, pregnancy, etc)**
[X]	**Other IBD (not UC)**
[X]	**Infective colitis only**
[X]	**Other non-IBD diagnosis (specify)**

Please fax all pages completed so far to 01792 606599 as soon as possible.

Section 6: Progress (after 2 days IV steroid treatment)

NOTE: When entering data onto GeneCIS, Section 6 of the Cohort CRF: *Progress (after 2 days of IV steroids)* can be found on the separate questionnaire: '04 - Cohort Progress'

GeneCIS

After 2 days treatment with intravenous (IV) hydrocortisone, a decision should be made regarding the participant's response.

6a – Steroid treatment

6a.i Has IV hydrocortisone treatment been initiated at any point following admission?

[X] **No** ***Go to Section 6b***

[ ] Yes

Date IV steroid therapy initiated: *d d m m y y y y*

Time IV steroid therapy initiated: *h h m m* *(using 24h clock)*

Date of transfer from IV to oral steroids: *d d m m y y y y*

Date of decision regarding response to **IV** steroids: *d d m m y y y y*

6a.ii Participant's response to **IV** hydrocortisone treatment:

[X] **Good response within approx 2-5 days**

Truelove & Witts score on day 5 / at discharge (whichever is sooner): [ ]

[ ] Inadequate response within approx 2-5 days

Criteria for non-response decision:

[ ] Stool frequency >8 per day

[ ] Stool frequency of 3-8 per day with CRP > 45mg/L

[ ] Clinical judgement *(state basis for opinion)*

6b – Surgery

Is clinical judgement that the participant requires a colectomy without further medical treatment?

	No - COHORT CRF COMPLETED
[X]	**Yes**

Which type of surgery was performed:

	Panproctocolectomy
	Subtotal colectomy
	Ileoanal pouch with stoma
	Ileoanal pouch without stoma
	Formation of ileostomy
	Other surgical procedure (please state)

_____

Date of surgery:

d	d	m	m	y	y	y	y

You have now reached the end of the Cohort CRF.

Please fax all pages to the CONSTRUCT Trial Office on 01792 606599 as soon as possible.

If some information is outstanding, please record it as soon as possible and refax that page.

NOTE: If participant is still potentially eligible for the RCT at this point (i.e. no exclusion criteria [X] have been recorded on this Cohort CRF), please complete an **RCT Screening Form** using the responses to the eligibility questions on this CRF.

Appendix 11 Randomised controlled trial case report form

construct
building the evidence

www.construct.swansea.ac.uk **EudraCT Number:** 2008-001968-36 **Email:** CONSTRUCTHelpdesk@swansea.ac.uk

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

Study Centre Name (i.e. Trust / Health Board name)

Study Site Name (i.e. Hospital name)

Participant study ID						

Complete Sections 1 & 2 of this CRF 7 days prior to the participant's scheduled follow up appointment to assess the participant's eligibility for follow up and fax to the Trial Office.

Complete Sections 3 to 11 after the participant's routine follow up appointment for their ulcerative colitis approximately 3m after their trial treatment. These sections refer to the time from the date of randomisation/discharge up to and including the date of their 3m follow up appointment.

- Once each page has been completed, the person completing it should initial and sign their name and record the date of completion at the bottom of that page.
- **Section 10** relates to blood ciclosporin levels and should **only** be completed if the participant was randomised to receive Sandimmun®.
- Any amendments to the CRF should be done by crossing out the error **once**, initialling and dating that action. The new entry should be written in alongside as clearly as possible.
- If you have any queries relating to the completion of this CRF, please contact the CONSTRUCT Helpdesk by email on CONSTRUCTHelpdesk@swansea.ac.uk

Initials of person completing this page:		Signature		**Date** page completed:	

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

Please complete 7 days before the participant's routine 3m follow up appointment with the healthcare professional is due.

Section 1: Participant demographics - update

Please check whether any of the following information about the participant has changed **since the date of discharge**.

- If there is no change to existing data, tick "No".
- If information about the participant has changed, tick "Yes" and record the new details.

Field	No	Yes	Change to…
Title			
Surname			
Address			
Postcode			
Tel number			
GP name			
GP practice			

- If any of this section of the CRF has been completed with a "Yes", please **detach it and fax it separately** to the CONSTRUCT Trial Office.
- Section 1 must be filed separately in a secure place.

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

Please complete 7 days before the participant's routine 3m follow up appointment with the healthcare professional is due.

Section 2: Patient eligibility for follow up

2a) Details of death of participant

Has the participant died since the **date of discharge**?

☐ No (**Go to Section 2b**)

☐ Yes *(Please record date of death and also complete an **AE Screening Form** for the event leading to the death)*

Date of death: | *d* | *d* | *m* | *m* | *y* | *y* | *y* | *y* |

2b) Details of withdrawal of participant

Has the participant withdrawn from any aspect of the trial **since the date of discharge**?

☐ No (**Go to Section 3**)

☐ Yes *(Complete a **Participant Withdrawal Form*** and also complete below*)*

Which of the following has the participant withdrawn from? (Instructions for completion of follow up data collection forms are in brackets)

☐ **Access to medical records AND completion of participant questionnaires**

(3m RCT CRF - UP TO DATE OF WITHDRAWAL. Do not send PFQ)

☐ **Access to medical records only**

(3m RCT CRF - UP TO DATE OF WITHDRAWAL. PFQ can be sent)

☐ **Completion of participant questionnaires only**

(3m RCT CRF – complete in full. Do not send PFQ)

☐ **Completion of trial treatment only**

(3m RCT CRF – complete in full. PFQ can be sent)

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

Complete Sections 3-10 as soon as possible after the participant's 3m follow up appointment with their healthcare professional as part of their ongoing care for their ulcerative colitis.

Please ensure that the information in this CRF corresponds to the information collected since the **date of the randomisation up to and including the date of the participant's 3m follow up appointment** with the PI / other authorised person.

All tests, etc done since the 3m follow up appointment will be collected in the 6m RCT CRF. To prevent double-counting, please ensure that the data in this CRF relates to information up to and including the 3m follow up appointment date but not beyond.

DATES FOR REFERENCE:	
Date of **randomisation**:	Date of **3m follow up** appointment:
d d m m y y y y	d d m m y y y y

Section 3: Treatment continuation

Was the trial treatment discontinued prematurely **by the PI** (or other authorised person)?

- ☐ No (**Go to Section 4**)
- ☐ Yes *(Please complete the rest of **Section 3**)*

Date treatment discontinued: d d m m y y y y

Reason for discontinuation:

- ☐ Adverse event occurred *(If so, also complete an **AE Screening Form**)*
- ☐ Surgery required *(If so, also complete an **AE Screening Form**)*
- ☐ Other *(please state)*

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

Section 4: Surgery details

Has the participant had **colitis-related** surgery since the **date of randomisation**?

☐ No **(Go to Section 5)**

☐ Yes (*Complete the rest of **Section 4** AND also complete an **AE Screening Form***)

Type of surgery	Date surgery performed	Tick if done as an emergency
Panproctocolectomy	d d m m y y y y	
Subtotal colectomy	d d m m y y y y	
Ileoanal pouch with stoma	d d m m y y y y	
Ileoanal pouch without stoma	d d m m y y y y	
Formation of ileostomy	d d m m y y y y	
A reversal procedure	d d m m y y y y	
Resuture procedure	d d m m y y y y	
Abscess drainage	d d m m y y y y	

Other colitis-related surgical procedure(s) *(please state what, the date it was performed and whether it was done as an emergency)*

_____ d d m m y y y y |

Date of admission: d d m m y y y y

Date of discharge: d d m m y y y y

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

Section 5: Participant follow up events - New conditions

Please tick in the "Yes" or "No" column to indicate whether, according to the hospital notes, the participant has been diagnosed with any of the following **since they were randomised up to and including the date of the 3m follow up appointment** (include all diagnoses made during the 3m follow up appointment in this CRF).

The participant will be asked the same questions during their follow up appointment in the PFQ to capture all non-hospital diagnoses (e.g. GP diagnosis of a serious infection).

If "Yes" is ticked, record the site(s) of the condition and the date(s) of the diagnosis.

IMPORTANT: AN AE SCREENING FORM IS REQUIRED FOR EACH CONDITION.

Incidence of ….	No	Yes	Site(s) of condition	Date of diagnosis
Colorectal malignancies				d d m m y y y y
				d d m m y y y y
Other GI malignancies				d d m m y y y y
				d d m m y y y y
Non-GI malignancies				d d m m y y y y
				d d m m y y y y
Pneumonia				d d m m y y y y
				d d m m y y y y
Abscesses				d d m m y y y y
				d d m m y y y y
Other serious bacterial infections				d d m m y y y y
				d d m m y y y y
Renal disorders				d d m m y y y y
				d d m m y y y y

Please enter any additional sites and dates under the headings listed on the **Additional Comments Form** if there is insufficient space on this page.

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

For Section 6 onwards, please complete the data that relates to the study centre (i.e. the Trust / Health Board) where they were recruited, not just that particular hospital and include tests for any condition, not just their bowel condition.

Section 6: Healthcare contacts / episodes

Complete this section with **counts of the number of contacts / episodes** by the participant at the study centre (not just at the hospital where they were recruited).

Contact type (for any condition)	**Number of contacts**
1. Clinic visits (**Include** further Remicade® infusions (if relevant) and the 3m follow up appointment) since randomisation	
2. A&E attendances since randomisation	

Nights spent as an inpatient (for any condition)	**Number of nights**
1. Number of nights as an inpatient during the original episode that led to them being entered into the trial	
2. Number of nights as an inpatient since their discharge following their **first** infusion	

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

Section 7: Drugs given as an inpatient since randomisation

Complete the details of any drugs **given as an inpatient** since the ***date of randomisation to the date of the 3m follow up appointment***. Include any drugs given in response to an adverse event (AE) whilst an inpatient. Some common drugs have been listed for your convenience. Please write in any additional drugs not listed in the empty rows.

Drug name	Strength	Number per dose	Dose frequency	Number of days given (in total)	Used to treat an AE?
Adalimumab					
Azathioprine					
Mercaptopurine					
Methotrexate					
Prednisolone					
Septrin					

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

Section 8: Tests & procedures performed

Complete the **number of each test listed** performed at that **study centre** for **any condition** between **date of randomisation** and **date of 3m follow up appointment.**

INCLUDE all tests done as part of the 3m follow up appointment in this section.

Test type	N°. of tests / procedures performed
BLOOD TESTS	
1. Ciclosporin levels	
2. Full blood count	
3. C-Reactive Protein (CRP)	
4. Erythrocyte Sedimentation Rate (ESR)	
5. Urea & electrolytes	
6. Calcium & phosphate	
7. Liver function tests (LFTs)	
8. Clotting profile	
9. Thiopurine Methyltransferase (TPMT)	
PROCEDURES	
10. Oesophogastroduodenoscopy (OGD)	
11. Barium meal	
12. Barium follow through	
13. Barium enema	
14. Colonoscopy with biopsy	
15. Colonoscopy without biopsy	
16. Flexible sigmoidoscopy	
17. Rigid sigmoidoscopy	
18. CT scan	
19. MRI scan	
20. Abdominal x-ray	
21. Chest x-ray	
22. Stool culture/testing	

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

Section 9: 3m follow up appointment test results

Please record the results of the **tests done at the 3m follow up appointment with the healthcare professional**.

- Where tests use different units of measurement, please record the information as it is displayed locally, remembering to include local units of measurement
- Place a **cross** in the final column if the test has not been requested, either routinely or on this occasion.

9a – Clinical measurements at 3m follow up appointment

Measurement	Result		Test NOT requested (X)
Weight		*(Kg)*	
Pulse		*(bpm)*	
Temperature		*(°C)*	
Systolic blood pressure		*(mm Hg)*	
Diastolic blood pressure		*(mm Hg)*	
Stool frequency		*(per day)*	
Bloody stool frequency		*(per day)*	

(Continued overleaf)

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

9b – Blood results at 3m follow up appointment

Measurement	Result		Test NOT requested (X)
Haemoglobin	_____	(*g/dL*)	
Urea	_____	(*mmol/L*)	
Creatinine	_____	(*mmol/L*)	
Sodium	_____	(*mmol/L*)	
Potassium	_____	(mmol/L)	
Chloride	_____	(mmol/L)	
Bicarbonate	_____	(mmol/L)	
C-Reactive protein (CRP)	_____	(mg/L)	
Erythrocyte Sedimentation Rate (ESR)	_____	(mm/hr)	
Alanine transaminase (ALT)	_____	(U/L)	
Aspartate transaminase (AST)	_____	(*U/L*)	
Alkaline phosphatase (ALP)	_____	(*U/L*)	
Total bilirubin	_____	(*µmol/L*)	
Gamma glutamyl transpeptidase (GGT)	_____	(*U/L*)	
Albumin	_____	(*g/L*)	
Total cholesterol	_____	(*mmol/L*)	
Glomerular Filtration Rate (GFR)	_____	*(mL/min/m^2)*	

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

Section 10: Blood ciclosporin levels

Participant allocated to Sandimmun® & Neoral®:

	No – Go to Section 11
	Yes – complete section below

Date of each test	**Result** (ng/mL)
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	
d d m m y y y y	

Section 11: Date of 6m follow up appointment

Complete this section when a date has been allocated: d d m m y y y y

Once completed, fax this CRF to the CONSTRUCT Trial Office on 01792 606599.

Do not wait for Section 11 to be completed before faxing. Refax this page once the 6m follow up appointment date is known.

Appendix 12 Post-Colectomy Questionnaire

construct

www.construct.swansea.ac.uk

EudraCT number: 2008-001968-36

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

construct

building the evidence

Post Colectomy Questionnaire

(v1-0 30Apr2012)

(for completion by patients with colectomy or reversal)

Please tick to indicate which time period this questionnaire refers to:	
On discharge	
4 weeks post discharge	
8 weeks post discharge	
12 weeks post discharge	

CONSTRUCT

Swansea University College of Medicine, Singleton Park, Swansea SA2 8PP

Phone: +44(0)1792 513411/513405 Fax: +44 (0)1792 606599

Email: construct@swansea.ac.uk
Website: www.construct.swansea.ac.uk

Please read all the instructions before completing this questionnaire.

Thank you for agreeing to continue participating in this study. The answers you give for this questionnaire will help us to find out whether the treatments you receive are helpful for your condition.

The information you provide will be completely confidential and will not be accessible by any third parties.

Please answer all the questions. Although it may seem that some questions are asked more than once, it is still important that you answer every one.

If you find it difficult to answer a question, please do the best you can. If you are unsure what the question is asking, please ask the research professional to explain it when you meet.

Please follow the instructions for each section of the questionnaire carefully as the sections ask you to think back about different periods of time.

Please return the completed questionnaire to **CONSTRUCT, College of Medicine, Swansea University, FREEPOST SWC4951, Swansea SA2 8ZZ**

If you have any questions about the questionnaire, please contact us on XXXX or email XXXX.

Date questionnaire started:	*d*	*d*	*m*	*m*	*y*	*y*	*y*	*y*
Time questionnaire started:	*h*	*h*	*m*	*m*	*(using 24h clock)*			
Date questionnaire completed:	*d*	*d*	*m*	*m*	*y*	*y*	*y*	*y*
Time questionnaire completed:	*h*	*h*	*m*	*m*	*(using 24h clock)*			
Patient initials:								

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

Section A: Crohn's and Colitis Questionnaire (CCQ)

The following questions ask for your views about your bowel problem and how it has affected your life over the **last two weeks**.

The terms bowel problem or bowel condition refer to all aspects of your bowel illness and its related treatments. If you have had some bowel surgery you may wish to answer questions 1, 2, 6, 9, 24 and 26 using the "not applicable" response.

Please answer **all the questions**. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

1. On how many days over the last **two weeks** have you had loose or runny bowel movements?

   ☐ days ☐ *Not Applicable*

2. On how many days in the last **two weeks** have you noticed blood in your stools?

   ☐ days ☐ *Not Applicable*

3. On how many days over the last **two weeks** have you felt tired?

   ☐ days

4. In the last **two weeks** have you felt frustrated?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

5. In the last **two weeks**, has your bowel condition prevented you from carrying out your work or other normal activities?

   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

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

6. On how many days over the last **two weeks** have you opened your bowels more than three times a day?

☐ days ☐ *Not Applicable*

7. On how many days over the last **two weeks** have you felt full of energy?

☐ days

8. In the last **two weeks** did your bowel condition prevent you from going out socially?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

9. On how many days over the last **two weeks** have your bowels opened accidentally?

☐ days ☐ *Not Applicable*

10. On how many days over the last **two weeks** have you felt generally unwell?

☐ days

11. In the last **two weeks** have you felt the need to keep close to a toilet?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

12. In the last **two weeks**, has your bowel condition affected your leisure or sports activities?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

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

13. On how many days over the last **two weeks** have you felt pain in your abdomen?

	days

14. On how many nights over the last **two weeks** have you been unable to sleep well (days if you are a shift worker)?

	nights (or days)

15. On how many nights in the last **two weeks** have you had to get up to use the toilet because of your bowel condition after you have gone to bed?

	nights

16. In the last **two weeks** have you felt depressed?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

17. In the last **two weeks** have you had to avoid attending events where there was no toilet close at hand?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

18. On how many days over the last **two weeks**, have you had a problem with large amounts of wind?

	days

19. On how many days over the last **two weeks** have you felt off your food?

	days

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

20. Many patients with bowel problems have worries about their illness. How often during the last **two weeks** have you felt worried?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

21. On how many days over the last **two weeks** has your abdomen felt bloated?

☐ days

22. In the last **two weeks** have you felt relaxed?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

23. In the last **two weeks** have you been embarrassed by your bowel problem?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

24. On how many days over the last **two weeks** have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?

☐ days ☐ *Not Applicable*

25. In the last **two weeks** have you felt upset?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

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

26. On how many days over the last **two weeks** have you had to rush to the toilet?

☐ days ☐ *Not Applicable*

27. In the last **two weeks** have you felt angry as a result of your bowel problem?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

28. In the last **two weeks**, has your sex life been affected by your bowel problem?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

29. On how many days over the last **two weeks** have you felt sick?

☐ days

30. In the last **two weeks** have you felt irritable?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

31. In the last **two weeks** have you felt lack of sympathy from others?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

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

32. In the last **two weeks** have you felt happy?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

33. How has your quality of life changed since the last time you filled in a questionnaire? Please circle one of the five statements below:

1	**2**	**3**	**4**	**5**
Mucn better now	Somewhat better	About the same	Somewhat worse	Much worse

What date did you complete the last questionnaire?

d	*d*	*m*	*m*	*y*	*y*	*y*	*y*

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

Supplementary question

Do you have a stoma?

Yes Please continue with the questions below

No Please go straight to **Section B** on page 13

For patients with a stoma

The following questions ask for your views about your **stoma** and how it has affected your life over the **last two weeks**.

Please choose only **one** answer for each of the questions. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

---

1 On how many days over the last **two weeks** have you been afraid that other people might hear your stoma?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

2 On how may days over the last **two weeks** have you been worried that other people might smell your stools?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

3 On how many days over the last **two weeks** have you been worried about possible leakage from your stoma bag?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

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

4 On how many days over the last **two weeks** have you had problems with care for your stoma?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

5 On how many days over the last **two weeks** have you found the skin around your stoma irritated?

a) None
b) On one or two days only
c) On three to seven days
d) On eight to fourteen days (i.e. more than every other day)

6 In the last **two weeks** have you felt embarrassed because of your stoma?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

7 In the last **two weeks** have you felt less complete because of your stoma?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

8 In the last **two weeks** have you felt less attractive as a result of your stoma?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

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

9 In the last **two weeks** have you felt less feminine / masculine as a result of your stoma?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

10 In the last **two weeks** have you been dissatisfied with your body as a result of your stoma?

a) No, not at all
b) Yes, some of the time
c) Yes, most of the time
d) Yes, all of the time

If you did not complete any of the questions in Section A (including the stoma questionnaire), please record the question number(s) below and, if possible, give a reason why it was not completed.

Question N°	Reason for non-completion

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

Section B: SF-12

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please tick the **one box** that best describes your answer.

---

1. **In general**, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
b) Climbing several flights of stairs	☐	☐	☐

3. During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	☐	☐	☐	☐	☐
b) Were limited in the kind of work or other activities	☐	☐	☐	☐	☐

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

4. During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	☐	☐	☐	☐	☐
b) Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

5. During the past **4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

6. These questions are about how you feel and how things have been with you during the past **4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past **4 weeks**…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
b) Did you have lots of energy?	☐	☐	☐	☐	☐
c) Have you felt downhearted and low?	☐	☐	☐	☐	☐

7. During the past **4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

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

Section C: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today**.

Mobility

I have no problems in walking about	❑ A
I have some problems in walking about	❑ B
I am confined to bed	❑ C

Self-Care

I have no problems with self-care	❑ A
I have some problems washing or dressing myself	❑ B
I am unable to wash or dress myself	❑ C

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	❑ A
I have some problems with performing my usual activities	❑ B
I am unable to perform my usual activities	❑ C

Pain/Discomfort

I have no pain or discomfort	❑ A
I have moderate pain or discomfort	❑ B
I have extreme pain or discomfort	❑ C

Anxiety/Depression

I am not anxious or depressed	❑ A
I am moderately anxious or depressed	❑ B
I am extremely anxious or depressed	❑ C

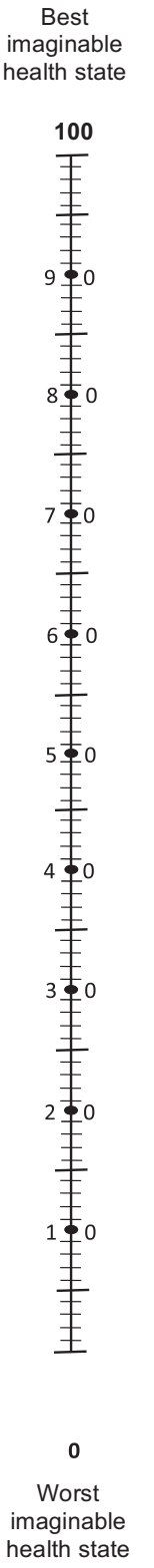
Participant study ID: | | | | | | | |

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Office use only:

Health state indicated *(whole number between 0 and 100).*

Appendix 13 First interview schedule (randomised controlled trial only)

First interview schedule for CONSTRUCT participants (RCT only)
Pt Interview Schedule V3-0 05Aug2011

Patients will be contacted to arrange a convenient date/time. Explanation about interview will include 'Your information will be very valuable/helpful and inform us of things we don't know about and therefore I would like to speak to you uninterrupted for up to one hour'.

At the start, brief background information will be requested, eg when diagnosed, when admitted, which drug given as inpatient, whether treated with infliximab or ciclosporin in the past.

Firstly, I want to ask you questions about your health and well-being and then I will ask you questions about the treatment you received (*make sure patient knows which episode of treatment*). The next questions are about your health and well-being.

1. What is important to you about your health?

2. What does good health mean to you? }
3. What does bad health mean to you? } if time short, drop these

4. What were the main difficulties your illness was causing you before the treatment?
   (past symptoms / quality of life)

5. How has the illness affected your quality of life?

Before we move on to the second part of the interview about your recent treatment, when I will ask 9 questions, are there any other comments you would like to make about your health that we have not covered.

I would now like to ask you some questions about the treatment you received (*make sure patient understands which episode of treatment*).

6. In what form were the medicines administered?
7. How easy was that to manage?
8. What were the positive aspects of having the medicines given in this way?
9. What were the challenging aspects of having the medicines given in this way?
10. How has the treatment affected you?
    (side effects)
11. How long do you think the effects, good or bad, of the treatment lasted?
12. If you found that the positive effects were short-term, do you consider it was worthwhile having the treatment?
13. Can you describe what difference the treatment has made to your daily life
14. How does the treatment regimen that you are on now compare with other therapies or treatments you might have had in the past?
    (Perceptions of safety & implications of having this treatment. Surgery – if last resort why?)
15. To conclude, we have covered a whole range of issues, I would like to finish by asking what are your views of the medicines you are currently taking?

I have finished asking the set questions - are there any other comments you would like to make?
NB –remember to say will be contacting again in 9 months' time to interview again

Appendix 14 First interview schedule (colectomy)

First interview schedule for CONSTRUCT RCT participants who have colectomy
Surgery Pt Interview Schedule V2-0 05Aug2011

Patients will be contacted to arrange a convenient date/time. Explanation about interview will include 'Your information will be very valuable/helpful and inform us of things we don't know about and therefore I would like to speak to you uninterrupted for up to one hour'.

At the start, brief background information will be requested, eg when diagnosed, when admitted, whether treated with infliximab or ciclosporin in the past.

Firstly, I want to ask you questions about your health and well-being and then I will ask you questions about the treatment you received (*make sure patient knows which episode of treatment*). The next questions are about your health and well-being.

1. What is important to you about your health?

2. What does good health mean to you? }
   } if time short, drop these
3. What does bad health mean to you? }

4. What were the main difficulties your illness was causing you before the treatment?
   (past symptoms / quality of life)

5. How has the illness affected your quality of life?

Before we move on to the second part of the interview about your recent treatment, when I will ask 10 questions, are there any other comments you would like to make about your health that we have not covered.

I would now like to ask you some questions about the treatment you received (*make sure patient understands which episode of treatment*).

6. I understand you have had surgery, when was this?
7. When you agreed to take part in CONSTRUCT you were going to be given a drug treatment. Did you have this before the operation? (*clarify which one and what they thought about it)*?
8. Why did you have the operation?
9. Can you describe what difference the operation has made to your daily life?
10. How has the operation affected your quality of life?
11. How are you coping with the ileostomy *(mentally and phsically)?*
12. How has it affected your relationships with others?
13. Do you think you would you prefer to be on long term treatment for your colitis rather than have had a colectomy?
    (Perceptions of safety & implications of having different treatments. Surgery – if last resort why?)
14. Do you feel the decision to go ahead with the operation was good or bad?
15. To conclude, we have covered a whole range of issues, are there any other comments you would like to make?

NB –remember to say will be contacting again in 9 months' time to interview again

Appendix 15 Second interview schedule (randomised controlled trial and surgery)

Second interview schedule (12 months) for CONSTRUCT participants

***

Patients will be contacted to arrange a convenient date/time. Explain that this is the second of the interviews they agreed to take part in when they consented to CONSTRUCT, information will be very valuable, help us to understand what happens after treatment and therefore I would like to speak to you uninterrupted for up to one hour.

1st transcript to be read before interview, pertinent things said by patient to be noted and available to aid interview. Will also help with validation of previous interview and understanding of change over time.

***

Firstly, I want to ask you questions about your health and well-being and then I will ask you questions about the treatment you received. The next questions are about your health and well-being.

1. When I spoke to you 9 months ago, you told me the following things …… were having an effect on your health or your views about your health. Have those changed in any way, for the better or perhaps for the worse?

2. 9 months ago you told me a range of practical and personal problems relating to UC. Are you aware of any changes that I should know about?

3. Has anything about your quality of life changed since 9 months ago?
(*social, physical, emotional, mental)*

Before we move on to the second part of the interview are there any other comments you would like to make about your health that we have not covered.

I am interested in what has happened treatment-wise over the past 9 months since we last spoke, so the next questions will be about this.

4. Nine months ago you described the treatment you were having as xxxx. What treatment(s) have you had since then?
(have to hand the date of CONSTRUCT treatment)
(A ? Has had more of the drug they were randomised to - infliximab or ciclosporin)
(B ? Has had treatment with the drug they were not randomised to)
(C ? Had different drug treatments)
(D ? pt may have had surgery since last interview)

5. What are your views about the treatment(s) you have received in the last 9 months?
   a. What were the positive aspects of the medicines you were given?
   b. What were the challenging aspects of the medicines you were given
   (+&- *about impact on UC)*
   (*side effects, treatment lasted or not, ? worth it)*
   c. Positive and challenging aspects of the way the medicines were administered?
   (+ &- aspects of being given it-convenience, process, impact)

6. Has there been a change in your daily life compared to 9 months ago
(Treatment, care, lifestyle, routine?)

Questions for drug treatment only	Questions for surgery pts
If participant has been treated with both infliximab & ciclosporin since randomisation in CONSTRUCT ask: 7. Which of the medicines/treatments did you prefer and why? a. If had infliximab & ciclosporin – specifically which preferred b. ? because that treatment regime suits your lifestyle? I would now like to ask: 8. What do you think of the care you are currently receiving for UC? (*trying to find out about access to service/IBD nurses etc)* 9. What is your opinion about the time that it takes you to access that care? 10. What has changed in your relationship with doctors and nurses since we last spoke (*way communicate or interact)* a. Is that because i. Change in treatment / drugs? ii. Lack of change in treatment / drugs? iii. ? surgery iv. Better or worse communication with you? v. Something else? b. What has brought about that change or lack of change (in treatment, drugs, surgery, something else)? 11. Does bringing up your illness with you again now, through questionnaires and interviews, bother you?	7. Thinking back to the drug treatment you had a year ago, what are your views about it now? *If have been treated with infliximab & ciclosporin over the year, which did they prefer?* 8. Since your surgery, can you describe what difference the operation has made to your daily life? 9. Since the surgery, how has the operation affected your quality of life? 10. Have you had a reversal operation since the surgery? If yes, when was that and how are you now? If no, do you anticipate having a reversal? 11. Since I last asked, how are you coping with the ileostomy *(mentally, emotionally, phsically)?* a. Has that changed? 12. How has it affected your relationships with others? a. Friends & family b. Doctors and nurses and other healthcare professionals 13. Do you think you would you prefer to be on long term treatment for your ulcerative colitis rather than have had a colectomy? Have your views changed? *(Perceptions of safety & implications of having different treatments. Surgery – if last resort why?)* 14. Do you feel the decision to go ahead with the operation was good or bad? Have your views changed since we last spoke? 15. Of all the treatments you have had for UC which would you consider as the most successful and why?
CONSTRUCT Pt Interview Schedule RCT V3-0 05Aug2011.doc	CONSTRUCT Surgery Pt Interview Schedule V2-0 05Aug2011.doc

I have finished asking the set questions - are there any other comments you would like to make?

NB –remember to thank the participant for taking part in 2 interviews

Appendix 16 Health-care professional interview schedule 1

Health Care Professional interview schedule – high trial recruitment

PI/Nurse interviews. Judgement sampling, sites with **high trial recruitment.**

1. What are your views about administering IV ciclosporin?

2. What are your views about administering infliximab?

3. a. What are your views about treating a patient with infliximab?

   b. What are your views about treating a patient with ciclosporin?

4. a. What are your views about treating a patient with infliximab in the longer term?
   Outcomes for pt
   b. What are your views about treating a patient with ciclosporin in the longer term?
   Outcome for pt

5. a. **Consultant only**
   What do you think your nursing staff feel about administering these drugs – are their views different to yours and if so, why?

   b. Nurse only
   What do you think the doctors feel about administering these drugs – do they have a different perspective on administering the drug to you?

6. Do you have a treatment preference? Why?

7. What are your views about colectomy as a treatment for acute severe colitis as opposed to medical intervention?

8. What are your views on NICE guidance which states that infliximab can only be used in acute severe UC when ciclosporin is contraindicated?

9. NICE also allows use of infliximab in research because there is not enough evidence. Should it be used 'only in research', ie in CONSTRUCT – what are your views about that?
   (depending on answer to above, can explore question of equipoise – in context of trial do you have an open mind about both the drugs? Trying to find out if have patients who they think should have infliximab so didn't put into the trial)

Nurse interviews only:

10. Can you give me a feel for roughly how long during an infusion of ciclosporin you were prevented from doing other duties?
    (if they can put a figure on it, that's great but they may well not be able to be that specific. It may be that they say it didn't prevent them but they just kept a close eye on the participant, kept checking them out of the corner of their eye)

PI interviews only:

In summary, you have told us about your personal preference regarding the two drugs and your views on NICE guidelines and negotiating care with patients, but it is very important to us that we have a good understanding of your site's view on the two drugs, as issues of equipoise have already arisen in other site interviews, so:

11. Can you clarify where your site stands on the effectiveness of the two drugs, what we might call "scientific equipoise"?

12. And, we would also like clarification on where your site stands on the experience of using the two drugs, what we might call "administering equipoise"?

13. Do you feel that this has in any way influenced your site's participation in the trial?

Appendix 17 Health-care professional interview schedule 2

Health Care Professional interview schedule – high cohort recruitment, no or low trial recruitment/poor overall recruitment

PI interviews. Judgement sampling, sites which have **high cohort recruitment with no or low trial recruitment or poor overall recruitment.**

1. What are your views about administering IV ciclosporin?
   a. If not administering ciclosporin – What are the reasons for this?

2. What are your views about administering infliximab?
   a. If not administering infliximab – What are the reasons for this?

3. As you are aware the methods of delivery are different for the two drugs with ciclosporin having longer administration time. Do you think this has an effect on which drug is administered?

4. Infliximab and ciclosporin have different cost implications: Ciclosporin in considered to be cheaper than infliximab.
   a. Do you have any views on whether this has an effect on which drug is administered?

5. a. What are your views about treating a patient with infliximab?
   b. What are your views about treating a patient with ciclosporin?

6. a. What are your views about treating a patient with infliximab in the longer term?
      Outcomes for pt
   b. What are your views about treating a patient with ciclosporin in the longer term?
      Outcome for pt

7. If you are not currently administering either of the drugs:

   a. Have you ever administered them in the past? (ciclosporin/infliximab)
   b. If yes, what were your views on administering them?
   c. Do you think this has affected your treatment preference now? Why?

8. Consultant – what do you think your nursing staff feel about administering these drugs – are their views different to yours and if so, why?

9. Do you have a treatment preference? Why?

10. Do you have any views on whether there is a conflict between professional preference and what is available to prescribe for treatment of ulcerative colitis. (ciclosplorin/infliximab)

11. What are your views about colectomy as a treatment for acute severe colitis as opposed to medical intervention?

12. What are your views on NICE guidance which states that infliximab can only be used in acute severe UC when ciclosporin is contraindicated?

13. NICE also allows use of infliximab in research because there is not enough evidence. Should it be used 'only in research', ie in CONSTRUCT – what are your views about that?

Appendix 18 McMaster IBDQ, UKIBDQ, CUCQ and CUCQ+ questions and response options

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
How frequent have your bowel movements been during the last 2 weeks? *McMaster response option A*	On how many days over the last 2 weeks have you had loose or runny bowel movements? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you had loose or runny bowel movements? *CUCQ response option A*	On how many days over the last 2 weeks have you had loose or runny bowel movements? *CUCQ+ response option C*
How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? *McMaster response option B*	On how many days over the last 2 weeks have you felt tired? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you felt tired? *CUCQ response option A*	On how many days over the last 2 weeks have you felt tired? *CUCQ+ response option A*
How often during the last 2 weeks have you felt frustrated, impatient, or restless? *McMaster response option B*	In the last 2 weeks have you felt frustrated? *UK-IBDQ response option B*	In the last 2 weeks have you felt frustrated? *CUCQ response option B*	In the last 2 weeks have you felt frustrated? *CUCQ+ response option B*
How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? *McMaster response option B*	In the last 2 weeks has your bowel condition prevented you from carrying out your work or other normal activities? *UK-IBDQ response option B*	In the last 2 weeks has your bowel condition prevented you from carrying out your work or other normal activities? *CUCQ response option B*	In the last 2 weeks has your bowel condition prevented you from carrying out your work or other normal activities? *CUCQ+ response option B*
How much of the time during the last 2 weeks have your bowel movements been loose? *McMaster response option B*	On how many days over the last 2 weeks have you opened your bowels more than three times a day? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you opened your bowels more than three times a day? *CUCQ response option A*	On how many days over the last 2 weeks have you opened your bowels more than three times a day? *CUCQ+ response option C*
How much energy have you had during the last 2 weeks? *McMaster response option C*	On how many days over the last 2 weeks have you felt full of energy? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you felt full of energy? *CUCQ response option A*	On how many days over the last 2 weeks have you felt full of energy? *CUCQ+ response option A*
How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? *McMaster response option B*	In the last 2 weeks have you been worried about being admitted to hospital because of your bowel problem? *UK-IBDQ response option B*	No comparable question	No comparable question
How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? *McMaster response option B*	In the last 2 weeks did your bowel condition prevent you from going out socially? *UK-IBDQ response option B*	In the last 2 weeks did your bowel condition prevent you from going out socially? *CUCQ response option B*	In the last 2 weeks did your bowel condition prevent you from going out socially? *CUCQ+ response option B*

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
No comparable question	On how many days over the last 2 weeks have your bowels opened accidentally?	On how many days over the last 2 weeks have your bowels opened accidentally?	On how many days over the last 2 weeks have your bowels opened accidentally?
	UK-IBDQ response option A	*CUCQ response option A*	*CUCQ+ response option C*
How often during the last 2 weeks have you felt generally unwell?	On how many days over the last 2 weeks have you felt generally unwell?	On how many days over the last 2 weeks have you felt generally unwell?	On how many days over the last 2 weeks have you felt generally unwell?
McMaster response option B	*UK-IBDQ response option A*	*CUCQ response option A*	*CUCQ+ response option A*
How often during the last 2 weeks have you been troubled because of fear of not finding a washroom?	In the last 2 weeks have you felt the need to keep close to a toilet?	In the last 2 weeks have you felt the need to keep close to a toilet?	In the last 2 weeks have you felt the need to keep close to a toilet?
McMaster response option B	*UK-IBDQ response option B*	*CUCQ response option B*	*CUCQ+ response option B*
How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks?	In the last 2 weeks has your bowel condition affected your leisure or sports activities?	In the last 2 weeks has your bowel condition affected your leisure or sports activities?	In the last 2 weeks has your bowel condition affected your leisure or sports activities?
McMaster response option D	*UK-IBDQ response option* B	*CUCQ response option B*	*CUCQ response option B*
How often during the last 2 weeks have you been troubled by pain in the abdomen?	On how many days over the last 2 weeks have you felt pain in your abdomen?	On how many days over the last 2 weeks have you felt pain in your abdomen?	On how many days over the last 2 weeks have you felt pain in your abdomen?
McMaster response option B	*UK-IBDQ response option A*	*CUCQ response option A*	*CUCQ+ response option A*
How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?	On how many nights over the last 2 weeks have you been unable to sleep well (days if you are a shift worker)?	On how many nights over the last 2 weeks have you been unable to sleep well (days if you are a shift worker)?	On how many nights over the last 2 weeks have you been unable to sleep well (days if you are a shift worker)?
McMaster response option B	*UK-IBDQ response option A*	*CUCQ response option A*	*CUCQ+ response option A*
How often during the last 2 weeks have you felt depressed or discouraged?	In the last 2 weeks have you felt depressed?	In the last 2 weeks have you felt depressed?	In the last 2 weeks have you felt depressed?
McMaster response option B	*UK-IBDQ response option B*	*CUCQ response option B*	*CUCQ+ response option B*
How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand?	In the last 2 weeks have you had to avoid attending events where there was no toilet close at hand?	In the last 2 weeks have you had to avoid attending events where there was no toilet close at hand?	In the last 2 weeks have you had to avoid attending events where there was no toilet close at hand?
McMaster response option B	*UK-IBDQ response option B*	*CUCQ response option B*	*CUCQ+ response option B*
Overall, in the last 2 weeks how much of a problem have you had with passing large amounts of gas?	On how many days over the last 2 weeks have you had a problem with large amounts of wind?	On how many days over the last 2 weeks have you had a problem with large amounts of wind?	On how many days over the last 2 weeks have you had a problem with large amounts of wind?
McMaster response option E	*UK-IBDQ response option A*	*CUCQ response option A*	*CUCQ+ response option A*

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
No comparable question	On how many days over the last 2 weeks have you felt off your food? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you felt off your food? *CUCQ response option A*	On how many days over the last 2 weeks have you felt off your food? *CUCQ+ response option A*
Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? *McMaster response option B*	Many patients with bowel problems have worries about their illness. How often during the last 2 weeks have you felt worried? *UK-IBDQ response option B*	Many patients with bowel problems have worries about their illness. How often during the last 2 weeks have you felt worried? *CUCQ response option B*	Many patients with bowel problems have worries about their illness. How often during the last 2 weeks have you felt worried? *CUCQ+ response option B*
How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? *McMaster response option B*	On how many days over the last 2 weeks has your abdomen felt bloated? *UK-IBDQ response option A*	On how many days over the last 2 weeks has your abdomen felt bloated? *CUCQ response option A*	On how many days over the last 2 weeks has your abdomen felt bloated? *CUCQ+ response option A*
How often during the last 2 weeks have you felt relaxed and free of tension? *McMaster response option B*	In the last 2 weeks have you felt relaxed? *UK-IBDQ response option B*	In the last 2 weeks have you felt relaxed? *CUCQ response option B*	In the last 2 weeks have you felt relaxed? *CUCQ+ response option B*
How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? *McMaster response option B*	On how many days over the last 2 weeks have you noticed blood with your bowel movements? *UK-IBDQ response option A*	On how many days in the last 2 weeks have you noticed blood in your stools? CUCQ response option A	On how many days in the last 2 weeks have you noticed blood in your stools? *CUCQ+ response option C*
How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? *McMaster response option B*	In the last 2 weeks have you been embarrassed by your bowel problem? *UK-IBDQ response option B*	In the last 2 weeks have you been embarrassed by your bowel problem? *CUCQ response option B*	In the last 2 weeks have you been embarrassed by your bowel problem? *CUCQ+ response option B*
How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? *McMaster response option B*	On how many days over the last 2 weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels? CUCQ response option A	On how many days over the last 2 weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels? *CUCQ+ response option C*
How much of the time during the last 2 weeks have you felt tearful or upset? *McMaster response option B*	In the last 2 weeks have you felt upset? *UK-IBDQ response option B*	In the last 2 weeks have you felt upset? *CUCQ response option B*	In the last 2 weeks have you felt upset? *CUCQ+ response option B*

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? *McMaster response option B*	On how many days over the last 2 weeks have you had to rush to the toilet? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you had to rush to the toilet? CUCQ response option A	On how many days over the last 2 weeks have you had to rush to the toilet? *CUCQ+ response option C*
How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? *McMaster response option B*	In the last 2 weeks have you felt angry as a result of your bowel problem? *UK-IBDQ response option B*	In the last 2 weeks have you felt angry as a result of your bowel problem? *CUCQ response option B*	In the last 2 weeks have you felt angry as a result of your bowel problem? *CUCQ+ response option B*
To what extent has your bowel problem limited sexual activity during the last 2 weeks? *McMaster response option F*	In the last 2 weeks has your sex life been affected by your bowel problem? *UK-IBDQ response option B*	In the last 2 weeks has your sex life been affected by your bowel problem? *CUCQ response option B*	In the last 2 weeks has your sex life been affected by your bowel problem? *CUCQ+ response option B*
How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? *McMaster response option B*	On how many days over the last 2 weeks have you felt sick? *UK-IBDQ response option A*	On how many days over the last 2 weeks have you felt sick? *CUCQ response option A*	On how many days over the last 2 weeks have you felt sick? *CUCQ+ response option A*
How much of the time during the last 2 weeks have you felt irritable? *McMaster response option B*	In the last 2 weeks have you felt irritable? *UK-IBDQ response option B*	In the last 2 weeks have you felt irritable? *CUCQ response option B*	In the last 2 weeks have you felt irritable? *CUCQ+ response option B*
How often during the past 2 weeks have you felt a lack of understanding from others? *McMaster response option B*	In the last 2 weeks have you felt lack of sympathy from others? *UK-IBDQ response option B*	In the last 2 weeks have you felt lack of sympathy from others? *CUCQ response option B*	In the last 2 weeks have you felt lack of sympathy from others? *CUCQ+ response option B*
How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? *McMaster response option G*	In the last 2 weeks have you felt happy? *UK-IBDQ response option B*	In the last 2 weeks have you felt happy? *CUCQ response option B*	In the last 2 weeks have you felt happy? *CUCQ+ response option B*
How often during the last 2 weeks have you been troubled by cramps in your abdomen? *McMaster response option B*	No comparable question	No comparable question	No comparable question
Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? *McMaster response option E*	No comparable question	No comparable question	No comparable question

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
No comparable question	No comparable question	On how many nights in the last 2 weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed? *CUCQ response option A*	On how many nights in the last 2 weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed? CUCQ+ response option A
Stoma-specific questions			
No comparable question	No comparable question	No comparable question	On how many days over the last 2 weeks have you been afraid that other people might hear your stoma? *CUCQ+ response option D*
No comparable question	No comparable question	No comparable question	On how many days over the last 2 weeks have you been worried that other people might smell your stools? *CUCQ+ response option D*
No comparable question	No comparable question	No comparable question	On how many days over the last 2 weeks have you been worried about possible leakage from your stoma bag? *CUCQ+ response option D*
No comparable question	No comparable question	No comparable question	On how many days over the last 2 weeks have you had problems with care for your stoma? *CUCQ+ response option D*
No comparable question	No comparable question	No comparable question	On how many days over the last 2 weeks have you found the skin around your stoma irritated? *CUCQ+ response option D*
No comparable question	No comparable question	No comparable question	In the last 2 weeks have you felt embarrassed because of your stoma? *CUCQ+ response option B*
No comparable question	No comparable question	No comparable question	In the last 2 weeks have you felt less complete because of your stoma? *CUCQ+ response option B*
No comparable question	No comparable question	No comparable question	In the last 2 weeks have you felt less attractive as a result of your stoma? *CUCQ+ response option B*

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
No comparable question	No comparable question	No comparable question	In the last 2 weeks have you felt less masculine/ feminine as a result of your stoma? *CUCQ+ response option B*
No comparable question	No comparable question	No comparable question	In the last 2 weeks have you been dissatisfied with your body as a result of your stoma? *CUCQ+ response option B*
Questionnaire response options			
McMaster IBDQ response options	*UK-IBDQ response options*	*CUCQ response options*	*CUCQ+ response options*
A: 1 = Bowel movements as or more frequent that they have ever been 2 = Extremely frequent 3 = Very frequent 4 = Moderate increase in frequency of bowel movements 5 = Some increase in frequency of bowel movements 6 = Slight increase in frequency of bowel movements 7 = Normal, no increase in frequency of bowel movements B: 1 = All of the time 2 = Most of the time 3 = A good bit of the time 4 = Some of the time 5 = A little of the time 6 = Hardly any of the time 7 = None of the time	A: None, 1–2; 3–7; 8–14 (i.e. more than every other) days B: No, not at all; yes, some of the time; yes, most of the time; yes, all of the time	A: Open response option (0–14) B: No, not at all; yes, some of the time; yes, most of the time; yes, all of the time	A: Open response option (0–14) B: No, not at all; yes, some of the time; yes, most of the time; yes, all of the time C: Open response (0–14) Not applicable option for bowel surgery patients D: None, 1–2; 3–7; 8–14 (i.e. more than every other) days

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
C: 1 = No energy at all 2 = Very little energy 3 = A little energy 4 = Some energy 5 = A moderate amount of energy 6 = A lot of energy 7 = Full of energy D: 1 = A great deal of difficulty; activities made impossible 2 = A lot of difficulty 3 = A fair bit of difficulty 4 = Some difficulty 5 = A little difficulty 6 = Hardly any difficulty 7 = No difficulty; the bowel problems did not limit sports or leisure activities E: 1 = A major problem 2 = A big problem 3 = A significant problem 4 = Some trouble 5 = A little trouble 6 = Hardly any trouble 7 = No trouble F: 1 = No sex as a result of bowel disease 2 = Major limitation as a result of bowel disease 3 = Moderate limitation as a result of bowel disease 4 = Some limitation as a result of bowel disease			

McMaster IBDQ: question and response	UK-IBDQ: question and response	CUCQ: question and response	CUCQ+: question and response
5 = A little limitation as a result of bowel disease 6 = Hardly any limitation as a result of bowel disease 7 = No limitation as a result of bowel disease G: 1 = Very dissatisfied, unhappy most of the time 2 = Generally dissatisfied, unhappy 3 = Somewhat dissatisfied, unhappy 4 = Generally satisfied, pleased 5 = Satisfied most of the time, happy 6 = Very satisfied most of the time, happy 7 = Extremely satisfied, could not have been more happy or pleased			

Appendix 19 Health professional interview analysis framework

Introduction
This document presents the analysis framework which was constructed using thematic lines of enquiry from Health Professional interviews (consultants and nurses).

Health Professional Interviews
A total of 23 semi-structured interviews were carried out with consultants (15 Principal Investigators from high (n=8) and low recruiting sites (n=7)) and nurses responsible for administrating and monitoring infliximab and ciclosporin (n=8 from high recruiting sites) from across the 52 CONSTRUCT sites. Interviews addressed the ease of handling a range of drugs for Ulcerative Colitis, aspects of provision which might influence professional preference for one drug over another, and impressions about other groups' contribution to treatment and care.

Data Analysis
Transcripts underwent rigorous analysis by standard thematic analysis based on the health professional interview schedule. Thematic analysis is in keeping with a structured approach to data collection, analysis focuses on examining and identifying explicit and implicit themes within the data. The method emphasises organisation and rich description of the data using a coding process which recognises important moments in the data. Three researchers individually coded transcripts from the health professional interviews as they were completed. Following coding of four of the interviews with consultants, the three researchers worked together to agree a coding structure and developed an analysis framework. This analysis framework then guided coding of the remaining consultant interview transcripts and data were entered as interviews were completed. Following analysis of the nurse interview transcripts, the three researchers convened again to asses and amend, if necessary, the framework in light of any differences between nurse and consultant data. No amendments were made to the framework at this point and data from nurse interviews were entered into the existing framework.

The following framework presents the outcomes of analysis. Each section contains quotes from participants which are labelled by participant code name and the line number in the transcript that the quote has been taken from. Data presented within this framework is a representation of the full dataset collected. Comments specific to ciclosporin appear in the left column and to infliximab in the right column, with more general comments across the two columns at the bottom of each section.

Key - Colour of typeface

	Level of recruitment by site	Interview ID
	Poor overall recruitment	HP2, HP5, HP6
	High cohort, low or no RCT	HP1, HP3, HP4, HP7
	High RCT recruitment (PIs)	HP9, HP10, HP11, HP12, HP13, HP14, HP16
	High RCT recruitment (N)	HPN18, HPN19, HPN20, HPN21, HPN22, HPN23a, HPN24, HPN25a, HPN25b

Drug administration and management

Lead up to treatment

Ciclosporin	Infliximab
+ve	**+ve**
HP7 less attentive to making patients aware of adverse events in long terms, work up to treatment is less than Inflix, less of an issue (45 / 46)	HPN24 it's very easy because it's more common... there's no problem giving.. there's no problem even with the calculation and with preparation for the drug.pharmacy it's always readily available too (68, 70)
-ve	**-ve**
HP3 a lot of work for pharmacy, bringing it, solution, make it up (102) HPN5a To prepare intravenous drugs so that's two nurses off the ward you know mixing and preparing the drugs and taking it to the patient (182). HP13 it required more input from nurses in terms of making up the infusions (20) HP11 the patient needs to be counselled about the risks (cicl) (67)	HP11 there is a problem at weekends and out of hours...logistical problems with Pharmacy (34) HP12 preparation is challenging in some instances HP12 the pre-screening is the issue (39) HPN18 the patient has to have a chest x ray, they have to preferably have been seen all that kind of stuff done, they have to have the TB testing and all that. So they would normally have a period before they would start patients on infliximab (102) HPN19 it's quite a lengthy drawing up process, you can't aggravate the vials when your mixing them...slightly more time consuming because you have to wait for it to dissolve...and because they are in 100ml vials that tends to make it a longer process as well because you're drawing up 3-5 of those.... but it's not too complicated once you know how to do it (53,56,57, 62) HPN24 we have to discuss it first, we have to go through it first with the patient (225) HPN19 the whole process involves talking to the patient and educating them as to why you are giving it (inflix) (94)
General comments about criteria used to assess UC	
HP5 we follow the Oxford 5-day rule (steroids then decide) depends also on patients' age, co-morbidity, colon's state, likely benefits of medications, there are always both options open (115) HP1 If patient fit for surgery (life-saving) and have not improved by 5 days would rather have it (92) HP2 Oxford criteria for monitoring patients daily and promptly (believe in strongly) (117) HP10 the burden of administration , is in making it up, setting it up, rather than monitoring during the infusion (both drugs) (56) HP16 there's a question around TB screening though really it shouldn't be much different for ciclosporin... but in practice because of the area we live in we have got a very low endemic TB, so it's not really much of an issue (180) HPN18 in a general setting these nurses would be making the cicl themselves... as a clinical trial it comes up in an infusion bag already, they don't cannulate the patients, their cannualted by one of the doctors (time of nurses on cicl due to trial context reduced 15-20.) (419, 424)	

Drug administration

Ciclosporin	Infliximab
+ve	**+ve**
HP2 Longer administration time doesn't impact on choice of drug. Not a problem as proper administration of both in inpatients is important (53)	HP2 Inflix used frequently for Crohn's now and acute UC (40)
HP5 comfortable with administering Cicl as long as you take all precautions and watch lipids (5)	HP2 I'm more familiar with it (47)
HP5 patients are not going anywhere and are severely ill so practicalities-wise no problem (12)	HP2 Inflix [nurses] more used to it, advantages over Cicl no monitoring needed compared to level for Cicl (42)
HP5 I have had problems with sepsis of pelvis when we don't look carefully enough (39)	HP5 with severe colitis administering Inflix is not a problem (12)
HP6 comfortable with administering Cicl (13)	HP5 Inflix is easier than Cicl as you don't have to worry about electrolytes and reactions (18)
HP6 last used it when I was a registrar (10 yrs ago) bridge therapy, good experience (84)	HP5 Inflix is more straightforward than administering Cicl (19)
HP4 no problem with administration of the drug on the ward, (7)	HP5 Out of personal choice, Inflix and with younger people using it as first line of treatment as less toxic [than ciclosporin] (26/32)
HP7 no concerns about administering, well established, well used (15)	HP5 In in-patients it is nicer for something 'in and out' like Inflix over and above Cicl (84)
HP7 adverse sides to it, but equally well accepted and well established (19)	HP6 Happy to administer Inflix personally, better guidelines around administering it (37)
HP9 we've got quite well organised so it doesn't cause us any problems (16)	HP6 Always prescribed Inflix in his hospital, consultants are more comfortable with it (26,35)
HP10 I still use it and believe it is a safe approach (11)	HP1 Fully functional infrastructure in place and a lot of experience of Inflix administering (29)
HP10 rather more relaxed about it, paradoxically, simply because I know when the IV infusion is stopped, the drug disappears (75)	HP1 Inflix deserves a chance in selected patients (35) HP3 administering is time consuming but not as time consuming as Cicl (16)
HP11 We have no problem it (13)	HP3 administering is only repeated every 8 weeks (17)
HP11 we have always used Ciclo (18)	HP3 sensible and good experience of this drug 'when it works it is fantastic' (23-25)
HP 11 we're comfortable with it (21)	HP3 would go for Inflix if no contraindication. If contraindicated would have to go for Cicl (40)
HP13 its more complicated than inflix but when people get used to it, its fine (15)	HP4 no problem with administering Inflix (11)
HP14 the nice thing about cicl is you can stop it (144)	HP4 no barriers on the ward to administering (34)
HP14 I think these patients are equally likely to need surgery and I think being able to get them off their treatment is really good so in many cases I think cicl is preferable from that point of view (147)	HP7 newer than Cicl (only 15 years) more used to using it with Crohns than UC (24)
	HP7 data suggests it is effective, easier to administer, simpler regime, less palava (28)
	HP9 it's really straightforward, we have a good system for doing it (23)

HP14 I think it's a good drug as a rescue drug (65) HP14 I think it can be used reasonably safely and I think it's quite a nice drug (65) HP16 we're pretty happy and confident giving ciclosporin....we've a reasonable amount of experience with it (23, 28) HP16 rather than changing the bags we run a bag over 24 hours...much as they do in oxford...makes it a little bit easier (51, 56, 61) HP15 it's easier time wise and nursing hours it's easier to do than the infliximab (217) HPN21 to actually mix it up and give it to the individual is quite easy to do (54) HPN25b To be honest it does feels like you know it's just part of what we do so it's not like a thing you would think about really. (252) HP19 I suppose you could argue on the other side, infliximab... maybe just the inconvenience of coming in to have infusions once you've gone home (136)	HP9 we all feel pretty comfortable using infliximab because we use it a lot for Crohns (39) HP9 deep down have a sort of comfort with it that is slightly not there with ciclosporin (44) HP10 very short infusion (22) HP12 administration ease wise, it is much easier (23) HP12 it's about convenience and it's certainly more convenient, if you take cost out of the equation to give inflix (78) HP13 its pretty straightforward and I think inflix has an advantage because of its frequency in use in Chrons disease (63) HP13 it has an advantage, a familiarity advantage (70) HP14 infliximab has an advantage in that it's just a 2 hour infusion and then it's done (26) HP14 there's no problem with infliximab. I think it's a good drug to administer, I think it's an easy drug to administer (30) HP14 I like inflix because once you've done it, you've done it for 2 weeks (33) HP14 if the 2 were equally efficacious and equally cost effective, I would choose infliximab because of that reason (practicality of administration) (138) HP14 and yet for ease of administration, the inflix is easier (168) HP14 it's quite easy to give (290) HP16 staff are completely au fait with giving inflix (165) HP16 it's straightforward, it's easy and I think from my point of view the most important thing is about an hour later it's in and you know the full dose is in (169) HP15 compared to a continuous infusion of cicl it's a lot easier (42) HPN18 I prefer it when they have inflix... I think it's easier for the patient... because it's just one infusion... it's a couple of hours instead of being hooked.... I mean keep in mind they have got proffusive diarrhoea... I think it's easier to administer as a nurse and it is easier for the patient to receive it as a patient (165, 169, 173, 178, 189) HPN19 we do huge amounts of inflix and it's not an issue at all... one infusion over 2 hours and that's it (48, 58) HPN23a I find it an easy drug to administer (28)

	HPN24 it's very easy because it's more common... there's no problem giving…there's no problem even with the calculation and with preparation for the drug..pharmacy it's always readily available too (68, 70) HPN25a I've done that for quite a number of years now and that's really straightforward. (58) HPN25a It's easy to make, it's easy to give and just give the first, here we give the first three infusions over two hours and then subsequent infusions over an hour so it's really quite simple (64)
-ve	**-ve**
HP2 More troublesome than Inflix (perhaps because used less frequently, less general confidence in it, or higher dose when first introduced than now makes level monitoring more important) (32) HP6 Ciclosporin not used much in this hospital (14) HP6 not the length of administering that is the problem, rather there are more safety aspects, it is a more dangerous drug (44) HP1 No experience of Cicl IV in UC before (23) HP1 only administered to one patient so far and that was 10 years ago, before becoming consultant, and that was a failed medical therapy experience (negative experience) (12/17) HP3 administering [infliximab] is time consuming but not as time consuming as Cicl (16) HP3 administering is time consuming for staff (11) HP3 they [nurses] think it's quite labouring and need extra work (78) HP3 'is a bit debateable although I use it' (29) - Worry about toxicity and the liver, use it half-heartedly, when no choice (that or colectomy) (32/33) HP3 hassle to administer and takes a long period of time (7/11/33) HP3 lot of work for pharmacy (102) HP4 slight worries about availability of Cicl levels (12) makes people perceive it's a more difficult drug to use (18, 25) HP7 disadvantage is slight – continual infusion over long period of time, have to check levels (17) HP9 I guess there is a slight disadvantage to ciclosporin, because it's the infusion, it's continuous thing rather than infliximab which is sort of give it and then done (30)	HP3 'labouring work' but works well (25) HP7 treating people with Inflix go through risk counselling, unknown risks, no data re cancer or 10-15 years hence, potentially greater adverse effects need to make patients aware of that (35) HP10 have greater anxiety in administering infliximab in acute severe UC than ciclosporin.....concerned about duration that infliximab stays in the circulation (24) HP10 if they have had an infective complication then infliximab still around....potential for exacerbating it (should be administered in a "timely manner" if surgery is needed)(27) HP11 we often find there is a problems at weekends ad out of hours if we are going to prescribe it... logistical problems with pharmacy (33) HP14 after inflix they're going to have it for 19 weeks they're going to be immunosuppressed, you know for a long while (issues with surgery) (164) HP16 the only concern we have is if you give it and it doesn't work, if it's still in the system (249) HPN18 we needed to inform the IBD Clinical Nurse Specialist because they need to ensure that the patient was given the blood form to have blood taken a week later at a GP surgery, so when they came in for their second infusion which would have been done in a completely different setting because it would have been as an inpatient, that the bloods were in keeping with what's standard for giving inflix, so there were issues with that (74) HP13 there are differences in recommendations north and south of the border so we just can't use it (inflix) unless we go through a process called the Individual Patient Treatment Panel (SMC restrictions) (229) HP19 it's not just as if you've has the dose over, you know cos you go onto tablets and therefore don't have to come back into hospital as such other than monitoring... I think there are pros and cons to both (134)

HP10 the 6 hr infusion makes it slightly more labour intensive than the 2hr infusion of infliximab (16) HP12 difficult (9) HP12 fairly cumbersome both for the staff and equally important for patients because once you are tied to the drip and associated dript stand, it sort of restricts patients moving around (10) HP12 the staff find it fairly challenging (12) HP12 changing it every 6hrs, the bags etc, would be and will be challenging (16) HP13 it goes on over a longer period of time obviously, so the need to continue to make up bags and things over a longer time rather than just a one off infusion (25) HP13 there is a learning curve with cicl …. Because you're not familiar with it (123, 126) HP14 its quite difficult to the IV as a continuous infusion (13) HP14 you have to get the right dose and you have to get the patient connected up to a continuous drip and it tend to get behind, the nurses tend to find that it takes 8 hours instead of 6 to give each bag (14) HP14 it requires the patient to be on the ward and not go anywhere and um I think it's a bit cumbersome (19) HP14 it's more cumbersome to give (289) HP16 knowing that we're giving the right drug at the right level and first of all that the infusions are continuous, that they're put up, what are the gaps, how long is it before the next infusion is put up, all that sort of thing can sometimes cause problems (72) HP16 you can end up with having periods of delay where patients don't get their drug... I think that's potentially a significant problem... and it's difficult to get around that (87,92,96) HP16 we don't have ciclosporin levels on site so we send them off... in practice that generally means that though you can get a level back, you probably can't get a level back and act on it (levels of cicl in blood) (115) HP16 it's certainly more of a faff for the nursing staff and you've got that more prolonged period of time to wait and try and keep the patient in (285) HP16 I think they (nurses) find it far more difficult, more complex, more time consuming,	

there's maybe a little bit of a familiarity issue (398) HP15 its time consuming and slightly messy. You know it's complicated and err it's work for the nursing staff (19) HP15 They have to change the infusion every six hours because the issue about not being stable in the containers and it's a nuisance for the patients in that they have to be connected up to a drip all of the time (28) HP15 more fiddly (97) HPN18 you had to be mindful that the continuous infusion had to be prescribed to cover the weekend until Monday (27) HPN18 once the patient has been on cicl for 24 hours they have to have bloods and if the cicl are too high then they tended to stop it . Now the issue we have is because they are having continuous cicl they have got cic going through their veins, so their levels would always be too high. So they tended to sort of mess about and putting them on oral earlier than they needed to and things so I think from that point of view it was difficult (32) HPN18 12-20 min (bag change) (464) HPN19 time consuming (17) HPN19 having to make it up every six hours was time consuming, changing lines, always having to have two nurses to check it, because the way the GI Unit is split here is there's a corridor up between the two wards so obviously bed cover etc etc but only have one trained each side so this a bit at times, a bit difficult....geography of the wards...we've no one else to check the drug (21, 28, 29) HPN19 you prime your line with your medication as well, was run the bag for 4 hours then put a flush up to get the last 2 hrs of the ciclosporin that was in the line, so you're going back to the patient quite a lot (37) HPN20 you need two registered nurses cos our student nurses aren't allowed to check anything like that....Probably 10 – 15 mins. Make up the bags, go to the patient, check the patient, change the bag four times a day, probably an hour anyway.... over a 24 hour period probably about ¾ - 1hr would be spent dealing only with ciclosporin. (263...270) HPN21 because the patient is on an infusion for longer they can be a little bit frustrated...longer period of time than...inflix (98) HPN22 they (nurses) are a little bit uncomfortable with it, but only because they are not familiar with it (27)	

HPN22 any new drug that you're not familiar with, its time consuming, and of course with time pressures on the ward, they can find that quite difficult (29) HPN24 It's difficult with the cicl because we were told we are not supposed to stop it we have to continue, not supposed if patient goes off ward and needs to be continued..... there will be side effects if we stop it (24, 39) HPN24 it was a bit difficult and also we have to work out about how many mls, because we didn't work it out ourselves it was the DR who gave use the prescription so no-one has actually taught us how to do it...even the pharmacy they also had difficulty (46) HPN25a my experience is from years and years and years ago when I worked on a ward and it was a bit of a nuisance....it was just a nuisance for me as the nurse looking after ten other patients. (29, 38) HPN25b patients don't particularly like being hooked up to it for such a long period....its restrictive (52, 57) HPN25b it's intensive in that first period...it's a fairly significant drug to be administering (208, 211) HP14 if you get rid of the IV then you get rid of the question of the difficulty we have with cicl which is the administration because it then leap frogs over inflix and becomes the easier drug to administer rather than the more difficult to administer (263) HPN19 I suppose there are a few downsides with cicl, not that there aren't with inflix...within the trial, they went onto cicl tablets and had to be monitored more frequently that say inflix so that's slightly more logistics for the patient so that kind of scenario (134)	
General comments about the administration of ciclosporin & infliximab	
HP3 nurses need training up (to administer both drugs) (72) HP4 Administering is a challenge for this particular unit, actually that is not entirely true...(6) HP4 The concern is the availability of ciclosporin levels and people's perception is it's a more difficult drug but not true. No different administering either drug not difficult to do, we should be clear about that (13) HP4 there is a perception that Cicl is difficult drug to use but reality is there is equal access to both drugs and equal availability of both (18) HP9 we basically order it and the nurses are very experienced in giving both, so it doesn't really cause us problems (34) HP9 at one stage I felt ciclosporin might be the slightly more effective of the two drugs but that infliximab was a bit easier to manage, so the two were reasonable offset by each other (47) HP10 the burden of administration, is in making it up, setting it up, rather than monitoring during the infusion (both drugs) (56) (we make it up on the ward (136)) HP12 cicl we know because there is so much data out there. Inflix the answer is yet to be resolved and so some people might take that as a negative aspect in relation to inflix (51)	

HP14 so on the one hand you've got the convenience of doing infliximab and on the other hand you've got the convenience of being able to stop cicl (151)

HP14 if I think they are really heading home but they need a bit more then I'd give them inflix and if they are really heading for surgery but they want last roll of the dice I'd give them cicl (174)

HP15 I would stress that the differences are not massive (455)

HPN18 I don't really have any views on administering it (cicl) it's a drug, we administer it (14, 18)

HPN19 it's (cicl) more involved because it's a longer period but it's slightly less involved because it's a longer period, if you know what I mean, so once you set it going, as long as you don't completely ignore them, you know, it's sort of done for 24 hours so it's kind of up and down as to whether it's helpful to have a longer infusion or a shorter one (30)

HPN21 I can't say I've seen any sort of difference between the two regarding administration (95)

HPN22 I don't see there's much difference to be honest with you in the practicalities of it (inflix vs cicl) (67)

Effectiveness

Ciclosporin	Infliximab
HP4 tend to use ciclosporin as acting more quickly (171)	HP3 sensible and good experience of this drug 'when it works it is fantastic' (23-25)
HP7 had good benefits with good effects from ciclosporin pts in past (92)	HP3 'labouring work' but works well (25)
HP9 felt ciclosporin may be the slightly more effective of the two drugs (47)	HP7 data suggests it is effective, easier to administer, simpler regime, less palava (28)
HP9 we've always been very cautious with it and as I say I've always offset that by thinking it was an effective drug (63)	HP11 this is the one thing I don't like about inflix because there is no data to give us a clear timescale or timeline for decision making (94)
HP11 one of the things I like about it (cicl) is the response or non response is very clear and clear cut and has a very short time scale (81)	HP12 the other slight issue with inflix is the speed of response (39)
HP16 I think cicl is effective (272)	HP12 the response is slightly sort of slower (45)
HP16 I don't see it being any more effective than inflix but I'd accept that it probably does work and it probably works well (276)	HP12 sometimes it is a bit challenging that you have given the inflix if they are going to take a sort of week to 10 days time, would you hold the nerve (47)
HPN24 it takes a while to settle down. As far as I can remember it took a while for that patient to settle down with his bowels ...day 3 they still feel bas they still feel worse (102,105)	HP12 it's at least as effective as ciclosporin with the additional benefit of convenience and potentially less toxic (222)
HPN25b the patients that have been using it seem to have responded really well I've not seen anybody that's had to go onto you know to anything else having had ciclosporin everyone that I've seen using it have responded well. (74)	HP16 it's very clear to me it's a very effective treatment for a proportion of patients with really severe colitis and there's no doubt that we've had some patients with toxic dialation, who've really been at the far end of the spectrum who have responded perfectly immediately (215)
	HP16 I think that the efficacy is best...at worst is broadly similar (409)

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	HP16 though anecdotally I would probably feel that my infliximab response rate ...the inflix works better (414) HP15 the good thing about infliximab is that you know fairly rapidly whether it is going to work and once it's worked and patients have a dramatic benefit (106) HP15 It's quite difficult to stop it and that's actually one of the biggest issues, the clinical decision is about when to stop the drug (108) HP16 you probably get patients out of hospital quicker with inflix (287) HPN18 I felt that when they were randomised to infliximab they has a greater chance of not going to surgery ... but that's my personal gut feeling (219, 224) HPN20 the patients that were on the trial, the vast majority of the inflix ones seemed to do better (179) HPN20 very beneficial (81) HPN23a I think those that are sensitive to it, it works very very well (57) HPN23a I think we definitely see much more progress with people on inflix (122) HPN24 it worked really well on that patient (33) HPN24 there's a quicker response with inflix...patients pass comments and they always tell me I feel much better after this one (118) HPN25a it seems like a very good drug because I've seen so many successful outcomes... but that's mainly with Chron's disease and my views about ulcerative colitis are slightly mixed because the outcomes haven't been as successful but I think perhaps they've been treated a little bit later (87, 92, 95)
General comments about the effectiveness of ciclosporin & infliximab	
HP6 in terms of efficacy – sort of good similar experiences with both drugs (87) HP9 infliximab as safer and easier to manage but maybe not quite so effective and ciclosporin as a bit more sort of a fiddle, little bit more risky for the patient but perhaps a little bit more effective (91) HPN19 inflix was the new boy on the block as such and cicl was maybe seen as bit older, you know maybe less effective drug (26) HPN21 they all seem to do quite well on it (inflix) the same with cicl (84)	

Adverse events

Ciclosporin	Infliximab
HP5 I have had problems with sepsis of pelvis when we don't look carefully enough (39)	HP6 can watch out for any infusion side effects easily, with regular obs every ½ hr or so (78)
HP5 Inflix is easier than Cicl as you don't have to worry about electrolytes and reactions (18)	HP5 Inflix is easier than Cicl as you don't have to worry about electrolytes and reactions (18)
HP5 Out of personal choice, Inflix and with younger people using it as first line of treatment as less toxic [than ciclosporin] (26/32)	HP4 patients tend to tolerate infliximab better than ciclo (184)
HP6 safety aspects – thought ciclosporin was more of a dangerous drug to give (44/49), Used inf because of safety aspect (72)	HP7 treating peo with Inflix go through risk counselling, unknown risks, no data re cancer or 10-15 years hence, potentially greater adverse effects need to make patients aware of that (35)
HP6 don't really want to continue long term because of side effects (99)	HP11 It certainly has a risk of side effects profile which is no less worrying than cicl (58)
HP3 worry about toxicity & liver, use it half-heartedly, when no choice (that or colectomy) (32/33)	HP11 anaphylactic reaction (149)
HP7 adverse sides to it, but equally well accepted and well established (19)	HP12 hold off on inflix for older individuals (68)
HP9 potentially quite significant side effects that can happen… slightly uncomfortable feeling about it (60)	HP16 you don't have this concern of canullas tissuing (171)
HP9 there's the hassle of the levels and a lot of patients in my experience, end up with toxicity, tremor particularly (153)	HP16 anecdotally we don't see a significant increase in complications or infections post-operatively in those patients (inflix remains in system) (259)
HP11 I think that in the long term the risks of renal failure are significant (125)	HP15 there are less risks (69)
HP11 The patient needs to be counselled on the risks (11)	HPN19 most of the time it goes without incident (83)
HP11 patients are most worried about are surprisingly seizures,,,, renal toxicity (68)	HPN21 have only ever seen minor reactions to the inflix, patients don't seem too worried by it (82)
HP11 renal toxicity is what worries me most of all if I don't have a reliable system to make sure that these patients are monitored (72)	HPN24 there were no side effects (99)
HP12 comorbidities in relation to toxicity and hypertension etc, renal toxicity and hypertension again in the same group elderly (76)	HPN25a I've had very few problems with infusion reactions. (59)
HP16 I'm always a little bit more nervous with it.. and I think that's from the side effects, of renal impairment...I think the side effect profile of cicl although it's maybe not come out in studies still concerns us more (278, 281)	HP11 Every bad reaction I have seen with infliximab has been in older patients (220)
HP15 Risk benefit ratio compared to inflix is slightly worse (82)	
HP15 we've treated lots and lots of patients with ciclosporin over many years and most	

of them are OK, but they are more likely to get hypertension, ...slight parathesia, most...very subtle change in renal function... some of get other neurological side effects, slight tremor (87) HPN20 it's more the potential for reaction to these drugs and the increased observations really that pose a problem for a busy unit (56) HPN25b in the early stages we would monitor them for the first few hours to make sure they weren't having any reactions (182) HPN24 we have to monitor this patient closely for any side effects ... it takes 3 hrs because you've got to do obs for a couple of hours, but then sometimes we tend to forget because we get busy with other patients... so ideally it should be one to one..because we handle 9 patients (249, 255)	

Monitoring

Ciclosporin	Infliximab
HP2 Inflix [nurses] more used to it, advantages over Cicl no monitoring needed compared to level for Cicl (42) HP4 concerns re availability of ciclo levels (54), sent to another hospital, take approx 3 days for result (61) HP7 disadvantage is slight – continual infusion over long period of time, have to check levels (17) HP12 monitoring is sort of more labour intensive for nursing staff point of view (139) HP12 they have more monitoring after they leave hospital (276) HP15 you have to monitor the levels which don't currently do for inflix (92) HPN18 once the patient has been on cicl for 24 hours they have to have bloods and if the cicl are too high then they tended to stop it . Now the issue we have is because they are having continous cicl they have got cic going through their veins, so their levels would always be too high. So they tended to sort of mess about and putting them on oral earlier than they needed to and things so I think from that point of view it was difficult (32) HPN18 most research staff are only around Monday to Friday 9-5 it is very difficult to monitor what is going on with the patient (44) HPN18 they don't monitor the patient, the patient doesn't need any monitoring (12 hour	HPN20 we kind of treat both as the same, we make sure the individual is monitored every 30 mins for a period of time.. The only difference with inflix is that the infusion only last 2 hours but you're observing that patient for 4 hours, so really when you put the two together they are very similar (66)

infusion site) (442) HPN21 time consuming with regards to observation, particularly on a busy ward when you've got one nurse to 10 patients, it can take quite a huge part of your workload (16) HPN20 we're doing observations very, very frequently within a 30 minutes period over maybe 4-6 hours just to make sure that the individual is fine and comfortable (36) HPN20 your with that individual for up to 4 hours when you've got demands of other patients, that's when it becomes difficult, but that's more a time management issue and sort of staffing issue (51) HPN20 we kind of treat both as the same, we make sure the individual is monitored every 30 mins for a period of time.. The only difference with inflix is that the infusion only last 2 hours but you're observing that patient for 4 hours, so really when you put the two together they are very similar (66) HPN24 we have to monitor this patient closely for any side effects ... it takes 3 hrs because you've got to do obs for a couple of hours, but then sometimes we tend to forget because we get busy with other patients... so ideally it should be one to one..because we handle 9 patients (249, 255) HPN24 care assistants can also monitor blood pressure (269) HPN25b from a nursing point of view there are obviously monitoring issues. (41) HPN25b in the early stages we would monitor them for the first few hours to make sure they weren't having any reactions (182) HPN25b we would probably monitor them more closely over the first six hours over the first bag (232)	

Longer term maintenance

Ciclosporin	Infliximab
HP5 mostly the effect is useful acutely but after that no much use in terms of maintaining remission (60) HP5 Cicl is not good in longer-term, for maintenance (62) HP6 don't want to use in long-term because of side effects, switch to Azathioprine soon as poss (99)	HP5 Published studies show longer-term benefit of Inflix, similar to Crohns (50) HP5 issue of not being able to continue with infliximab - would you want to start with something you can't continue? (69-71) HP6 Can only give 3 Inflix infusions, not allowed to continue on maintenance basis, unlike for Crohn's (94)

HP6 if pt already on Azathioprine no point in starting ciclosporin as nowhere to go (101)	HP1 Longer term giving of Inflix, not sure, twitchy of long-term treatment (with Crohn's perspective) tell patients to come off or I take them off if they are in very deep remission (49)
HP1 Little experience of longer-term treatment for patients on Cicl 6 months to a year would be OK then I would get worried would then look to Azathiorpine (66)	HP3 personally prefer to give Inflix and over the longer-term, as maintenance too (52)
HP3 long-term renal failure wouldn't give Cicl over three months (57)	HP4 Have to argue for infliximab on named pt basis for those we need 2nd or 3rd induction and maintenance agents because have life events meaning don't want to consider surgery (199-204)
HP7 don't use Cicl long-term either switch to oral after 3 months no-one is on it long-term (74)	HP4 do have 1 or 2 pts using outside NICE guidance (206)
HP9 there's the hassle of the levels and a lot of patients in my experience, end up with toxicity, tremor particularly (153)	HP7 use Inflix for max of 12 months then stop unless they absolutely need it afterwards, maybe azathioprine is then adequate (wait and see policy) (60)
HP9 isn't particularly effective ....so would see that again as a bridge to getting them on Azathioprine (157)	HP9 there are funding concerns (121)
HP10 the real risks there are risk of infection because the deaths related to ciclosporin have generally been associated with extended use (119)	HP9 I wasn't all that impressed with it as a drug, I didn't really get the feeling it was making a huge difference for patients (125)
HP10 I give it for a limited period (ciclo) but simply because the evidence for giving cicl on a long term basis and retaining remission is ....well there is none (124)	HP9 as a maintenance option I still have some concerns about it (127)
HP11 I don't (treat patient in longer term with cicl) (116)	HP9 concern about its long term effect based on fairly limited use in UC (133)
HP11 I think that in the long term the risks of renal failure are significant (125)	HP10 first attack I would usually use infliximab as a bridge to immunomodulators with Azathioprine. If patient has relapsed..... there's a much stronger case for using infliximab as maintenance therapy (85)
HP12 absolutely no, no longer term, not at all (118)	HP10 all the infliximab in every other clinical chronic inflammatory condition shows that continued use provides continued benefit (100)
HP12 we don't have any patients pre-trial and post-trial who have continued ciclosporin more than 3mth period (122)	HP11 problems come up with NICE, we are getting increasing pressure in our area, to show that we are following NICE guidance so that becomes a problems (100)
HP12 no evidence for long term use of cic in UC setting anywhere (132)	HP11 I tend not to (101)
HP13 I don't think there is any evidence for that. (162)	HP11 There are cost implications, there are immunosuppressant implications so if it is possible for a disease which is essentially curable with surgery then I'm not sure that it's the right thing (108)
HP13 I would often stop it before that (12 weeks) or sometimes I would stop it before that if they run into complications of therapy and I have to say it really is a bridge to using azathioprine or mercaptopurine for immunosuppression (166)	HP12 we clearly individualise patients (longer term care, inflix) (95)
HP13 if somebody comes in on Azathioprine you could argue there's not much point in giving the ciclosporin because there's not a get out strategy (173)	HP12 longer term after 12 months it is clearly individualised and based on sort of consensus at the MDT (97)
HP14 I think it's limited to the bridging effect so I think on the other hand although I have access to use it long term. I don't use it long term (60)	HP12 we don't have any patient in xxxx at the moment with UC who have gone past 13mth period, that just puts it into perspective (103)

HP14 we tend not to, I think we've had a couple of patients over the years who've had longer term cicl, you've got to watch their blood pressure and their renal function. I think it's probably not an acceptable long term treatment after 3 months, I'd be cautious about doing that (86) HP14 I don't think there is the trial evidence to support it (96) HP16 I would treat someone with cicl for between 3 and 6 months... then stop it (357, 362) HP16 I can use cicl as a bridge to getting them into another effective therapy (364) HP16 I see it as a short term treatment (384) HP15 we don't generally, I've got only one or two patients, most of them only have it for three months (179) HP15 long term toxicity (189) HP15 I think that in young people where there is a significant risk of renal damage long term then I'm very very wary about using it long term (189) HP15 in some ways it's easier to make that decision for cicl because the risks are greater for long term therapy (195) HPN18 As long as it's tolerated there's no issues with continuing ciclosporin in the long term (207) HPN19 (discussing longer term cicl) again if it works for the patient, sometimes it comes down to an individual decision then I would be happy to do that (202) HPN22 if it works for them, then yes, absolutely (115)	HP13 I think the published data is not great (134) HP13 I would like to have it available for a few selected people who I don't think are quite ready for colectomy (135) HP13 I don't have anybody left on it and I've tried but for one reason or another people have failed treatment and come off it (141) HP13 if you rescued somebody like that with inflix then they should continue on the drug (179) HP14 I think the current NICE guidelines are um, a bit tricky because I think if you are going to give a patient infliximab you need to give them…., and then they respond to it, if they do respond to it you want to be able to continue the treatment and I think it may have more of a long term use than the NICE guidelines that we're currently using (38) HP14 if a patient is responding well to infliximab I think there's a case for them continuing it (54) HP14 It's what we do in Crohn's disease, we're familiar with doing it, it feels comfortable, patients do well and I don't have any problem with it (71) HP16 if you get someone who responds very well then we will give them three doses and we will try and assess them at the end of this and if they are better we'll stop it but if they relapse then we will continue (332) HP15 it works fantastic (102) HP15 it is generally well tolerated in young people (long term) ... and actually when they are on it and have has a really dramatic response it's much more difficult then to withdraw it (200,205) HPN18 the patients seem to do quite well on it generally (201) HPN19 we now have to request the funding for patients with UC on long term inflix...so that's a bit of a challenge and it means that decisions are made differently to whether a patient is going on to maintenance inflix (154, 156) HPN19 (discussing longer term inflix) it sometimes comes down to a very individualised decision because it depends on how the patients are, how they feel you know.(183) HPN22 It's already an issue because we can't really treat as maintenance with inflix so obviously if a patient responds well we've had to get exceptional funding and thing like that and so there is a case for it I think (103) HPN23a Some (patients) prefer it longer but some go onto Humira, the Adalimumab, the

	injections that they have but some are happy to just have the inflix and it works for them ... I think they are quite happy to have that done because they feel great benefit from it (71, 78) HPN23a We've got some who have been having it in excess of 5 years (86) HPN25a Most of the patients we treat have have been on it long term or do continue to have it long term....over a year... And many of our patients have been on it for much longer than that... a lot of the patients that we try to withdraw treatment end up going back on it because they relapse. (122, 126, 130, 133)
General comments about the use of ciclosporin & infliximab as longer term maintenance	
HP5 In an acute situation you tailor your support according to your gut feeling (76) HP1 Depends what is best for the patient (54/56)	

Personal preference and involvement in the trial

Consultants' personal preferences

Ciclosporin	Infliximab
HP5 I have more experience of Cicl and am more cautious, looking for infection foci (38) HP5 I have a lot of good experience with this drug but I am more wary than I am with Inflix (42) HP6 last time I really used a lot of ciclo was 10-11 yrs ago but only about 3 or 4 pts (84) HP4 Only tend to use Cicl as acting more quickly (171) HP9 a sort of slightly uneasy feeling about ciclosporin that I think I do have (56) HP10 rather more relaxed about it, paradoxically, simply because I know when the IV infusion is stopped, the drug disappears (75) HP11 I might reach a preference with cicl a the moment (155) HP11 I've used it for a long time and I'm comfortable with it (160) HP13 if I was looking at the data and assuming efficacy is equal I would favour cicl (270) HP13 unless you've got a bloody good reason you should be using cicl (444)	HP2 I'm more familiar with it (47) HP5 My own personal preference would be Inflix (103) HP5 Out of personal choice, Inflix and with younger people using it as first line of treatment as less toxic (26/32) HP6 personally prefer Inflix see results more quickly can watch out for side effects, seen good outcomes, I would choose it if I had the choice (77) HP1 treatment preference based on familiarity for nurses and me (from Crohns treatment) (86) HP3 sensible and good experience of this drug 'when it works it is fantastic' (23-25) HP3 Inflix personal preference, 'absolutely' but follows NICE guidelines (unfortunately) (116) HP3 would go for Inflix if no contraindication. If contraindicated would have to go for Cicl (40) HP4 I suspect my prejudice is towards infliximab, if I had to have one. Probably because of lack of availability of Cicl and not having the ability to monitor it closely as I would like (164) HP7 newer than Cicl (only 15 years) more used to using it with Crohns than UC (24)

HP14 i don't much like it (9) HP14 I would be more likely to use oral cicl than I would IV cicl ... I don't think IV ciclosporin is what I would use in the future but we've used it for the trial (259, 262) HP16 I'm a little bit relunctant to treat with cicl anybody who's already on azathioprine (313)	HP9 probably slightly in favour of infliximab just due to ease and sort of slight feeling that it's a bit more predictable and the side effects are easier to manage (190) HP11 I personally am yet to be convinced that it has anything to offer in terms of advantage over and above cicl (36) HP11 I don't feel comfortable using it (60) HP11 (on inflix) if there is data to suggest that it significantly better in terms of avoiding surgery in terms of success of treatment then I'm willing to change my mind (62) HP12 that is a difficult one but I would say yes at the moment if I had to choose between the two I would go for infliximab because there is, although not good quality RCT data... but there is clinical experience data (85) HP12 I mean personal preference would be for offering infliximab and then colectomy (159) HP14 if the 2 were equally efficacious and equally cost effective, I would choose infliximab because of that reason (practicality of administration) (138) HP16 my treatment preference is inflix...my reasoning for that is that I think that the efficacy is best.....at worst broadly similar (405, 409) HP15 My personal view is that they probably have equal efficacy, I think inflix have overall my clinical impression is that it has less side effects so if I was given a free choice, if it was asking it for me or if my loved ones, I would opt for infliximab (65) HP15 my treatment preference is slightly in the direction of inflix (222) HP15 when a patient was given inflix I was rather please and when they were given cicl I was less enthusiastic...we wondered about the tolerance for the patient and the convenience for the patients (380, 394
General comments on PI personal preference	
HP4 the subtleties of which sub-group of people respond to a certain drug, you will always be slightly biased by personal preference (183) HP4 find that patients tend to tolerate Inflix better than Cicl, but that is general impression, not data-based, but I am more in favour of ensuring appropriate medical rescue is provided rather than giving preference to one drug (185) HP7 I don't have a treatment preference happy to administer either (90) HP14 I want the one that's more effective (141) HP14 some patients I'd choose and some other patients I'd choose the other (170)	

Consultants' views on nurses' preferences

Ciclosporin	Infliximab
HP6 I often find that nursing staff aren't as comfortable with it (13)	HP2 Inflix more used to it, advantages over Cicl no monitoring needed compared to level for Cicl (42)
HP6 Clinicians don't like using ciclo (21) and attitude has infiltrated down through the nursing staff, so they weren't happy using it either (30)	HP2 most nurses more familiar with Inflix (41/91)
HP6 the only thing is with unfamiliarity with using it (108)	HP2 specialist IBD nurses more comfortable with Inflix (92)
HP3 they [nurses] think it's quite labouring and need extra work (78)	HP5 nurses think that Inflix is easier to handle (81)
HP11 nurses on the ward are very familiar with it (44)	HP5 nurses think Inflix is less problematic (82)
HP14 the problem they have with cicl is keeping up with the drips (115)	HP5 nurses think Inflix is quicker (85)
HP16 I think that they would wish that we didn't prescribe cicl again (389)	HP5 nurses prefer to give Inflix (82)
HP16 I think they find it far more difficult, more complex, more time consuming, there's maybe a little bit of a familiarity issue (398)	HP6 Attitude of gastro consultants has filtered down to nurses to prefer Inflix (30)
	HP6 nurses are happier administering Inflix, (36/37)
	HP6 nurses unfamiliar with Cicl, used to Inflix, happier with it, fear of the unknown 112)
	HP6 preference for infliximab (116-8)
	HP6 would like to use for grumbling colitic pts who aren't severe enough to require admission but not that well on drugs in the community (124)
	HP1 nurses prefer Inflix from the experience and numbers they have treated so far (79)
	HP1 one patient with Cicl compared to 30-40 Inflix means more familiarity with Inflix, more comfort (80)
	HP1 treatment preference based on familiarity for nurses and me (from Crohns treatment) (86)
	HP3 one specialist nurse gives Inflix only (70)
	HP3 nurses are used to giving Inflix (108)
	HP7 prefer Inflix, more familiar, used more generally, simpler, easier to prepare and administer (83)

	HP12 they prefer, clearly infliximab, primarily because it (cicl) is challenging reconstituting is messy as well as changing bags every 6 hrs, monitoring is sort of more labour intensive for nursing staff point of view (137) HP13 we find umm, infliximab easier (189) HP12 you could sometimes get from the nurses reaction after we got the randomisation, immediately you can see they are relieved if it is infliximab as opposed to ciclosporin (17)
General consultant comments about nurses preferences about ciclosporin & infliximab	
HP3 nurses are not happy giving any of them (72) HP3 nurses agree with me that it is all time consuming (77) HP3 nurses don't have experience of both drugs (68) HP4 nurses don't have a problem with either drug, fully conversant with both (150, 154) HP9 I think they're OK with both 1(171) HP9 historically they probably have more experience of using ciclosporin on the wards than infliximab but now it's pretty equal. I don't think that's a barrier to the use of it really (172) HP11 I've never heard any complaints about either drug (135) HP14 they don't have big problems with either of them. They are more familiar with inflix than they are with cicl and the problem they have with cic is keeping up with the drips (114)	

Consultants' views on colleagues' preferences

Ciclosporin	Infliximab
HP2 most specialists are confident with Inflix and more familiar, level monitoring of Cicl is problematic (81) HP5 My unit is more likely to use Cicl (107) HP6 some gastro colleagues less used to using ciclo (20) HP6 Gastroenterologists who have worked there a long time don't like Cicl. They didn't like it from the word go (21) HP4 perception that Cicl is more cumbersome (25) HP4 outside the trial (where there is no choice because of randomisation) people's perception is that Cicl is more difficult (lack of availability, Cicl levels more	HP2 most specialists are confident with Inflix and more familiar, level monitoring of Cicl is problematic (81) HP2 (pro Inflix) most specialists feel 'well if I'm given a choice why don't I go down the path of least resistance which is human nature' (83) HP2 my colleagues are more familiar with Infliximab, they favour Inflix given the choice (47) HP6 Always prescribed Inflix in this hospital, consultants are more comfortable with it (26,35) HP6 colleagues prefer prescribing biological (26) HP9 there might be a preference towards infliximab just in terms of sort of ease and comfort (66)

unpredictable, more cumbersome) (54, 66) HP9 it's a drug we don't use very often (referring to unease with cicl) (58) HP12 cicl is the devil who you know because we have used it for many years (40)	HP9 something that is there in all of us in a way (referring to preference for infliximab) HP12 I would suspect that other colleagues mostly favour infliximab (252) HP16 think if they were given the option they would tend to favour inflix simply, I think it's done and its done and it's a much more well trodden pathway (612) HP15 I think most of them would be very keen to use the infliximab if they got the chance (340)
General comments on consultant views of colleague preferences	
HP2 Not all colleagues are happy to use either drug equally (73) HP4 personal view we pre-decide what happens in drug use for each individual patient according to what drugs they were on before, long term sensible goals, what is acceptable, pre-defined outcome (95) HP4 the subtleties of which sub-group of people respond to a certain drug, you will always be slightly biased by personal preference (183) HP7 I don't have a treatment preference happy to administer either (90) HP9 some colleagues were strict ciclorsporin users because of what the HTA [think he means NICE] had said and then there were others who were coming down on the infliximab side (300) HP14 I run it as a dictatorship so it's the same as (laughs) my views about, I'm in charge (laughs) so yea I think we appreciate they are equally effective (252) HP14 equally effective and there isn't a scientific preference between the two (255)	

Nurses' personal preferences

Ciclosporin	Infliximab
HPN19 I think their view is that they're not so keen on it but that's not necessarily based in any facts or knowledge it's just their opinion (20) HPN25a I don't have anything to do with ciclosporin so I probably if I was on a ward though I would prefer to use infliximab because it's easier to mix.... It's (cicl) much more high maintenance for the nurse so if I was on the ward and had the choice I probably would still go for infliximab (174)	HPN18 I prefer it when they have inflix... I think it's easier for the patient... because it's just one infusion... it's a couple of hours instead of being hooked.... I mean keep in mind they have got profusive diarrhoea... I think it's easier to administer as a nurse and it is easier for the patient to receive it as a patient (165, 169, 173, 178, 189) HPN18 Myself it would be infliximab but basically my reason for that..my background it haematology/oncology as we used a lot of the group of MAB therapies... we have has some really good, you know reactions with them (264) HPN19 I'm happy to treat patients with it (93) HPN19 I think there are pros and cons to both to be quite honest..... I don't rule out cicl as a treatment, but I think it's still, patient wise and other nurses and I think the general feeling it

	that infliximab is seen as better rightly or wrongly (144, 146) HPN19 probably still say it is inflix... and I probably fall into the same category or it's a recent drug and its...maybe again it's personal experience because I've probably seen the effects of inflix more... I speak to patients and find out their experiences and I don't see cicl (232, 236) HPN21 it's quite a good drug to be honest with you (119) HPN21 Personally I feel that the inflix is better but that's only because of the experiences we've had with the inflix rather than the cicl ... seen patients do very well on it, particularly when before there perhaps wouldn't have been any other outcome than surgery for them (209...217) HPN22 I've always considered infliximab is a good drug (77) HPN22 I kind of lean towards inflix but obviously, you know if the evidence tell us something different....just because I'm more familiar with it, that I see more patients have a good effect from it, but that's probably just because we've used it more (145, 150) HPN23a for most of the patients it a wonder drug, so I'm definitely all for it (28) HPN23a my own experience with inflix is a positive one, you know for patients so I can only think that it's a great thing to have (190) HPN23a I just think it's a great treatment, I think it's very good it's very effective and it's nice to see that it's actually being used widely with it being such an expensive one (254) HPN25a I don't have anything to do with ciclosporin so I probably if I was on a ward though I would prefer to use infliximab because it's easier to mix.... It's (cicl) much more high maintenance for the nurse so if I was on the ward and had the choice I probably would still go for infliximab (174)
General comments on nurses personal preferences	
HPN20 I can't say I do, I can't say I don't (179)	

Nurses' views on consultants' preferences

Ciclosporin	Infliximab
	HPN18 My feeling , that the doctors think that there is more value in giving someone infliximab than perhaps continuing with standard care (cicl) (237) HPN19 I think there is still the perception that there is still the perception that inflix is better....because it is the new one...not necessarily the consultants but maybe the doctors who aren't as experienced or a new rotation or new into it as such that maybe they don't

	necessarily know cic (211,214) HPN25a I don't know that that's what they would choose but I think now if they could use infliximab they probably would. And if they can use it they do (155, 160)
General comments on nurses views of consultant preferences	
HPN19 I think they're happy to do both (211) HPN20 (doctors considering practicalities for nurses) No they give no consideration whatsoever I would say (laughs) (168) HPN20 I don't think they know enough about it, if I'm being honest with you, because we have a 3 month changeover for our medical team on the ward that they simply don't have enough confidence with the drug, they rely heavily on the nurses to tell them what it is and how they must prescribe it and again if there's a reaction, what they need to do about it, they don't seem to have the knowledge base as perhaps they should… they seem to be quite unconfident with it, purely from a lack of education, I feel (164…176) HPN22 (doctors views on administering drugs) I don't think they actually probably consider it to be honest with you...no I don't think they think about the actual administration at all (121) HPN23a They're just of the opinion that if it suits the patient and they get relief from it then they're quite happy for them to have it....it's an expensive drug (inflix) to have but it's just very effective so I don't think they mind at all (97) HPN25a don't think they have much opinion on the practicalities of it because it's not for them to worry about.... Yeh I don't think they give any consideration to that to be honest I think they you know they're more interested in the outcomes for the patient. (160, 165)	

Equipoise and views on trial

HP2 Efficacy of both drugs is equal, so not choosing one over the other on those terms (65)
HP2 Both drugs are equally available in the Trust (103)
HP2 Not all colleagues are happy to use either drug equally (73)
HP5 we haven't been successful in the Trial, we don't have nurses who can support it (169/173)
HP5 support for recruitment has not been there, only one single-handed nurse specialist (179)
HP5 'I'm fighting my corner again [for research support], as usual, story of my life' (180)
HP5 Trial nurses support the Trials Unit but they won't cover the wards where patients are both treated and recruited (189)
HP5 the Trial is good, very useful, very important. (197)
HP5 'I would like to make a thing about the Trial' (196) paperwork is hard for us to get, too much of it, too much for different departments to handle (R&D, pharm), much more than usual, top-heavy (197) (207)

HP5 the drug we choose ultimately depends on the patient (75)

HP5 you can always find reasons why Cicl is contraindicated! So you can say that Inflix is indicated for patients with acute colitis because, for example, they were at risk of infection (142)

HP1 I would give both Inflix and Cicl info to patients in an open setting if they want (41)

HP3 did not have any admissions severe enough to recruit to the RCT (191)

HP3 we had lots of people in the cohort but all responded to steroids (191)

HP3 luckily for the patients no one was eligible up to now for the RCT (192)

HP3 no patients have gone to to Cicl or have had colectomies for UC so no one ready yet (200)

HP4 quite well equipoised for this, so there would not have been a cost issue colouring our thinking, we do use both drugs (74)

HP4 There is a big difference in cost but it wouldn't drive our decision making outside this trial (80)

HP4 if choice has already been made about drugs, for those patients obviously don't want to be randomised to the trial – would obviously be a great number of patients in that situation (129)

HP4 I am aware that our numbers who have gone to randomisation are small but our cohort is reasonably big, trying to think why this might be (136)

HP4 we are not actively not getting them randomised into the trial, we have a research nurse and do 11 o'clock ward round to pick patients up (146)

HP4 you can use Inflix for acute rescue in the context of the trial, which is good and appropriate for the trial (204)

HP4 "I feel increadibly embarrassed that we have only had 1 randomisation and I know I am very proactive when I am on the ward and I know some patients will have been missed because inevitably no system is perfect…" (245)

HP4 "It is going to prompt me to look back at the cohort… because I do want to understand why so few people needed to go on….is proactively driven by my colleague… it either means all our patients are going into remission or we are failing to recognise that they need to be offered medical therapy and then not being randomised in the context of the trial… don't quite know what all the variables are to explain our very low recruitment" (252)

HP4 "it is high on the agenda and our nurse comes to a daily ward round" (279)

HP4 "exceptionally well run and organised trial" (288)

HP4 "I think you should be congratulated" (293)

HP4 "I'm just sorry we haven't got more patients actually in the randomised cohort" (294)

HP9 I think it was a good trial for use because we were slightly divided and reasonably neutral going into it (303)

HP9 we did go into it sort of excepting that it was a good clinical question that we didn't know the answer to nd we needed to move on with that (329)

HP11 (on inflix) if there is data to suggest that it significantly better in terms of avoiding surgery in terms of success of treatment then I'm willing to change my mind (62)

HP11 we have both been very keen to give every patient with colitis who was, fits the inclusion criteria be considered for the trial (257)

HP11 we have has a lot of patients who just did not want to go to the trial because you know patients come with their own pre-conceived ideas of what's better (261)

HP12 all of them were given the same (balanced view) even the colleagues who had been using cicl for a number of years gave the same view that we know this devil but we don't that much about the other devil but these are the pros and cons so the feeling from them all was that they were comfortable (259)

HP12 we were completely open (293)

HP13 you sort of has this feeling that infliximab was going to be better but actually as the trial progressed I don't think that was true (99)

HP13 my attitude changed over the course of the trial (110)

HP13 we couldn't give people infliximab without CONSTRUCT so we tried to enter everybody. I don't think you can anticipate any selection bias from our point of view (376)

HP13 there's a big down time when people think about it and then you start to persuade people and then they enter one and it just runs from that (411)

HP13 and by the end of the study you know it was just sort of taken as red within the unit that if someone came in with acute severe colitis they would have been consent for CONSRUCT and there's just the time taken for that change in mindset (417)

HP14 In terms of the outcome of the trial yeh, we were happy to use either of them, I didn't feel "oh no it's they've got this one or oh no I've got that one when I randomised them I was quite happy (241)

HP14 equally effective and there isn't a scientific preference between the two (255)

HP14 we were happy that it was a genuine equipoise decision (320)

HP14 but there were sites, I mean the site up the road North Tyneside up the road said we don't do that trial cos we believe the infliximab is better ad we're going to give inflix (324)

HP14 I think believing that the question is real and that there is equipoise is fundamentally important to the recruitment (327)

HP16 most of my colleagues is that the efficacy is probably broadly similar between the two but that for ease and convenience and side effect profile and familiarity of use within a hospital setting a biological would edge it, but we're quite happy giving cicl to the appropriate patients (560)

HP16 if the result was that cicl was a lot better we'd use it and it the results were that inflix was a lot better, we'd use it (622)

HP16 from the point of view from patient selection, it would have been difficult for us to introduce an enormous amount of bias (662)

HP16 most patients when they read about it probably intended to favour.. they were hoping they would get inflix, from reading the literature (673)

HP15 I would say that there probably isn't equipoise here, that we're slightly on the side of infliximab.... but of course at the beginning of the trial that view would have been different because of course they was less data available...more data equivalence of efficacy, but I still think people favour inflix cos it's better tolerated.... put all patients in, we were absolutely fair about it (345, 350, 360, 368, 372)

HP15 the difference (between drugs) is not sufficiently dramatic that I would say it was unethical to put them into a randomised study (460)

HPN18 pretty much from a personal point of view, every patient that I approached came into the trial. I mean they didn't all randomise, they didn't all go into the RCT, sometimes that was clinician's decision, sometime it was because they had read the little bit in the inflix leaflet that suggests that they could end up with some type of cancer (382)

HPN19 sometimes it depended on the individual clinician particularly in the beginning I always got the impression that there was… people had specific opinions but I think once they worked within the trial, working with the two drugs I think they were a lot more open to it as it developed (318)

HPN22 I can think of a couple of occasions a least over the last few years, where a consultant decided that no they wanted one particular one over another (191)

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HPN22 I can think of a couple of occasions a least over the last few years, where a consultant decided that no they wanted one particular one over another (191)

HP13 from a pragmatic point of view because if someone comes in now and they're not in construct then they get cicl because the SMC (Scottish Medicines Consortium) say we can't use inflix (218)

Consultants' and nurses' views on surgery (colectomy)

HP2 cannot generalise on whether to go for surgery or not, go by patient's experience (120)

HP2 no preference (surgery or keep on drugs) rely on clinical judgement re individual patient (121)

HP6 some patients should go for colectomy others worth trying to salvage their colons with drugs (146)

HP6 case by case decision, surgery for some is not a failure – it is what is needed for them at the time (147)

HP6 patient shouldn't regard colectomy as failure as such (148, 155)

HP1 If patient fit for surgery (life saving) and have not improved by 5 days would rather have it (92)

HP1 preference for colectomy but would go with what patient wants (cannot put colon back) (116-117)

HP3 anti-surgery and most patients agree with me they want to keep colon (126)

HP4 Colectomy still an important option often delayed by poor decision-making (213)

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HP4 conservation of the colon is important but need to look at whole picture (disease history, risk benefit, surgical salvage, level of disease, previous rescue with other drugs) (225)

HP4 patients sometimes delay coming in or have delayed contact once they are in or go to another team for a while effectively delaying the inevitable and poor decision making leads to the inappropriate delay of surgery (224)

HP7 patient views as important as anything else, combined with weighing up risks and benefits, involve them hugely (103-109)

HP7 depends on patient view of taking drugs long-term, view of surgery, views on bag (young women don't want it) (110-116)

HP7 colectomy = cure, there is long term risk of using infliximab & ciclosporin or azathioprine, all powerful drugs (105)

HP9 nice to have an option for patients that isn't colectomy (204)

HP9 I think colectomy still has a role (209)

HP9 feels a little bit disappointing having to go for colectomy because it means obviously the treatments haven' worked (for patient and doctor) (210)

HP10 lifesaving (156)

HP10 timely colectomy has reduced the mortality of patients with acute sever UC, it's about saving lives, it's not about saving colons (156)

HP10 colectomy is one of the other treatment options..... contingency planning (162, 165)

HP11 It's something we do because we have to (176)

HP11 most patients would rather keep their colon, I don't think colectomy is a cure as many surgeons put it (178)

HP11 I think we need to give medical therapy a good try because that is what patients want us to do (184)

HP12 I wouldn't say to anybody that surgery is the next step and the only step without offering them the option of inflix (69)

HP12 we do offer patients colectomy probably more than a lot of other centres, I would presume (141)

HP12 I mean personal preference would be for offering infliximab and then colectomy (159)

HP12 there is some variability but we are not adverse to offering somebody colectomy because we have excellent surgical backup (161)

HP12 you have to individualised the patient, their circumstances (181)

HP13 I think in the right circumstances absolutely the right thing to do (308)

HP13 you just talk to the patients, you know, the number of people I've met who've sort of said "you know I had that operation x number of years ago and I feel fantastic I wish I'd done it years before" (311)

HP13 I'm not saying that operations get rid of every problem, you know there are clearly problems with pouches and stomas and things like that (315)

HP13 from a quality of life point of view and from a data point of view and from a personal point of view, that surgery is right in many circumstances, not for everybody by any means (319)

HP13 but equally the ones who haven't had it are very nervous about having anything like that, it's a last ditch, it's a very difficult decision (330)

HP13 I guess if there's one truth in life when it comes out you can't put it back (338)

HP14 I think it's good but um it really does depend on the patient....it usually depends on the psychology and situation of the patient ..... they almost all say "I wish I'd had it earlier"(179, 189, 194)

HP14 we've rarely regretted sending anyone for surgery (203)

HP16 colectomies clearly can be life saving and necessary in the right patient (431)

HP16 I'd be uncomfortable with a young patient who's not been exposed to a second line agent having a colectomy unless it's because of an emergency deterioration in their symptoms (426)

HP15 it's a brilliant treatment, it's just that ileostomy and or potentially pouch procedure that you need afterwards that's the problem (232)

HP15 I think in this day and age it's actually a very safe treatment for severe UC, it just the consequences which are disabling for patients (237)

HP15 some of our patients just will not have a colectomy unless they are at death's door (243)

HP15 it's always a difficult discussion with families about when to have surgery (253)

HP15 nowadays the more medical treatments that are available the more we try to delay the surgery and then of course it becomes a little bit more difficult to make that decision (263)

HP15 (referring to acute cases, recently diagnosed) it's very much more difficult for them... they haven't lived with it (277, 281)

HPN18 with UC generally speaking if they have the surgery it generally goes away and it doesn't come back (297)

HPN18 you need to do everything you can to preserve you bowel. So my gut feeling is that we shouldn't just go straight to colectomy, we should try all possible therapies out there (309)

HPN19 I've got patients who are happy to be on medication and they want to put off colectomy as long as possible because they see it as this big bad evil and I have other patients who are more willing to accept surgery and colectomy because they want to get over the symptoms and they've such poor quality of life that they want more, better and sometimes there's that middle row as well who aren't not sure about surgery but have it and actually are really quite satisfied because it's an end to all the symptoms and the loss of quality of life and things. Though it does depend on an individual decision as well so it's very difficult (183)

HPN19 I think it comes down to personal decision, I think it's very important to have lots of discussions about all the options, medical or surgical... it's very difficult if they're newly diagnosed and they come in with their first presentation ... some people come with obvious preconceived ideas about things anyway and I think it's important to explore those feeling and how they feel and then kind of gets you to a decision because I think there are some patients who are adamant they want to try everything they possibly can medically before they go down the surgical route .. there are patients who actually get to a point where they want their life back and this is pretty ultimate... the surgery being the ultimate solution (254,267)

HPN20 I think sometimes they can carry on with the medical treatment too long, that's my opinion. (192)

HPN20 (doctors don't get to see the outcomes for patients) they probably don't see them that often after colectomy.(211)

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HPN21 I think it has to be very individual... I'm sort of on neutral ground with it... from a medical background, feel that they should be given the chance for a medical intervention before we go straight to surgery (236, 238)

HPN21 sometime they may be looking for a very quick fix (241)

HPN21 it's always a last resort, it's not something I'm particularly comfortable sending them off to have (247)

HPN22 I think it's an option and I think it's different for each patient and I think that they need to be given the choice and have all the information because for some patients it can be a very good treatment and give them back their quality of life (157)

HPN23a I think it has its place, you know if the medical intervention is just not working...I think it's a very hard thing to come to terms with, patients need counselling...I think they (patients) all prefer to try the medical treatment first (140, 147)

HPN24 that would be their last resort, their last option.... I think I would rather treat it conservatively first and then see what happens (190, 193)

HPN25a well I suppose it depends on patient by patient basis I mean I have seen lots of patients who've struggled for many years with different medicine..... And had all the you know all that's available to them and still struggled and eventually gone for a colectomy and wished they'd done it years ago.... on the other hand I've seen lots of patients then have problems post surgery I mean anyway..... I think I've got mixed views about it but I'm a medical nurse so I'd probably would always plum for the medical option (189, 194, 198, 208)

HPN25b my personal thoughts are that you know that that's a last resort and I think the majority of patients feel the same that they would rather try any form of medical management.... be fair the majority of them that do end up having surgical intervention are just just relieved to be at the end of all the, you know, of the symptoms really... at the right when time it's the right thing to do but it think it you know it should always be a last resort (137, 144, 149)

Negotiated care and shared decision making

HP2 (pro Inflix) most specialists feel 'well if I'm given a choice why don't I go down the path of least resistance which is human nature' (83)

HP5 our surgeons are very active [in decision making], and Multi Disciplinary Team meetings twice a week (121)

HP5 the drug we choose ultimately depends on the patient (75)

HP1 I would give both Inflix and Cicl info to patients in an open setting if they want Cicl (41) 'I don't have experience do I' (42) 'I have never given it personally' (43-4)

HP1 preference for colectomy but would go with what patient wants (cannot put colon back) (116-117)

HP3 anti-surgery and most patients agree with me they want to keep colon (126)

HP4 Care is negotiated with the patient, patient input is important, but pre-defined pathways according to previous discussions (113)

HP4 [surgery] patients come and say I have got to that point in my career where colectomy might be acceptable then we often try to operate (127)

HP4 if we are in a situation where we are just buying time, there will already have been a choice made (129)

HP4 patients sometimes delay coming in or have delayed contact once they are in or go to another team for a while (delaying the inevitable) (224)

HP4 surgery tailored to pt's previous history, patient's wishes (239)

HP7 patient views [re surgery] as important as anything else, combined with weighing up risks and benefits, involve them hugely (103-109)

HP7 [surgery] depends on patient view of taking drugs long-term, view of surgery, views on bag (young women don't want it) (110-116)

HP10 I like to tailor the treatment to the individual patient (144)

HP11 we don't choose it lightly we of course counsel the patients about the risks etc, but they face surgery at that point (Cicl) (28)

HP11 the patient needs to be counselled about the risks (cicl) (67)

HP11 I think we need to give medical therapy a good try because that is what patients want us to do (184)

HP11 I think the majority of people are quite fond of their colon and don't want a stoma or a big operation (196)

HP12 I wouldn't say to anybody that surgery is the next step and the only step without offering them the option of inflix (69)

HP12 we clearly individualise patients (longer term care, inflix) (95)

HP12 longer term after 12 months it is clearly individualised and based on sort of consensus at the MDT (97)

HP12 you have to individualised the patient, their circumstances (181)

HP12 we actually see the patients and talk to them together (colectomy) (196)

HP12 surgeons disagree amongst themselves across the country, whether it is wise to do or not but we have no qualms (204)

HP14 some patients I'd choose on and some other patients I'd choose the other (170)

HP15 it's always a difficult discussion with families about when to have surgery (253)

HPN19 more of the time they're on their last option so patients are quite happy to have the drug and therefore it makes it easier to give it or treat a patient with it because they are more accepting...they have limited options left (87, 91)

HPN19 the whole process involves talking to the patient and educating them as to why you are giving it (inflix) (94)

HPN19 (discussing longer term inflix) it sometimes comes down to a very individualised decision because it depends on how the patients are, how they feel you know.(183)

HPN19 (discussing longer term cicl) again if it works for the patient, sometimes it comes down to an individual decision then I would be happy to do that (202)

HPN19 I think it comes down to personal decision, I think it's very important to have lots of discussions about all the options, medical or surgical... it's very difficult if they're newly diagnosed and they come in with their first presentation ... some people come with obvious preconceived ideas about things anyway and I think it's important to explore those feeling and how they feel and then kind of gets you to a decision because I think there are some patients who are adamant they want to try everything they possibly can medically before they go down the surgical route .. there are patients who actually get to a point where they want their life back and this is pretty ultimate... the surgery being the ultimate solution (254,267)

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HPN22 it's whatever is best for the patient (139)

HPN22 I think it's an option and I think it's different for each patient and I think that they need to be given the choice and have all the information because for some patients it can be a very good treatment and give them back their quality of life (157)

HPN19 more of the time they're on their last option so patients are quite happy to have the drug and therefore it makes it easier to give it or treat a patient with it because they are more accepting...they have limited options left (87, 91)

Costs

Costs of the two drugs and comparative costs

Ciclosporin	Infliximab
HP6 Cost of Cicl is cheaper than Inflix so in this hospital they have to complete a form saying when they wish to start using biological drugs, patient must try Cicl (unless already tried and had adverse reaction first time around) (64) HP6 Hospital policy favouring Cicl is all based on cost whereas for consultants want Inflix because of safety aspects (70) HP3 cheaper - that is the reason that change is impeded to move to favouring Inflix (160) HP3 cost will add up though. It is more than just cost of drugs, especially if patients have complications (argument against just favouring Cicl because it is cheaper) (172)	HP9 there are funding concerns (referring to long term maintenance use) (121) HP11 it's very very expensive so I bare that in mind (54) HP11 There are cost implications (long term maintenance) 108) HP11 25% complete remission for a cost of what we pay for infliximab is probably no justifiable really (236) HP12 it's about convenience and it's certainly more convenient, if you take cost out of the equation to give inflix (78) HP12 the only counteracting point is the cost (225) HP13 that's not an excuse to use it (inflix) given the huge cost differential, that's assuming that efficacy is relatively equal (37) HP13 if CONSTRUCT shows that cicl and inflix are equivalent on terms of efficacy…. I don't think there's any good excuse then to continue using a vastly more expensive drug (inflix) (48) HP14 it's expensive its £10,000 per year (73) HP14 but if you limit it to patients who've had a good response then its £10,000 per successful treatment (75) HP14 I mean the problem is that the expense of it, they've (NICE) got to come to terms with the cost of the drug, that's the problem (219)

	HP15 there is an issue of cost of course, we're pushed all the time to stop it for cost reasons (120) HP15 (referring to NICE guideline restrictions on inflix) it's done for financial reasons.... it's cheaper to take someone's colon out and that's the bottom line (292,297) HPN19 we now have to request the funding for patients with UC on long term inflix...so that's a bit of a challenge and it means that decisions are made differently to whether a patient is going on to maintenance inflix (154, 156) HPN22 It's already an issue because we can't really treat as maintenance with inflix so obviously if a patient responds well we've had to get exceptional funding and thing like that and so there is a case for it I think (103) HPN22 It's a costly drug so there has to be some kind of guidance doesn't there (NICE)(178) HPN23a They're just of the opinion that if it suits the patient and they get relief from it then they're quite happy for them to have it....it's an expensive drug (inflix) to have but it's just very effective so I don't think they mind at all (97) HPN23a more of an expensive treatment (169) HPN23a I just think it's a great treatment, I think it's very good it's very effective and it's nice to see that it's actually being used widely with it being such an expensive one (254) HP13 it is quite closely policed here (254)
General comments about cost of ciclosporin & infliximab	
HP2 Cost does not come into clinician's mind when it comes to drug choice as a rule (60) HP5 Should use either drug when the situation is acute and not consider the money (67) HP3 where are the calculations about which is the cheaper drug in the long run? (164) HP4 although there is a big difference in cost it wouldn't be a driver in our decision making outside of the trial (80) HP13 sent us how much we'd spent on the 2 drugs during the study and there was a massive difference. That if there's not a substantial differences in efficacy I just don't think there's any way that you can justify, you know, giving 2 drugs but picking the vastly cheaper one just because it's a bit easier (276) HP13 I think total healthcare costs are vital (298) HP15 cost is a huge issue here (490)	

Evidence and guidelines

Evidence (not related to National Institute for Clinical Evidence (NICE) guidelines)

Ciclosporin	Infliximab
HP5 evidence-base for Cicl is pretty good for it now (6) HP4 use of drugs is influenced by the European trial but I think there may well be equivalence with the 2 drugs (90) HP9 going with ciclosporin because it was perhaps had a bit more evidence base (87) HP10 I give it for a limited period (ciclo) but simply because the evidence for giving cicl on a long term basis and retaining remission is ....well there is none (124) HP12 no evidence for long term use of cic in UC setting anywhere (132) HP13 I don't think there is any evidence for that (use of cicl longer term) (162) HP14 I don't think there is the trial evidence to support it actually (long term use) (96)	HP5 Published studies show longer-term benefit of Inflix, similar to Crohns (50) HP5 there is evidence (e.g. CYSIF) follow-up data on patients acutely treated with Inflix, now time for pragmatic approach (151) HP6 better delivering something with use of a protocol (37) HP6 better guidelines around administering Inflix (37) HP1 Should be rolled out from research to practice, if you want to give a good try with med therapy (115) HP7 as we have data Inflix should be used in clinical practice HP7 data suggests it is effective, easier to administer, simpler regime, less palava (28) HP10 a recent article in APT suggesting that infliximab should always be used in acute severe UC and not ciclosporin (45) HP10 it's clear that continued use is effective in reducing colectomy rates (based on published literature, ACT 1 & 2 studies) (99) HP12 Inflix in the acute setting, there is not a great deal of trial data because most of the trials in the 2 licensing trials were moderate severe ones rather than acute sever ones (41) HP13 I think that the published data is not great (long term use inflix) (134) HP16 I don't think there is much evidence that really that this is, that we're switching off the disease so I think we're just a little bit behind where we were with chrohn's (345)

Evidence (related to NICE guidelines)

HP3 Inflix not licensed according to NICE you only give 3 doses, no maintenance (48)

HP3 Inflix personal preference, 'absolutely' but follows NICE guidelines (unfortunately) (116)

HP3 should be using more Inflix (132), not only in research (140), need guidance to change (134)

HP3 [NICE} should be using more Inflix, sooner the better (144)

HP4 NICE is constraining us re use of Inflix (197)

HP4 NICE is awkward, but we do have some patients using drugs outside of NICE guidance on specific argument of special cases(response rates, outcomes, reduction in colectomy rates, continuation of drugs (206)

HP7 as we have data Inflix [NICE] should be used in clinical practice (123/130)

HP7 NICE guidance not now appropriate now we have data, slightly outdated (123)

HP7 NICE will wait for x amount of studies before they will happily use Inflix in practice and 'Cicl is cheaper so driving a little bit the lack of impetus' (133)

HP2 Very frustrated by NICE guidelines they are one or 2 years behind what is available. They have a vast number of thingsthat they need to do, so cannot keep up with guidance (129)

HP2 Use research setting or database setting, there is nothing else, but Inflix should be used more widely as the evidence is there just NICE haven't approved it yet (138)

HP5 NICE will recommend Inflix in time (56)

HP5 the drug we choose ultimately depends on the patient (75)

HP5 you can always find reasons why Cicl is contraindicated! So you can say that Inflix is indicated for patients with acute colitis because, for example, they were at risk of infection (142)

HP5 we are past the point where there is a question, you [NICE] should be able to use Inflix acutely (154)

HP6 NICE guidelines can only give 3 Inflix infusions cannot continue on as maintenance (94)

HP6 professionally would like to use Infix, but my hands are tied, bound by NICE (127, 131)

HP6 NICE very restricting why can't we be allowed to use Inflix (otherwise talking about surgery for patients who have severe enough symptoms to warrant a trial of Inflix) (13)

HP6 would be good if NICE guidelines were changed (161)

HP9 you can usually find a reason why ciclosporin would not be indicated and give the option (232)

HP9 I don't think it's a particularly sensible NICE guidance based on the lack of evidence that they have to make the decision on and therefore, in all honesty, because we can, we slightly ignore it (236)

HP9 I sort of treat it with a bit of contempt (239)

HP9 I think NICE promoting research when there is a question to answer is a good thing (266)

HP10 (referring to Infliximab as maintenance therapy) I know NICE don't approve but I think that NICE are behind the times and not for the first time (89)

HP10 it's a no-brainer to find a way of getting him on to infliximab again (113)

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HP10 I think it's outdated, its manifestly inappropriate (196)

HP10 I think that they've got an effective drug which clearly works and I think should be allowed to use accordingly to license (217)

HP11 problems come up with NICE, we are getting increasing pressure in our area, to show that we are following NICE guidance so that becomes a problems (100)

HP11 I think it is difficult because up to recently there hasn't been convincing data to support it to be honest (207)

HP11 I think that NICE at the end of the day is also about health economics (211)

HP11 but I would support NICE at this point until there is better data (225)

HP12 statement made at a time based on the two licensing trials which did not include acute severe patients and there wasn't enough clinical practice data in the literature. So at the time probably that was a right statement, but now, you know, it is sort of unreasonable.

HP12 (should inflix only be used in research) no, because... its at least as effective as ciclosporin with the additional benefit of convenience and potentially less toxic (222)

HP13 NICE have written that guideline and I would interpret that as people can do what they want (laughs) … But we don't have that freedom (Scotland governed by SMC) (245, 250)

HP13 I'm not a massive NICE supporter but I actually think their guidance has been pretty sensible (346)

HP13 they as a national body have to have their eye on healthcare costs and I think to favour the cheaper drug if in a situation where there is such a big difference between the 2 drugs is sensible, but also to acknowledge that it's not absolutely the right drug for everybody (429)

HP14 I think the current NICE guidelines are um, a bit tricky because I think if you are going to give a patient infliximab you need to give them…., and then they respond to it, if they do respond to it you want to be able to continue the treatment and I think it may have more of a long term use than the NICE guidelines that we're currently using (38)

HP14 I think it's unduly restrictive and I think it will eventually change. I think it's actually quite hard to adhere to actually as well. I mean you've got a patient who you want to give treatment to, you're duty bound to give them the best treatment available and in some cases that's going to be inflix (208)

HP14 I mean the problem is that the expense of it, they've got to come to terms with the cost of the drug, that's the problem (219)

HP16 I think it's completely wrong (restriction of inflix) (447)

HP16 I think it's not backed up by data..so I think NICE is probably doing itself a major dis-service with this particular guidance because I think they lose credibility... this is an algorithm based on cost effectiveness that is probably outdated. (463)

HP16 I think there's been an interpretation of the results by NICE that is out of step with received gastroenterological opinion in the UK by experts in this area (504)

HP16 It's very hard to find anyone who supports the NICE guidance in its present format (516)

HP16 I'm pleased we can get access to biological in trials and I think a lot of our patients at the moment are in trials to get access to biologicals (519)

HP16 NICE guidance is from 2008 so you know the world has moved on a lot from there (528)

HP15 we bend the rules just slightly and feel it's not in their interest to have cicl, then we could use inflix... but it's bending the rules just a little bit and I'm always quite wary about that (162)

HP15 (referring to NICE guideline restrictions on inflix) it's done for financial reasons.... it's cheaper to take someone's colon out and that's the bottom line (292,297)

HP15 I think we should be allowed to use it (inflix) for UC if we use it for Crohn's disease (308)

HPN18 I think you have to have parameters there but I think there should be some kind of you know some leeway where it is not set in stone where somebody can make a decision as long as they can back it up with some kind of rationale (327)

HPN18 I don't think it (inflix) should be specifically just for research (340)

HPN19 I don't particularly agree with the NICE guidelines....NICE guidelines are key to funding issues because they go by them and strictly by them (287, 290)

HPN19 NICE kind of has a few things to answer for such as because it make these decisions and for UC there isn't a great deal of options (291)

HPN19 very personal opinion is that a bit closed minded of NICE, they need to be more open minded and flexible (294)

HPN19 (inflix in research) from a personal point of view I think having more information, having more data about different drugs and about how they affect patients I think it brilliant and I think it should be encouraged because it's the way to make informed decisions in the future (304)

HPN20 (inflix for research only) No...It works (laughs). I mean we've been using it up here for years and years as our first line treatment for our IBD patients. (245, 249) (Scotland site, NICE guidelines not applicable)

HPN21 (inflix in research only) I think it you took that element out people would be more happy to take it on board because when we mention research I think they seem to feel that it's maybe not proven to work...there's stigma around it and a bit of fear (265)

HPN22 I think it ties our hands a little bit (167)

HPN22 It's a costly drug so there has to be some kind of guidance doesn't there (178)

HPN23a more of an expensive treatment (169)

HPN23a I'm surprised at that statement (infliximab for research only) (185)

HPN25a I didn't know was if the ciclosporin is contraindicated I thought you could use it (inflix)..... I thought that erm it would we were able to use it for acute UC if I had any views it would be that I think it should be able to be used before it was acutely severe. (221, 231)

HPN25a I don't think it should only be in research. If it's a very expensive treatment I can see why NICE say that because it's incredibly expensive they'll probably compare the cost of a colectomy I can understand that point completely but I don't think if I had UC then I would want it available to me so I would think so. (251)

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Nurse time on ciclosporin (health economics)

Nurses time on ciclosporin (Health Economics additional question)
HPN20 you need two registered nurses cos our student nurses aren't allowed to check anything like that....Probably 10 – 15 mins. Make up the bags, go to the patient, check the patient, change the bag four times a day, probably an hour anyway.... over a 24 hour period probably about¾ - 1hr would be spent dealing only with ciclosporin. (263...270)
HPN21 each first administration of it is going to require at least 4-5 hours of my time, bulk of which is observations, so quite a big chunk really (laughs) but after that the impact is much reduced, it's really just the initial dose it you like, the first infusion that they have. It varies because it very much depends on how much staff I've got as well (294)
HPN22 to prepare it, talk to the patient, set the patient up, do the observations and things that can take up to an hour.. and having to go back... it's about the same...for cicl and inflix , they're both time consuming 208, 232)
HPN24 usually the first few hours we would go for 2-4 hours , for the first 24 hours...we have to monitor the patient closely for side effects...but then it takes 2-4 hours because you've got the obs for a couple of hours...care assistants can also monitor blood pressure (246, 255, 269)
HPN25a from my memory it's just because you have to change the drip a number of times per shift and then you have to take another nurse to go and check it with you, you have to do their blood pressure you know I I just think it's erm as far as I remember it was quite time consuming. (269)
HPN25b in the early stages we would monitor them for the first few hours to make sure they weren't having any reactions..... After that then as you say the bags are changed six hourly so at that six hourly point, you know the patient may be on six hourly observations anyway so we would do observationsobviously check the access site and change the bag over with the intravenous additives guidelines now it's a two registered nurse procedure.... To prepare intravenous drugs so that's two nurses off the ward you know mixing and preparing the drugs and taking it to the patient.... Which I suppose could take perhaps from start to finish with our obs observe and an access check 20 minutes perhaps every six hours.....it's intensive that first period... We would probably monitor them more closely over the first six hours over the first bag..... To be honest it does feels like you know it's just part of what we do so it's not like a thing you would think about really. (169, 174,182,188, 208,232,252)

General comments about the trial

General comments about the trial
HP13 (cicl) previously we would have just written it up and then would have made it up and given and because we were doing the trial we, you know wrote a specific sort of SOP so we were clear that we were doing the right thing and doing the same thing to everybody (209)
HP13 we just thought we actually liked taking part (429)
HP14 our pharmacy made the trial as difficult as possible because they insisted we try to use trial supplies rather than normal supplies (292)
HP16 it's a relatively straightforward trial to take part in (566)
HPN18 because it is a clinical trial, we are having to make sure that things are prescribed and stuff like that (67)
HPN18 we'd actually increased her workload (IBD specialist nurse) sort of quite significantly as a result of the trial (135)
HPN18 in a general setting these nurses would be making the cicl themselves... as a clinical trial it comes up in an infusion bag already, they don't canulate the patients, their canualted by one of the doctors (time of nurses on cicl due to trial context reduced 15-20.) (419, 424)

Assessment of quality of interviews

According to Guba[106] the following criteria should be applied to qualitative data to assess their trustworthiness, corresponding to constructs employed by positivistic researchers such as internal and external validity, reliability and objectivity:

- credibility (in preference to internal validity) – 'congruence of findings with reality'
- transferability (in preference to external validity/generalisability) – 'application of findings to other situations'
- dependability (in preference to reliability) – 'processes in the study reported in enough detail that others can repeat the work'
- confirmability (in preference to objectivity) – 'findings are the result of participants' experiences and ideas not researcher preference'.

Credibility can be assessed according to whether or not the operational methods that are being applied to the concepts under study are applied correctly.[108] We would argue that the questions asked in this study, and the adoption of both face-to-face interviewing methods and telephone interviewing, with both health-care professionals and participants, over an extended trial period, gave enough detail and sufficient information to clarify people's views. Interviews were undertaken not at a static time point but over time, as participants (patients) were brought on board, at 3 months and then again at 12 months post drug treatment. This also included patients who had also undergone surgery. The extensive data sets collected were also rich in detail and captured information across the study aims in accordance with a question schedule that related not only to both drugs being administered but also to people's views of their health, their health care, their relationship with professionals and others, their illness and personal preferences for drug allocation (professionals' interviews). Indeed, additional information was obtained from health-care professionals, using these qualitative methods, about the trial itself and about professionals' hope for trial information to guide them in their future practice.

Transferability can be assessed, in qualitative terms, according to Denscombe[107] and Stake,[110] if a particular study can be seen as an example within a broader group. This can be assured if sufficient contextual information is supplied about the sites involved and the participants within those sites, so any reader can make this kind of transfer.[111] In this trial we are confident that we have supplied sufficient detail of participant characteristics, participant views and trial site allocation across all UK locations for the reader to build a picture of what occurred and with whom. We have also provided information of how participants and sites were involved in this trial, differences between locations and differences between groups of participants. In addition, we have explained how health-care professionals were chosen for interview and how they were recruited, so that this work can be repeated by others in other settings with other drug groups if appropriate.

In qualitative data terms, **dependability** suggests that the work processes should be reported in enough detail so that any future researcher could repeat the work; thus, the research design can be viewed as a 'prototype model'.[109] Shenton reminds us that this kind of detail allows the reader to also be reassured that appropriate research practices were followed or, at the very least, that the extent to which they were followed can be assessed. We have demonstrated in this report how participants were approached, the kinds of questions they were asked and the order in which those questions were asked. We have also reported their comments in quotation form and described how we assured participants (both patients and health-care professionals) that ethical standards would be upheld throughout the trial. This included assurances about each individual's anonymity. We provided participants with information about the removal of aspects of data from the study data sets if they so wished and explained that they could withdraw from the study at any stage if they so wished. We were keen to clarify the research design in this report and to explain the qualitative data capture and analysis methods in the 'methods' sections, so that others might follow similar procedures in their own work.

Confirmability is the 'qualitative investigator's comparable concern to objectivity'.[109] Confirmability ensures that findings link clearly and precisely to the study informants' data rather than to the assumptions, preferences or personal opinions of any one of the qualitative researchers involved in a study or to others with whom they work. In this study, we always worked as a team during analytic framework development and data assessment, in terms of both participant and health-care professional data. We developed out trial analytic frameworks from both data sets independently, and conferred about all key findings, which were shared with the wider team. We were aware of the need to achieve consensus of opinion in group discussion and conferred on not only the iterative process of revealing the thematic results but also the emergent key and incidental themes. During each group analysis meeting, we made sure that three qualitative researchers, including the qualitative trial lead, were present to discuss aspects of data capture, data content and analysis. In addition, we worked with the wider team (seven additional members) through a half-day group-working session that employed schema analysis to triangulate patient data, and through the group-working process we were able to add to the veracity of working methods. During schema analysis the core team (three qualitative researchers) examined whether or not their views aligned appropriately and sufficiently with the wider group and whether or not data were being appropriately managed and clarified. We were assured that this was the case, that no new themes were suddenly revealed and that consensus of opinion regarding key emergent themes could be achieved in a manner that was uncontested.

We therefore believe that our qualitative data are robust, although the number of interviewees is inevitably small in comparison with the quantitative data. The data we obtained were extensive, not only about patient and professional views of the interventions but also about participants' views about the impact of colitis on their health and lifestyle. Participants were willing to speak very openly about their disease, and the views we obtained came from adults of all ages and from across the UK. We thus feel that the data are important and deserve careful consideration alongside the clinical effectiveness and cost-effectiveness results.

Appendix 20 MATRICS proforma

MATRICS

Layer 1: effects sought[a]

Effects on patients	Effects on the NHS specialty being investigated	Effects on the rest of NHS and society

a Derived from the aims and objectives of the study.

Layer 2: methods used

Code	Method

Layer 3: findings reported

Code(s)	Finding(s)
Effects on patients	
Effects on NHS specialty being investigated	
Effects on the rest of NHS and society	

Appendix 21 Data Monitoring and Ethics Committee charter

CONSTRUCT DMEC charter

Lead authors	***Ian Russell and Michelle Grey***
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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

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26/01/09	V1-3	DMEC members as listed in V1-3
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	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)

Appendix 22 A personal experience

I am a 64-year-old male who prior to retirement was a Senior Officer in the Fire and Rescue Service. In 1999 I was diagnosed with Inflammatory Bowel Disease (IBD) and in 2005 I had a total colectomy following a steroid-resistant flare-up. I have been a member of Crohn's and Colitis UK for 15 years and it was via them that I was invited to join the Trial Management Group (TMG) of the Construct Trial.

My first encounter with the professional researchers working on the trial was not easy and for the first few meetings I did feel out of my depth. I initially had the fear that I was only there because the National Institute for Health Research (NIHR) make public/patient involvement mandatory in the trials they sponsor. After my first couple of meetings it became apparent that my earlier misgivings were unfounded and could not be further from the truth. The Lead Researcher, Professor Williams, always made a point of involving me in discussions and my views were considered along with those of the other members.

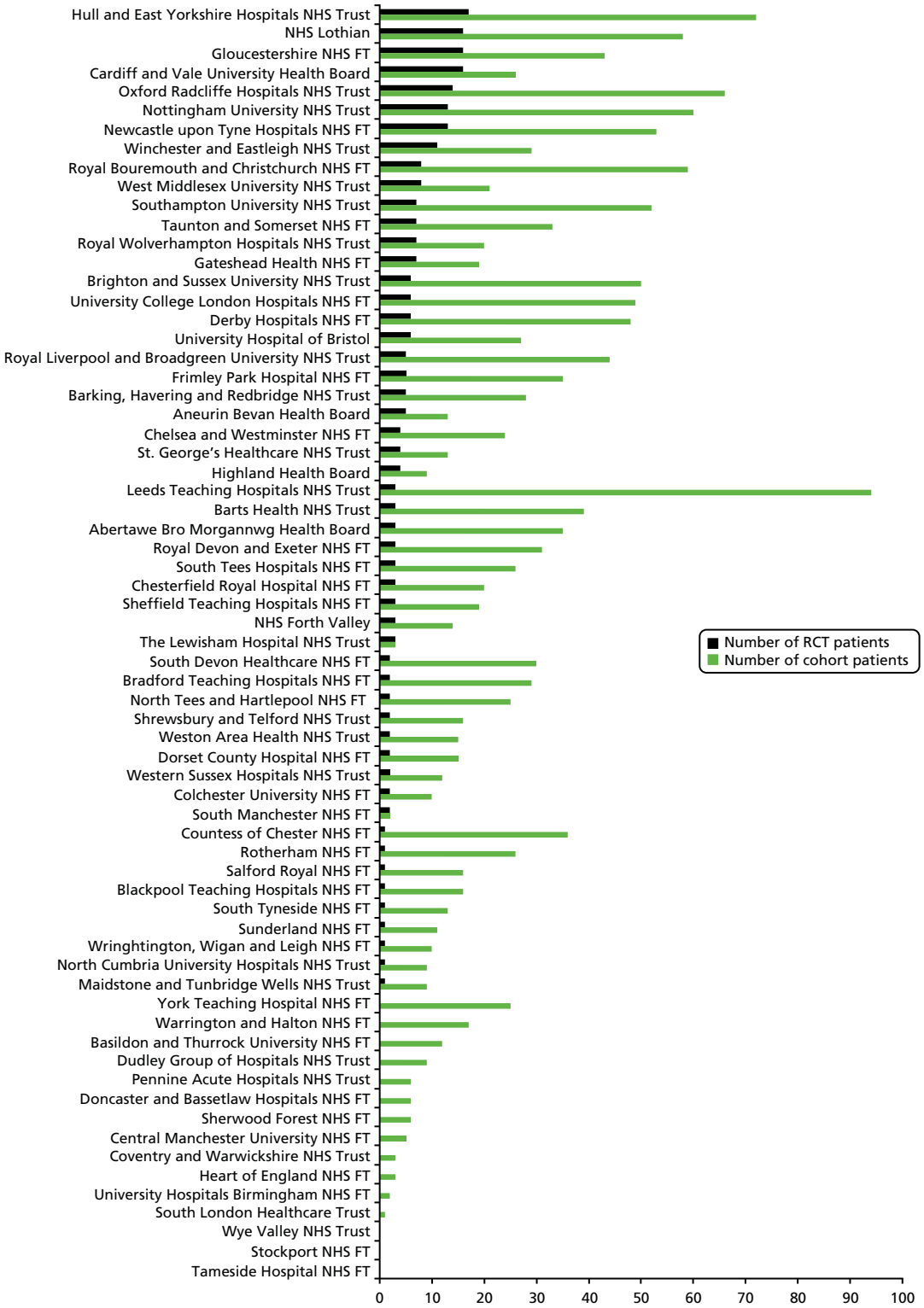
I found that my membership of the TMG was a two-way process and that I was able to feed in information from my personal experience of IBD. This I believe helped the professional researchers to more fully understand how IBD impacts on the life of individuals. I also gained a lot more knowledge about Ulcerative Colitis and its medical effects on the body and the various treatments which are available.

One of the main ways I was able to get involved outside of the normal TMG meetings was in the production of the health questionnaires. In particular the one which dealt with patients who had had surgery when their treatment failed. In these cases the individuals are left with a temporary or permanent Stoma. My personal experience of both the physical and mental trauma of this procedure and the long-term effects were helpful in shaping some of the questions. It is all too easy when you are highly trained in a subject to devise questions which are not explicit or easy for people to understand. I worked on the theory that if I could understand the questions other patients would have a fighting chance.

At one point in the trial we had a recurring problem with patients who where taking part in the trial but not returning questionnaires. It was agreed that a joint letter from Professor Williams and myself would be sent to the individuals who had not returned the questionnaires. This did have some impact, which may have been because the recipients of the letters were influenced by the fact that a fellow sufferer was writing to them in conjunction with the Lead Researcher.

Being a member of a Trial Management Group is a long-term commitment covering years rather than months. My advice would be if you have the time, energy and the will, you may be able to help improve the lives of people you are unlikely to meet and that can be very rewarding.

Appendix 23 Participant recruitment



Appendix 24 Participant analysis framework

1. Longevity of disease.
   Living with UC.
   Time.
   Course of disease: over longer period; short-term unpredictability.
2. Serious suffering.
   Description of suffering.
   Intensity of suffering.
   Negative experience of suffering.
   Loss of bodily control/function: gradual/sudden demise.
   Unpredictability of symptoms/relapse.
   (Toileting.) (Pain.)
3. Acceptance, coping, toleration.
   Positive perception of life.
   Surprise at positive moments.
   Counter-intuitive return to better state.
   Normalising illness/wellness/taken for granted.
   Trivialising illness (within relationships).
4. Knowledge and information sharing.
   Nurse.
   Crohn's and Colitis UK: self-help group low profile/some groups disbanded.
   Internet.
   Shared decision-making.
   Media: UC low profile, not publicised.
   Health-care professional/service want issues highlighted.
   Containment: people not forthcoming about illness.
   Trial removes treatment decision.
5. Life changes.
   Being overwhelmed by illness.
   Taking different and unexpected paths.
   Taken off guard.
   Stopping doing things.
   Giving up control/taking control.
   Restriction/constraint: unpredictability of disease.
6. Body: core of disease.
   Within the body but ability to reflect on.
   Failure of the body to function: different type of failure to other chronic conditions/physical consequences.
   IBD inside/outside.
   Loss of body parts.
   Defining self (loss of colon).
   Body centric.
   Visceral notion of UC.
7. Physical, mental and emotional impact.
   Trajectory from physical to mental, to social to emotional impact.
   Stress (leading to flare-ups).
   Directional change (physical becomes mental).
   Fear and despair/uncertainty.
   Impact of physical, mental, emotional impact on relationships.
   (Defining self by symptoms.)

Loss of hope.
Physically fit/mentally vulnerable.

8. Expectations of health and well-being.
   'Normal' life.
   Happy/unhappy life.
   Comfort/discomfort.
   Inconvenience.
   Managing life/practicalities.
   Freedom/imprisonment.
   Having energy.
   Being fit and healthy.
   Link between good and bad health.
9. Cacophony of drugs.
   Other treatments alongside drugs.
   Other treatments instead of drugs.
   Number of drugs taken together.
   Complex drugs pathway.
   Unpredictable drug pathway.
10. Process and outcome of treatment.
    Treatment practicalities.
    What treatment has achieved/meant to patients.
    Surgical intervention.
    Side effects.
    Unpredictability of treatment.
    Proactive: difficult for health-care professional because of unpredictably.
    Health-care professional aim is for people to live normal live.
11. Hindsight.
    Post-surgery views.
    Changes in perception.
    Living with colostomy.
    Views about reversal.
    Stoma.
    Submissive regarding choices.
12. Relationships.
    Family, friends, professionals.
    Support.
    Understanding.
    Giving.
    Sharing/withholding information: work.
    Infertility: awareness/lack of impact of disease (male and female).
    Pregnancy: awareness/lack of impact of disease (male and female).
    Disclosure.
    Lack of awareness of others.
    Lack of awareness of concerns.
13. Work.
    Impact before treatment on work.
    Positive effects of treatment on work.
    Aftermath: future work arrangements.
    Work identity: share with colleagues.
    Impact of UC on career/work.

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