Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

Final protocol 22nd November 2013

1. Title of the project:

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262)

2. Name of TAR team and 'lead'

TAR team

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3. Plain English Summary

Ulcerative colitis is recognised as the most common form of inflammatory bowel disease in the UK, having an incidence of approximately 10 per 100,000 per year and a prevalence of approximately 240 per 100,000.[1] Peak incidence is between 15 and 25 years of age, with a potential second peak between 55 and 65 years.[1] The majority (approximately 80%) of incident cases are reported to be of mild or moderate severity. An estimated 132,600 people in England and Wales have been diagnosed with ulcerative colitis. It is a chronic disease of unknown cause with symptoms including the development of bloody diarrhoea, abdominal pain, weight loss, fatigue, anaemia and an urgent need to defecate. Symptoms may vary according to the degree and severity of bowel inflammation. The condition has no current cure and the disease course is relapsing-remitting in pattern. A range of factors have been suggested as potentially influencing the risk of relapse.[2] There is evidence to indicate that severity of disease may be associated with younger age at diagnosis.[3,4] Complications of ulcerative colitis include primary sclerosing cholangitis (inflamed and damaged bile ducts),

bowel cancer, osteoporosis and toxic megacolon (swelling of colon due to trapped gases). The aim of clinical management is to induce and maintain disease remission and to avoid potential complications and surgical intervention.[5]

4. Decision problem

4.1 Purpose of the decision to be made

This assessment will address the question "what is the clinical effectiveness and cost-effectiveness of infliximab, adalimumab and golimumab in the treatment of moderately to severely active ulcerative colitis after the failure of conventional therapy as compared against each other and standard clinical management?"

4.2 Clear definition of interventions

Three interventions will be considered within this assessment. Infliximab, adalimumab and golimumab are monoclonal antibodies which inhibit the activity of TNF-α.

(1) Infliximab (Remicade, Merck Sharp and Dohme)

Infliximab has a UK marketing authorisation for the treatment of moderately to severely active ulcerative colitis in adults, who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications against such therapies.[6]

Infliximab also has a UK marketing authorisation for the treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications against such therapies.[6]

Infliximab for the treatment of ulcerative colitis is administered by intravenous infusion at a dosage of 5 mg/kg followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 8 weeks thereafter.[6]

Biosimilar versions of infliximab (Remsima, Celltrion Healthcare; Inflectra, Hospira) are also licensed for the same indications. These will also be included as part of the evidence base for infliximab in this assessment.

(2) Adalimumab (Humira, AbbVie)

Adalimumab has a UK marketing authorisation for the treatment of moderately to severely active ulcerative colitis in adults who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications against such therapies.[7]

Adalimumab for the treatment of ulcerative colitis is administered subcutaneously according to an induction dose regimen of 160 mg at Week 0 and 80 mg at Week 2 followed by a recommended maintenance dosage of 40 mg every other week (increased to 40 mg every week if clinical response is insufficient).[7]

(3) Golimumab (Simponi, Merck Sharp and Dohme)

Golimumab has a UK marketing authorisation for the treatment of moderately to severely active ulcerative colitis in adults who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications against such therapies.[8]

Golimumab for the treatment of ulcerative colitis is administered subcutaneously according to body weight. Patients with body weight less than 80 kg receive an initial dose of 200 mg, followed by 100 mg at week 2, then 50 mg every 4 weeks, thereafter. Patients with body weight greater than or equal to 80 kg receive an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter.[8]

4.3 Place of the intervention in the treatment pathway(s)

As outlined in the final scope and NICE clinical guideline 166 ('Ulcerative colitis: Management in adults, children and young people'),[1] conventional treatment options for moderately to severely active (non-systemic) ulcerative colitis include the use of oral or topical aminosalicylates, corticosteroids and/or immunosuppressants (NB: Some conventional treatment options did not have marketing authorisation at the time of clinical guideline publication [June 2013]). Recommended conventional treatment options may vary according to the extent and location of colitis.[1] Colectomy may be considered in the event of inadequate control of symptoms and/or poor quality of patient life on conventional treatment.

Infliximab, adalimumab and golimumab will be assessed in this current technology assessment in line with licensed indications as treatment options for moderately to severely active ulcerative colitis after the failure of conventional therapy.

Infliximab was not previously recommended by NICE for the treatment of "subacute" manifestations of moderately to severely active ulcerative colitis (NICE technology appraisal guidance 140).[9] NICE technology appraisal 262 (adalimumab for the treatment of moderately to severely active ulcerative colitis) was terminated as no evidence submission was provided by the manufacturer.[10]

4.4 Relevant comparators

Interventions may be compared against each other. Other relevant comparators include standard clinical management options, which, as described in the final scope, may include a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), thiopurines (mercaptopurine or azathioprine), calcineurin inhibitors or elective surgical intervention.

Emergency surgical intervention will not be considered as a comparator in this assessment (as acute severe ulcerative colitis is stated in the final scope as being outside the remit of this assessment).

4.5 Population and relevant sub-groups

The assessment will consider the following two populations:

(1) Adults aged 18 years and over with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications against such therapies.

It is anticipated that severity of disease in adults will be defined according to the modified Truelove and Witts' severity index (1955) (as referred to in the final scope and as categorised and tabulated in NICE clinical guideline 166).[1]

The following interventions are indicated for use in adults:

- Adalimumab
- Infliximab
- Golimumab

(2) Children and adolescents aged 6 to 17 years (inclusive) with severely active ulcerative colitis, who have had an inadequate response to conventional therapy including

corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications against such therapies.

It is anticipated that the severity of ulcerative colitis in children and adolescents will be made using the Paediatric Ulcerative Colitis Activity Index (PUCAI) (as categorised and tabulated in NICE clinical guideline 166).[1]

The following intervention is indicated for use in children and adolescents:

- Infliximab

Specific subgroups and treatment effect modifiers of interest include duration of disease, as specified in the final scope.

4.6 Key factors to be addressed

The objectives of the assessment are to:

- evaluate the clinical effectiveness of each intervention
- evaluate the adverse effect profile of each intervention
- evaluate the incremental cost-effectiveness of each intervention compared (i) against each other and (ii) against all comparators
- estimate the overall NHS budget impact in England and Wales

4.7 Factors that are outside the scope of the appraisal

The evaluation of interventions in the following groups are outside of the appraisal scope and will not be considered in this assessment:

- Children with mildly or moderately active ulcerative colitis (as defined by the PUCAI measure)
- Adults with mildly active ulcerative colitis (as defined by the modified Truelove and Witts' [1955] criteria)
- Adults and children with acute severe (systemic) ulcerative colitis

5. Methods for the synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'[11] and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).[12]

5.1. Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness literature relating to infliximab, adalimumab and golimumab within their licensed indications for the treatment of moderately to severely active ulcerative colitis after the failure of conventional therapy.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Search strategies will be used to identify relevant trials (as specified under the inclusion criteria below) and systematic reviews/meta-analyses (for the identification of additional trials). The following databases will be searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid)
- Embase (Ovid)
- Cochrane Database of Systematic Reviews (Wiley Interscience)
- Cochrane Central Register of Controlled Trials (Wiley Interscience)
- Cumulative Index to Nursing and Allied Health Literature (EBSCO)
- Science Citation Index (ISI Web of Knowledge)
- Social Sciences Citation Index (ISI Web of Knowledge)
- BIOSIS (Web of Knowledge)
- Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effectiveness and Health Technology Assessment (CRD DARE and HTA)

Current research registers (e.g. UK Clinical Research Network Portfolio Database, ClinicalTrials.gov) will also be searched for ongoing and recently completed research projects. Citation searches of key included studies will also be undertaken using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science.

Searches will not be restricted by language or date or publication type. The MEDLINE search strategy is presented in Appendix 1. High precision search filters designed to retrieve clinical trials and systematic reviews will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases. Industry submissions and relevant systematic reviews will also be handsearched in order to identify any further relevant clinical

trials. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

5.2 Inclusion and exclusion criteria

5.2.1 Inclusion criteria

Inclusion criteria have been defined in line with the final scope provided by NICE and are outlined below.

5.2.1.1 Populations

(1) Adults aged 18 years and over with moderately to severely active (non-systemic) ulcerative colitis (defined as patients with moderately active disease according to the modified Truelove and Witts' criteria [1955] only) whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant of or have medical contraindications to such therapies.

ii) Children aged 6 to 17 years with severely active (non-systemic) ulcerative colitis (as classified by the PUCAI measure) whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant of or have medical contraindications to such therapies.

5.2.1.2 Interventions

For adults (defined by the Assessment Group as aged 18 years and over):

- Adalimumab
- Infliximab
- Golimumab

For children and adolescents aged 6 to 17 years (inclusive):

- Infliximab

Interventions will be assessed in line with licensed indications.

5.2.1.3 Comparators

Interventions may be compared with each other. Interventions will be compared with standard clinical management, which may include a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), thiopurines (mercaptopurine or azathioprine), calcineurin inhibitors or elective surgical intervention.

5.2.1.4 Outcomes

The outcome measures to be considered include:

- Mortality
- Measures of disease activity
- Rates of and duration of response, relapse and remission
- Rates of hospitalisation
- Rates of surgical intervention (both elective and emergency)
- Time to surgical intervention (both elective and emergency)
- Adverse events of treatment (including leakage and infections following surgery)
- Health-related quality of life

Mucosal healing will not be included as an outcome in this assessment.

5.2.1.5 Study design

Randomised controlled trials (RCTs) will be included in the clinical effectiveness systematic review. If no RCTs are identified for an intervention, non-randomised studies may be considered for inclusion. Non-randomised studies may also be included, where necessary, as a source of additional evidence (e.g. relating to adverse events, long-term effectiveness etc) associated with the interventions.

Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an assessment of the methodology and results to be undertaken.

5.2.2 Exclusion criteria

The following types of studies will be excluded:

- Studies which include adults with mildly active ulcerative colitis (as defined by the modified Truelove and Witts' [1955] criteria)
- Studies which include children with mildly or moderately active ulcerative colitis (as defined by the PUCAI measure)
- Studies which include adults with severely active ulcerative colitis as defined by the modified Truelove and Witts' [1955] criteria (representing patients who are systemically ill and are excluded as being outside the remit of this appraisal)
- Studies which include adults, adolescents or children with acute severe ulcerative colitis, whose disease is systemic (as shown by tachycardia, fever, anaemia or a raised erythrocyte sedimentation rate) (representing patients who are excluded as being outside the remit of this appraisal)

- Studies which include patients with inflammatory bowel disease other than ulcerative colitis (e.g. Crohn's disease)
- Studies where interventions are administered not in accordance with licensed indications
- Systematic reviews and clinical guidelines (these may be used as sources of references)
- Studies which are considered methodologically unsound in terms of study design or the method used to assess outcomes
- Studies which are only published in languages other than English
- Studies based on animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as abstracts or conference presentations only, where insufficient details are reported to allow an assessment of study quality or results.

Trials retrieved for full paper screening which are subsequently excluded will be listed in an appendix to the report with reasons justifying their exclusion.

5.2.3 Study selection

Retrieved studies will be selected for inclusion according to the inclusion and exclusion criteria specified in Sections 5.2.1 and 5.2.2. Studies will be assessed for relevance first by title/abstract, and then finally by full text, excluding at each step studies which do not satisfy the inclusion criteria. One reviewer will examine titles and abstracts for inclusion, and a second reviewer will check at least 10% of citations. Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion and exclusion criteria. Discrepancies will be resolved by discussion, with involvement of a third team member when necessary.

5.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form. A draft data extraction form is presented in Appendix 2. Data will be extracted with no blinding to authors or journal. Where multiple publications of the same study are identified, data will be extracted and reported as a single study. A second reviewer will check at least 10% of data extraction forms. Discrepancies will be resolved by discussion. The Assessment Group's approach to handling data obtained from the manufacturers' submissions is detailed in Section 7.

5.4 Quality assessment strategy

The methodological quality of each included RCT will be assessed using the Cochrane Risk of Bias tool[13] or (adapted) criteria based on those proposed by the NHS Centre for Reviews and Dissemination for RCTs.[11] The purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, to inform potential exclusions from any sensitivity analysis. Each included study will be quality assessed by one reviewer and a second reviewer will check at least 10% of quality assessment forms.

5.5. Methods of analysis/synthesis

Pre-specified outcomes will be tabulated and discussed in a narrative synthesis.

If considered appropriate, meta-analysis may be carried out using fixed and/or random effects models using the Cochrane Collaboration Review Manager© software (version 5.1). Heterogeneity may be explored through consideration of the study populations, methods, and interventions and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic. If appropriate, a simultaneous comparison of all interventions will be performed. This will be done using a random effects network meta-analysis assuming that the trials form a connected network of evidence. Network meta-analyses will be implemented using the freely available software WinBUGS 1.4.3.

5.6 Methods for estimating quality of life

Health-related quality of life (HRQoL) data available from studies included in the clinical effectiveness systematic review will be extracted. In the absence of such evidence, the mathematical model may use evidence on HRQoL drawn from alternative sources.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

A comprehensive search will be undertaken to systematically identify cost-effectiveness literature relating to infliximab, adalimumab and golimumab within their licensed indications for the treatment of moderately to severely active ulcerative colitis after the failure of conventional therapy.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field

- Scrutiny of bibliographies of retrieved papers

Search strategies will be used to identify relevant economic papers.

The following databases will be searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid)
- Embase (Ovid)
- Cumulative Index to Nursing and Allied Health Literature (EBSCO)
- Science Citation Index (ISI Web of Knowledge)
- Social Sciences Citation Index (ISI Web of Knowledge)
- Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment and NHS Economic Evaluations Database (CRD DARE, HTA and EED)
- EconLit (Ovid)
- BIOSIS (Web of Knowledge)

Citation searches of key included studies will also be undertaken using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science.

Searches will not be restricted by language or date or publication type. The MEDLINE search strategy is presented in Appendix 1. High precision search filters designed to identify existing economic evaluations of interventions for the treatment of moderately to severely active ulcerative colitis will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

Additional searches, for example to inform the decision-analytic model, where required in the course of the project, will be undertaken through consultation between the team.

Any existing health economic analyses identified by the searches will be critically appraised using published checklists.[14,15] In addition, any economic analyses presented in the sponsor submissions to NICE will also be critically appraised using these checklists. Existing cost-effectiveness analyses may also be used to identify sources of evidence to inform structural assumptions and parameter values for the Assessment Group model.

6.2 Development of a *de novo* economic model

A *de novo* economic evaluation will be undertaken from the perspective of the UK NHS and Personal Social Services (PSS). The model will draw together evidence concerning treatment efficacy, withdrawal, treatment-related adverse events, relevant imaging/diagnostic interventions, chronic care costs, and HRQoL. Costs on drug acquisition, administration, hospitalisation, adverse events and primary care will be identified through literature searches and national formularies. In line with current recommendations, costs and health outcomes will be discounted at 3.5%. The primary health economic outcome of the model will be expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. The cost-effectiveness of all interventions and comparators will be compared incrementally against each other.

Sensitivity analysis will be undertaken to examine the key determinants of cost-effectiveness. Probabilistic sensitivity analysis (PSA) will be undertaken to generate information on the likelihood that each treatment produces the greatest amount of net benefit. The results of this PSA will be presented as cost-effectiveness acceptability curves (CEACs).

7. Handling the company submission(s)

Data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 14th March 2014. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on economic model submission, will be assessed for clinical validity, reasonableness of assumptions, and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or by developing a *de novo* model.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in turquoise in the assessment report (followed by an indication of the relevant company name, e.g. in brackets). Any academic in confidence data will be underlined and highlighted in yellow.

8. Competing interests of authors

None

9. Appendices

Appendix 1: Search strategy

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1946 to Present>

1. Colitis, Ulcerative/
2. ulcerative colitis.tw.
3. colitis ulcerosa.tw.
4. uc.tw.
5. colitis ulcerative.tw.
6. Colitis/
7. colitis.tw.
8. colitides.tw.
9. Inflammatory Bowel Diseases/
10. inflammatory bowel disease$.tw.
11. ibd.tw.
12. or/1-11
13. adalimumab.af.
14. humira.af.
15. d 2e7.af.
16. d2e7.af.
17. 331731-18-1.rn.
18. infliximab.af.
19. remicade.af.
20. 170277-31-3.rn.
21. ta650.af.
22. ta 650.af.
23. inx.af.
24. remsima.af.
25. inflectra.af.
26. ct p13.af.
27. ctp13.af.
28. golimumab.af.
29. simponi.af.

30. cnto148.af.
31. cnto 148.af.
32. 476181-74-5.rn.
33. or/13-32
34. 12 and 33

Search strings 1-11 are terms for the condition, ulcerative colitis, with string 12 combining these terms with OR.
Search strings 13-32 are terms for the interventions, adalimumab, infliximab and golimumab, with string 33 combining these terms with OR.
Search string 34 combines the condition and intervention terms together to retrieve studies about the condition and intervention.

The filters provided below will each be combined with the search above to retrieve trials, systematic reviews and economic literature on the condition and intervention.

RCT search filter for Ovid MEDLINE(R)

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Systematic Reviews search filter for Ovid MEDLINE(R)

1. Meta-Analysis/
2. meta analy$.tw.
3. metaanaly$.tw.
4. meta analysis.pt.
5. (systematic adj (review$1 or overview$1)).tw.
6. exp Review Literature/

7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.
11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list$.ab.
18. bibliograph$.ab.
19. hand-search$.ab.
20. relevant journals.ab.
21. manual search$.ab.
22. or/17-21
23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. review.pt.
27. 25 and 26
28. comment.pt.
29. letter.pt.
30. editorial.pt.
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34

Economic search filter for Ovid MEDLINE(R)

1. exp "costs and cost analysis"/
2. economics/
3. exp economics, hospital/
4. exp economics, medical/
5. economics, nursing/

6. exp models, economic/
7. economics, pharmaceutical/
8. exp "fees and charges"/
9. exp budgets/
10. budget$.tw
11. ec.fs
12. cost$.ti
13. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab
14. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti
15. (price$ or pricing$).tw
16. (financial or finance or finances or financed).tw
17. (fee or fees).tw
18. (value adj2 (money or monetary)).tw
19. quality-adjusted life years/
20. (qaly or qalys).af.
21. (quality adjusted life year or quality adjusted life years).af.
22. or/1-21

Appendix 9.2. Draft data extraction form

DRAFT DATA EXTRACTION FORM (VERSION 1.1)	
TRIAL DETAILS	
Author, year	
Objective	
Study design (e.g. RCT)	
Publication type (i.e. full report or abstract)	
Country of corresponding author	
Sources of funding	
INTERVENTIONS	
Focus of interventions (comparisons)	
Description	
Intervention group	
Intervention name	
Intervention dosing regimen and route of administration	
Comparator group	
Comparator name	
Comparator dosing regimen and route of administration	

Geographical Setting (number of study sites, geographical location details)	
Length of study and latest time point available with data	
Duration of treatment	
Length of follow-up (if different)	
STUDY CHARACTERISTICS	
Method of randomisation	
Description	
Generation of allocation sequences	
Allocation concealment	
Blinding level	
Numbers included in the study	
Numbers randomised	
POPULATION CHARACTERISTICS	
Target population (describe)	
Inclusion / exclusion criteria (n)	
Diagnosis method applied	
Recruitment procedures used (participation rates if available)	
Characteristics of participants at baseline	
Age	
Gender	
Ethnicity	
Extent of disease severity at baseline	
Duration of disease	
Comorbidities at baseline	
Details of any previous colorectal surgical intervention for ulcerative colitis	
Any details of previous conventional treatments (including type, dose and duration)	
Proportion receiving steroids at baseline	
Details of any other medication at baseline and whether discontinued	
Concomitant medications during study	
Any other relevant information	
Were intervention and control groups comparable?	
OUTCOMES	
Measures of disease activity	
Mortality	

Rates of and duration of response, relapse and remission	
Rates of hospitalisation	
Rates of surgical intervention	
Time to surgical intervention	
Adverse events of treatment (including leakage and infections following surgery)	
Health-related quality of life	
Any evidence of selective reporting of outcomes?	
ANALYSIS	
Statistical techniques used	
Intention to treat analysis?	
Power calculation?	
Any rescue therapy / early escape option?	
Attrition rates	
Was attrition adequately dealt with?	
Number (%) followed-up	
RESULTS	
Measures of disease activity	
Mortality	
Rates of and duration of response, relapse and remission	
Rates of hospitalisation	
Rates of surgical intervention	
Time to surgical intervention	
Adverse events of treatment (including leakage and infections following surgery)	
Health-related quality of life	
Other information	
SUMMARY	
Authors' overall conclusions	
Reviewers' comments	

Appendix 9.3. Timetable/milestones

Milestone	**Date**
Draft protocol	1st November 2013
Final protocol	22nd November 2013
Progress report	21st March 2014
Draft assessment report	27th May 2014
Final Assessment report	24th June 2014

10. References

(1) NICE. Ulcerative colitis: Management in adults, children and young people. CG166. 2013.

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(3) Roth LS, Chande N, Ponich T, Roth ML, Gregor J. Predictors of disease severity in ulcerative colitis patients from Southwestern Ontario. *World J Gastroenterol* 2010; 16(2):232-236.

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