Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final protocol 30th May 2007

[redacted]

1. Title of the project:

Use of tumour necrosis factor alpha (TNF α) inhibitors (adalimumab, certolizumab pegol and infliximab [review]) and natalizumab for Crohn's disease

2. Name of TAR team and 'lead'

West Midlands Health Technology Assessment Collaboration (WMHTAC)

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3. Plain English Summary

Crohn's disease is a chronic inflammatory disease of the digestive system. It usually affects the lower part of the small intestine or the large intestine, where it can cause ulcers and scarring. The main symptoms are pain in the abdomen, urgent diarrhoea, anal lesions, rectal bleeding, fever, fistulae, general tiredness and loss of weight. People usually suffer recurrent acute flares of the disease with periods of remission in between. There is no cure for Crohn's disease. Surgery is necessary in up to two thirds of patients, for example when fistulae develop: fistulae are small passages that connect the intestine with other organs or the skin.

There are a number of drugs that can be used to reduce symptoms. Conventional treatment consists of corticosteroids and/or aminosalicylates, both of which can reduce inflammation. Immunosuppressants may also be tried. Some patients do not respond to these treatments, or cannot tolerate the side effects. A drug called infliximab can then be used. This is one of a group of drugs called cytokine inhibitors. Cytokines are small protein molecules, which occur in the body and are involved in inflammatory conditions. Infliximab binds to these molecules and inhibits the inflammatory response. Adalimumab, also a cytokine inhibitor, has recently received a pre-licence positive opinion for use in Crohn's disease. A further cytokine inhibitor, certolizumab pegol is currently being investigated in clinical trials. Natalizumab is a member of a new class of molecules known as selective adhesion molecule (SAM) inhibitors, which are also involved in blocking the inflammatory response. Certolizumab pegol and natalizumab also have licensing agreements pending.

The aim of this report is to gather all the evidence from clinical trials on the effectiveness of infliximab, adalimumab, certolizumab pegol and natalizumab in patients with moderate to severe, active Crohn's disease who have not responded to conventional treatment. Effectiveness will be measured by how much patients' quality of life improves, how long they survive, how long the periods of remission are and whether they need surgery. We will also look at the side effects of

the drugs. Finally, we will look at how much the drugs cost and whether they provide good value for money.

4. Decision Problem

4.1 Purpose of the decision to be made

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract. Its aetiology is unknown, but is thought to involve genetic, environmental, infectious and immunological factors. It affects approximately 60,000 people in the UK (about 1 in 1000) and between 3,000 and 6,000 new cases are diagnosed each year. [1] Any age group can be affected but onset (diagnosis) is most common in teenagers and young adults.[2]

It most commonly affects the small intestine and/or colon and causes inflammation, deep ulcers and scarring to the wall of the intestine. Main clinical features are pain in the abdomen, urgent diarrhoea, anal lesions, rectal bleeding, fever, fistulae, general tiredness and loss of weight.[1,3] Medically or surgically induced remissions are interspersed with relapses.[4] Complications of the disease include the occurrence of obstructions, perianal disease and fistulae. Perianal disease comprises fissures, fistulae and abscesses. Fistulae may develop between loops of bowel adjacent to the bladder or vagina, or to the skin.[3] Surgery is required in up to two thirds of patients to treat intractable haemorrhage, perforation, persistent or recurrent obstruction, abscess or unresponsive fulminant disease. [2]

The disease is neither medically nor surgically curable and treatment is aimed at reducing symptoms and improving quality of life. A range of treatments are currently employed including drug treatment with aminosalicylates, antimetabolites, corticosteroids, immunosuppressive drugs, antibiotics or dietary or surgical intervention. The goal of treatment is to induce and then maintain remission. Medications that are effective in the short term may not result in sustained remission, and in contrast, drugs used for maintenance may have minimal effects of active disease. Long-term use of some drugs may result in high rates of relapse or unacceptable toxicity. [4]

A range of disease activity measures exist, including the Crohn's Disease Activity Index (CDAI), the Perianal Disease Activity Index (PDAI) and the Harvey-Bradshaw Activity Index (HBDAI). The Inflammatory Bowel Disease Questionnaire (IBDQ) measures health related quality of life. The CDAI is often used to describe disease severity, with a score of <150 being associated with remission and a score of >450 with very severe disease.[5] Values of between 220 and 400 are often described as being associated with moderate to severe Crohn's disease.

Infliximab was the first tumour necrosis factor inhibitor (anti-TNF-α antibody) to be licensed for use in patients with severe active Crohn's disease or fistulating active Crohn's disease, who have not responded to conventional treatment or who have experienced toxicity from these treatments.[6] A previous TAR[7] investigated the cost-effectiveness of infliximab as a second or third line treatment and found some evidence of short-term benefit to the patients based on 3 completed randomised controlled trials and one ongoing trial. There was limited evidence on long-term suppression of the disease, long-term tolerability and optimal dose and frequency of dosing. Infliximab has recently received a positive opinion for use in children.

Adalimumab, also an anti-TNF-α antibody, has recently received a positive opinion for use in Crohn's disease. Two further drugs are currently being trialled in Crohn's disease patients with refractory disease: certolizumab pegol, also an anti-TNF-α antibody, and natalizumab, a selective adhesive molecule (SAM) inhibitor. Neither of these drugs are currently licensed in the UK.

[redacted]

The main aims of the report are:

- to update the previous TAR[7] on the clinical and cost-effectiveness of infliximab and to integrate previous results with any new evidence identified
- to review the evidence on the clinical and cost-effectiveness of adalimumab, certolizumab pegol and natalizumab compared to conventional treatment (including no treatment)

4.2 Definition of the intervention

Infliximab, certolizumab pegol and adalimumab are all tumour necrosis factor inhibitors (anti-TNF-α antibodies). TNF-α is a cytokine, a small protein molecule acting as a cell messenger and involved in inflammatory conditions. It is a key mediator of the inflammation associated with Crohn's disease and can be detected in diseased areas of the bowel wall and in blood and faeces of patients with the disease. [8] Infliximab, certolizumab pegol and adalimumab are manufactured antibodies that bind to and inhibit TNF-α thus preventing the inflammatory response.[9]

Infliximab (marketed as Remicade, Schering-Plough) is a chimaeric monoclonal antibody with a human IgG Fc region and murine antigen-binding regions that are highly specific for TNF. It is given by intravenous infusion. 5 mg/kg are given over a period of 2 hours; additional infusions of 5 mg/kg can be given at 2 and 6 weeks, followed by infusions every 8 weeks (maintenance). Alternatively an infusion of 5mg/kg can be given if signs and symptoms reappear (readministration). This is the case for both severe, active Crohn's disease and for fistulating Crohn's disease.

Adalimumab (Humira, Abbott Laboratories) is similar to Infliximab, but is a fully human antibody, and is given by subcutaneous injection. [9]Certolizumab pegol (Cimzia, UCB) is a polyethylene glycolated Fab' fragment of a humanized anti-TNF-α monoclonal antibody intended for subcutaneous administration.[8]

Natalizumab (Tysabri, Elan Pharmaceuticals and Biogen Idec) is a member of a new class of molecules known as selective adhesion molecule (SAM) inhibitors. It is a recombinant humanised IgG4 monoclonal antibody that blocks adhesion and subsequent migration of leukocytes into the gut. Crohn's disease is associated with migration of leukocytes into gut tissue resulting in inflammation.[10]

Dosing guidelines are not yet available for adalimumab, certolizumab pegol or natalizumab or for infliximab in children.

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

Infliximab (Remicade) is licensed for use as a second or third line treatment where conventional treatment has failed or could not be tolerated. The Summary of Product Characteristics (SPC) states that:

"*Remicade is indicated for:*
- *treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies*
- *treatment of fistulating, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).*"

Maintenance therapy can be given at 2 and 6 weeks after the initial dose followed by infusions every 8 weeks. Alternatively, if the signs and symptoms recur, Remicade can be readministered within 16 weeks of the last infusion. The SPC states however that the safety and efficacy of readministration after a drug free interval of more than 16 weeks has not been established. There is still a lack of data on the benefits and risks of the alternative strategies for continued treatment.

The EMEA post-authorisation summary of positive opinion for Humira[11] states that:

"Humira is indicated for treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or and immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. For induction treatment, Humira should be given in combination with corticosteroids. Humira can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate."

The Summary of Product Characteristics (SPC) is not yet available.

[redacted]

[redacted]

There are currently no guidelines on maintenance dosing or readministration for certolizumab pegol or natalizumab.

4.4 Relevant comparators

Given that (anticipated) licences for all four drugs are for use only when conventional treatment has failed, it is unlikely that the drugs would be compared to conventional treatment within the same trial population. It should be noted that conventional treatment may include infliximab. Therefore the most likely comparator will be no treatment or placebo where all patients are receiving conventional therapy. Another relevant comparator may be a different dosing regimen of the same drug.

For comparisons between the four drugs under review, head-to-head comparisons of two or more drugs within the same trial would be the ideal scenario. Scoping searches have indicated that we will identify mainly trials where the individual drugs have been compared to placebo.

4.5 Population and relevant sub-groups

Infliximab is licensed only for use in adults at the moment, and for *severe*, active Crohn's disease or fistulating disease resistant to treatment. Adalimumab is licensed for *severe*, active Crohn's disease; current information does not indicate whether this is in adults only.

[redacted]

There is no standard definition for what constitutes *severe* Crohn's disease. NICE guidance defines *severe* as a score of >300 on the Crohn's Disease Activity Index (CDAI) or 8 to 9 on the Harvey-Bradshaw index. The group that developed the CDAI defines values of 150 and below as quiescent disease and values above 450 as extremely severe disease; no intermediate cut-off point is given for *severe* disease.[5]

The NICE scope for the current appraisal states that the population of interest consists of patients with *moderate to severe* Crohn's disease; there is no standard definition of what constitutes *moderate to severe.* Trials have described patients with a CDAI of 220-400 as having moderate to severe Crohn's disease.[12,13]

4.6 Key factors to be addressed

Key factors are:
- the clinical effectiveness of infliximab, adalimumab, certolizumab pegol and natalizumab particularly in terms of enhancing patient quality of life, maintenance of remission, delaying disease progression and prolonging survival
- the cost-effectiveness of infliximab, adalimumab, certolizumab pegol and natalizumab from the perspective of the NHS

4.7 Areas outside the scope of the appraisal
N/A

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy
A search will be undertaken to identify existing good quality systematic reviews in order to document the evidence base to date. This will follow the ARIF search protocol (Appendix 1). Searches for primary studies will be restricted to RCTs. There will be no language restrictions. A sample MEDLINE search strategy can be found in Appendix 1.

The following resources will be searched for relevant primary studies:

- Bibliographic databases: Cochrane Library, MEDLINE(Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), EMBASE(Ovid), from 2000 to the current date.. Searches will be based on index and text words that encompass the condition: Crohn's disease and the interventions: adalimumab, certolizumab pegol, infliximab and natalizumab. If appropriate, a methodological 'filter' will be applied to identify randomised controlled trials.
- EMEA and FDA and other relevant websites.
- Citations of relevant studies will be examined.
- Further information will be sought from contacts with experts.
- Research registries of ongoing trials including National Research Register, Current Controlled Trials, Clinical Trials.gov
- Industry submissions.

5.2 Types of studies included

Inclusion criteria

Study Design: Randomised controlled trials (RCTs)

Population: Adults (≥ 18 years) and children (6-17 years) with moderate to severe, active Crohn's disease intolerant or resistant to conventional treatment for all 4 drugs; adults (≥ 18 years) with fistulating Crohn's disease resistant to conventional treatment for infliximab only; 'moderate to severe' disease will include patients with an average CDAI score of 220 or above or those that are described by trial authors as having moderate to severe disease.

It should be noted that the licence indications for infliximab and adalimumab specify patients with *severe* disease, rather than *moderate to severe* as specified in the scope. [redacted]. However, as trials are likely to include a spectrum of patients and there are no standard definitions for severe or moderate-to-severe Crohn's disease, we propose to use the above inclusion criterion and look at sub-groups of patients if feasible (see 5.3).

[redacted]

Intervention: Infliximab *or* adalizumab *or* certolizumab pegol *or* natalizumab (any dosage/treatment regimen)

Comparator:

- Conventional treatment without natalizumab or TNF-α inhibitors including no treatment, placebo, dietary intervention, drug treatment with aminosalicylates, methotrexate, corticosteroids (prednisolone, budesonide and hydrocortisone), azathioprine, metronidazole or surgical intervention); given that we are looking at treating patients intolerant or resistant to conventional treatment, it is more likely that the comparator will be placebo where all patients are receiving some form of conventional treatment
- Any combination of drugs listed under intervention compared to each other
- Different dosage or treatment regimens of the same drug

Outcomes – studies that investigate at least one of the following outcomes:
Overall survival, progression free survival, health-related quality-of-life, disease activity (remission, response, relapse, changes in disease activity indices, number of fistulae for fistulating disease), need for surgery, adverse effects of treatment

Both trials that look at induction and maintenance of remission will be included.

Exclusion criteria

We will exclude study designs other than RCTs.

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.3 Sub-groups to be examined

If we find that trial populations fall distinctly into different sub-groups according to disease severity, e.g. more moderate end of disease spectrum compared to very severe disease, we will present trial results according to the different sub-groups.

Results for children aged 6-17 years will be presented separately where possible.

Trials in patients with fistulating disease will be analysed separately. Where there is a mixture of patients with and without fistulating disease we will extract data separately if the published paper allows this.

5.4 Data extraction strategy

Data on study characteristics, study quality and results will be extracted independently by two reviewers, or by one reviewer and checked by a second. A standardized data extraction form will be used, based on the form designed for the previous TAR on infliximab (see Appendix 2). Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary.

5.5 Quality assessment strategy

A suitable quality checklist for RCTs will be used, based on guidelines suggested by the Cochrane collaboration inviting consideration of threats arising from selection, performance, attrition and detection bias. Study quality will be assessed independently by two reviewers, or by one reviewer and checked by a second. Any disagreements will be resolved by consensus or involvement of a third reviewer where necessary.

5.6 Methods of analysis/synthesis

Results from all relevant trials will be tabulated and described and compared qualitatively. Where possible, data will be pooled across studies using meta-analysis. This will depend on the availability of a suitable number of trials with the same intervention and comparator using the same or similar outcome measures, and the availability of adequately reported data within those trials. Where meta-analysis is performed, clinical and statistical heterogeneity will be assessed. Analysis of sub-groups will be explored where appropriate.

At the date of protocol completion, certolizumab pegol and natalizumab had not yet been licensed. Where possible, we will include an analysis on whether the identified evidence (based on the inclusion/exclusion criteria) relating to these drugs, is consistent with the evidence relevant to the actual licence indications/SPCs once these become available. Should licensing information become available very late in the course of the project we may highlight any potential discrepancies (or consistencies) between identified evidence and evidence relevant to the licence indications in the discussion section or in an addendum to the report.

5.7 Methods for estimating quality of life

Information on impact on quality-of-life will ideally be obtained from the same sources as the effectiveness data, where standardised and validated scoring scales have been used. A single utility score for quality of life is required for a cost-utility analysis. Ideally this will be obtained from instruments used in the effectiveness trials that are designed to produce utility weights. In the absence of such data we will examine the literature for studies reporting relationships between the outcome measures and appropriate preference based health related quality of life measures. If such studies do not exist we will explore the feasibility of estimating such relationships from publicly available data. If necessary we will use expert opinion to estimate adult utility weights for use in the cost effectiveness analyses.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Systematic review of literature relevant to economic evaluation

A comprehensive search for literature on the cost and cost-effectiveness of infliximab, adalimumab, certolizumab pegol and natalizumab for the treatment of Crohn's disease from the perspective of the United Kingdom will be conducted.

Studies on costs, quality of life, cost effectiveness and modelling will be identified from the following sources:

- Bibliographic databases: MEDLINE (Ovid), EMBASE (Ovid), Cochrane Library (NHS EED and DARE), and HEED database.
- Industry submissions
- Internet sites of national economic units

Searches will run from 2000 and there will be no language restrictions. Studies conducted in any country will be included.

Standard approaches to applying inclusion/ exclusion criteria will be employed. Quality assessment for cost-effectiveness studies will be done using standard criteria.[14] Papers may be excluded at this stage on the basis of quality assessment. Justification for the exclusion of papers will be presented. The papers that remain in the review will be summarised on the basis of key items of information, an example of which is listed below.

- Details of the study characteristics such as form of economic analysis, comparators, perspective, time horizon and modelling used.
- Details of the effectiveness and cost parameters such as: effectiveness data; health state valuations; resource use data; unit cost data; price year; discounting assumptions; productivity costs.
- Details of the results and sensitivity analysis.

6.2 Economic Evaluation

A model-based economic evaluation will be conducted as part of this appraisal. The cost-effectiveness analysis estimates the expressed incremental cost per quality adjusted life year (QALY) for each treatment compared to usual care. Analyses will be undertaken for patients with moderate to severe active Crohn's disease and for patients with fistulating disease (infliximab only). Calculation of a cost/QALY will be dependent on the availability of robust utility data or the ability to map disease specific scores to utility scores.

Any models supplied by the manufacturers will be appraised and where possible used to rerun analyses using the effectiveness estimates obtained as part of the systematic review. Given that this is a chronic disease where patients can move between varying states of disease, a Markov model is likely to be the most suitable model structure. If it is necessary to develop a *de novo* model, this will be done in collaboration with clinical experts in order to ensure that the patient pathway is represented adequately.

Sensitivity analyses will be performed around key parameters, such as proportion of patients responding to treatment (and re-treatment), (age-dependent) utility gains, duration of benefit, proportion avoiding surgery and costs of different treatment regimens. These will take the form of both conventional one and multi-way analyses and probabilistic sensitivity analysis (PSA). The use of PSA will involve specifying distributions around model parameters (such as transition rates, side effects, costs, utilities, etc.) and using Monte Carlo simulation to randomly sample from these distributions. This process will allow the propagation of the uncertainty around the model inputs through the model and thereby the quantification of the impact of this uncertainty on the uncertainty around the model outputs. The results of the PSA will be presented as scatter

plots on the cost-effectiveness plane and as cost-effectiveness acceptability curves. The expected net benefit for each intervention will be estimated assuming a cost effectiveness threshold (lambda) = £20,000 per QALY.

The perspective for the reference case model will be NHS/PSS. The time horizon of our reference case analysis would ideally be over a patient's lifetime to reflect the chronic nature of the condition; this will be dependent on the availability of long-term data on effectiveness. We anticipate that there will be higher levels of uncertainty associated with the effectiveness of longer-term treatment. A secondary analysis will explore the feasibility of incorporating this uncertainty into the model by specifying the effectiveness as a time dependent function, and having uncertainty around the parameters in this function. Costs and outcomes will be discounted at 3.5% p.a.

As certolizumab pegol and natalizumab have not been licensed at the time of protocol completion, the economic model will be based on the anticipated licence indications as outlined in the protocol, or the actual licence indications if and when they become available. The model will be available to NICE to run additional calculations should there be late changes in the licence indications.

7. Handling the company submission(s)

Company submissions by the manufacturers/sponsors will be considered if received by the assessment group no later than the 6th August 2007. Data arriving after this date will not be considered. Any clinical data meeting the inclusion criteria for the review 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 presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the assessment group judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing *de-novo* modelling.

Any 'commercial in confidence' data taken from a company submission will be highlighted in the assessment report.

8. Competing interests of authors

Martin Connock-none
Janine Dretzke-none
Anne Fry-Smith-none
Christopher McCabe-none
Catherine Meads-none
Natalie Rowles-none
Tariq Iqbal-tbc

9. Appendices

Appendix 1 DRAFT Search Strategies

ARIF search protocol (scoping searches for systematic reviews)

1. Cochrane Library
- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database
An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments and Evidence Based guidelines
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes, Public Health excellence
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- STEER Reports (no longer published)
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases
- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts
- Cochrane Collaboration (via Cochrane Library)

- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

Sample search strategy MEDLINE (clinical effectiveness primary studies)

1 (adalimumab or humira).mp.
2 (certolizumab or cimzia).mp.
3 (infliximab or remicade).mp.
4 (natalizumab or tysabri).mp.
5 or/1-4
6 Crohn Disease/
7 crohn$.mp.
8 or/6-7
9 5 and 8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 randomized controlled trials.sh.
13 random allocation.sh.
14 double blind method.sh.
15 single blind method.sh.
16 or/10-15
17 (animals not human).sh.
18 16 not 17
19 clinical trial.pt.
20 exp clinical trials/
21 (clin$ adj25 trial$).ti,ab.
22 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
23 placebo$.ti,ab.
24 random$.ti,ab.
25 placebos.sh.
26 research design.sh.
27 or/19-26
28 27 not 17
29 28 not 18
30 18 or 29
31 9 and 30
32 limit 31 to yr="2000 - 2007"

Appendix 2 DRAFT Data Extraction Form

Data Extraction Form – Moderate to severe Active Crohn's disease

Title of Study

Reference:
Geographical location of the study:

Baseline Characteristics	Placebo/ other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=
Mean Age ±SD					
Sex					
Ethnicity					
Mean weight ± SD					
Mean height ± SD					
Number smokers					
Mean duration of Crohn's disease (years) ± SD					
Intestinal area involved Ileum only Colon only Ileum/colon					
Previous surgery for Crohn's					
Mean baseline CDAI ± SD					
Mean baseline IBDQ ± SD					
Mean C-reactive protein mg/L ± SD					
Concurrent medication					
Prednisolone equivalent < 20mg/day ≥ 20 mg/day					
Mercaptopurine					
Azathioprine					
Oral aminosalicylate					
Antibiotic					

Other: Specify					

Notes: (Identify any statistically significant differences)

Study design/methodology - See flow chart

Was ITT analysis used: **YES/NO**

Outcomes: ITT population / efficacy population

Outcome 1

Mean CDAI ± SD	Placebo/other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=
Baseline					
1st timepoint					
P vs placebo					
2nd timepoint					
P vs placebo					
Endpoint Specify week					

Repeat table for all relevant outcomes

Duration of response

Mean duration of response (SD)	Placebo/other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=

Notes

Data Extraction Form – Fistulating Crohn's disease

Reviewer:
Date:

Title of Study

Reference:
Geographical location of the study:

Characteristic	Placebo/other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=
Mean Age ±SD					
Sex					
Ethnicity					
Mean weight kg ± SD					
Mean height cm ± SD					
Number smokers (%)					
Mean duration of Crohn's disease (years) ± SD					
Intestinal area involved Ileum only (%) Colon only (%) Ileum/colon (%)					
Previous surgery for Crohn's					
Mean baseline CDAI ± SD					
Mean baseline IBDQ ± SD					
Mean C-reactive protein mg/L ± SD					
Number of fistulas 1 >1					
Location of fistula Perianal (%) Abdominal (%)					
Duration of fistula					
Mean PDAI score					
Concurrent medication					
Prednisolone equivalent (%) ≤ 40mg/day					

> 40 mg/day					
Mercaptopurine (%)					
Azathioprine (%)					
Oral aminosalicylate (%)					
Antibiotic (%)					
Other: Specify					

Notes: *Identify any statistically significant differences*

Study design/methodology - See flow chart

Was ITT analysis used: YES/NO

Outcomes - ITT population/ efficacy population

Outcome 1

Mean/ Median CDAI ± SD or IQR	Placebo/other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=
Baseline					
1st timepoint					
P vs placebo					
2nd Timepoint					
P vs placebo					
Endpoint Specify week					

Repeat table for each outcome

Length of time to beginning of response

Days	Placebo/other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=
Mean/ Median					
SD / IQR					

Duration of response

Duration - days	Placebo/other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=
Mean/ median					
SD or IQR					

Safety: Data extraction – All studies Reviewer:
Title of Study: Date:
Reference:

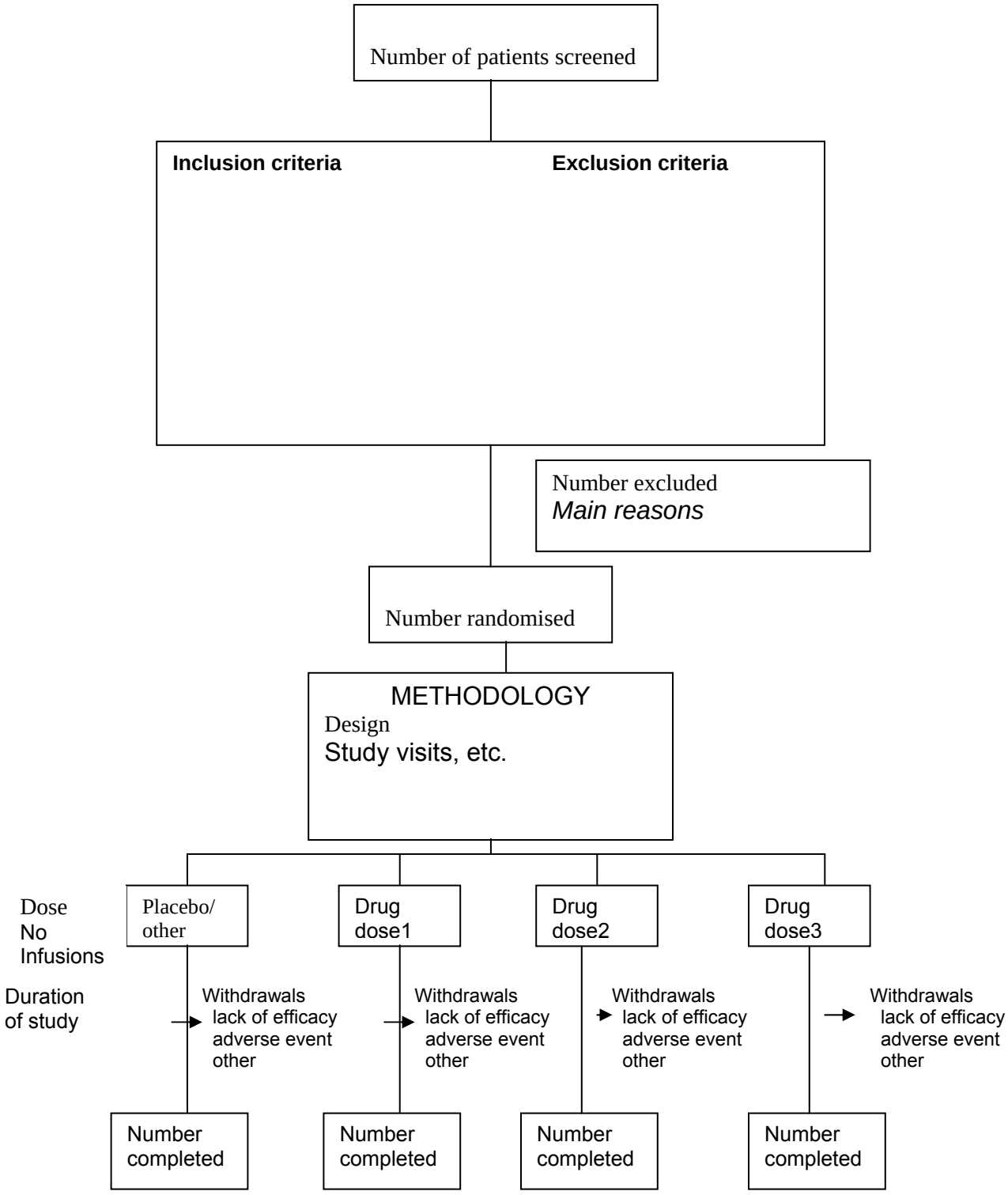
Adverse event		Placebo/other treatment n=	Drug dosage 1 n=	Drug dosage 2 n=	Drug dosage 3 n=	Total drug n=
Average follow up						
Any Adverse Event (%)						
DEATH						
Adverse event leading to withdrawal						
GI:	Nausea					
	Vomiting					
	Abdo. Pain					
CNS:	Headache					
	Pain					
	Fatigue					
Infection:	URTI					
	Other infection					
	Serious infection					
	TB					
Haematological						
Cardiovascular	Chest pain					
	Hypotension					
	Hypertension					
Skin	Pruritus					
	Injection site Reaction					
Hypersensitivity	Acute					
	Delayed					
Respiratory	Dyspnoea					
Other	Myalgia					
	Fever					
	Abscess					
	Antibodies to DNA					

	Human anti-cA2					
	Lupus arthritis					
	AE during or within 2 hrs of infusion					
	Other					
	Other					

Title of study

Reviewer:
Date:

Reference



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