National Institute for Health and Care Excellence

Final

Addendum to Clinical Guidelines 152, Crohn's disease: management in adults, children and young people

Clinical Guideline Addendum 152.1

Methods, evidence and recommendations

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Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on Crohn's disease: management in adults, children and young people (NICE guideline CG152) was reviewed in April 2015 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence that supported the need for an update of the guideline in relation to the following area: the clinical and cost-effectiveness of tumour necrosis factor (TNF)-alpha inhibitor biologics (infliximab and adalimumab) in combination with immunosuppressants compared with infliximab or adalimumab alone. The full surveillance report can be found here.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Information for consultation

You are invited to comment on the new recommendation in this update. This is marked as **[new 2016].**

1.2 Recommendations

1. **When a person with Crohn's disease is starting infliximab or adalimumab (in line with recommendations 1.2.12, 1.2.15, 1.2.17 and 1.2.20), discuss options of:**
    - **monotherapy with one of these drugs, or**
    - **combined therapy (either infliximab or adalimumab, combined with an immunosuppressant)**

   and tell the person there is uncertainty about the comparative effectiveness and long-term adverse effects of monotherapy and combined therapy. [new 2016]

1.3 Patient-centred care

This guideline offers best practice advice on the care of adults, children and young people with Crohn's disease.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the person is under 16, their family or carers should also be given information and support to help the child or young person make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with Crohn's disease. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1.4 Methods

This update was developed based on the process and methods described in the guidelines manual 2014. For details specific to the evidence review, see Section 2.3.1.

2 Evidence review and recommendations

2.1 Introduction

Crohn's disease is a long-term condition characterised by inflammation of the lining of the digestive system. Typically people with Crohn's have recurrent acute exacerbations ('flares') interspersed with periods of remission or less active disease.

Incidence of Crohn's disease is greatest in people aged between 15 and 30 years. However it may affect people of any age: 15% are older than 60 years at diagnosis while 20–30% are younger than 20 years.

Crohn's disease is not medically or surgically curable. The aim of treatment is to supress the inflammatory process, provide symptom relief, and maintain or improve quality of life while minimising short- and long-term adverse effects. Clinical management depends on disease activity, site, and behaviour (inflammatory, stricturing or fistulising), response to previous medications, and extra-intestinal symptoms. Current treatment includes aminosalicylates, corticosteroids, immunosuppressants, certain biologic agents, antibiotics, nutritional supplementation and dietary measures.

The NICE guideline for the management of Crohn's disease (CG152) covers strategies for treating acute disease (to induce remission) and for preventing relapse (maintaining remission). This update is concerned with treatment to induce remission in active Crohn's disease.

A routine surveillance review of CG152 highlighted evidence on the combined use of tumour necrosis factor (TNF)-alpha inhibitor and immunosuppressant medications for inducing remission in people with severe active Crohn's disease. The NICE treatment pathway currently recommends treatment with a TNF alpha inhibitor biologic (namely, infliximab or adalimumab) for adults and children with severe active Crohn's, whose disease has either not responded to conventional therapy (including immunosuppressants and/or corticosteroids, and primary nutrition therapy in the case of children), or who are intolerant or have contraindications to conventional therapy. However, it is not explicit in the current guideline whether immunosuppressant therapy should be continued (or added, if it was previously stopped) when treating patients with infliximab or adalimumab. This is because recommendations on the use of these biologics were incorporated directly into CG152 from an earlier NICE technology appraisal (NICE TA187). The review of evidence relating to these technologies was limited in the technology appraisal to their existing marketing authorisations and only considered trials in which the randomised comparison was between licensed doses of infliximab or adalimumab versus placebo. No account was taken of concomitant treatment with immunosuppressant medication.

This update aims to provide guidance on the relative efficacy, safety and cost-effectiveness of the combined use of TNF alpha inhibitor biologics (infliximab or adalimumab) together with an immunosuppressant medication, compared with biologic medication given alone.

2.2 Review question

What is the clinical and cost-effectiveness of TNF alpha inhibitor monoclonal antibodies (infliximab and adalimumab) given in combination with immunosuppressants compared with infliximab or adalimumab alone for inducing remission in adults and children (6-17 years) with active Crohn's disease?

2.3 Clinical evidence review

A systematic search of the literature was conducted (see Appendix D:) which identified 3,417 articles. The titles and abstracts were screened and 97 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C:). A further 12 full text articles, identified from cross-checking reference lists, were also reviewed. Of the 109 articles reviewed, 99 were excluded as they did not meet the criteria and 10 met the criteria and were included.

A review flowchart is provided in Appendix E:, and the excluded studies (with reasons for exclusion) are shown in Appendix F:.

2.3.1 Methods

The review protocol was developed in consultation with the topic expert members and approved by the core Committee before the review was carried out. The following outcomes were considered important for decision-making:

- disease remission (at three time periods following the start of treatment: early (4-6 weeks), middle (10-12 weeks) and late (15+ weeks);
- serious adverse events;
- quality of life;
- whether patients are corticosteroid-free at 6 and 12 months;
- rates of surgery at 6 and 12 months;
- hospital admissions;
- growth (as measured by height velocity standard deviation score, HVSDS) – in paediatric populations only.

During discussion of outcomes, topic experts noted that limited evidence would be available from randomised controlled trials (RCTs) relating to the specific serious adverse events of interest (namely, serious infections requiring hospitalisation, lymphoma, other malignancies and mortality) given the relatively short time horizon of trials of therapies for inducing remission in patients with Crohn's disease. It was therefore agreed, for the adverse events outcome only, to also include evidence from observational studies in which the two treatment groups of interest were compared over a minimum 12 month period.

The population for the review was 'adults and children (6-17 years) with active Crohn's disease'. The topic experts were keen to keep the population criteria broad to ensure inclusion of patients who may not have had therapy with an immunosuppressant prior to starting a biologic, and also patients who may have lost response to biologic medication (due to the formation of antibodies). Topic experts were also keen not to specify 'severe' active Crohn's as a population criterion as this would require a setting a threshold definition for 'severe'. Patients who are losing response to a biologic might not meet this threshold but may still warrant being given an additional immunosuppressant to reduce immunogenicity.

Three RCTs met the review protocol criteria and were included in the efficacy analyses. A further 7 observational studies were included for the review of serious adverse events. For a summary of included studies please see Table 1 and Table 2 (for the full evidence tables see Appendix G:).

The TNF-alpha inhibitor medication used in all 3 of the included RCTs was infliximab. The study populations were all adults. No paediatric studies, and no trials of adalimumab combined with any immunosuppressant medication met the review protocol criteria.

In one double-blind RCT, the immunosuppressant medication azathioprine (AZA) was administered concomitantly with infliximab and compared to treatment with infliximab + placebo (Colombel et al. 2010). Methotrexate was the immunosuppressant medication used

in combination with infliximab in the two other included RCTs: one a double-blind trial (Feagan et al. 2014), the other an open-label study (Schroder et al. 2006). Azathioprine (and mercaptopurine (MP), a chemically related immunosuppressant drug) suppress the immune response via a different mechanism to methotrexate. The current NICE guideline (CG152) recommends methotrexate only in patients who cannot tolerate AZA/MP, or who are contraindicated due to deficiencies in the enzyme thiopurine methyltransferase (TPMT). Therefore, separate analyses were undertaken in this review for the two following comparisons:

i. AZA + infliximab versus infliximab monotherapy, and
ii. MTX + infliximab versus infliximab monotherapy.

Where more than one study assessed an outcome for a given comparison, data were combined using pair-wise meta-analyses. The Mantel-Haenszel and inverse variance methods were used for dichotomous and continuous outcomes respectively. A fixed effects model was applied because the studies used the same medication and dose, and were therefore assumed to estimate the same treatment effect. The I^2, chi^2 and tau^2 statistics were calculated to assess heterogeneity. For most efficacy outcomes, evidence was available from only one study for each comparison. Estimates of effect size and 95% confidence intervals were calculated in Review Manager. Forest plots showing the outcome of these analyses are included in Appendix I:. Forest plots were not generated for the serious adverse events specified in the review protocol (serious infections, lymphoma and other malignancies and mortality) due to lack of consistency in reporting and analysis across the included observational studies.

There were some deviations from the review protocol in the analyses. The time period for 'early' clinical remission was expanded from 4-6 weeks to include a 2 week time point reported in Schroder (2006). Similarly, the middle time period specified in the review protocol (10-12 weeks) was widened to include remission data reported at 14 weeks in the study by Feagan (2014). Clinical response to treatment (a reduction of ≥70 points on the Crohn's Disease Activity Index, CDAI) was omitted from analyses because the focus of the review was on remission of disease; inclusion of many different definitions of remission risks overstating the evidence for this outcome. Rates of 'corticosteroid-free *clinical remission'* reported by Colombel (2010) and Feagan (2014) were included but analysed separately from data reported by Schroder (2006) which matched the outcome as it was specified in the review protocol: 'corticosteroid-free' (some patients may achieve withdrawal from corticosteroids without full remission of symptoms).

There were insufficient data across included studies to do the subgroup analyses proposed in the review protocol (Appendix C:). However one study reported some subgroup comparisons that approximately matched those in the review protocol. The primary outcome in those analyses was 'corticosteroid-free clinical remission' at 26 weeks (Colombel 2010). Forest plots for the relevant comparisons are presented in Appendix I.1.1. The presence of a subgroup effect was assessed by examining the statistical significance of a test for subgroup differences. A p-value less than 0.05 was taken as possible evidence for a significant subgroup effect. No significant differences were found for any of the subgroup comparisons.

The quality of the overall evidence for each outcome for each comparison was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group. For the specified adverse events of interest (serious infections, lymphoma and other malignancies and mortality), a GRADE quality rating was derived for each outcome and study, rather than a summary across studies, because the data could not be pooled. For full GRADE profiles please see Appendix H:.

Risk of bias was assessed by considering whether there were serious or very serious limitations in study design in those studies contributing to each outcome. Lack of blinding of RCT participants and investigators was a reason for downgrading certain efficacy outcomes

for risk of bias. Observational studies are inherently at risk of selection bias and therefore start with a GRADE rating of 'low quality'. Evidence on adverse events was further downgraded for risk of bias if studies had failed to take account of known treatment group differences or controlled for potential confounding factors in analyses.

Indirectness was assessed by noting whether the evidence directly applied to the parameters specified in the review protocol. The majority of efficacy outcomes and all observational studies reporting adverse event data were downgraded one level for serious indirectness. In one trial, the study population was limited to patients who were naïve to both immunosuppressant and anti-TNF alpha medications (Colombel 2010). The evidence from this trial may not be generalizable to patients with active Crohn's disease who are being 'stepped up' to treatment with anti-TNF alpha therapy having failed (or lost response to) prior conventional therapy, as currently recommended in the NICE pathway for induction of remission in Crohn's disease. In another trial (Feagan 2014), approximately one-third of the study population was already in prednisolone-induced remission at baseline, so did not meet the review population of patients with active Crohn's disease. Similarly, comparative evidence on serious adverse events of interest came from observational studies in which patients received the study treatment both to induce remission and for longer-term maintenance once the disease was in clinical remission.

Inconsistency (variability in the results from different trials) was only assessed when data were combined in meta-analyses. The degree of heterogeneity was assessed and 95% confidence intervals were examined to determine whether serious inconsistency was present, using the methods described by the GRADE working group.

Imprecision was assessed by determining whether 95% confidence intervals for effect estimates incorporated thresholds for clinically important harm, no effect and clinically important benefit. The original guideline development group had considered a 15% relative increase in remission rate to be clinically important when assessing evidence for a different therapeutic comparison (of conventional corticosteroids versus budesonide for the induction of remission in Crohn's disease). In consultation with topic experts, the same minimally important difference (MID) threshold was used to assess imprecision of the evidence for induction of remission in this review. The original guideline also used an MID of 16.8 for change in IBDQ score when assessing evidence for quality of life; it was agreed to apply the same threshold in this review. For other outcomes, a routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimally important difference (MIDs). No information was identified in the COMET database. MIDs were also sought from other published literature but none were found, so GRADE default MIDs were used (RR 0.75 and 1.25 for dichotomous outcomes, and -0.5 and 0.5 standardised mean differences for continuous outcomes). When assessing imprecision of the evidence, if the confidence interval for an outcome incorporated both MID thresholds for clinically important benefit and harm, imprecision was judged to be very serious and downgraded two levels. If the 95%CI incorporated one of the MID thresholds, imprecision was considered serious and the evidence downgraded one level.

Among other factors considered, potential publication bias was not a serious concern. However, two studies used non-randomised subgroup data from placebo-controlled RCTs to present a pooled analysis of comparative rates of adverse events in patients who were, and those who were not taking immunosuppressant medication at study initiation (Osterman et al. 2014, Jones et al. 2015). In neither case was it possible to verify the results of these pooled analyses with reference to the individual published trials because both had used unpublished data obtained from the original trial investigators.

Overall, evidence for the efficacy outcomes in the review was of low quality. This was largely due to imprecision of effects, and concerns about generalisability. Evidence for serious adverse events came mostly from observational studies and was of very low quality overall,

due to risk of bias, very imprecise effect estimates, and concerns about applicability to the population of interest.

Table 1: Summary of included studies – randomised controlled trials

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
Colombel (2010) 'SONIC' trial Double-blind, multi-centre RCT 30 week trial (with optional 20 week extension). Two of 3 active treatment arms were included in this review	N=338 adults ≥21yrs[a] with active Crohn's disease of ≥6 weeks duration; CDAI score 220-450 points; immunosuppressant and biologic naïve; corticosteroid-dependent *or* failed to respond to mesalamine / budesonide therapy *or* being considered for second course. Median age: 34.0yrs 50.9% male Duration of disease (years): median: 2.2yrs Baseline CDAI score (mean): 268.7	Combination infliximab + azathioprine vs. Infliximab + placebo Infliximab infusions at weeks 0, 2, 6, 14, and 22. Dose: 5mg/kg bodyweight. Azathioprine oral capsules given daily. Dose: 2.5mg/kg bodyweight. Optional 20 week extension trial (with blinding maintained): infliximab infusions at weeks 30, 38, and 46 (*plus* azathioprine capsules daily through to week 50 for those in intervention arm or placebo capsules in comparator group).	• Remission - clinical remission (CDAI<150) - Mucosal healing • Quality of life • Corticosteroid-free remission • Adverse events - Any adverse events (not specified) - Serious infections	Setting: multinational (92 centres) Corticosteroids at baseline: 29.3% Prior immunosuppressants: none 68.6% of randomised patients completed 30wk trial 60.1% of randomised patients enrolled in 20wk extension trial.
Feagan (2014) 'COMMIT' trial Double-blind, multi-centre RCT 14 week induction trial (additional 36	N=126 patients with Crohn's disease who had initiated corticosteroids (prednisolone) for active symptoms within 6 weeks of screening visit; infliximab naïve; no methotrexate in the past year or previous methotrexate failure; no azathioprine within 8 weeks prior to randomisation. Mean age: 39.5yrs 56.3% male	Combination infliximab + methotrexate vs. Infliximab + placebo Infliximab infusions at weeks 1, 3, 7, and 14. Dose: 5mg/kg bodyweight. Methotrexate given weekly by subcutaneous injection. Dose: initial 10mg/wk increased using dose-escalation strategy to 20mg at week 3,	• Clinical remission at week 14 • Quality of life • Corticosteroid-free remission • Rates of surgery	Setting: Canada (15 centres). Corticosteroids at baseline: 100% Prior immunosuppressants: 25%

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
week maintenance extension only for patients in corticosteroid-free remission at week 14)	Disease duration (years) – mean (sd): 10.3 (9.3) Baseline CDAI score (mean): 207.7	then 25 mg at week 5 with continuation through to week 14. Maintenance extension trial for patients in corticosteroid-free remission at 14 weeks: infliximab infusions given at weeks 22, 30, 38 and 46 (*plus* weekly subcutaneous 25mg methotrexate injections for those in intervention arm, or placebo injections in comparator group).		Approximately 30% of patients across both groups were already in steroid-induced remission (CDAI < 150 points) at baseline so do not meet review protocol criterion for 'active Crohn's disease'.
Schroder (2006) Open-label randomised controlled pilot study. 48 weeks	N=19 patients with active Crohn's disease refractory to / dependent on corticosteroids; resistant or intolerant to azathioprine; naïve to anti-TNF-alpha treatment. Mean age: 33.7yrs 42.1% male Disease duration (years) – mean (sd): 8.8 (6.3) Baseline CDAI score (mean): 268.7	Combination infliximab + methotrexate vs. Infliximab monotherapy Infliximab infusions at weeks 0 and 2. Dose: 5mg/kg bodyweight. Methotrexate (20mg/week) by infusion between weeks 0 to 5, then orally to 48 weeks	• Clinical remission - (CDAI<150) at week 12, week 24 • Quality of life • Corticosteroid-free • Adverse events - Any serious adverse events (not specified)	Setting: Germany (1 centre). Corticosteroids at baseline: 79% Prior immunosuppressants: 100% (89.5% resistant to AZA/MP; 10.5% intolerant)

(a) After 2 years recruitment the minimum age for study participants was raised from 18 to 21 following reports of hepatosplenic T-cell lymphoma in adolescents and very young adults receiving combination therapy with anti-TNF-alpha and immunosuppressant agents.

Table 2: Summary of included studies – observational and cohort studies reporting adverse events of interest

Study reference (including study design)	Study population	Comparison groups	Outcomes reported	Comments
Hamzaoglu (2010) Retrospective cohort study	N=297 consecutive patients treated with infliximab for Crohn's disease between October 1998 and January 2005. Mean age: 40 years[a] 40% male[a] Disease duration – median: 13.9yrs (range 1 - 48)	Data extracted for: ○ N=61 treated with combined infliximab + AZA/MP ○ N=160 treated with infliximab monotherapy	• Adverse events - Serious infections - Malignancy - Death	Setting: USA (1 centre) Patients taking concomitant corticosteroids at start of infliximab treatment are excluded from analyses.
Jones (2015) Meta-analysis of non-randomised subgroup data from placebo-controlled RCTs	N=1,055 patients with Crohn's disease randomised to anti-TNF-alpha treatment in placebo-controlled trials, stratified by concomitant immunosuppressant use at baseline. Patient characteristics not reported.	Infliximab [pooled data from 5 trials]: ○ N=152 treated with combined infliximab + immunosuppressant (IS) ○ N=302 treated with infliximab monotherapy Adalimumab [pooled data from 4 trials]: ○ N=260 treated with combined adalimumab + IS ○ N=341 treated with adalimumab monotherapy	• Adverse events - Serious infections - Malignancy - Death	Setting: multiple countries (pooled data from RCTs). Corticosteroids at baseline: not reported. Prior immunosuppressants: not reported.
Kinney (2003) Retrospective cohort	N=117 patients treated with episodic ('on demand') infliximab for Crohn's disease between October 1998 and	○ N=58 treated with combined infliximab + AZA/MP	• Adverse events - Death	Setting: USA (1 centre)

Study reference (including study design)	Study population	Comparison groups	Outcomes reported	Comments
study	March 2001. Mean age: 42 years 42% male Disease duration (years) – mean: 13.1	○ N=23 treated with combined infliximab + Methotrexate (MTX) ○ N=36 treated with infliximab monotherapy		55% of overall cohort were treated with concomitant corticosteroids. Prior immunosuppressants: not reported.
Lichtenstein (2014) Retrospective cohort study	N=3,764 patients with Crohn's disease who were treated with infliximab during or within a year before enrolment in the prospective, observational TREAT registry (average patient follow-up: 5.2 years). Mean age at enrolment: 41 years 41% male Disease duration (years) – mean (sd): 11.2 (9.8)	○ N=3,517 treated with infliximab + IS ○ N=247 treated with infliximab only	• Adverse events - Malignancy	Setting: USA (multicentre). Corticosteroid use in previous year (across cohort): 48% Immunosuppressant use in previous year (across cohort): 52%
Marehbian (2009) Retrospective cohort study	N=8,581 longitudinal cohort of patients identified from private health insurance claims (2002-2005) by presence of at least one claim for Crohn's disease and with a minimum of 1 year of information without a CD diagnosis before the index diagnosis. Mean age: 48 years 44% male	○ Combined anti-TNF-alpha + IS therapy (representing 162 person-years of exposure) ○ Anti-TNF-alpha monotherapy (representing 292 person-years of exposure)	• Adverse events - Serious infection (sepsis) - Malignancies: (lymphoma; solid tumours)	Setting: USA (nationwide). Analyses excluded patients prescribed steroids.

Study reference (including study design)	Study population	Comparison groups	Outcomes reported	Comments
	Disease duration: not known.			
Osterman (2014) Pooled analysis of data from placebo-controlled RCTs and a prospective observational study of adalimumab treatment for the induction or maintenance of remission.	N=1,594 patient participants in six trials of adalimumab (representing 3,050 person-years of adalimumab exposure). Mean age: 38 years 39% male Disease duration (years): approximately 8 (range: 0 to 47 years)	Pooled data from 6 studies: ○ N=694 treated with adalimumab + any IS (representing 1401 person-years of adalimumab exposure) ○ N=563 treated with adalimumab + AZA/MP (representing 1145 person-years of adalimumab exposure) ○ N=900 treated with adalimumab only (representing 1649 person-years of adalimumab exposure)	• Adverse events - Malignancies: (non-melanoma skin cancer, NMSC; other malignancies)	Setting: multiple countries (pooled data from RCTs) Corticosteroids at baseline: 51% Prior ant-TNF-therapy use: 70%
Osterman (2015) Retrospective cohort study	N=1,994 new users of anti-TNF-alpha therapy for the treatment of Crohn's disease between February 2007 and December 2010 identified from Medicare records. Age ranges (years): 20-39yrs: 22%; 40-59yrs: 35% 60yrs+ 43% 37% male Disease duration: not known.	Infliximab: ○ N=381 treated with combined infliximab + IS ○ N=912 matched patients treated with infliximab monotherapy Adalimumab: ○ N=196 treated with combined adalimumab + IS ○ N=505 matched patients treated with adalimumab monotherapy	• Adverse events - Serious infections	Setting: USA (nationwide) 9% treated with steroids within 28 days of start of anti-TNF-alpha therapy 87% of combination therapy patients were taking immunosuppressants before starting anti-TNF-alpha therapy ('step-up' therapy)

(a) Based on overall sample of 297 study patients whose records were reviewed. Data were not extracted for patients treated with corticosteroids (with or without immunosuppressant therapy) at the start of infliximab treatment.

2.4 Health economic evidence review

2.4.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to TNF alpha inhibitor biologics (infliximab or adalimumab) in combination with immunosuppressants compared with infliximab or adalimumab alone for Crohn's disease in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 08.10.2015. The health economic search strategies are detailed in appendix J.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual 2014*.
- Extracted key information about the studies' methods and results into full economic evidence tables (appendix M).
- Generated summaries of the evidence in economic evidence profiles.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix L).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

Table 3 explains the information contained in the economic evidence profile.

Table 3: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental	The difference between the mean health effect associated with the intervention

Item	Description
effect	and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case.
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

2.4.2 Results of the economic literature review

The search returned 1038 articles. 1026 of these were excluded based on title and abstract. Full papers were obtained for 12 articles. 11 full text articles were excluded. Only one study from the published literature was included.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix K. Appendix L contains a list of excluded studies and the reason for their exclusion.

Table 4 contains the economic evidence profile for the review question summarising the results of the study included in the systematic review. Full economic evidence tables are contained in appendix M.

Table 4: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
Saito et al. 2013 Cost-utility analysis Infliximab (IFX) vs. infliximab + azathioprine (IFX + AZA) United Kingdom	Partially applicable [(a)]	Very serious limitations [(b)]	Decision tree with 1-year time horizon, comparing IFX vs. IFX + AZA in a hypothetical cohort of 25-year-old men, weighing 60 kg, who were biologic-naïve CD patients refractory to conventional non-anti-TNF-α therapy	£1593.35	0.064 QALYs	£24,917 per QALY	A probabilistic analysis showed that combination therapy has 75% probability of being cost effective at threshold of £30,000. However, at an investment of £20,000 per QALY, only 13.0% (read off graph) of the simulations showed that combination therapy was cost effective. The one-way sensitivity analysis demonstrated that ICERs remain in the £17,147-£45,564 per QALY range, and that quality of life utilities for nonresponding active disease had the highest impact on ICER (45,564 per QALY over IFX monotherapy).

Acronyms

AZA: azathioprine; ICER: incremental cost-effectiveness ratio; IFX: infliximab; QALY: quality-adjusted life year

[(a)] UK study from an NHS perspective. Population consistency with current NICE recommendations questionable. Sources of costs not always from relevant UK sources.

[(b)] Short time horizon. Adverse effects not adequately captured. £30,000 per QALY gained ICER threshold used in probabilistic analysis.

2.5 Evidence statements

2.5.1 Clinical evidence statements

Combination infliximab and azathioprine versus infliximab monotherapy

In one study, 338 participants (with a mean disease duration of 2.2 years), who were naïve to both immunosuppressant and TNF alpha inhibitor therapy, were treated with a combination of infliximab and azathioprine or infliximab alone for the induction of remission. Treatment duration was 6 months with an optional extension to 12 months. Low quality evidence favoured combination therapy in terms of clinical remission (CDAI<150) at 10 and 18 weeks following initiation of treatment, and corticosteroid-free remission at 6 and 12 months. In 210 patients with endoscopic evidence of ulceration at baseline, low quality evidence suggested higher rates of mucosal healing at 6 months favouring combination therapy. There was very low quality evidence of fewer (unspecified) serious adverse events up to 54 weeks in patients treated with combination therapy. In all cases, the effects favouring combination therapy were of uncertain clinical importance.

Moderate quality evidence showed no difference in quality of life between the two treatment groups at 10 weeks.

The study reported analyses that showed there were no differences in corticosteroid-free remission at 6 months between the following subgroups: younger, middle and older-age patients; males and females; Caucasian and non-Caucasian patients; steroid dose at baseline (≤20mg or >20mg daily prednisolone); and whether or not patients had undergone previous Crohn's disease-related surgery.

Combination infliximab and methotrexate versus infliximab monotherapy

In two studies, 145 participants (mean duration of disease: 8-10 years), who were not naïve to immunosuppressant therapy but were naïve to a TNF alpha inhibitor, were treated with combination infliximab and methotrexate therapy or with infliximab alone for the induction of remission. There was no clinically important difference in remission or quality of life between the two treatment groups at 10-14 weeks (low quality evidence). For all other reported outcomes of interest, the evidence was inconclusive and of very low quality.

Specified serious adverse events

Serious adverse events of specific interest (serious infections, lymphoma and other malignancies, and mortality) were reported in one RCT and 7 observational studies comparing combination therapy and TNF alpha inhibitor monotherapy. Evidence was very low quality and inconclusive, with the exception of evidence from one observational study of infliximab with or without concomitant azathioprine, which showed higher rates of serious infections in patients taking combined therapy, and one study of pooled data from RCTs of adalimumab monotherapy that showed higher rates of non-melanoma skin cancer and other malignancies in patients who were taking an immunosuppressant (azathioprine/mercaptopurine or methotrexate) at study initiation (and hence the comparison was observational in nature). In both cases the evidence was very low quality and of uncertain clinical importance.

2.5.2 Health economic evidence statements

One partially applicable study with very serious limitations was included in the economic literature review. This cost-utility analysis investigated the cost effectiveness of infliximab + azathioprine versus infliximab alone in immunomodulator- and biologic-naïve people with

active Crohn's disease over a 1-year time horizon. It found that the combination therapy was unlikely to be cost effective with an incremental cost effectiveness ratio of £24,917 per QALY (combination therapy has 13% probability of being cost effective at the threshold of £20,000).

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The review compared medication strategies to induce remission in Crohn's disease. The types of medicine under consideration, TNF-alpha inhibitors (infliximab and adalimumab) and immunsouppressants (azathioprine / mercaptopurine and methotrexate), all have known side effects and possible long-term health risks associated with their use. The Committee therefore valued disease remission and serious adverse events as the most important outcomes for decision-making. The Committee discussed the various definitions of remission included in the review protocol and the problem of potentially overstating the evidence for this outcome due to multiple counting of the same patients. Topic experts felt it was important to consider both mucosal healing and clinical remission: • Mucosal (endoscopic) healing is increasingly used as a 'gold standard' endpoint in clinical trials because research suggests it is associated with longer-term outcomes, including lower rates of steroid use, surgery and hospitalisations. However, an appropriate duration of follow-up to establish mucosal healing is not agreed, detection requires endoscopy or a surrogate marker, and a precise definition (beyond absence of ulceration) is also currently lacking; • The Crohn's Disease Activity Index (CDAI) is frequently used in clinical practice to monitor disease activity and assess the impact of medical treatment. Clinical remission (defined as a CDAI score ≤150 points or, in children and adolescents, a score ≤10 on the Paediatric Crohn's Disease Activity Index, PCDAI) is likely to be more important to patients than mucosal healing because, when experiencing a 'flare' of Crohn's disease, patients' concern is to reduce the number and severity of daily symptoms and feel better as soon as possible after starting treatment; • Young people living with Crohn's disease may prioritise symptom control and improved functioning over longer-term outcomes. The Committee agreed it was important to also take account of quality of life as an outcome for decision-making. The Committee discussed the importance of achieving remission that can be sustained independent of the need for corticosteroids, due to potential side effects of their long-term use.
Quality of evidence	The Committee acknowledged the lack of efficacy evidence relating to adalimumab combined with any immunosuppressant medication, as no adalimumab RCTs were identified that met the review protocol criteria. They also noted the absence of any evidence directly applicable to paediatric patients (6-17 years). **Infliximab + azathioprine versus infliximab monotherapy** Combination treatment with infliximab and azathioprine was associated with higher rates of clinical remission (CDAI≤150) at 10 and 18 weeks, mucosal healing at 6 months, and corticosteroid-free remission at 6 and 12 months when compared with infliximab monotherapy. However the Committee noted that only one study was included in this comparison (the SONIC trial, Colombel 2010), and evidence of improved rates of remission was of low

	Committee discussions
	quality due to two issues: 1. Potential indirectness of the study population The SONIC study population comprised patients who were relatively newly diagnosed (mean disease duration: 2.2 years) and who were naïve to both TNF-alpha inhibitors and immunosuppressant medication at baseline. The evidence may not therefore generalise to patients being considered for treatment with infliximab or adalimumab in accordance with current recommendations in NICE CG152. This is because the NICE treatment pathway recommends infliximab or adalimumab in patients with severe, active Crohn's whose disease has not responded to prior treatment with conventional therapy (including immunosuppressants and/or corticosteroids); 2. Imprecision of effect estimates In all remission outcomes favouring combined treatment, the 95% CIs around the effect estimates were wide, crossing the agreed minimally important difference (MID) of 15% (RR 1.15), indicating serious uncertainty in the clinical importance of the reported results. There were fewer serious adverse events associated with combined treatment in the SONIC trial. However the Committee noted this evidence was very low quality and of serious clinical uncertainty. The 95% CI was wide, crossing the default GRADE MID (RR 0.63 95%CI 0.41 to 0.98), and the outcome is indirect because it is not possible to determine from the published study what specific events were included. Separate reporting of rates of colon carcinoma, sepsis, mortality (zero events in either treatment group) and rates of serious infections (discussed in more detail below) suggest that this composite outcome, labelled 'any serious adverse effects', included events other than those specified in the review protocol. A topic expert confirmed that an improvement in symptoms would generally be expected around 12 weeks after starting therapy with infliximab or adalimumab. A 10-14 week time point for assessing the impact of treatment on patients' on quality of life would therefore seem appropriate. The Committee noted there was no clinically important difference in quality of life at 10 weeks between the two treatment groups in the SONIC trial (as measured by the Inflammatory Bowel Disease Questionnaire, IBDQ), and that this evidence was of moderate quality. **Infliximab + methotrexate versus infliximab monotherapy** Evidence for this treatment comparison came from two RCTs which the Committee felt more closely matched the population of patients who would be considered for TNF-alpha inhibitor treatment within the current NICE pathway for inducing remission. Study patients had a mean disease duration of 10-12 years, and were not required to be immunosuppressant-naïve for inclusion, although none were taking immunosuppressant medicines at baseline. However, the evidence was all of low or very low quality due to imprecision of effect estimates and study design issues: one study was open-label (Schroder 2006) while almost a third of patients did not have active Crohn's disease (CDAI≥150) at baseline in the study by Feagan (2014). **Specific serious adverse events** The Committee noted that the comparative evidence for serious infections, lymphomas and other malignancies, and mortality was all of very low quality due to the following reasons:

	Committee discussions
	○ the majority of evidence was observational, and studies failed to adequately control for potential confounders in analyses; ○ indirectness of study populations; ○ very serious or serious imprecision of reported effect estimates. The Committee discussed the validity of the evidence relating to non-melanoma skin cancer and other malignancies. It was felt that detection of a significant difference between treatment groups would require a follow-up period exceeding that quoted for this analysis (median 1.61 years, range 0.04 to 5.5 years).
Trade-off between benefits and harms	Topic experts confirmed that, in the absence of current evidence-based guidance, UK clinicians often continue immunosuppressant medication in people with active symptoms whose disease has failed to respond to the treatment added on to corticosteroids, and who are subsequently escalated to treatment with infliximab or adalimumab. In patients prescribed a recommended 12-month course of TNF-alpha inhibitor who are not already taking a concomitant immunosuppressant, one would generally be added. A perception of synergy was cited as driving current clinical practice: concomitant immunosuppressants have been shown to reduce immunogenicity in patients taking TNF-alpha inhibitors (Baert et al. 2003; Vermeire et al. 2007). This reduces the risk of infusion reactions (which are often a reason for early patient withdrawal from treatment) and may help sustain response, which can become compromised over time due to build-up of antibodies to the TNF-alpha inhibitor. In terms of this perceived benefit of combination therapy, it was noted that two studies (Colombel 2010 and Feagan 2014) both reported a significant reduction in antibodies to infliximab, favouring combination treatment. However, any differential rates of infusion reaction were not reflected in early withdrawal from treatment, as attrition rates did not differ significantly between treatment groups in either study. The Committee acknowledged the importance of this issue: antibody formation to TNF-alpha inhibitor treatment during induction may adversely affect longer term outcomes and should be considered by the clinician and explained to the person considering treatment. Topic experts explained that it was not included as a patient-important outcome in the review protocol because the primary focus was on induction of remission and there were other important outcomes to consider. The topic experts noted that patients (or their carers) may, however, prefer not to take two types of medication that both suppress the immune system, or may have experienced side effects which dissuade them from continuing an immunosuppressant when starting treatment with infliximab or adalimumab. Clinicians are increasingly cautious of prescribing combination therapy in young men because of reported cases of rare and usually fatal hepatosplenic T-cell lymphoma (HSTCL) in this patient group and, in all cases, concomitant immunosuppressant therapy would only be prescribed after eliciting the preferences of patients and/or their carers. After considering the evidence the Committee felt unable to make a recommendation either in favour of or against offering combination therapy to patients prescribed infliximab or adalimumab to induce remission. This is due to insufficient, directly applicable evidence of the comparative benefits and harms of the two treatment options.

	Committee discussions
	The Committee were unconvinced by the low quality efficacy evidence favouring combined therapy reported by the SONIC trial. They did not feel this evidence could be generalised to people who may have already experienced failure of therapy using an immunosuppressant added to conventional corticosteroid treatment. Furthermore, the very low quality evidence, mainly from observational studies, of possible associations with specific serious adverse events was too uncertain to inform decision-making. The Committee felt the only course of action was to recommend that clinicians advise patients when starting infliximab or adalimumab treatment of the option for combination therapy, but explain that there is current uncertainty regarding evidence of benefits and long-term adverse effects compared with monotherapy. The Committee acknowledged that patients may have preferences for the attributes of different treatment options, such as mode of administration (oral versus injectable). These preferences should be elicited during decision-making in order to optimise patient choice, which may improve outcomes. The Committee acknowledged that people starting infliximab or adalimumab who are already taking an immunosuppressant may need to be on the immunosuppressant for maintenance therapy once the anti-TNF agent is withdrawn (which may be as soon as 12 months, in accordance with the current NICE pathway). Because immunosuppressants require 3-6 months to take full effect, it may be more practical to continue with an immunosuppressant throughout treatment with the TNF-alpha inhibitor. The Committee felt that clinical practice is not currently supported by a clear evidence base. Limitations in our current knowledge of the implications of combining two different types of immunosuppressant treatment mean that firm recommendations cannot yet be made. They agreed that it was appropriate to make a research recommendation, given the current lack of evidence of the comparative benefits and harms of these two treatment modalities in adults and children with severe, active Crohn's whose disease has not responded to conventional prior therapy and who are being considered for treatment with infliximab or adalimumab. Study follow-up would need to be of sufficient duration to capture the serious adverse effects of specific concern.
Trade-off between net health benefits and resource use	One economic evaluation was included in the systematic review. It was a cost-utility analysis of combination therapy with infliximab plus azathioprine compared with infliximab monotherapy for Crohn's disease patients refractory to conventional non-immunomodulatory and non-anti-TNF-α therapy, showing that combination therapy is unlikely to be a cost effective treatment in that patient group. The Committee noted that the available economic evidence pertained to immunosuppressive-naïve patients only and was therefore of limited applicability to the NICE pathway. Moreover, it suffered from very serious limitations, most importantly short time horizon (1-year) which was not sufficiently long to capture all important differences in costs and outcomes. Furthermore, the study did not use EQ-5D but a disease-specific measure (the Inflammatory Bowel Disease Questionnaire) to derive utility data, which is not in line with the NICE reference case. In the light of the extensive limitations of the included study, the Committee members came to a conclusion that, although it is currently the best available evidence by which to assess the cost effectiveness of combination

	Committee discussions
	therapy with infliximab plus azathioprine versus infliximab alone in patients with Crohn's Disease, it should not be considered for decision making. The Committee highlighted that, there was no economic evidence available on non immunomodulator-naïve patients. Also, there was no evidence on the cost-effectiveness of adalimumab given in combination with immunosuppressants versus adalimumab monotherapy. The only immunosuppressant considered in the published economic evaluation was azathioprine (used in combination with infliximab). The Committee discussed extensively the relevance and feasibility of *de novo* economic modelling in this case. The Committee members were of the opinion that the main advantage of economic modelling would be explicitly quantifying the trade-off between the potential for an increased chance of remission compared with the side effects of concurrent immunosuppressant treatment, in terms of both health and cost consequences. The Committee raised questions about whether mapping from disease-specific measures such as the Inflammatory Bowel Disease Questionnaire to EQ-5D utility values was an option, which was deemed practicable. The Committee acknowledged that because the additional cost of immunosuppressant treatment itself was minimal, any differences in cost-effectiveness were likely to be driven by differences in efficacy and long-term adverse effects. They therefore concluded that the usefulness of modelling was dependent on the availability and interpretation of the identified clinical evidence. Analysis of the evidence available from the immunosuppressant-naïve population showed that the benefit of combination therapy was uncertain. Also the Committee agreed that these data would not be generalised to the non immunosuppressant-naïve population. The Committee deemed it unreasonable to use the evidence indirectly, because effectiveness of combination therapy (biologic + immunosuppressant) may vary depending on patients' previous exposure and response to immunosuppressive therapy. The benefits of combination therapy may not extend to patients who are already known to be non-responders to immunosuppressants. The only available evidence from the non immunosuppressant-naïve population was of low quality and suggested no clinically important differences. Long-term safety data were of very low quality, sparse, inconclusive or uncertain. The Committee therefore concluded that, overall, economic modelling was unfeasible in this case and should not be performed as it could not resolve uncertainty over the long-term costs and consequences of the compared treatment options. Also the evidence on long term safety and adverse events from the clinical review was sparse and had very low quality and consequently could not be used to populate a model. Further research is needed that could provide the necessary data.
Other considerations	**Equalities issues** Age was identified as a potential equalities issue because the highest incidence of Crohn's disease occurs in adolescents and young adults. The Committee heard from topic experts how young people may face difficulties and discrimination in learning environments and the workplace due to impact of the disease on their daily functioning, and absence due to sickness and the need to attend frequent health appointments. Younger people may have difficulties adhering to therapies, particularly during periods of less active disease, and may prefer to take fewer types of medication. The Committee agreed that it was important to take account of patients' health-related quality of life as well as evidence of clinical benefits and potential risks during their decision-making. Gender was highlighted as a potential equalities issue. Cases of rare and

	Committee discussions
	usually fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported, associated with TNF alpha inhibitor and azathioprine/mercaptopurine treatment for Crohn's disease or ulcerative colitis. Cases have been predominantly young males (≤35 years). Comparative evidence of serious adverse events (including lymphomas) was reviewed for this update but was mostly inconclusive and all of very low quality. The review did not include non-comparative registry data or case studies. However, the Committee noted that the summary of product characteristics and information leaflets supplied with infliximab and adalimumab carry warnings advising caution when considering combination therapy in adolescent and young adult male patients. Race was identified as a potential equalities issue. A topic expert noted that there is a perception among clinicians that non-White patients, particularly those of south Asian descent, have a poorer response to TNF alpha inhibitor agents which has led to inequities in access. Only one study included in the review undertook a sub-group analysis which showed no difference in corticosteroid-free remission rates among Caucasian and non-Caucasian patients for either combined or monotherapy. The Committee noted the importance of all ethnic groups having equal access to TNF-alpha inhibitor treatment. Because methotrexate has potential teratogenic effects it should not be prescribed in pregnancy. CG152 states that "the GDG were aware of serious precautions associated with methotrexate in the BNF (for example, the need to avoid conception for three months after stopping the drug in both men and women because of its teratogenic effect)". This issue was noted by the Standing Committee for this update, but not discussed further as no evidence was found favouring combined therapy with a TNF alpha inhibitor and methotrexate. The management of Crohn's disease in pregnancy may require special consideration, and is addressed in more detail in Chapter 12 of the NICE guideline CG152.

2.7 Recommendation

1. **When a person with Crohn's disease is starting infliximab or adalimumab (in line with recommendations 1.2.12, 1.2.15, 1.2.17 and 1.2.20), discuss options of:**
    - **monotherapy with one of these drugs, or**
    - **combined therapy (either infliximab or adalimumab, combined with an immunosuppressant)**

   and tell the person there is uncertainty about the comparative effectiveness and long-term adverse effects of monotherapy and combined therapy. [new 2016]

2.8 Research recommendation

1. **Does combined therapy of a tumour necrosis factor (TNF) alpha inhibitor with an immunosuppressant improve clinical outcomes and reduce the risk of serious adverse events in adults and children (6-17 years) with severe, active Crohn's**

disease who are starting a TNF alpha inhibitor (infliximab or adalimumab) for the induction of remission, where previous conventional therapy has failed?

Why is this important?

There is a current lack of directly applicable evidence of the comparative benefits and harms of the two treatment options in the populations specified to enable recommendations to be made.

Table 5: Criteria for selecting high-priority research recommendations

PICO	**Population:** Adults (or children: 6-17 years) with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments, and primary nutrition therapy in children), or who are intolerant of or have contraindications to conventional therapy. **Intervention:** Therapy with an immunosuppressant medication (azathioprine/mercaptopurine or methotrexate) given in combination with an anti-TNF alpha agent (infliximab or adalimumab). **Comparison:** Infliximab or adalimumab monotherapy. **Outcomes:** Remission; adverse events (serious infections requiring hospitalisation, lymphoma, other malignancies, mortality); quality of life; rates of surgery; hospital admissions; growth as measured by height velocity (paediatric population only).
Current evidence base	There are currently only three comparative trials in this area (total N=483). Low quality efficacy evidence favouring combined infliximab and azathioprine over infliximab monotherapy was reported by the SONIC trial (Colombel et al. 2010), but in a population that cannot be generalised to the population in the current NICE treatment pathway. Two smaller trials of infliximab combined with methotrexate report mostly inconclusive evidence which is of low or very low quality. Duration of patient follow-up in all three trials was insufficient to capture serious adverse effects of specific concern. Current evidence comparing the two treatment modalities in relation to serious adverse events comes mostly from observational studies, is inconclusive and of very low quality.
Study design	One year RCT with extended patient follow-up (minimum 2 years)

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4 Glossary and abbreviations

Please refer to the NICE glossary.

Adjunctive therapy - one treatment associated with or assisting another treatment.

Aminosalicylates / 5-aminosalicylate - treatment including mesalazine, olsalazine and balsalazide as well as sulfasalazine.

Azathioprine (AZA) - an immunosuppressant medication, a prodrug of 6-mercaptopurine (6MP/MP).

Biologics - a class of protein-based therapeutics produced by means of biological processes involving recombinant DNA technology.

Concomitant treatment – two (or more) medicines given at or almost at the same time.

Corticosteroid (or steroid-)-dependent - patients whose Crohn's disease flares when corticosteroid therapy is reduced or stopped.

Crohn's Disease Activity Index (CDAI) – a system for scoring clinical signs and symptoms, used to monitor disease activity and the effects of treatment.

Endoscopic (mucosal) healing – the intestinal lumen appears normal with no evidence of ulceration when seen on endoscopy.

Fistulising – a complication of Crohn's disease where inflammation causes abnormal tunnels to form between the bowel and other structures, causing small leaks of faecal matter and abscesses to form.

Fulminating- when symptom onset is sudden and rapidly worsening.

Harvey Bradshaw Index (HBI) – a scoring system similar to the CDAI, used to measure activity and severity in Crohn's disease.

Histological healing - a pathological interpretation of intestinal biopsies in which samples no longer show signs of either acute or chronic inflammation.

Inflammatory Bowel Disease (IBD) - chronic, non-specific disorders of unknown aetiology. Includes Crohn's disease and ulcerative colitis.

Inflammatory Bowel Disease Questionnaire (IBDQ) - a disease-specific health-related quality of life measure.

Immunogenicity – the induction of an undesirable immune response to protein-based therapeutics.

Immunosuppressants (also referred to as immunosuppressives / immunomodulators) - drugs that weaken activity of the immune system.

Monotherapy – use of a single drug to treat a disorder or disease.

Mercaptopurine (MP) / 6-mercaptopurine (6MP) - an immunosuppressant medication.

Methotrexate (MTX) - an immunosuppressant medication.

Mucosal (endoscopic) healing - an endoscopic appearance where the mucosa shows no visual evidence of inflammation. Ideally it should be supported by evidence of histological healing.

Neutropenia - the presence of abnormally few neutrophils in the blood, leading to increased susceptibility to infection.

Paediatric Crohn's Disease Activity Index (PCDAI) – paediatric version of the CDAI

Remission (also sometimes referred to as 'quiescent disease') – when the patient is symptom free and has no endoscopic or radiological evidence of disease activity.

Steroid-sparing– reducing or eliminating the need for corticosteroid therapy

Stricturing – a complication of Crohn's disease where chronic inflammation causes narrowing of the lumen of the intestinal tract, which may then cause obstruction.

Thiopurine S-methyl- transferase (TPMT) - a genetic deficiency of this enzyme leads to increased risk of bone marrow suppression with the use of immunosuppressant medications.

Appendices

Appendix A: Standing Committee members and NICE teams

A.1 Core members

Name	Role
Susan Bewley	Chair
Gita Bhutani	Associate Director for Psychological Professions
Simon Corbett	Cardiologist
Gail Fortes Mayer	Commissioner
John Graham	Vice Chair (Oncologist)
Peter Hoskin	Oncologist
Roberta James	SIGN Programme Lead - methodologist
Jo Josh	Lay member
Asma Khalil	Obstetrician
Manoj Mistry	Lay member
Amaka Offiah	Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Paediatric Radiologist
Mark Rodgers	Research Fellow - methodologist
Nicholas Steel	PH/Academic in primary care
Sietse Wieringa	GP

A.2 Topic expert Committee members

Name	Role
Nadeem Afzal	Consultant in Paediatric Gastroenterology
Jamie Dalrymple	Principal in General Practice
Bonnie Huggett	Clinical Nurse Specialist
Jayne Kranat	Lay member
Alan Lobo	Consultant Gastroenterologist
John Mayberry	Consultant Gastroenterologist

A.3 NICE project team

Name	Role
Martin Allaby	Clinical Adviser
Jessica Fielding	Public Involvement Adviser
Rupert Franklin	Guideline Commissioning Manager
Bhash Naidoo	Technical Lead (Health Economics)
Sharon Summers-Ma	Guideline Lead
Judith Thornton	Technical Lead
Trudie Willingham	Guideline Co-ordinator

A.4 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Adviser
Emma Banks	Co-ordinator
Kathryn Hopkins	Technical Analyst Quality Assurance
Wes Hubbard	Information Specialist
Nick Lowe	Administrator
Hugh McGuire	Technical Adviser
Nicki Mead	Technical Analyst
Susannah Moon	Programme Manager
Lorraine Taylor	Associate Director
Anna Zaremba	Health Economist

Appendix B: Declarations of interest

B.1 Core Committee

Name	Interest declared	Type of interest	Action
Susan Bewley	Self-employed academic and obstetric expert.	Non-specific Personal Financial	Declare & participate
Susan Bewley	100 hour per annum teaching contract with Kings College London.	Non-specific Personal Financial	Declare & participate
Susan Bewley	Received income/fee for Teaching (BSc law and ethics tutor at KCL, occasional fees for lectures on obstetrics)	Non-specific Personal Financial	Declare & participate
Susan Bewley	Received income/fee for Medico-legal reports (approx. 2/year) and Medical Defence Union cases committee and council	Non-specific Personal Financial	Declare & participate
Susan Bewley	Received income/fee for external reviews for NHS organisations related to my obstetric expertise (serious incident and maternal mortality investigations, RCOG review)	Non-specific Personal Financial	Declare & participate
Susan Bewley	Received royalties from edited books	Non-specific Personal Financial	Declare & participate
Susan Bewley	Expressed views in publications about obstetric matters, largely based on evidence.	Non-specific Personal Non-financial	Declare & participate
Susan Bewley	A trustee and committee member of Healthwatch (a charity devoted to evidence and "for treatments that work") and a trustee of Sophia (a charity devoted to women with HIV and the UK arm of the Global Coalition for Women and AIDS).	Non-specific Personal Non-financial	Declare & participate
Susan Bewley	Member of the following editorial boards: Medical Law Review, International Journal of Childbirth, Journal Article Summary Service; Member All-Parliamentary Party Group on Maternity; Trustee of Maternity Action (a charity which aims to end inequality and improve the health and well-being of pregnant women, partners and young children), one of seven members of the Women's Health and Equality Consortium which is a Strategic Partner of the Department of Health.	Non-specific Personal Non-financial	Declare & participate
Susan Bewley	Part-time on call sexual offences examiner (forensic medical examinations) working at the Haven Camberwell Sexual Assault Referral Centre (Kings College Hospital)	Non-specific Personal Financial	Declare & participate
Susan Bewley	Received income/fee as Consultant for the World Health Organization (five days approx), for their updated guideline on Reproductive and Sexual Health and Human Rights for Women living with HIV	Non-specific Personal Financial	Declare & participate
Susan Bewley	Received fee as Chair of NICE Fertility Evidence Update	Non-specific Personal Financial	Declare & participate

Name	Interest declared	Type of interest	Action
Susan Bewley	Expert fee (one off piece of work) for medicolegal criminal case	Non-specific Personal Financial	Declare & participate
Susan Bewley	Expert fee (one off piece of work) for obstetric and managerial advice (overseas not- hospital) for-profit	Non-specific Personal Financial	Declare & participate
Susan Bewley	Expenses paid to lecture at the National RCOG trainees annual conference	Non-specific Personal Financial	Declare & participate
Susan Bewley	Expenses only lecture at the Royal Society of Medicine	Non-specific Personal Non-financial	Declare & participate
Susan Bewley	Expenses only lecture at the GLADD Annual conference	Non-specific Personal Non-financial	Declare & participate
Susan Bewley	Expenses only lecture at the FIL Annual conference	Non-specific Personal Non-financial	Declare & participate
Susan Bewley	Expenses only lecture at the RCOG Review training	Non-specific Personal Financial	Declare & participate
Susan Bewley	Expenses only lecture at the BPAS Annual Meeting Clinical Forum	Non-specific Personal Financial	Declare & participate
Susan Bewley	Expenses only lecture at the WOW Festival	Non-specific Personal Financial	Declare & participate
Susan Bewley	Expenses only lectures relating to publicising NICE intrapartum guidelines	Non-specific Personal Financial	Declare & participate
Susan Bewley	Lecture fee, at 'safe hands conference' Bolton	Non-specific Personal Financial	Declare & participate
Susan Bewley	Unpaid (but travel, hotel and subsistence) trip to two not-for-profit maternity hospitals in return for four days teaching/ expert advice, India	Non-specific Personal Financial	Declare & participate
Susan Bewley	Al Jazeera: studio fee for commenting as an obstetric expert about egg freezing	Non-specific Personal Financial	Declare & participate
Susan Bewley	PRP: fee for review of NIHR policy research programme domestic violence report	Non-specific Personal Financial	Declare & participate
Susan Bewley	Birmingham University: fee for assisting NICE training tool development	Non-specific Personal Financial	Declare & participate
Susan Bewley	Choitham Hospitals, India: fee for maternity services advice	Non-specific Personal Financial	Declare & participate

Name	Interest declared	Type of interest	Action
Susan Bewley	Fee for lecture on egg freezing (debate at British Fertility Society, January 2016)	Non-specific Personal Financial	Declare & participate
Susan Bewley	Fee for lecture on domestic violence (Faculty of Sexual and Reproductive Healthcare, RCOG)	Non-specific Personal Financial	Declare & participate
Susan Bewley	Fee for lecture on reproductive health as public health issue (European society for human reproduction and embryology)	Non-specific Personal Financial	Declare & participate
Susan Bewley	Fee for lecture on female genital mutilation (Liverpool medical society)	Non-specific Personal Financial	Declare & participate
Gita Bhutani	Chair of Psychological Professions Network North West	Non-specific Personal Non-financial	Declare & participate
Gita Bhutani	Member of British Psychological Society; Division of Clinical Psychology; Faculty of Leadership and Management Committee Member	Non-specific Personal Non-financial	Declare & participate
Gita Bhutani	Project lead on BPS Division of Clinical Psychology project on 'Comprehensively representing the complexity of psychological services'	Non-specific Personal Non-financial	Declare & participate
Gita Bhutani	Analytical support in partnership with Liverpool University on Liverpool Health Partners project on Patient Quality and Safety	Non-specific Personal Non-financial	Declare & participate
Gita Bhutani	Joint project lead on Health Education North West funded project on Schwartz Rounds	Non-specific Personal Non-financial	Declare & participate
Simon Corbett	Network Service Adviser for the British Cardiovascular Society. This role incorporates the regional specialty adviser role for the Royal College of Physicians.	Non-specific Personal Non-financial	Declare & participate
Simon Corbett	Director for Clinical Effectiveness for employer (University Hospital Southampton NHS Foundation Trust). Part of this role involves the dissemination and implementation of NICE guidance in the Trust.	Non-specific Personal Non-financial	Declare & participate
Simon Corbett	Independent cardiologist on the Trial Steering Committee of the randomised controlled AVATAR trial, a randomised trial of medical therapy vs ablation in patients with atrial fibrillation. The study is sponsored by Imperial College London and is part funded by Medtronic. Travel expenses are paid by Imperial.	Personal Non-financial	Declare & participate
Gail Fortes Mayer	None	Not applicable	Declare & participate
John Graham	Director of National Collaborating Centre for Cancer – this post is funded through a contract with NICE to produce NICE's clinical guidelines.	Non-specific Non-personal Financial	Declare & participate
John Graham	Principal investigator for Ongoing clinical trials in prostate cancer: 1) With Custirsen funded by OncoGenex Technologies Inc and Teva Pharmaceutical Industries Ltd. 2) Orteronel Affinity Trial funded by Millenium	Non-specific Non-personal Financial	Declare & participate

Name	Interest declared	Type of interest	Action
	Pharmaceuticals Inc 3) Principal investigator for a study of radium-223 in prostate cancer that is funded by Bayer Pharmaceuticals 4) Principal investigator in 2 trials of radium-223 in breast cancer funded by Bayer Pharmaceuticals.		
John Graham	Principal investigator for 8 Ongoing clinical trials in breast and prostate cancer run via the National Cancer Research Network (not pharmaceutical industry funded)	Non-specific Non-personal Financial	Declare & participate
John Graham	Member of the trial management groups for 2 prostate cancer trials: RT01 and CHHIP. Both are closed to recruitment but continuing to report trial results.	Non-specific Personal Non-financial	Declare & participate
John Graham	Council member of the South-West England Clinical Senate	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Investigator in research studies sponsored by various companies with payment for expenses to NHS Trust and department which fund research staff. Recent studies have been on behalf of Millenium, Astellas, Ipsen and Amgen.	Non-specific Non-personal Financial	Declare & participate
Peter Hoskin	Fellow of the Royal College of Radiologists and member of Faculty Board, Specialist Training Board and Chair of Exam Board.	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Consultant to the IAEA; Undertake by invitation lectures and working group meetings for which expenses may be paid.	Non-specific Personal Financial	Declare & participate
Peter Hoskin	Department reimbursed for studies on alpharadin by Astellas.	Non-specific Non-personal Financial	Declare & participate
Peter Hoskin	Department reimbursed for studies on MDV 3100 by Medivation. and Astellas	Non-specific Non-personal Financial	Declare & participate
Peter Hoskin	Department receives grants from Astellas for trials in prostate cancer.	Non-specific Non-personal Financial	Declare & participate
Peter Hoskin	Department receives grants from Bayer for trials in prostate cancer.	Non-specific Non-personal Financial	Declare & participate
Peter Hoskin	Department received grants from Millennium for trials in prostate cancer.	Non-specific Non-personal Financial	Declare & participate
Peter Hoskin	Trustee for funding research within the unit/department. Funded by Donations/Legacies.	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Member of the Steering Group for National Cancer Intelligence Network (NCIN)	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Member of the faculty board of the Royal College of Radiologists.	Non-specific Personal Non-financial	Declare & participate

Name	Interest declared	Type of interest	Action
Peter Hoskin	Member of the specialist training committee for the Royal College of Radiologists.	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Editorial board member for the Journal of Contemporary Brachytherapy.	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Member of the East of England senate.	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Member of the NICE standing committee for rapid updates / and non-Hodgkin's lymphoma GDG.	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Member European Society for Radiotherapy and Oncology (ESTRO) Board	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Member HTA Clinical Evaluation and Trials Board	Non-specific Personal Non-financial	Declare & participate
Peter Hoskin	Clinical Editor, radiotherapy and Oncology	Non-specific Personal Non-financial	Declare & participate
Roberta James	Programme Lead at Scottish Intercollegiate Guidelines Network	Non-specific Personal Financial	Declare & participate
Roberta James	Member of Guideline Implementability Research and Application Network	Non-specific Personal Non-financial	Declare & participate
Roberta James	Expert group member of Project on a Framework for Rating Evidence in Public Health	Non-specific Personal Non-financial	Declare & participate
Jo Josh	Governor at SASH NHS Foundation Trust: governor representing the voluntary sector.	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Steering Group Member at UK Community Advisory Board (UK-CAB)	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Trustee at Surrey Community Action	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Member of HIV ad hoc communications support	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Mental health ad hoc communications support: member of ENRICH panel,	Non-specific Personal Non-financial	Declare and participate
Jo Josh	NHS East Surrey Clinical Commissioning Group: patient representative	Non-specific Personal Non-financial	Declare and participate

Name	Interest declared	Type of interest	Action
Asma Khalil	Member of the National Clinical Reference Group for Fetal Medicine	Non-specific Personal Non-financial	Declare & participate
Asma Khalil	Co-chair of the "Improving Outcomes" working group, South West London Maternity Network	Non-specific Personal Non-financial	Declare & participate
Asma Khalil	Associate Editor for the journal Biomedical Central Pregnancy and Childbirth	Non-specific Personal Non-financial	Declare & participate
Asma Khalil	Member of the Maternal and Fetal Medicine National Clinical Study Group	Non-specific Personal Non-financial	Declare & participate
Asma Khalil	Assistant Convenor for the MRCOG Part1 course, RCOG	Non-specific Personal Non-financial	Declare & participate
Asma Khalil	Principal Investigator at St George's Hospital for several NIHR funded studies, e.g. Non-invasive Prenatal Testing	Non-specific Non-personal Financial	Declare & participate
Asma Khalil	Chief Investigator for Cardiovascular changes in Pregnancy study and Quantitative fetal fibronectin, Cervical length and ActimPartus® for the prediction of Preterm birth in Symptomatic women (QFCAPS)	Non-specific Non-personal Financial	Declare & participate
Asma Khalil	Collaboration with commercial companies, such as USCOM®, Roche Diagnostics®, Alere Diagnostics® and proact medical Ltd® (research equipment and/or consumables)	Non-specific Non-personal Financial	Declare & participate
Manoj Mistry	Public member of Pennine Care NHS FT in the capacity as a carer	Non-specific Personal Non-financial	Declare & participate
Manoj Mistry	PPI representative for the Primary Care Research in Manchester Engagement Resource group at the University of Manchester.	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Carer representative on NICE Guideline Development Group: 'Transition between inpatient hospital settings and community or care home settings for adults with social care needs.'	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Lay representative for the MSc Clinical Bioinformatics at the University of Manchester	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Lay Educational Visitor with the Health and Care Professions Council, London	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Lay representative at the Clinical Research Facility (collaboration between Central Manchester University Hospital NHS FT/University of Manchester)	Non-specific Personal Financial	Declare & participate

Name	Interest declared	Type of interest	Action
Manoj Mistry	Public Representative Interviewer at the Medical School, Lancaster University	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Public Member of NIHRs 'Research for Patient Benefit Programme Committee' (North West region)	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Member of the Patient Panel at NIHRs 'The Collaboration for Leadership in Applied Health Research and Care' Greater Manchester	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Member of the Patient and Public Involvement Group, Liverpool Clinical Trials Unit, University of Liverpool	Non-specific Personal Financial	Declare & participate
Manoj Mistry	PPI panel assisting research into Information Systems: Dashboard: Monitoring and Managing from Ward to Board at the University of Leeds	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Member of the Study Steering Committee for the research project: ''Comprehensive Longitudinal Assessment of Salford Integrated Care (CLASSIC): a study of the implementation and effectiveness of a new model of care for long term conditions ''(University of Manchester/ Salford Royal).	Non-specific Personal Financial	Declare & participate
Manoj Mistry	Patient-Public Representative for the new postgraduate 'Advanced Clinical Skills' course at Manchester Pharmacy School, The University of Manchester, England, UK	Non-specific Personal Financial	Declare & participate
Manoj Mistry	PPI representative at the Centre for Engagement and Involvement, Faculty of Medicine and Human Sciences, University of Manchester	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Lay Member of the Prescribed Specialised Services Advisory Group, Department of Health	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Lay Representative for the research project: "Understanding how frontline staff use patient experience data for service improvement- an exploratory case study evaluation and national survey " at the Department of Primary Care Health Sciences, University of Oxford, England.	Non-specific Personal Financial	Declare and participate
Amaka Offiah	Provision of expert advice to Her Majesty's Courts in cases of suspected child abuse.	Non-specific Personal Financial	Declare & participate
Amaka Offiah	Recipient of honoraria and/or expenses for lectures and/or guidelines development from BioMarin, InfoMed and Alexion.	Non-specific Personal Financial	Declare & participate
Amaka Offiah	Chairperson Skeletal Dysplasia Group for Teaching and Research	Non-specific Personal	Declare & participate

Name	Interest declared	Type of interest	Action
		Non-financial	
Amaka Offiah	Chairperson Child Abuse Taskforce of the European Society of Paediatric Radiology.	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Member Joint RCR/RCPCH NAI Working Party for Guideline Update - Imaging in Suspected Non-Accidental Injury.	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Member of the Royal College of Radiology Academic Committee.	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Committee member of the International Consortium for Vertebral Anomalies and Scoliosis.	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Vice Chair of South Yorkshire (Sheffield) Research Ethics Committee.	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Medical Academic Staff Committee Representative of the Yorkshire Regional Council of the BMA	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Partner Governor of the Sheffield Children's NHS Foundation Trust (representing the University of Sheffield)	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Editorial Committee Member of the journal Paediatric Radiology	Non-specific Personal Non-financial	Declare & participate
Amaka Offiah	Recipient of research funding from NIHR, ARUK, The Sheffield Children's Charity, Skeletal Dysplasia Group for Teaching and Research	Non-specific Non-personal Financial	Declare & participate
Amaka Offiah	Member of the Sheffield Children's Hospital Research and Innovations Committee	Non-specific Personal Non-financial	Declare & participate
Mark Rodgers	Associate editor of the journal Systematic Reviews that publishes research on health and social care.	Non-specific Personal Non-financial	Declare & participate
Mark Rodgers	Research fellow in health services research; has provided independent academic reviews of clinical effectiveness and diagnostic accuracy evidence for funders including NIHR and NICE.	Non-specific Non-personal Financial	Declare & participate
Mark Rodgers	Employee of the Centre for Reviews and Dissemination (University of York) which provides Evidence Review Group reports and Technology Assessment Reports as part of the NICE technology appraisals process.	Non-specific Non-personal Financial	Declare & participate
Nicholas Steel	Work as the principal investigator on a National Institute of Health Research funded project on: 'Are NICE clinical guidelines for primary care based on evidence from primary care?'	Non-specific Non-personal Financial	Declare & participate
Nicholas Steel	National Institute for Health Research Health Services & Delivery Research Programme Healthcare Delivery Research Panel member	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	NIHR Regional Advisory Committee for the Research for	Non-specific	Declare &

Name	Interest declared	Type of interest	Action
	Patient Benefit Programme East of England region	Personal Non-financial	participate
Nicholas Steel	Norfolk & Suffolk Primary & Community Care Research Steering Group	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	Advisory Committee on Clinical Excellence Awards East of England	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	'Implementation Science' Editorial Board member	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	'Quality in Primary Care' Editorial Board member	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	Faculty of Public Health Part A MFPH Examiner	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	Faculty of Public Health Part A MFPH Development Committee	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	Honorary Public Health Academic Consultant, Public Health England	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	Various publications on clinical practice guidelines and primary care	Non-specific Personal Non-financial	Declare & participate
Nicholas Steel	Research grant: 'Primary Care capacity building for GPs' (Principal investigator 5%); CLAHRC East of England Research Capability Funding	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	Research grant: 'Anticholinergics, Benzodiazepines, Cognition and Dementia' (co-applicant 1%); Alzheimer's Disease Society	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	Research grant: 'English Longitudinal Study of Ageing UK Funders application' (co-applicant 10%); Consortium of UK Government departments	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	Research grant: 'Can a practice based approach using Significant Event Audit identify key factors that might reduce avoidable non-elective hospital admissions? A feasibility study' (co-applicant 5%); National Institute for Health Research – Research for Patient Benefit	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	PhD supervision: 'Improving access to high quality primary care for socio-economically disadvantaged older people in rural areas'; National Institute for Health Research Doctoral Research Fellowship	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	PhD supervision: 'Life expectancy with chronic conditions'	Non-specific Non-personal Financial	Declare and participate
Sietse Wieringa	At the Centre for Primary care & Public Health at Barts & The London School of Medicine & Dentistry/Queen Mary	Non-specific Personal	Declare & participate

Name	Interest declared	Type of interest	Action
	University I am working on a literature review of 'mindlines' (related to communities of practice) and a qualitative study of a large group of GPs on a virtual social network sharing medical knowledge. I was funded for this via an NIHR In practice fellowship.	Financial	
Sietse Wieringa	Board member of the Platform of Medical Leadership in the Netherlands, via which I am involved in a mixed methods study for the development of a medical leadership competency framework. The study group receives funds from KNMG (Royal Dutch College of Medicine) and SBOH which receives its funds from the Dutch Ministry of Health.	Non-specific Non-personal Financial	Declare & participate
Sietse Wieringa	Member of Generation Next, a think tank and network of young GPs. It's indirectly funded by the Ministry of Health.	Non-specific Personal Non-financial	Declare & participate
Sietse Wieringa	Member of NHG (Dutch GP Society), which produces guidelines and I worked for this organisation in the past.	Non-specific Personal Non-financial	Declare & participate

Topic Experts

Name	Interest declared	Type of interest	Action
Jayne Kranat	None	Not applicable	Declare and participate
John Mayberry	None	Not applicable	Declare and participate
Alan Lobo	Member, Advisory Board, Takeda UK (Manufacturers of vedolizumab)	Non-specific Personal Financial	Declare and participate
Alan Lobo	Member, Advisory Board, Vifor Pharma (Ferinject parenteral iron preparation)	Non-specific Personal Financial	Declare and participate
Alan Lobo	Accommodation and travel to attend European Crohn's and Colitis Organisation (ECCO 2015) meeting, funding from Vifor Pharma.	Specific Personal Non-financial	Declare and participate
Alan Lobo	Participant in sponsored post-marketing study of vedolizumab, Takeda. All funding through Trust R and D mechanisms	Non-specific Non-personal Financial	Declare and participate
Alan Lobo	Conference attendance travel and accommodation VEGW 2015 Tillotts Pharma (manufacturers of Octasa)	Non-specific Personal Non-financial	Declare and participate
Bonnie Huggett	Received support from Remsima and Falk for registration and accommodation to attend European Crohn's and Colitis Organisation (ECCO)	Specific Personal Financial	Declare & attend to answer specific questions during discussion of evidence agenda items. Leave the meeting for formulation of

Name	Interest declared	Type of interest	Action
			recommendations agenda item.
Bonnie Huggett	Sponsorship from NAPP for registration for ECCO 2016 Amsterdam	Specific Personal Financial	
Bonnie Huggett	Sponsorship from Dr Falk Pharma for ECCO 2016 accommodation	Specific Personal Financial	

Appendix C: Review protocol

	Details
Review Question	What is the clinical and cost-effectiveness of TNF alpha inhibitor monoclonal antibodies (infliximab and adalimumab) given in combination with immunosuppressants compared with infliximab or adalimumab alone for inducing remission in adults and children (6-17 years) with active Crohn's disease?
Objectives	A recent review of the NICE guideline on Crohn's disease (CG152) identified evidence on the effectiveness of TNF alpha inhibitor biologics (infliximab or adalimumab) given in combination with an immunosuppressant for inducing remission in people with severe active Crohn's disease. This drug combination is not currently explicitly considered in the NICE pathway as it was outside the remit of the relevant technology appraisal for infliximab/adalimumab (TA187). The update aims to provide guidance on the efficacy, safety and cost-effectiveness of this combination therapy compared with treatment with infliximab/adalimumab alone in cases where conventional prior therapy has failed to induce remission in people with active Crohn's disease.
Types of study to be included	- Randomised controlled trials - Systematic reviews of RCTs If no RCTs are found reporting adverse events of importance, the following may be considered: - Comparative observational studies with a minimum timeframe of 12 months
Language	English language only
Status	Published papers (full text only)
Population	Adults (aged 18yrs+) and children (6-17yrs) with active Crohn's disease
Intervention	An immunosuppressant used in the treatment of Crohn's disease (azathioprine/mercaptopurine or methotrexate) given in addition to a TNF alpha inhibitor (infliximab or adalimumab)
Comparator	- Infliximab or adalimumab only - Placebo given in addition to infliximab or adalimumab
Outcomes	○ Remission - as defined by any of: absence of clinical symptoms (determined by investigator); Crohn's Disease Activity Index (CDAI) score ≤150 or Paediatric Crohn's Disease Activity Index (PCDAI) score ≤10 points at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15+ (late) following initiation of therapy +/- fall of > 70 points in CDAI; Harvey Bradshaw Index (HBI) < 3; Endoscopic healing; Fistula healing ○ Adverse events (restricted to: serious infections (requiring hospitalisation), lymphoma, other malignancies, mortality) ○ Quality of life (any generic or disease-specific scale) ○ Corticosteroid-free (at 6 months; at 12 months) ○ Rates of surgery (at 6 months; at 12 months) ○ Hospital admissions

	Details
	○ growth (as measured by height velocity standard deviation score, HVSDS) - paediatric studies only
Any other criteria for inclusion / exclusion of studies	Exclusion - ulcerative colitis - significant abscess - mixed IBD population, unless treatment and outcome data are separately available for people with Crohn's disease Selection of papers: i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will not be conducted due to the nature of the review question (narrow question with clearly defined straightforward inclusion and exclusion criteria). ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). Other mechanisms will be in place for QA: - The Committee will be sent the list of included and excluded studies prior to the Committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they have known of which haven't been picked up by the searches.
Analysis of subgroups or subsets	Age: - Younger vs. older age children (suggested age ranges: 6-10yrs; 11-17yrs) - Young / middle / older age adults (suggested age ranges: 18-30yrs; 31-65;yrs 65+yrs) Gender Ethnicity Medication prior to trial Disease location: - Small bowel - Colon - Small bowel and colon - Perianal Disease severity: - Moderate vs. severe disease* * Severe as defined in CG152: very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (2-4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. The clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score ≥ 300 / Harvey-Bradshaw Index (HBI) score ≥ 9 (adults) or a Paediatric Crohn's Disease Activity Index (PCDAI) score ≥40 (children)
Data extraction and quality assessment	Key features of included studies and reported outcomes will be extracted into evidence tables. The quality of evidence for each outcome will be assessed using the approach for intervention questions outlined by the GRADE working group.

	Details
	Double quality appraisal will not be undertaken. For QA, the Committee will be asked to cross-check GRADE tables to ensure agreement with all assigned ratings.
Strategy for data synthesis	Data for each outcome from different studies will be synthesised using pairwise meta-analysis where possible. Where synthesis by meta-analysis is not possible, data will be presented for individual studies.
Searches	Sources to be searched: - Clinical searches - Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records), HTA, and PubMed - Economic searches - Medline, Medline in Process, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied Supplementary search techniques: - None identified Limits: - No date limit will be set - Studies reported in English - Animal studies will be excluded from the search results - Conference abstracts will be excluded from the search results where insufficient data are reported and no related published study can be identified.

Appendix D: Search strategy

Two literature searches were undertaken: one to identify systematic reviews and randomised controlled trials relevant to the review question, the second to identify additional evidence on adverse events from comparative observational and cohort studies, as per the review protocol (Appendix C: The databases that were searched, together with the number of articles retrieved from each database are shown in Table 6 and Table 8 respectively. The search strategies used for each search are shown in Table 7 and Table 9 respectively.

Table 6: Clinical search summary: efficacy

Database	Date searched	Version/files	Number retrieved
MEDLINE (Ovid)	06/10/2015	Ovid MEDLINE(R) 1946 to September Week 4 2015	691
MEDLINE In-Process (Ovid)	06/10/2015	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 05, 2015	47
Embase (Ovid)	06/10/2015	Embase 1974 to 2015 Week 40	2,803
Cochrane Database of Systematic Reviews (CDSR)	06/10/2015	Cochrane Database of Systematic Reviews : Issue 10 of 12, October 2015	13
Cochrane Central Register of Controlled Trials (CENTRAL)	06/10/2015	Cochrane Central Register of Controlled Trials : Issue 9 of 12, September 2015	118
Database of Abstracts of Reviews of Effect (DARE)	06/10/2015	Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015	6
Health Technology Assessment (HTA Database)	06/10/2015	Health Technology Assessment Database : Issue 3 of 4, July 2015	1
PubMed	06/10/2015	-	35

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The Pubmed translation consisted of an abbreviated strategy run at the end of the process designed to capture references that had not yet appeared in the Medline in Process database. Randomised Controlled Trial and Systematic Review filters were used to identify the study designs specified in the Review Protocol.

Table 7: Clinical search terms – efficacy (Medline and Medline in process)

Line number/Search term/Number retrieved
1 Crohn Disease/ (32787)
2 ((crohn* or cleron) adj4 (disease* or syndrome* or colitis or enteritis)).tw. (32667)
3 ((regional* or terminal or granuloma*) adj4 (enteritis or enterocolitis or colitis or ileiti* or

Line number/Search term/Number retrieved
epithelioid)).tw. (3909)
4 ileocoli*.tw. (1642)
5 ((ileum or cecum*) adj4 (inflam* or irritat* or sore* or tender* or swell*)).tw. (393)
6 Inflammatory Bowel Diseases/ (15321)
7 (inflamm* adj1 bowel).tw. (28796)
8 or/1-7 (62884)
9 Immunosuppressive Agents/ (81340)
10 (immunosuppress* or immunodepress* or immunomodulator*).tw. (133214)
11 (immun* adj4 (suppressant* or suppressive*)).tw. (2451)
12 ((antirejection or anti-rejection) adj4 medic*).tw. (46)
13 Azathioprine/ (13771)
14 (azathioprine or azasan or imurel or imuran or Immuran).tw. (12632)
15 (arathioprin* or aza-q or azafalk or azahexal or azamedac or azamun* or azanin or azapin or azapress or azaprine).tw. (4)
16 (azarek or azarex or azathiodura or azathiopine or azathioprim or azathioprin or azathiopurine or azathropsin or azatioprina).tw. (222)
17 (azatox or azatrilem or azopi or azoran or azothioprin* or aseroprin or azafor or azafrine or azaimun or azadus).tw. (35)
18 (colinsan or berkaprine).tw. (0)
19 (immuthera or imunen or imuprin or imurane or imurek or imurel or imuren or imazan or imussuprex or immunoprin).tw. (57)
20 (oprisine or thioazeprine or thioprine or transimune or zinothin or zytrim).tw. (4)
21 6-Mercaptopurine/ (5733)
22 (mercaptopurin* or purimethol or purinethol or puri nethol or leupurin*).tw. (3763)
23 (allmercap or capmerin or classen or empurine or flocofil or ismipur or leukerin or loulla).tw. (13)
24 (mercaleukin or mercap or mercaptina or mercapto or mercapurene or mern or merpurin or mycaptine).tw. (2256)
25 (puri-nethol or purinethiol or purinetone or purixan).tw. (12)
26 (thiohypoxanthine or thiopurine or varimer or xaluprine).tw. (1455)
27 Methotrexate/ (33369)
28 (methotrexat* or amethopterin* or mexate).tw. (31685)
29 (abitrexate or ametopterine or antifolan or biotrexate or canceren).tw. (2)
30 (ebetrex or emtexate or emthexat* or emtrexate or enthexate).tw. (2)
31 (farmitrexat* or farmotrex or folex).tw. (3)
32 (matrex or maxtrex or metex or methoblastin or methohexate or methotrate or methrotrexate or meticil or metoject or metothrexate or methylaminopterin* or meticil or metoject or metotrex* or metrex).tw. (262)
33 (ifamet or imeth or intradose MTX or lantarel or ledertrexate).tw. (1)
34 (neotrexate or novatrex or otrexup or rasuvo or reumatrex or rheumatrex).tw. (4)
35 (texate or texorate or trexall or xaken or zexate).tw. (2)
36 or/9-35 (234119)
37 Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors] (12232)
38 ((tumo?r necrosis factor alpha or TNF-alpha) adj4 (inhibitor* or antagonist*)).tw. (4514)
39 ((anti-TNF alpha or anti tumo?r necrosis factor alpha) adj4 agent*).tw. (537)
40 (infliximab or avakine or inflectra or remicade or remsima or revellex).tw. (7491)
41 (adalimumab or humira or exemptia or trudexa).tw. (3086)
42 or/37-41 (20770)
43 8 and 36 and 42 (1508)
44 Animals/ not Humans/ (4021057)
45 43 not 44 (1498)
46 limit 45 to english language (1338)

Line number/Search term/Number retrieved	
47	Randomized Controlled Trial.pt. (411120)
48	Controlled Clinical Trial.pt. (91645)
49	Clinical Trial.pt. (504928)
50	exp Clinical Trials as Topic/ (300823)
51	Placebos/ (33988)
52	Random Allocation/ (86176)
53	Double-Blind Method/ (134903)
54	Single-Blind Method/ (21328)
55	Cross-Over Studies/ (37182)
56	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (800434)
57	(random$ adj3 allocat$).tw. (22537)
58	placebo$.tw. (162559)
59	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (131927)
60	(crossover$ or (cross adj over$)).tw. (59921)
61	or/47-60 (1481974)
62	animals/ not humans/ (4021057)
63	61 not 62 (1381596)
64	Meta-Analysis.pt. (59963)
65	Meta-Analysis as Topic/ (14897)
66	Review.pt. (2008719)
67	exp Review Literature as Topic/ (8394)
68	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (71181)
69	(review$ or overview$).ti. (290861)
70	(systematic$ adj5 (review$ or overview$)).tw. (66031)
71	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4901)
72	((studies or trial$) adj2 (review$ or overview$)).tw. (27118)
73	(integrat$ adj3 (research or review$ or literature)).tw. (6082)
74	(pool$ adj2 (analy$ or data)).tw. (15925)
75	(handsearch$ or (hand adj3 search$)).tw. (5754)
76	(manual$ adj3 search$).tw. (3448)
77	or/64-76 (2181046)
78	animals/ not humans/ (4021057)
79	77 not 78 (2041776)
80	63 or 79 (3166210)
81	46 and 80 (691)

Table 8: Clinical search summary: serious adverse events

Database	Date searched	Version/files	Number retrieved
MEDLINE (Ovid)	09/10/2015 [23/10/2015]	Ovid MEDLINE(R) <1946 to October Week 1 2015>	565 (160[1]) [1[2]]
MEDLINE In-Process (Ovid)	09/10/2015	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 08, 2015>	25 (11)
Embase (Ovid)	09/10/2015	Embase 1974 to 2015 Week 40	2,655 (438)

[1]*Numbers in circular brackets represent unique results for this strategy when compared with the general update strategy.*

[2]Number in square bracket represents missing record due to issue with Medline English language search limit between 23rd September and 12th October 2015.

The MEDLINE search strategy is presented below. This was translated for use in the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

Table 9: Clinical search terms – serious adverse events (Medline and Medline in process)

Line number/Search term/Number retrieved
1 exp Crohn Disease/ (32912)
2 ((crohn* or cleron) adj4 (disease* or syndrome* or colitis or enteritis)).tw. (32841)
3 ((regional* or terminal or granuloma*) adj4 (enteritis or enterocolitis or colitis or ileiti* or epithelioid)).tw. (3918)
4 ileocoli*.tw. (1653)
5 ((ileum or cecum*) adj4 (inflam* or irritat* or sore* or tender* or swell*)).tw. (398)
6 Inflammatory Bowel Diseases/ (15432)
7 (inflamm* adj1 bowel).tw. (29008)
8 or/1-7 (63237)
9 Immunosuppressive Agents/ (81649)
10 (immunosuppress* or immunodepress* or immunomodulator*).tw. (133888)
11 (immun* adj4 (suppressant* or suppressive*)).tw. (2467)
12 ((antirejection or anti-rejection) adj4 medic*).tw. (47)
13 Azathioprine/ (13797)
14 (azathioprine or azasan or imurel or imuran or Immuran).tw. (12680)
15 (arathioprin* or aza-q or azafalk or azahexal or azamedac or azamun* or azanin or azapin or azapress or azaprine).tw. (4)
16 (azarek or azarex or azathiodura or azathiopine or azathioprim or azathioprin or azathiopurine or azathropsin or azatioprina).tw. (222)
17 (azatox or azatrilem or azopi or azoran or azothioprin* or aseroprin or azafor or azafrine or azaimun or azadus).tw. (35)
18 (colinsan or berkaprine).tw. (0)
19 (immuthera or imunen or imuprin or imurane or imurek or imurel or imuren or imazan or imussuprex or immunoprin).tw. (57)
20 (oprisine or thioazeprine or thioprine or transimune or zinothin or zytrim).tw. (4)
21 6-Mercaptopurine/ (5756)
22 (mercaptopurin* or purimethol or purinethol or puri nethol or leupurin*).tw. (3781)
23 (allmercap or capmerin or classen or empurine or flocofil or ismipur or leukerin or loulla).tw. (13)
24 (mercaleukin or mercap or mercaptina or mercapto or mercapurene or mern or merpurin or mycaptine).tw. (2263)
25 (puri-nethol or purinethiol or purinetone or purixan).tw. (12)
26 (thiohypoxanthine or thiopurine or varimer or xaluprine).tw. (1465)
27 Methotrexate/ (33574)
28 (methotrexat* or amethopterin* or mexate).tw. (31830)
29 (abitrexate or ametopterine or antifolan or biotrexate or canceren).tw. (2)
30 (ebetrex or emtexate or emthexat* or emtrexate or enthexate).tw. (2)
31 (farmitrexat* or farmotrex or folex).tw. (3)
32 (matrex or maxtrex or metex or methoblastin or methohexate or methotrate or methrotrexate or meticil or metoject or metothrexate or methylaminopterin* or meticil or metoject or metotrex* or metrex).tw. (264)
33 (ifamet or imeth or intradose MTX or lantarel or ledertrexate).tw. (1)
34 (neotrexate or novatrex or otrexup or rasuvo or reumatrex or rheumatrex).tw. (4)
35 (texate or texorate or trexall or xaken or zexate).tw. (2)

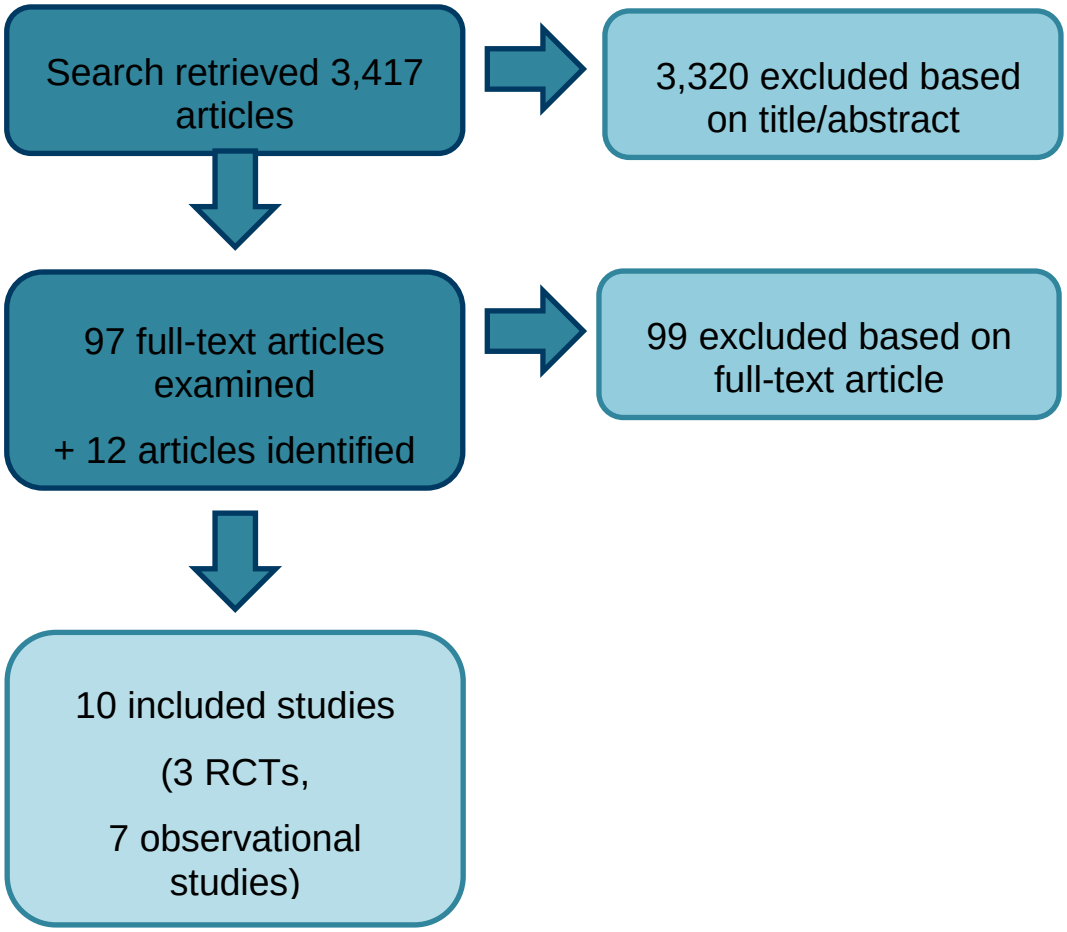
Line number/Search term/Number retrieved
36 or/9-35 (235242)
37 Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors] (12299)
38 ((tumo?r necrosis factor alpha or TNF-alpha) adj4 (inhibitor* or antagonist*)).tw. (4536)
39 ((anti-TNF alpha or anti tumo?r necrosis factor alpha) adj4 agent*).tw. (539)
40 (infliximab or avakine or inflectra or remicade or remsima or revellex).tw. (7524)
41 (adalimumab or humira or exemptia or trudexa).tw. (3116)
42 or/37-41 (20882)
43 exp "Drug-Related Side Effects and Adverse Reactions"/ (94447)
44 ADRs.tw. (1983)
45 ((adverse or side or undesirable or toxic) adj4 (event* or effect* or react* or outcome*)).tw. (463910)
46 exp Safety/ (59221)
47 (drug adj4 (toxic* or safe* or tolerabl*)).tw. (21984)
48 Azathioprine/ae (2556)
49 6-Mercaptopurine/ae (746)
50 Methotrexate/ae (6468)
51 exp Immunologic Deficiency Syndromes/ (289270)
52 immunodeficienc*.tw. (105190)
53 (immun* adj4 (deficienc* or depress* or supress* or incompetenc*)).tw. (18283)
54 exp infection/ (667570)
55 exp Bacterial Infections/ (770554)
56 infect*.tw. (1248864)
57 exp Virus Diseases/ (793042)
58 ((virus or viral) adj4 disease*).tw. (35108)
59 exp Mycoses/ (108755)
60 mycos?s.tw. (11515)
61 (fung* adj4 disease*).tw. (4173)
62 (sepsis or py?emia* or septic?emia* or pyohemia*).tw. (80320)
63 (blood adj4 poison*).tw. (476)
64 ((Epstein Barr or EBV or herpesvirus 4 or herpes virus 4) adj4 infect*).tw. (9386)
65 Cytomegalovirus/ (18378)
66 (cytomegalovirus or HHV 5 or herpesvirus 5).tw. (34596)
67 ((salivary gland or cytomegol*) adj4 virus*).tw. (212)
68 (zona or zoster or shingles).tw. (24920)
69 exp hypersensitivity/ (295466)
70 (allerg* or hypersensitiv* or erethism).tw. (193033)
71 exp anemia/ (142925)
72 an?emia*.tw. (108848)
73 Neutropenia/ (15908)
74 neutrop?enia*.tw. (26865)
75 exp Thrombocytopenia/ (41534)
76 (thrombocytop?enia* or thrombopenia*).tw. (38278)
77 ((thrombocyte* or platelet*) adj4 deficienc*).tw. (745)
78 exp lymphoma/ (153686)
79 (lymphoma* or reticulolymphosarcoma* or germinoblastoma*).tw. (133251)
80 (germinoblastic adj4 sarcoma*).tw. (1)
81 ((lymph node or lymphocytic or lymphoid) adj4 (tumo?r* or neoplasm* or malignanc*)).tw. (17345)
82 Leukopenia/ (7679)
83 (leukopenia* or leucopenia* or leukocytopenia* or leucocytop?enia*).tw. (13284)
84 exp Carcinoma, Squamous Cell/ (111440)
85 ((squamous cell or epidermoid or planocellular or prickle cell) adj4 (carcinoma* or cancer* or

Line number/Search term/Number retrieved
neoplasm* or epitheli*)).tw. (72616)
86 exp Skin Neoplasms/ (103549)
87 (skin adj4 (carcinoma* or cancer* or neoplasm* or tumo?r*)).tw. (29798)
88 Cholangiocarcinoma/ (6064)
89 cholangiocarcinoma*.tw. (7215)
90 ((cholangiocellular or bile tract or biliary or gall duct) adj4 (carcinoma* or cancer* or neoplasm*)).tw. (3613)
91 (myelosuppression* or myelotoxic*).tw. (9236)
92 (bone marrow adj4 (toxic* or depress* or supress*)).tw. (2477)
93 exp Cholestasis/ (30136)
94 cholestas*.tw. (11600)
95 ((biliary or bile duct) adj4 (stas* or obstruct* or stasis or stenosis)).tw. (7996)
96 exp Fibrosis/ (56386)
97 (fibrosis or fibroses or cirrhosis).tw. (181341)
98 exp Pancreatitis/ (45415)
99 pancreatiti*.tw. (45217)
100 ((liver or kidney or pancrea*) adj4 (damag* or impair* or inflamm*)).tw. (36274)
101 exp Stomatitis/ (14175)
102 (stomatiti* or mucositi* or oromucusiti*).tw. (18315)
103 ((mouth or oral) adj4 inflamm*).tw. (2152)
104 hepatitis B.tw. (58772)
105 tuberculos?s.tw. (142254)
106 (koch* adj4 disease).tw. (42)
107 exp Pneumonia/ (78646)
108 (pneumoni* or pneumocyst* or lobitis).tw. (131918)
109 ((lung or pulmonary) adj4 inflam*).tw. (17305)
110 exp Psoriasis/ (31676)
111 psorias*.tw. (27529)
112 ((psoriasiform or psoriatic) adj4 (dermat* or lesion* or rash* or skin)).tw. (3446)
113 exp Neuritis/ (6034)
114 (neuriti* or polyneuriti* or neuraxiti*).tw. (12539)
115 Vitiligo/ (4220)
116 vitiligo*.tw. (4500)
117 Jaundice, Obstructive/ (2802)
118 ((cholestatic or obstructive or mechanical) adj4 jaundice).tw. (7538)
119 exp Alopecia/ (11520)
120 (alopecia or baldness or pseudopelade or atrichosis or hairlessness).tw. (12787)
121 (hair adj4 loss).tw. (5173)
122 exp Demyelinating Diseases/ (84233)
123 demyelination*.tw. (11758)
124 (demyelinating adj4 (disease* or disorder* or syndrome* or encephalopath*)).tw. (6540)
125 ((multiple or disseminated or insular or multiplex) adj4 sclerosis).tw. (51434)
126 or/43-47,51-125 (4269434)
127 8 and 36 and 42 and 126 (834)
128 or/48-50 (9255)
129 128 and 8 and 42 (98)
130 127 or 129 (850)
131 Animals/ not Humans/ (4033465)
132 130 not 131 (848)
133 limit 132 to english language (757)
134 Randomized Controlled Trial.pt. (413275)

Line number/Search term/Number retrieved	
135	Controlled Clinical Trial.pt. (91856)
136	Clinical Trial.pt. (506578)
137	exp Clinical Trials as Topic/ (302041)
138	Placebos/ (34034)
139	Random Allocation/ (86446)
140	Double-Blind Method/ (135365)
141	Single-Blind Method/ (21423)
142	Cross-Over Studies/ (37337)
143	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (805096)
144	(random$ adj3 allocat$).tw. (22676)
145	placebo$.tw. (163224)
146	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (132423)
147	(crossover$ or (cross adj over$)).tw. (60143)
148	or/134-147 (1489295)
149	animals/ not humans/ (4033465)
150	148 not 149 (1388520)
151	Observational Study as Topic/ (1064)
152	Observational Study/ (14998)
153	Epidemiologic Studies/ (6416)
154	exp Case-Control Studies/ (753260)
155	exp Cohort Studies/ (1499259)
156	Cross-Sectional Studies/ (205280)
157	Controlled Before-After Studies/ (62)
158	Historically Controlled Study/ (29)
159	Interrupted Time Series Analysis/ (86)
160	Comparative Study.pt. (1743878)
161	case control$.tw. (84095)
162	case series.tw. (37631)
163	(cohort adj (study or studies)).tw. (96258)
164	cohort analy$.tw. (4061)
165	(follow up adj (study or studies)).tw. (38187)
166	(observational adj (study or studies)).tw. (48181)
167	longitudinal.tw. (145668)
168	prospective.tw. (367853)
169	retrospective.tw. (289815)
170	cross sectional.tw. (176682)
171	or/151-170 (3533414)
172	Meta-Analysis.pt. (60532)
173	Meta-Analysis as Topic/ (14958)
174	Review.pt. (2017139)
175	exp Review Literature as Topic/ (8417)
176	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (71806)
177	(review$ or overview$).ti. (292384)
178	(systematic$ adj5 (review$ or overview$)).tw. (66608)
179	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4931)
180	((studies or trial$) adj2 (review$ or overview$)).tw. (27283)
181	(integrat$ adj3 (research or review$ or literature)).tw. (6112)
182	(pool$ adj2 (analy$ or data)).tw. (16051)
183	(handsearch$ or (hand adj3 search$)).tw. (5805)
184	(manual$ adj3 search$).tw. (3465)
185	or/172-184 (2190340)

Line number/Search term/Number retrieved	
186	animals/ not humans/ (4033465)
187	185 not 186 (2050777)
188	150 or 171 or 187 (6008516)
189	133 and 188 (565)

Appendix E: Review flowchart



Appendix F:Excluded studies

Study	Reason for Exclusion
Absah,I., Stephens,M. (2013) Adjunctive treatment to antitumor necrosis factor in pediatric patients with refractory Crohn's disease. Current Opinion in Pediatrics 25: 624-628	Not primary research (narrative review / commentary).
Affronti,A., Orlando,A., Cottone,M. (2015) An update on medical management on Crohn's disease. Expert Opinion on Pharmacotherapy 16: 63-78	Not primary research (narrative review / commentary).
Afif,W., Sandborn,W.J., Faubion,W.A., Ret al. (2013) Risk factors for lymphoma in patients with inflammatory bowel disease: a case-control study. Inflammatory Bowel Diseases 19: 1384-1389	Incorrect population (mixed IBD).
Akobeng,A.A., Sandborn,W.J., Bickston,S.J. (2014) Tumor necrosis factor-alpha antagonists twenty years later: What do Cochrane reviews tell us? Inflammatory Bowel Diseases 20: 2132-2141	Not primary research (narrative review / commentary).
Akobeng,A.K., Zachos,M. (2004) Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews, CD003574	Incorrect intervention/comparator (systematic review of placebo-controlled studies of anti-TNF-alpha monotherapy). Adverse event data not stratified by IS use.
Arnott,I.D., Watts,D., Satsangi,J. (2003) Azathioprine and anti-TNF alpha therapies in Crohn's disease: a review of pharmacology, clinical efficacy and safety. Pharmacological Research 47: 1-10	Not primary research (narrative review / commentary).
Beaugerie,L.(2012) Inflammatory bowel disease therapies and cancer risk: where are we and where are we going? Gut 61: 476-483	Not primary research (narrative review / commentary).
Beaugerie,L., Brousse,N., Bouvier,A.M., et al. (2009) Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 374: 1617-1625.	Incorrect population (mixed IBD); rates of lymphoproliferative disorder not reported for anti-TNF alpha monotherapy.
Beigel,F., Steinborn,A., Schnitzler,F., et al. (2014) Risk of malignancies in patients with inflammatory bowel disease treated with thiopurines or anti-TNF alpha antibodies. Pharmacoepidemiology & Drug Safety 23: 735-744	Incorrect population (mixed IBD).
Biancone,L., Zuzzi,S., Ranieri,M., et al. (2012) Fistulizing pattern in Crohn's disease and pancolitis in ulcerative colitis are independent risk factors for cancer: A single-center cohort study. Journal of Crohn's and Colitis 6: 578-587	Cohort includes patients treated certolizumab.
Bouguen,G., Sninsky,C., Tang,K.L., et al. (2015) Change in erythrocyte mean corpuscular volume during combination therapy with azathioprine and infliximab is associated with mucosal healing: a post hoc analysis from SONIC. Inflammatory Bowel Diseases 21:	Post-hoc analysis of included study (Colombel et al. 2010).

Study	Reason for Exclusion
606-614	
Bressler,B., Siegel,C.A.(2014) Beware of the swinging pendulum: Anti-tumor necrosis factor monotherapy vs combination therapy for inflammatory bowel disease. Gastroenterology 146: 884-887	Commentary / opinion on included study (Osterman et al. 2014)
Chande,N., Tsoulis,D., MacDonald,J. (2013). Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews CD000545	Incorrect intervention (systematic review of AZA/MP). Includes one study already included in review (Colombel et al. 2010).
Chang,C.W., Wei,S.C., Chou,J.W., et al. (2014) Safety and Efficacy of Adalimumab for Patients With Moderate to Severe Crohn's Disease: The Taiwan Society of Inflammatory Bowel Disease (TSIBD) Study. Intestinal Research 12: 287-292	Retrospective cohort study. Adverse event data not stratified by IS use.
Colombel,J., Sandborn,W.J., Rutgeerts,P., et al. (2007) Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. Gastroenterology 132: 52-65	Placebo-controlled trial of maintenance treatment; adverse event data stratified by IS use but denominators cannot be determined.
Colombel,J-F. (2012) When should combination therapy for patients with Crohn's disease be discontinued? Gastroenterology and Hepatology 8: 259-262	Not primary research (narrative review / commentary).
Colombel,J.F., Reinisch,W., Mantzaris,G.J., et al. (2015) Randomised clinical trial: deep remission in biologic and immunomodulator naive patients with Crohn's disease - a SONIC post hoc analysis. Alimentary Pharmacology & Therapeutics 41: 734-746	Post-hoc analysis of included study (Colombel et al. 2010).
Connor,V. (2011) Anti-TNF therapies: a comprehensive analysis of adverse effects associated with immunosuppression. Rheumatology International 31: 327-337	Non-systematic review / commentary. No CD-specific comparative adverse event data reported.
Cozijnsen,M., Duif,V., Kokke,F., et al. (2015) Adalimumab therapy in children with Crohn disease previously treated with infliximab. Journal of Pediatric Gastroenterology & Nutrition 60: 205-210	Observational cohort study; adverse event data not stratified by IS use.
Cozijnsen,M.A., Escher,J.C., Griffiths,A., et al. (2015) Benefits and risks of combining anti-tumor necrosis factor with immunomodulator therapy in pediatric inflammatory bowel disease. Inflammatory Bowel Diseases 21: 951-961	Non-systematic review. Includes mixed IBD populations and non-randomised designs. Used for cross-checking.
Cross,R.K. (2015) Which patients with inflammatory bowel disease should receive combination therapy? Expert Review of Gastroenterology and Hepatology 9: 715-717.	Not primary research (narrative review / commentary).
Dassopoulos,T., Sultan,S., Falck-Ytter,Y.T., et al. (2013) American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology 145: 1464-1478	Systematic review / guideline. Used for cross-checking. No additional studies identified.

Study	Reason for Exclusion
Deepak,P., Stobaugh,D.J., Ehrenpreis,E.D. (2013) Infectious complications of TNF-alpha inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: analysis of the Food and Drug Administration Adverse Event Reporting System. Journal of Gastrointestinal & Liver Diseases 22: 269-276	Incorrect population (mixed IBD).
D'Haens,G., Baert,F., van,Assche G., et al. (2008) Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 371: 660-667	Incorrect comparator (conventional 'step up' management).
D'Haens,G.R., Panaccione,R., Higgins,P., et al. (2011) The London position statement of the World Congress of gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organization: When to start, when to stop, which drug to choose, and how to predict response. American Journal of Gastroenterology 106: 199-212	Expert opinion/ guideline based on non-systematic review. Used for cross-checking.
Dretzke,J., Edlin,R., Round,J., et al. (2011) Connock,M., Hulme,C., Czeczot,J., et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technology Assessment 15: 1-250	Incorrect intervention/comparator.
Dulai,P.S., Siegel,C.A., Colombel,J.F., et al. (2014) Systematic review: Monotherapy with antitumour necrosis factor alpha agents versus combination therapy with an immunosuppressive for IBD. Gut 63: 1843-1853	Systematic review - does not meet review protocol. Includes non-randomised studies and anti-TNF alpha agents not of interest.
Dulai,P.S., Siegel,C.A., Peyrin-Biroulet,L. (2014) Anti-tumor necrosis factor-alpha monotherapy versus combination therapy with an immunomodulator in IBD. Gastroenterology Clinics of North America 43: 441-456	Non-systematic review / commentary. Used for cross-checking.
Dulai,P.S., Thompson,K.D., Blunt,H.B., et al. (2014) Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clinical Gastroenterology & Hepatology 12: 1443-1451	Systematic review - includes studies of mixed IBD populations and case series; does not report outcomes stratified by concomitant IS use.
Dwyer,J.P., Lim,D.L., Mitchell,B. (2014) Long-term outcomes in inflammatory bowel disease patients treated with infliximab or adalimumab in an Australian regional center. Journal of Gastroenterology and Hepatology 29: 111	Abstract only: no full text article available.
Fidder,H., Schnitzler,F., Ferrante,M., et al. (2009) Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. Gut 58: 501-508	Incorrect population (mixed IBD).
Garcia-Vidal,C., Rodriguez-Fernandez,S., Teijon,S. et al. (2009). Risk factors for opportunistic infections in infliximab-treated patients: The importance of screening in prevention. European Journal of Clinical Microbiology and Infectious Diseases 28: 331-337	Incorrect population: includes patients with a range of different infliximab indications.
Gisbert,J.P., Chaparro,M. (2013) Safety of anti-TNF agents during	Non-systematic review.

Study	Reason for Exclusion
pregnancy and breastfeeding in women with inflammatory bowel disease. American Journal of Gastroenterology 108:, 1426-1438	Does not report adverse effects stratified by concomitant IS use.
Gonzalez-Lama,Y., Lopez-San,Roman A., Marin-Jimenez,I., et al. (2008) Open-label infliximab therapy in Crohn's disease: a long-term multicenter study of efficacy, safety and predictors of response. Gastroenterologia y Hepatologia, 31: 421-426	Retrospective cohort study; does not report serious adverse events stratified by concomitant IS use.
Grossi,V., Lerer,T., Griffiths,A., et al. (2015) Concomitant Use of Immunomodulators Affects the Durability of Infliximab Therapy in Children With Crohn's Disease. Clinical Gastroenterology and Hepatology 13: 1748-1756	Prospective cohort study. Outcome not specified in review protocol.
Hanauer,S.B. (2007) Risks and benefits of combining immunosuppressives and biological agents in inflammatory bowel disease: Is the synergy worth the risk? Gut 56: 1181-1183	Not primary research (narrative review / commentary).
Hanauer,S.B. (2012) What to take from TREAT? American Journal of Gastroenterology 107: 1423-1425	Not primary research (narrative review / commentary).
Hanauer,S.B., Feagan,B.G., Lichtenstein,G.R.,et al. (2002) Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. Lancet 359: 1541-1549	Incorrect intervention (compares regimens of infliximab to placebo in responders); adverse events not reported by concomitant IS use.
Hanauer,S.B., Sandborn,W.J., Rutgeerts,P., et al. (2006) Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial, Gastroenterology 130: 323-332	Incorrect intervention/comparator (compares regimens of adalimumab with placebo); adverse event data for adalimumab-treated patients not stratified by concomitant IS use
Hanauer,S.B., Wagner,C.L., Bala,M., et al. (2004) Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clinical Gastroenterology & Hepatology 2: 542-553	Incorrect intervention/comparator (compares regimens of adalimumab with placebo); outcomes not specified in review protocol (infusion reactions and antibody response).
Hazlewood,G.S., Rezaie,A., Borman,M., et al. (2015) Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology 148: 344-354	Systematic review did not meet protocol: does not include all relevant outcomes. Used for cross-checking. No additional relevant studies identified.
Herrinton,L.J., Liu,L., Weng,X., et al. (2011) Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. American Journal of Gastroenterology 106: 2146-2153	Incorrect population (mixed IBD).
Hradsky,O., Copova,I., Zarubova,K., et al. (2015) Seroprevalence of Epstein-Barr Virus, Cytomegalovirus, and Polyomaviruses in Children with Inflammatory Bowel Disease. Digestive Disease and Sciences 60: 3399-3407	Incorrect population (mixed IBD).

Study	Reason for Exclusion
Hyams,J., Crandall,W., Kugathasan,S., et al. (2007) Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 132: 863-873	Incorrect intervention/comparator (compares two regimens of maintenance infliximab in responders).
Hyams,J.S., Griffiths,A., Markowitz,J., et al. (2012) Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology 143: 365-374	Incorrect intervention/comparator (compares maintenance regimens of adalimumab); both groups permitted IS, but adverse events not reported stratified by concomitant IS use.
Hyams,J.S., Ruemmele,F., Colletti,R.B., et al. (2014) Impact of concomitant immunosuppressant use on adalimumab efficacy in children with moderately to severely active Crohn's disease: Results from Imagine 1. Gastroenterology 146: S-214.	Abstract only: no full text article available.
Kamm M.,Hanauer S., Panaccione R., et al. (2011) Adalimumab sustains steroid-free remission after 3 years of therapy for Crohn's disease. Alimentary Pharmacology and Therapeutics 34: 306-317	Post-hoc analysis of CHARM trial (Colombel et al. 2007). Adverse event data stratified by baseline corticosteroid not immunosuppressant use.
Khanna R., Bressler B., Levesque B., et al. (2015) Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster-randomised controlled trial. Lancet [e-pub]. (http://dx.doi.org/10.1016/S0140-6736(15)00068-9)	Incorrect comparator (conventional 'step up' management).
Khanna,R., Feagan,B.G. (2015) Safety of infliximab for the treatment of inflammatory bowel disease: current understanding of the potential for serious adverse events. Expert Opinion on Drug Safety 14: 987-997	Non-systematic review / expert opinion. Used for cross-checking.
Kierkus,J., Iwanczak,B., Wegner,A., et al. (2015) Monotherapy with infliximab versus combination therapy in the maintenance of clinical remission in children with moderate to severe Crohn disease. Journal of Pediatric Gastroenterology & Nutrition 60: 580-585	Incorrect comparison (withdrawal vs continuation of IS in two groups treated with maintenance infliximab).
Kierkus,J., Iwanczyk,B., Wegner,A., et al. (2013) Efficacy infliximab with immunomodulator and infliximab alone of maintenance therapy in children with Crohn's disease multicenter randomized study. Journal of Crohn's & Colitis 7: S220-S221	Abstract only: no full text article available.
Kopylov,U., Al-Taweel,T., Yaghoobi,M., et al. (2014) Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. Database of Abstracts of Reviews of Effects 1632-1641	Systematic review did not meet protocol: does not include all relevant outcomes. Used for cross-checking. No additional studies identified.
Kotlyar,D.S., Osterman,M.T., Diamond,R.H., et al. (2011) A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clinical Gastroenterology & Hepatology 9: 36-41	Case study analysis of known cases of HSTCL.
Lemann,M., Mary,J.Y., Duclos,B., et al. (2006) Infliximab plus	Incorrect comparator

Study	Reason for Exclusion
azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. Gastroenterology 130: 1054-1061	(AZA/MP monotherapy).
Lichtenstein,G.R. (2011) Steroid-free clinical remission in the SONIC study. Gastroenterology and Hepatology 7: 3-4	Post-hoc analysis of included study (Colombel et al. 2010).
Lichtenstein,G.R., Diamond,R.H., Wagner,C.L., et al. (2009) Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. Alimentary Pharmacology & Therapeutics 30: 210-226	Pooled analysis of data from two placebo-controlled infliximab trials already included in Jones (2015) meta-analysis (analyses were cross-checked and verified).
Lichtenstein,G.R., Feagan,B.G., Cohen,R.D., et al. (2006) Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clinical Gastroenterology & Hepatology 4: 621-630	Cohort study but does not report outcomes for anti-TNF alpha therapy stratified by concomitant IS use.
Lichtenstein,G.R., Feagan,B.G., Cohen,R.D., et al. (2012) Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREATTM registry. American Journal of Gastroenterology 107: 1409-1422	Cohort study but does not report outcomes for anti-TNF alpha therapy stratified by concomitant IS use.
Lichtenstein,G.R., Panaccione,R., Mallarkey,G. (2008) Efficacy and safety of adalimumab in Crohn's disease. Therapeutic Advances in Gastroenterology 1: 43-50	Non-systematic review / commentary. Used for cross-checking.
Lichtenstein,G.R., Rutgeerts,P., Sandborn,W.J., et al. (2012) A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. American Journal of Gastroenterology 107,: 1051-1063	Includes data from same CD trials as Jones et al. (2015); analysis by concomitant IS use includes placebo groups, so comparator does not match review protocol.
Lin,Z., Bai,Y., Zheng,P. (2011) Meta-analysis: efficacy and safety of combination therapy of infliximab and immunosuppressives for Crohn's disease. European Journal of Gastroenterology & Hepatology 23: 1100-1110	Systematic review / meta-analysis. Includes trials with incorrect comparator. Used for cross-checking. No additional studies identified.
Long,M.D., Herfarth,H.H., Pipkin,C.A. (2010) Increased Risk for Non-Melanoma Skin Cancer in Patients With Inflammatory Bowel Disease, Clinical Gastroenterology and Hepatology 8: 268-274	Study type (retrospective nested case-control study).
Long,M.D., Martin,C., Sandler,R.S., Kappelman,M.D. (2013) Increased risk of herpes zoster among 108,604 patients with inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 37: 420-429	Study type (retrospective nested case-control study).
Long,M.D., Martin,C.F., Pipkin,C.A et al. (2012) Risk of melanoma and non-melanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 143: 390-399	Study type (retrospective nested case-control study).
Lorenzetti,R., Zullo,A., Ridola,L., et al. (2014) Higher risk of tuberculosis reactivation when anti-TNF is combined with	Systematic review - includes RCTs in non-IBD

Study	Reason for Exclusion
immunosuppressive agents: a systematic review of randomized controlled trials. Annals of Medicine 46: 547-554	populations; outcomes not reported separately for Crohn's disease.
Love,B.L., Smith,L.S., Sarbah,S.A., Fowler,F.C. (2011) Azathioprine and infliximab: Monotherapy or combination therapy in the treatment of Crohn's disease. Clinical Medicine Insights: Gastroenterology 4: 21-30	Non-systematic review / commentary. Used for cross-checking.
Magro,F., Santos-Antunes,J., Albuquerque,A., et al. (2013) Epstein-Barr virus in inflammatory bowel disease-correlation with different therapeutic regimens. Inflammatory Bowel Diseases 19: 1710-1716	Prospective cohort study. Incorrect population (mixed IBD).
Mantzaris G, Ployzou P, Karagiannidis A., et al. (2004) A prospective, randomised trial of infliximab and azathioprine for the induction and maintenance of remission of steroid-dependent Crohn's disease. Gastroenterology 126: A54.	Abstract only: no full text article available.
Mason,M., Siegel,C.A. (2013) Do inflammatory bowel disease therapies cause cancer? Inflammatory Bowel Diseases 19: 1306-1321,	Non-systematic review (includes studies in non-IBD populations). Used for cross-checking.
McDonald-John,W.D., Wang,Yongjun, Tsoulis,David , et al. (2014) Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database of Systematic Reviews: CD003459	Incorrect intervention (methotrexate). Includes data from two studies already included in review.
McNamara,D.A., Brophy,S., Hyland,J.M. Perianal Crohn's disease and infliximab therapy. Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland,2: 258-263	Non-systematic review / commentary.
Meier,J., Sturm,A. (2010) Concomitant use of immunomodulators with anti-TNF in Crohn's disease: Yes or no?, Current Drug Targets.11: 176-178	Non-systematic review / commentary.
Miheller,P., Lakatos,P.L., Horvath,G., et al. (2009) Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe--a Hungarian nationwide observational study, BMC Gastroenterology 9: 66	Observational cohort study. Does not report SAEs of interest stratified by IS use.
Mosli,M.H., Feagan,B.G. (2015) Combination therapy for the treatment of Crohn's disease. Expert Opinion on Biological Therapy 15: 1429-1442	Non-systematic review / commentary. Used for cross-checking.
Moss A., Kim K., Fernandez-Becker N., et al. (2010) Impact of concomitant immunomodulator use on long-term outcomes in patients receiving scheduled maintenance infliximab. Digestive Disease and Sciences 55: 1413-1420.	Retrospective cohort study – adverse events reported by concomitant IS use, but denominators cannot be determined.
Naganuma,M., Kunisaki,R., Yoshimura,N., et al. (2013) A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. Journal of Gastroenterology 48: 595-600	Incorrect population (mixed IBD).
Narula,N., Peyrin-Biroulet,L., Colombel,J.-F. (2014) Combination therapy with methotrexate in inflammatory bowel disease: Time to COMMIT? Gastroenterology146 : 608-611	Commentary on included study (Feagan et al. 2014)

Study	Reason for Exclusion
Panaccione R, Colombel J, Sandborn W., et al. (2010). Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. Alimentary Pharmacology and Therapeutics 31: 1296-1309	Post-hoc analysis of CHARM trial (Colombel et al. 2007). Adverse event data not stratified by baseline concomitant IS use.
Peyrin-Biroulet,L., Reinisch,W., Colombel,J.F., et al. (2014) Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut 63: 88-95	Post-hoc analysis of data from included trial (Colombel et al. 2010
Present D, Rutgeerts P, Targan S., et al. (1999) Infliximab for the treatment of fistulas in patients with Crohn's disease. New England Journal of Medicine 340: 1398-1405	Incorrect intervention/comparator (infliximab vs. placebo). Adverse event data not stratified by concomitant IS use.
Reenaers,C., Louis,E., Belaiche,J., et al. (2012) Does co-treatment with immunosuppressors improve outcome in patients with Crohn's disease treated with adalimumab? Alimentary Pharmacology and Therapeutics 36: 1040-1048	Retrospective cohort study; focus on efficacy (no serious adverse effects meeting the review protocol criteria were reported).
Rosh,J.R., Gross,T., Mamula,P., et al. (2007) Hepatosplenic T-cell lymphoma in adolescents and young adults with Crohn's disease: A cautionary tale? Inflammatory Bowel Diseases 13: 1024-1030	Review of HSTCL cases and commentary. No comparative risk data
Rutgeerts P, D'Haens G, Targan S., et al. (1999). Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 117: 761-769	Incorrect intervention/comparator (infliximab Vs. placebo). Adverse event data not stratified by concomitant IS use.
Rutgeerts P, vanAssche G, Sandborn W., et al. (2012) Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 142: 1102-1111.	Incorrect intervention/comparator (adalimumab Vs. placebo). Adverse event data not stratified by concomitant IS use.
Sandborn,W.J., Hanauer,S.B., Rutgeerts,P., et al. (2007) Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 56: 1232-1239	Incorrect intervention/comparator. Serious adverse events not reported stratified by concomitant IS use.
Sandborn,W.J., Rutgeerts,P., Enns,R., et al. (2007) Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial. Annals of Internal Medicine.146 : 829-838	Incorrect intervention/comparator. Serious adverse events not reported stratified by concomitant IS use.
Sands,B.E., Anderson,F.H., Bernstein,C.N., et al. (2004) Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. New England Journal of Medicine 350: 876-885	Incorrect intervention/comparator. Serious adverse events not reported stratified by concomitant IS use.
Siegel C., Marden S., Persing S., et al. (2009) Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a	Meta-analysis includes data from case series studies. Denominators for reported

Study	Reason for Exclusion
meta-analysis. Clinical Gastroenterology and Hepatology 7: 874-881	adverse events cannot be determined.
Soh,J.S., Yun,W.J., Kim,K.-J., et al. (2015) Concomitant use of Azathioprine/6-mercaptopurine decreases the risk of anti-TNF-induced skin lesions. Inflammatory Bowel Diseases 21: 832-839	Incorrect population (mixed IBD); not an outcome specified in review protocol.
Sokol,H., Seksik,P., Carrat,F., et al. (2010) Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. Gut 59: 1363-1368	Incorrect population (mixed IBD).
Targan S., Hanauer S., van Deventer S., et al. (1997) A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. New England Journal of Medicine 337: 1029-1035.	Incorrect intervention/comparator. Serious adverse events not reported stratified by concomitant IS use.
Toruner,M., Loftus,E.V.,Jr., Harmsen,W.S., et al. (2008) Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 134: 929-936	Incorrect population (mixed IBD).
van,Assche G., Lewis,J.D., Lichtenstein,G.R., et al. (2011) The London position statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis organisation: Safety. American Journal of Gastroenterology 106: 1594-1602	Expert opinion/ guideline based on non-systematic review. Used for cross-checking.
van,Assche G., Magdelaine-Beuzelin,C., D'Haens,G., et al. (2008) Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 134: 1861-1868	Incorrect comparison (withdrawal vs continuation of IS in two groups treated with maintenance infliximab).
van,Assche G., Vermeire,S., Rutgeerts,P. (2009) Immunosuppression in inflammatory bowel disease: traditional, biological or both? Current Opinion in Gastroenterology 25: 323-328	Not primary research (narrative review / commentary).
Veereman-Wauters,G., de,Ridder L., Veres,G., et al. (2012) Risk of infection and prevention in pediatric patients with IBD: ESPGHAN IBD Porto Group commentary. Journal of Pediatric Gastroenterology & Nutrition 54: 830-837	Not primary research (narrative review / commentary).
Vermeire S., Noman M., van Assche G., et al. (2007) Effectiveness of concomitant immunosuppressive therapy in supressing the formation of antibodies to infliximab in Crohn's disease. Gut 56: 1226-1231	Prospective cohort study; does not report adverse events of interest.
Wang,Z., Wang,J., Fu,L., et al. (2015) Effectiveness and risk associated with infliximab alone and in combination with immunosuppressors for Crohn's disease: a systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine 8: 4846-4854.	Systematic review did not meet protocol: does not include all relevant outcomes. Used for cross-checking. No additional relevant studies identified.
Watanabe M., Hibi T., Lomax K., et al. (2012) Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. Journal of Crohn's and Colitis 6: 160-173.	Incorrect intervention/comparator. Serious adverse events not reported stratified by concomitant IS use.

Appendix G: Evidence tables

G.1 Randomised controlled trials included in the review

Bibliographic reference	**Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.**
Study type	Double-blind, multi-centre RCT
Aim	To compare the efficacy and safety of infliximab and azathioprine therapy alone or in combination for Crohn's disease.
Patient characteristics	Recruitment: March 2005 to November 2008. Inclusion criteria: - adults aged ≥21yrs* - Crohn's disease of ≥6 weeks duration - CDAI score 220-450 points - immunosuppressant and biologic naïve - corticosteroid-dependent (CDAI ≥220 after reduction of dose), *or* being considered for a second course of steroids within 12 months, *or* no response to ≥ 4 weeks of mesalamine (≥2.4g per day) or budesonide (≥ 6mg per day) Exclusion criteria: - short bowel syndrome - an ostomy - a symptomatic stricture - an abscess - recent history of tuberculosis or other granulomatous infection - positive chest radiograph / TB skin test - recent history of opportunistic infection (past 6m)

Bibliographic reference	Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.

- active hepatitis B or C, or HIV infection
- multiple sclerosis, cancer, homozygous mutant or heterozygous TPMT phenotype

*Note: minimum age was raised from 18 to 21 in March 2007 after reports of hepatosplenic T-cell lymphoma in adolescents and very young adults receiving combination biologic + immunosuppressant therapy.

Baseline demographic characteristics:	Intervention (n=169)	Control (n=169)
Male sex - n (%)	88 (52.1)	84 (49.7)
Median age (yrs)	34.0 (range:19-68)	35.0 (range:18-80)
White ethnic group - n (%)	142 (94.0)	146 (93.0)

Other baseline characteristics:	Intervention (n=169)	Control (n=169)
Median body weight (kg)	72.0	68.9
Median disease duration (yrs)	2.2	2.2
Crohn's Disease Activity Index score (CDAI) – mean (sd)	289.9 (55.0)	284.8 (62.1)
Inflammatory Bowel Disease Questionnaire (IBDQ) score – mean (sd)	125.3 (28.9)	126.7 (30.3)
Mucosal ulcerations detected on ileocolonoscopy	111 (65.7)	99 (58.6)
Gastrointestinal area involved – n/total no. (%)		
○ Ileum or colon	167/169 (98.8)	163/169 (96.4)
- Ileum only	54/167 (32.3)	54/163 (33.1)
- Colon only	40/167 (24.0)	45/163 (27.6)
- Ileum and colon	73/167 (43.7)	64/163 (39.3)

Bibliographic reference	Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.		
	○ Proximal gastrointestinal tract	16/169 (9.5)	12/169 (7.1)
	Past fistula - n (%) - Perianal - Enterocutaneous - Rectovaginal - Other Current fistula – n (%) - Perianal - Enterocutaneous - Rectovaginal - Other	32 (18.9) 27 (84.4) 4 (12.5) 1 (3.1) 0 (0.0) 25 (14.8) 23 (92.0) 2 (8.0) 2 (8.0) 0 (0.0)	33 (19.5) 26 (78.8) 9 (27.3) 4 (12.1) 2 (6.1) 13 (7.7) 11 (84.6) 4 (30.8) 1 (7.7) 0 (0.0)
	Extra-intestinal manifestations - n (%) ○ Total number of patients with history	82 (48.5)	75 (44.4)
	Previous Crohn's disease-related surgery - n (%)	82 (48.5)	75 (44.4)
	Smoking status - n (%) ○ Current smoker ○ Not smoking - Former smoker (≤1 year ago) - Former smoker (≥1 year ago) - Non-smoker	 65 (38.5) 104 (61.5) 8 (7.7) 29 (27.9) 67 (64.4)	 71 (42.0) 98 (58.0) 9 (9.2) 19 (19.4) 70 (71.4)
	Treatment at baseline:		
	Systemic corticosteroids – no. (%) ○ None	 122 (72.2)	 117 (69.2)

Bibliographic reference	**Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.**

○ <20 mg daily	14 (8.3)	19 (11.2)
○ ≥20 mg daily	33 (19.5)	33 (19.5)
Budesonide – no. (%)	19 (11.2)	28 (16.6)
5-Aminosalicylic compounds – no. (%)	85 (50.3)	87 (51.5)

Note: Other treatments and steroid tapering schedule

- ○ Oral mesalamine was continued at stable dose
- ○ Systemic corticosteroids could be initiated (for patients not receiving them at baseline), with dose maintained, increased or decreased until week 14 (maximum dose allowed = 40mg per day). After week 14, dose was tapered at rate of at least 5mg per week.
- ○ During the main study, 58 (34.3%) patients in the combined therapy group and 60 (35.5%) patients in the infliximab monotherapy group received systemic corticosteroids.
- ○ Budesonide could be maintained or decreased until week 14 (maximum dose 9mg per day). After week 14 budesonide was tapered at a rate of 3mg every 2 weeks to a dose of 6mg per day or less.

Number of Patients

508 patients randomised to 3 groups:

- Azathioprine monotherapy, n=170 - excluded from this review
- Infliximab + azathioprine combination therapy, n=169 – intervention group
- Infliximab monotherapy, n=169 – comparator group

Attrition rates

Intervention group: Infliximab + azathioprine combination therapy (n=169):

121 (72%) completed 30 week trial. Reasons for discontinuation:

- not eligible, n=2
- withdrew consent, n=7
- had an adverse event, n=28
- lost to follow-up, n=2

Bibliographic reference	Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.
	- other reasons (not specified), n=9 108 (64%) were enrolled in study extension to 50 weeks. 90 (53%) completed. Comparison group: Infliximab monotherapy (n=169): 111 (66%) completed 30 week trial. Reasons for discontinuation: - not eligible, n=8 - withdrew consent, n=9 - had an adverse event, n=20 - lost to follow-up, n=5 - other reasons (not specified), n=16 97 (57%) were enrolled in study extension to 50 weeks. 85 (50%) completed.
Intervention	Combined therapy: Infliximab + azathioprine - Infliximab iv infusions at weeks 0, 2, 6, 14 and 22, *plus* - Azathioprine oral capsules given daily Optional extension (with blinding maintained) from week 30 to 50: infliximab infusions at weeks 30, 38, and 46 *plus* azathioprine capsules daily through to week 50 Infliximab dose: 5mg per kilogram bodyweight Azathioprine dose: 2.5mg per kilogram bodyweight
Comparison	Monotherapy: Infliximab + placebo - Infliximab infusions at weeks 0, 2, 6, 14 and 22, *plus* - Placebo oral capsules given daily Optional extension (with blinding maintained) from week 30 to 50: : infliximab infusions at weeks 30, 38, and 46 *plus* placebo capsules daily through to week 50 Infliximab dose: 5mg per kilogram bodyweight

<table>
<tr><td>Bibliographic reference</td><td>Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.</td></tr>
<tr><td>Length of follow up</td><td>30 weeks (with optional extension to 50 weeks)

Monitoring for adverse events and use of corticosteroids was performed through to week 54.</td></tr>
<tr><td>Location</td><td>Multi-national (92 participating centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Outcomes extracted:
◦ Rate of any remission (defined as Crohn's Disease Activity Inventory (CDAI) score < 150 points) at weeks 6 (early), 10 (middle), 18 (late)
◦ Mucosal healing at 26 weeks (as % of those with ulcerations at baseline) – assessed with ileocolonoscopy
○ Inflammatory Bowel Disease Questionnaire (IBDQ) score – assessed at week 10 (middle)
○ Corticosteroid-free remission (at 26 weeks, 50 weeks)
○ Adverse events (through to week 54)

Reported but not extracted:
○ Rates of corticosteroid-free clinical remission (- only extracted for week 26 and week 50 as the outcome does not match the agreed definitions of 'remission' specified in the review protocol) [1]
○ Response-70 (reduction from baseline CDAI score of ≥70 points) [1]
○ Response-100 (reduction from baseline CDAI score of ≥100 points)[1]
○ Corticosteroid dose[1]
○ Change in C-reactive protein (CRP) from baseline to week 26
○ Use of concomitant medication (through to week 54)

Remission
<table>
<tr><th></th><th>Combined therapy (intervention), N=169</th><th>Infliximab monotherapy (comparator), N=169</th><th>p-value for combined therapy vs. infliximab monotherapy[2]</th></tr>
<tr><td colspan="3">Any clinical remission (CDAI<150) – n (%)</td><td></td></tr>
<tr><td>- Week 6 (early)</td><td>88 (52.1)</td><td>83 (49.1)</td><td>0.56</td></tr>
<tr><td>- Week 10 (middle)</td><td>101 (59.8)</td><td>80 (47.3)</td><td>0.02</td></tr>
<tr><td>- Week 18 (late)</td><td>102 (60.4)</td><td>84 (49.7)</td><td>0.05</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.

Mucosal healing			
Patients included in 26 week analysis[3] Mucosal healing – n (%)	**N=107** 47 (43.9)	**N=93** 28 (30.1)	 0.06
Quality of life: Inflammatory Bowel Disease Questionnaire (IBDQ) scores: change from baseline - mean (sd)			
- Week 10	42.4 (34.7)	37.8 (35.6)	0.15
Corticosteroid-free remission (ITT analysis)			
- Week 26 - Week 50	96 (56.8) 78 (46.2)	75 (44.4) 59 (34.9)	0.02 0.04

Adverse events through to week 54[4]

	Combined therapy (intervention), N=163[5]	**Infliximab monotherapy (comparator), N=179[5]**	**p-value for combined therapy vs. infliximab monotherapy[2]**
- Any (unspecified) serious adverse event – n (%) - Serious infection – n (%)	27 (15.1) 7 (3.9)	39 (23.9) 8 (4.9)	0.04 0.79

Rates of surgery (at 6 months; at 12 months)

Not reported

Bibliographic reference	**Colombel J, Sandborn W, Reinisch W, et al. (2010) Infliximab, azathioprine, or combination therapy for Crohn's disease. [The SONIC trial]. New England Journal of Medicine 362: 1383-1395.**
	Hospital admissions Not reported **Growth (paediatric studies only)** Not applicable Note: Antibodies to infliximab were detected at week 30 in 1 of 116 (0.9%) patients receiving combination therapy and 15 of 103 (14.6%) patients receiving infliximab monotherapy – this is not an outcome specified in the review protocol.
Source of funding	Research grants from Centocor Ortho Biotech (manufacturers of Remicade (infliximab) and Schering-Plough
Comments	**Randomisation:** centralised, computer-generated. **Allocation concealment:** random allocation using computerised procedure stratified according to centre, duration of Crohn's disease (<3 years or ≥3 years) and steroid dose (<20 mg daily or ≥20 mg daily) **Blinding:** researchers and study participants were blind to treatment allocation. All colonoscopies were videotaped and interpreted by a single reviewer blinded to treatment allocation and timing of procedure (i.e. baseline or 26 weeks). **Indirectness:** Study participants were all immunosuppressant naïve **Other comments:** - Study power calculation reported; recruitment target achieved - ITT efficacy analyses (patients who required surgery for Crohn's or who withdrew from the study were considered not to be in remission). - Safety population for the combination therapy group included 11 patients who were assigned to one of the two monotherapy groups in the trial but were inadvertently given at least one dose of both active oral and intravenous therapy

[1] *Measured at each data-collection point (i.e. week 0, 2, 6, 10, 18, 26; and for those in extension trial: weeks 34, 42, and 50); however, data are only extracted up to 18 weeks ('late' remission), as specified in the review protocol.*

[2] *Reported p-values were calculated using the Mantel-Haenszel test, stratified according to duration of Crohn's disease and dose of systemic corticosteroids at baseline (equivalent to 0-<20mg or ≥20mg daily prednisolone. P-values for change from baseline in IBDQ scores are based on ANOVA on van der Waerden scores adjusting for duration of Crohn's disease and corticosteroid treatment at baseline.*

[3] *Four intervention and 6 comparator group patients were excluded from analysis of mucosal healing at 26 weeks because they underwent endoscopy before or after 26 weeks; patients with baseline ulceration and missing data at 26 weeks (either because they did not undergo endoscopy at week 26 or who had results that could not be evaluated) were assumed to have a lesion (intervention n=31/107 (29%); comparator n=29/93 (31.2%))*
[4] *There was zero incidence of malignancy, sepsis or death in either treatment arm.*
[5] *The safety population for the combination therapy group included 11 patients who were assigned to one of the two monotherapy groups in the trial but were inadvertently given at least one dose of both active oral and intravenous therapy.*

Bibliographic reference	**Feagan B, McDonald J, Panaccione R, et al. (2014) Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. [The COMMIT trial]. Gastroenterology 146: 681-688.**
Study type	Double-blind, multi-centre RCT
Aim	To evaluate the potential superiority of combination therapy over infliximab alone in patients with active Crohn's disease who were recently also treated with corticosteroids
Patient characteristics	Recruitment: December 2005 to February 2008 Inclusion criteria: - patients with diagnosis of Crohn's disease who had initiated prednisolone (15-40 mg/day) for active symptoms within 6 weeks of screening visit Exclusion criteria: - received methotrexate within the past year - failed to respond to previous methotrexate - previous treatment with infliximab - risk factors for infliximab toxicity (e.g. latent TB, demyelinating disorders, congestive heart failure, current malignancy or malignancy within past 5 years) - received azathioprine/6-MP within 8 weeks prior to randomisation - immediate need for surgery - symptomatic stenosis or ileal / colonic strictures with prestenotic dilatation - bowel resection within 6 months prior to screening - short-bowel syndrome - a stoma - signs, symptoms or laboratory tests indicating clinically significant medical disease - chronic or serious infection within 6 months prior to screening

Bibliographic reference	Feagan B, McDonald J, Panaccione R, et al. (2014) Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. [The COMMIT trial]. Gastroenterology 146: 681-688.

- allergy to murine proteins, infliximab, methotrexate and/or prednisolone
- pregnancy
- known substance abuse

Baseline demographic characteristics:	Combined therapy (intervention), N=63	Infliximab monotherapy (comparator), N=63
Male sex - n (%)	34 (54.0)	37 (58.7)
Age in years - mean (sd)	40.4 (13.3)	38.5 (12.9)
White ethnic group - n (%)	60 (95.2)	57 (90.5)

Other baseline characteristics:	Intervention (N=63)	Control (N=63)
Body weight (kg) – mean (sd)	72.4 (15.4)	71.4 (16.2)
Duration since diagnosis (months) – mean (sd)	130.9 (119.7)	115.4 (103.2)
Crohn's Disease Activity Index score (CDAI) – mean (sd)	207.8 (110.8)	207.6 (100.3)
CDAI score ≥150 points – n (%)	43 (68.3)	46 (73.0)
SF-36 - Physical component score (PCS) – mean (sd) - Mental component score (MCS) – mean (sd)	 39.4 (9.6) 42.7 (1.5)	 36.6 (9.5) 41.6 (1.5)

Bibliographic reference	Feagan B, McDonald J, Panaccione R, et al. (2014) Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. [The COMMIT trial]. Gastroenterology 146: 681-688.		
	Gastrointestinal area involved – n (%) ○ Ileum or colon - Ileum only - Colon only - Ileum and colon ○ Unknown	 11 (17.5) 0 (0.0) 38 (60.3)	 13 (20.6) 1 (1.6) 35 (55.6)
	CRP level (mg/L) – median, (interquartile range)	2.95 (2.0 to 11.0)	6.0 (3.0 to 14.5)
	Haemoglobin level(g/L) – mean (sd)	134.2 (15.7)	131.4 (18.0)
	White cell count (10^9/L) – mean (sd)	10.6 (3.7)	11.0 (3.1)
	Platelet count (10^9/L) – mean (sd)	352 (113)	363 (110)
	Previous Crohn's disease-related surgery - n (%)	36 (57.1)	29 (46.0)
	Smoking status - n (%) ○ Current smoker ○ Not smoking - Former smoker - Non-smoker	 24 (38.1) 16 (25.4) 23 (36.5)	 25 (39.7) 11 (17.5) 27 (42.9)
	Other Crohn's treatment:		
	- Prior AZA / MP therapy, n (%) - Time since prednisolone initiation (weeks) – mean (sd) - Prednisolone dose at randomisation (mg/day) – mean (sd)	15 (23.8) 3.2 (2.3) 22.7 (9.2)	16 (25.4) 3.4 (2.3) 26.5 (10.5)

Bibliographic reference	**Feagan B, McDonald J, Panaccione R, et al. (2014) Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. [The COMMIT trial]. Gastroenterology 146: 681-688.**
	Note: Other treatments and steroid tapering schedule ○ Both groups received oral folic acid (1mg/day) to prevent methotrexate toxicity ○ Ondansetron (4mg oral tablet) was given before administration of the study drug if patients developed nausea ○ Aminosalicylates, budesonide, probiotics, systemic antibiotics for treating luminal CD, other non-study immunosuppressants, parenteral nutrition, investigational agents, or topical aminosalicylates or corticosteroids were not permitted. Antibiotics were allowed for non-CD indication and active perianal disease for maximum 14 consecutive days. ○ All patients were required to discontinue prednisolone by week 14. Tapering of prednisolone began 7 days after randomisation: - patients on >20mg daily decreased by 5mg/wk until 20mg/day was reached - patients on ≤20mg decreased daily dose by 2.5mg/wk
Number of Patients	126 patients randomised to 2 groups: - Infliximab + methotrexate combination therapy, n=63 – intervention group - Infliximab + placebo, n=63 – comparator group **Attrition rates** Intervention group: Infliximab + methotrexate combination therapy (n=63): 28 patients (44.4%) discontinued the trial after 14 weeks due to: - failure to achieve remission at week 14, n=15 - CDAI relapse (score ≥150 or increase of more than 70 points higher than week 14 score), n=8 - required prohibited therapy for CD, n=3 - had an adverse event, n=2 Comparison group: Infliximab monotherapy (n=63): 27 (42.9%) discontinued the trial after 14 weeks due to: - failure to achieve remission at week 14, n=14 - CDAI relapse (score ≥150 or increase of more than 70 points higher than week 14 score), n=9 - withdrew consent, n=2 - had an adverse event, n=1 - lost to follow-up, n=1

Bibliographic reference	**Feagan B, McDonald J, Panaccione R, et al. (2014) Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. [The COMMIT trial]. Gastroenterology 146: 681-688.**
Intervention	Combined therapy: infliximab + methotrexate - Infliximab iv infusions at weeks 1, 3, 7, and 14, *plus* - Methotrexate by weekly subcutaneous injection Maintenance phase for patients in remission at week 14 through to week 50: infliximab infusions at weeks 22, 30, 38 and 46 *plus* weekly subcutaneous methotrexate injections. Infliximab dose: 5mg per kilogram bodyweight. 200mg dose of iv hydrocortisone administered 30 mins prior to each infliximab infusion to minimise risk of infusion reactions and sensitisation. Methotrexate dose: initial dose of 10mg/wk increased using dose-escalation strategy to 20mg at week 3, then 25 mg at week 5 with continuation through to week 50. Mean methotrexate dose at week 50 (or end of treatment) was 22.3mg
Comparison	Monotherapy: Infliximab + placebo - Infliximab iv infusions at weeks 1, 3, 7, and 14, *plus* - Placebo by weekly subcutaneous injection Infliximab dose: 5mg per kilogram bodyweight. 200mg dose of iv hydrocortisone administered 30 mins prior to each infliximab infusion to minimise risk of infusion reactions and sensitisation.
Length of follow up	14 weeks induction phase – all patients 50 weeks maintenance phase - only those in corticosteroid-free remission at week 14 SF-36 data collected throughout and at a post-study follow-up visit at week 66
Location	Canada (15 centres)
Outcomes measures and effect size	**Outcomes extracted:** ○ Prednisolone-free remission at week 14[1] and week 50 (ITT) ○ SF-36 Physical and Mental Component Summary Scores (PCS, MCS) at week 14[2]

Bibliographic reference	**Feagan B, McDonald J, Panaccione R, et al. (2014) Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. [The COMMIT trial]. Gastroenterology 146: 681-688.**

- Proportion of patients experiencing adverse events and undergoing surgery

Reported but not extracted:

- Time to treatment failure (defined as failure to enter corticosteroid-free remission (CDAI<150) at week 14 or failure to maintain this remission through to week 50)
- SF-36 Physical and Mental Component Summary Scores at week 50
- Mean CDAI score at week 14 and week 50
- Median change in serum CRP concentration at week 14 and week 50
- Proportion of patients achieving overall treatment success at week 50
- Median serum infliximab concentration
- Proportion of patients developing antibodies to infliximab

	Combination N=63	**Monotherapy N=63**	**p-value**
Remission			
Prednisolone-free remission (ITT)[1]			
- Week 14	48 (76.2)	49 (77.8)	0.83
- Week 50	35 (55.6)	36 (57.1)	0.86
Quality of Life			
SF-36 scores - mean, (sd)[3]			
Physical Component Summary score	**N=59**	**N=59**	
- Week 14	45.2 (9.7)	46.1 (9.7)	0.65
Mental Component Summary score	**N=59**	**N=59**	
- Week 14	44.7 (11.5)	47.1 (11.5)	0.27
Rates of surgery (through to week 50)			
Surgery[4]	3 (4.8)	1 (1.6)	0.34[5]

Bibliographic reference	**Feagan B, McDonald J, Panaccione R, et al. (2014) Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. [The COMMIT trial]. Gastroenterology 146: 681-688.**
	Adverse events No clear reporting of serious adverse events of interest **Hospital admissions** Not reported **Growth (paediatric studies only)** Not applicable <u>Note:</u> A significant reduction in risk of developing antibodies to infliximab was reported for patients in combination therapy group (4% vs. 20% in monotherapy group, p=0.01) – this outcome was not specified in review protocol
Source of funding	Supported by the Crohn's and Colitis Foundation of America, Merck / Schering Plough, Canada, and Prometheus Laboratories, Inc.
Comments	**Randomisation:** centralised, computer-generated. **Allocation concealment:** random allocation using computerised minimisation procedure to balance treatment groups on basis of (i) treatment with or without a purine metabolite in past 12 months; (ii) prednisolone dose <20 mg or ≥20mg; and (3) CDAI < 150 or ≥150 at randomisation **Blinding:** researchers and study participants were blind to treatment allocation. Blood counts and aminotransferase levels monitored by independent unblinded clinician (with no study patient contact). Methotrexate dose adjustments were made if leukopenia developed; dose adjustments were also made in placebo group to preserve blinding **Indirectness:** Approximately 30% of patients across both groups were in steroid-induced remission (CDAI < 150 points) at baseline, therefore do not meet review protocol criterion for 'active Crohn's disease' **Other comments:** - Study power calculation reported; recruitment target achieved. - Weeks 14-50 were a trial of maintenance therapy; only those patients in steroid-free remission at 14 weeks were eligible to be entered, therefore outcome data beyond week 14 were not analysed.

[1] *Note that all patients were required to have stopped prednisolone by 14 weeks, so 'prednisolone-free remission at 14 weeks' has been treated for analysis purposes as 'in clinical remission (CDAI<150) – (middle time point)'*

[2] *The SF36 Physical Component Summary (PCS) score was used in analyses as this is likely to correlate more closely with the IBDQ than the Mental Component Summary score*
[3] *All standard deviations calculated by reviewer from reported standard errors*
[4] *3 patients in combination therapy (intervention) group had a bowel resection and 1 patient in infliximab monotherapy underwent surgery for perianal abscess*
[5] *p-value calculated by reviewer*

<table>
<tr><th>Bibliographic reference</th><td>Schroder O, Blumenstein I and Stein J. (2006) Combining infliximab with methotrexate for the induction and maintenance of remission in refectory Crohn's disease: a controlled pilot study. European Journal of Gastroenterology & Hepatology 18: 11-16.</td></tr>
<tr><th>Study type</th><td>Open-label, randomised, controlled pilot study</td></tr>
<tr><th>Aim</th><td>To assess the safety and efficacy of an induction scheme of infliximab combined with long-term immunosuppressive therapy with methotrexate in patients with refractory Crohn's disease resistant or intolerant to azathioprine.</td></tr>
<tr><th>Patient characteristics</th><td>Recruitment: September 2001 to September 2003

Inclusion criteria:
- active Crohn's disease, refractory to / dependent on corticosteroids
- resistant or intolerant to azathioprine

Exclusion criteria:
- previous treatment with infliximab or any other anti-TNF-alpha agent

<table>
<tr><th>Baseline demographic characteristics:</th><th>Combined therapy (intervention), N=11</th><th>Infliximab monotherapy (comparator), N=8</th></tr>
<tr><td>Male sex - n (%)</td><td>6 (54.5%)</td><td>2 (25%)</td></tr>
<tr><td>Age in years - mean (sd)</td><td>31.6 (9.4)</td><td>36.5 (7.3)</td></tr>
</table>

<table>
<tr><th>Other baseline characteristics:</th><th>Intervention (N=11)</th><th>Control (N=8)</th></tr>
<tr><td>Duration of disease (years) – mean (sd)</td><td>8.2 (6.0)</td><td>9.6 (6.8)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Schroder O, Blumenstein I and Stein J. (2006) Combining infliximab with methotrexate for the induction and maintenance of remission in refectory Crohn's disease: a controlled pilot study. European Journal of Gastroenterology & Hepatology 18: 11-16.**

Crohn's Disease Activity Index score (CDAI) – mean (sd)	251 (61)	293 (93)
Inflammatory Bowel Disease Questionnaire score (IBDQ) – mean (sd)	113 (23)	106 (17)
Location of disease – n (%) ○ Ileum or colon - Terminal ileum - Colon - Ileum and colon ○ Whole GI tract	 1 (9.1) 1 (9.1) 7 (63.6) 2 (3.2)	 1 (12.5) 1 (12.5) 5 (62.5) 1 (12.5)
Other Crohn's treatment:		
Azathioprine failure – n (%) - Intolerance - Resistance Concomitant medication – n (%) - Corticosteroids - 5-Aminosalicylates	 1 (9.1) 10 (90.9) 8 (72.7) 2 (18.2)	 1 (12.5) 7 (87.5) 7 (87.5) 3 (37.5)

Note: Other treatments and steroid tapering schedule

- Aminosalicylates at a dose of ≥4g per day were permitted if the dose had been stable for 6 weeks prior to screening visit;
- Corticosteroids (prednisolone) at a dose ≤40mg/day were permitted if the dose had been stable for 4 weeks prior to screening
- Tapering of prednisolone began on signs of improvement in patient's condition:
  - patients on >20mg daily decreased dose by 5mg/wk
  - patients on ≤20mg daily decreased dose by 2.5mg/wk

Number of Patients	19 patients, randomised to two treatment groups:

Bibliographic reference	**Schroder O, Blumenstein I and Stein J. (2006) Combining infliximab with methotrexate for the induction and maintenance of remission in refectory Crohn's disease: a controlled pilot study. European Journal of Gastroenterology & Hepatology 18: 11-16.**
	- Infliximab + methotrexate combination therapy, n=11 – intervention group - Infliximab monotherapy, n=8 – comparator group Attrition rates Intervention group: Infliximab + methotrexate combination therapy (n=11): 4 patients (36.4%) discontinued the trial before week 48 due to lack of efficacy Comparison group: Infliximab monotherapy (n=8): 2 patients (25.0%) discontinued the trial before week 48 due to lack of efficacy
Intervention	Combined therapy: Infliximab + methotrexate - Infliximab iv infusions at weeks 0 and 2 *plus* - Methotrexate by weekly infusion between weeks 0 to 5 inclusive (six infusions), followed by oral methotrexate to 48 weeks Infliximab dose: 5mg per kilogram bodyweight administered IV in 250ml saline over 2 hours. Methotrexate dose: 20mg/week
Comparison	Infliximab monotherapy - Infliximab iv infusions at weeks 0 and 2 Infliximab dose: 5mg per kilogram bodyweight administered IV in 250ml saline over 2 hours.
Length of follow up	48 weeks
Location	Germany (one centre)
Outcomes measures and effect size	**Outcomes extracted:** o Clinical remission (defined as CDAI<150) at weeks 2 (early), 12 (middle), 24 (late) o Serious adverse events (to week 48) o Mean IBDQ score at week 12 (middle)[1]

Bibliographic reference	**Schroder O, Blumenstein I and Stein J. (2006) Combining infliximab with methotrexate for the induction and maintenance of remission in refectory Crohn's disease: a controlled pilot study. European Journal of Gastroenterology & Hepatology 18: 11-16.**

- Corticosteroid-free at 48 weeks

Reported but not extracted:

- Clinical remission at week 48
- Mean IBDQ at weeks 2, 24 and 48
- Median time to achieve remission
- Clinical remission at any point during the trial
- Mean CDAI at weeks 2, 12, 24 and 48 – presented graphically

Remission	**Combination N=11**	**Monotherapy N=8**	**p-value**
Clinical remission (defined as CDAI<150) – n (%) - Week 2 (early) - Week 12 (middle) - Week 24 (late)	 7 (63.6) 9 (81.8) 6 (54.5)	 2 (25.0) 4 (50.0) 3 (37.5)	 0.16 0.32 0.65
Adverse events (through to week 48)			
Serious adverse events – n (%) Serious infections – n (%)	0 0	1 (12.5) 0	0.49 n/a
Quality of life: Inflammatory Bowel Disease Questionnaire (IBDQ) score - mean (sd)[1]			
- Week 12	172 (38)	142 (38)	Not reported
Corticosteroid-free at week 48			
Corticosteroid-free – n (%) of all patients	7 (63.6)	2 (0.25)	0.16

Rates of surgery (at 6 months; at 12 months)

Not reported

Bibliographic reference	**Schroder O, Blumenstein I and Stein J. (2006) Combining infliximab with methotrexate for the induction and maintenance of remission in refectory Crohn's disease: a controlled pilot study. European Journal of Gastroenterology & Hepatology 18: 11-16.**
	Hospital admissions Not reported **Growth (paediatric studies only)** Not applicable
Source of funding	Not reported
Comments	**Randomisation:** procedure not reported. **Allocation concealment:** procedure not reported **Blinding:** open label study

[1] *Mean score and standard deviation estimated from graph*

G.2 Comparative observational and cohort studies included in safety analyses

Bibliographic reference	**Hamzaoglu H, Cooper J, Alsahli M, et al. (2010) Safety of infliximab in Crohn's disease: a large single-center experience. Inflammatory Bowel Diseases 16: 2109-2116.**
Study type	Retrospective cohort study
Aim	To evaluate the safety profile of infliximab in clinical practice in patients with Crohn's disease attending a single centre.
Patient characteristics	Consecutive patients treated with infliximab for Crohn's disease between October 1998 and January 2005.

Bibliographic reference	**Hamzaoglu H, Cooper J, Alsahli M, et al. (2010) Safety of infliximab in Crohn's disease: a large single-center experience. Inflammatory Bowel Diseases 16: 2109-2116.**
	Characteristics[1]: Age (yrs) – mean (sd): 40 (range 19 – 84) Male sex – n (%): 119 (40.1) Duration of disease at first infliximab infusion (years) – median: 13.9 (range 1 - 48) Location of disease – n (%) - Small bowel: 27 (9) - Colon: 110 (37) - Ileocolitis: 148 (50) - Other: 12 (4) Indications for infliximab: - Active luminal disease: 175 (59) - Active fistulising disease: 107 (36) - Other: 12 (4) Concomitant medication at start of infliximab treatment: - None: 160 (53.9) - Azathioprine / mercaptopurine only: 61 (45) - Corticosteroids only: 50 (36) - Methotrexate only: 1 (0.7) - AZA/MP + corticosteroids: 25 (18)
Number of Patients	N=297 patients. Data extracted for 221 patients as follows: - concomitant azathioprine / mercaptopurine at start of infliximab therapy (n=61) - treated with infliximab only (n=160)
Intervention	Combined infliximab + AZA/MP therapy

<table>
<tr><td>Bibliographic reference</td><td>Hamzaoglu H, Cooper J, Alsahli M, et al. (2010) Safety of infliximab in Crohn's disease: a large single-center experience. Inflammatory Bowel Diseases 16: 2109-2116.</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Comparison</td><td>Infliximab monotherapy</td></tr>
<tr><td>Length of follow up</td><td>297 patients followed up for total of 261 patient years. Median follow-up (months): 14.3 (range: 1 – 83)</td></tr>
<tr><td>Location</td><td>USA (one centre)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Adverse events:</th><th>Infliximab + concomitant AZA/MP (N=61)</th><th>Infliximab monotherapy (N=160)</th><th>p-value</th></tr>
<tr><td>Serious infections – n (%)</td><td>3 (4.9)</td><td>0</td><td>0.005</td></tr>
<tr><td>Malignancy – n (%)</td><td>2 (3.3)</td><td>2 (1.3)</td><td>0.31</td></tr>
<tr><td>Death – n (%)</td><td>1 (1.6)</td><td>0</td><td>0.11</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Risk of bias: observational study. No significant differences in patient characteristics between groups treated with concomitant immunosuppressants (+/-corticosteroids) and those treated with infliximab monotherapy. Analyses do not control for potential confounders, including previous exposure to immunosuppressants among the monotherapy group.
Indirectness: Not clear if study population had active Crohn's for duration of follow-up
Other:
- Outcome data were not extracted for patients taking corticosteroids at start of infliximab treatment (with or without immunosuppressants).</td></tr>
</table>

[1] *Characteristics correspond to full sample of 297 patients; data were analysed for 221 patients (74%) treated either with concomitant infliximab + thiopurine therapy or infliximab monotherapy; patients taking corticosteroids at the start of infliximab treatment (with or without immunosuppressants) were excluded.*

Bibliographic reference	**Jones J, Kaplan G, Peyrin-Biroulet L, et al. (2015). Effects of concomitant immunomodulatory therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease; a meta-analysis of placebo-controlled trials. Clinical Gastroenterology and Hepatology 13: 2233-2240.**
Study type	Meta-analysis of non-randomised subgroup data from placebo-controlled RCTs.
Aim	To compare the efficacy and safety of combined anti-TNF and immunosuppressant therapy versus anti-TNF monotherapy in Crohn's disease, using data for the anti-TNF exposed patients in placebo-controlled trials, comparing subgroups who were and were not treated with a concomitant immunosuppressant.
Patient characteristics	Not reported (pooled analysis of RCTs)
Number of Patients	N=454 infliximab-treated patients [pooled data from 5 trials]: - treated with combined infliximab + immunosuppressant (IS): N=152 - treated with infliximab monotherapy: N=302 N=601 adalimumab-treated patients [pooled data from 4 trials]: - treated with combined adalimumab + IS: N=260 - treated with adalimumab monotherapy: N=341
Intervention	Combination infliximab or adalimumab therapy + an immunosuppressant (azathioprine / mercaptopurine / methotrexate)
Comparison	Infliximab or adalimumab monotherapy
Length of follow up	Various (pooled analysis of RCTs)
Location	Various (pooled analysis of RCTs)
Outcomes measures and effect size	

Adverse events:	**Summary estimate: combined anti-TNF agent + immunosuppressant compared to monotherapy (OR; 95% CI)**

Bibliographic reference	**Jones J, Kaplan G, Peyrin-Biroulet L, et al. (2015). Effects of concomitant immunomodulatory therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease; a meta-analysis of placebo-controlled trials. Clinical Gastroenterology and Hepatology 13: 2233-2240.**
	Serious infections - Infliximab: 0.56 (0.15 to 2.09) - Adalimumab: 1.18 (0.30 to 4.60) Malignancy - Infliximab: 8.6 (0.34 to 214.38) - Adalimumab: n/a Death - Infliximab: 0.93 (0.04 to 23.22) - Adalimumab: n/a
Source of funding	Not reported
Comments	**Risk of bias**: observational study (patients not randomised to concomitant immunosuppressants). Patient characteristics at baseline not compared across included trials. Those on immunosuppressant medication at trial enrolment may have had more severe disease. Prior exposure to immunosuppressants among monotherapy patients is not known. Differences in concomitant corticosteroid use between treatment groups is not known. **Indirectness**: Included trials of anti-TNF-alpha therapy for both induction and maintenance of remission in patients with Crohn's disease. **Other:** - Analyses included patient-level data obtained directly from 3 pharmaceutical sponsors of the original trials so results could not be verified with reference to original trial publications. - Only data from placebo-controlled trials of infliximab or adalimumab were extracted and included in this review; 2 trials of certolizumab were excluded.

Bibliographic reference	**Kinney T, Rawlins M, Kozarek R, et al. (2003). Immunomodulators and 'on demand' therapy with infliximab in Crohn's disease: clinical experience with 400 infusions. American Journal of Gastroenterology 98: 608-612.**
Study type	Retrospective cohort study

<table>
<tr><td>Bibliographic reference</td><td>Kinney T, Rawlins M, Kozarek R, et al. (2003). Immunomodulators and 'on demand' therapy with infliximab in Crohn's disease: clinical experience with 400 infusions. American Journal of Gastroenterology 98: 608-612.</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Aim</td><td>To examine, in patients receiving infliximab with and without concomitant immunosuppressant therapy, whether these medications have an effect on clinical response or length of remission between infliximab doses.</td></tr>
<tr><td>Patient characteristics</td><td>Study period: October 1998 to March 2001.

Inclusion: Patients with Crohn's disease receiving infliximab infusions who completed more than 2 weeks of follow-up (total of 400 infusions).

<table>
<tr><th>Patient characteristics:</th><th>Infliximab + azathioprine / mercaptopurine (N=58)</th><th>Infliximab + methotrexate (N=23)</th><th>Infliximab monotherapy (N=36)</th></tr>
<tr><td>Age (years) – mean</td><td>40</td><td>43</td><td>46</td></tr>
<tr><td>Male:Female</td><td>1:0.9</td><td>1:1.3</td><td>1:3.5</td></tr>
<tr><td>Disease duration (years) – mean</td><td>12</td><td>13</td><td>15</td></tr>
<tr><td>Follow-up (weeks) – mean</td><td>53</td><td>65</td><td>40</td></tr>
</table>

Disease location (multiple sites in some patients, therefore % total more than 100) – n (%):
- Stomach: 5 (4)
- Duodenum: 8 (7)
- Small bowel: 73 (62)
- Colon: 75 (64)
- Rectum: 41 (35)
- Perianal: 19 (16)

Other co-therapies – n (%):
- Prednisolone: 64 (54.7)
- Mesalamine: 51 (43.6)
- Antibiotics: 16 (13.7)</td></tr>
</table>

Bibliographic reference	**Kinney T, Rawlins M, Kozarek R, et al. (2003). Immunomodulators and 'on demand' therapy with infliximab in Crohn's disease: clinical experience with 400 infusions. American Journal of Gastroenterology 98: 608-612.**
Number of Patients	N=117 patients
Intervention	Combined infliximab + AZA/MP *or* MTX therapy Infliximab iv infusions given 'on demand' following initial infusion Dose: 5mg / kg bodyweight AZA/MP dose: 1.5-2.0 mg / kg bodyweight MTX dose: not reported. Mean number of infusions per patient: Infliximab + azathioprine: 3 Infliximab + methotrexate: 4
Comparison	Infliximab monotherapy Infliximab iv infusions given 'on demand' following initial infusion Dose: 5mg / kg bodyweight Mean number of infusions per patient: 3
Length of follow up	Study period: October 1998 to March 2001. Mean overall length of follow-up: 52 weeks.
Location	USA (one centre)
Outcomes measures and effect size	

Adverse events:	**Combined Infliximab + AZA/MP (N=58)**	**Infliximab + MTX (N=23)**	**Infliximab monotherapy (N=36)**

Bibliographic reference	**Kinney T, Rawlins M, Kozarek R, et al. (2003). Immunomodulators and 'on demand' therapy with infliximab in Crohn's disease: clinical experience with 400 infusions. American Journal of Gastroenterology 98: 608-612.**
	Death – n (%) | 0 | 0 | 1
Source of funding	Not reported
Comments	**Risk of bias**: Ratio of males:females differed between combination therapy (1:1) and monotherapy (1:3.5) groups. Analyses did not control for differences between groups or for potential confounding factors, including disease severity, prior immunosuppressant exposure or concomitant corticosteroids (not reported). **Indirectness**: Not all study patients meet review protocol criteria for active Crohn's disease (26-36% of patients across treatment groups achieved remission during study period) **Other**: - 1 death in infliximab monotherapy group due to small bowel perforation 3 weeks after initial infliximab infusion.

Bibliographic reference	**Lichtenstein G, Feagan B, Cohen R, et al. (2009) Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ registry. American Journal of Gastroenterology 109: 212-223.**
Study type	Retrospective cohort study
Aim	To examine the potential relationship between risk of malignancy and treatment with TNF antagonists.
Patient characteristics	Patients with Crohn's disease enrolled between January 1999 and March 2004 in the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT™) registry, who were treated with infliximab during or within a year before registry enrolment Inclusion: - Adults 18yrs+ - Not in a clinical trial Patient characteristics at enrolment[1]

Bibliographic reference	**Lichtenstein G, Feagan B, Cohen R, et al. (2009) Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ registry. American Journal of Gastroenterology 109: 212-223.**
	Age (years) – mean (sd): 40.5 (14.0) Male – n (%): 1,382 (41.0) Caucasian ethnicity – n (%): 3,044 (90.4) Disease duration (years) – mean (sd): 11.2 (9.8) Disease severity – n (%) - Remission: 465 (14.2) - Mild-moderate: 1,728 (52.7) - Moderate-severe: 1,004 (30.6) - Severe-fulminant: 83 (2.5) Intestinal area involvement – n (%): - Ileum only: 869 (26.3) - Colon only: 971 (29.4) - Ileum and colon: 1,468 (44.4) Medication use within previous year – n (%): - Antibiotics: 1,094 (32.0) - Immunosuppressants: 1,780 (52.0) - Prednisolone: 1,635 (47.8)
Number of Patients	N=3,764 patients: o treated with infliximab + IS (n=3,517) o treated with infliximab only (n=247)

<table>
<tr><td>Bibliographic reference</td><td>Lichtenstein G, Feagan B, Cohen R, et al. (2009) Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ registry. American Journal of Gastroenterology 109: 212-223.</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Intervention</td><td>Combined infliximab + IS therapy</td></tr>
<tr><td>Comparison</td><td>Infliximab monotherapy</td></tr>
<tr><td>Length of follow up</td><td>Mean patient follow-up: 5.2 years</td></tr>
<tr><td>Location</td><td>USA (data from approximately 350 participating gastroenterologists enrolling up to 150 patients)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Adverse events:</th><th>Combined infliximab + IS therapy (n=3,517)</th><th>Infliximab monotherapy (n=247)</th><th>p-value</th></tr>
<tr><td>Malignancy – n (%)</td><td>119 (3.4)</td><td>5 (2.0)</td><td>0.25[2]</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>TREAT™ registry sponsored by Janssen Biotech, Horsham, PA, USA (manufacturer of infliximab).</td></tr>
<tr><td>Comments</td><td>Risk of bias: Patient characteristics for combined versus monotherapy group not reported; not clear if malignancy incidence analysis by use of infliximab/immunosuppressants controlled for confounding factors
Indirectness: not clear whether patients included in malignancy incidence analysis all met review protocol criteria for active Crohn's disease</td></tr>
</table>

[1] *Based on sample of 3,420 patients who were treated with infliximab at time of enrolment in TREAT registry (demographic and disease characteristics data not available for all patients); analyses include a further 97 patients who were treated with infliximab within 1 year of enrolment.*

[2] *p-value calculated by reviewer*

Bibliographic reference	**Marehbian J, Arrighi H, Hass S, et al. (2009). Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. American Journal of Gastroenterology 104: 2524-2533.**

Bibliographic reference	**Marehbian J, Arrighi H, Hass S, et al. (2009). Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. American Journal of Gastroenterology 104: 2524-2533.**
Study type	Retrospective cohort study
Aim	To determine whether (i) Crohn's disease itself is associated with increased risk of morbidity from a variety of infectious, malignant and neurological adverse events compared with healthy controls; (ii) monotherapy with any one of steroids, immunosuppressants, and anti-TNF agents increases risk of these adverse events compared with patients with CD not taking these medications, and (iii) the risk of combination therapy with these agents is greater than monotherapy.
Patient characteristics	Longitudinal cohort of patients identified from private health insurance claims (2002-2005) by presence of at least one claim for Crohn's disease Inclusion (longitudinal cohort): Minimum of 1 year of information without a CD diagnosis before the index diagnosis. Exclusions: History of HIV infection Solid organ transplant recipients <1 year of continuous health plan coverage after first (index) CD diagnosis Demographic characteristics: Age (years) – mean (sd): 48 (16) Male – n (%): 3,776 (44%)
Number of Patients	N=8,581 (longitudinal cohort) representing a total of 17,609 person years of exposure, of whom: - 5% had used an anti-TNF agent - 13% had used IS medications - 35% had used steroids - 15% had used some combination of these three drug groups

<table>
<tr><td>Bibliographic reference</td><td>Marehbian J, Arrighi H, Hass S, et al. (2009). Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. American Journal of Gastroenterology 104: 2524-2533.</td></tr>
<tr><td></td><td>Anti-TNF agents included infliximab and adalimumab
IS medication included azathioprine, mercaptopurine and methotrexate
Steroid medication included prednisolone and budesonide.

Event data were extracted only for patients classified as treated with (i) combined anti-TNF-alpha + IS therapy, or (ii) anti-TNF-alpha monotherapy. Patients prescribed steroids were excluded from analyses.</td></tr>
<tr><td>Intervention</td><td>Combined anti-TNF-alpha + IS therapy (representing 162 person years of exposure)</td></tr>
<tr><td>Comparison</td><td>Anti-TNF-alpha monotherapy (representing 292 person years of exposure)</td></tr>
<tr><td>Length of follow up</td><td>Minimum of 1 year follow-up</td></tr>
<tr><td>Location</td><td>USA (nationwide)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Adverse events:</th><th>Combined anti-TNF-alpha + IS therapy (total: 162 person years)[1]</th><th>Anti-TNF-alpha monotherapy (total: 292 person years)[1]</th></tr>
<tr><td>Serious infection (sepsis) – n</td><td>23</td><td>48</td></tr>
<tr><td>Lymphoma – n</td><td>1</td><td>2</td></tr>
<tr><td>Solid tumours – n</td><td>20</td><td>2</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Supported by research grant from Elan Pharmaceuticals, South San Francisco, CA, to Health Benchmarks, Woodland Hills, CA.</td></tr>
<tr><td>Comments</td><td>Risk of bias: observational study. No comparison of patient characteristics across treatment groups. Data were analysed as 'time to event' adjusted for potential confounding factors (including age, gender, comorbidities) but not disease duration or severity.
Indirectness: not clear whether all patients met review protocol for active Crohn's disease for duration of follow-up</td></tr>
</table>

[1] *Number of patients per treatment group not known, therefore % event rates cannot be calculated.*

<table>
<tr><td>Bibliographic reference</td><td>Osterman M, Sandborn W, Colombel J, et al. (2014) Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology 146: 941-949.</td></tr>
<tr><td>Study type</td><td>Pooled analysis of data from randomised, placebo-controlled trials of adalimumab for the induction or maintenance of remission in Crohn's disease patients (CLASSIC I and II, GAIN, CHARM, EXTEND and the long-term open-label extension study ADHERE).</td></tr>
<tr><td>Aim</td><td>To determine (i) the risk of malignancy[1] in patients with Crohn's disease treated with adalimumab monotherapy compared with the general population, and (ii) the risk of malignancy in patients treated with combination adalimumab and immunosuppressant therapy compared with adalimumab monotherapy</td></tr>
<tr><td>Patient characteristics</td><td>Patients who received at least one dose of adalimumab during the six trials, classified according to exposure to immunosuppressants at study baseline.
<table>
<tr><th>Baseline characteristics</th><th>Combined adalimumab + any IS therapy (N=694)</th><th>Combined adalimumab + thiopurine therapy (N=563)</th><th>Adalimumab monotherapy (N=900)</th></tr>
<tr><td>Age (years) – mean (sd)</td><td>36.2 (12.1)</td><td>35.8 (12.2)</td><td>38.7 (11.6)</td></tr>
<tr><td>Male gender – n (%)</td><td>269 (38.8)</td><td>223 (39.6)</td><td>348 (38.7)</td></tr>
<tr><td>Caucasian ethnicity – n (%)</td><td>642 (92.5)</td><td>517 (91.8)</td><td>835 (92.8)</td></tr>
<tr><td>Smoking status – n (%)
- Current
- Past</td><td>
228 (32.9)
163 (23.5)</td><td>
175 (31.1)
134 (23.8)</td><td>
336 (37.3)
228 (25.3)</td></tr>
<tr><td>Disease duration (years) – median (range)</td><td>7.7 (0-46.8)</td><td>7.5 (0-46.8)</td><td>8.4 (0-44.1)</td></tr>
<tr><td>Baseline CDAI – mean (sd)</td><td>310.4 (60.2)</td><td>308.1 (60.3)</td><td>310.4 (63.2)</td></tr>
<tr><td>Fistuala(e) at baseline – n (%)</td><td>99 (14.3)</td><td>87 (15.5)</td><td>123 (13.7)</td></tr>
<tr><td>Baseline corticosteroid use – n (%)</td><td>282 (40.6)</td><td>222 (39.4)</td><td>314 (34.9)</td></tr>
<tr><td>Prior anti-TNF use – n (%)</td><td>404 (58.2)</td><td>308 (54.7)</td><td>406 (45.1)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Osterman M, Sandborn W, Colombel J, et al. (2014) Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology 146: 941-949.</td></tr>
<tr><td>Number of Patients</td><td>N=1594 patient participants in six clinical trials of adalimumab (representing 3,050 person-years of adalimumab exposure), of whom:
- treated with combination adalimumab + AZA/MP therapy, n=563
- treated with combination adalimumab + MTX therapy, n=131
- treated with adalimumab monotherapy, n=900</td></tr>
<tr><td>Intervention</td><td>Combination adalimumab + AZA/MP/MTX therapy ('Combined adalimumab + any IS therapy')
- Cumulative duration of adalimumab exposure: 1401 person-years

Combination adalimumab + AZA/MP therapy (= 'Combined adalimumab + thiopurine therapy')[2]
- Cumulative duration of adalimumab exposure: 1145 person-years</td></tr>
<tr><td>Comparison</td><td>Adalimumab monotherapy
- Cumulative duration of adalimumab exposure: 1649 person-years</td></tr>
<tr><td>Length of follow up</td><td>Combined adalimumab + any IS therapy (n=694): median 1.61 years (range: 0.04 to 5.52)
Combined adalimumab + thiopurine therapy (n=563): median 1.25 years (range: 0.04 to 5.54)
Adalimumab monotherapy (n=900): median 1.61 years (range: 0.04 to 5.52)</td></tr>
<tr><td>Location</td><td>Multiple countries (pooled analysis of RCTs)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Adverse events:</th><th>Combined adalimumab + any IS therapy (N=694; 1401 person-years)</th><th>Combined adalimumab + thiopurine therapy (N=563; 1145 patient-years)</th><th>Adalimumab monotherapy (N=900; 1649 patient-years)</th></tr>
<tr><td>Non-melanoma skin cancer (NMSC)
- n (%) of patients treated</td><td>11 (1.6)</td><td>10 (1.8)</td><td>4 (0.44)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Osterman M, Sandborn W, Colombel J, et al. (2014) Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology 146: 941-949.**

- per 100 patient-years of adalimumab exposure	0.79	0.87	0.24
Adjusted RR (95% CI)[3]	3.46 (1.08 to 11.06)	4.01 (1.24 to 13.00)	Reference
Other malignancies (exc. NMSC)			
- n (%) of patients treated	14 (2.0)	10 (1.8)	6 (0.67)
- per 100 patient-years of adalimumab exposure	1.0	0.87	0.36
Adjusted RR (95% CI)[3]	2.82 (1.07 to 7.44)	2.61 (0.93 to 7.31)	Reference

Source of funding	AbbVie funded the studies and was responsible for the study design, research analysis, data collection and review and approval of the publication.
Comments	**Risk of bias**: observational study (patients not randomised to concomitant immunosuppressants). Those on immunosuppressant medication at study initiation may have had more severe disease. Analyses adjusted for a number of potential confounders (including age, sex, race, weight, smoking status, disease duration, baseline CDAI, baseline corticosteroid use, prior use of anti-TNF alpha medication). Prior exposure to immunosuppressants (including among monotherapy patients) was not controlled for. **Indirectness**: Included trials of adalimumab for both induction and maintenance of remission in patients with Crohn's disease, therefore not all patients meet the review protocol inclusion criteria for active Crohn's disease. **Other**: - analyses could not be verified with reference to original published trials suggesting unpublished data were obtained from trial investigators.

[1] *Treatment-emergent malignancy - defined as a malignancy occurring during adalimumab therapy and up to 70 days after the last dose of adalimumab.*
[2] *'Combined adalimumab + thiopurine therapy' was reported separately to 'Combined adalimumab + any IS therapy' because the former is the most frequently used treatment combination.*
Relative risk (RR) calculated using Poisson regression with follow-up time censored at the time of the first neoplastic event, as reported by investigator.

Bibliographic reference	**Osterman M, Haynes K, Delzell E, et al. (2015). Effectiveness and safety of immunomodulators with anti-tumor necrosis factor therapy in Crohn's disease. Clinical gastroenterology and Hepatology 13: 1293-1301.**
Study type	Retrospective cohort study.
Aim	To assess the effectiveness and safety of immunosuppressants[1] when combined with anti-TNF therapy, compared with anti-TNF monotherapy, in patients with Crohn's disease.
Patient characteristics	Study period for identifying eligible patients: February 2007 to December 2010. New users of anti-TNF therapy (infliximab or adalimumab) for the treatment of Crohn's disease, identified from Medicare drug benefits. Inclusion: - newly initiated treatment with infliximab or adalimumab (defined as not receiving a prescription for any anti-TNF agent in previous 12 months) - at least 1 diagnostic code for Crohn's disease in the 12 months prior to starting anti-TNF therapy Exclusions: - patients hospitalised with IBD during the 8 weeks prior to date of index anti-TNF prescription - patients who experienced any serious or opportunistic infections that were the focus of the study in the 183 days prior to starting anti-TNF therapy - patients who were hospitalised (with CD as discharge diagnosis) or had CD-related surgery before the first 120 days after the start of anti-TNF therapy - patients who experienced any of the opportunistic or serious infections that were the focus of the study before the first 120 days after the start of anti-TNF therapy

	Infliximab		**Adalimumab**	
Patient characteristics	**Combination therapy (n=381)**	**Monotherapy (n=912)**	**Combination therapy (n=196)**	**Monotherapy (n=505)**
Age group (years) – n (%)				
20-39	67 (17.6)	170 (18.6)	59 (30.1)	149 (29.5)
40-59	115 (30.2)	280 (30.7)	85 (43.4)	219 (43.4)

Bibliographic reference	**Osterman M, Haynes K, Delzell E, et al. (2015). Effectiveness and safety of immunomodulators with anti-tumor necrosis factor therapy in Crohn's disease. Clinical gastroenterology and Hepatology 13: 1293-1301.**

60+	199 (52.2)	462 (50.7)	52 (26.5)	137 (27.1)
Male – n (%)	145 (38.1)	341 (37.4)	72 (36.7)	175 (34.7)
Caucasian ethnicity – n (%)	334 (87.7)	789 (86.5)	166 (84.7)	430 (85.1)
Oral steroids – n (%) - Started ≤ 28 days prior - Started ≥ 28 days prior - None within 90 days	 36 (9.4) 153 (40.2) 192 (50.4)	 83 (9.1) 358 (39.3) 471 (42.3)	 19 (9.7) 78 (39.8) 99 (50.5)	 48 (9.5) 190 (37.6) 267 (52.9)

Number of Patients	N=1,994 classified according to therapy regimen as follows: - patients treated with combined infliximab + IS therapy[1], N=381 - matched patients with infliximab monotherapy, N=912 - patients treated with combined adalimumab + IS therapy[1], N=196 - matched patients treated with adalimumab monotherapy, N=505
Intervention	Combined therapy with either infliximab or adalimumab + any immunosuppressant[1]
Comparison	Infliximab monotherapy or adalimumab monotherapy
Length of follow up	Median 1.4 to 1.7 years
Location	USA (nationwide)
Outcomes measures and effect size	**Infliximab analysis**

	Infliximab combination therapy	**Infliximab monotherapy**

Bibliographic reference	**Osterman M, Haynes K, Delzell E, et al. (2015). Effectiveness and safety of immunomodulators with anti-tumor necrosis factor therapy in Crohn's disease. Clinical gastroenterology and Hepatology 13: 1293-1301.**

Adverse events: serious infections[2]	**(per 100 patient-years)**	**(per 100 patient-years)**
Events - n per 100 patient-years	6.8	8.0
Adjusted HR (95% CI)	0.80 (0.48 to 1.34)	Reference

Adalimumab analysis

Adverse events: serious infections[2]	**Adalimumab combination therapy (per 100 patient-years)**	**Adalimumab monotherapy (per 100 patient-years)**
Events - n per 100 patient-years	9.0	7.4
Adjusted HR (95% CI)	1.22 (0.57 to 2.30)	Reference

Source of funding	Supported with funding from grants from Agency for Healthcare Research and Quality and National Institute for Health.

Comments	**Risk of bias**: observational study. Data were analysed as 'time to event'. Potential covariates were controlled for as a single propensity score estimated from logistic regression modelling (covariates included: age, sex, ethnicity, comorbidities, surgery and medication indices of severity of CD). Duration of disease and smoking status were not included as covariates due to unreliability of data. **Indirectness**: majority of infliximab and adalimumab combination therapy users (86% and 89% respectively) had received prior immunosuppressants, indicating a 'stepping-up' of therapy. However, analyses of serious infection were limited to incidence >120 days after start of anti-TNF alpha therapy, so it is likely that a proportion of patients did not meet the review protocol criteria for active Crohn's disease. **Other**: - Approximately 50% of patients were treated with oral steroids in the 90 days prior to start of anti-TNF therapy. - Analyses were adjusted for oral steroid use in a time-updating manner.

[1] *Thiopurines (azathioprine / 6-mercaptuopurine) constituted 92% and 89% of the immunosuppressant use among combined infliximab and combined adalimumab therapy cohorts respectively.*

[2] *Because the cohort was relatively old, primary analyses were all tested for an interaction by age (<65 years or ≥65 years). No evidence of an interaction was found for any outcomes.*

[3] *Serious infections= hospitalised bacterial infections identified using ICD codes on principal discharge diagnosis.*

Appendix H: GRADE profiles

H.1 Combined infliximab + azathioprine versus infliximab monotherapy

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome: Remission (CDAI<150): early (6 weeks) – Figure 1											
1[1]	RCT	No serious	Serious[2]	n/a	Serious[3]	No serious	88/169 (52.1%)	83/169 (49.1%)	RR 1.06 (0.86 to 1.31)	29 more per 1000 (from 69 fewer to 152 more)	LOW
Outcome: Remission (CDAI<150): middle (10 weeks) - Figure 2											
1[1]	RCT	No serious	Serious[2]	n/a	Serious[3]	No serious	101/169 (59.8%)	80/169 (47.3%)	RR 1.26 (1.03 to 1.54)	123 more per 1000 (from 14 more to 255 more)	LOW
Outcome: Remission (CDAI<150): late (18 weeks) - Figure 3											
1[1]	RCT	No serious	Serious[2]	n/a	Serious[3]	No serious	102/169 (60.4%)	84/169 (49.7%)	RR 1.21 (1.00 to 1.48)	104 more per 1000 (from 0 more to 239 more)	LOW
Outcome: Mucosal healing (26 weeks) - Figure 4											
1[1]	RCT	No	Serious[2]	n/a	Serious[3]	No serious	47/107	28/93	RR 1.46 (1.00 to	138 more per 1000	LOW

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
		Serious					(43.9%)	(30.1%)	2.13)	(from 0 more to 340 more)	
Outcome: Quality of life: measured with IBDQ (change from baseline score) - middle (week 10) (Better indicated by higher values) - Figure 5											
1[1]	RCT	No serious	Serious[2]	n/a	No serious	No serious	169	169	-	MD 4.6 higher (2.9 lower to 12.1 higher)	MOD
Outcome: Corticosteroid-free remission (CDAI<150): 26 weeks - Figure 6											
1[1]	RCT	No serious	Serious[2]	n/a	Serious[3]	No serious	96/169 (56.8%)	75/169 (44.4%)	RR 1.28 (1.03 to 1.59)	124 more per 1000 (from 13 more to 262 more)	LOW
Outcome: Corticosteroid-free remission (CDAI<150): 50 weeks - Figure 7											
1[1]	RCT	No serious	Serious[2]	n/a	Serious[3]	No serious	78/169 (46.2%)	59/169 (34.9%)	RR 1.32 (1.02 to 1.72)	112 more per 1000 (from 7 more to 251 more)	LOW
Outcome: Any serious adverse events (to week 54) - Figure 8											
1[1]	RCT	No serious	Very serious[2,4]	n/a	Serious[5]	No serious	27/179 (15.1%)	39/163 (23.9%)	RR 0.63 (0.41 to 0.98)	89 fewer per 1000 (from 5 fewer to 141 fewer)	VERY LOW

[1] *Colombel (2010)*

[2] All study patients were naïve to immunosuppressant (and biologic) medication; does not meet stated objectives of the review "to provide guidance on the efficacy, safety and cost-effectiveness of combination therapy compared with infliximab/adalimumab alone, in cases where conventional prior therapy has failed to induce remission in people with active Crohn's disease"
[3] 95% CI crosses MID for clinically important difference in remission (RR 1.15)
[4] Unclear what particular events were classed as 'serious adverse events': may have included events other than those specified in the review protocol (namely, serious infections, lymphomas and other malignancies, and mortality).
[5] 95% CI crosses default MID for clinically important reduction in serious adverse events (RR 0.75)

H.2 Combined infliximab + methotrexate versus infliximab monotherapy

Quality assessment							No of patients		Effect estimate		
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	Quality
Outcome: Remission (CDAI<150): early (2 weeks) - Figure 14											
1[1]	RCT	Serious[2]	No serious	n/a	Very serious[3]	No serious	7/11 (63.6%)	2/8 (25%)	RR 2.55 (0.71 to 9.16)	387 more per 1000 (from 73 fewer to 1000 more)	VERY LOW
Outcome: Remission (CDAI<150): middle (12-14 weeks) - Figure 15											
2[4]	RCT	No serious	Serious[5]	No serious	Serious	No serious	57/74 (77%)	53/71 (74.6%)	RR 1.04 (0.86 to 1.25)	30 more per 1000 (from 105 fewer to 187 more)	LOW
Outcome: Remission (CDAI<150): late (24 weeks) - Figure 16											
1[1]	RCT	Serious[2]	No serious	n/a	Very serious[3]	No serious	6/11 (54.5%)	3/8 (37.5%)	RR 1.45 (0.51 to 4.13)	169 more per 1000 (from 184 fewer to 1000 more)	VERY LOW
Outcome: Quality of life: measured with multiple scales - middle (10-14 weeks) (Better indicated by higher values) - Figure 17											

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
2[4]	RCT	No serious	Serious[5]	Serious[6]	No serious	No serious	70	67	-	SMD 0.01 higher (0.32 lower to 0.35 higher)	LOW
Outcome: Rates of surgery (to week 50) - Figure 18											
1[7]	RCT	No serious	Serious[5]	n/a	Very serious[8]	No serious	3/63 (4.8%)	1/63 (1.6%)	RR 3.0 (0.32 to 28.07)	32 more per 1000 (from 11 fewer to 430 more)	VERY LOW
Outcome: Corticosteroid-free (at week 48) - Figure 19											
1[1]	RCT	Serious[2]	No serious	n/a	Very serious[8]	No serious	7/11 (63.6%)	2/8 (25%)	RR 2.55 (0.71 to 9.16)	387 more per 1000 (from 73 fewer to 1000 more)	VERY LOW
Outcome: Corticosteroid-free remission (at week 50) - Figure 20											
1[7]	RCT	No serious	Serious[5]	n/a	Very serious[8]	No serious	35/63 (55.6%)	36/63 (57.1%)	RR 0.97 (0.71 to 1.32)	17 fewer per 1000 (from 166 fewer to 183 more)	VERY LOW
Outcome: Any serious adverse events (to week 48) - Figure 21											
1[1]	RCT	Serious[2]	Serious[9]	n/a	Very serious[8]	No serious	0/11 (0%)	1/8 (12.5%)	RR 0.25 (0.01 to 5.45)	94 fewer per 1000 (from 124 fewer to 556	VERY LOW

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
										more)	

[1] *Schroder (2006)*
[2] *Open-label study*
[3] *95% CI crosses both MIDs for clinically important difference in remission (RR 0.85 and 1.15)*
[4] *Schroder (2006), Feagan (2014)*
[5] *Approximately 30% of study participants in Feagan (2014) did not have active Crohn's disease at baseline (CDAI≤150)*
[6] *I^2 = 62% indicating significant heterogeneity*
[7] *Feagan (2014)*
[8] *95% CI crosses both default MIDs for clinically important difference (RR 0.75 and RR 1.25)*
[9] *Unclear what particular events were classed as 'serious adverse events': may have included events other than those specified in the review protocol (namely, serious infections, lymphomas and other malignancies, and mortality).*

H.3 Combined versus monotherapy: Specified serious adverse events (no forest plots)

Quality assessment							No of patients		Effect estimate	Quality
Study	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative Risk /Odds Ratio /Hazard Ratio (95% CI)	
Outcome: Serious infections										
Infliximab studies										
Colombel (2010)	RCT	No serious	Serious[1]	n/a	Very serious[2]	No serious	7/163 (4.3%) [AZA]	8/179 (4.5%)	RR 0.96 (0.36 to 2.59)	VERY LOW
Hamazaoglu (2010)	Observational	Serious[3]	Serious[4]	n/a	Serious[5]	No serious	3/61 (4.9%) [AZA/MP]	0/160 (0%)	RR 18.18 (0.95 to 346.84)	VERY LOW
Jones (2015)	Observational	Serious[6]	Serious[7]	Not reported	Very serious[2]	Serious[8]	152 [Any IS]	302	OR 0.56 (0.15 to 2.09)	VERY LOW
Osterm	Obser	No	Serious[9]	n/a	Very	No serious	381	912	HR 0.80 (0.48 to	VERY

Quality assessment							No of patients		Effect estimate	
Study	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative Risk /Odds Ratio /Hazard Ratio (95% CI)	Quality
an (2015)	vational	serious			serious[2]		[Any IS]		1.34)	LOW
Adalimumab studies										
Jones (2015)	Observational	Serious[6]	Serious[7]	n/a	Very serious[2]	Serious[8]	260 [Any IS]	341	OR 1.18 (0.30 to 4.60)	VERY LOW
Osterman (2015)	Observational	No serious	Serious[9]	n/a	Very serious[2]	No serious	196 [Any IS]	505	HR 1.22 (0.57 to 2.30)	VERY LOW
Unspecified TNF-alpha inhibitor studies										
Marehbian (2009)	Observational	Serious[10]	Serious[4]	n/a	Very serious[11]	No serious	n/k [Any IS]	n/k	T=14.2 per 100 person years C=16.4 per 100 person years	VERY LOW
Outcome: Malignancies										
Infliximab studies										
Hamazaoglu (2010)	Observational	Serious[3]	Serious[4]	n/a	Very Serious[2]	No serious	2/61 (3.3%) [AZA/MP]	2/160 (1.3%)	RR 2.62 (0.38 to 18.21)	VERY LOW
Jones (2015)	Observational	Serious[6]	Serious[7]	Not reported	Very serious[2]	Serious[8]	152 [IS-not specified]	302	OR 8.6 (0.34 to 214.38)	VERY LOW
Lichtenstein (2014)	Observational	Serious[12]	Serious[4]	n/a	Very serious[2]	No serious	119/3,517 (3.4%) [IS – not specified]	5/247 (2.0%)	RR 1.67 (0.69 to 4.05)	VERY LOW
Adalimumab studies										
Osterman (2014)	Observational	Serious[13]	Serious[7]	Not reported	(i) Serious[5] (ii) Serious[5]	Serious[8]	(i) 11/694 (1.6%) [Any IS] (ii) 10/563	4/900 (0.44%)	Non-melanoma skin cancer (i) RR 3.46 (1.08 to 11.06)	VERY LOW

Quality assessment							No of patients		Effect estimate	
Study	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative Risk /Odds Ratio /Hazard Ratio (95% CI)	Quality
							(1.8%) [AZA/MP]		(ii) RR 4.01 (1.24 to 13.00)	
Osterman (2014)	Observational	Serious[13]	Serious[7]	Not reported	(i) Serious[5] (ii) Serious[5]	Serious[8]	(i) 14/694 (2.0%) [Any IS] (ii) 10/563 (1.8%) [AZA/MP]	6/900 (0.67%)	Other malignancies (i) RR 2.82 (1.07 to 7.44) (ii) 2.61 (0.93 to 7.31)	VERY LOW
Unspecified TNF-alpha inhibitor studies										
Marehbian (2009)	Observational	Serious[10]	Serious[4]	n/a	Very serious[11]	No serious	n/k [IS – not specified]	n/k	Lymphoma T=0.62 per 100 person years C=0.69 per 100 person years	VERY LOW
Marehbian (2009)	Observational	Serious[10]	Serious[4]	n/a	Very serious[11]	No serious	n/k [IS – not specified]	n/k	Solid tumours T=12.35 per 100 person years C=0.69 per 100 person years	VERY LOW
Outcome: Mortality										
Infliximab studies										
Hamazaoglu (2010)	Observational	Serious[3]	Serious[4]	n/a	Very serious[2]	No serious	1/61 (1.6%) [AZA/MP]	0/160 (0%)	RR 7.79 (0.32 to 188.68)	VERY LOW
Jones (2015)	Observation	Serious[6]	Serious[7]	Not reported	Very serious[2]	Serious[8]	152 [IS – not	302	OR 0.93 (0.04 to 23.22)	VERY LOW

Quality assessment							No of patients		Effect estimate	
Study	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative Risk /Odds Ratio /Hazard Ratio (95% CI)	Quality
	al						specified]			
Kinney (2003)	Observational	Serious [3]	Serious[14]	n/a	Very serious[2]	No serious	0/81 (0%) [IS – not specified]	1/23 (2.8%)	RR 0.10 (0.00 to 2.32)	VERY LOW

Acronyms: AZA - azathioprine; MP - mercaptopurine; IS - immunosuppressant (any of azathioprine, mercaptopurine, methotrexate); TNF-alpha inhibitor - tumour necrosis factor-alpha inhibitor medication (infliximab or adalimumab)

[1] All study patients were naïve to immunosuppressant (and TNF-alpha inhibitor) medication; does not meet stated objectives of the review "to provide guidance on the efficacy, safety and cost-effectiveness of combination therapy compared with infliximab/adalimumab alone, in cases where conventional prior therapy has failed to induce remission in people with active Crohn's disease"
[2] 95% CI incorporates both default MIDs for clinical benefit and clinical harm (RR 0.75 and RR 1.25)
[3] Analyses do no to control for potential confounders such as prior exposure to immunosuppressants in the infliximab monotherapy group.
[4] Not clear if study population met review protocol criteria for active Crohn's disease for duration of study follow-up
[5] 95% CI incorporates default MID for clinical harm (RR 1.25)
[6] Patients taking immunosuppressant therapy at trial enrolment may have had more severe disease; prior exposure to immunosuppressants in the anti-TNF alpha monotherapy group not known; concomitant corticosteroid use not reported
[7] Not all patients had active Crohn's disease (pooled analysis of data from trials of anti-TNF alpha therapy for both induction and maintenance of remission)
[8] Analyses included patient-level data obtained directly from original trial investigators/sponsors, so results were unable to be verified with reference to original trial publications
[9] analyses limited to incidence of serious infections >120 days after start of anti-TNF alpha therapy, so it is likely that a proportion of patients did not meet the review protocol criteria for active Crohn's disease
[10] Differences in patient characteristics between treatment groups not reported; analyses do not control for disease duration or severity
[11] Group denominators not reported; effect estimate and 95% Cis cannot be determined
[12] Differences in patient characteristics between treatment groups not reported; not clear if analysis of malignancy incidence adjusted for potential confounding factors
[13] Patients taking immunosuppressant therapy at trial enrolment may have had more severe disease; prior exposure to immunosuppressants in the anti-TNF alpha monotherapy group not controlled for in analyses
[14] Not all study patients meet review protocol criteria for active Crohn's disease (26-36% of patients across treatment groups achieved remission during study period)

Appendix I: Forest plots

I.1 Combined infliximab + azathioprine versus infliximab monotherapy

Figure 1: Clinical remission (CDAI<150): early (6 weeks)

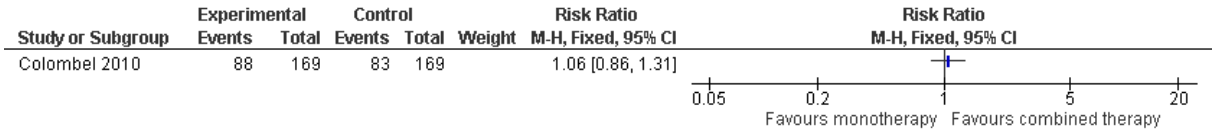


Figure 2: Clinical remission (CDAI<150): middle (10 weeks)

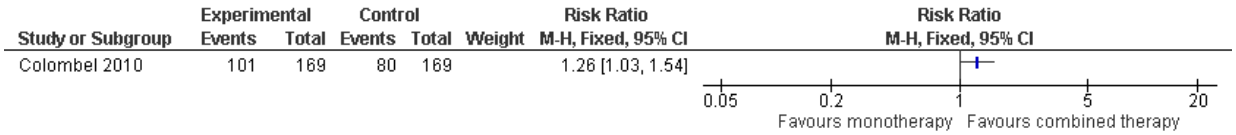


Figure 3: Clinical remission (CDAI<150): late (18 weeks)

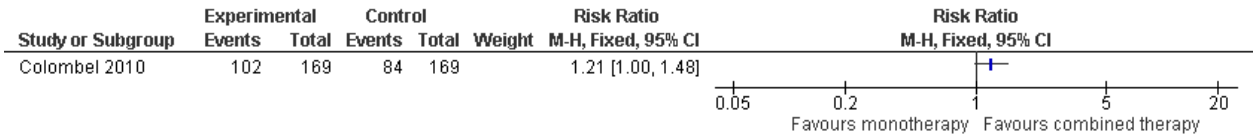


Figure 4: Remission: mucosal healing (26 weeks)

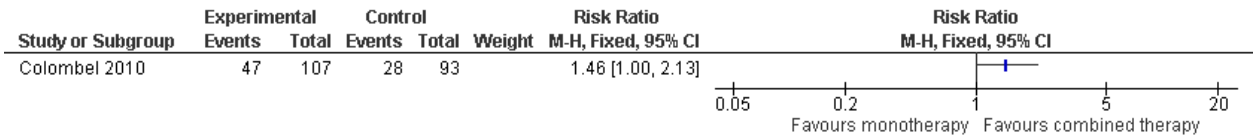


Figure 5: Quality of life: mean change from baseline IBDQ score: middle (10 weeks)

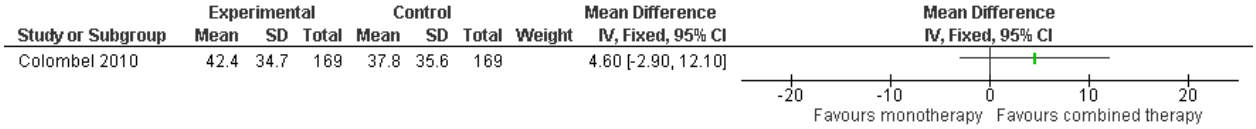


Figure 6: Corticosteroid-free clinical remission (26 weeks)

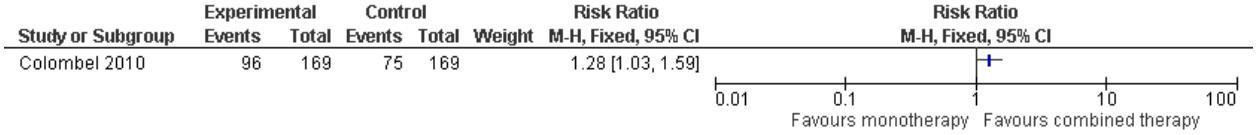


Figure 7: Corticosteroid-free clinical remission (50 weeks)

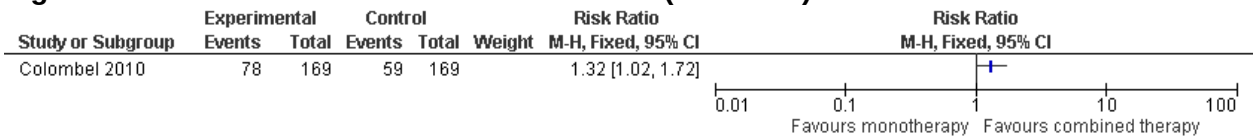
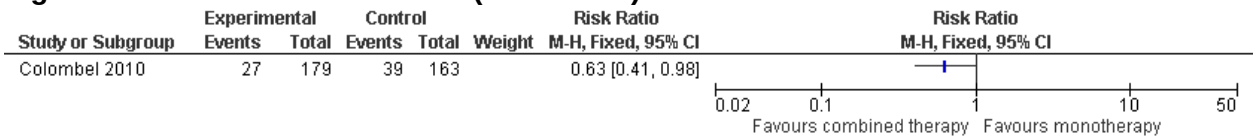


Figure 8: Serious adverse events (to week 54)



I.1.1 Subgroup analyses: patients in corticosteroid-free clinical remission at week 26

Figure 9: Males vs. females (p=0.27)

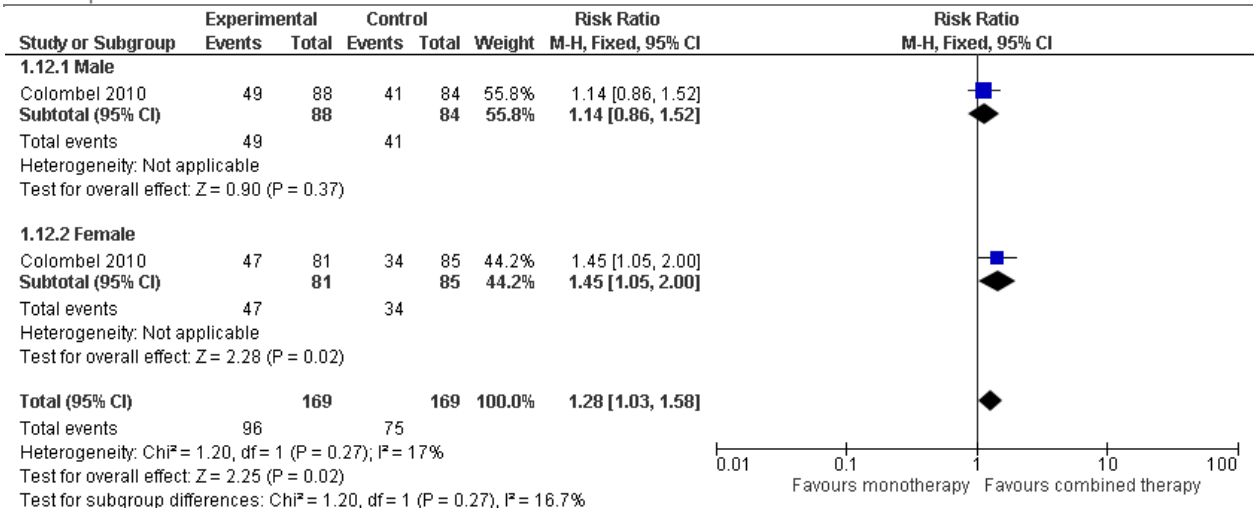


Figure 10: Adult age groups: 18-30 yrs / 30-50 yrs / over 50yrs (p=0.38)

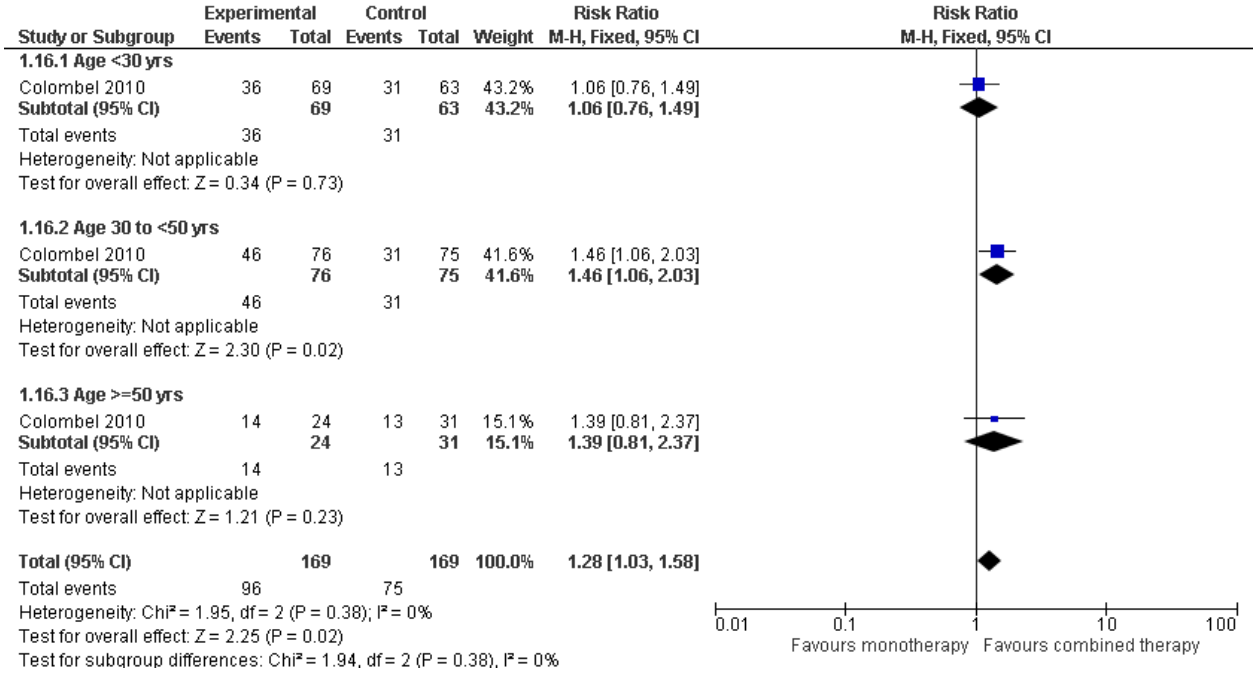
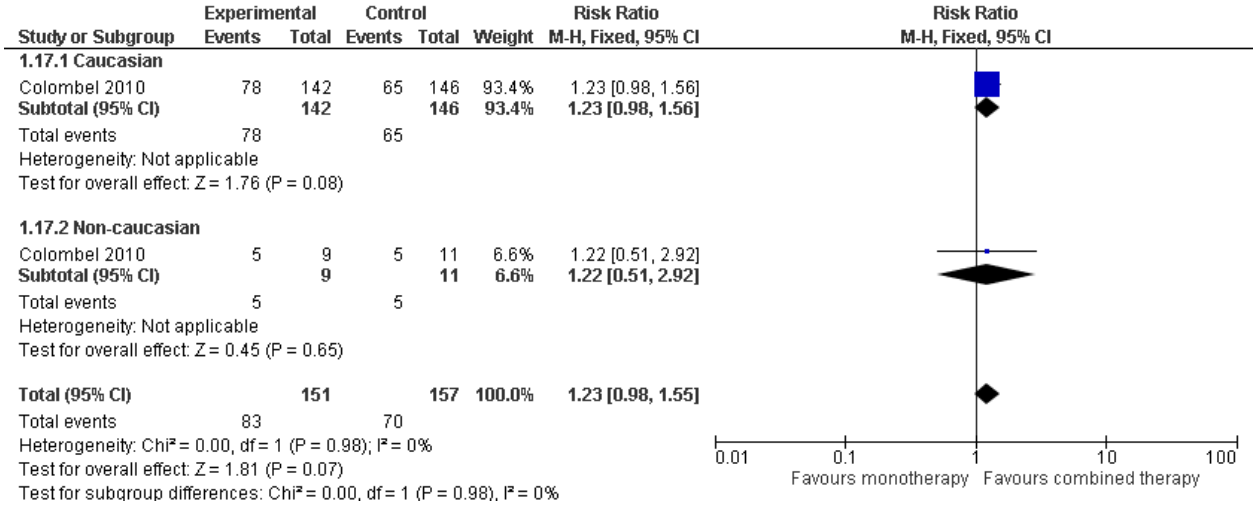


Figure 11: Ethnicity: Caucasian vs. non-Caucasian[1] (p=0.98)



1 Ethnicity was self-reported. Data were not collected for patients recruited to the study in France(18 in the combined AZA+infliximab group and 12 in the infliximab monotherapy group).

Figure 12: Disease severity: with previous Crohn's disease-related surgery vs. without previous surgery (p=0.36)

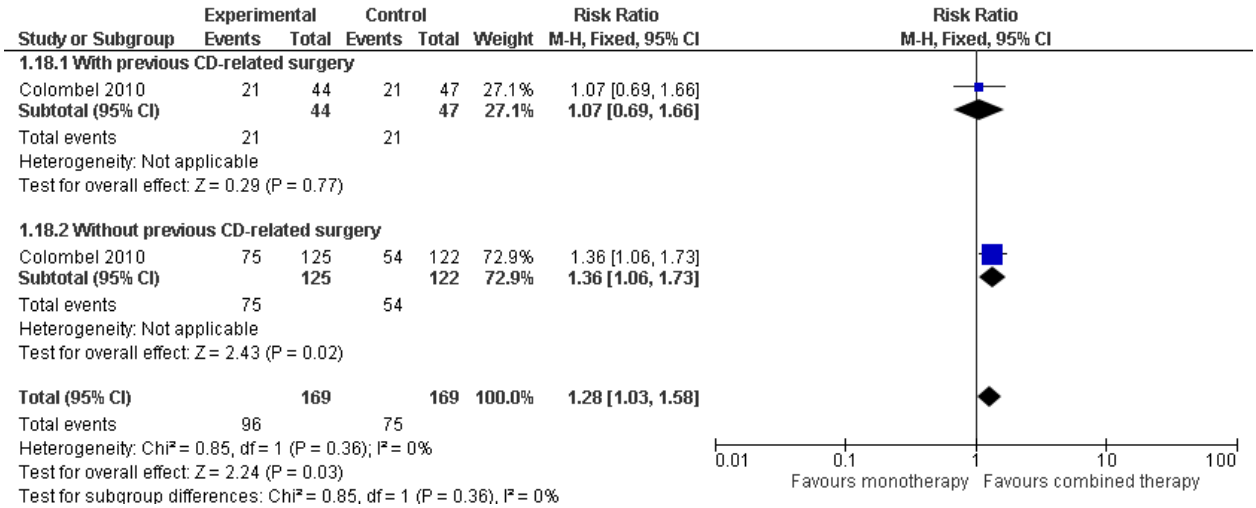
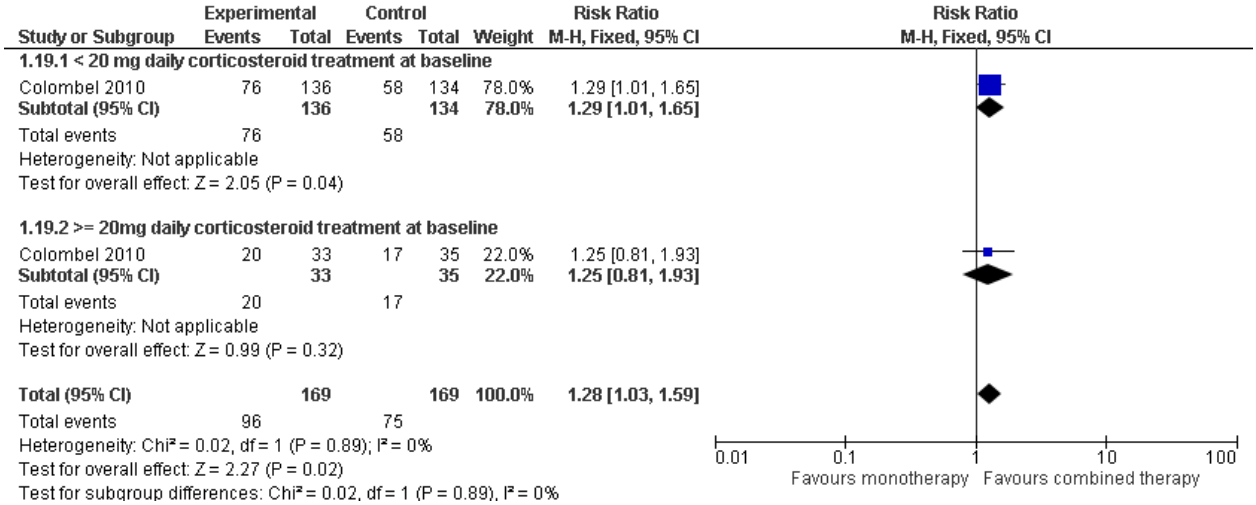


Figure 13: Baseline corticosteroid use[2] (p=0.89)



[2] *<20 mg daily includes patients not taking any corticosteroids at baseline.*

I.2 Combined infliximab + methotrexate versus infliximab monotherapy

Figure 14: Clinical remission (CDAI<150): early (2 weeks)

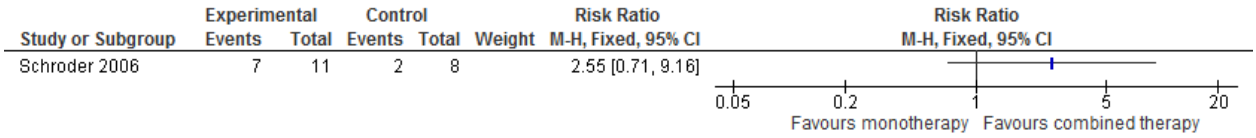


Figure 15: Clinical remission (CDAI<150): middle (12-14 weeks)

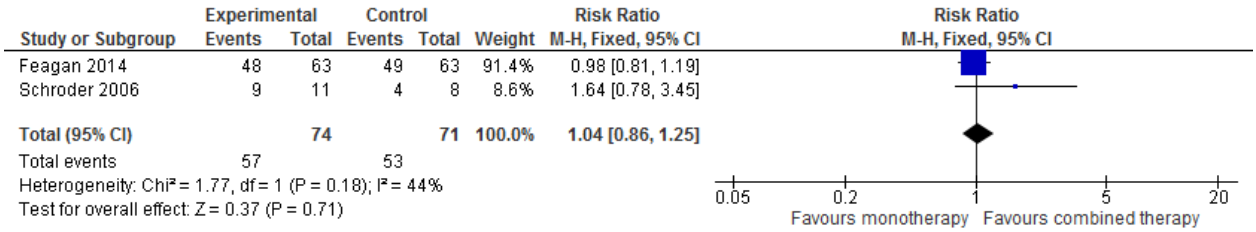


Figure 16: Clinical remission (CDAI<150): late (24 weeks)

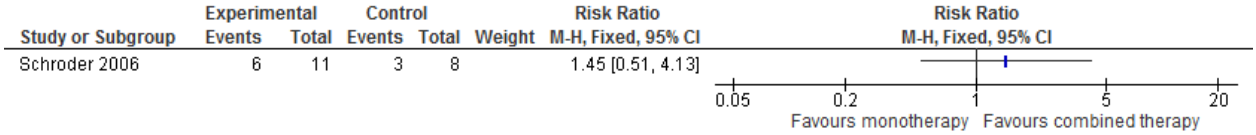


Figure 17: Quality of life (mean SF30 Physical Component Summary score, Feagan 2014; mean IBDQ score, Schroder 2006): middle (12-14 weeks)

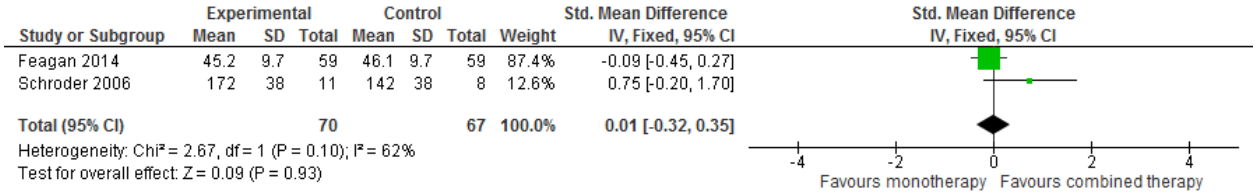


Figure 18: Rates of surgery (to week 50)

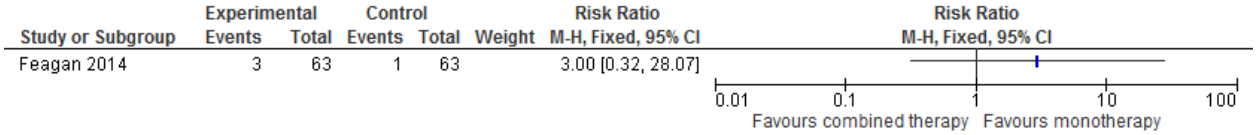


Figure 19: Corticosteroid-free (at 48 weeks)

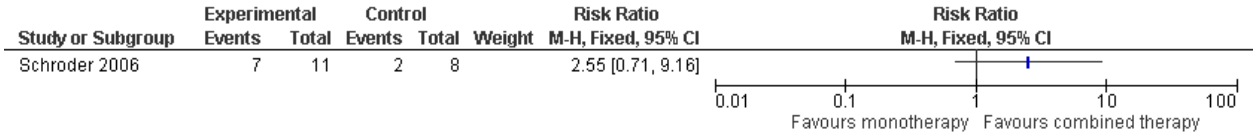


Figure 20: Corticosteroid-free remission (at 50 weeks)

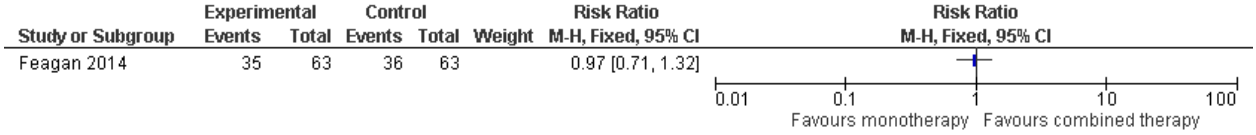
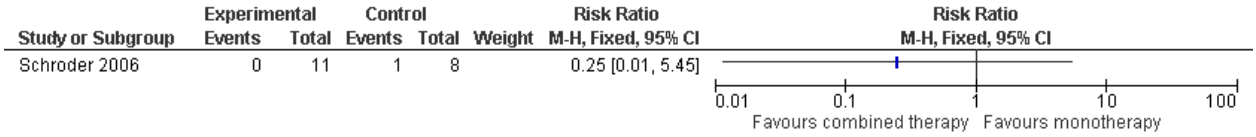


Figure 21: Any serious adverse events (through to week 48)



Appendix J: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in table 10. The search strategy is shown in table 11. The same strategy was translated for the other databases listed.

Table 10: Economic search summary

Database	Date searched	Version/files	Number retrieved
MEDLINE (Ovid)	08/10/2015	Ovid MEDLINE(R) 1946 to October Week 1 2015	142
MEDLINE in Process (Ovid)	08/10/2015	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 07, 2015	11
Embase (Ovid)	08/10/2015	Embase 1974 to 2015 Week 40	1,006
NHS Economic Evaluation Database (NHS EED) (legacy database)	08/10/2015	NHS Economic Evaluation Database : Issue 2 of 4, April 2015	2
Health Technology Assessment (HTA Database)	08/10/2015	Health Technology Assessment Database : Issue 3 of 4, July 2015	1

Table 11: Economic search strategy

Database: Medline
Strategy used: Database: Ovid MEDLINE(R) 1946 to October Week 1 2015 Search strategy: 1 Crohn Disease/ (32912) 2 ((crohn* or cleron) adj4 (disease* or syndrome* or colitis or enteritis)).tw. (32841) 3 ((regional* or terminal or granuloma*) adj4 (enteritis or enterocolitis or colitis or ileiti* or epithelioid)).tw. (3918) 4 ileocoli*.tw. (1653) 5 ((ileum or cecum*) adj4 (inflam* or irritat* or sore* or tender* or swell*)).tw. (398) 6 Inflammatory Bowel Diseases/ (15432) 7 (inflamm* adj1 bowel).tw. (29008) 8 or/1-7 (63237) 9 Immunosuppressive Agents/ (81649) 10 (immunosuppress* or immunodepress* or immunomodulator*).tw. (133888) 11 (immun* adj4 (suppressant* or suppressive*)).tw. (2467) 12 ((antirejection or anti-rejection) adj4 medic*).tw. (47) 13 Azathioprine/ (13797) 14 (azathioprine or azasan or imurel or imuran or Immuran).tw. (12680) 15 (arathioprin* or aza-q or azafalk or azahexal or azamedac or azamun* or azanin or azapin or azapress or azaprine).tw. (4) 16 (azarek or azarex or azathiodura or azathiopine or azathioprim or azathioprin or azathiopurine or azathropsin or azatioprina).tw. (222) 17 (azatox or azatrilem or azopi or azoran or azothioprin* or aseroprin or azafor or azafrine or azaimun or azadus).tw. (35) 18 (colinsan or berkaprine).tw. (0) 19 (immuthera or imunen or imuprin or imurane or imurek or imurel or imuren or imazan or imussuprex or immunoprin).tw. (57)

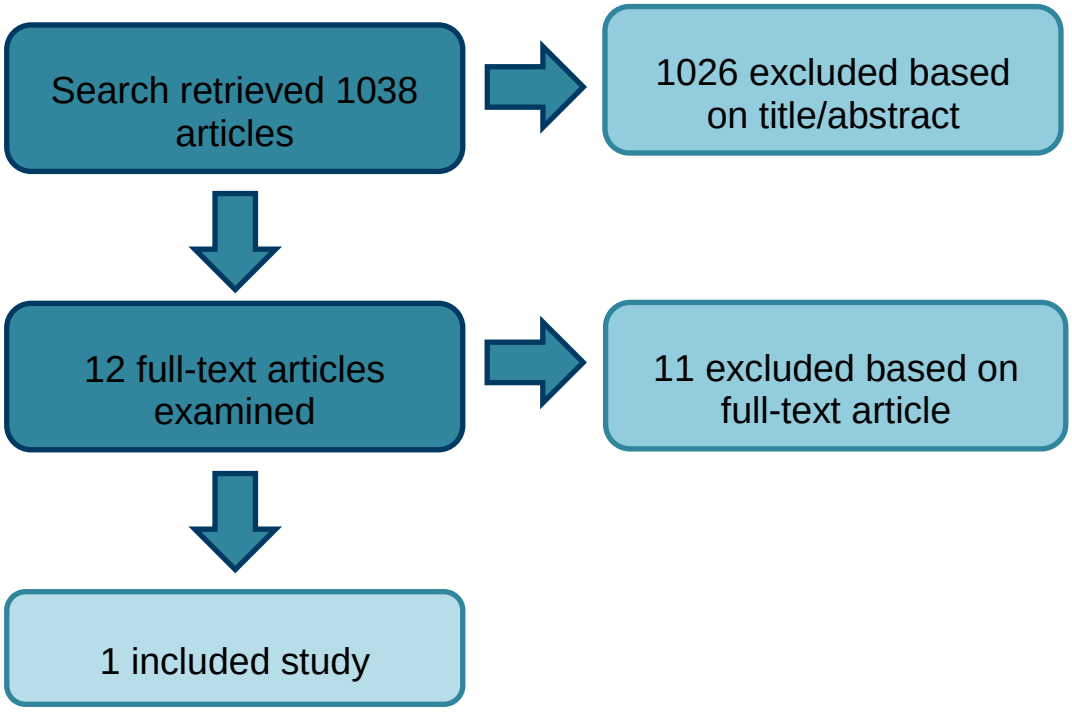
Database: Medline

20 (oprisine or thioazeprine or thioprine or transimune or zinothin or zytrim).tw. (4)
21 6-Mercaptopurine/ (5756)
22 (mercaptopurin* or purimethol or purinethol or puri nethol or leupurin*).tw. (3781)
23 (allmercap or capmerin or classen or empurine or flocofil or ismipur or leukerin or loulla).tw. (13)
24 (mercaleukin or mercap or mercaptina or mercapto or mercapurene or mern or merpurin or mycaptine).tw. (2263)
25 (puri-nethol or purinethiol or purinetone or purixan).tw. (12)
26 (thiohypoxanthine or thiopurine or varimer or xaluprine).tw. (1465)
27 Methotrexate/ (33574)
28 (methotrexat* or amethopterin* or mexate).tw. (31830)
29 (abitrexate or ametopterine or antifolan or biotrexate or canceren).tw. (2)
30 (ebetrex or emtexate or emthexat* or emtrexate or enthexate).tw. (2)
31 (farmitrexat* or farmotrex or folex).tw. (3)
32 (matrex or maxtrex or metex or methoblastin or methohexate or methotrate or methrotrexate or meticil or metoject or metothrexate or methylaminopterin* or meticil or metoject or metotrex* or metrex).tw. (264)
33 (ifamet or imeth or intradose MTX or lantarel or ledertrexate).tw. (1)
34 (neotrexate or novatrex or otrexup or rasuvo or reumatrex or rheumatrex).tw. (4)
35 (texate or texorate or trexall or xaken or zexate).tw. (2)
36 or/9-35 (235242)
37 Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors] (12299)
38 ((tumo?r necrosis factor alpha or TNF-alpha) adj4 (inhibitor* or antagonist*)).tw. (4536)
39 ((anti-TNF alpha or anti tumo?r necrosis factor alpha) adj4 agent*).tw. (539)
40 (infliximab or avakine or inflectra or remicade or remsima or revellex).tw. (7524)
41 (adalimumab or humira or exemptia or trudexa).tw. (3116)
42 or/37-41 (20882)
43 8 and 36 and 42 (1522)
44 Animals/ not Humans/ (4033465)
45 43 not 44 (1512)
46 limit 45 to english language (1344)
47 Economics/ (27199)
48 exp "Costs and Cost Analysis"/ (194377)
49 Economics, Dental/ (1887)
50 exp Economics, Hospital/ (20822)
51 exp Economics, Medical/ (13966)
52 Economics, Nursing/ (3955)
53 Economics, Pharmaceutical/ (2637)
54 Budgets/ (10205)
55 exp Models, Economic/ (11174)
56 Markov Chains/ (10978)
57 Monte Carlo Method/ (22012)
58 Decision Trees/ (9399)
59 econom$.tw. (169950)
60 cba.tw. (8989)
61 cea.tw. (17210)
62 cua.tw. (825)
63 markov$.tw. (12889)
64 (monte adj carlo).tw. (22718)
65 (decision adj3 (tree$ or analys$)).tw. (9170)
66 (cost or costs or costing$ or costly or costed).tw. (333573)
67 (price$ or pricing$).tw. (24919)

Database: Medline

68 budget$.tw. (18407)
69 expenditure$.tw. (37694)
70 (value adj3 (money or monetary)).tw. (1441)
71 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2976)
72 or/47-71 (704982)
73 "Quality of Life"/ (132361)
74 quality of life.tw. (153758)
75 "Value of Life"/ (5517)
76 Quality-Adjusted Life Years/ (8051)
77 quality adjusted life.tw. (6804)
78 (qaly$ or qald$ or qale$ or qtime$).tw. (5557)
79 disability adjusted life.tw. (1415)
80 daly$.tw. (1372)
81 Health Status Indicators/ (21128)
82 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16740)
83 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1057)
84 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3006)
85 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
86 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (342)
87 (euroqol or euro qol or eq5d or eq 5d).tw. (4519)
88 (qol or hql or hqol or hrqol).tw. (27689)
89 (hye or hyes).tw. (60)
90 health$ year$ equivalent$.tw. (38)
91 utilit$.tw. (123006)
92 (hui or hui1 or hui2 or hui3).tw. (929)
93 disutili$.tw. (242)
94 rosser.tw. (71)
95 quality of wellbeing.tw. (5)
96 quality of well-being.tw. (349)
97 qwb.tw. (179)
98 willingness to pay.tw. (2531)
99 standard gamble$.tw. (696)
100 time trade off.tw. (803)
101 time tradeoff.tw. (220)
102 tto.tw. (644)
103 or/73-102 (350481)
104 72 or 103 (1007707)
105 46 and 104 (142)

Appendix K: Economic review flowchart



Appendix L: Economic excluded studies

Reference	Reason for exclusion
Arseneau,K.O., Cohn,S.M., Cominelli,F., Connors,A.F.,Jr., Cost-utility of initial medical management for Crohn's disease perianal fistulae, Gastroenterology 2001 120 p.1640-1656	Not applicable: Incorrect population.
Bodger,K., Cost effectiveness of treatments for inflammatory bowel disease, PharmacoEconomics 2011 29 (5) p.387-401	Not applicable: Incorrect interventions examined (combination therapy defined as infliximab or adalimumab with immunosuppressants not included).
Bressler,B., Siegel,C.A, Beware of the swinging pendulum: Anti-tumor necrosis factor monotherapy vs combination therapy for inflammatory bowel disease, Gastroenterology.146 (4) (pp 884-887), 2014.Date of Publication: April 2014. 2014 p.884-887	Not applicable: No cost-effectiveness data included.
Cohen,R.D., Cominelli,F., Arseneau,K.O., Connors,Jr, Cost utility of initial medical management for Crohn's disease perianal fistula [3] (multiple letters), Gastroenterology.122 (4) (pp 1187-1190), 2002.Date of Publication: 2002. 2002 p.1187-1190	Not applicable: Incorrect population and study type (comment and critique on Arseneau 2001).
Doherty,G.A., Miksad,R.A., Cheifetz,A.S., Moss,A. C., Comparative cost-effectiveness of strategies to prevent postoperative clinical recurrence of Crohn's disease, Inflammatory Bowel Diseases 2012 18 p.1608-1616	Not applicable: Incorrect population and interventions examined (combination therapy not included).
Hanauer,S.B., Turning traditional treatment strategies on their heads: Current evidence for "step-up" versus "top-down", Rev Gastroenterol Disord 2007 7 p.S17-S22	Not applicable. No cost-effectiveness data included.
Jaisson-Hot,I., Flourie,B., Descos,L., Colin,C., Management for severe Crohn's disease: a lifetime cost-utility analysis, International Journal of Technology Assessment in Health Care 2004 20 p.274-279	Not applicable: Incorrect intervention (combination therapy not included).
Marchetti,M., Liberato,N.L., Di,Sabatino A., Corazza,G.R., Cost-effectiveness analysis of top-down versus step-up strategies in patients with newly diagnosed active luminal Crohn's disease, European Journal of Health Economics 2013 14 p.853-861	Not applicable: Incorrect intervention (TNF alpha inhibitor biologics (infliximab or adalimumab) monotherapy not included as a comparator to combination therapy) and population.
Kuznar,W., Writer,M., Step-up therapy program for anti-inflammatory biologic agents does not increase cost nor adversely affect patient outcomes, American Health and Drug Benefits.6 (3) , 2013.Date of Publication: 2013.	Not applicable: Incorrect interventions (combination therapy not included) and costing data (American costs used).
Ruffolo,C., Scarpa,M., Bassi,N., Infliximab, azathioprine, or combination therapy for Crohn's disease, New England Journal of Medicine 2010 363 p.1086-1087	Not applicable: No cost-effectiveness data included.

Reference	Reason for exclusion
Scott,F.I., Vajravelu,R.K., Bewtra,M., Mamtani,R., Lee,D., Goldberg,D.S., Lewis,J.D., The benefit-to-risk balance of combining infliximab with azathioprine varies with age: a markov model, Clinical Gastroenterology & Hepatology 2015 13 p.302-309	Not applicable: No cost-effectiveness data included.

Appendix M: Economic evidence table

These are the full evidence tables for included economic studies.

Table 12: Full economic evidence tables

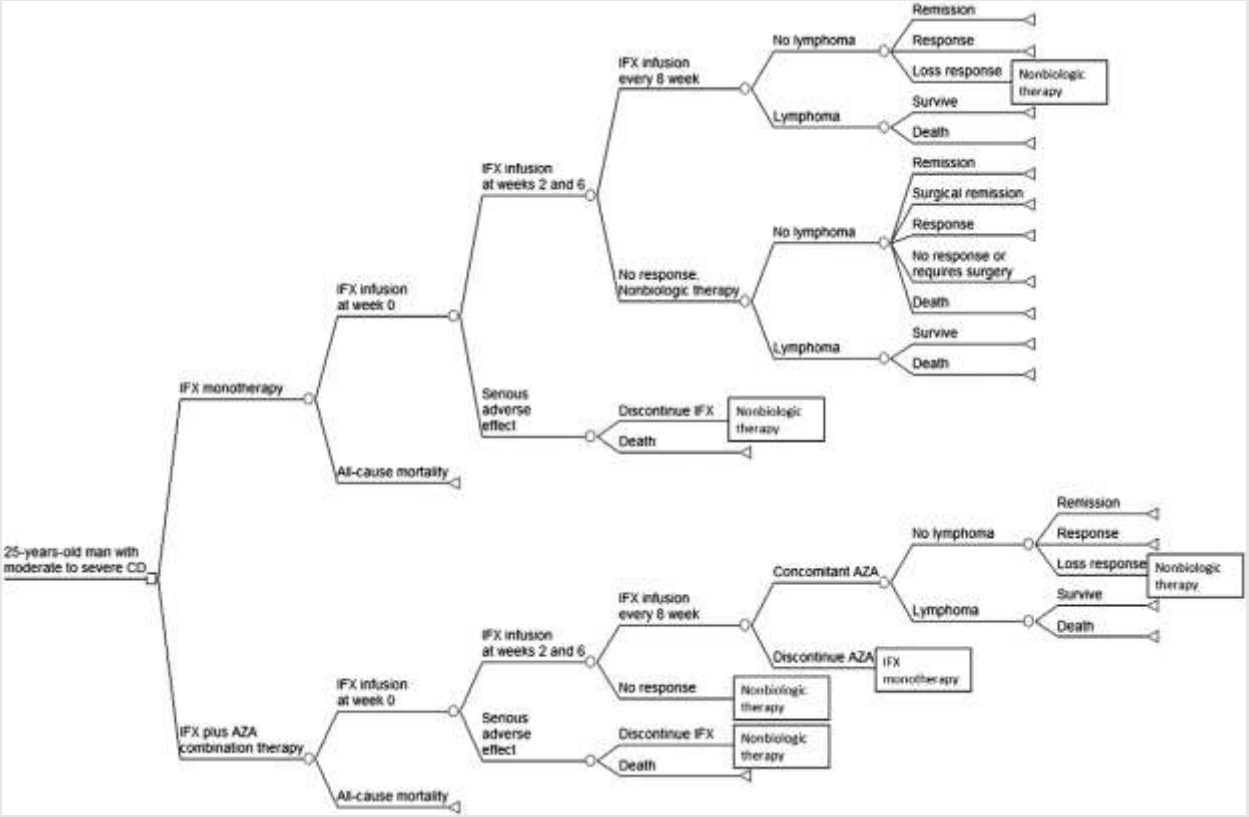
Bibliographic reference	**Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174**
Evaluation design	

Interventions	Intravenous infusion of infliximab (IFX) 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter
Comparators	Combination therapy, i.e. oral azathioprine (AZA) capsules at a dose of 2.5 mg/kg daily in addition to equivalent IFX therapy
Base-line cohort characteristics	A hypothetical cohort of 25-year-old men, weighing 60 kg, who were biologic-naïve CD patients refractory to conventional non-anti-TNF-α therapy and who had a score of 220 to 450 points on the Crohn's Disease Activity Index (CDAI)
Type of Analysis	Cost-utility analysis
Structure	Decision tree
Cycle length	Not applicable [not Markov]
Time horizon	1 year
Perspective	UK National Health Service
Country	United Kingdom
Currency unit	£
Cost year	Not specified
Discounting	Not applicable
Other comments	Key assumptions: • clinical response defined as a reduction from the baseline CDAI score of at least 70 points or 25% (whichever was the greater), and clinical remission defined as a CDAI score of less than 150 points; • if any serious adverse effects related to IFX occurred, then this occurrence was at initial infusion (i.e., at week 0); • patients who did not achieve clinical response at 12 weeks would not be offered retreatment with IFX;

Bibliographic reference	Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174

- nonresponders would have the same prognosis as those receiving nonbiologic therapy;
- nonbiologic therapy included treatment with 5-aminosalicylic acid, antibiotics, immunomodulators, corticosteroids, or surgery;
- in the combination therapy, AZA discontinuation could occur for patients who received IFX maintenance therapy.

The following figure shows the structure of the Crohn's Disease decision tree for the cost-utility analysis (IFX monotherapy vs. IFX plus AZA combination therapy). It has been sourced from the original article.



Bibliographic reference	**Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174**
	Software: TreeAge Pro 2009
Results	

Comparison	IFX vs. IFX plus AZA
Incremental cost	£1593.35
Incremental effects	0.064 QALYs
Incremental cost effectiveness ratio	£24,917 per QALY
Conclusion	Since the ICER is lower than the £30,000 per QALY limit, the combination therapy can be considered to be cost effective in comparison with infliximab monotherapy.

Data sources

Base-line data	An age of 25 years was chosen as the entry age since CD onset typically occurs in the late teens to age 30. No further explanation or justification for the assumptions adopted has been provided.
Effectiveness data	Effectiveness data were derived from published literature: ➢ clinical response rate at week 12 (sourced from a Hungarian nationwide multicenter report): - IFX monotherapy: 0.735 (0.609-0.861) - combination therapy with IFX plus AZA: 0.882 (0.846-0.918) ➢ maintenance remission rate (from the weighted means of randomized controlled trials, however since response rates were not reported, the response rate at 1 year for each therapy was assumed to be 1.35-fold of the remission rate reported by the ACCENT 1 trial): - IFX monotherapy: sustained remission at 1 year: 0.309 (0.234-0.384); sustained response at 1 year[a]: 0.487; loss of response: 0.513 - combination therapy with INF plus AZA: sustained remission at 1 year: 0.446 (0.358-0.535); sustained response at 1 year[a]: 0.705; loss of response: 0.295 ➢ adverse effect (determined according to meta-analyses and the most recent single-center safety profile data): - associated with IFX: discontinue IFX because of serious adverse effect: 0.111 (0.075-0.147); death due to serious adverse effect: 0.004 (0.000-0.010) - associated with AZA: discontinue AZA because of adverse effect: 0.089 (0.060-

Bibliographic reference	Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174	
		0.127); lymphoma risk: annual incidence of lymphoma per 100,000 in general population based on the most recent surveillance epidemiology and end results data: 27.1 (10.0-100.0); baseline risk of lymphoma for a patient with CD according to a recent meta-analysis: RR = 1.00; risk of lymphoma in CD patients treated with AZA according to a recent meta-analysis: RR=4.18 (2.07-7.51); death from lymphoma within 1st year: 0.297 ➢ nonbiologic therapy (from a previous analysis using a Markov model of European CD patients who did not receive biological therapy): remission: 0.068; post-surgery remission: 0.015; improvement to mild level of disease: 0.201; remain drug refractory: 0.711, death related to CD: 0.005 ➢ age-specific death rates per 100,00 (25-year-old man) estimated from data for England and Wales between 2001 and 2007: 71.8
	Cost data	Annual care cost (£) sourced from published literature: • IFX monotherapy: - drug cost of IFX: £10,742.24 (single infusion cost (5 mg/kg) = £1,342.78) - other costs except IFX: remission[b]: £1660.78; mild disease: 2214.37 (1304.27-3108.29) • combination therapy with IFX plus AZA: - drug cost of IFX: £10,742.24 - drug cost of AZA: £428.76 (AZA 1 month of maintenance treatment cost (2,5 mg/kg daily) = £35.73) - other costs except IFX and AZA: remission[b]: 1,660.78; mild disease: 2214.37 (1304.27-3108.29) • non-biologic therapy: - overall cost: 4965.20 • lymphoma treatment: - cost related to CD: 4965.20 - cost related to lymphoma[c]: 4908.43
	Utility data	Sourced from published literature (a standard gamble approach was used to define utility scores with CDAI). Since utility scores were not given for nonresponding active disease or lymphoma complicated by CD, a utility of 0.4 was assigned to the non-responding active state based on a consultation with a panel of UK gastroenterologists reported in published literature and it was assumed that the lymphoma state decreased utility scores by 0.15

Bibliographic reference	**Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174**	
		following published literature. Remission[d]: 0.89 (0.80-0.98) Post-surgery remission[d]: 0.86 (0.77-0.95) Mild disease[d]: 0.77 (0.69-0.85) Nonresponding active disease[e]: 0.40 (0.18-0.62) Lymphoma[f]: 0.25 (0.03-0.47) Death: 0
Uncertainty		
	One-way sensitivity analysis	One-way sensitivity analyses were conducted by adjusting parameters such as treatment efficacy, adverse effect rate, lymphoma risk, annual care cost, and quality of life utility scores. Results are presented in the table below:

Parameter	Base-case estimate	Sensitivity estimate	ICER (£/QALY)
IFX monotherapy			
Initial response rate	0.735	0.609	24,326
		0.861	25,907
Maintenance remission rate	0.309	0.234	24,203
		0.384	26,300
Combination therapy with IFX +AZA			
Initial response rate	0.882	0.846	25,113
		0.918	24,757
Maintenance	0.446	0.358	26,366

Bibliographic reference	Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174

remission rate		0.535	24,757
Percentage of responders (%)	135	120	24,009
		150	25,687
IFX serious adverse effect rate	0.111	0.075	24,197
		0.147	24,197
Mortality associated with IFX	0.004	0.000	24,197
		0.010	24,197
AZA adverse effect rate	0.089	0.060	24,944
		0.127	24,880
Annual incidence of lymphoma	27.1	10.0	24,854
		100.0	25,192
Lymphoma risk	RR = 4.18	2.07	24,849
		7.51	25,026
CD-related cost post-IFX	2214.37	1,304.27	22,769
		3,108.29	27,027
Percentage of costs in remission (%)	75	50	23,730
		100	26,105

Bibliographic reference	Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174

Lymphoma-related cost	4908.43	2454.21	24,901
		7362.65	24,934
Utility of remission	0.89	0.80	30,125
		0.98	21,200
Utility of post-surgery remission	0.86	0.77	24,820
		0.95	25,016
Utility of mild disease	0.77	0.69	25,255
		0.85	24,589
Utility of nonresponding active disease	0.40	0.18	17,147
		0.62	45,564
Decrement utility of lymphoma	0.15	0.00	24,893

Probabilistic sensitivity analysis	Probabilistic sensitivity analysis was performed using Monte Carlo simulations involving 10,000 samples. At an investment of £30,000 per QALY, 75.0% of the simulations showed that combination therapy was cost-effective. At an investment of £20,000 per QALY, only 13.0% (read off graph) of the simulations showed that combination therapy was cost-effective.

Bibliographic reference	**Saito,S., Shimizu,U., Nan,Z., Mandai,N., Yokoyama,J., Terajima,K., Akazawa,K., Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis, Journal of Crohn's & Colitis 2013 7 p.167-174**
Applicability	**Partially applicable** Population as defined in the study consists of immunomodulatory- and biologic-naïve patients with moderate to severely active CD who are refractory to conventional drug therapy. The NICE pathway currently recommends starting a biologic only in those patients with refractory CD that have not responded to prior therapy, including corticosteroids with or without additional immunosuppressants. This is in line with infliximab and adalimumab licensed indications. Effectiveness of biologic monotherapy as well as combination therapy with immunosuppressants may depend on patients' previous exposure and response to immunosuppressive therapy. The benefits of combination therapy may not extend to patients who are already known to be nonresponders to, for example, AZA. Costs data used are unlikely to accurately represent costs currently experienced in 2015. Furthermore, an annual cost of lymphoma complicated by CD was sourced from a study of illness cost in Germany, which may not be representative of relevant UK costs. All costs of lymphoma were converted into GBP using 2008 exchange rates reported by the Organization for Economic Co-operation and Development.
Limitations	**Very serious limitations** 1-year time horizon is not sufficiently long to reflect all important differences in costs and outcomes. In particular, the rate of lymphoma in the 1st year is likely to be low, but the main concern is around long-term risk of developing lymphoma or other malignancies in patients receiving combination therapy instead of biologics alone. Moreover, a number of IFX- and AZA-related adverse effects were not included. A cost-effectiveness threshold of £30,000 per QALY gained was used. **Conflicts** Nil. The study was funded by a grant from CISA (the platform for Clinical Information Statistical Analysis; NTT DATA Co., Tokyo, Japan.

Acronyms
AZA: azathioprine; CD: Crohn's Disease; CDAI: Crohn's Disease Activity Index; ICER: incremental cost-effectiveness ratio; IFX: infliximab; QALY: quality-adjusted life year; RR: relative risk
[a] *Responders include both patients in remission and patients who had a clinical response; response rate was assumed to be 1.35-fold (range = ±0.15) of the remission rate.*
[b] *Other costs for a patient in remission were assumed to be 0.75-fold (range = ±0.25) of the mild disease.*
[c] *Germany data (range= ±50%)*
[d] *Range was assumed to be ±10%.*
[e] *Expert opinion data (range = ±0.22)*
[f] *Decrement of 0.15 was assigned.*