Exploration of post-market evidence of effectiveness and safety of TNF-alpha inhibitors in Crohn's and colitis

Erika MacDonald

Thesis submitted to the

Faculty of Graduate and Postdoctoral Studies

in partial fulfillment of the requirements

for the Master's degree in Epidemiology

School of epidemiology, public health and preventive medicine

Faculty of Medicine

University of Ottawa

Table of Contents

List of Tables

List of Figures

Legend

IBD: Inflammatory bowel disease

TNF-α inhibitors: tumour-necrosis factor-alpha inhibitors

95% CI: 95% confidence interval

OR: odds ratio

RR: relative risk

RD: risk difference

RCT: randomized controlled trial

Abstract

The objectives of this thesis were to synthesize existing RCT evidence and post-market observational evidence of TNF-α inhibitors in inflammatory bowel disease. Two separate systematic reviews were performed: an overview of systematic reviews of RCTs, and a systematic review of post-market observational studies of TNF-α inhibitors in Crohn's disease and ulcerative colitis. The overview of systematic reviews included 37 studies. RCT evidence demonstrated superiority of all agents to placebo in Crohn's disease and ulcerative colitis, with no increased risk of malignancy or serious adverse events. Network meta-analyses have not shown superiority of any agent compared to another. The second systematic review included 255 studies. Included studies were deemed to be unamenable to pooling with substantial methodological and clinical diversity. Available evidence is insufficient to determine real-world effectiveness and safety, but points towards no increased risk of malignancy and no difference in efficacy between adalimumab and infliximab.

Executive Summary

Background: Use of TNF-α inhibitors in Crohn's disease and ulcerative colitis is increasing despite unknown long-term effectiveness and safety of these medications. The relative short duration and small sample size of pre-market clinical trials is not conducive to determination of the long-term effectiveness of medications and the risk of rare and long-term adverse events. Owing to a theoretical potential for increased risk of malignancy and the lifelong nature of inflammatory bowel disease, post-market research is particularly important for the TNF-α inhibitors.

Objectives: The objectives of this thesis were (1) to assess existing evidence on effectiveness and safety of TNF-α inhibitors in Crohn's disease and ulcerative colitis from previously published systematic reviews of RCTs, (2) To review available post-market evidence of effectiveness and safety of TNF-α inhibitors in Crohn's disease and ulcerative colitis, and (3) To propose a plan for post-market surveillance of TNF-α inhibitors in Crohn's disease and ulcerative colitis to address current gaps in knowledge.

Methods: Two separate systematic reviews were performed: an overview of pre-existing systematic reviews of RCTs of TNF-α inhibitors in IBD, and a systematic review of post-market observational studies. Two separate comprehensive literature searches were performed. Studies were screened for eligibility independently by two reviewers. Data was extracted into distiller SR systematic review software. Quality of studies was assessed using the AMSTAR quality assessment tool for systematic reviews and the applicable SIGN 50 methodology checklist for observational studies.

Results: Thirty-seven studies were included in the overview of systematic reviews: eleven systematic reviews of TNF-α inhibitors in ulcerative colitis, 18 in Crohn's disease, and seven in both. There was substantial overlap of included RCTs within the systematic reviews: 74% of ulcerative colitis RCTs and 49% of Crohn's Disease RCTs were included in more than one of the systematic reviews. All agents were more effective than placebo and no increased risk of malignancy was found. No single agent was found to be superior in indirect treatment comparisons. Two-hundred and fifty-five met eligibility criteria for the systematic review of observational studies. Of these, there were nine comparative cohort studies and seven case-control studies with some form of adjustment for confounding. All but two of these studies lacked rigorous control for confounding, and none were deemed to be of high quality. Two comparative cohort studies of acceptable quality

found no difference in efficacy or safety endpoints between infliximab and adalimumab, and another found no difference in risk of malignancy between users and non-users of TNF-α inhibitors. The only case-control study deemed to be of acceptable quality found a decreased risk of colorectal cancer with TNF-α inhibitors compared to non-use. Due to methodological and clinical diversity, the studies were deemed to be unamenable to pooling in meta-analysis.

Conclusions: Systematic reviews of RCTs have shown consistently that TNF-α inhibitors are more effective than placebo in Crohn's disease and ulcerative colitis. Post-market observational evidence points towards no increased risk of malignancy with TNF-α inhibitors and no difference in efficacy between adalimumab and infliximab, but is of insufficient quality and quantity to determine whether real-world effectiveness and safety is consistent with pre-market RCTs. Additional post-market observational studies with rigorous control for confounding, large sample sizes, and long duration of follow-up assessing outcomes of importance to patients could address this knowledge gap.

Acknowledgements

I would first like to express my sincere gratefulness for the opportunity to work with my supervisor, Dr. George Wells. He has shared with me what I'm sure is only a small glimpse of his immense knowledge, over several hours of meetings that hardly ever seemed rushed despite his intensely busy schedule. I would also like to thank my co-supervisor Dr. Lise M Bjerre for her very practical suggestions throughout the entire process and for her thought-provoking questions.

I'd like to recognize my thesis advisory committee member Dr. Rostom for his valuable input and support throughout this process.

I am fortunate to have worked with Shuching Hsieh, with her attention to detail as a second reviewer, as well as Becky Skidmore, with her similar level of attention to detail for the literature searches. I'd like to thank Tushar Shukla for his work screening articles, Nazmun Nahar for procuring a very large number of full texts, Anne Gray for always helping me find Dr. Wells when I need him, Shannon Kelly and the rest of Dr. Wells' research team at the University of Ottawa Heart Institute for letting me hang out in their office space and for answering my questions.

I'd like to thank my fellow classmates for many educational discussions and for inspiring me with their hard work and enthusiasm, and my friends for not dis-owning during these recent anti-social years.

My dad is deserving of recognition for "making me" go into Pharmacy which is a profession that I have come to know and love, and I'd like to thank my mom for not ever making me do anything work or school related.

And lastly but certainly not least importantly, I'd like to thank my husband Russ for his support throughout my pursuit of this degree and absolutely everything else, and my son Rigby for being an excellent sleeper from a very young age and super fun to have around.

Introduction

Rationale

Although tumour-necrosis factor-alpha (TNF-α) inhibitors are in widespread use for lifelong conditions, their long-term safety and efficacy are not known. The three TNF-α inhibitors currently indicated for the treatment of Crohn's disease and ulcerative colitis in Canada are infliximab (Remicade®), adalimumab (Humira®), and golimumab (Simponi®). Infliximab was first licensed in Canada for treatment of Crohn's disease in 2001, and adalimumab in 2010. Golimumab was licensed for use in ulcerative colitis in 2014.

There are several existing systematic reviews, meta-analyses, and network meta-analyses of short-term randomized controlled trials (RCTs) assessing efficacy and safety of TNF-α inhibitors in Crohn's disease and ulcerative colitis. Systematic reviews, meta-analyses and network meta-analyses of RCTs are at the top of the 'evidence hierarchy' and RCTs form the basis for market approval of medications. Despite this, evidence from RCTs have their own limitations including lack of external validity due to restrictive eligibility criteria, relatively short duration of treatment, and a small number of exposed individuals relative to the number of patients that will eventually receive the drug.(1, 2) All of this leads to an incomplete picture of the safety and effectiveness of medications at the time of market approval. A lack of long-term safety data is of particular concern in chronic diseases such as Crohn's disease and ulcerative colitis, where the need for medication is often life-long.

The potential increased risk of malignancy associated with TNF-α inhibitors is of particular concern to patients and clinicians. Because the relative short duration and small number of patients in clinical trials on which market authorization of TNF-α inhibitors for Crohn's disease and ulcerative colitis were based do not enable detection of rare and long-term adverse events, risk of malignancy will be the focus of this thesis.

Although observational study design is subject to increased risk of bias and confounding, such studies are a necessary supplement to pre-market RCTs which are inadequate for determination of safety and real-world effectiveness of medications. An in-depth exploration of the available observational post-market evidence may shed some much-needed light on the real-world and/or long-term effectiveness and safety of this relatively new class of medications, which have now been

in use for a much longer period of time than the studies on which their market authorization was based. This approach may also identify remaining knowledge gaps that should be addressed in future studies.

The current system of post-market surveillance of drugs in Canada relies heavily on passive reporting of adverse drug events by health professionals, patients, and manufacturers. It is well recognized that this is inadequate to ensure the safety of currently marketed pharmaceuticals.(3) Health Canada has identified the need to improve post-market surveillance of medications and is working towards this goal.(4, 5)

Objectives

The objectives of this thesis are:

(1) To assess existing evidence on effectiveness and safety of TNF-α inhibitors in Crohn's disease and ulcerative colitis from previously published systematic reviews of RCTs,

(2) To review available post-market evidence of effectiveness and safety of TNF-α inhibitors in Crohn's disease and ulcerative colitis, and

(3) To propose a plan for post-market surveillance of TNF-α inhibitors in Crohn's disease and ulcerative colitis to address current gaps in knowledge.

Description of upcoming chapters

Chapter 1 provides broad background information relevant to all of the chapters to come. This includes a description of the epidemiology and the personal and economic burden of the two forms of inflammatory bowel disease (Crohn's disease and ulcerative colitis), the general approach to treatment, the current role of TNF-α inhibitors in therapy, known adverse effects of TNF-α inhibitors, reasons for concern regarding the long-term risk of malignancy with TNF-α inhibitors, a description of the clinical efficacy endpoints used in the management of inflammatory bowel disease, limitations of pre-market RCTs, and post-market surveillance of medications in Canada.

Chapter 2 is an overview of systematic reviews of RCTs. A systematic review was performed to identify pre-existing systematic reviews, meta-analyses and network meta-analyses of TNF-α inhibitors in Crohn's disease and ulcerative colitis in order to assess the safety and efficacy of these agents. This Chapter contains relevant background information, methods, results and discussion.

Chapter 3 is a systematic review of post-market observational studies. The purpose of this chapter is to assess the real-world and long-term safety and effectiveness of TNF-α inhibitors using evidence from available observational studies. Results of post-market observational studies are compared with the results of RCTs. This chapter contains relevant background, methods, results and discussion.

Chapter 4 describes post-market surveillance strategies currently in use in other jurisdictions and provides recommendations for post-market surveillance of TNF-α inhibitors in Canada to address current knowledge gaps and improve the system of post-market surveillance in Canada.

Chapter 1: Background

Crohn's disease and ulcerative colitis, the two major forms of Inflammatory Bowel Disease (IBD), are chronic immune-mediated diseases with no known cure. IBD is more prevalent in Canada than any other country in the world.(6, 7) The estimated prevalence of IBD in Canada in 2012 was 0.67% of the total population; an estimated 129 000 Canadians were living with Crohn's disease, while 104 000 were living with ulcerative colitis.(7) A study using provincial health administrative databases in five Canadian provinces (Nova Scotia, Manitoba, Saskatchewan, Alberta and British Columbia) found that incidence rates vary widely between provinces, ranging from 8.8 per 100000 person years in British Columbia to 20.2 in Nova Scotia for Crohn's disease, and from 9.9 in British Columbia to 19.5 in Nova Scotia for ulcerative colitis. Although the reason for the West-East gradient remains unknown, it is hypothesized be due to an environmental causal factor in the development of IBD.(6)

The etiologies of both Crohn's disease and ulcerative colitis remain unknown, however the current thinking is that dysregulation of the host immune system causing inflammation and ulceration of the gastrointestinal tract results from intestinal bacteria or environmental stimuli. There also appears to be a genetic component. IBD has a peak in onset between 15-30 years of age.(8)

While ulcerative colitis is a mucosal disease involving the rectum and possibly part or all of the colon, Crohn's disease can affect any part of the gastrointestinal tract, "from mouth to anus"(8) and, unlike ulcerative colitis, does not typically involve the rectum. Also unlike ulcerative colitis, Crohn's is a transmural disease: one-third of patients suffer from perirectal fissures, abscesses, and anal stenosis.

For up to 15% of patients diagnosed with IBD a differentiation between Crohn's disease and ulcerative colitis cannot be made initially. In the great majority of cases of 'indeterminate colitis', a diagnosis of a specific form of IBD will eventually be made later on in the disease course.(8)

Symptoms of IBD can range from mild to extremely severe and disabling. The burden of disease can be very high for patients, with quality of life affected more negatively as severity of disease increases.(7) The "major symptoms of ulcerative colitis are diarrhea, rectal bleeding, tenesmus,[1] passage of mucus, and crampy abdominal pain."(8) Symptoms of Crohn's disease vary depending on

[1] The feeling that stool needs to be passed even though the bowels are empty

the disease location: nausea, vomiting and epigastric pain occur with upper gastrointenstinal tract involvement, “low-grade fevers, malaise, diarrhea, crampy abdominal pain and sometimes hematochezia”[2] typically occur with colonic disease, “incontinence, large hemorrhoidal tags, anal strictures, anorectal fistulae, and perirectal abscesses” are symptoms of perianal disease, “recurrent episodes of right lower quadrant pain and diarrhea” are typically associated with ileocolitis, and malabsorption and steatorrhea[3] are possible symptoms of jejunoileitis[4].(8)

Not only is the burden of disease high for patients, but it is also costly to the healthcare system. Total direct costs of IBD in Canada in 2012 were over $1.2 billion. Medications made up the largest component at over $0.5 billion, and hospitalizations were second at $395 million, together accounting for 76% of the total cost of IBD care in Canada.(7).

Both diseases can be categorized according to Montreal Classification.{Satsangi, 2006 #75} Crohn’s disease is categorized according to age at diagnosis, location of disease, and disease behaviour, and ulcerative colitis is categorized according to extent and severity of disease.

Malignancy in Inflammatory Bowel Disease

It has been long recognized that patients with inflammatory bowel disease are at an increased risk of colorectal cancer, although this is less well-studied in Crohn’s disease than in ulcerative colitis. An estimated 1 in 6 deaths in ulcerative colitis patients and 1 in 12 deaths in Crohn’s disease patients are attributed to malignancy.(9) Lifetime prevalence of colorectal cancer in the Canadian population overall is 6.3% in males and 7.2% in females.(10) Known risk factors of colorectal cancer in IBD include a younger age at diagnosis, family history of colorectal cancer, duration of disease, extent of anatomic involvement, persistent inflammation, and concurrent primary sclerosing cholangitis.(9, 11)

Inflammatory bowel disease patients may also be at increased risk of other cancers, such as lymphoma and leukemia, as compared to the general population.(8) However, many population-based studies have failed to show an association between lymphoma and IBD in itself, unlike rheumatoid arthritis, which is a known risk factor for lymphoma. There is evidence of an association of increased risk of lymphoma associated with the thiopurines (azathioprine and 6-mercaptopurine).(12) There is less evidence surrounding the association of methotrexate with

[2] Bright red blood in stool
[3] An excess of fat in the stool
[4] Inflammation of the jejunum and ileum of the small intestine

lymphoma, especially in IBD patients, but the risk appears to be lower.(12) An association between TNF-α inhibitors and lymphoma has been more difficult to quantify, and is a focus of this thesis.

Approach to treatment of Crohn's disease and ulcerative colitis

Prior to the availability of the biologics, pharmacologic options for treatment of the inflammatory bowel diseases included corticosteroids, aminosalicylates, and immunomodulators such as azathioprine and methotrexate.

Corticosteroids have not been shown to be effective for maintenance of remission in IBD, and their use is limited to short-term treatment of acute illness due to significant adverse effects inherent in long-term use.(13) Budesonide is a corticosteroid with extensive first pass metabolism and low systemic activity. Although it can be used for up to three months, it has not shown to be effective for maintenance of remission in IBD.(14, 15)

Aminosalicylates, including sulfasalazine, 5-aminosalicylic acid, and mesalazine, are available in multiple formulations including enemas, suppositories, tablets, and sustained release tablets, are first-line treatment for induction and maintenance of remission in ulcerative colitis, however their use is limited to mild to moderate disease.(13, 16) Efficacy of aminosalicylates in Crohn's disease for maintenance of remission is controversial, with conflicting results from available trials. Despite this, they are often used as first-line for mild to moderate disease involving the colon or distal ileum.(13, 17) These agents are ineffective for the systemic symptoms of Crohn's disease.(17) This class of drugs is generally well-tolerated, with the exception of sulfasalazine which is discontinued in up to 40% of patients due to adverse effects.(13)

Thiopurines (azathioprine and 6-mercaptopurine) have been shown to be effective maintenance therapy compared to placebo in both Crohn's disease and ulcerative colitis, however a slow onset of action limits their usefulness in active disease and many patients will eventually become refractory or experience intolerable adverse effects.(16, 17) Routine monitoring is required due to the risk of myelosuppression and hepatotoxicity.(13)

Methotrexate is an option for treatment of active Crohn's disease refractory to other treatments and its efficacy for maintenance of remission has been demonstrated in patients in whom remission was induced with this agent.(13, 17) Evidence of efficacy of methotrexate in ulcerative colitis is limited.(13, 16)

Evidence of benefit of calcineurin inhibitors, cyclosporine and tacrolimus, for induction therapy in active Crohn's disease is conflicting and limited.(17, 18) Cyclosporine is an option for induction of remission in severe ulcerative colitis based on two small placebo controlled trials,(16) however it is not approved for this indication. Many patients will eventually require surgery, which is not curative.(7, 19)

The anti-integrins, natalizumab and vedolizumab, are newer biologic agents emerging for treatment of IBD. Natalizumab is reserved for treatment of Crohn's disease in patients with nonresponse or intolerance to other therapies, owing to an unacceptably high risk of progressive multifocal leukoencephalopathy, which is a demyelinating brain disorder caused by an opportunistic viral infection.(13, 20) Vedolizumab is a promising new alternative to natalizumab for IBD refractory to treatment with TNF-α inhibitors. Its advantage over natalizumab is thought to relate to its selectivity for the gut and because of this selectivity it appears to not have the same increased risk of progressive multifocal leukoencephalopathy. It may be more effective in ulcerative colitis than in Crohn's disease.(21)

TNF-α inhibitors in Crohn's disease and ulcerative colitis

Infliximab, adalimumab, certolizumab and golimumab are monoclonal antibodies to human tumour necrosis factor (TNF), a cytokine whose proinflammatory effects play an important role in Crohn's disease and ulcerative colitis. These biologic response modifiers bind with high affinity to soluble and membrane-bound TNF, which in turn prevents TNF from binding to its receptors.(13, 22) Infliximab is administered intravenously, while adalimumab, certolizumab and golimumab are administered by subcutaneous injection.

Two TNF-α inhibitors are currently available in Canada for treatment of IBD: infliximab (Remicade®), adalimumab (Humira®), and golimumab (Simponi®). Infliximab, the first biologic agent for treatment of IBD, became available in Canada in 2001 for use in Crohn's disease, and ulcerative colitis in 2006.(23) Infliximab is approved for treatment of moderate to severe Crohn's disease and ulcerative colitis in patients refractory to conventional therapies, and in fistulising Crohn's disease. It is also indicated for rheumatoid arthritis.(24), Adalimumab became available for use in Canada in 2010 for Crohn's disease and was approved for ulcerative colitis in 2013. It is indicated for treatment of moderate to severe Crohn's refractory to conventional therapy, including for patients "who have lost response to or are intolerant of" infliximab, or for ulcerative colitis, with inadequate response or intolerance to conventional therapies. Adalimumab and infliximab are also both approved in

Canada for treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.(24, 25) Golimumab was approved for use in ulcerative colitis is Canada in 2014 for refractory moderate to severely active ulcerative colitis or in patients with contraindications to conventional therapy. It is also approved for the treatment of psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.{Janssen, 2014 #92} Certolizumab was approved for use in Crohn's disease by the Federal Drug Agency (FDA) in 2008,(26) but it is not currently approved for use in either form of IBD by the European Medicines Agency (EMA).(27)

The Canadian Gastroenterology Association guidelines for use of TNF-α inhibitors in Crohn's disease recommend initiation in patients refractory to conventional therapy (immunosuppressants and/or corticosteroids), those who have fistulizing disease, or in hospitalized patients in whom a fast onset of action is desirable.(28) Moderate to severe Crohn's disease is traditionally defined as a Crohn's Disease Activity Index (CDAI) between 220 and 400,(28) while a Mayo Clinic score of 6 or greater is indicative of Moderate to severe ulcerative colitis.(29)

The costs of treatment with TNF-α inhibitors are high relative to other available therapies at approximately $4000 per 8 week cycle for infliximab and $3000 for adalimumab.(30) North American economic analyses have found that they generally exceed traditional thresholds of cost-effectiveness.(31)A Canadian cost-utility analysis found an incremental cost-effectiveness ratio of $193,305 per quality adjusted life-year for adalimumab and $222,955 for infliximab over a 5-year time horizon as compared to usual care.(30) Despite this, their use has been increasing in recent years and they represent a large proportion of direct costs of IBD in Canada.(7)

Table 1.1 describes the four TNF-α inhibitors currently marketed for Crohn's disease and ulcerative colitis.

Table 1.1: Therapeutic doses of TNF-α inhibitors and countries with regulatory approval (as of April 3 2014)

TNF-α inhibitor, generic name (brand name)	Countries with regulatory approval for Crohn's or Colitis*	Induction dose	Maintenance dose	Additional Comments	Dosing Source
Infliximab (Remicade)	Canada, USA, EMA/UK,	Intravenously: 5mg/kg at 0, 2,	5mg/kg every 8 weeks	Consider increasing to	Canada

	France (13 August 1999),	and 6 weeks		10mg in some situations	
Adalimumab (Humira)	Canada, USA, EMA/UK, France (08 september 2003 for Crohn's, April 4 2012 for UC),	Subcutaneously: 160mg at week 0, 80mg at week 2	40mg every 2 weeks	"dose escalation may be considered" in patients experiencing flare (Crohn's)	Canada
Certolizumab (Cimzia)	USA (Crohn's), not Canada, not EMA/UK, not France (RA only)	Subcutaneously: 200mg at weeks 0, 2 and 4 (Crohn's)	400mg every 4 weeks (Crohn's)		USA
Golimumab (Simponi)	USA (ulcerative colitis), EMA/UK (ulcerative colitis), France (UC, Sept 29 2013), not Canada	Subcutaneously: 200mg at week 0, 100mg at week 2 (ulcerative colitis)	100mg every 2 weeks (ulcerative colitis)		USA

*Within EU, France, UK, Canada, US, or New Zealand. Medications approved under EMA's "centralised authorization procedure" will have regulatory approval in all EU countries plus Iceland, Liechtenstein and Norway. The TNF-α inhibitors are in this category.

Source: Remicade and Humira, Canadian Product Monographs, Drugs@FDA. US Food and Drug Administration Website. Accessed April 3 2014. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, European Public assessment reports, available from: European Medicines Agency. Human Medicines. 2014. Accessed April 3 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124, MedSafe (New Zealand Medicines and Medical Devices Safety Authority). Medicines Data Sheets. Accessed April 3 2014. http://www.medsafe.govt.nz/profs/datasheet/datasheet.htm#S

Adverse effects of TNF-α inhibitors

As with other immunosuppressant agents, an important risk of treatment with the TNF-α inhibitors is infection. TNF-α inhibitors are believed to increase the risk of serious infections including tuberculosis, candidiasis, listeriosis, legionellosis and pneumocystis.(13, 24, 25) Infusion-reactions, serum sickness-like reactions, hepatic failure, demyelinating disorders, congestive heart failure, psoriatic skin rashes, and hematologic reactions have also been observed. Antibody formation leading to attenuation or elimination of efficacy later on in therapy, or development of immune reactions to the medications are other possible adverse events and are likely of more concern in patients receiving episodic or interrupted treatment with these agents. These reactions are less likely to occur in patients receiving other concomitant immunosuppressants (i.e. azathioprine, methotrexate). The potential association of these agents with malignancy is also gaining attention; this is a focus of this thesis and is discussed in more detail below.(13)

In a questionnaire administered to 84 patientTs with IBD attending gastroenterology clinics at teaching hospitals, 83% reported, appropriately so, that they had no knowledge of the long-term safety of biologics. Lack of knowledge of long-term side effects of aminosalicylates, corticosteroids, and the thiopurines were reported at 50%, 43% and 64% respectively.(32)

TNF-α inhibitors and risk of malignancy

The name "tumour necrosis factor" originates from this cytokine's ability, recognized in 1975, to lyse tumours in vitro and in mice. It is therefore not surprising that there is evidence that TNF-α is active against cancer. This leads to the legitimate concern that inhibitors of TNF may increase risk of malignancy.(33)

It is difficult to quantify the potential relationship between TNF-α inhibitors and malignancy for many reasons, namely: (1) Patients with IBD already have an increased risk of malignancy due to their underlying disease (see above); and (2) other medications used to treat IBD such as methotrexate and the thiopurines (azathioprine and 6-mercaptopurine) have also been associated with increased risk of malignancy, and these agents are often used prior to treatment with TNF- α inhibitors, which makes it difficult to attribute malignancy to a specific therapy; and (3) clinical trials, which form the basis for licensing decisions, are of limited duration and exclude patients with prior malignancy.(33)

The latest Health Canada-issued alert concerning increased risk of malignancy with TNF- α inhibitors was issued in August 2009. This "safety update" communicated that Health Canada was working

with manufacturers of TNF-inhibitors agents (which include infliximab, adalimumab, etanercept, golimumab, and certoluzimab) to update labelling to highlight the increased risk of certain types of cancers in younger patients. The letter stated that: "The role of TNF blockers in the development of cancer is not known. Health Canada has communicated in the past on the risk of the development of certain types of cancers, including lymphoma, associated with the use of these drugs".(34)

In 2006 a "dear healthcare professional letter" warned of a possible association between infliximab and hepatosplenic T-cell lymphoma (HSTCL), a rare form of non-hodgkin's lymphoma, based on 6 case reports in children and young adults. It was noted in this letter that in all 6 of these cases, other immunosuppressants had also been administered, and that "a causal relationship between REMICADE® and the development of HSTCL has not been clearly established."(35)

This 2006 letter referenced a 2004 advisory informing Canadians of a revision to the product monograph stating that malignancies have been associated with TNF-α inhibitors including infliximab in clinical trials and post-market. It was noted that the rate of lymphoma was higher than that in the general population, but that patients with Crohn's disease may have a several-fold higher risk of lymphoma than those without the disease, even without TNF-α inhibitors. The advisory states that **"**the role of TNF-blockers in the development of malignancy is not known."(36)

In addition to similar advisories to Health Canada described above, in March 2013 the FDA released a MedWatch Safety alert describing labelling changes for Remicade: "Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including REMICADE… Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer."(37)

The Canadian product monographs of Humira and Remicade address the potential increased risk of malignancy. Excerpts from these product monographs are included in Table 1.2 below.

Table 1.2: Excerpts from Humira and Remicade product monograph sections relevant to risk of malignancy

Humira (adalimumab) (25)	**Remicade (infliximab) (24)**
<u>"Serious Warnings and Precautions</u> **Hepatosplenic T-Cell Lymphoma** Very rare post-marketing reports of	**<u>"Serious Warnings and Precautions</u>** **Hepatosplenic T-cell Lymphoma** Postmarketing cases of hepatosplenic T-cell

hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with HUMIRA® (adalimumab). Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for Crohn's disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA® should be carefully considered. The causal association of HSTCL with HUMIRA® is not clear. **Pediatric Malignancy** Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including HUMIRA®. See (WARNINGS AND PRECAUTIONS, Malignancies)." **"Warnings and Precautions: Malignancies** In the controlled portions of clinical trials of some TNF-blocking agents, including HUMIRA®, more cases of malignancies have been observed among patients receiving those TNF-blockers compared to control patients. In the controlled and uncontrolled open-label portions of clinical trials of HUMIRA®, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung, and melanoma. Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Patients with rheumatoid arthritis may be at a higher risk (up to 2-fold) than the general population for the development of leukemia, even in the absence of TNF-blocking therapy."	lymphoma have been reported in patients treated with TNF blockers including REMICADE®. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All REMICADE® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were reported in adolescent or young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to REMICADE® (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis). **Pediatric Malignancy** Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE® (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis)." **"Adverse Reactions: Malignancies/Lymphoproliferative Disease** In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients… Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE®, more cases of non-lymphoma malignancies have

	been observed in patients receiving those TNF-blockers compared with control patients…Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of non-lymphoma malignancies among REMICADE®-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. The potential role of TNF-blocking therapy in the development of malignancies is not known. Rates in clinical trials for REMICADE® cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE® treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE®."

Clinical efficacy endpoints in IBD

The Disease Activity Index (aka Mayo Score) is the most widely used scale for measuring efficacy of therapies for ulcerative colitis in clinical trials, however the definition of remission using this index can vary from trial to trial.(38) The Mayo Clinical Score incorporates clinical and endoscopic findings into a 12-point scale with 4 subscales pertaining to stool frequency, rectal bleeding, endoscopic findings, and physician global assessment. In Crohn's disease, almost all clinical trials use the Crohn's Disease Activity Index (CDAI) to measure disease activity.(39) This scale incorporates 8 clinical variables into a single numerical score.(40) Induction and maintenance of response and remission according to these scales have formed the basis for regulatory approval of medications for the treatment of IBD. A recent review suggests that assessments are best made at 4-6 weeks for induction trials if CDAI is only determined once, plus at 8 or 12 weeks if made twice to limit the bias due to placebo effect. The authors recommended assessments at 6-8 weeks for ulcerative colitis, but earlier (7-14 days) if patients are hospitalized with severe disease. Placebo effect according to the CDAI has been estimated to be 13-24% and 2-12% for the Mayo Score.(39)

Although corticosteroid withdrawal, corticosteroid-free remission and corticosteroid-free response are important clinically relevant endpoints, these have not been used in pre-market RCTs leading to

market authorization. Mucosal healing ("restitution of epithelial integrity") is a commonly considered efficacy endpoint used to assess therapies for ulcerative colitis and has been shown to improve prognosis. In Crohn's Disease it has only started to be used in clinical trials. However, mucosal healing as an endpoint also lacks standardization in both Crohn's disease and ulcerative colitis. The majority of trials in Crohn's disease have used "absence of ulcers" as the defining criteria, but validated indices for ileocolonoscopic assessment do exist. These include the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscropic Score for Crohn's Disease (SES-CD). It remains unclear which is the most appropriate definition of mucosal healing for use in ulcerative colitis trials. There is a subscore of the Mayo Clinic Score relevant to determination of mucosal healing, but this is subjective. Sigmoidoscopy has been considered sufficient but is limited as it does not allow visualization of the entire colon.(39)

Maintenance trials typically assess maintenance of response (e.g. change in CDAI 70 or 100 at all time points) but some also assess maintenance of remission (CDAI <150 at all time points). Sustained or durable remission refers to achievement of remission (i.e. CDAI <150 or Mayo Clinical Score ≤2 with no subscore >1) at all follow-up points. It is important to note that in most maintenance trials, patients enter the maintenance trials only after an initial response to the agent being studied. These trials will therefore overestimate efficacy for the population in which the treatments were initiated, which would include the non-responders in the induction trials that did not continue into the maintenance trial.(39)

Although achievement of remission is the (short-term) clinical endpoint currently accepted by patients, clinicians and regulatory authorities, it has not been shown to prevent long-term complications associated with IBD or to alter the disease course. "Deep clinical remission" ("a composite of symptoms control and mucosal healing") is attainable in Crohn's disease and may be a more appropriate and clinically important endpoint, however the ideal outcome for assessment of efficacies of therapy in IBD remains to be determined.(41) Long-term studies assessing structural damage such as development of strictures, perforations and need for surgery would be ideal to determine the true clinical impact of therapies for IBD.(39)

Limitations of RCTs

Of all new medications approved for use in Canada, 4.2% will eventually be withdrawn from the market due to safety concerns.(42) Limitations of pre-market clinical trials in identifying important adverse reactions and drug interactions are part of this problem. Of the 34 biologic agents with 37

indications approved by the FDA between 2005 and 2012, pivotal efficacy trials leading to approval of these agents included a median of 217 patients in the intervention group (IQR 70-410), and were of a median duration of 24 weeks (IQR 18.0-49.6). The mean total safety population was 890 patients (IQR 288-1839).(43) This represents the total number of patients exposed in the RCTs leading to regulatory approval for any indication on which approval was based for biologic agents. This small number of patients and short duration is insufficient for detection of rare and of long-term adverse reactions that can take years to develop, such as malignancy. Another important limitation of RCTs relates to external validity: patients taking TNF-α inhibitors in the real world may differ from clinical trial participants in several respects; for example, use of concomitant medications, presence of other illnesses, level of follow-up, adherence to medications and other physician recommendations (such as attendance to follow-up appointments, dietary restrictions).

Post-market surveillance

Health Canada is responsible for regulatory approval of medications in Canada. They have identified a need to improve post-market surveillance of medications and are working towards this goal.(4) The current system of post-market surveillance relies mostly on passive methods of surveillance: adverse reaction reporting by health professionals, patients and manufacturers. Whereas adverse reaction reports are voluntarily submitted by health professionals and patients, drug manufacturers are required to report any adverse reactions they are aware of to Health Canada. This system is known to be inadequate. Only between 1 and 10% of all adverse reactions are reported, with some estimates much lower. Even in France, where adverse reaction reporting by health professionals is mandatory, their reporting rates are similar to other countries.(3)

A recent advance in the system of post-market surveillance of medications in Canada was the establishment of the Drug Safety and Effectiveness Network (DSEN). The objectives of DSEN are to "increase capacity to perform high quality research in the area of post-market surveillance of medications and to improve knowledge of safety and effectiveness of medications available to Canadians".(44) The creation of DSEN is an important step in improving post-market surveillance of pharmaceuticals in Canada. Because funding is obviously not unlimited and DSEN would not have the capacity to conduct research on all currently available medications, effective prioritization of research is key to optimizing safety of pharmaceuticals currently available to Canadians.

Other jurisdictions use a variety of active surveillance strategies. For example, the recently developed Sentinel system in the U.S. will facilitate signal detection, and the FDA has also recently

implemented a requirement for risk management plans to be submitted at the time of market authorization, as does the European Medicines Agency.(45)

A more active approach to post-market surveillance of TNF-α inhibitors in Canada may be warranted. Their potential for long-term use, high up-front costs, and potential association with increased risk of cancer makes this class of medications particularly suited for an in depth assessment of the existing evidence of their safety and effectiveness.

Chapter 2: Overview of systematic reviews in Crohn's disease and ulcerative colitis

BACKGROUND

Randomized controlled trials are the 'gold standard' for evidence of efficacy and are generally required for market authorization of pharmaceuticals. Systematic reviews and meta-analyses provide a method of synthesizing available RCT evidence to facilitate incorporation of available evidence from multiple studies.

A newer method gaining increasing acceptance is that of network-meta analysis. In the absence of direct evidence comparing two interventions, a network meta-analysis allows a comparison of two interventions by comparing each one with a common comparator, thus enabling a so-called indirect comparison between two treatments. In the presence of both direct and indirect evidence, a network meta-analysis can increase precision of effect estimates and allows incorporation of more of the available evidence as compared to traditional pairwise meta-analyses.(46, 47) Network meta-analyses can use either a frequentist or a Bayesian approach. In a frequentist analysis, similar to most traditional pair-wise meta-analyses, results are presented as point estimates with 95% confidence intervals. Although the analysis itself is complex and not as well-understood by the users of the information, the results of a Bayesian network meta-analysis are arguably more easily interpretable. The probability of each intervention being best can be reported, which is of interest to decision-makers. The statistical model used for a Bayesian analysis combines a prior distribution with a likelihood distribution using the data of the included RCTs. The prior distributions are typically non-informative or 'vague'.(46)

Increasing acceptance and awareness of meta-analysis and network meta-analysis methods may have contributed to more frequent production of this type of research. Duplication in systematic reviews has been observed previously and occurs frequently.(48, 49) Prospero provides an avenue through which protocols of systematic reviews addressing health outcomes can be prospectively registered. This can prevent duplication, holds investigators accountable to their original planned research, and increases transparency.

A method for quantifying the amount of overlap between systematic reviews was recently developed. The authors suggested that overviews of systematic reviews should report overlaps and

that this could be done effectively by calculating a "corrected covered area" (CCA). The CCA is calculated by first creating a 'citation matrix', where one systematic review is represented in each column, and index primary publications are represented in each row. An 'X' is marked wherever a primary publication is included in a systematic review. The CCA, which is the proportion of actual to potential number of non-unique citations, is calculated using the following formula: (N-r) / (rc-r), where N is the total number of publications in all reviews, counting all occurrences (i.e. the numbers of 'x' in the citation matrix), r is the number of rows (number of index publications) and c is the number of columns (number of systematic reviews). Some limitations of this approach are that it does not account for "multiple publications" of an index primary publication, or that a single study could be included in several different reviews with no actual overlap of data extracted for analyses, if for instance each systematic review was interested in a different outcome within the same RCT. With a broader research question, the amount of overlap would be expected to decrease because different SRs could be looking at completely different interventions and different outcomes, and if systematic reviews included different publications types this could artificially decrease overlap because the calculation does not account for the weight given to each of the studies in the systematic reviews. The authors state that "The CCA is comprehensive and easy to understand. Nevertheless, more practical examples of the CCA are needed to verify our measure."(50)

Because of the large number of previously published systematic reviews, meta-analyses and network meta-analyses of RCTs focusing on the efficacy and safety of the TNF-α inhibitors in Crohn's disease and ulcerative colitis, a systematic review was performed to identify, critically appraise and summarize pre-existing systematic reviews of RCTs. Quality, recentness and directness of included systematic reviews was considered to best answer the clinical questions of efficacy and safety. Overlap of included RCTs within the systematic reviews and reasons for discrepancies in results were explored.**Research questions:**

1. In adult patients with Crohn's disease naïve to TNF-α inhibitors, what is the efficacy of the TNF-α inhibitors (adalimumab, infliximab, certolizumab, golimumab) compared to each other, to conventional therapy or to surgery, whether with or without concomitant immunosuppressants for (i) induction of response (ii) induction of remission (iii) maintenance of response (iv) maintenance of remission (v) mucosal healing (vi) hospitalization and (vii) surgery.

2. In adult patients with ulcerative colitis naïve to TNF-α inhibitors, what is the efficacy of the TNF-α inhibitors (adalimumab, infliximab, certolizumab, golimumab) compared to each other, to

conventional therapy or to surgery, whether with or without concomitant immunosuppressants for (i) induction of response (ii) induction of remission (iii) maintenance of response (iv) maintenance of remission (v) mucosal healing (vi) hospitalization and (vii) surgery

3. In adult patients with ulcerative colitis or Crohn's disease naïve to TNF-α inhibitors, what is the risk of (i) serious adverse events, (ii) discontinuation of treatment/withdrawals due to adverse events and (iii) malignancy with TNF-α inhibitors compared to conventional therapy or to surgery, whether with or without concomitant immunosuppressants?

METHODS

The study protocol for this overview of systematic reviews was registered in PROSPERO, registration number CRD42014009321.

Eligibility

Studies were assessed for eligibility based on the following criteria:

Population: Adults (18 years or older) naïve to previous TNF-α inhibitor therapy, diagnosed with (1) Crohn's disease, moderate to severe or (2) ulcerative colitis, moderate to severe. The population of interest for this overview was restricted to adults, because pediatric-onset disease is of greater extent and severity, and there other differential considerations affecting therapy and outcomes.(51) The population was restricted to TNF-α inhibitor naïve patients because efficacy and safety in TNF-α inhibitor experienced patients would be expected to differ, depending on the reason for stopping the first TNF-α inhibitor. Because many of the pivotal RCTs included both TNF-α inhibitor naïve and experienced patients and systematic reviews for the most part did not provide an overall percentage of included patients who were TNF-α inhibitor naïve, systematic reviews were eligible for inclusion as long as they did not restrict to TNF-α inhibitor experienced patients.

Intervention: TNF-α inhibitors (infliximab, adalimumab, golimumab, certolizumab) initiated within the approved therapeutic dose range, alone or in combination with immunosuppressants, for (1) Crohn's disease or (2) ulcerative colitis

Comparison: Placebo, traditional care, surgery, or a TNF-α inhibitor alone or in combination with immunosuppressants.

Outcome(s): Induction of remission, induction of response, maintenance of remission, maintenance of response, mucosal healing, hospitalization, surgery, any malignancy, any serious adverse event (overall serious adverse events, as defined in each study), and withdrawal/discontinuation of therapy due to adverse events.

Study design(s): Systematic reviews of randomized controlled trials (RCTs) and controlled clinical trials (CCTs). A CCT is a non-randomized or quasi-randomized experimental study with a control group.

Exclusion criteria: Studies assessing TNF-α inhibitors for surgically-induced remission, studies assessing TNF-α inhibitors in pregnancy or in the pediatric population only, and studies assessing TNF-α inhibitors in patients who previously failed therapy or were intolerant to another TNF-α inhibitor.

Search Strategy

A comprehensive peer-reviewed literature search of several major databases (PubMed, Medline, EMBASE, Cochrane) and a search of grey literature (including unpublished studies, using CADTH 'grey matters' guide)(52) was performed in collaboration with an information specialist in May 2014. A comprehensive list of key words and relevant subject headings (i.e. MeSH terms) pertaining to the diseases of interest (e.g. Crohn's disease, Ulcerative colitis, Inflammatory Bowel Disease), the drugs of interest (e.g. the names of each of the drugs and their brand names, variations of terminology for the class of medications) and study design (e.g. systematic review, meta-analysis, network meta-analysis) were combined with 'and'. The full search strategy is provided in Appendix 2.1. Reference lists of included systematic reviews were reviewed for additional citations.

Selection of studies for inclusion

At the first level of screening, after removal of duplicate citations by a single reviewer (EM), two independent reviewers (EM, TS) applied eligibility criteria relating to the population, intervention, comparison and study design to screen titles and abstracts of all citations from the database and grey literature searches to identify for which studies full-texts would be retrieved for a more in-depth review. Screening criteria is provided in APPENDIX 2.2. At the second level of screening, full-text articles of all retrieved studies were independently assessed for inclusion by two reviewers (EM, SH), and the level of inter-rater agreement was measured using the kappa statistic. Disagreements were resolved through discussion and consensus. Any disagreements remaining unresolved after discussion were brought to a third reviewer (GW) to make a final decision regarding study eligibility.

Justification for chosen safety outcome measures

Occurrence of malignancy was specifically chosen as a safety outcome of interest. Although there is a suspected increased risk of malignancy with the TNF-α inhibitors, the magnitude of this risk is not yet known. This outcome is of particular importance to patients when weighing the risks and benefits of therapy, especially in the long-term. The other chosen safety endpoints (overall serious

adverse events, and withdrawal/discontinuation of therapy due to adverse events) were selected to broadly quantify adverse events and enable a comparison between the results of the systematic review of systematic reviews with those of the systematic review of post-market observational studies (Chapter 4). A potential limitation to this is that RCTs in the included systematic reviews can inconsistently define *'serious adverse event'.* A serious adverse event (or reaction) is defined by the International Conference on Harmonization as *"any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect."*(53) If a definition of 'serious adverse event' was reported in the included study, this information was extracted.

Subgroup Analysis

Subgroups of interest included level of disease severity at baseline (moderate disease, severe disease), hospitalization at baseline, duration of disease prior to treatment initiation, concomitant methotrexate use, concomitant thiopurine use, and whether patients were naïve to prior immunosuppressant use.

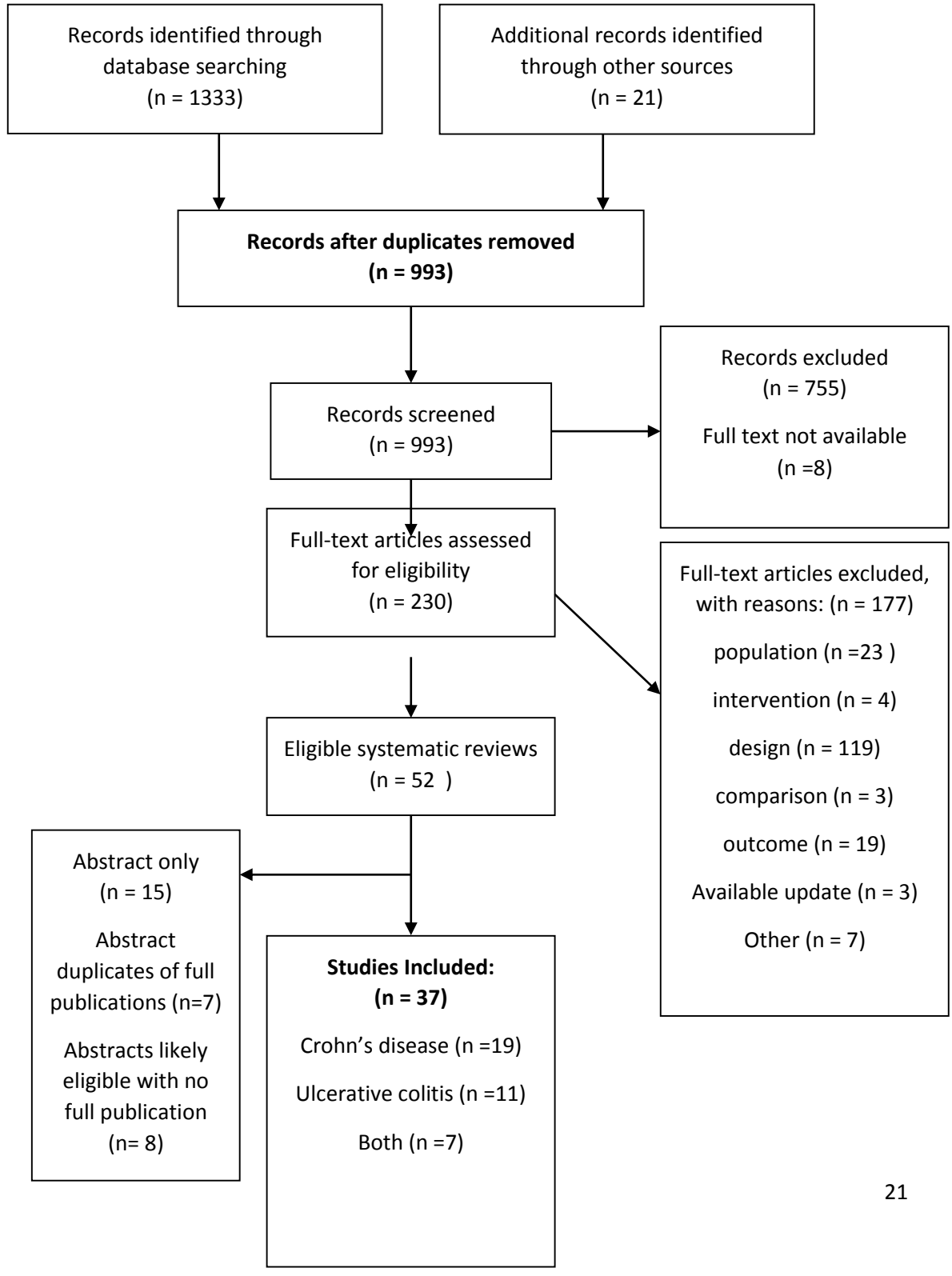
Data extraction and quality assessment

Information to be extracted pertaining to the patient population, intervention, comparison, outcome(s), study design and methods, and items relating to study quality was pre-defined and entered into Distiller SR (Ottawa, Canada) using a data extraction form first piloted on 5 studies. Data extraction was performed by one reviewer (EM), and the data extraction of a 10% sample of studies was checked by a second reviewer (SC). A purposeful sample of studies was selected to reflect a range of methodologies and those found to be the most challenging to extract data from. A quality assessment instrument, AMSTAR,(54) was used to assess the quality of included systematic reviews. The AMSTAR tool and guidelines are provided in APPENDIX 2.3. A literature review and consultation with experts in the area of reporting and assessment of systematic reviews revealed that there is currently no validated tool for assessment of quality of network meta-analyses. The network meta-analyses were assessed on the AMSTAR items for the quality of the systematic review. In addition, the ISPOR report on interpreting indirect treatment comparisons was used as a benchmark for high quality reporting. The **checklist of good research practices for conducting and reporting network-meta-analysis studies is summarized in Appendix 2.4.** Included network meta-analyses were given an assessment of high quality, acceptable, or unacceptable according to this

criteria.(46) Quality assessment was done in duplicate for a purposeful sample of six of the included systematic reviews. This sample included all of the network meta-analyses and the systematic reviews for which the first reviewer had the greatest difficulty applying the quality assessment tool. Disagreements were resolved through consensus. Any disagreements remaining unresolved after discussion between the two reviewers were brought to a third reviewer (GW). It was decided not to contact study investigators for further information to clarify incomplete or unclear information, because of the potential introduction of ascertainment bias from this approach.

RESULTS

A total of 993 unique records were identified by the database and grey literature searches. Figure 2.1, a PRISMA flow diagram outlining the study selection process, is shown below.



After title and abstract screening, 230 records were retrieved for full text review. Thirty-seven systematic reviews were included: eleven systematic reviews of TNF-α inhibitors in ulcerative colitis including three network meta-analyses, 19 in Crohn's disease including one network meta-analysis, and seven in both forms of inflammatory bowel disease (IBD) including a network meta-analysis of safety across indications. Characteristics of all systematic reviews meeting eligibility criteria are shown in Table 2.1.

Table 2.1: Characteristics of included systematic reviews						
Review (author, year) and method of data synthesis	**Search date (mm/yyyy)**	**Population (Disease and inclusion criteria)**	**Relevant intervention(s)**	**Comparison (s)**	**Relevant outcome(s) for which data were reported**	**Overall quality[a] and limitations**
Systematic reviews in Crohn's disease						
Akobeng, 2009 (Cochrane review) **Meta-analysis**	06/2003	**Crohn's disease** Active CD	Any TNF-α inhibitor (included infliximab)	Placebo or other medication	Induction of remission and response, any malignancy, lymphoma	**High Quality** -Outdated (search date 2003)
Assasi, 2010 **Meta-analysis**	11/2008	**Crohn's disease** Active or fistulising CD, refractory to conventional therapy, 18 years or older. Not restricted to TNF-α inhibitor naïve.	Infliximab, adalimumab, etanercept	Conventional therapies, anti-TNF-α drugs, surgical interventions, placebo	Induction and maintenance of remission and response, hospitalization, serious adverse events, surgery	**High quality** -Reasons for not pooling studies were not explicitly stated
Behm, 2009 (Cochrane review)	07/2007	**Crohn's disease** Patients with clinical response induced by	Any TNF-α inhibitor (including infliximab, adalimumab,	Placebo or other medication	Maintenance of remission and response	**High quality**

Meta-analysis		TNF-α inhibitors, and patients unable to wean corticosteroids. Not restricted to TNF-α inhibitor naïve.	certolizumab)			
Chande, 2013 **(Cochrane review)** **Meta-analysis**	06/2012	**Crohn's disease** Adults with acute (active) CD defined by conventional clinical, radiographic, and endoscopic criteria.	Azathioprine, 6-mercaptopurine (including in combination with infliximab)	Not specified; included infliximab	Induction of remission, mucosal healing, withdrawal due to adverse events, severe adverse events	**High Quality**
Da, 2013 **Meta-analysis**	12/2011	**Crohn's disease** Not restricted to TNF-α inhibitor naïve.	Certolizumab	No comparison specified in eligibility criteria	Remission and response (induction and maintenance)	**High Quality** -Important characteristics of included studies were not presented
De Cruz, 2014 **Qualitative review**	08/2011	**Crohn's disease**	"Current therapies" (including TNF-α inhibitors infliximab, adalimumab, certolizumab)	Eligibility criteria not reported, so no comparison specified	Mucosal Healing	**Unacceptable** -No specific eligibility criteria was presented -The relevant research question was not specific -No list of included studies or quality assessment -Results of relevant studies were qualitatively

						described in text
Dretzke, 2011 **Qualitative**	06/2007	**Crohn's disease** Adults and children with moderate-to-severe active or fistulising CD intolerant or resistant to conventional treatment	Infliximab, adalimumab	Any other treatment, including different dosage regimens	Induction and maintenance of remission and response, hospitalization, surgery	**High quality** -No relevant pooled analyses
Huang, 2011 (Crohn's) **and Huang, 2011 (Crohn's, chinese)** **Meta-analysis**	06/2010	**Crohn's disease** Adults aged 18-75. Not restricted to TNF-α inhibitor naïve.	Adalimumab	Comparison not specified; Placebo was the comparison in the included studies.	Induction and maintenance of remission, induction of response, serious adverse events	**Unacceptable** -Table of "results of included trials" was not clear and had minimal information -Study selection process was not described and eligibility criteria was very broad -Outcomes were not stated in methods section
Hutfless, 2014 **Meta-analysis**	06/2011	**Crohn's disease** Not restricted to TNF-α inhibitor naïve, however subgroup analysis was presented.	All interventions for (excluding probiotics, antibiotics, enteral and parenteral nutrition), including infliximab, adalimumab, certolizumab.	Any comparison, apart from different doses of the same medication	Induction and maintenance of remission, mucosal healing, any malignancy, lymphoma, cervical cancer, surgery	**High quality**

Kawalec, 2013 **Meta-analysis**	11/2012	**Crohn's disease** Moderate to severe or fistulising CD. Not restricted to TNF-α inhibitor naïve.	Adalimumab, infliximab, certolizumab	Placebo or another TNF-α inhibitor	Remission and response (induction and maintenance), severe adverse events	**High Quality** -Not all pre-specified sub-group analyses were reported
Lian, 2006 **Chinese study** **Meta-analysis**	01/2009	**Crohn's disease** Adults with disease duration >12 weeks	TNF-α inhibitors (infliximab, adalimumab and certolizumab)	Placebo or traditional care	Induction and maintenance of remission, induction and maintenance of response, serious adverse events	**Unacceptable** Study selection and data extraction not performed in duplicate, lack of study characteristics, insufficient detail provided for results
McDonald, 2012 **(Cochrane review)** **Meta-analysis**	06/2012	**Crohn's disease** Active CD in adults over 17.	"Trials where at least one arm of the study received oral or parenteral methotrexate" (including methotrexate + infliximab)	Any comparison (including infliximab)	Induction of remission, serious adverse event, withdrawal/discontinuation of therapy due to adverse event	**High quality** -Unable to pool results due to significant heterogeneity
Mills, 2011	12/2009	**Crohn's disease**	Infliximab	Comparison	Remission	**Unacceptable**

Qualitative review				not specified; placebo was the comparator in included studies.	(induction and maintenance)	-Eligibility criteria, data extraction and quality assessment not described -Study selection not performed in duplicate -List of included studies not provided
Nikfar, 2014 **Meta-analysis**	07/2012	**Crohn's disease** Not restricted to TNF-α inhibitor naïve.	Certolizumab pegol	No comparison specified: "studies that investigated efficacy of Cp in CD".	Remission (induction and maintenance), response (induction)	**Acceptable** -Eligibility criteria not clearly described -Unclear distinction between induction and maintenance, with only induction reported for response but both for remission
Peyrin-Boulet, 2008 **Meta-analysis**	12/2006	**Crohn's disease** Adults. Not restricted to TNF-α inhibitor naïve.	Any anti-TNF (including adalimumab, infliximab, certolizumab)	Placebo	Induction and maintenance of remission, any malignancy	**Acceptable** -Use of online appendices and tables to report important outcome results
Rahimi, 2007 **Meta-**	12/2005	**Crohn's disease** Active CD patients of any age, naïve to TNF-α inhibitors	Any anti-TNF (including infliximab and certolizumab)	Placebo	Induction of remission and response	**Unacceptable** -Conclusions do not consider substantial heterogeneity and that individual agents may have

analysis						different effects
Stidham, 2014 (Crohn's) **Network Meta-analysis**	08/2013	**Crohn's disease** Not restricted to TNF-α inhibitor naïve	Infliximab, adalimumab or certolizumab	Placebo	Induction and maintenance of remission and response	**High quality** -No description or justification of model used
Zhang, 2013 **Meta-analysis**	06/2012	**Crohn's disease** 18 years or older, without malignancy, and a follow-up of at least 24 weeks. Not restricted to TNF-α inhibitor naïve.	TNF-α inhibitors (including adalimumab, certolizumab, infliximab, golimumab) with or without TNF-α inhibitor treatment as induction therapy	Placebo	Serious adverse event, any malignancy	**Acceptable** -All participants in 8 of 13 included RCTs received TNF-α inhibitors as induction therapy for 0-6 weeks. It is plausible that short-term exposure can lead to long-term adverse effects. -Maximum of 56 weeks therefore long-term risk of adverse effects cannot be ruled out -Two included studies assessed CDP 571 which is not marketed
Systematic reviews in Crohn's disease and ulcerative colitis						
Assasi, 2009	04/2008	**Crohn's disease and**	Infliximab, adalimumab,	Placebo, traditional	Induction and maintenance of	**High quality**

Meta-analysis		**ulcerative colitis** Adults, not responsive to conventional treatment. Not restricted to TNF-α inhibitor naïve.	etanercept	care, another TNF-α inhibitor, surgery	remission and response, malignancy, surgery, hospitalization	-Reason for not pooling data in meta-analyses for many outcomes was not explicitly stated
Costa, 2013 **Meta-analysis**	05/2012	**Crohn's disease and ulcerative colitis** Adults. Not restricted to TNF-α inhibitor naïve.	Infliximab	Placebo, traditional-care, another TNF-α inhibitor	IBD-related hospitalization, major surgeries	**High Quality**
Ehteshami-Afshar, 2011 **Meta-analysis**	02/2011	**Crohn's disease and ulcerative colitis**	Infliximab	Comparison not specified; placebo was the comparator in included studies.	Surgery (colectomy)	**Unacceptable** -Number of articles included/excluded does not add up -No discussion of substantial heterogeneity -unclear timing of endpoint assessment for colectomy -Lack of characteristics of included studies
Ford, 2011	12/2010	**Crohn's disease and ulcerative colitis**	"Biological therapy at any dose or regimen" (including	Placebo	Remission (induction and maintenance),	**High quality** -Risk of bias assessment

Meta-analysis		Adults (>90% over aged 16) with active, quiescent, or fistulising disease. Not restricted to TNF-α inhibitor naïve.	adalimumab, infliximab and certolizumab)		severe adverse events	results not reported
Singh, 2011 **Network meta-analysis**	01/2010	**Crohn's disease and ulcerative colitis** "Adults (aged 16 years or older) with any disease (except HIV/ AIDS) included in studies of any of the nine biologics..." Relevant subgroup analyses of IBD studies were presented	"Any of the nine biologics", (including adalimumab, certolizumab, golimumab, infliximab)	Any other therapy or placebo	Serious adverse events, withdrawal or discontinuation of therapy due to adverse events, lymphoma, leukemia	**Acceptable** -Details of included studies for the relevant subgroup analysis are not reported
Neurath, 2012 **Qualitative review**	03/2012	**Crohn's disease and ulcerative colitis**	"anti-inflammatory or immunosuppressive agents" (including Infliximab, adalimumab, golimumab and certolizumab)	No comparison specified	Mucosal healing	**Unacceptable** -No list of included studies or quality assessment -Broad research question -Eligibility, selection of studies and data extraction -no description of risk of bias assessment
Williams, 2014	11/2013	**Crohn's disease and ulcerative colitis**	Infliximab, adalimumab,	Placebo	Any type of malignancy,	**High quality** -Lack of patient

Meta-analysis		Studies in which >90% of the population were >16, a minimum treatment duration of 14 days, and malignancies reported in both arms. Not restricted to TNF-α inhibitor naïve.	golimumab, certolizumab		specific types of malignancy	characteristics (i.e. age, sex, or duration of disease) of included studies -Mean length of follow-up of 205 days is "inadequate to exclude a risk of malignancy" with TNF-α inhibitors
Systematic reviews in ulcerative colitis						
Baggenstos, 2013 **Qualitative**	09/2012	**Ulcerative colitis** Aim was to identify all RCTs addressing treatment outcome in UC, and identify the elderly population (60 years or older) represented in these studies. Not restricted to TNF-α inhibitor naïve.	Any intervention (including TNF-α inhibitors)	Any comparison	None specified (any treatment outcome)	**Unacceptable** -Data extraction not described -No quality assessment of included studies -Included RCTs did not provide sufficient evidence to "evaluate efficacy of treatment and adverse effects from treatment for UC in the elderly."
Chang, 2013 **Meta-analysis**	05/2012	**ulcerative colitis** "acute, severe, refractory UC"	Infliximab	Cyclosporine	Colectomy	N/A; only observational studies were identified by the review, therefore no data was extracted.
Danese, 2014	12/2013	**ulcerative colitis** Moderately to severely	Infliximab, adalimumab,	Each other and placebo	Remission, response,	**High quality SR. High quality NMA.**

Network meta-analysis		active UC defined as "a Mayo Clinic Score of 6 to 12 points with an endoscopic subscore of 2 or 3." Efficacy analyses were restricted to patients naïve to biological agents	golimumab and vedolizumab		mucosal healing, (induction and maintenance); serious adverse events, withdrawal or discontinuation of therapy due to adverse events	-The probability of each treatment being best was not reported -Lack of characteristics of included studies
Gisbert, 2006 **Meta-analysis**	01/2006	**Ulcerative colitis**	Infliximab	None specified	Induction and maintenance of remission and response	**Acceptable** -Study selection and data extraction not described. -Timing of outcome assessment not reported
Huang, 2011 (ulcerative colitis) **AND Huang, 2011 (UC Chinese)** **Meta-analysis**	03/2010	**Ulcerative colitis** Moderate to severe UC	TNF-α blockers (including infliximab and adalimumab)	placebo, glucocorticoid or other drug	Induction and maintenance of remission (short-term and long-term 'relief') and response, mucosal healing, severe adverse reactions, malignant tumor,	**Acceptable** -Pooled analyses included studies with infliximab and adalimumab versus either placebo or corticosteroids as control -Timing of outcome assessment not reported -Outcomes and eligibility criteria were not well-defined

					colectomy	
Lawson, 2006 **(Cochrane review)** **Meta-analysis**	05/2006	**Ulcerative colitis** Active UC, "defined by a combination of clinical, radiographic, endoscopic and histologic criteria"	TNF-α inhibitors (including infliximab)	Placebo or other drugs	Mucosal healing, induction of remission and response, lymphoma, colectomy	**High quality**
Lv, 2006 **Meta-analysis**	07/2013	**Ulcerative colitis** "UC resistant to conventional therapy of corticosteroids and/or immunosuppressive agents, or refractory to intravenous corticosteroids" At least 12 weeks follow-up. Not restricted to TNF-α inhibitor naïve.	Any anti-TNF therapy (including adalimumab, certolizumab, infliximab, golimumab)	Placebo or other intervention	Clinical remission (distinction between induction and maintenance not made), mucosal healing, 'serious side effects', colectomy	**High quality** -The authors conclude that TNF-α blockers are effective and safe for induction and maintenance of long-term remission, however there is no differentiation between induction and maintenance outcomes -They also conclude that infliximab and cyclosporine appear to be comparable, however this is not consistent with the reported results and there are no comparative studies.
Nikfar, 2011	09/2010	**Ulcerative colitis**	Infliximab	Placebo or corticosteroid	Induction of remission,	**Unacceptable** -clinical response was listed

Meta-analysis		Active UC		s	serious adverse events (although induction of response listed as a key outcome, results not reported)	as a 'key outcome' in the methods, results were not reported -No differentiation between induction or maintenance of remission, and timing of outcome assessment is not reported -Characteristics of individual studies are not reported -Several included RCTs were of poor quality and this was not explicitly considered
Stidham, 2014 **Network meta-analysis**	13/08/2013	**ulcerative colitis** Adults with UC. Not restricted to anti-TNF naïve; prior anti-TNF was allowed in two of the seven included RCTs.	Infliximab, adalimumab and golimumab	Each other and placebo	Remission, response (induction and maintenance)	**High quality SR. High quality NMA.** -No description or justification of model used
Thorlund, 2014 **Network meta-**	30/10/2013	**ulcerative colitis** Adults with moderate to severe UC, non-hospitalized, refractory to conventional	Infliximab and adalimumab	Each other and placebo	Remission, response, mucosal healing (induction and maintenance), serious adverse	**Acceptable SR. Acceptable NMA.** -Industry-funded by Janssen Inc. -No assessment of risk of

analysis		treatments, naïve to TNF-α inhibitors			events, withdrawal due to adverse events	bias of included studies -Did not include all relevant comparators -No sensitivity analyses were described -Lack of justification of model choice and of prior distributions -Probability of each intervention being best was not reported
CD = Crohn's disease, TNF = tumor-necrosis factor, UC = ulcerative colitis [a]Quality assessed with AMSTAR						

It was decided by the investigators at the point of full-text screening that because reports published only as abstracts or conference proceedings did not provided enough information to fully assess eligibility and/or sufficient detail for quality assessment, inclusion would be restricted to full reports of systematic reviews. See Appendix 2.5 for a list of articles excluded at full text review.

Apart from obvious reasons for discrepancies of results across systematic reviews such as the existence of new studies since publication of the systematic review and the choice of effect measure (OR versus RR for example), it was evident that certain key characteristics might lead to differences in the effect size estimate, including: Definition of outcome measure (of particular importance for *response* outcomes in Crohn's disease), timing of outcome measurement, whether analyses were restricted to subgroups of participants receiving particular doses, whether 'maintenance' analyses were restricted to subgroups of participants who had an initial response or remission with induction therapy (of particular importance for Crohn's disease), the number of included studies and participants (related to other key characteristics), and use of a random or fixed effects model in the analysis. Pooled effect size estimates from included studies and the key characteristics leading to differences in efficacy estimates are presented in Table 2.2 for ulcerative colitis, Table 2.4 for Crohn's disease, and Table 2.6 for safety outcomes in the combined IBD population, within the relevant sections below.

Because the included network meta-analyses were very recent, encompassed all of the TNF-α inhibitors of interest, and were all of acceptable to high quality, these results are described in more detail. Newer RCTs have been published since many of the included systematic reviews, especially in ulcerative colitis, therefore the recent network meta-analyses are more reflective of the current available RCT evidence.

ULCERATIVE COLITIS

Systematic reviews and meta-analyses in ulcerative colitis

A total of 18 systematic reviews assessing efficacy and/or safety of TNF-α inhibitors in ulcerative colitis were included. Seven included both forms of IBD; of these, one is a network meta-analysis assessing the safety of biologics for any indication.(55) Three others are network meta-analyses and are discussed in the following section.(56-58) A Canadian Health Technology Assessment report from the Canadian Agency for Drugs and Technology in Health (CADTH) (30) assessed infliximab and

adalimumab for both Crohn's disease and ulcerative colitis. Another systematic review was a Chinese version of an English publication, with just slight differences between them and so these are presented together.(59, 60) Outcome data from three of the included systematic reviews was not amenable to extraction: in Chang 2013, a systematic review assessing infliximab versus cyclosporine, no RCTs were identified in the literature search.(61). Baggenstos 2013 aimed to review evidence for biologics in the elderly from available RCTs.(62) Results and information pertaining to age of included participants from was reported for 20 RCTs, but there were no pooled results presented for any outcomes. Neurath 2012, although meeting eligibility criteria for this systematic review, did not provide a list of included studies.(63)

Costa 2013 assessed the efficacy of infliximab in avoiding IBD-related hospitalizations and major surgeries in both Crohn's disease and Ulcerative colitis.(64) A separate analysis was performed for observational studies and clinical trials. Only the results of the systematic review of clinical trials are included in this review.

Efficacy and Safety outcomes in systematic reviews and meta-analyses in ulcerative colitis

Pooled effect size estimates from included studies and the key characteristics leading to differences in efficacy estimates are presented in Table 2.2 for ulcerative colitis.

Table 2.2: Efficacy and safety of TNF-alpha inhibitors in ulcerative colitis							
Study and search date	**Intervention / Comparison**	**Outcome definition; timing**	**Notable population and intervention characteristics[c]**	**Fixed *or* random effects model**	**participants; studies**	**Effect size (95% CI)**	**Comments**
Induction of response							
Assasi, 2009 April 2008	Infliximab / placebo	Clinical response[c]; timing NR	Analysis restricted to 5mg/kg dose	Fixed	492; 3	RR 2.03 (1.67, 2.48)	
Gisbert, 2006 January 2006	Infliximab / placebo	"defined by the authors of each study as partial or complete symptomatic response"; timing NR		Fixed	782; 4	OR 3.60 (2.67, 4.85)	"Short-term response" 5mg/kg subgroup: 535; 4, OR (3.64, 2.59-5.11). RCTs comparing infliximab to corticosteroids were not included in the pooled analyses.
Huang, 2011 March 2010	TNF-alpha inhibitors (adalimumab and infliximab) / placebo or corticosteroids	Not defined; timing NR	Pooled comparisons included either TNF-alpha inhibitor and any control	Random	1272; 5	OR 2.36 (1.34, 4.15)	Called “short-term response” in the paper
Lawson, 2006 May 2006	Infliximab / placebo	“as defined by the authors”; timing NR		Fixed	728; 2	RR 1.99 (1.65, 2.41)	
Stidham, 2014	Infliximab / placebo	“decrease by at least 3 points and/or 30 percent from baseline in the total Mayo	Analysis restricted to 5mg/kg dose.	Random	486; 2	RR 2.00 (1.64, 2.44)	Analysis not restricted to TNF-naïve patients.

		Score, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of at least 1 or 0"; 6-8 weeks					
Stidham, 2014	TNF-alpha inhibitors (infliximab, adalimumab, golimumab)	"		Random	1780; 5	RR 1.65 (1.37, 1.99)	"
Stidham, 2014	Adalimumab / placebo	"		Random	778; 2	RR 1.36 (1.13, 1.64)	"
Stidham, 2014	Golimumab / placebo	"		Not applicable	516; 1	RR 1.75 (1.40, 2.19)	"
Induction of remission							
Assassi, 2009 April 2008	Infliximab / placebo	Clinical remission[b]; timing NR	5mg/kg dose	Fixed	550; 4	RR 2.93 (2.06, 4.15)	It was noted that for all analyses there were too few studies to assess heterogeneity therefore a fixed effects model was used.
Ford, 2011 December 2010	Infliximab / placebo	Hierarchical definition provided[a]; up to 4 months	*Sands, Probert, ACT 1 and 2, Jarnerot*	Random	827; 5	RR 1.39 (1.10, 1.75)	RR was reported as 0.72 (0.57, 0.91) for "failure to induce remission". Statistically significant heterogeneity (I-squared 70%)

Gisbert, 2006 January 2006	Infliximab / placebo	"defined by the authors as complete symptomatic response"; timing NR		Random	728; 2	OR 4.56 (1.98, 10.52)	“short-term remission” 5mg/kg subgroup: 486; 2 OR 5.28 (2.30, 12.09)
Huang, 2011 March 2010	TNF-alpha inhibitors (adalimumab, infliximab) / placebo or corticosteroids	Not defined; timing NR	*One adalimumab (Reinisch 2010), 4 infliximab RCTs*	Random	1311; 5	OR 2.42 (1.22, 4.81)	This outcome is called "short-term relief" in the paper. One adalimumab and four infliximab RCTs.
Lawson, 2006 April 2006	Infliximab / placebo	"as defined by the primary studies"; 8 weeks		Fixed	728; 2	RR 3.22 (2.18, 4.76)	Results of 5mg/kg subgroup vs placebo also reported: RR 3.54 (2.36, 5.31). *Although 4 included RCTs assessed this outcome for IFX vs placebo, only ACT1 and ACT2 included in the pooled analysis;* *Also, single RCTs comparing infliximab to methylprednisolone (n=20) and prednisolone (n=13) were reported separately. These were pooled together with placebo comparator in another SR*
Nikfar, 2011 September 2010	Infliximab / placebo	Not defined, and no distinction between induction and remission; timing NR		Fixed	NR;5	RR 1.93 (1.62, 2.30)	*ACT1, ACT2, Probert, Jarnerot, Sands*
Nikfar,	Infliximab /	Not defined, and no		Random	NR;3	RR 1.07	Random effects was used

2011 September 2010	corticosteroids	distinction between induction and remission; timing NR				(0.87, 1.31)	because of few included studies, according to the authors
Stidham 2014	TNF-alpha inhibitors (infliximab, adalimumab, golimumab)	"defined by Mayo Score or ulcerative colitis symptom score"; within 8 weeks	5mg/kg dose	Random	1823; 6	RR 2.45 (1.72, 3.47)	
Stidham 2014	Infliximab / placebo	"	5mg/kg dose	Random	529; 3	RR 2.76 (1.29, 5.90)	
Stidham 2014	Adalimumab / placebo	"	5mg/kg dose	Random	778; 2	RR 1.87 (1.27, 2.75)	
Stidham 2014	Golimumab / placebo	"	5mg/kg dose	Random	516;1	RR 3.00 (1.75, 5.14)	
Maintenance of response							
Assassi, 2009 April 2008	Infliximab / placebo	Clinical response[c]; timing NR		Fixed	486; 2	RR 2.02 (1.55, 2.64)	
Danese, 2014 December 2013	Infliximab / placebo	"decrease from baseline in the MCS of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute rectal bleeding subscore of 0 or 1."		Fixed	NR; 2	OR 2.89 (1.96, 4.28)	

Danese, 2014 December 2013	Adalimumab / placebo	“		Fixed	NR; 2	OR 1.90 (1.27, 2.86)	
Danese, 2014 December 2013	Golimumab / placebo	“	Only responders to induction treatment continued into maintenance phase.	Fixed	NR; 1	OR 2.24 (1.41, 3.56)	In maintenance golimumab trials, only responders to induction treatment continued into maintenance phase.
Gisbert, 2006 January 2006	Infliximab / placebo	"defined by the authors of each study as partial or complete symptomatic response"; timing NR		Fixed	773; 3	OR 3.40 (2.52, 4.59)	Called “long-term response”. 5mg/kg subgroup: 531; 3, OR 2.92 (2.05, 4.16). *Other*
Huang, 2011 March 2010	Infliximab / placebo or corticosteroids (prednisolone)	Not defined; timing NR		Fixed	741;3	OR 3.22 (2.28, 4.55)	Called “long-term response” in this paper.
Stidham, 2014 August 2013	TNF-alpha inhibitors (infliximab, adalimumab, golimumab) / placebo	"decrease by at least 3 points and/or 30 percent from baseline in the total Mayo Score, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of at least 1 or 0"; maintained for at		Random	1070; 3	RR 1.76 (1.46, 2.14)	Sensitivity analysis excluding “studies that continued maintenance therapy on those that responded to the induction therapy (n=1) did not substantively affect composite treatment effects.”

		least 52 weeks					
Stidham, 2014 August 2013	Infliximab / placebo	"		Random	242; 1	RR 2.29 (1.52, 3.45)	
Stidham, 2014 August 2013	Adalimumab / placebo	"		Random	518; 1	RR 1.68 (1.21, 2.33)	
Stidham, 2014 August 2013	Golimumab / placebo	"	The included RCT (Sandborn 2010) continued maintenance therapy only in those that responded to induction therapy.	Random	310; 1	RR 1.61 (1.22, 2.13)	
Maintenance of remission							
Assassi, 2009 April 2008	Infliximab / placebo	Clinical remission[b]; timing NR	5mg/kg dose	Fixed	486; 2	RR 2.23 (1.54, 3.22)	
Danese 2014 December 2013	Infliximab / placebo	"an MCS of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing was defined as an absolute subscore for endoscopy of 0 or 1."		Fixed	NR; 2	OR 2.78 (1.75, 4.41)	

Danese 2014 December 2013	Adalimumab / placebo	"		Fixed	NR; 2	OR 2.30 (1.37, 3.86)	
Danese 2014 December 2013	Golimumab / placebo	"		Fixed	NR; 1	OR 1.81 (1.10, 3.00)	In maintenance golimumab trials, only responders to induction treatment continued into maintenance phase.
Gisbert, 2006 January 2006	Infliximab / placebo	"defined by the authors of each study as complete symptomatic response"; timing NR		Fixed	728; 2	OR 2.72 (1.92, 3.86)	"long-term response" 5mg/kg subgroup: 486; 2, OR 2.61 (1.69, 4.03)
Huang, 2011 March 2010	Infliximab / placebo or corticosteroids	Not defined; timing NR		Fixed	782; 5	OR 2.82 (1.91, 4.16)	Called "long-term relief" in this paper
Lv, 2014 July 2013	TNF-alpha inhibitors (infliximab or adalimumab) / placebo or glucocorticoids	"Unless otherwise defined in the primary study, clinical remission was defined either as a total Mayo score#2 with no individual subscore exceeding 1 points"/ 13-56 weeks		Fixed	1279; 6	RR 2.00 (1.57, 2.53)	"Clinical remission", noted to be "maintenance" in text of article, but in conclusions the authors refer to induction and maintenance of remission.
Lv, 2014 July 2013	TNF-alpha inhibitors (infliximab or adalimumab) / placebo	"		Fixed	1222; 3	RR 2.29 (1.73, 3.03)	"
Lv, 2014	Infliximab /	"		Fixed	57; 3	RR 1.01	No studies comparing

July 2013	glucocorticoids					(0.73, 1.42)	adalimumab to glucocorticoids, therefore infliximab is the only intervention for this comparison
Stidham 2014 August 2013	TNF-alpha inhibitors (infliximab, adalimumab, golimumab) / placebo	"defined by Mayo Score or ulcerative colitis symptom score"; maintained after 52 weeks		Random	1070; 3	RR 2.00 (1.52, 1.62)	
Stidham 2014 August 2013	Infliximab / placebo	"	5mg/kg dose	Random	242; 1	RR 2.10 (1.31, 3.36)	
Stidham 2014 August 2013	Adalimumab / placebo	"	5mg/kg dose	Random	518; 1	RR 2.06 (1.26, 3.38)	
Stidham 2014 August 2013	Golimumab / placebo	"	5mg/kg dose	Random	310; 1	RR 1.86 (1.19, 2.90)	
Mucosal healing							
Danese, 2014 December 2013	Infliximab / placebo	"an absolute subscore for endoscopy of 0 or 1"		Fixed	NR; 2	OR 2.65 (1.79, 3.92)	
Danese, 2014	Adalimumab / placebo	"		Fixed	NR; 2	OR 1.99 (1.30,	

December 2013						3.06)	
Huang, 2011 March 2010	TNF-alpha inhibitors (Infliximab and adalimumab) / placebo or corticosteroids	Not defined; timing NR		Random	1325; 6	OR 1.59 (0.91, 2.78)	Statistically significant heterogeneity. Included studies compared infliximab or adalimumab to placebo or corticosteroids.
Lawson, 2006 May 2006	Infliximab / placebo	Not defined; 8 weeks		Fixed	728; 2	RR 1.88 (1.54, 2.28)	
Lv, 2014 July 2013	TNF-alpha inhibitors (infliximab, adalimumab) / placebo, prednisolone or cyclosporine	"Unless otherwise defined in the primary study... mucosal healing was defined as an endoscopy subscore of 0 or 1."; 13-56 weeks		Fixed	1345; 5	RR 1.72 (1.44, 2.05)	Statistically significant heterogeneity (I-squared 65%)
Lv, 2014 July 2013	TNF-alpha inhibitors (infliximab and adalimumab) / placebo	"		Fixed	1222; 3	RR 1.89 (1.55, 2.31)	
Lv, 2014 July 2013	Infliximab / prednisolone	"		Not applicable	13; 1	RR 0.88 (0.31, 2.44)	
Lv, 2014 July 2013	Infliximab / cyclosporine	"		Not applicable	51; 1	RR 1.04 (0.70, 1.55)	
Hospitalization							

Costa, 2013 May 2012	Infliximab / placebo	Hospitalization related to IBD; 6-54 weeks		Random	NR; 2	OR 0.54 (0.35, 0.84)	Ulcerative colitis subgroup; also reported as a pooled analysis for all IBD patients.
Surgery							
Assassi, 2009 April 2008	Infliximab / placebo	Results of 4 RCTs described narratively for this outcome					See text
Costa, 2013 May 2012	Infliximab / placebo	"overall major surgery rate (such as any resection of a part of the gut, strictureplasty, or ostomy)"; 6-54 weeks		Random	NR; 4	OR 0.55 (0.40, 0.76)	Unlike with hospitalization outcome from this study, results not pooled for IBD.
Ehteshami-Afshar, 2011 February 2011	Infliximab / placebo	Colectomy; Timing NR	Ulcerative colitis	Random	NR; 3	RR 1.17 (0.6, 2.28)	Only RCTs in ulcerative colitis were identified, however Crohn's RCTs were also eligible
Huang, 2011 March 2010	Infliximab / placebo	Colectomy; timing NR		Fixed	784;3	OR 0.31 (0.20, 0.48)	The systematic review compared any anti-TNF to any control. The three included RCTs for this comparison *(Sands, Jarnerot, Sandborn)* compared infliximab to placebo
Lawson, 2006	Infliximab / placebo	Colectomy; Timing NR		Not applicable	45; 1	RR 0.44 (0.22, 0.87)	*Results for colectomy for 1 study only; Jarnerot*

May 2006							
Lv, 2014 July 2013	Infliximab / placebo or cyclosporine or methylprednisolone	Colectomy; 13-56 weeks		Fixed	1591; 3	RR 0.76 (0.54, 1.08)	
Lv, 2014 July 2013	Infliximab / placebo	Colectomy; 13-56 weeks		Not applicable	1212; 1	RR 0.64 (0.43, 0.97)	
Lv, 2014 July 2013	Infliximab / methylprednisolone	Colectomy; 13-56 weeks		Not applicable	20; 1	RR 3.00 (0.14, 65.90)	
Lv, 2014 July 2013	Infliximab / cyclosporine	Colectomy; 13-56 weeks		Not applicable	22; 1	RR 1.2 (0.57, 2.60)	
Serious adverse events							
Assassi, 2009 April 2008	Infliximab / placebo	Not defined; timing NR.		NA	742; 4	RD/ARR -7.1 (p = 0.019)	Only proportion and number in each group and p-value reported
Ford, 2011 December 2010	Infliximab / placebo	Not defined; Up to 4 months		Random	782; 4	RR 0.64 (0.41, 1.00)	From induction trials only. No 'maintenance' outcomes reported for UC in this systematic review.
Huang, 2011 March 2010	TNF-alpha inhibitors (infliximab, adalimumab) / placebo or corticosteroids	'severe adverse drug reactions'; timing NR		Fixed	1347; 6	OR 0.65 (0.48, 0.89)	
Lv, 2014 July 2013	TNF-alpha inhibitors (infliximab or	"Serious side effects were defined by each primary study."; 13-56		Fixed	2088; 5	RR 0.81 (0.68, 0.98)	

	adalimumab) / placebo or cyclosporine	weeks					
Lv, 2014 July 2013	TNF-alpha inhibitors (infliximab or adalimumab) / placebo	"		Fixed	1973; 4	RR 0.83 (0.69, 1.00)	
Lv, 2014 July 2013	Infliximab / cyclosporine	"		Fixed	115; 1	RR 0.63 (0.30, 1.34)	
Nikfar, 2011 September 2010	Infliximab / placebo	Not defined; timing NR		Random	NR; 3	RR 0.83 (0.44, 1.54)	Random effects used because of "few included studies." Infliximab vs corticosteroids NR for this comparison.
Withdrawal or discontinuation of therapy due to adverse events							
Only reported in included NMAs							
Malignancy							
Assassi, 2009 April 2008	NA	NR		NA	NA	NA	Reported that "No data on the incidence of malignancy were reported."
Huang, 2011 March 2010	TNF-alpha inhibitors (infliximab or adalimumab) / placebo or corticosteroids	"malignant tumour"; timing NR		Fixed	NR	OR 0.57 (0.17, 1.90)	"malignant tumor was reported in two papers; four patients in the treatment group vs three patients in the control group." No details given re: interventions /comparisons.

95% CI=95% confidence interval; RR=relative risk; OR=odds ratio; NR=not reported; NA=not applicable

[a]Definition of UC remission: Hierarchy of endpoint definitions was used: “UC remission: endoscopic evidence of complete remission (most stringent definition available, for example, complete mucosal healing), clinical assessment as complete remission, recognized scoring system of complete remission (for example, Truelove and Witt (6)), other author-defined criteria for remission."

[b]Definition of UC remission: “Mayo score is 2 or less with no individual subscore greater than 1, Data on clinical remission that were collected using other instruments and definitions (such as Truelove-Witts score, Ulcerative Colitis Symptoms Score, and Seo index)”

[c]Definition of UC response: “A decrease in Disease Activity Index (or Mayo score) of three points or more from the baseline, which should be at least 30% of the baseline score; and a decrease in the subscore for rectal bleeding of one point or more, or an absolute subscore for rectal bleeding of 0 or 1, or clinical response according to other definitions”

To explore the magnitude of the differences in effect estimates between systematic reviews, effect estimates for induction and maintenance of remission in both Crohn's disease and ulcerative colitis were converted to risk differences standardized to a common baseline prevalence if they were not reported as such already in the systematic review. The calculation was done using placebo rates from randomized controlled trials in IBD patients as the baseline prevalence, due to lack of better available baseline prevalence data. See Appendix 2.6 for calculations used to convert relative risks and odds ratios to risk differences, and justification for the baseline prevalences used. The risk differences were calculated for the remission outcomes because it was the most frequently reported outcome in included systematic reviews. Results from the included systematic reviews are not pooled together because this would be inappropriate; there is substantial overlap of RCTs in the included systematic reviews, and the more recent RCTs would be underrepresented. Forest plots displaying the results for induction of remission and maintenance of remission are presented in Figures 3.2 through 3.5.

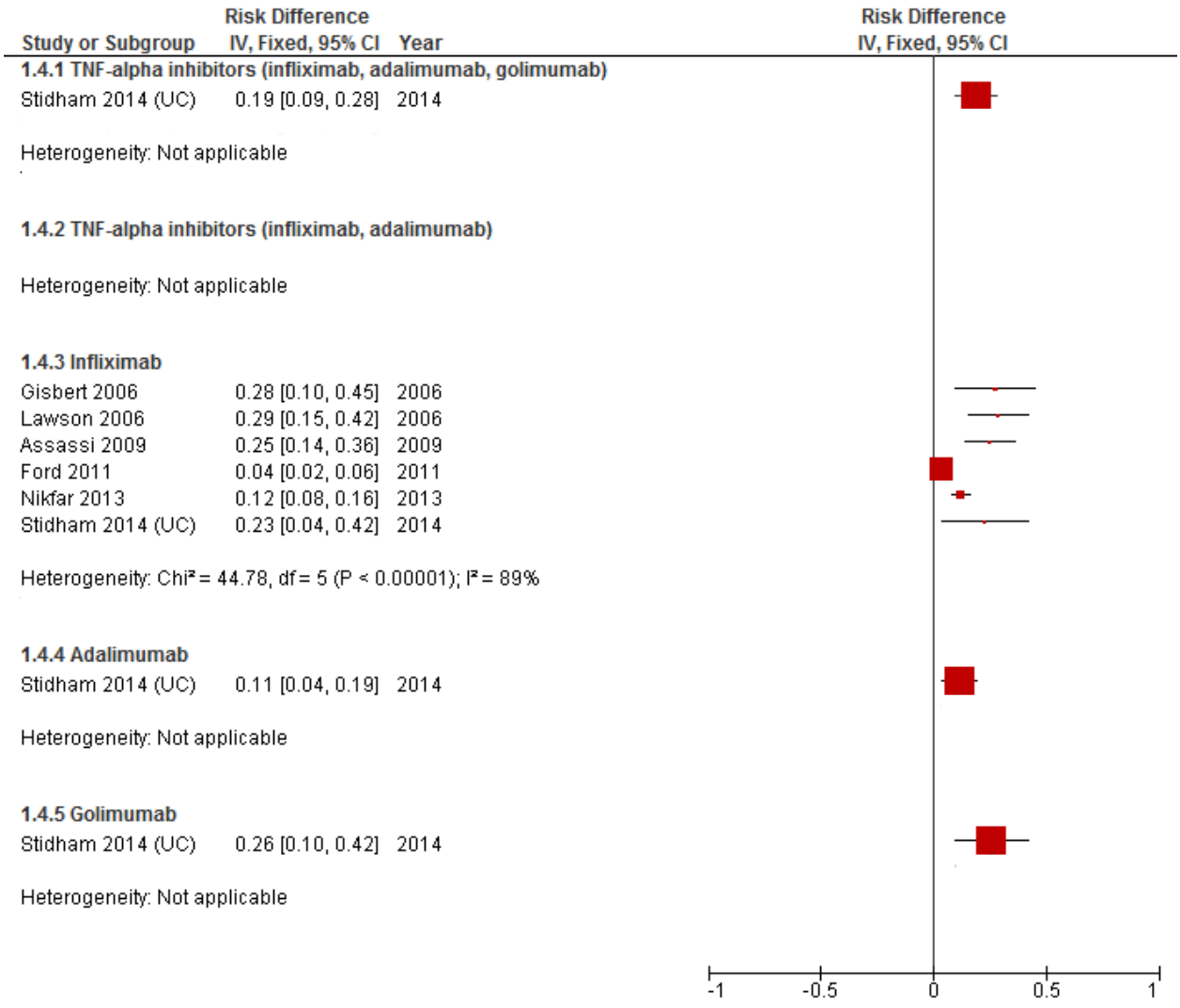
Unlike most RCTs of "maintenance" treatment with TNF-α inhibitors for Crohn's disease, RCTs assessing maintenance of response and remission with TNF-α inhibitors in ulcerative colitis did not restrict enrolment to initial responders/remitters, with the exception of a pivotal golimumab RCT *(Sandborn 2014, Pursuit maintenance)*.

Induction of remission and response

All pooled comparisons of TNF-α inhibitors as a class and as individual agents versus placebo were statistically significant for superiority for induction of remission and response. Only Assasi 2009 and Stidham 2014 restricted analyses to the 5mg/kg dose for infliximab. Different RCTs were included in the pooled analyses across the systematic reviews, and not related to publication date; the assessment of infliximab versus placebo consistently included ACT1 and ACT2, whereas other smaller RCTs with differences in timing and definitions of outcomes and treatment regimens (65) were included by some systematic reviews and excluded by others.

A forest plot displaying the risk differences and 95% confidence interval for the systematic reviews reporting pooled estimates for induction of remission is displayed in Figure 2.2, as a visual depiction of the comparability of meta-analysis results.

Figure 2.2: Forest plot of comparison: TNF-alpha inhibitors vs placebo in ulcerative colitis. Outcome: Induction of remission



Calculation of risk differences standardized to a common baseline prevalence revealed a much smaller risk difference for Ford 2011 and statistically significant heterogeneity between the systematic reviews. This difference between systematic reviews did not dissipate with the use of higher or lower estimates of baseline prevalence. One characteristic that differed between Ford 2011 and others was the timing of the outcome assessment, which was up to four months in Ford 2011 whereas the others were eight weeks. Nikfar 2011 also had a lower estimated risk difference

than the other studies as well, possibly due to an error in their analysis; the forest plot in Nikfar 2011 shows an RCT (*Sands 2001*) favoring placebo for induction of remission, which contradicts the other included systematic reviews in which the results of this RCT were displayed correctly as being in favor of the intervention.

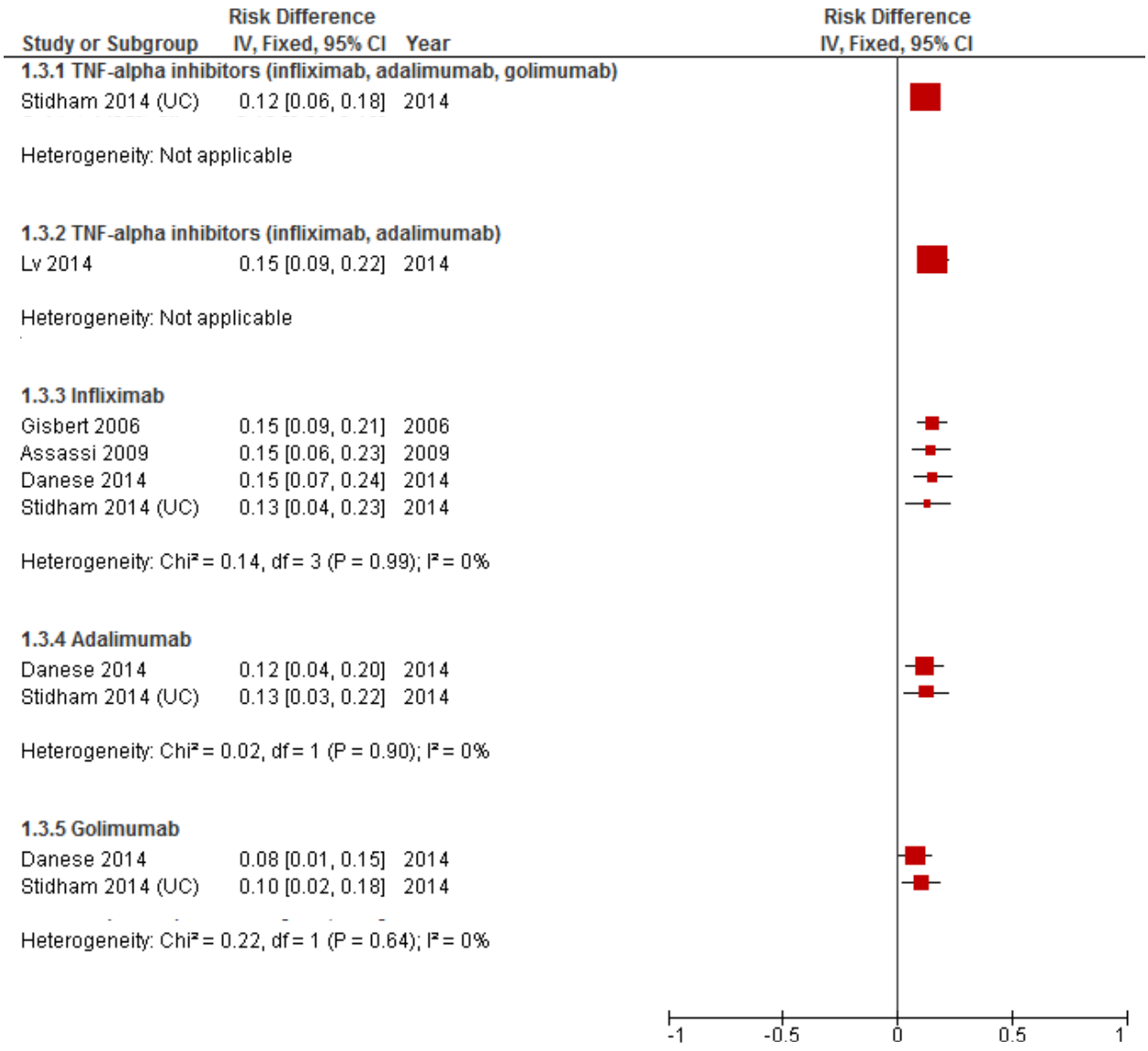
Maintenance of remission and response

TNF-α inhibitors were again consistently superior to placebo for maintenance of remission and response in all pooled analyses. Only a golimumab maintenance RCT required an initial response prior to randomization.

The standardized risk difference estimates were consistent across the four systematic reviews reporting pooled estimates for the comparison of infliximab versus placebo for maintenance of remission, and the two systematic reviews reporting pooled estimates for adalimumab and golimumab.

A forest plot displaying the risk differences and 95% confidence interval for the systematic reviews reporting pooled estimates for maintenance of remission is displayed in Figure 2.3.

Figure 2.3: Forest plot of comparison: TNF-alpha inhibitors vs placebo in ulcerative colitis. Outcome: Maintenance of remission



Mucosal healing

Four included systematic reviews comparing TNF-α inhibitors to placebo consistently reported statistically significant superiority of TNF-α inhibitors.

Hospitalization and surgery

Costa 2013 reported an OR of 0.54 for infliximab versus placebo for hospitalization. For surgery outcomes, all comparisons were of infliximab versus placebo or other control reported in five systematic reviews. With the exception of one systematic review, the included systematic reviews found infliximab to be statistically significantly superior to placebo for prevention of colectomy or major surgery.

Serious adverse events

All estimates showed no difference or fewer serious adverse events with TNF-α inhibitors versus placebo or other control.

Withdrawal or discontinuation due to adverse events

No included systematic reviews reported pooled results for this outcome.

Malignancy

A single included systematic review, Huang 2011, reported a non-significant OR of malignancy of 0.57 (95% CI 0.17, 1.90) for TNF-α inhibitors (infliximab or adalimumab) versus control (placebo or corticosteroids) in ulcerative colitis.

Quality Assessment of systematic reviews and meta-analyses in ulcerative colitis

Details of the quality assessments are provided in Appendix 2.7. Six of the included systematic reviews of ulcerative colitis were of high quality (Williams, Costa, Ford, Lawson, Lv, Assasi), three were of acceptable quality (Chang, Huang, and Gisbert), and four were of unacceptable quality (Baggenstos, Neurath, Ehteshami, Nikfar). Only one systematic review provided an a priori design (Lawson) and only three provided lists of excluded studies in addition to included studies (Lawson, Lv, Assasi).

Network meta-analyses in ulcerative colitis

There are three very recently published network meta-analyses evaluating TNF-α inhibitors in ulcerative colitis.(56, 66, 67) All three network meta-analyses included RCTs comparing TNF-α inhibitors to placebo. The networks in Danese 2014 and Sitdham 2014 included three TNF-α inhibitors: infliximab, adalimumab and golimumab, whereas Thorlund 2014 included only adalimumab and infliximab in the network. These were the two agents approved for ulcerative

colitis in Canada at the time of the study. Danese also included vedolizumab in the network, which is a biologic agent that does not act through inhibition of TNF-α.

The analyses by Danese and Thorlund were restricted to patients who were TNFα inhibitor naïve; for RCTs reporting data in patients with prior TNF-α inhibitor exposure, only data on naïve patients were used in their analyses for efficacy outcomes. Safety outcomes were not reported separately for naïve versus experienced patients in the included RCTs, therefore naïve patients were not analyzed separately for these outcomes in any of three the network meta-analyses. Two of the 7 RCTs in Stidham's analysis included both patients who were TNF-α inhibitor naïve and experienced.

Unlike the other two network meta-analyses, Danese did not perform a network meta-analysis comparing of agents for maintenance outcomes. This was justified as follows: "Given the mixture of study designs involved in the maintenance trials and the fact that persons who responded to induction may be more likely to achieve a positive clinical outcome in the long term than those who did not respond, we decided not to synthesize indirect effect estimates but simply summarize the available direct evidence using frequentist fixed- effects models."

Safety outcomes were not assessed by Stidham. The safety outcomes reported by Danese were not analyzed in a network meta-analysis; event rates per treatment group were reported. None of the three studies reported subgroup analyses.

Although there was substantial overlap with respect to the RCTs included in the three network meta-analyses, there were some notable differences between them. With respect to RCTs of infliximab and adalimumab, Thorlund 2014 excluded *Probert 2003* because the outcomes of interest were only assessed at 6 weeks, not 8 weeks. The sensitivity analysis in which Stidham 2014 excluded *Probert 2003* did not "substantively affect composite treatment effects". Danese 2014 included a Japanese RCT, *Suzuki 2014*, not included by either of the others, possibly because it was not available at the time of publication. Two other infliximab studies included by Thorlund 2014 and not the other two Network meta-analyses were analyses of colectomy and quality of life of an RCT included by this and the other two Network meta-analyses (*Rutgeerts 2005; ACT 1*). While Danese 2014 chose not to synthesize maintenance trial data to form indirect effect estimates because of the mixture of study designs, Stidham 2014 performed a sensitivity analysis excluding studies that required response to induction (a single golimumab RCT) and found that it did not "substantively

affect composite treatment effects." Thorlund's paper did not include 52 week results from ULTRA-1 given that patients that did not have a response to placebo were allowed to cross-over to adalimumab. "ULTRA-2 trial allowed patients with inadequate response 12 weeks or later to either switch to adalimumab or escalate their dose – patients who chose to switch were analyzed using "non-responder" imputation." The corrected covered area (CCA) for these network meta-analyses was calculated to be 0.4 (or 40%). As described by Pieper et al a CCA of more than 15% is considered to be a very high degree of overlap. However, this 15% cut-off was not justified by the authors.(50)

Efficacy outcomes in network meta-analyses of TNF-α inhibitors in ulcerative colitis

The efficacy results of TNF-α inhibitors for induction and maintenance of remission, response, and mucosal healing for the three network meta-analyses in ulcerative colitis are presented in Table 2.3.

Table 2.3: Efficacy of TNF-alpha inhibitors in network meta-analyses in ulcerative colitis								
		Any Anti-TNF vs placebo	Adalimumab vs placebo	Infliximab vs placebo	Golimumab vs placebo	Infliximab vs adalimumab	Infliximab vs golimumab	Golimumab vs adalimumab
Induction of remission (OR, 95% CI or 95% CrI)								
	Danese	NA	1.91 (0.98,3.72)	5.33 (2.28,13.63)	2.90 (1.19,6.54)	2.79 (0.95-8.83)	1.84 (0.58-6.92)	1.52 (0.50-4.28)
	Stidham[a]	RR=2.45 (1.72,3.47)	RR=1.87 (1.27,2.75)	RR=2.76 (1.29,5.90)	RR=3.00 (1.75,5.14)	RR=2.08 (0.32-12.03)	RR=1.18 (0.13-10.63)	RR for adalimumab vs golimumab = 1.75 (0.17-16.86)
	Thorlund	NA	2.22 (1.23,3.98)	5.26 (2.94,9.99)	NA	**2.38 (1.03,5.26)**	NA	NA
Induction of response (OR, 95% CI)								
	Danese	NA	1.76 (1.19-2.56)	4.13 (2.39-7.16)	2.11 (1.18-3.28)	**2.36 (1.22-4.63)**	1.96 (0.99-4.48)	1.20 (0.60-2.12)
	Stidham[a]	RR=1.65 (1.37-1.99)	RR=1.36 (1.13-1.64)	RR=2.00 (1.64-2.44)	RR=1.75 (1.40-2.19)	RR=2.12 (0.73-5.80)	RR=1.48 (0.38-4.69)	RR=1.46 (0.42-5.38)
	Thorlund	NA	1.87 (1.18-2.97)	4.15 (2.53-6.82)	NA	**OR for adalimumab vs infliximab = 0.45 (0.23-0.89)**	NA	NA
Maintenance of remission (OR, 95% CI)								
	Danese[b]	NA	2.78 (1.75-4.41)	2.30 (1.37-3.86)	1.81 (1.10-3.00)[c]	NA	NA	NA
	Stidham[a]	RR=2.00 (1.52-2.62)	RR=2.06 (1.26-3.38)	RR=2.10 (1.31-3.36)	RR=1.86 (1.19-2.90)	RR=1.18 (0.19-8.02)	RR=1.22 (0.18-8.43)	RR for adalimumab vs golimumab = 1.04 (0.16-6.96)
	Thorlund	NA	1.99 (1.08-3.89)	2.73 (1.50-5.14)	NA	OR for adalimumab vs infliximab =	NA	NA

						0.72 (0.31-1.76)		
Maintenance of response (OR, 95% CI)								
	Danese[b]	NA	2.89 (1.96-4.28)	1.90 (1.27-2.86)	2.24 (1.41-3.56)[c]	NA	NA	NA
	Stidham[a]	RR=1.76 (1.46-2.14)	RR=1.68 (1.21-2.33)	RR=2.29 (1.52-3.45)	RR=1.61 (1.22-2.13)	RR=1.70 (0.17-16.59)	RR=1.47 (0.15-14.43)	For adalimumab vs golimumab, RR=1.14 (0.11-10.92)
	Thorlund	NA	1.81 (1.09-3.05)	3.39 (1.94-6.06)	NA	OR for adalimumab vs infliximab = 0.54 (0.25-1.13)	NA	NA
Mucosal healing, induction (OR, 95% CI)								
	Danese		1.64 (1.18-2.31)	3.31 (2.07-5.32)	1.84 (1.18-2.81)	**2.02 (1.13-3.59)**	1.80 (0.96-3.46)	1.12 (0.64-1.92)
	Stidham	NA	NA	NA	NA	NA	NA	NA
	Thorlund	NA	1.51 (0.96-2.39)	3.26 (2.21-0.84)	NA	**OR for adalimumab vs infliximab = 0.46 (0.25-0.84)**	NA	NA
Mucosal healing, maintenance (OR, 95% CI)								
	Danese[b]	NA	1.99 (1.30-3.06)	2.65 (1.79-3.92)	NA	NA	NA	NA
	Stidham	NA	NA	NA	NA	NA	NA	NA
	Thorlund	NA	1.91 (1.12-3.31)	3.77 (2.12-6.89)	NA	OR for adalimumab vs infliximab = 0.50 (0.23-1.11)	NA	NA

NA= not applicable; CI= confidence interval; CrI= credible interval

Bolded results are statistically significant indirect comparisons (95% CrI does not include 1)

[a]traditional pair-wise meta-analyses were used for all direct comparisons (all placebo comparisons). Statistically significant heterogeneity was found only with infliximab for

induction of remission: I-squared = 0.728 [b]pair-wise frequentist meta-analyses were performed for maintenance outcomes [c]In included trials, “included only persons who responded to induction in their maintenance phases”

Results are generally similar across the three network meta-analyses, with slight discrepancies explained by differences in included RCTs, the number of comparators included in the networks, and the use of relative risks by Stidham versus odds ratios by Danese and Thorlund. A comparison of the odds ratios in the studies by Thorlund 2014 and Danese 2014 reveals that for all efficacy outcome measures except induction of remission, Thorlund's estimates for efficacy of infliximab versus placebo are slightly higher while the estimates for efficacy of adalimumab versus placebo are all slightly lower. In Thorlund 2014 the comparison of infliximab versus adalimumab for induction of remission is still statistically significant, whereas in Danese 2014 it is not. Although the point estimate for this association is slightly lower in Thorlund 2014 at 2.38 as compared to 2.79, the 95% credible interval (CrI) is much narrower. All of the TNF-α inhibitors were consistently statistically significantly superior to placebo for all measures of efficacy with the exception of adalimumab for induction of mucosal healing in Thorlund 2014.

The author's conclusions in the 3 included studies are presented in Box 3.1:

Box 3.1: Conclusions of network meta-analyses of TNF-α inhibitors in Ulcerative colitis

Stidham 2014	"…compared to placebo, infliximab, adalimumab and golimumab are all effective for the induction and maintenance of remission in ulcerative colitis. However, network meta-analysis demonstrates that no single agent is clinically superior to the others…"
Danese 2014	"Biological agents are effective treatments for UC, but head-to-head trials are warranted to establish the best therapeutic option."
Thorlund 2014	"…both infliximab and adalimumab are superior to placebo in the treatment of moderate to moderately severe ulcerative colitis. While infliximab is statistically more effective than adalimumab in the induction of remission, response, and mucosal healing at 8 weeks, infliximab and adalimumab are comparable in efficacy at 52 weeks of maintenance treatment."

Safety outcomes in network meta-analyses of TNF-α inhibitors in ulcerative colitis

Two of the ulcerative colitis network meta-analyses assessed safety. In Danese 2014, measures of association were not calculated for safety outcomes; occurrence of serious adverse events, and adverse events leading to study discontinuation were reported as "event rates" (%) in each intervention group. The point estimate of frequency of serious adverse events, as well as adverse

events leading to withdrawal of study drug, were actually higher in all of the placebo comparator groups versus the TNF-α inhibitor intervention groups, except for the withdrawal of drug due to adverse events in golimumab placebo group versus active treatment which was 2.7% and 3.1% respectively. Thorlund 2014 reported results of a Bayesian network analysis for safety outcomes. Consistent with Danese 2014, risk of serious adverse events and discontinuation due to adverse events was lower in the TNF-α treatment groups (OR<1) for all comparisons versus placebo for any time point as well as at the 52 week time point, although differences were not statistically significant. Indirect comparison of infliximab versus adalimumab revealed more frequent occurrence of serious adverse events and discontinuation due to adverse events with adalimumab, except for an OR of 0.72, 95% CI 0.20-2.52 for discontinuation due to adverse events results at 52 weeks, although the differences were not statistically significant.

Quality assessment of network meta-analyses in ulcerative colitis

Quality was assessed using the AMSTAR quality assessment tool for the systematic review portion, and the ISPOR report on interpreting indirect treatment comparisons was used as a benchmark for high quality of the network meta-analysis portion specifically.(46) Details of the quality assessments are provided in Appendix 2.7. Two of the three Network meta-analyses were deemed to be of high quality according to AMSTAR criteria in addition to network meta-analysis specifically (Danese 2014 and Stidham 2014) and the third (Thorlund 2014) was of acceptable quality for both assessments. Only Danese 2014 provided an a priori design, and only Thorlund 2014 provided a list of excluded studies.

CROHN'S DISEASE

Systematic Reviews and meta-analyses in Crohn's disease

Twenty-six systematic reviews meeting eligibility criteria assessed efficacy and/or safety of TNF-α inhibitors in Crohn's disease, seven of which included both types of IBD. One systematic review was reported in two separate publications: Assasi 2009 and Assasi 2010, a 2009 Canadian Health Technology assessment from CADTH including both forms of IBD and a separate publication on the results for Crohn's disease specifically. Another systematic review was a Chinese publication which contained just slightly more information than a related English publication; therefore, these are presented together: Huang 2011 (Chinese) and Huang 2011 (English). Three systematic reviews'

results were not amenable to extraction; a list of included studies was not provided in two, De Cruz 2013 and Neurath 2012, and Mills 2011 did not include any RCTS, only systematic reviews that were already assessed for eligibility for this overview.

Efficacy and safety outcomes in systematic reviews and meta-analyses in Crohn's disease

Pooled effect sizes for efficacy and safety endpoints from included systematic reviews are reported in Table 2.4 below. Results of systematic reviews intending to pool results for studies that found only one RCT for a given outcome are also included in this table.

Table 2.4: Efficacy and safety outcomes for TNF-alpha inhibitors in Crohn's disease							
Study and search date	**Intervention / Comparison**	**Outcome definition; timing**	**Notable population and intervention characteristics[c]**	**Fixed *or* random effects model**	**Participants; studies**	**Effect size (95% CI)**	**Comments**
Induction of response							
Akobeng, 2009 June 2003	Infliximab / placebo	CR70; 4 weeks		NA	108 (1)	RR 4.07 (1.63, 10.12)	One study only (Targan 1997)
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Adalimumab / placebo	CR70; not specified	Restricted to the 160/80mg induction dose subgroup	Fixed	475 (2)	RR 1.60 (1.29, 1.98)	Fewer patients than Huang, 2011 despite same number of studies because of the dose subgroup
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Infliximab / placebo	CR70; not specified		Not applicable	2 studies	Results not pooled; see text	RCTs: Targan and Lemann; results not pooled.
Da, 2013 December 2011	Certolizumab / placebo	"Defined by Harvey–Bradshaw index or CD activity index"; 4-12 weeks		Fixed	807;3	OR 1.234 (0.912, 1.671)	An "overall" analysis that did not separate induction/maintenance included 5 studies (not reported here).
Huang, 2011 and Huang 2011(Chinese) June 2010	Adalimumab / placebo	Not defined; 4 weeks		Fixed	624 (2)	OR 1.93 (1.33, 2.79)	*Hanauer and Sandborn (GAIN and CLASSIC 1)*
Kawalec, 2013	TNF-alpha	CR70; 4 weeks		Fixed	Not	"Relative	Results of individual agents

November 2012	inhibitors (infliximab, adalimumab, certolizumab) / placebo				reported	Benefit" (RB) 1.64 (1.37, 1.95)	not reported for CR70; only for adalimumab and certolizumab for CR 100.
Kawalec, 2013 November 2012	Adalimumab / placebo	CR100; 4 weeks		Fixed	612;3	"Relative Benefit" (RB) 1.31 (0.53, 3.24)	
Kawalec, 2013 November 2012	Certolizumab / placebo	CR100; 4 weeks		Fixed	1173; 3	"Relative Benefit" (RB) 1.23 (0.99, 1.53)	
Lian 2006	TNF-alpha inhibitors (infliximab, adalimumab, certolizumab) / placebo	decreased CDAI score from the baseline >=100 or 70, or CDAI<=150; 4-52 weeks		Random	Not reported	RR 1.28 (1.11, 1.48)	Results for induction and maintenance outcomes were reported as subgroup analyses, with very few details provided.
Nikfar, 2012 July 2012	Certolizumab / placebo	CR100; timing not reported (included studies ranged from 4-26 weeks)	Restricted to the 400mg dose	Fixed	Not reported;5	RR 1.38 (1.22, 1.56)	Distinction between 'maintenance' and 'induction' not made for this outcome. Only 'induction' reported for response, both maintenance and induction for remission.
Rahimi, 2007 December 2005	TNF-alpha inhibitors (adalimumab, infliximab, certolizumab (CDP 870), CDP 571) / placebo	Not defined; 4 weeks	Other TNF-alpha inhibitors that have not received market authorization for IBD were included in the analysis	Random	Not reported (6)	OR 1.68 (0.96, 2.96)	Irrelevant comparison. Despite statistically significant heterogeneity, agents were not analyzed separately, and it was concluded that TNF-alpha inhibitors were ineffective.
Stidham, 2014	TNF-alpha	CD100 (except		Random	1771	RR 1.43 (1.17,	This study was a network

(Crohn's) August 2013	inhibitors (adalimumab, certolizumab, infliximab) / placebo	in one study,(Targan 1997); Up to 12 weeks			(6)	1.73)	meta-analysis, however pairwise meta-analyses were performed for placebo comparisons.
Stidham, 2014 (Crohn's) August 2013	Infliximab / placebo	CD70; Up to 12 weeks		Random	52 (1)	RR 4.01 (1.29, 12.44)	
Stidham, 2014 (Crohn's) August 2013	Adalimumab / placebo	CD100; Up to 12 weeks		Random	475 (2)	RR 1.71 (1.31, 2.24)	
Stidham, 2014 (Crohn's) August 2013	Certolizumab / placebo	CD100; Up to 12 weeks		Random	1244 (3)	RR 1.25 (1.07, 1.46)	
Induction of remission							
Akobeng, 2009 June 2003	Infliximab/ placebo	CDAI <150; 4 weeks		Not applicable	108 (1)	RR 8.13 (1.16, 56.89)	
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Adalimumab / placebo	CDAI less than 150; 2 weeks	Represents a subgroup who received the 160/80mg induction dose	Fixed	475 (2)	RR 2.94 (1.86, 4.66)	Results of 2 RCTs not pooled for infliximab vs placebo
Chande, 2013 June 2012	Azathioprine / infliximab	"clinical remission as measured with a validated outcome"; through 26		Fixed	339 (1)	RR 0.66 (0.51, 0.87)	

		weeks					
Chande, 2013 June 2012	Infliximab + azathioprine / infliximab	"clinical remission as measured with a validated outcome"; through 26 weeks		Fixed	338 (1)	RR 1.26 (1.03, 1.54)	
Da, 2013 December 2011	Certolizumab / placebo	"Defined by Harvey–Bradshaw index or CD activity index"; 4-12 weeks		Fixed	807 (3)	OR 1.361 (0.974, 1.901)	
Ford, 2011 December 2010	TNF-alpha inhibitors (infliximab, adalimumab, certolizumab) / placebo	See Below[a] ; Up to 4 months		Random	2756 (10)	RR 0.87 (0.80, 0.94)	RR is for failure to induce remission (less than 1 favors the intervention)
Ford, 2011 December 2010	Infliximab / placebo	See Below[a] ; Up to 4 months		Random	562 (3)	RR 0.68 (0.52, 0.90)	RR is for failure to induce remission (less than 1 favors the intervention)
Ford, 2011 December 2010	Adalimumab / placebo	See Below[a] ; Up to 4 months		Random	714 (3)	RR 0.85 (0.79, 0.91)	RR is for failure to induce remission (less than 1 favors the intervention)
Ford, 2011 December 2010	Certolizumab / placebo	See Below[a] ; Up to 4 months		Random	1480 (4)	RR 0.95 (0.90, 1.01)	RR is for failure to induce remission (less than 1 favors the intervention)
Huang, 2011 and Huang, 2011(Chinese) June 2010	Adalimumab / placebo	Not defined; 4 weeks		Fixed	624 (2)	OR 2.98 (1.78, 4.99)	*)*

Hutfless, 2014 June 2011	TNF-alpha inhibitors (infliximab, adalimumab, certolizumab)	"Disease activity measures (remission as measured by the CDAI, PCDAI, HBI, or other disease activity measurements)"; 2 weeks	Relevant Subgroup analysis: "In four trials that allowed prior TNF-alpha inhibitor use: RR 2.1 (95% CI, 1.5 to 3.0)". In three trials that excluded patients with prior use: RR of 1.5 (95% CI, 1.1 to 2.2; P=0.03)	Random	2208 (7)	RR 1.8 (1.4, 2.4)	This was the only pooled result reported in Hutfless, 2014 (AHRQ report).
Kawalec, 2013 November 2012	TNF-alpha inhibitors (Infliximab, adalimumab, certolizumab) / placebo	CDAI less than or equal to 150; 4 weeks		Fixed effects	2277 (8)	RR 1.90 (1.55, 2.33)	
Kawalec, 2013 November 2012	Infliximab / Placebo	CDAI less than or equal to 150; 4 weeks		Fixed	98 (1)	RR 4.88 (0.72, 33.24)	
Kawalec, 2013 November 2012	Adalimumab / Placebo	CDAI less than or equal to 150; 4 weeks		Fixed	714 (3)	RR 2.42 (1.60,3.63)	
Kawalec, 2013 November 2012	Certolizumab/ Placebo	CDAI less than or equal to 150; 4 weeks	Included a study where certolizumab was administered IV (Winter)	Fixed	1365 (4)	"Relative Benefit": 1.63 (1.32, 2.13)	
Lian, 2006 January 2006	TNF-alpha inhibitors (infliximab,	CDAI<=150		Random	Not reported	RR 1.31 (1.05, 1.63)	

	adalimumab, certolizumab)						
Nikfar 2013, July 2012	Certolizumab/ placebo	CDAI less than or equal to 150; timing not reported	Analysis restricted to 400mg dose	Random effects	Not reported; 2	RR 1.24 (0.99,1.54)	
Peyrin-Boulet, 2008 December 2006	TNF-alpha inhibitors as a class (infliximab, adalimumab, certolizumab)	CDAI less than or equal to 150; 4 weeks	In dose-ranging studies all doses were included, however it was noted that "exclusion of treatment groups receiving 80/40 or 40/20 of adalimumab or 100 and 200 of certolizumab did not change the overall efficacy of anti-TNF therapy."	Random	Not reported	RD 0.14 (0.09, 0.19)	This SR separated outcomes as short term induction of remission, long-term induction of remission, and maintenance after open-label induction; "short-term induction," defined as within 4 weeks. This result is excludes CDP571, onercept and etanercept trials.
Peyrin-Boulet, 2008 December 2006	Adalimumab / placebo	CDAI less than or equal to 150; 4 weeks	"	Random	Not reported (2)	RD 0.14 (0.08, 0.20)	
Peyrin-Boulet, 2008 December 2006	Certolizumab / placebo	CDAI less than or equal to 150, 4 weeks	"	Random	Not reported (3)	RD 0.10 (0.06, 0.14)	
Rahimi, 2007 December 2005	TNF-alpha inhibitors as a class (infliximab,	Not defined; 4 weeks		Random	Not reported (7)	OR 1.67 (0.94, 2.96)	Irrelevant comparison

	certolizumab, CDP 571, etanercept) / placebo						
Stidham, 2014 (Crohn's) August 2013	TNF-alpha inhibitors (Infliximab, adalimumab, certolizumab) / placebo	CDAI score of less than 150; up to 12 weeks	Restricted to current approved doses	Random	1771 (6)	RR 1.66 (1.17, 2.36)	
Stidham, 2014 (Crohn's) August 2013	Infliximab / placebo	CDAI score of less than 150; up to 12 weeks	Restricted to 5mg/kg dose subgroup	Random	52 (1)	RR 3.70 (0.87, 15.80)	
Stidham, 2014 (Crohn's) August 2013	Adalimumab / placebo	CDAI score of less than 150; up to 12 weeks	Restricted to 160mg/80mg dose subgroup	Random	475 (2)	RR 2.94 ((1.86, 4.66)	
Stidham, 2014 (Crohn's) August 2013	Certolizumab / placebo	CDAI score of less than 150; up to 12 weeks	Restricted to 400mg dose subgroup; Study assessing IV certolizumab not included (Winter 2004)	Random	1244 (3)	RR 1.22 (1.00, 1.50)	
Maintenance of response							
	Certolizumab / placebo	CD100; 24-30 weeks	Analysis restricted to 400mg dosing; Included an RCT with randomization before induction	Random	1088 (2)	RR 1.64 (1.37, 1.97)	
Assassi, 2009	Infliximab /	Decrease in	These results	Fixed	287	RR 2.75	Results for 5mg/kg and

and Assassi, 2010 April 2008 and November 2008	placebo	CDAI of 70 points or a decrease in 70-100 and 25% improvement from baseline; not specified	represent a subgroup receiving the 5mg/kg dose Randomization after response to induction	effects	(2)	(1.72, 4.40)	10mg/kg reported separately
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Adalimumab / placebo	CR70 or a decrease in CDAI of 70-100 and 25% improvement from baseline; not reported	These results represent a subgroup receiving 40mg every other week	Fixed	379 (2)	RR 2.03 (1.51, 2.71)	Results for 40mg weekly and every two weeks are reported separately. I-squared 91%. Fixed and random effects models were reported in Assasi 2009; random effects was not statistically significant: RR 1.63, 95% CI 0.67-3.98.
Behm, 2009 July 2007	Infliximab / placebo	Response "as defined by the primary studies"; not reported	Patients with response to induction therapy with an anti-TNF agent	Random	404 (2)	RR 2.19 (1.27, 3.75)	
Behm, 2009 July 2007	Adalimumab / placebo	Response "as defined by the primary studies"; not reported	Patients with response to induction therapy with an anti-TNF agent	Random	499 (1)	RR 2.69 (1.88, 3.86)	
Behm, 2009 July 2007	Certolizumab / placebo	Response "as defined by the primary studies"; not reported	Patients with response to induction therapy with an anti-TNF agent	Random	425 (1)	RR 1.74 (1.41, 2.13)	

Da, 2013 December 2011	Certolizumab / placebo	"Defined by Harvey–Bradshaw index or CD activity index"; Timing not reported (both studies were 26 weeks long)	Includes an RCT with randomization before induction (Sandborn 2007) and initial open-label response to certolizumab (Schreiber 2007)	Fixed	1084 (2)	OR 2.171 (1.644, 2.866)	
Kawalec, 2013 November 2012	TNF-alpha inhibitors (infliximab, adalimumab)/ placebo	CR70; 48-56 weeks	All included RCTS randomized after initial response or remission to induction	Fixed	Not reported; 5	RB 2.06 (1.32, 3.23)	Results for individual agents not reported for CR70.
Kawalec, 2013 November 2012	TNF-alpha inhibitors (Certolizumab, adalimumab) / placebo	CR100; 26-56 weeks	All included RCTS randomized after initial response or remission to induction	Fixed	1117; 4	RB 2.03 (1.48, 2.78)	I-squared 63%
Kawalec, 2013 November 2012	Adalimumab / placebo	CR100; 26-56 weeks	All included RCTS randomized after initial response or remission to induction	Fixed	692;3	RB 2.21 (1.40, 3.51)	
Kawalec, 2013 November 2012	Certolizumab / placebo	CR100; 26-56 weeks	All included RCTS randomized after initial response or remission to induction	Fixed	425;2	RB 1.74 (1.41, 2.13)	
Lian 2006 January 2006	TNF-alpha inhibitors (infliximab, adalimumab, certolizumab)	Decreased CDAI score from the baseline >=100 or 70, or CDAI<=150; 4-		Random	Not reported	RR 1.62 (1.23, 2.14)	Results for induction and maintenance outcomes were reported as subgroup analyses, with very few details provided.

	/ placebo	52 weeks					
Stidham 1003	TNF-alpha inhibitors (certolizumab, adalimumab) / placebo	CD100; 24-30 weeks	Analysis restricted to current approved doses. Included an RCT (certolizumab, Sandborn 2007) with randomization before induction.	Random	1467 (4)	RR 1.68 (1.46, 1.93)	The outcome was defined as a decrease in CDAI of 100 or 70 or more from baseline within 12 weeks; CD100 was reported for certolizumab and adalimumab, and it was reported that "compatible data not available for infliximab".
Stidham 1003	Adalimumab / placebo	CD100; 24-30 weeks	Analysis restricted to 40mg every other week dosing	Random	379 (2)	RR 1.69 (1.19, 2.41)	
Maintenance of remission							
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Infliximab / placebo	CDAI = 150 points or CDAI is less than 150 points and it is decreased by 50 to 100 points; not reported	Only reported pooled results for infliximab maintenance for 10mg/kg dose; Included RCTs randomized participants with initial response or remission	Fixed	295 (2)	RR 2.80 (1.83, 4.30)	
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Adalimumab / placebo	CDAI = 150 points or CDAI is less than 150 points and it is decreased by 50 to 100 points; not reported	Analysis specific to 40mg every other week; Included RCTs randomized participants with initial response or remission to	Fixed	379 (2)	RR 2.66 (1.83, 3.86)	Assassi 2009 reported fixed effects even though I-squared = 65%; Assassi 2010 reported both: Random effects = RR 2.31 (1.23, 2.62).

			open-label or placebo/adalimumab				
Behm, 2009 July 2007	Infliximab / placebo	Not defined; timing not specified	Patients with response to induction therapy with an anti-TNF agent	Fixed	404 (2)	RR 2.50 (1.64, 3.80)	
Behm, 2009 July 2007	Certolizumab / placebo	Not defined; timing not specified	Patients with response to induction therapy with an anti-TNF agent	NA	425 (1)	RR 1.68 (1.30, 2.16)	
Da, 2013 December 2011	Certolizumab / placebo	"Defined by Harvey–Bradshaw index or CD activity index"; timing not reported but each included study was 26 weeks	Included an RCT with randomization before induction	Fixed	1084 (2)	OR 1.888 (1.390, 2.565)	
Dretzke	Results not pooled for any comparisons. See text.						
Ford, 2011 December 2010	TNF alpha inhibitors (infliximab, adalimumab, certolizumab) / placebo	See below;[b] At least 6 months.	Rather than "maintenance of remission", the outcome was termed "prevention of relapse of quiescent CD";	Random	1390 (5)	RR 0.71 (0.65, 0.76)	Sensitivity analyses: included only the 3 studies that randomized those who responded to or achieved remission after open-label treatment with anti-TNF (as opposed to anti-TNF or placebo) and found almost

			Only studies randomizing after an initial response or remission were included in the analysis				identical results: (RR 0.71, 95% CI 0.66-0.77)
Ford, 2011 December 2010	Infliximab / placebo	See below;[b] At least 6 months	Only studies randomizing after an initial response or remission were included in the analysis for this outcome.	Random	408 (2)	RR 0.72 (0.63, 0.83)	
Ford, 2011 December 2010	Adalimumab / placebo	See below;[b] At least 6 months	Only studies randomizing after an initial response or remission were included	Random	554 (2)	RR 0.54 (0.27, 1.07)	
Ford, 2011 December 2010	Certolizumab / placebo	See below;[b] At least 6 months	Only studies randomizing after an initial response or remission were included	Random	428 (1)	RR 0.73 (0.63, 0.85)	
Huang, 2011 and Huang, 2011(Chinese) June 2010	Adalimumab / placebo	Not defined; 56 weeks	Included studies only randomized remitters or responders	Fixed	554 (2)	OR 4.79 (2.96, 7.73)	
Hutfless, 2014	Results not pooled.						

June 2011							
Kawalec, 2013 November 2012	TNF-alpha inhibitors (Infliximab, adalimumab) / placebo	CDAI less than or equal to 150; 48-56 weeks	See next two	Fixed	1141 (6)	RR 2.75 (2.13, 3.54)	This result is for 48-56 weeks, so only infliximab and adalimumab were pooled.
Kawalec, 2013 November 2012	Infliximab / placebo	CDAI less than or equal to 150; 48-56 weeks	Included RCTs randomized participants with initial response to placebo or infliximab or to open label infliximab	Fixed	408 (2)	RB 2.28 (1.48, 3.50)	
Kawalec, 2013 November 2012	Adalimumab / placebo	CDAI less than or equal to 150; 48-56 weeks	Included 1 RCT with randomization before induction. Other included RCTs randomized participants with initial response or remission to open-label or placebo/adalimumab.	Fixed	733 (4)	RB 3.03 (2.21, 4.16)	
Kawalec, 2013 November 2012	Certolizumab / placebo	CDAI less than or equal to 150; 20-30 weeks	Included an RCT with randomization before induction	Fixed	Not reported (2)	RB 1.64 (1.36, 1.99)	
Lian, 2006 January 2006	TNF-alpha inhibitors (infliximab, adalimumab,	4-56 weeks		Random	Not reported	RR 1.96 (1.39, 2.76)	Results for induction and maintenance outcomes were reported as subgroup analyses, with very few details

	certolizumab) / placebo						provided.
Mills, 2011 December 2009	Infliximab / placebo	*NA*	*NA*	*NA*	*NA*	*NA*	Results of other systematic reviews are described qualitatively
Nikfar, 2013 July 2012	Certolizumab / placebo	CDAI less than or equal to 150; not reported	Randomization occurred before induction in two of the Included RCTs. Analysis restricted to 400mg dose.	Random ("Homogeneous, but too few studies to apply fixed effects")	Not reported (3)	RR 1.54 (1.26, 1.89)	The only Certolizumab maintenance comparison to have 3 studies; one of them appears to be a "short-term" 12-week induction study.
Peyrin-Boulet, 2008 December 2006	TNF-alpha inhibitors as a class (adalimumab, certolizumab, infliximab) / placebo	CDAI less than or equal to 150, 48-52 weeks	Participants with Initial response to TNF-alpha; patients responding to placebo were not included in the analysis.	Random	Not reported (4)	RD 0.23 (0.18, 0.29)	"When considering responders and non-responders after open-label induction in 3 trials, mean difference and 95% CI = 11.6, 5-18" at weeks 20-30.
Peyrin-Boulet, 2008 December 2006	Infliximab / placebo	CDAI less than or equal to 150, 48-52 weeks	Participants with initial response to a TNF-alpha inhibitor	Random	Not reported (2)	RD 0.19 (0.11, 0.27)	Results for certolizumab and adalimumab not reported individually; one study each.
Stidham, 2014 (Crohn's) August 2013	TNF-alpha inhibitors (adalimumab, certolizumab, infliximab) / placebo	CDAI score of less than 150; 24-30 weeks	Included an RCT (*Sandborn 2007*) with randomization before induction.	Random	1690 (5)	RR 1.78 (1.51, 2.09)	
Stidham, 2014	Infliximab /	CDAI score of		Not	223	RR 1.86 (1.21,	

(Crohn's) August 2013	placebo	less than 150; 24-30 weeks		applicable	(1)	2.86)	
Stidham, 2014 (Crohn's) August 2013	Adalimumab / placebo	CDAI score of less than 150; 24-30 weeks	Included RCTs randomized participants with initial response or remission to open-label or placebo/adalimumab,	Not applicable	379 (2)	RR 2.06 (1.50, 2.82)	
Stidham, 2014 (Crohn's) August 2013	Certolizumab / placebo	CDAI score of less than 150; 24-30 weeks	Included an RCT (Sandborn 2007) with randomization before induction.	Not applicable	1088 (2)	RR 1.62 (1.30, 2.02)	
Mucosal Healing							
Chande, 2013 June 2012	Azathioprine / infliximab	Not defined; Through 26 weeks		NA	214 (1)	RR 0.55 (0.33, 0.94)	
Chande, 2013 June 2012	Infliximab + azathioprine / infliximab	Not defined; Through 26 weeks		NA	210 (1)	RR 1.50 (1.02, 2.19)	
Hospitalization							
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Results of included RCTs described narratively (3 infliximab and one adalimumab RCT).						
Costa, 2013	Infliximab/ placebo	Hospitalization related to IBD;		Random	Not report	OR 0.48 (0.34, 0.67)	Results for Crohn's and ulcerative colitis also reported

		6-54 weeks			ed (3)		as a pooled estimate.
Surgery							
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Results of included RCTs described narratively (2 infliximab and 1 adalimumab)						
Costa, 2013 May 2012	Infliximab / placebo	"overall major surgery rate (such as any resection of a part of the gut, strictureplasty, or ostomy)"; 6-54 weeks		Random	Not reported; 2	OR 0.31 (0.15, 0.64)	Results for Crohn's and ulcerative colitis not pooled for this outcome.
Serious Adverse Events							
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Infliximab / placebo	Not defined; not reported			395 (5)	RD -6.6 (p=0.065)	
Assassi, 2009 and Assassi, 2010 April 2008 and November 2008	Adalimumab / placebo	Not defined; not reported			1457 (4)	RD -4.7 (p=0.001)	
Chande, 2013 June 2012	Azathioprine / infliximab	Through 54 weeks		NA	324 (1)	RR 1.12 (0.77, 1.62)	
Chande, 2013	Infliximab +	Through 54		NA	342	RR 0.63 (0.41,	Fewer SAEs with combination

June 2012	azathioprine / infliximab	weeks			(1)	0.98)	therapy
Ford, 2011 December 2010	TNF-alpha inhibitors as a class / placebo	Not defined; Up to 4 months		Random	2309 (8)	RR 0.97 (0.64, 1.49)	Severe adverse events were reported only for induction trials; "too few data to perform any other meaningful analyses with respect to adverse events for the maintenance trials." Only reported for these drugs as a class.
Huang, 2011 and Huang, 2011(Chinese) June 2010	Adalimumab / placebo	Not defined; 56 weeks		Fixed	833 (2)	OR 0.51 (0.33-0.80) (P= 0.003)	
Kawalec, 2013 November 2012	TNF-alpha inhibitors (infliximab, adalimumab, certolizumab) / placebo	26-56 weeks (maintenance)		Fixed	2295 (7)	RR 0.70 (0.58, 0.86)	Also assessed SAEs for induction trials.
Kawalec, 2013 November 2012	Infliximab / placebo	26-56 weeks (maintenance)		Fixed	855 (2)	RR 0.78 (0.61, 1.00)	
Kawalec, 2013 November 2012	Adalimumab / placebo	Through 56 weeks (maintenance)		Fixed	1012 (4)	RR 0.55 (0.38, 0.79)	
Kawalec, 2013 November 2012	Certolizumab / placebo	Through 56 weeks (maintenance)		Not applicable	428 (1)	RR 0.84 (0.40, 1.78)	
Lian, 2006	TNF-alpha inhibitors	Not reported; 4-56 weeks		Random	Not report	RR 0.87 (0.73, 1.04)	

January 2006	(infliximab, adalimumab, certolizumab) / placebo				ed (11)		
McDonald, 2012 June 2012	Infliximab + Methotrexate / infliximab	Not defined; Not reported		Not applicable (1 study)	19 (1)	RR 0.25 (0.01, 5.45)	
Zhang, 2013 June 2012	infliximab, adalimumab, certolizumab, and CDP 571 / placebo	"adverse events which require intervention to prevent life-threatening impairment or damage."; minimum 24 weeks	In 8 of the 13 studies, all participants received induction therapy with TNF-alpha inhibitors.	Fixed	4257 (13)	OR 0.80 (0.67, 0.96)	Two of the included studies assessed CDP 571.
Zhang, 2013 June 2012	Adalimumab / placebo	"adverse events which require intervention to prevent life-threatening impairment or damage."; minimum 24 weeks		Fixed	1129 (5)	0.57 (0.39, 0.84)	
Withdrawal or discontinuation of medication due to adverse effects							
Chande, 2013 June 2012	Azathioprine / infliximab	Not defined; Not reported			324 (1)	RR 1.47 (0.96, 2.23)	
Chande, 2013 June 2012	Infliximab + azathioprine / infliximab	Not defined; Not reported			342 (1)	RR 1.16 (0.75, 1.80)	More withdrawals due to adverse events in the combination therapy group (not statistically significant),

							although more SAEs in the monotherapy group
McDonald, 2012 June 2012	Infliximab + methotrexate / infliximab	Not defined; 2 studies – results not pooled.					Extracted data from each study separately; not in this table.
Malignancy							
Peyrin-Boulet, 2008 December 2006	TNF-alpha inhibitors as a class (Adalimumab, infliximab, certolizumab, etanercept, onercept, CDP571) / placebo	Any malignancy; timing not reported	Overall analysis included trials of any design; subgroup analyses of short-term induction trials, short and long-term induction trials, and maintenance trials with randomization after open-label induction were reported.	Random	Not reported (21)	RD 0.0004 (-0.002-0.003) "No difference in frequency of malignancies between anti-TNF and control groups in short-term induction trials."	More studies were included in the safety than in the efficacy analyses; studies were excluded from efficacy analyses for non-standard design or when information about pre-specified outcomes was not available.
Williams, 2014 November 2013	TNF-alpha inhibitors as a class (adalimumab, certolizumab, golimumab, infliximab) / placebo	Any malignancy; timing not reported	**BOTH TYPES of IBD.** Only RCTs reporting occurrence of malignancy in both arms were included.	Random	7054 (22)	RR 0.77 (0.37, 1.59)	"[Results] remained nonsignificant throughout the numerous pre-defined subgroup analyses we conducted according to type of IBD, anti-TNFa agent used, duration of therapy, concomitant use of immunosuppressants, exposure to anti-TNFa therapies during induction of remission, study design and risk of bias of studies."

Zhang, 2013 June 2012	TNF-alpha inhibitors (Infliximab, adalimumab, certolizumab, CDP 571) / placebo	"a medical condition, especially tumors, characterized by anaplasia, invasiveness and metastasis"; from 24 weeks		Fixed	2969; 6	OR 0.47 (0.19-1.16)	Results for individual agents not reported. One of the included studies is for CDP 571.

95% CI=95% confidence interval; RR=relative risk; OR=odds ratio; NR=not reported; NA=not applicable; CR70 = “a reduction of CDAI of 70 or more points from baseline”; CR 100 = “a reduction of CDAI of 100 or more points from baseline” (Quoted from Kawalec 101

[a] Hierarchy of endpoint definitions was used: "Luminal CD remission : Crohn’s disease activity index (CDAI) <150 (or other validated index), endoscopic evidence of complete remission (most stringent definition available, for example, complete mucosal healing), clinical assessment of complete remission, or other author-defined criteria for remission.

[b] Luminal CD relapse : CDAI ≥ 150, endoscopic/ radiological evidence of relapse (most stringent definition available), other CDAI cutoff, clinical assessment as relapsed, or other author-defined criteria for relapse.

[c]Notable population and intervention characteristics include restricted to a specific dose, *or* restricted to remitters/responders for maintenance studies. Where systematic reviews restricted analyses to certain doses this is noted; otherwise all active arms vs placebo were included in the analyses.

The most frequently analyzed outcomes in the included systematic reviews were induction and maintenance of remission. Point estimates of efficacy of TNF-α inhibitors versus placebo consistently demonstrated superiority of TNF-α inhibitors. However, the magnitude of the estimates differed between systematic reviews. To explore the magnitude of the differences in effect estimates between studies, effect estimates for induction and maintenance of remission in both Crohn's disease and ulcerative colitis were converted to risk differences if these were not reported already in the study. The calculation was done using results of a systematic review of placebo remission rates from RCTs in IBD patients, due to lack of better baseline prevalence data. Forest plots of risk differences for induction and maintenance of remission from the included systematic reviews are presented in the sections below. See Appendix 2.6 for relevant calculations and an explanation regarding the baseline prevalence values that were chosen.

Although most of the included systematic reviews pooled results from included RCTs for the individual TNF-α inhibitors and/or TNF-α inhibitors as a class of medications, in Dretzke's systematic review, a National Institutes of Health Research (NIHR) Health Technology Assessment, investigators determined that it was inappropriate to pool results for any comparisons of any outcomes. Only adalimumab and infliximab were included in this systematic review. Specifically with respect to induction, the authors state: "The two adalimumab trials differed with respect to their populations: CLASSIC I excluded patients if they had previously received any TNF-α inhibitor treatment while the GAIN trial recruited only patients who had previously experienced infliximab treatment but had proved intolerant or unresponsive; because of these clear population differences results from the two trials were not pooled. The existence of only a single induction trial for infliximab in this population precluded pooling."(68) Detailed results of each of the included RCTs are reported in the systematic review. The Agency for Healthcare Research and Quality (AHRQ) report of comparative effectiveness of pharmacologic therapies for Crohn's disease, Hutfless 2014, reported only one pooled comparison. In this report it was stated that pooled results were not reported in the case of substantial statistical heterogeneity, defined as: "(1) a chi-squared test with a significance level of α less than or equal to 0.10 and (2) an I-squared statistic with a value of 50 percent or more, indicating substantial heterogeneity."(18)

Induction of response and remission

Systematic reviews that reported pooled estimates for the three TNF-α inhibitors as a class versus placebo for induction of remission found fairly consistent results: Kawalec 2013 found an RR 1.90

for infliximab versus placebo (95% CI 1.55, 2.33), Assasi 2009 found a similar RR of 1.8 (95% CI 1.4, 2.4) in a systematic review that included one less RCT, Ford 2011 found an RR 0.87 (95% CI 0.80, 0.94) with a switch of event and non-event, and Hutfless 2014 reported a risk difference of 0.14 (95% CI 0.09, 0.19). Most comparisons of TNF-α inhibitors as individual agents versus placebo for induction of remission reached statistical significance, with the exception of four of the six systematic reviews pooling data for certolizumab (Stidham 2014, Ford 2011, Da 2013, Nikfar 2012), and one of the three systematic reviews reporting results for infliximab, Stidham 2014. Results from Stidham 2014 were from a single RCT; this systematic review restricted analyses to the 5mg/kg dose and therefore had a smaller sample size.

Although Assasi 2009 pooled results for adalimumab versus placebo and Hutfless 2014 for TNFα inhibitors as a class versus placebo, induction of remission results were not pooled for other comparisons.

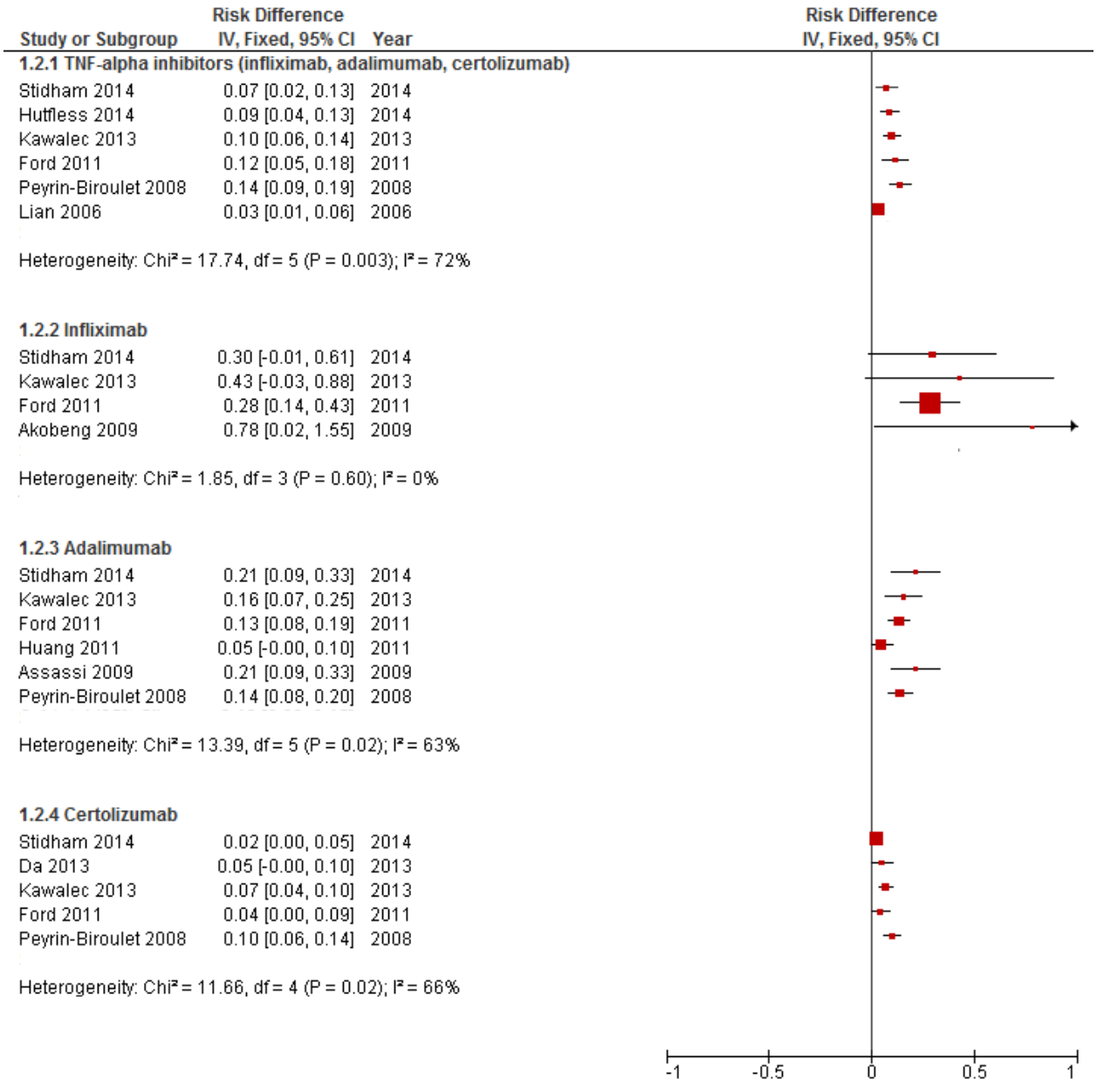
A systematic review (Chande 2013) reporting the results of a single RCT showed that combination therapy of infliximab + azathioprine was statistically significantly superior to infliximab for induction of remission with a RR 1.26 (1.03, 1.54). McDonald 2012 did not pool results for two studies, one with a RR of 1.07 (0.57, 2.03) and another with a RR of 0.73 (0.31, 1.69) for induction of remission.

Two systematic reviews pooled results from studies of all three relevant TNF-α inhibitors versus placebo for induction of response (Kawalec 2013 and Lian 2006), and both found that these agents were statistically significantly superior to placebo. Adalimumab was statistically significantly superior to placebo in three of the included systematic reviews but only trended towards superiority in Kawalec 2013. Results from a single infliximab RCT described in the Cochrane review, Akobeng 2009, were statistically significant for induction of response. Results for certolizumab were somewhat inconsistent, likely owing to the inconsistency in which RCTs were included in the systematic reviews for this outcome; RCTs characterized as “maintenance” studies in the AHRQ report, for example, were included as “induction” RCTs in Nikfar’s 2014. Certolizumab was statistically significantly superior to placebo in Nikfar 2014 and Stidham 2014 and trended towards superiority in Da 2013 and Kawalec 2013.

The converted risk differences for induction of remission are displayed in Figure 2.4. Risk differences were statistically heterogeneous among the included systematic reviews for TNF-alpha inhibitors as a class versus placebo, adalimumab versus placebo, and certolizumab versus placebo. When a single

systematic review of unacceptable quality was removed, Lian 2006, the I^2 for the comparison of TNF-alpha inhibitors versus placebo dropped from 72% to 0%. Similarly, when Huang 2011, a systematic review of unacceptable quality, was removed from the adalimumab group of studies the I^2 dropped from 63% to 0%. No single study appears to explain the statistical heterogeneity observed among the certolizumab estimates, however. These statistical differences could be explained by differences in the included RCTs; Da 2012 did not include an RCT included by the others for unclear reasons, and an RCT in which certolizumab administered IV instead of subcutaneously *(winter 2012)* was included by some systematic reviews and not others. Also, the placebo rate used to calculate the risk difference (11%) was substantially lower than the overall placebo rate reported in the certolizumab RCTs (over 20%).

Figure 2.4: Forest plot of comparison: TNF-alpha inhibitors vs placebo in Crohn's disease. Outcome: Induction of remission



Maintenance of response and remission

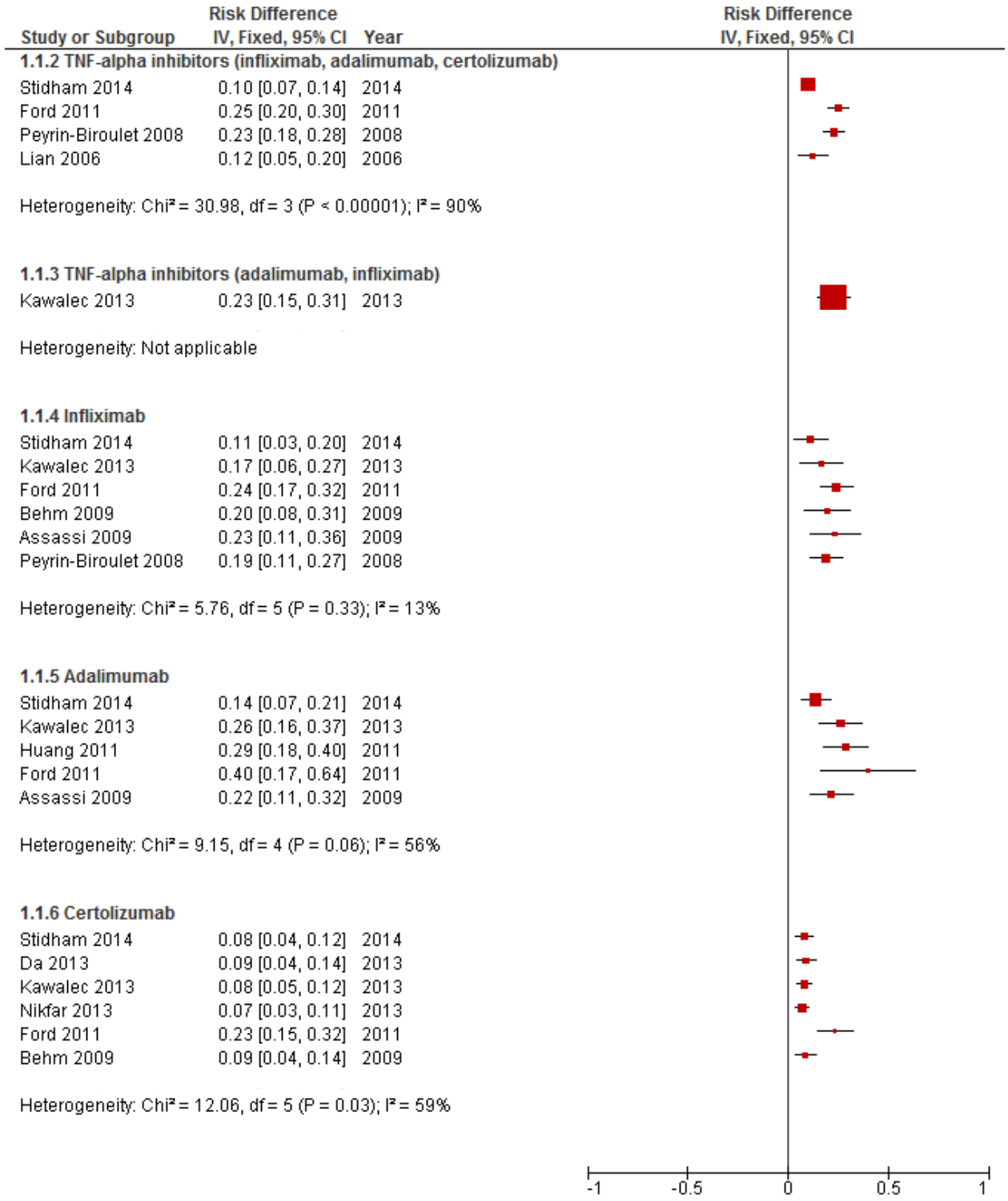
Timing of outcome measurement for maintenance of response and remission ranged from 20 to 56 weeks, but was most often from 48-56 weeks. Studies pooling comparisons of all three relevant TNF-α inhibitors versus placebo (Ford 2011 and Peyrin-Biroulet 2008) as well as infliximab and

adalimumab together versus placebo (Kawalec 2013), found that as a class they were statistically significantly superior to placebo for maintenance of remission. Individual agents were consistently statistically significantly superior to placebo for maintenance of remission, with the exception of adalimumab in one of the five studies reporting pooled analyses (Ford 2011). Behm 2009, a Cochrane review, reported results from the two adalimumab RCTs separately for this outcome due to heterogeneity.

Again, as for the induction outcomes, Dretzke 2011 did not pool results for any comparisons for maintenance of remission or maintenance of response. They stated that the two adalimumab trials "differed fundamentally with respect to populations analysed for outcome results," in agreement with the Cochrane review, Behm 2009. With respect to infliximab, "the pre-maintenance 'induction' phases of the two trials were very different, so the populations analysed for maintenance outcomes were likely to be quite different at the start of maintenance…(up to sixfold difference in exposure, different requirement in duration of response 70, and between four- and sixfold difference in duration of induction phase) is that the populations were unlikely to be sufficiently similar for the pooling of results to be informative."(68) Results of included RCTs are described narratively in Dretzke 2011.

When converted to risk differences, pooled estimates for maintenance of remission differed substantially between systematic reviews for the comparison of certolizumab versus placebo, as shown in Figure 2.5.The conversion of risk ratio or odds ratio to risk difference was calculated again using a placebo event rate of 28.5%, taken from the certolizumab RCT that was included in these systematic reviews. This made the calculated risk differences for Behm 2009 and Ford 2011 identical at 0.19, whereas they are quite different when calculated using a baseline prevalence of 13%, at 0.08 and 0.23 as reported in the Forest plot below. Ford 2011 also has the highest calculated Risk Difference for the comparisons of Adalimumab versus placebo and TNF-alpha inhibitors as a class versus placebo.

Figure 2.5: Forest plot of comparison: TNF-alpha inhibitors vs placebo in Crohn's disease. Outcome: Maintenance of remission



All pooled comparisons of TNF-α inhibitors as a class or as individual agents versus placebo for maintenance of response were statistically significant for superiority.

Mucosal healing

Results for mucosal healing were not pooled for any comparisons of TNF-α inhibitors versus placebo in Crohn's disease, however De Cruz 2013 and Neurath 2012 narratively described relevant studies. Observational studies, a sub-study of an infliximab RCT, a 52-week adalimumab RCT of 135 patients (*EXTEND*) and an open-label uncontrolled certolizumab study (*MUSIC*) are described. Chande 2013 found combination therapy of infliximab and azathioprine versus infliximab alone to be statistically significantly superior to infliximab for mucosal healing with a relative risk of 1.50 (95% CI 1.02, 2.19) in a single RCT, and the relative risk of mucosal healing with azathioprine compared to infliximab was 0.55 (95% CI 0.33, 0.94) in a single RCT.

Hospitalization and surgery

Only Costa 2013 reported pooled results for hospitalization or surgeries for TNF-α inhibitors versus placebo in Crohn's disease. With respect to hospitalizations, the pooled OR from five clinical trials in IBD patients was 0.51 (95% CI 0.40-0.65) for IBD patients, and was 0.48 (95% CI 0.34-0.67) from three Crohn's disease RCTs. The pooled OR for major surgeries was 0.31 (0.15, 0.64) from two Crohn's disease trials.

Serious adverse events

Effect size estimates differed across the included systematic reviews with respect to serious adverse events, however, there was a consistent trend towards fewer serious adverse events with TNF-α inhibitors as a class and individually as compared to placebo. Interestingly, Chande 2013 found fewer serious adverse events with combination versus monotherapy with infliximab.

Withdrawal or discontinuation of therapy due to adverse events

No included systematic reviews reported pooled analyses for this outcome. Chande 2013, a Cochrane review reporting a comparison of azathioprine versus infliximab and a combination of azathioprine and infliximab versus infliximab, included one RCT for each comparison. McDonald 2012, another Cochrane review, reported results of two RCTs comparing a combination of infliximab and methotrexate versus infliximab alone but did not pool the results.

Malignancy

Williams 2014 (which included both types of IBD), Peyrin-Biroulet 2008 and Zhang 2013 reported pooled analyses for the risk of malignancy in Crohn's disease. In all three of the systematic reviews, there was no difference between TNF-α inhibitors and control with a point estimate trending towards less malignancy with TNF-α inhibitors. Malignancy was specified as an outcome of interest by other systematic reviews (Akobeng 2009, Chande 2013, and Assasi 2009) but results were not reported. Assasi 2009 noted that malignancy was not reported in included RCTs. Hutfless 2014 reported results for lymphoma and other cancers in but did not present pooled results.

Quality Assessment of systematic reviews and meta-analyses in Crohn's disease

Details of the quality assessments are provided in Appendix 2.7. Thirteen of the included systematic reviews in Crohn's disease were of high quality (Williams, Costa, Ford, Assasi, Kawalec, Chande, McDonald, Da, Assasi, Akobeng, Behm, Dretzke, Hutfless), three were of acceptable quality (Nikfar, Zhang, Peyrin-Biroulet) and 7 were of unacceptable quality (De Cruz, Neurath, Ehteshami, Mills, Rahimi, Huang, Lian). Only seven provided lists of excluded studies as well as included studies (Nikfar, Chande, McDonald, Lv, Akobeng, Assasi and Hutfless) and only one provided an a priori design (McDonald).

Network meta-analyses in Crohn's disease

There is one available full report of a Network Meta-analysis evaluating TNF-α inhibitors in Crohn's disease (Stidham 2014),(69) as well as two published as abstracts.(70, 71) Similar to the same authors' network meta-analysis of TNF-α inhibitors in ulcerative colitis, Stidham et al assessed four efficacy endpoints (induction and maintenance of remission and response) for three TNF α inhibitors (infliximab, adalimumab and certolizumab). Three of the six induction RCTs and three of the five maintenance RCTs included in the network meta-analysis allowed patients with prior TNF-α treatment after a washout period. There were no subgroup analyses performed, and results were not reported separately for TNF-α naïve and TNF-α experienced patients. No safety outcomes were reported.

Two network meta-analyses were not included because are available as abstract only. Briefly, Tongbram 2013 included natalizumab in addition to the three TNF-α inhibitors. Induction of

response and remission in moderate to severe Crohn's disease were assessed. Rezaie 2013 included the same three TNF-α inhibitors along with methotrexate and thiopurines or combination therapies and assessed comparative efficacy for maintenance of remission. This network meta-analysis addresses a relevant question that has not been addressed by other systematic reviews, of combination therapy versus monotherapy.

Dretzke 2011, a systematic review performed as part of a National Institute for Health Research (NIHR) Health Technology assessment, decided against performing indirect comparisons, citing the following reasons: variation in the placebo arm results in induction trials, lack of similarity of placebo arms in maintenance trials, and the reporting of results for responders only in many of the maintenance RCTs.(68)

Efficacy and safety results of network meta-analyses in Crohn's disease

Frequentist pair-wise comparisons of TNF-α inhibitors versus placebo from Stidham 2014 are reported in Table 2.4 above. Results of indirect comparisons are reported below in Table 2.5 below.

Table 2.5: Efficacy of TNF-alpha inhibitors in network meta-analyses in Crohn's disease								
	Study	Any Anti-TNF vs placebo	Adalimumab vs placebo	Infliximab vs placebo	Certolizumab vs placebo	Infliximab vs adalimumab	Infliximab vs certolizumab	Adalimumab vs certolizumab
Induction of remission (OR, 95% CI or 95% CrI)								
	Stidham 2014	RR 1.66 (1.17, 2.36)	2.94 (1.86, 4.66)	3.70 (0.87, 15.80)	1.22 (1.00, 1.50)	1.52 (0.20, 17.46)	4.29 (0.65, 46.09)	2.93 (1.21, 7.75)
Induction of response (OR, 95% CI or 95% CrI)								
	Stidham 2014	RR 1.43 (1.17, 1.73)	1.71 (1.31, 2.24)	4.01 (1.29, 12.44)	1.25 (1.07, 1.46)	3.17 (0.53, 22.96)	5.36 (0.91, 40.15)	1.73 (0.69, 4.25)
Maintenance of remission (OR, 95% CI or 95% CrI)								
	Stidham 2014	RR 1.78 (1.51, 2.09)	2.06 (1.50, 2.82)	1.86 (1.21, 2.86)	1.62 (1.30, 2.02)	REVERSE: 1.42 (0.17, 9.27)	1.23 (0.26, 13.14)	1.81 (0.55, 8.51)
Maintenance of response (OR, 95% CI or 95% CrI)								
	Stidham 2014	RR (adalimumab and certolizumab only): 1.68 (1.46, 1.93)	1.69 (1.19, 2.41)	"compatible infliximab data not available"	1.64 (1.37, 1.97)	"Compatible infliximab data was not available"	"Compatible infliximab data was not available"	1.45 (0.36, 6.08)
NA= not applicable; CI= confidence interval; CrI= credible interval, OR= odds ratio, RR= relative risk Traditional pair-wise meta-analyses were used for all direct comparisons (all placebo comparisons)								

None of the indirect comparisons were statistically significant, with the exception of adalimumab versus certolizumab for induction of remission with an OR of 2.93 (95% CI: 1.21, 7.75). However, this does not rule out a clinically important difference for other comparisons; 95% CrIs were wide, most notably for comparisons of infliximab versus certolizumab with a 95% CrI of 0.65 to 46.09 for induction of remission. Safety was not an outcome of interest in Stidham 2014.

Quality assessment of network meta-analyses in Crohn's disease

Details of the quality assessments are provided in Appendix 2.7. Stidham 2014 was a high quality systematic review and network meta-analysis, however neither an a priori design nor a list of excluded studies was provided.

BOTH CROHN'S DISEASE AND ULCERATIVE COLITIS: SAFETY

Williams 2014 pooled data from 22 placebo-controlled RCTs of TNF-α inhibitors in both Crohn's disease and ulcerative colitis patients.(72) Only RCTs reporting malignancies in both arms of the trial were included. This could introduce bias, because RCTs not reporting malignancies may have actually had no occurrence of malignancy therefore not including these in the analysis could inflate the results. The occurrence of malignancy was very low despite this, however. The authors note that "follow-up in individual RCTs was never longer than 392 days, and mean length of follow-up was 205 days."

Singh 2011, an 'overview' and network meta-analysis, assessed safety of nine biologics (including adalimumab, certolizumab, golimumab and infliximab) for any indication other than HIV. A subgroup analysis of IBD patients was performed.

Outcomes in systematic reviews assessing safety in both Crohn's disease and ulcerative colitis

Pooled effect sizes for safety endpoints from included systematic reviews that reported safety endpoints in both forms of IBD together are reported in Table 2.6 below.

Table 2.6: Safety of TNF-alpha inhibitors in IBD across indications						
Study and search date	**Intervention / Comparison**	**Outcome definition; timing**	**Fixed *or* random effects model**	**Number of participants; studies**	**Effect size (95% CI)**	**Comments**
Serious adverse events						
Singh, 2011 January 2010	TNF-alpha inhibitors (adalimumab, certolizumab, golimumab, infliximab, etanercept) / 'control' (not specified)	"Number of serious adverse events (SAEs): counted as the total number of SAEs, as listed in each study."; timing not reported	Frequentist network meta-analysis; not specified fixed vs random	Not reported	OR 0.70 (0.31-1.6)	This was a subgroup analysis of an overall analysis of safety across all indications for biologics with the exception of HIV
Withdrawal or discontinuation of therapy due to adverse events						
Singh, 2011 January 2010	TNF-alpha inhibitors (adalimumab, certolizumab, golimumab, infliximab, etanercept) / 'control' (not specified)	"defined in a standard manner in studies"	Frequentist network meta-analysis; fixed vs random not reported	Not reported	OR 1.01 (0.37, 2.77)	This was a subgroup analysis of an overall analysis of safety across all indications for biologics with the exception of HIV
Malignancy						
51 Williams	TNF-alpha inhibitors as a class (adalimumab, certolizumab, golimumab, infliximab) / placebo	Any malignancy; timing not reported	Random	7054 (22)	RR 0.77 (0.37, 1.59)	Only RCTs reporting occurrence of malignancy in both arms were included. "[Results] remained nonsignificant throughout the numerous pre-defined subgroup analyses we conducted according to type of IBD, anti-TNFa agent used, duration of therapy, concomitant use of

						immunosuppressants, exposure to anti-TNFa therapies during induction of remission, study design and risk of bias of studies."
NA= not applicable; CI= confidence interval; CrI= credible interval, OR= odds ratio, RR= relative risk						

There was no difference in occurrence of malignancy, with an estimated RR of 0.77 (95% CI 0.37, 1.59) for TNF-α inhibitors versus placebo in Williams 2014. Results remained non-significant across the subgroup analyses performed, including type of IBD, the specific TNF-α inhibitor used, and concomitant immunosuppressant use. The mean length of follow-up in the included RCTs was 205 days, therefore results cannot be extrapolated to long-term use. The network meta-analysis assessing safety of biologics across indications, Singh 2011, found an OR of 1.01 for malignancy in RCTs of TNF-α inhibitors versus control; this was reported as a subgroup analysis of an overall analysis including RCTs for any indication.

Quality assessment of systematic reviews and meta-analyses assessing safety across IBD indications

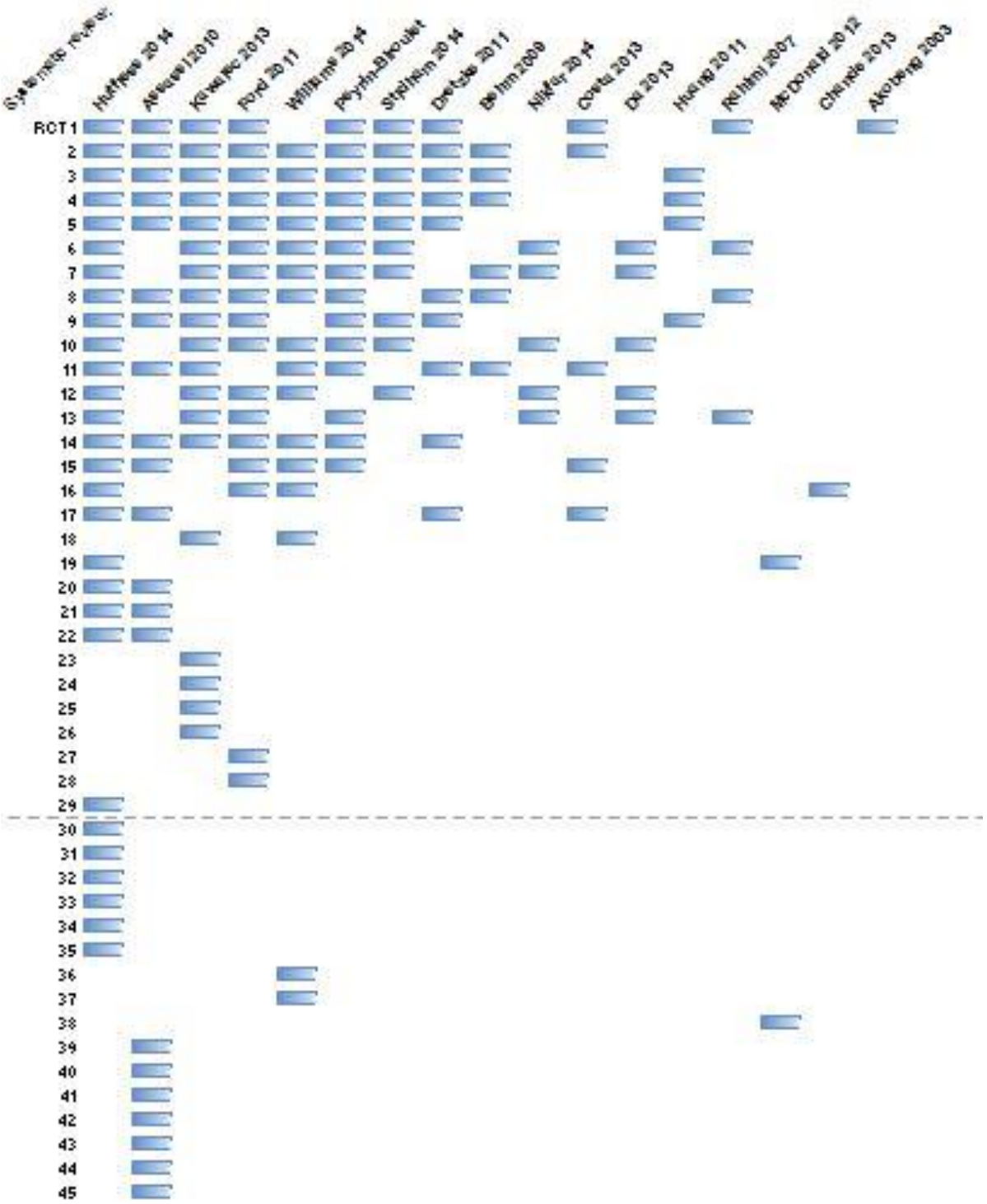
Williams 2014 was of high quality and Singh 2011 was of acceptable quality. Although Singh 2011 provided an a priori design, neither study provided a list of excluded studies.

Overlap in existing systematic reviews

A 'citation matrix' was created to examine the overlap of RCTs included in the systematic reviews; one for Crohn's disease and another for ulcerative colitis, as shown in Figures 3.6 and 3.7.

Figure 2.6: Ulcerative colitis citation matrix

Figure 2.7: Crohn's disease citation matrix



A single column represents each of the included systematic reviews and each row represents the first occurrence of an RCT within any of the included systematic reviews. Only citations of included RCTs relevant to TNF-α inhibitors in IBD were extracted from included systematic reviews. Because some systematic reviews included RCTs in both Crohn's disease and ulcerative colitis, there are RCTs in each citation matrix for some of the systematic reviews. A list of all of the RCTs included in one or more of these systematic reviews is included in Appendix 2.8.

There were a total of 19 primary publications in 14 ulcerative colitis systematic reviews. Fourteen (74%) of these RCTs were included in more than one systematic review. The covered area was 32.7% and the corrected covered area was 27.5%, indicating substantial overlap between the systematic reviews.

There were a total of 45 primary publications in 17 included Crohn's disease systematic reviews. Twenty-two of these RCTs (48.8%) were included in more than one systematic review. The covered area was 22% and the corrected covered area 17%, indicating substantial overlap with respect to RCTs of TNF-α inhibitors in Crohn's disease.

DISCUSSION

Randomized controlled trials have shown that TNF-α inhibitors are more effective than placebo for induction and maintenance of response, remission, and reduction of hospitalization and surgery in ulcerative colitis and Crohn's disease patients. It is still not known whether any of the TNF-α inhibitors are superior to any of the others. A single industry-funded network meta-analysis in ulcerative colitis patients did find that infliximab was statistically significantly superior to adalimumab for induction outcomes,(67) however two other network meta-analyses did not reach statistical significance for most of the estimates of comparative efficacy between agents.(56, 66) It is not possible to rule out that there may be a clinically important difference between TNF-α inhibitors, however; the reported 95% CrIs were wide, and encompassed clinically important estimates for all indirect comparisons of efficacy. The question of whether any of the agents have superior efficacy for ulcerative colitis remains unanswered after three separate network meta-analyses of acceptable to high quality, therefore it is likely that a more definitive answer on comparative efficacy of the TNF-α inhibitors would require an RCT comparing different agents. Similar for ulcerative colitis, a single high quality network meta-analysis of TNF-α inhibitors in Crohn's disease found that TNF-α inhibitors are superior to placebo, however differences in efficacy between agents were not statistically significant with the exception of adalimumab versus certolizumab for induction of remission.

What is missing from the existing network meta-analyses of TNF-α inhibitors in IBD are potentially important subgroup analyses, such as patients naïve to any prior therapy and patients receiving concomitant immunomodulator therapy. However, with the wide CrIs observed in the analyses of the full RCT populations it is unlikely that further dividing into subgroups would provide meaningful results. Additionally, there are no network meta-analyses in ulcerative colitis that include combination therapy of TNF-α inhibitors with an immunosuppressant (i.e. azathioprine or 6-MP in combination with a TNF-α inhibitor) as compared to monotherapy with TNF-α inhibitors, likely owing to the lack of RCT data. In Crohn's disease, Rezaie 2013 reports the results of network meta-analyses including combination therapy as a comparator, but this report is currently available only as a conference abstract.(71) There are likely important differences in efficacy and safety of TNF-α inhibitors in combination with immunosuppressants as compared to monotherapy, and this warrants further research. Available evidence points towards superiority of combination therapy

compared to monotherapy for induction of remission and mucosal healing in Crohn's disease, without increased risk of adverse events in the short-term. If there were adequate RCT evidence, this important question could be addressed using a network meta-analysis. According to the AHRQ report of comparative effectiveness of therapies for Crohn's disease,(18) there are seven RCTs assessing monotherapy of TNF-α inhibitors versus placebo and four assessing combination therapy of TNF-α inhibitors with a thiopurine or methotrexate versus placebo for induction of remission. There is also an RCT comparing infliximab combination therapy to infliximab monotherapy, which would close a loop in the network.(18)

There was substantial overlap in the included systematic reviews with respect to the included RCTs. Of the three recent network meta-analyses in ulcerative colitis, for example, only Danese 2014 had been registered in Prospero in July 2013. None of the network meta-analyses cited any of the others, which is not surprising since they were all published within just a few months of each other. Although the research questions were slightly different with respect to the interventions and populations of interest, these studies likely represent unnecessary duplication of research efforts. The occurrence of unnecessary duplication of systematic reviews has been reported previously.(48, 49) A search of Prospero performed July 14th 2014 revealed a fourth network meta-analysis, registered in December 2013, with an estimated completion date of June 2014 (Archer et al. PROSPERO 2013:CRD42013006883 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006883). This "Technology Assessment Report commissioned by the NIHR HTA programme on behalf of the National Institute for Health and Care Excellence", will be assessing infliximab, adalimumab and golimumab for treatment of moderately to severely active ulcerative colitis after the failure of conventional therapy. Although this will also include the pediatric population in addition to the adult population, it is likely that there will be substantial overlap with the already available network meta-analyses.

Presumably, each of the systematic reviews required substantial investment in resources for literature search and selection of studies, and the identification and determination of studies for eligibility would likely be very similar across studies. An overview such as this one provides a list of relevant RCTs that could easily be used by subsequent systematic reviews. Searches and subsequent screening of articles for eligibility could be limited to articles published since the last high quality systematic review.

There was inconsistency as to whether RCT results were pooled in the included systematic reviews. A systematic review of TNF-α inhibitors infliximab and adalimumab commissioned by NIHR determined that it was inappropriate to perform meta-analyses or indirect comparisons for any of the relevant comparisons.(68) The included RCTs were pooled in meta-analyses and network meta-analyses by many other systematic reviews. Dretzke 2011 presents valid arguments against pooling results. Their reasons relate to the clinical diversity of the included RCTs, specifically population differences. Although the decision not to pool the results was justified, the consequence is that the results of this systematic review are more difficult to interpret for clinicians, decision makers, and possibly more difficult to use for economic modeling purposes. Inevitably, it will be necessary to summarize the results of the included studies somehow. In Dretzke's systematic review, the point estimates of effect sizes from included studies are presented as a range in the abstract/summary. This distribution of estimates is arguably less meaningful than a pooled estimate and 95% confidence interval with underlying clinical heterogeneity, as this presented a range of point estimates could reflect outlying poor quality studies. The term heterogeneity, or 'statistical heterogeneity', refers to a statistical difference in effect estimates between studies. However, the term heterogeneity can also be used to describe clinical diversity across studies (i.e. differences in the intervention, population, or outcomes) or methodological diversity (i.e. differences in the study design and risk of bias). Methodological and clinical diversity can lead to statistical heterogeneity, because differences in study methods and characteristics can lead to different effect estimates.(73) The extent to which clinical heterogeneity is accepted should depend on the end goal of the researchers. If it is to estimate an effect size for drugs as a class for estimates of impact in the entire disease population, some diversity in the population and intervention and outcome(s) should not preclude combining the results. In the case of TNF-α inhibitors, for example, adalimumab and infliximab could have different levels of efficacy, but if the question of the researchers is whether as a whole this class of medications is effective for induction of remission of Crohn's disease, it could be appropriate to combine results of RCTs of the different agents. On the other hand, if the end-goal of the research is to compare cost-effectiveness of medications listed on formularies, the overall precise point estimate that is gained by combining all of the studies of TNF-αinhibitors versus placebo would be of little use. A network-meta-analysis reporting indirect comparisons of agents available in the decision makers' jurisdiction would be most relevant. Options for overcoming the issue of clinical and methodological heterogeneity in RCTs in order to facilitate combining their data could include restricting analyses to subgroups of a more homogeneous

population where possible, and doing sensitivity analyses excluding certain RCTs to determine how and if results are affected. Where substantial statistical heterogeneity is identified in a systematic review, it would be appropriate to conclude that either 1) the initial research question was too broad; differences in clinical characteristics between studies meeting eligibility criteria appear to have led to different effect estimates, 2) methodological differences resulting in different types of bias led to different results, therefore some studies' estimates are closer to the true effect estimate, 3) differences in effect estimates between studies are due to chance, or 4) a combination of these. If clinical heterogeneity leading to statistical heterogeneity precludes combining of results of studies, then an appropriate course of action would be to determine which particular characteristics differed between studies to explain this difference, and to describe this succinctly in the conclusions, perhaps by dividing responses the initial clinical question and its responses into subgroups. In other words, rather than concluding that studies were too heterogeneous to combine, it would be concluded that the initial question was too broad. When methodological diversity leads to statistical heterogeneity due to different levels and types of bias, choosing to combine some studies, excluding those with the highest risk of bias in sensitivity analyses, or selection of the "best" RCTs to answer the clinical question would result in a more relevant answer to the clinical question than simply describing all of the results narratively. If methodological and clinical diversity cannot be identified to explain statistical heterogeneity, then there is also the possibility that differences between studies were due to chance. If there are no signs of clinical or methodological diversity between studies and it is likely that differences between studies were due to chance, combining the results of the studies could still be appropriate; however it would be very difficult to rule out methodological or clinical diversity.

The AHRQ report (18) and CADTH report (30) pooled results for some comparisons, while others were not pooled due to statistical heterogeneity. Statistical measures of heterogeneity could differ across outcomes in a systematic review because of the inclusion of different RCTs for different outcomes. However, if the relevant RCTs considered for pooling of results are the same for multiple outcome(s) and it is deemed appropriate to report pooled estimates for one of those outcomes, then arguably results for all outcomes should be amenable to pooling. The exception would be where there is a concern unique to that outcome with respect to clinical or methodological diversity. Cut-offs for determination of heterogeneity (i.e. I-squared greater than 0.5) are arbitrary; there is no number that defines statistical heterogeneity, and statistical heterogeneity is a direct result of either clinical or methodological diversity of the included RCTs. Deciding to pool results for

one outcome but not others from the same included RCTs implies that either 1) the pooled results may not be valid, or 2) it may have been appropriate to pool results for the other outcome.

Limitations

Data extraction and quality assessment were performed by a single reviewer, with a proportion of extracted data checked by a second reviewer. The definition of systematic review that was used to determine study eligibility was based on the Cochrane library definition with some additional aspects and was quite stringent; studies calling themselves a systematic review that did not meet the criteria were excluded. With the stringent definition of systematic review used, it is possible that some systematic reviews were excluded due to poor reporting.

CONCLUSIONS

Several systematic reviews of varying quality address efficacy and safety of TNF-α inhibitors in Crohn's disease and ulcerative colitis. Recentness, quality, and directness of the evidence provided by included systematic reviews were considered in determining which systematic review best answered the clinical questions.

TNF-α inhibitors versus placebo in Crohn's disease

A recent high quality systematic review with network meta-analysis, Stidham 2014, provides estimates of efficacy for induction and maintenance of remission and response for infliximab, adalimumab, and certolizumab versus placebo in Crohn's disease that are consistent with results of previous systematic reviews. This study found a statistically significant RR of 1.66 for induction of remission, 1.43 for induction of response, 1.78 for maintenance of remission and 1.68 for induction of response for TNF-α inhibitors as a class versus placebo. Individual agents versus placebo were statistically significantly superior for all comparisons with the exception of infliximab versus placebo for induction of remission where only one small RCT was included. No agent was found to be statistically superior for any indirect comparisons, with the exception of Adalimumab versus certolizumab for induction of remission. Infliximab had the highest probability of being best for the induction outcomes, whereas adalimumab had the highest probability of being best for maintenance of remission (versus certolizumab and infliximab) and response (versus certolizumab). A single high quality systematic review, Costa 2013, reported statistically significant reductions in

hospitalization and major surgeries for infliximab versus placebo. A recent systematic review of acceptable quality, Kawalec 2013, reported fewer serious adverse events with TNF-α inhibitors versus placebo with a RR 0.70. There were fewer serious adverse events reported for all three individual agents versus placebo as well, and this was statistically significant for the comparison of adalimumab versus placebo.

Discontinuation of therapy due to adverse events was not reported in any of the Crohn's systematic reviews. In a systematic review of IBD patients overall there was no difference between TNF-α inhibitors and placebo for withdrawal or discontinuation of therapy due to adverse events. A recent high quality systematic review, Williams 2014, did not find a difference in risk of malignancy for the TNF-α inhibitors versus placebo with a RR 0.77 (95% CI 0.37, 1.59) in IBD.

No pooled analyses of RCTs of TNF-α inhibitors for mucosal healing in Crohn's disease were identified.

TNF-α inhibitors versus placebo in ulcerative colitis

A recent high quality systematic review with network meta-analysis restricting analyses to patients naïve to TNF-α inhibitors, Danese 2014, did not report comparisons of TNF-α inhibitors as a class versus placebo, but found that individual agents were statistically significantly superior to placebo for outcomes of induction and maintenance of response and remission as well as mucosal healing. With the exception of infliximab versus adalimumab for induction of response and mucosal healing, indirect comparisons between agents were not statistically significant; however, the 95% CrIs do not rule out a potential clinically important difference between agents. Risk of colectomy is reduced with infliximab versus placebo, but statistical significance is lost when pooled with RCTs using other comparators according to another recent high quality systematic review (Lv 2014). Infliximab decreased IBD-related hospitalizations as compared to placebo in another systematic review of high quality, Costa 2013.

Similar to Crohn's disease, there were fewer serious adverse events reported in treatment versus control groups in Lv 2014, a recent high quality systematic review comparing infliximab and adalimumab to placebo, with an RR 0.81. A network meta-analysis encompassing both forms of IBD, Singh 2011, reported no difference between TNF-α inhibitors and placebo for discontinuation of therapy due to adverse events or risk of malignancy.

Combination versus monotherapy of TNF-α inhibitors

A single Cochrane review of high quality, Chande 2013, identified a single RCT comparing combination therapy of infliximab + azathioprine versus infliximab in Crohn's disease. Combination therapy was found to be statistically significantly superior for induction of remission and mucosal healing and less likely to cause serious adverse events, with no significant difference in withdrawals due to adverse events. Another Cochrane review, McDonald 2012, identified two small RCTs comparing combination therapy of infliximab and methotrexate to infliximab alone in Crohn's disease. There were no differences in efficacy between combination versus monotherapy, however these RCTs were of small size and results were not pooled due to heterogeneity. No systematic reviews assessing combination therapy versus monotherapy in ulcerative colitis were identified.

Chapter 3: Systematic review of observational post-market studies of TNF-α inhibitors in Crohn's disease and ulcerative colitis

BACKGROUND

There was a lack of knowledge regarding long-term safety and efficacy of TNF-alpha inhibitors at the time that they become available for use in Canada. Crohn's disease and ulcerative colitis are chronic diseases with no cure and for which the TNF-α inhibitors are currently in widespread use.

Limitations of RCTs

Although RCTs and systematic reviews/meta-analyses of RCT's sit atop of the 'evidence hierarchy', they are known to have their own limitations, including: (1) The close monitoring and follow-up that occurs in the RCT environment as compared to the real world limits generalizability, as do the usually strict inclusion criteria (resulting in inclusion of patients most likely to respond to treatment and least likely to experience adverse events due to therapy); (2) If there is a subgroup in which a treatment under study is expected to have different effects, it is often the case that this subgroup is not adequately represented (resulting in inadequate power) to draw concrete conclusions; (3) The usual limited duration of clinical trials leads to a lack of knowledge regarding true treatment efficacy and safety over the course of time that a patient would actually be taking the medication; (4) because many RCTs are industry funded trials leading to market authorization, there is potential for bias with the involvement of industry in data analysis and interpretation of results; (5) sample sizes do not allow for detection of rare adverse events, and; (6) Participation in an RCT has been shown to result in improved outcomes regardless of the intervention being studied because of increased medical attention.(2),(74) (75)

As an example of the limitations of using RCT's for assessment of safety of TNF-α inhibitors, a recent systematic review and meta-analysis of 22 RCT's comparing TNF-α inhibitors to placebo (with or without concomitant treatment) in patients with IBD found no difference in malignancy with an RR of 0.77 (95% CI 0.37–1.59), a non-significant difference in favour of the intervention. However a very important consideration in the interpretation of these results is that none of the included RCT's

provided data on malignancy beyond 1-year, making it impossible to draw any conclusions regarding risk of malignancy with longer-term treatment with these agents.(72)

Gathering evidence on adverse effects

There is a lack of consensus regarding the optimal strategy for gathering and assessing evidence on adverse effects. Although RCTs are known to have limitations in their ability to detect adverse effects (due to close monitoring, a controlled environment, limited duration and healthy population less likely to experience adverse effects), observational trials are subject to bias and their results are less likely to be amenable to meta-analysis.

The Cochrane handbook for systematic reviews of interventions' Chapter on adverse effects discusses the low likelihood of observing rare or long-term adverse events in clinical trials, and this justifies the inclusion of cohort studies, case-control studies, and sometimes case reports of case series in these cases. It has been proposed that these observational studies "offer some of the best chances for unbiased observational studies. This idea was empirically verified by a comparison of randomized and observational studies of adverse effects, which found that, if anything, risk estimates from observational studies were lower." It is also noted that in systematic reviews of observational studies, the limitations of such evidence must be carefully considered.(76)

An analysis of data from 58 meta-analyses compared estimates of harm in observational studies and RCTs. Generally, the odds ratio (OR) for the occurrence of adverse events results were similar across study types (ratio of ORs=1.03; 95% CI 0.93–1.15), although there were examples of discrepant results. The authors suggest that systematic reviews of adverse event outcomes not be limited to a particular trial design, and that special attention be given to the contribution of confounding factors to the differences in risk estimates between RCT and observational study data.(77)

The Chapter in the Cochrane Handbook for Systematic reviews of interventions' on adverse effects presents advantages and disadvantages of several approaches to systematic reviews of adverse effects. The authors state that "Interventions may have many different adverse effects, and reviews may need to focus on a few important ones in detail, together with a broader, more general summary of other potential adverse effects."(76) Although a narrow focus of outcomes is easier and can perhaps result in more meaningful conclusions, the scope may be too narrow, and it would only be appropriate for adverse effects that are known. A broad focus could allow for analyses of

previously unknown adverse effects, but the volume of data collection required could be problematic.(76)

Justification for a systematic review of post-market observational studies

An observational study is one where "allocation occurs in the course of usual treatment decisions or peoples' choices".(78)

The Cochrane Non-randomized Studies Methods Group lists three main reasons for including non-randomized studies in a Cochrane review: 1) To examine the case for undertaking a randomized trial by providing explicit evaluation of weaknesses of available non-randomized studies; 2) To provide evidence of the effects of interventions that cannot be or are unlikely to be studied in randomized trials; and 3) To provide evidence of effects that cannot be adequately studied in randomized trials, such as long-term and rare outcomes, or outcomes that were not known to be important when randomized trials were conducted.(78)

The final point adds to the justification for this systematic review. RCTs were of inadequate duration considering the life-long course of IBD, and a concern for potential long-term risk of malignancy requires long-term data in sample sizes larger than would be available from RCTs.

IBD patients in the 'real-world' are different from those included in pivotal pre-market clinical trials. This was demonstrated in a cohort of 206 patients presenting to a medical centre for adjustment or escalation of their medical therapy, with moderate to severe disease activity and an established diagnosis of IBD.(79) Criteria for eligibility from seven pivotal RCTs of biologics (including natalizumab) in Crohn's disease and two pivotal RCTs for ulcerative colitis were applied to the patients in the cohort. The investigators found that only 34% of patients would have qualified for at least one of the applicable RCTs. Proportion eligible for inclusion was highest for the CHARM and PRECISE 1 trials at only 27% of Crohn's disease patients. For the ulcerative colitis patients only 25% would have been eligible for participation in the ACT study. Crohn's disease patients in the cohort who were found not to be eligible for inclusion in the RCTs did not differ from eligible patients with respect to age, duration of disease, location of disease, or gender. In the cohort, the most frequent reason for "exclusion" from the RCT in Crohn's disease patients would have been a non-perianal abscess or symptomatic stricture (62.2% of ineligible patients). Other reasons for ineligibility in the Crohn's patients were (1) recent exposure to or prior non-response to TNF-alpha inhibitor therapy in 51.2%, (2) high dose steroid use in 18.3%, and (3) comorbid conditions (e.g. cardiovascular

disease, COPD, malignancy) in 25.6%. Current use of topical rectal 5-ASA or corticosteroids was the most common reason for trial ineligibility in UC patients (56.7%); for eligibility in ACT, patients must not have used topical agents for two weeks prior to enrollment. Other reasons that UC patients were ineligible for inclusion were because (1) they were steroid/immunomodulator naïve (45%), (2) newly diagnosed (16.7%), and (3) were found to need 'probable colectomy' (15%). Half of these patients deemed ineligible for inclusion in any of the RCTs either were newly initiated on anti-TNF treatments, had an increase in dose of current TNF-alpha inhibitor treatment, or switched to a different TNF-alpha inhibitor. In ineligible Crohn's disease patients, 24.7% and 6.2% newly initiated TNF-alpha inhibitor mono or combination therapy with an immunomodulator, respectively, and 31.7% of UC patients newly initiated TNF-alpha inhibitor therapy.(79)

A Cochrane overview and network meta-analysis assessed the occurrence of adverse effects of 9 biologics (including the TNF-α inhibitors adalimumab, certolizumab, golimumab and infliximab) in studies in which they were being used for any indication (including Crohn's and Colitis). The analysis included 163 RCT's with a mean duration of 6 months and 46 open-label extension studies with a mean duration of 13 months. The occurrence of serious adverse effects, lymphoma, and heart failure was not statistically significantly different than control, although the biologics as a group were found to be statistically significantly associated with withdrawal due to adverse effects (OR 1.47, 95% CrI 1.20-1.86) and serious infection (OR 1.37, 95% CrI 1.04-1.82). The authors concluded that there is "a need for more research regarding the long-term safety of biologics and an urgent need for comparative safety reports of different biologics preferably without industry involvement."(55)

Although observational study design is subject to increased risk of bias and confounding as compared to RCTs, pre-market RCTs are sometimes inadequate for determination of safety and real-world effectiveness of medications.(1, 2) TNF-α inhibitors have been approved for use in Canada for over 10 years. A systematic review and meta-analysis of observational post-market evidence may shed some much-needed light on the real-world and/or long-term effectiveness and safety of this relatively new class of medications, and also identify remaining knowledge gaps that should be addressed in future post-market surveillance studies.

Because of the RCT limitations in determining real-world effectiveness and safety, long-term efficacy and safety outcomes, and rare adverse events, an exploration of available post-market observational evidence was performed.

Research questions for the exploration of post-market evidence:

1. In adult patients with Crohn's disease naïve to TNF-α inhibitors, what is the efficacy of the TNF-α inhibitors (adalimumab, infliximab, certolizumab, golimumab) compared to each other, conventional therapy or surgery for (i) induction of response (ii) induction of remission (iii) maintenance of response and (iv) maintenance of remission (v) mucosal healing (vi) hospitalization and (vii) surgery

2. In adult patients with ulcerative colitis naïve to TNF-α inhibitors, what is the efficacy of the TNF-α inhibitors (adalimumab, infliximab, certolizumab, golimumab) compared to each other, conventional therapy or surgery for (i) induction of response (ii) induction of remission (iii) maintenance of response and (iv) maintenance of remission (v) mucosal healing (vi) hospitalization and (vii) surgery

3. In adult patients with ulcerative colitis or Crohn's disease naïve to TNF-α inhibitors, what is the risk of (i) serious adverse events, (ii) discontinuation of treatment/withdrawals due to adverse events and (iii) malignancy with TNF-α inhibitors compared to each other, conventional therapy, or surgery?

4. How does the post-market evidence of efficacy and safety compare to the results of available systematic reviews, meta-analyses and network meta-analyses?

METHODS

The study protocol for this systematic reviews of observational studies was registered on PROSPERO, registration number CRD42014009341.

Eligibility

Detailed selection criteria is provided in Appendix 3.1. Studies were assessed for eligibility based on the following criteria:

Inclusion criteria

Population: Adults (18 years or older) naïve to previous TNF-α inhibitor therapy, not pregnant, diagnosed with (1) Crohn's disease, moderate to severe disease or (2) Ulcerative colitis, moderate to severe disease.

Intervention: Each of the individual TNF-α inhibitors (infliximab, adalimumab, golimumab, certolizumab) initiated within the approved therapeutic dose range for (1) Crohn's disease or (2) ulcerative colitis, or for which regulatory approval is being sought in any jurisdiction for these conditions (therapeutic dose in Canada where applicable; EU or USA approved-dosing otherwise), as well as the TNF-α inhibitors as a group.

Comparison: Any comparison or no comparison

Outcome(s): Induction of remission, induction of response, maintenance of remission, maintenance of response, mucosal healing, hospitalization, surgery, any malignancy, any serious adverse event (as reported in each study), and withdrawal/discontinuation of therapy due to adverse events

Study Design: This systematic review will include post-market observational studies reporting any of the outcomes of interest. 'Post-market' status will be determined by assessing whether the TNF-α inhibitor had gained regulatory approval in the country in which the study was conducted at the time of beginning of patient enrolment in the study.

Exclusion criteria

Case reports and case series less than 10 patients were excluded. Studies with no comparison group 'between two or more groups of participants receiving different interventions' or 'within the same group of participants over time'(78) (i.e. descriptive studies, case series) were included, but the level

to which they were assessed after taking an inventory of included studies. Because open-label extensions of randomized controlled trials were initiated prior to market authorization, and would likely not represent 'real-world' effectiveness and safety (e.g. due to strict inclusion criteria, biases due to industry-funding) these will be excluded, even if they were ongoing after the time of market authorization in the jurisdiction in which they were conducted.

Justification for exclusion of care reports and case series less than 10 patients

Although spontaneous reporting systems and published case reports are a valuable component of post-market surveillance and identification of adverse drug reactions, it would be unlikely that a review of individual case reports (published, or reported to Health Canada/FDA) would add meaningful information to what is known already re: risk of malignancy with TNF-alpha inhibitors. Spontaneous adverse reaction reporting typically services as a means of 'signal detection' – a signal has been defined by WHO as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously",(80) and is a method of hypothesis generation used to guide further research. Certain characteristics of a drug/adverse event association lend to more easily drawing conclusions that a relationship is causal. These characteristics include a "strong temporal association with drug administration, a low or near absent frequency in the underlying population, are not part of the underlying illness being treated, are generally the result of exposure to a drug or other toxin, and have no other likely explanation. Aplastic anemia, agranulocytosis, acute liver failure, rhabdomyolysis, certain arrhythmias such as torsades de pointes, and serious skin reactions such as Stevens-Johnson syndrome are examples of adverse events whose relationship to a drug can often be established by case series."(80) The ability to reach conclusions on the causal association between a drug and an ADR based on case reports alone is the exception rather than the rule. If malignancy was caused by TNF-alpha inhibitors, this adverse event may not develop or be detected for years after drug administration, patients with IBD are already thought to be at higher risk of malignancy, and malignancy is associated with many other risk factors apart from exposure to medications. It would not be possible to draw any conclusions based on case reports of malignancy in patients receiving TNF-alpha inhibitors. Another limitation to using case reports to determine causality with the biologics specifically, is that patients are often receiving or have received other drugs that may cause the same adverse events, whereas a valid comparative study or larger case series could address this limitation.(81)

Search Strategy

Searches were performed August 6th 2014 and imported into Endnote for de-duplication of citations. The same comprehensive peer-reviewed search strategy of Medline, EMBASE, and Cochrane was used as with the literature search for systematic reviews/meta-analyses/network meta-analyses, using keywords and subject headings related to the disease of interest, as well as the drugs of interest combined with 'and'. The full search strategy is available in Appendix 3.2. Originally the intention was not to apply a study design concept to the search, because of a lack of valid "filters" for observational studies. After an initial search of EMBASE and Medline search including only the drug and disease concepts not limited to study design it was decided to apply a filter for observational study design developed by the Scottish Intercollegiate Network (SIGN) to the search strategy.(82) The available filter included keywords and subject headings relevant to observational study design, and this filter was expanded to include subject headings and a number of keywords relevant to post-market surveillance and a new MeSH term, in consultation with an information specialist. Although it is likely that some eligible studies would not be captured when applying this search filter, the review team felt that it was a reasonable approach given the impracticality of having two reviewers screen the large number of citations retrieved without the filter.

Prior to publication of this systematic review in a peer-reviewed journal, the database searches will be updated and a grey literature search will be performed.

Selection of studies for inclusion

At first level screening, two independent reviewers (EM, SH) applied eligibility criteria relating to the population, intervention, comparison and study design to screen titles and abstracts of all citations from the database search to identify for which studies full-texts would be retrieved for a more in-depth review. At first level screening, any article for which at least one reviewer felt that it was potentially eligible moved onto the next level of screening. Preliminary review of these citations revealed a much higher number of eligible studies than anticipated. It was noted that many of the citations were published only in abstract form. In addition to the lack of information available to adequately assess eligibility, outcomes and risk of bias, data published preliminarily in abstract form can be inconsistent with fully published reports.(83) The review team decided to exclude articles available only as abstracts from further review. Prior to retrieval of full-texts, a single investigator screened citations of all articles included after title and abstract screening to exclude all articles

published as abstract only. At the second level of screening, full-texts of all retrieved studies were again assessed for inclusion independently by two reviewers (EM, SH). Disagreements were resolved through discussion and consensus. Any disagreements remaining unresolved after discussion were brought to a third reviewer (GW) to make a final decision regarding study eligibility.

Justification for not expanding safety assessment to other indications

It is usually the case that an assessment of occurrence of adverse events should include studies from all indications (i.e., not restricted to IBD, as is being proposed in this study).(76) In this systematic review, the assessment of adverse events will be limited to the IBD population for several reasons: (1) It is plausible that a risk of malignancy associated with TNF-α inhibitors could differ by indication, so it may not be appropriate to combine data from Rheumatoid Arthritis and IBD patients, for example;(55) (2) results of the systematic review of systematic reviews, meta-analyses and network meta-analyses (restricted to Crohn's disease and ulcerative colitis) and results of the observational systematic review are being compared on both efficacy and safety endpoints; and (3) because systematic reviews of observational studies are resource-intensive, a review of observational studies across all indications is not feasible for this project. Limiting to the IBD population will allow for simultaneous screening for studies assessing efficacy, safety, or both.

Reporting

As with the systematic review of systematic reviews, meta-analyses and network meta-analyses, the systematic review of observational studies was reported in accordance with the PRISMA statement,(84) as well as the MOOSE guidelines which address specifically the reporting of results of systematic reviews and meta-analyses of observational studies.(85)

Handling "switching" of TNF-alpha inhibitors

In practice it is likely that patients on one TNF-α inhibitor will sometimes be switched to another. Any studies specifically designed to assess "switching" TNF-α inhibitors did not meet inclusion criteria because the patients in these studies were not be TNF-α inhibitor naïve at study start. Participants in these studies would most likely include people who initially failed therapy with infliximab and are being switched to adalimumab, for example. The exception would be if such a study was a continuation of an initial study that included only TNF-α inhibitor naïve patients, in which case it could have met inclusion criteria for the systematic review.

Subgroup analysis

Subgroups of interest included level of disease severity at baseline (moderate disease, severe disease), hospitalization at baseline, duration of disease prior to treatment initiation, concomitant methotrexate use, concomitant thiopurine use, whether patients were naïve to prior immunosuppressant use, and whether patients were switched from one TNF-α inhibitor to another. These were to be explored to the extent possible given the information available in the included studies.

Quality assessment and data extraction

It was decided a priori to take an inventory of study designs near the completion of second level full-text screening to determine the best approach to synthesis of included studies. Basic design characteristics were extracted for all included studies, and more detailed characteristics were extracted for studies with any relevant comparison. Outcome data and risk of bias was extracted only for comparative studies with some form of adjustment for confounding in the design or analysis stage, or adequate justification provided to not adjust for confounding variables. This included case-control studies, comparative cohort studies, and studies in which a comparison was made in some sort of multivariable analysis for a relevant intervention and comparison. The comparative cohort studies and case-control studies for which outcome data were extracted were deemed to be the studies potentially amenable to pooling in meta-analysis or network meta-analysis.

Information pertaining to the patient population, intervention, comparison, outcome, study design and methods, extent of industry involvement, and items relating to study quality was pre-defined and entered into a form in Distiller SR (Ottawa, Canada). Because of inconsistent nomenclature with respect to observational study design, information on study design 'features' was be extracted according to pre-defined criteria in accordance with the *Cochrane Handbook of Systematic Reviews of Interventions* and *Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews* (i.e. documenting 'Yes', 'Possibly', 'Possible for one group only', 'No' or 'Not Applicable' to features such as 'which parts of the study were prospective: Identification of participants?'.(78, 86) Unadjusted and adjusted effect estimates were extracted where reported.

The applicable SIGN 50 methodological checklist was used for quality assessment of included comparative cohort and case control studies. The checklists and associated notes are provided in appendices 3.3-3.6. In addition, data relating to confounding factors considered in the study, comparability of groups based on confounding factors, and methods used to control for confounding were extracted in detail. Expert opinion was sought and literature was reviewed to determine the domains of confounding that could be of importance for the outcomes assessed, and a checklist including these relevant confounding domains was incorporated into the outcome-level data extraction form. This checklist was adapted from *"Issues related to unmeasured and residual confounding to be assessed for each outcome specified in the review protocol"*.(86) Issues related to *selective outcome reporting* and *selective analysis reporting* were also considered according to these predefined checklists,(86) and each study was also be assessed for directness (applicability to the PICO elements).

Data extraction forms developed in Distiller SR were first piloted on five studies. Because of the complexity and time involved with data extraction and assessment of risk of bias in non-randomized studies, the extent to which a second reviewer would check extracted data was determined once it was known how many studies were to be included. Data extraction was checked by a second reviewer for all studies for which outcome data was extracted. Any disagreements remaining unresolved after discussion between the two reviewers was brought to a third investigator (GW). It was also decided not to contact authors for incomplete of unclear information reported for included studies, because of the potential introduction of bias and because it was anticipated that this would not have any impact on our results.

Data Analysis

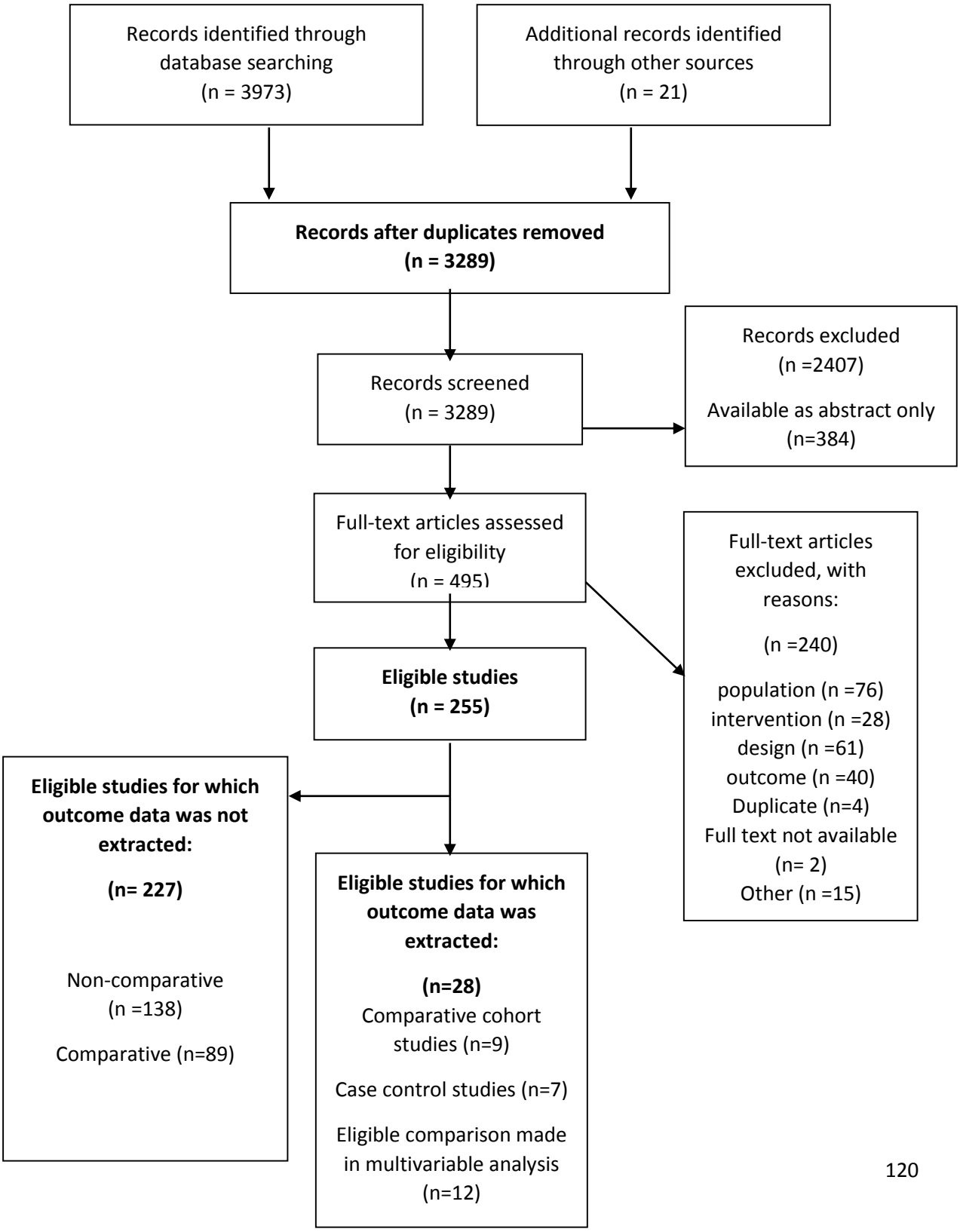
It is to be expected that the extent of heterogeneity in systematic reviews of observational studies is greater than with systematic reviews of RCTs. Depending on the extent and nature of any identified heterogeneity, it may be more appropriate to qualitatively report the results of systematic reviews than to pool the results. Prior to considering pooling study results in meta-analysis or network meta-analysis, heterogeneity was considered very carefully. Owing to substantial methodological and clinical diversity of included studies, it was deemed to be inappropriate to combine their results in meta-analysis. The rest of the section regarding data-analysis is described as how data analysis would have been performed if it had been pursued.

Meta-analysis: If it was determined that the results of included comparative observational studies were amenable to meta-analyses, data would be analyzed using Review Manager (revman) version 5.2. Heterogeneity of results across studies would be assessed through visual inspection of a forest plot, and consideration of the Cochran's Q and calculation of the I^2. Importantly, study characteristics and risks of bias would be considered to determine whether (and which) study results should be combined in a meta-analysis, and only studies with similar features were to be combined. Attempts would be made to explain any identified heterogeneity by considering differences in patient characteristics, risk of bias, and study design, and a random-effects model would be used. In studies where multiple effect estimates were reported (e.g. adjusted for different covariates), the results considered to be the primary analysis by the study authors would be used. Analyses would be performed in RevMan using an inverse variance weighted average for adjusted estimates. Sensitivity analyses would be performed including only studies deemed to be of relatively high quality, and excluding studies with high number of withdrawals (e.g. >30%).

Network meta-analysis: The possibility of performing a network meta-analysis of observational studies would be explored. Network meta-analyses traditionally include only RCTs or CCTs, so a network meta-analysis of observational studies would be a novel approach to synthesis of observational evidence. Similarity and consistency of included studies was to be assessed to determine whether it was appropriate to combine studies using a network meta-analysis approach.(87, 88) Bayesian modelling would be performed in WinBUGS (MRC Biostatistics Unit, Cambridge, UK) using the applicable code developed by the Multi-Parameter Evidence Synthesis Research Group out of the University of Bristol (Available at http://www.bristol.ac.uk/social-community-medicine/projects/mpes/). Deviance information criteria and residual deviance would be used to determine whether a fixed or random effects model will be used. Basic parameters would be assigned non-informative prior distributions; more informative prior distributions would be considered after evaluation of the information base. Model diagnostics, including trace plots and the Brooks-Gelman-Rubin statistic, will be used to assess model convergence. Two chains would be fit in WinBUGS for each analysis, employing at least 20,000 iterations, with a burn-in of at least 20,000 iterations. Results would be reported as point estimates with 95% CrIs, the probability of each treatment being best (based on Markov Chain Monte Carlo simulations), as well as mean ranks of each treatment.

RESULTS

A PRISMA flow diagram outlining the study selection process is show in Figure 3.1.



The electronic database search and review of reference lists retrieved 3289 records. A total of 255 studies have met eligibility criteria at the time of writing of this thesis. Of these, there were 28 studies for which there was a relevant comparison and some form of adjustment for confounding at either the design of the analysis stage, and for which outcome data was extracted. A list of excluded studies can be found in Appendix 3.7.

Characteristics of included studies:

Nine of these were cohort studies that were considered to be 'truly comparative' for the purposes of this systematic review: participants were divided into two or more distinct groups, outcomes were reported separately in each group, and there was some form of adjustment for confounding either at the design or the analysis stage or adequate justification provided to not adjust for confounding variables: one in ulcerative colitis,(89) seven in Crohn's disease,(90-96) and one in both forms of IBD.(97) These nine comparative cohort studies ranged in size from less than 50 patients, to greater than 56000 patients. With respect to method of adjustment for confounding, Kestens 2013, Choi 2014, Biancone 2011 were of matched design, Leombruno 2011 was a propensity-score matched analysis in which multivariable regression was also performed, Sussman 2012, Osterman 2014, Patil 2013 and Andersen 2014 adjusted for confounding in the analysis alone, and Gies 2010 justified not adjusting for confounding because no variables were found to be significant according to their pre-defined model-building approach. Table 3.1 below summarizes the characteristics of included 'truly comparative' cohort studies.

Table 3.1: Characteristics of 'truly comparative' cohort studies								
Study (author, year) **Location**	**Methods**	**Participant characteristics (whether naïve to any prior TNF-alpha inhibitor; hospitalized or outpatient at study start; sex; age (years); concomitant immunosuppressant use)**	**Disease characteristics (Type of IBD; Disease duration at initiation of treatment (years); Montreal classification UC: extent, CD: behaviour)**	**Intervention(s) / comparator(s)**	**Relevant Outcomes**	**N intervention / N comparison**	**Length of follow-up**	**Comments**
Andersen, 2014 Europe	Adj-A	Inpatient/outpatient NR, assumption is naïve to TNF-alpha inhibitors TNF-alpha inhibitors: Male 1993/4553 Mean age 33.7 c-AZA/6-MP 3860 c-MTX/CsA 823 Non-users: Male 23321/51593 Mean age 44.5 c-AZA/6MP 8427 c-MTX/CsA 1455	Crohn's disease and ulcerative colitis Duration NR; Behaviour (CD) and extent (UC) NR TNF-alpha inhibitors: CD 2459 UC 2094 Non-users: CD 15390 UC 36203	TNF-alpha inhibitors (infliximab, adalimumab or certolizumab) / non-users	Malignancy	4553/51593	Median 9.3 years	Did not report results separately by type of TNF-alpha inhibitor or by type of IBD

Biancone, 2011 Europe	Adj-M	Inpatient/outpatient NR; assumption is naïve to TNF-alpha inhibitors Never-treated: Male 130/287 c-IS 131 Infliximab: Male 153/304 c-IS 121 Age NR[a]	Crohn's disease Behaviour NR Infliximab: Median 13.8 years Never-treated: Median 14.8 years	Traditional care (never treated with infliximab) / infliximab	Any malignancy	304/287	Median 74 months	*Follow-up of a 2006 paper describing entire matched cohort of 808 patients*
Choi, 2014 Europe	Adj-M	Naïve to TNF-alpha inhibitors; inpatient/outpatient NR Adalimumab: Male 19/36 Mean age 39.4 c-IS 13/36 Infliximab: Males 18/36 Mean age 37.6 c-IS 20/36	Crohn's disease Adalimumab: Mean 11.6 years B1 23, B2 5, B3 8, p 6 Infliximab: Mean 8.2 years B1 21, B2 4, B3 9, p 8	Infliximab / adalimumab	Induction of response	36/36	Adalimumab: Mean 19.3 months Infliximab: Mean 20.5 months	Economic and clinical outcomes
Gies, 2010 North America (Canada)	N-Adj (see comment)	Outpatient; Naïve to TNF-alpha inhibitors *Induction*	Ulcerative colitis Duration NR *Induction*	Infliximab / adalimumab	Induction of response, maintenance of response	Induction: 28/25 Maintenance:	Median 1.3 years	Although the final model did not include any additional covariates, a

		Adalimumab: Male 14/25 Mean age 34 years c-IS 6 Infliximab: Male 18/28 Mean age 31 years c-IS 15 *Maintenance* Adalimumab: Male 11/20 Mean age 36 years c-IS 3 Infliximab: Male 12 /18 Mean age 31 years c-IS 11	Adalimumab: B1 0, B2 1, B3 24 Infliximab: B1 0, B2 3, B3 25 *Maintenance* Extent NR			18/20		model-building fashion was described in the methods to identify potential confounding variables, therefore will consider that this was adjusted for confounding. Characteristics and results for induction and maintenance studies were reported separately
Kestens, 2013 Europe	Adj-M	Naïve to TNF-alpha inhibitors; Hospitalized Adalimumab: Male 45/100 Mean age 37.8 C-IS 33% Infliximab: Male 45/100 Mean age 35.4	Crohn's disease Adalimumab: Mean 10.9 years B1 48, B2 33, B3 19, p 36 Infliximab: Mean 9.5 years B1 49, B2 35 B3 16, p 31	Infliximab / adalimumab	Maintenance of response, W/D due to adverse events, hospitalization, surgery	100/100	Min-Max 1-2 years	

		C-IS 66%						
Leombruno, 2011 North America (Canada)	Adj-M, Adj-A	Inpatient/outpatient NR; Assumed to be naïve to TNF-alpha inhibitors; c-IS NR Infliximab: Male 148/338 Mean age 35.1 years Non-user: Male 299/670 Mean age 33.6 years	Crohn's disease Behaviour NR Infliximab Mean 3.4 years Non-user Mean 3.1 years	Infliximab / non-infliximab	Hospitalization, surgery	338/670	Mean 1.96 years	Propensity-score matched analysis comparing infliximab to non-infliximab users
Osterman, 2014 North America (United States)	Adj-A	% naïve not reported; Age only reported as # per decade Adalimumab: Male 307/871 Outpatient 865/871 c-IS (new) 29 Infliximab: Male 553/1459 Outpatient 1445/1459	Crohn's disease Duration NR; B1, B2, B3 NR Adalimumab: P 101 Infliximab: P 184	Infliximab / adalimumab	Surgery, hospitalization	1459/ 871	Median 1.5 years	Analysis was "stratified by propensity score quintile"

		c-IS (new) 51						
Patil, 2013 North America (United States)	Adj-A	Inpatient/outpatient NR *Adalimumab or certolizumab:* Male 9/29 Mean age 31.7 c-IS 11 non-naive: *22* *Infliximab:* Male 13/31 Mean age 31.1 c-IS 10 non-naive: 3	Crohn's disease *Adalimumab or certolizumab:* Mean 8.5 years B1 7, B2 14, B3 8, p 8 *Infliximab:* Mean 5.8 years B1 7, B2 8, B3 16, p 9	Infliximab / Adalimumab or certolizumab	Induction and maintenance of remission	31/29	1 year	Separate analysis without 6 certolizumab-treated patients not shown; only reported that it was not different.
Sussman, 2012 North America (United states)	Adj-A	Inpatient/outpatient NR; naïve to TNF-alpha inhibitors; c-IS NR Infliximab: Male Age Adalimumab: Male Age	Crohn's disease Behaviour NR; Duration NR;	Infliximab / adalimumab	Hospitalization	623/623	6 months	Propensity-score matched Only known whether naïve to TNF-α inhibitors in the 6 months prior
Methods: Adj-A = Adjusted in the analysis; Adj-M = matched design Participant characteristics reported by intervention group where available, otherwise for overall study population Disease behaviour in Crohn's disease, Montreal classification: non-stricturing, non-penetrating = B1; stricturing = B2, penetrating = B3, perianal disease modifier = p (added to B1-B3 when present)								

Disease extent in ulcerative colitis, Montreal classification: Ulcerative proctitics = E1, Left-sided UC (distal UC) = E2; Extensive UC (pancolitis) = E3

NR= not reported; c-IS= concomitant immunosuppressant use; c-AZA/6-MP, c-MTX = concomitant azathioprine or 6-mercaptopurine, methotrexate

[a]Age reported only in original cohort study

The only ulcerative colitis study designated as truly comparative, Gies 2010, compared infliximab to adalimumab for induction and maintenance of response and remission in 53 patients over a median follow-up of 1.3 years. Although the final model in this study did not include any covariates, methods were considered to identify potential confounding variables and none were found, therefore outcome data was extracted for this study and quality was assessed.

Seven truly comparative cohort studies were of patients with Crohn's disease. Choi 2014 matched 36 infliximab and adalimumab patients, a total of 72 patients with Crohn's disease, and assessed induction of response. Osterman 2014 performed an analysis of 2330 patients stratified by propensity score quintile comparing infliximab to adalimumab for surgery and hospitalization after a median of 1.5 years of follow-up. Kesten 2013 performed a matched study of patients receiving infliximab and adalimumab in 200 patients and assessed maintenance of response, withdrawal due to adverse events, hospitalization, and surgery at 2 years. Patil 2013 performed an adjusted analysis of infliximab vs adalimumab or certolizumab in 60 patients for induction and maintenance of remission and one year of follow-up. In the study, adalimumab and certolizumab patients were considered together; an analysis comparing infliximab to only adalimumab, excluding six certolizumab patients, was not shown, however the authors reported that results were similar for analyses excluding the six certolizumab patients. Sussman 2012 compared infliximab to adalimumab in a propensity-score matched analysis of hospitalization in 1246 patients over 6 months. Biancone 2011 performed a matched cohort study of 591 patients comparing those treated with infliximab to those never treated with infliximab, for occurrence of any malignancy with a median follow-up of 74 months; this was a follow-up to a previous study reporting on the same cohort of patients in 2006. Leombruno 2011 performed a propensity score matched and multivariate analysis comparing 338 infliximab to non-infliximab users, for hospitalization and surgery, in a total of 1008 patients with a mean follow up of 1.96 years.

The single truly comparative cohort study including patients with either type of inflammatory bowel disease, Andersen 2014, compared TNF-α to non-TNF-α users in an adjusted analysis with a median follow-up of 9.3 years for occurrence of malignancy in 56146 patients from Denmark's national patient registry, 4553 of which were receiving TNF-α inhibitors (infliximab, adalimumab, or certolizumab). Results were not reported separately by type of TNF-α inhibitor, nor was any information given regarding the number of patients receiving specific TNF-α inhibitors. This study was supported in part by a grant from industry.

Of note, Lichtenstein 2014 reported results of the prospective “TREAT” registry in 6273 patients, 3764 of whom received infliximab.(98) Although meeting eligibility criteria for our systematic review, outcome data was not extracted for consideration or deemed appropriate to consider pooling in meta-analysis because reported results were not adjusted for confounding. The registry is sponsored by Janssen Inc., the manufacturer of infliximab. Unadjusted relative risks for infliximab vs non-infliximab treated patients were reported. A multivariable cox-regression analysis was performed to determine the “The relative influences of baseline patient and disease characteristics and medication use”, however none of the measures of association reported in the multivariable analysis were for comparisons of relevance; “infliximab alone" was a variable in the “Cox proportional hazards model of time to first (i.e., risk of) malignancy based on exposure (historical and at any time during registry participation) and adjusted for age, gender, and race,” however the reported HR represents a comparison of monotherapy with infliximab vs any other therapy, which would include combination therapy with infliximab or any other therapy.

Seven case control studies met eligibility criteria.(99-105) Characteristics are reported in Table 3.2 below.

Table 3.2: Characteristics of included case control studies							
Author, year **Design** **Continent**	**Participant characteristics** **age (years); concomitant immunosuppressant use**	**Type of IBD**	**Intervention(s)**	**Case definition and ascertainment**	**Control definition and ascertainment**	**Relevant Outcomes**	**Number of cases/controls** **Duration of follow-up** Comments
Baars, 2011 NCC Europe (The Netherlands)	Concomitant immunosuppressant use NR Patients >65 years at diagnosis or CRC were excluded Cases: Male 108/173 Age Mean 33 years (at diagnosis of IBD) Controls: Male 158/392 Age Mean 31 years (at diagnosis of IBD)	IBD Cases: 113 UC, 58 CD, 2 CU Controls: 175 UC, 207 CD, 10 CU	Anti-TNF, thiopurines, methotrexate, 5-ASA	Possible IBD-related colorectal cancer diagnosed in all 93 hospitals in The Netherlands. Cases were identified using the "nationwide network and registry of histo- and cytopathology (PALGA). Patients initially treated and diagnosed in an academic hospital and referred after cancer diagnosis were excluded.	Histologically confirmed IBD patients who had not developed CRC in the same time period, "matched with cases for the time period for being at risk for CRC." Control patients were identified from 22 randomly selected hospitals.	Colorectal cancer	173/392 Mean 15.5 years Medication use analyzed in logistic regression analysis; multivariate analysis using stepwise regression analysis Reported anti-TNF, thiopurine OR from multivariate analysis. Corrected for gender, location and type of IBD, concomitant primary sclerosing cholangitis,

							pseudopolyps, colonic surgery Determining whether anti-TNF increased risk of CRC was not a primary objective
Long, 2012 NCC	Patients 64 and older were excluded <u>Melanoma</u> Concomitant immunosuppressant use NR Cases: (n 209) Male 47% Age median 50 Controls: (n 823) Male 47.4% Age median 50 <u>NMSC</u> Age and sex NR Concomitant thiopurines: 31/1895 cases 40/8914 controls	IBD <u>Melanoma</u> Cases: CD 48.8% UC 49.8% Unknown 1.44% Controls: CD 48.9% UC 50.6% Unknown 0.6% <u>NMSC</u> Disease type NR	"Biologics" as a class (infliximab, adalimumab or certolizumab), 5-ASA, thiopurines, methotrexate, calcineurins, mycophenolate mofetil, natalizumab.	Diagnosis of melanoma: First, a claim containing a "CPT-4" code for interpretation of pathology from an office of surgical setting, accompanied by an ICD-9 diagnosis code of melanoma and (2) a claim containing a "CPT-4" code for excision of malignant lesions or Mohs stage 1 excision. Diagnosis of NMSC: (1) a claim containing a "CPT-4" code for interpretation of	"Disease-free" with melanoma of NMSC at the time of selection	Melanoma and non-melanoma skin cancer	<u>Melanoma</u> 209/823 <u>NMSC</u> 3288/12945 Age <64 and 12 months of continuous health plan enrollment were inclusion criteria. Cases were matched to up to 4 controls on sex, age within 2 years, region of the country, disease type, and month of the case's diagnosis.

				pathology from an office of surgical setting, accompanied by an ICD-9 diagnosis code of NMSC and (2) a claim containing a "CPT-4" code for destruction or excision and once of the ICD-9 codes for NMSC.			
Hutfless, 2008 NCC	Age 15-68 years; reported as % per decade Concomitant immunosuppressant use NR Only Women were included	IBD Cases: 7 UC, 3 CD Controls: 771 UC, 473 CD	Infliximab, any IBD medication, aminosalicylates, corticosteroids, infliximab, immune modulators	Cervical intraepithelial neoplasia grade 3 or greater (CIN-III or greater) as identified in the Kaiser Permanente Northern California Cancer Registry	Not diagnosed with cervical cancer	Cervical cancer	Association between infliximab and cervical cancer "not estimable", because no occurrences of cervical cancer in infliximab-treated patients
Singh, 2011	Characteristics not reported separately for case/control groups *Overall:* Male 45% Age median 36 years Concomitant IS use NR	Type of IBD NR	Infliximab, thiopurines, methotrexate, cyclosporine	Determined from the Manitoba Cancer Registry	Randomly selected from the same IBD database, matched for sex, age and area of residence	Nonmelanoma skin cancer	237/9381 Median 11.7 years Number of patients who received infliximab not reported

Long, 2010	Patients 64 and older were excluded; C-IS NR Cases: Male 389/742 Age Mean 42 Controls: Male 1556/2968 Age mean 49.2 years	Cases: CD 387 UC 355 Controls: CD 1548 UC 1420	Biologic (infliximab or adalimumab), thiopurine, methotrexate, calcineurin inhibitor, mycophenolate mofetil, any immunomodulator	First diagnosis of NMSC identified by claims database	IBD patients from the same medical claims database cohort, matched on gender, age, geographic region, IBD type, and duration of follow-up.	Nonmelanoma skin cancer	742/2968 Follow-up NR
Ananthakrishnan, 2009	C-IS NR Cases: Male 12/27 Age mean 40 Controls: Male 103/219 Age mean 44.1	Ulcerative colitis	Biologic therapy (infliximab), immunomodulator (methotrexate or azathioprine)	Colectomy Case ascertainment not described	Control ascertainment not described	Colectomy	27/219 Follow up NR Analysis of a database from a single academic IBD referral center. Reports ever use of immunomodulator (could be pre, post or during biologic therapy)
Solem, 2004 CC	C-IS NR Cases:	Crohn's disease	Infliximab, thiopurines, methotrexate,	Small bowel adenocarcinoma	Random generation of list of potential	Small bowel adenocarci	9/18 Median 3.5 years (cases) and 4.6

	Male 4/9 Age median 28 at diagnosis Controls: Male 8/18 Age median 31 at diagnosis		cyclosporine, 5-ASA	Diagnosis made at study institution. Case ascertainment not otherwise described.	controls from registry of Crohn's disease patients. Two age and gender-matched controls were selected for each case. Chart review verified absence of small bowel adenocarcinoma.	noma	years (controls)
NR= not reported; c-IS= concomitant immunosuppressant use; c-AZA/6-MP, c-MTX = concomitant azathioprine or 6-mercaptopurine, CRC= colorectal cancer							

Long 2012, a nested case-control study, analyzed separately the risk of melanoma and nonmelanoma skin cancer associated with IBD medications. Two hundred and nine melanoma cases were matched to 823 controls, and 3288 nonmelanoma skin cancer cases were matched to 12945 controls. This study was done in IBD overall, but results were presented separately for Crohn's disease and ulcerative colitis patients. Baars 2011 was a nested case-control study in IBD patients with 173 cases of colorectal cancer and 392 controls, followed for a mean of 15.5 years. Medication use was assessed as a yes or no variable in a stepwise multivariable regression analysis. Singh 2011 assessed the association of infliximab and other treatments with nonmelanoma skin cancer in a matched case control study of 237 cases and 9381 controls followed for a median of 11.7 years in IBD. Long 2010 was also a matched case control assessing the association of biologics (adalimumab or infliximab) with nonmelanoma skin cancer in 742 cases and 2968 controls in IBD. Ananthakrishnan 2009 assessed the association of infliximab with colectomy in ulcerative colitis in 27 cases and 219 controls from a database at a single academic IBD referral center. Solem, 2004 assessed the association of small bowel adenocarcinoma with infliximab and other treatments in a matched case control study with 9 cases followed for a median of 3.5 years and 18 controls followed for a median of 4.6 years. Hutfless 2008 reported no events in patients who ever used infliximab, so a measure of association between infliximab and cervical cancer was not calculated. Only 11 of 1165 patients in this nested case control study ever received a TNF-α inhibitor.

Twelve studies reported a comparison of interest as a dichotomous variable in multivariable analyses (i.e. concomitant immunomodulators yes or no, variably defined); these studies were not specifically aiming to compare two groups of patients, but rather, were assessing concomitant treatment with immunosuppressants as a "risk factor" for a given outcome, resulting in a relevant comparison of monotherapy vs combination therapy.(106-116)

There were also twelve eligible studies either with a before-after comparison, or where a comparison was made within the same group of participants over time. Seven of these compared a time period before to one after receiving TNF-α inhibitor therapy in Crohn's disease,(117-123) and a seventh involving both forms of IBD.(124) Another study was a propensity-score adjusted analysis of medicare databases looking at any lymphoma, any leukemia, any solid cancer, and nonmelanoma skin cancer.(125) In this study, medication use was treated as a "time-updated variable…such that patients could accrue follow-up time in one or both of the treatment arms sequentially and not

simultaneously. However, once patients were treated with a TNF inhibitor, they could not accrue follow-up time in the comparator cohort." Infliximab exposure status also varied over time in Abraham 2013, which compared infliximab use to non-use for hospitalization and surgery in IBD.(126) Reenaers 2012 compared efficacy and safety of adalimumab to adalimumab plus an immunosuppressant in Crohn's disease. Semesters with versus without concomitant immunosuppression were comopared.(127) Similarly, Sokol 2010 compared efficacy of semesters of use infliximab with versus without concomitant azathioprine or methotrexate in IBD patients.(128) ."

Seventy studies were comparative with no form of adjustment for confounding. Of these, 35 were aiming to make a comparison and 40 were not.

A summary of characteristics of comparative studies for which outcome data were not considered for potential pooling in meta-analysis (before/after or other within patient comparisons, no adjustment for confounding, outcome data was not extractable, or a comparison was made with a relevant comparator as a variable in multivariable analysis only) are provided in Appendix 3.8. Basic characteristics of eligible non-comparative studies are provided in Appendix 3.9.

Study results

A summary of findings of studies for which outcome data was extracted is provided in Tables 3.3 to 3.6. Results of included studies by type of IBD and outcome are also summarized below.

Table 3.3: Results of comparative cohort and case control studies of infliximab compared to adalimumab

Study Design	Outcome(s)	Effect size, 95% CI, p value (if available)	# Participants (IFX/ADA)	Overall Study Quality	Follow-up/Comments
Crohn's disease					
Choi, 2014 Cohort; Adj-M	Induction of response	RR 1, p=1	36/36	Low quality	At 12 weeks
Choi, 2014 Cohort; Adj-M	Withdrawal or discontinuation of therapy due to adverse event	RR 4, p=NR	36/36	Low quality	At 12 weeks 1/36 in Adalimumab vs 4/36 infliximab
Osterman, 2014	Hospitalization	HR 0.88, 95% CI: 0.72, 1.07	1445/865	Acceptable	1.5 years Analysis stratified by propensity

Cohort; Adj-A					score quintile
Osterman, 2014 Cohort; Adj-A	Surgery	HR 0.79, 95% CI: 0.60, 1.05	1445/865	Acceptable	1.5 years Analysis stratified by propensity score quintile
Kestens, 2013 Cohort; Adj-M	Maintenance of response	RD 8%, P= NR	100/100	Acceptable	At 2 years
Kestens, 2013 Cohort; Adj-M	Withdrawal or discontinuation of therapy due to adverse event	RD 3.2%, P=0.3	100/100	Acceptable	At 2 years
Kestens, 2013 Cohort; Adj-M	Hospitalization	RD -5.5%, P=0.4	100/100	Acceptable	At 2 years
Kestens, 2013 Cohort; Adj-M	Surgery	RD -5.7%, P=0.5	100/100	Acceptable	At 2 years
Sussman, 2012 Cohort; Adj-A	Hospitalization	RR 1.15, 95% CI NR, p=0.3070	623/623	Low quality	6 months Propensity-score matched
Ulcerative colitis					
Gies, 2010 (induction) Cohort[a]	Induction of response	RR 1.21, p=0.0889	28/25	Low quality	At 14 weeks
Gies, 2010 (Maintenance) Cohort[a]	Maintenance of response	RR 1.11 P=0.719	18/20	Low quality	54.5 weeks for ADA group and 64.5 weeks for IFX group
ADA= adalimumab; CZP= certolizumab pegol; IFX= infliximab; 95% CI= 95% confidence interval; HR= hazard ratio; RD= risk difference; RR= relative risk; OR = Odds ratio **Bold**= statistically significant [a]Gies, 2010: A plan for multivariate adjustment was described, but no variables were retained in the model					

Table 3.4: Results of comparative cohort and case control studies of infliximab compared to adalimumab or certolizumab

Study / design (cohort vs case control)	Outcome(s)	Effect size	# Participants (IFX/ADA or CZP)	Overall Study Quality	Follow-up/Comments

Crohn's disease					
Patil, 2013 Cohort, Adj-A	Induction of remission	OR 0.24, 95% CI: 0.04, 1.68	31/29	Low quality	2 months 6 patients received certolizumab; results not reported separately
Patil, 2013 Cohort, Adj-A	Maintenance of remission	OR 0.25, 95% CI: 0.03, 2.10	31/29	Low quality	12 months 6 patients received certolizumab; results not reported separately
ADA= adalimumab; CZP= certolizumab pegol; IFX= infliximab; 95% CI= 95% confidence interval; HR= hazard ratio; RD= risk difference; RR= relative risk; OR = Odds ratio **Bold**= statistically significant					

Table 3.5: Results of comparative cohort and case control studies of infliximab compared to traditional care

Study / design (cohort vs case control)	Outcome(s)	Effect size	# Participants (IFX/Traditional care)	Overall Study Quality	Follow-up/Comments
Crohn's disease					
Biancone, 2011 Cohort, Adj-M	Any malignancy	RR 0.944, p=0.95	304/287	Low quality	74 months A separate analysis of only remaining "matched" patients (221 in each group) was also reported as a subgroup analysis
Leombruno, 2011 Cohort, Adj-A	Surgery	**HR 0.57, 95% CI 0.43, 0.75, p<0.001**	338/670	Low quality	1.96 years Multivariable regression and propensity score matched
Leombruno, 2011 Cohort, Adj-A	Hospitalization	**HR 0.69, 95% CI 0.59, 0.81, p<0.001**	338/670	Low quality	1.96 years For any hospitalization; HR also reported for CD-related hospitalization Multivariable

					regression and propensity score matched
Solem, 2004 Case-control	Small bowel adenocarcinoma	OR 0.2, 95% CI 0.02-1.6, P=0.12	9/18	Low quality	Median 3.5 and 4.6 years follow-up for cases ad controls. Association of TNF-α inhibitors with outcome was not a primary objective of the study. Age and gender matched. Analysis adjusted for age and duration of follow-up.
Inflammatory bowel disease					
Singh, 2011 Case-control	Nonmelanoma skin cancer	HR 2.54, 95% CI 0.41, 15.82	NR Less than 5 cases in patients receiving infliximab, but numbers otherwise not reported.	Low quality	11.7 years Association of TNF-α inhibitors with outcome was not a primary objective of the study.
Ananthakrishnan, 2009 Case-control	Colectomy	**OR 3.12, 95% CI 1.21-8.07**	Cases: 14/13 Controls: 49/170	Low quality	Follow-up NR Association of TNF-α inhibitors with colectomy was not a primary objective of the study. Stepwise multivariate logistic regression to identify independent predictors of colectomy. Variables retained in the model not described.
Hutfless, 2008 Case-control	Cervical cancer	**OR not estimable** No cases in the infliximab group	Cases: 0/10 Controls: 11/1155	Low quality	10 cases of cervical cancer in 1165 IBD patients; 11 patients with ever use of infliximab
NMSC= nonmelanoma skin cancer					

ADA= adalimumab; CZP= certolizumab pegol; IFX= infliximab; 95% CI= 95% confidence interval; HR= hazard ratio; RD= risk difference; RR= relative risk; OR = Odds ratio
Bold= statistically significant

Table 3.6: Results of comparative cohort and case control studies of TNF-α inhibitors as a class (infliximab, adalimumab or certolizumab) compared to traditional care

Study / design (cohort vs case control)	Outcome(s)	Effect size	# Participants (IFX or ADA or CZP/Traditional care)	Overall Study Quality	Follow-up/Comments
Inflammatory bowel disease					
Andersen, 2014 Cohort, Adj-A	Any malignancy	Rate ratio 1.07, 95% CI 0.86, 1.33	4553/51593	Acceptable quality	9.3 years Did not report proportion of patients receiving each TNF-α inhibitor (IFX, ADA or CZP); analysis adjusted for type of IBD (CD or UC) but results not reported separately by type of IBD. Multivariable regression using propensity scores
Long, 2012 Nested Case-control	Melanoma, NMSC	<u>Melanoma</u> IBD overall: OR 1.88, 95% CI 1.08-3.29 <u>NMSC</u> IBD overall: OR 1.14, 95% CI 0.95, 1.36	<u>Melanoma</u> 82 (26 cases and 56 controls) /1032 <u>NMSC</u> NR	Low quality	Follow-up NR In a supplemental analysis: combined use of thiopurines and biologics for ≥1 year was associated with NMSC with adjusted OR 3.89, 95% CI 2.33, 6.46 as compared to no use of these medications. Persistent use of either alone was also associated with increased risk of NMSC vs no use of these medications. Adjusted for "utilization and comorbidities". Association of TNF-α inhibitors with outcome was not a primary objective of the study.
Baars, 2011 Nested Case-	Colorectal cancer	**OR 0.09, 95% CI 0.16, 0.56, p<0.001**	79 (4 cases and 75 controls)/ 472 (155	Acceptable	15.5 years OR suggests a protective effect of TNF-α inhibitors on colorectal cancer. Did not

control			cases and 317 controls)		report proportion of patients receiving each TNF-α inhibitor (IFX, ADA or CZP); analysis adjusted for gender, location and type of IBD, concomitant primary sclerosing cholangitis, pseudopolyps, colonic surgery. Also reported a protective effect with thiopurines. Did not report % of concomitant use, or OR for combination therapy.
Crohn's Disease					
Long, 2012 Nested Case-control	Melanoma, NMSC	<u>Melanoma</u> **CD subgroup: OR 1.94, 95% CI 1.03, 3.68** <u>NMSC</u> CD subgroup: OR 1.16 95% CI 0.95, 1.41	<u>Melanoma</u> 82 (26 cases and 56 controls) /1032 <u>NMSC</u> NR	Low quality	Follow-up NR Association of TNF-α inhibitors with outcome was not a primary objective of the study.
Long, 2010 Nested Case-control	NMSC	**OR 2.07, 95% CI 1.28, 3.33**	Cases: 38/704 Controls: 63/2968	Low quality	Follow-up NR Association of TNF-α inhibitors with NMSC was not a primary objective of the study. Study was in overall IBD population, but only analyzable for Crohn's disease. OR is for recent use of adalimumab or infliximab (within 90 days). OR for persistent use >365 days was also reported.
Ulcerative colitis					
Long, 2012	Melanoma, NMSC	<u>Melanoma</u>	<u>Melanoma</u>	Low quality	Follow-up NR

Nested Case-control		UC subgroup: OR 1.73, 95% CI 0.53, 5.63 <u>NMSC</u> UC subgroup: OR 1.06, 95% CI 0.69, 1.64	82 (26 cases and 56 controls) /1032 <u>NMSC</u> NR		Association of TNF-alpha inhibitors with outcome was not a primary objective of the study.
NMSC= nonmelanoma skin cancer ADA= adalimumab; CZP= certolizumab pegol; IFX= infliximab; 95% CI= 95% confidence interval; HR= hazard ratio; RD= risk difference; RR= relative risk; OR = Odds ratio **Bold= statistically significant result**					

Ulcerative colitis: efficacy outcomes

Gies 2010 found a non-significant RR of 1.21 for induction (at 14 weeks, in 58 patients) and 1.11 for maintenance of response for infliximab vs adalimumab (in 38 patients followed for over 1 year).

Ulcerative colitis: safety outcomes

Long 2012 reported a subgroup analysis of ulcerative colitis patients from the overall IBD population. No statistically significant association between melanoma or nonmelanoma skin cancer was found for this subgroup, with an OR of 1.73 (95% CI 0.53, 5.63) for melanoma, and an OR of 1.06 (95% CI 0.69, 1.64) for nonmelanoma skin cancer.

Crohn's disease: efficacy outcomes

Choi 2014, another matched cohort study in 72 patients, reported a RR of 1 (p=1) for induction of response with infliximab vs adalimumab. A non-statistically significant difference in hospitalization (HR 0.88, 95% CI 0.72, 1.07) and surgery (HR 0.79, 95% CI: 0.60, 1.05) was reported for the comparison of infliximab vs adalimumab an analysis of 2310 patients stratified by propensity-score quintile in Osterman 2014. Kestens 2013, a matched cohort study in 200 patients compared infliximab to adalimumab, also found no statistically significant difference for efficacy outcomes of maintenance of response with an RD 8% (p not reported), hospitalization with a RD of -5.5% (p= 0.4) or surgery with an RD of -5.7% (p=0.5). Patil 2013, a comparative cohort study adjusting for confounding in the analysis, compared infliximab vs either adalimumab or certolizumab for induction and maintenance of remission in 60 patients, and also found no statistically significant difference with an OR 0.24 (95% CI: 0.04, 1.68) and 0.25 (95% CI: 0.03, 2.10), respectively. Sussman

2012 was a propensity-score matched analysis comparison of infliximab to adalimumab, and found a non-significant RR of 1.15 for hospitalization in 1246 patients over a 6 month period. Leombruno 2011, a propensity-score matched analysis of 1008 patients that additionally adjusted for confounding in multivariable regression, found a statistically significant reduction in the risk of surgery and hospitalization with infliximab as compared to no infliximab, with an HR 0.57 (95% CI 0.43, 0.75) for surgery and HR 0.69 (95% CI 0.59, 0.81) for hospitalization.

Crohn's disease: safety outcomes

Andersen 2014 conducted a study of 56,146 patients, reporting a propensity-score adjusted non-significant rate ratio of 1.07 (95% CI 0.86, 1.33) for any malignancy for TNF-α inhibitors as a class (including infliximab, adalimumab and certolizumab) as compared to non-use. Choi 2014, a matched cohort study in 72 patients, reported a RR of 4 (p not reported) for withdrawal or discontinuation of therapy due to adverse events; of note, the event rate was low with only one event in the adalimumab group and four in the infliximab group. Kestens 2013 also reported no significant difference between infliximab and adalimumab for this same outcome, RD 3.2% (p=0.3). A single case-control study, Long 2012, reported a subgroup analysis of Crohn's disease patients from the overall IBD population. A statistically significant increased OR of 1.94 (95% CI 1.03, 3.68) for melanoma and 1.16 (95% CI 0.95, 1.41) for nonmelanoma skin cancer was found for TNF-α inhibitors vs non-use. Biancone 2011 reported a non-significant RR of 0.944 (p=0.95) for malignancy for infliximab vs non-use of infliximab in their matched cohort study of 591 patients. Long 2010 reported a statistically significant OR of 2.07 (95% CI 1.28, 3.33) for nonmelanoma skin cancer with recent use of infliximab or adalimumab. Although the study was in the entire IBD population, data was analyzable only for Crohn's disease. Solem 2004 found a non-significant OR of 0.2 (95% CI 0.02-1.6) for adenocarcinoma for infliximab vs non-use of infliximab in a small case-control study in Crohn's disease.

IBD overall: efficacy outcomes

Ananthakrishnan 2009, a case-control study, reported a significant OR of 3.12 (95% CI 1.21-8.07) for colectomy in IBD patients with infliximab use.

IBD overall: safety outcomes

Four case-control studies assessed safety of TNF-α inhibitors as a class in IBD patients. Long 2012 found an increased risk of melanoma with an OR of 1.88 (95% CI 1.08-3.29) and an OR of 1.14 (95% CI 0.95, 1.36) for nonmelanoma skin cancer. Baars 2011 found an OR of 0.09 (95% CI 0.16, 0.56) for

colorectal cancer which suggests a protective effect of TNF-α inhibitors overall including infliximab, adalimumab and certolizumab. Singh 2011 assessed safety of infliximab in IBD patients and reported a non-significant HR of 2.54 (95% CI 0.41, 15.82) for nonmelanoma skin cancer. An OR was not estimable in Hutfless 2008. There were no occurrences of cervical cancer in the 11 patients who ever used infliximab, of a total 1165 women with IBD.

Studies for which a comparison of interest was made in multivariable analysis

Outcome data was extracted from studies for which a comparison of interest was made through use of a dichotomous variable in multivariable analysis. Pooling of these studies, for which a measure of association was reported from a comparison made as a variable in a multivariable analysis, would be skewed substantially by publication bias and reporting bias towards a significant association. For example, the variable of interest may not have been significantly associated with the outcome in a univariate analysis, and therefore would not have been included in a multivariable analysis. Even if it was included in a multivariable analysis but not found to be significant, the measure of association may not have been reported in a final publication. Unless a study was specifically designed to compare two groups, methods of selecting confounding variables would not have been made with the intent of controlling confounding variables relevant for the comparison and outcomes of interest to this systematic review. Relevant outcome results from these studies are summarized in Table 3.7 below. It is important to consider the above source of bias when interpreting these results.

Table 3.7: Results of comparisons made in multivariable analyses

Study (Author, year)	Intervention / variable in multivariate analysis	Outcome	Effect measure, 95% confidence interval
Moran, 2014	TNF-α inhibitors / concomitant onset combination therapy[a]	Surgery	HR 1.57, 95% CI 0.73, 3.38
Armuzzi 2013	Infliximab / concomitant azathioprine	Maintenance of Remission	HR 2.20, 95% CI 1.10, 4.35
		Mucosal healing	OR 2.2, 95% CI 0.75, 6.63
Bortlik, 2013	Infliximab / concomitant thiopurine	"Loss of sustained clinical response	HR 1.00, 95% CI 0.49, 2.07
Eshuis, 2013	Infliximab / concomitant thiopurine	"failure of remission induction"	OR 2.10, 95% CI 1.22, 3.63
Chaparro, 2012	Infliximab / concomitant thiopurine	Surgery	HR 9.8, 95% CI 1.2, 78
Sprakes 2012	Infliximab / concomitant	“Failure to respond”	HR 0.76, 95% CI 0.39,

	immunomodulator		1.49
		"Sustained clinical benefit"	HR 0.78, 95% CI 0.44, 1.38
Chaparro, 2011	Infliximab / concomitant immunomodulator	Maintenance of response	HR 0.37, 95% CI NR
Takagi, 2010	Infliximab / no infliximab	Relapse	HR 0.245, 95% CI 0.12, 0.49
		Surgery	HR 0.65, 95% CI 0.17, 2.45
Miheller, 2009	Infliximab / concomitant azathioprine or methotrexate	Induction of response	OR 2.03, 95% CI 1.00, 4.17
Olsen, 2009	Infliximab / concomitant immunosuppressant	"Non-remission"	OR 0.38, 95% CI 0.04, 3.3
		Mucosal healing	OR 0.36, 95% CI 0.02, 4.7
Rudolph, 2008	Infliximab / concomitant immunomodulator	Maintenance of response	HR 0.58, 95% CI NR
Parsi, 2002	Infliximab / concomitant immunosuppressive	Induction of response (inflammatory)	OR 4.23, 95% CI 1.37, 3.07
		Induction of response (fistulising)	OR 0.91, 95% CI 0.15, 5.45
[a]combination therapy was defined as concomitant onset if both a thiopurine and anti-TNF agent were prescribed within 3 months of each other			

Consideration for pooling of results: inventory of eligible studies

Comparative studies with some form of adjustment for confounding in the design or analysis stage, or adequate justification provided not to adjust for confounding variables, were considered potentially amenable to pooling in meta-analysis or network meta-analysis.

In ulcerative colitis, there was an insufficient number of relevant studies to consider pooling any efficacy outcomes in meta-analysis or network meta-analysis, with no more than one relevant study per outcome.

For outcomes of induction and maintenance of response and remission in Crohn's disease, there was only one comparative study for each outcome. There were two comparative studies reporting an adjusted comparison of agents for withdrawal or discontinuation of therapy due to adverse

events, however, in one study the outcome was assessed after 12 weeks and in the other after two years, so it was decided not to further explore pooling these two studies.

For the outcomes of hospitalization and surgery, there was a sufficient number of studies with relevant comparisons to consider meta-analyses or network meta-analyses. Four studies reporting on these outcomes included one comparison of infliximab to usual care/no infliximab, and three comparisons of infliximab to adalimumab: three for hospitalization and two for surgery. For the outcome of malignancy, two studies, Andersen 2014 and Biancone 2011, would be potentially amenable to pooling of results in meta-analysis. Methodological and clinical diversity of studies was examined for each of these outcomes to determine whether studies were amenable to pooling, and is described below. Owing to the presence of clinical and methodological diversity for these outcomes, it was deemed to be inappropriate to pool their results.

Assessment of methodological diversity for studies reporting outcomes of hospitalization and surgery in Crohn's disease:

Kestens 2013 was a matched cohort study reporting risk differences of adalimumab and infliximab. Data was obtained from medical records. Osterman 2014 and Leombruno 2011 reported adjusted hazard ratios for the comparison of infliximab vs adalimumab and infliximab vs non-infliximab users, respectively, and were analyses of large medical claims databases. Sussman 2012 compared infliximab to adalimumab reporting hospitalization but not surgery outcomes in a propensity-score matched analysis of a medical claims database. Relative risk over six months was reported. Timing and definition of outcome measures and study design features were thought to be sufficiently similar to consider pooling. Neither surgery nor hospitalization outcomes were specifically defined in Kestens 2013. The surgical outcome in Osterman 2014 was bowel resection, whereas in Leombruno 2011 it consisted of "Bowel resection, creation of an ostomy, or surgical treatment of a perforation or abscess." Leombruno 2011 which compared infliximab to traditional care and Sussman 2012 were of low quality, while Kestens and Osterman were judged to be of acceptable quality.

Assessment of clinical diversity or studies reporting outcomes of hospitalization and surgery in Crohn's disease:

Not all population and intervention characteristics of interest were reported in the studies. Kestens 2013 included only patients who were initially hospitalized, whereas Osterman 2014 included only

outpatients. Duration of disease prior to initiation of therapy was not reported in Osterman 2014, but was approximately 10 years in Kestens 2013 vs three years in Leombruno 2011. The proportion of patients with perianal disease was different in Kestens 2013 (36% and 31%) as compared to Osterman 2014 (11.7% and 12.6%) , and was not reported in Leombruno 2011. In Sussman 2012, duration of disease, inpatient vs outpatient at initiation of treatment, and presence of perianal disease was not reported.

Assessment of methodological diversity for the outcome of malignancy, across both forms of IBD: Andersen 2014 compared TNF-α to non-TNF-α users in an adjusted analysis with a median follow-up of 9.3 years and reported rate ratios, and Biancone 2011 performed a matched cohort study of 591 patients comparing those treated with infliximab to those never treated with infliximab for occurrence of any malignancy with a median follow-up of 74 months, from which the relative risk was calculated. Andersen 2014 was judged to be of acceptable quality, whereas Biancone 2011 was deemed to be of low quality. Rate ratios are reported in Andersen 2014 whereas risk ratios are reported in Biancone 2011.

Assessment of clinical diversity for the outcome of malignancy, across both forms of IBD: "Confounding by indication" is less of a concern with harm as compared to efficacy outcomes, therefore the fact that Biancone 2011 included Crohn's Disease patients and Andersen 2014 included both Crohn's and ulcerative colitis patients would not preclude these studies' results from being pooled. Andersen 2014 reported rate ratios for all TNF-α inhibitors as a class and separate analyses by agent were not presented, whereas Biancone 2011 reported infliximab vs never use of infliximab.

Case-control studies: Of the six case-control studies for which outcome data was extracted, three reported the association of TNF-α inhibitors with nonmelanoma skin cancer in the overall IBD population. The intervention was classified differently in each of these studies: Singh 2011 assessed only infliximab, Long 2010 combined infliximab and adalimumab together, and Long 2012 combined infliximab, adalimumab and certolizumab. Results were not reported separately by subgroup of treatment in the two studies that combined different agents together. These three studies were deemed to be of low quality. It was decided not to further explore pooling the results of case-control studies.

Quality assessment

The SIGN 50 criteria for cohort and case control studies provided in Appendices 3.3-3.6 was applied to the nine comparative cohort studies with adjustment for confounding and the six case control studies for which outcome data was extracted. According to this criteria, high quality studies are defined as those meeting the majority of criteria in the SIGN 50 tool, with little or no risk of bias, and "Results unlikely to be changed by further research."(82) Acceptable studies are defined as meeting most of the criteria, and with "Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies", and low quality studies are those for which either most criteria are not met, there are "significant flaws relating to key aspects of study design", or conclusions are "likely to change in the light of further studies."(82)

Overall assessment of quality of included studies is included in the summary of findings tables, and additionally, a more detailed quality assessment is provided in Appendix 3.10.

None of the included comparative cohort studies or case control studies were deemed to be of high quality. Three of the included comparative cohort studies were deemed to be of acceptable quality: Kestens 2013 and Osterman 2014, which were both cohort studies comparing adalimumab to infliximab for the outcomes of hospitalization and surgery in Crohn's Disease, and Andersen 2014, which was a propensity-score adjusted analysis of a medical claims database comparing TNF-α inhibitor therapy to usual care for risk of malignancy. Only one of the case control studies, Baars 2011, was deemed to be of acceptable quality. The remaining comparative cohort studies and case control studies were deemed to be of low quality. Of note, all case control studies rated as low quality did not aim specifically to determine the association of TNF-α inhibitors with the outcomes of interest. Although these studies may have been of acceptable quality to answer their objectives, the reported associations between TNF-α inhibitors and outcomes of interest were thought to be highly biased.

Comparison of observational and RCT evidence

A qualitative comparison of observational and RCT evidence was performed. The measures of association (i.e. OR, RR, RD) for outcomes reported in a recent high quality systematic review were compared to individual observational cohort studies reporting the same outcome. Results were determined to be "consistent and overlapping" if the association was in the same direction with overlapping confidence intervals/credible intervals, "inconsistent and overlapping" if in different directions but confidence intervals/credible intervals overlapped, "consistent but not overlapping" if

in the same direction with confidence intervals that do not overlap, and "inconsistent and not overlapping" if in different directions with overlapping confidence/credible intervals. Outcomes and comparisons were included in this assessment for which there was both (1) available RCT data, including data generated from indirect treatment comparisons in network meta-analysis of RCTs, and (2) observational study data.

The only comparisons and outcomes for which there was both observational and RCT data available were hospitalization and surgery for infliximab vs placebo or non-use in Crohn's disease, induction of response in Crohn's disease, and malignancy for TNF-α inhibitors vs placebo or non-use in IBD. All results were either overlapping or consistent between observational and RCT data. These comparisons are summarized in Table 3.8 below:

Table 3.8: Comparison of RCT and observational evidence of efficacy and safety of TNF-α inhibitors in IBD

Outcome	Comparison	Systematic review	Observational study	Consistency of results
Crohn's Disease				
Surgery	Infliximab vs placebo or traditional care	Costa 2014 OR 0.31 (0.15, 0.64)	Leombruno 2011 HR 0.57, 95% CI 0.43, 0.75	Consistent Unable to assess whether overlapping
Hospitalization	Infliximab vs placebo or traditional care	Costa 2014 OR 0.48 (0.34, 0.67)	Leombruno 2011 HR 0.69, 95% CI 0.59, 0.81	Consistent Unable to assess whether overlapping
Maintenance of response	Infliximab vs adalimumab	Stidham 2014 "compatible infliximab data not available"	Kestens 2013 RD 8%, P= NR	N/A
Induction of response	Infliximab vs adalimumab	Stidham 2014 RR 3.17 (0.53, 22.96)	Choi 2014 RR 1, p=1	Consistent Unable to assess whether overlapping
IBD				
Any malignancy	TNF-α inhibitors vs placebo or non-used of TNF-α inhibitors	Williams 2014 RR of 0.77 (95% CI 0.37, 1.59)	Andersen 2014 Rate ratio 1.07, (95% CI 0.86, 1.33)	Inconsistent but overlapping
Any malignancy	TNF-α inhibitors vs	Williams 2014	Biancone 2011	Consistent

	placebo or non-used of TNF-α inhibitors	RR of 0.77 (95% CI 0.37, 1.59)	RR 0.944, p=0.95	Unable to assess whether overlapping

DISCUSSION

This systematic review of post-market observational studies identified over 200 studies meeting eligibility criteria, none of which were deemed to be of sufficient quality to answer the clinical questions of effectiveness or safety of TNF-α inhibitors in IBD. Of the nine identified comparative cohort studies for which outcome data were extracted, a lack of quality, together with methodological and clinical diversity precluding pooling, make it inappropriate to draw firm conclusions with respect to the real-world or long-term effectiveness or safety of any of the TNF-α inhibitors in Crohn's disease or ulcerative colitis. The same was true for the seven relevant case-control studies, with a lack of control for important confounding variables as the primary issue. The influence of bias in the results is evident when comparing studies; for example, a case-control study reports an increased risk of colectomy with infliximab as compared to traditional care,(103) whereas a comparative cohort study reports a reduced risk of hospitalization and surgery.(95)

When results of systematic reviews of RCTs were compared to results of observational systematic reviews for outcomes for which results of both study types were available, 95% confidence intervals consistently overlapped, when reported. However, a formal statistical analysis was not performed, to avoid overemphasizing these results which are based on limited evidence.

Previous systematic reviews of TNF-α inhibitors in IBD have included observational studies. Gisbert 2007 aimed to "systematically review the efficacy of infliximab for the treatment of UC".(129) Although eligibility was not restricted to randomized controlled trials, quality was only assessed for RCTs and these were the only studies considered for pooling in meta-analysis. Only basic characteristics and results of observational studies were presented. Costa 2013 aimed to "perform a systematic review and meta-analysis of all studies (experimental and observational) evaluating patients with IBD treated with infliximab and providing data on the rate of serious complications (hospitalizations and/or surgery)".(64) Eighteen observational studies were included, and the quality of included observational studies was assessed. Meta-analysis results were stratified according to study design – experimental vs observational. Their approach was "In case substantial heterogeneity was found in results between studies, we investigated whether clinical (therapy regimen, disease severity, follow-up length) or methodological (study quality and design and control type) differences between studies could, at least partially, explain the source of heterogeneity," in contrast to the present study, where it was first determined whether clinical or methodological diversity was present prior to pooling the results. The investigators noted that "the highest risk of bias existed for

potential unadjusted results' estimate because only one third of the studies clearly provided results after adjusting for potential prognostic imbalance variables," noting, however, that the quality of all included studies overall was good to moderate. A pooled OR of 0.29 (95% CI, 0.19, 0.43) was reported for the association of infliximab with hospitalization in IBD, from 10 observational studies of varying designs, however substantial statistical heterogeneity was found with an I^2 of 87%. Exclusion of "noncohort" designs dropped the I^2 substantially to 34% in the Crohn's disease analysis. The meta-analysis of surgical outcomes from observational studies in Crohn's (OR=0.32; 95% CI, 0.21, 0.49) and ulcerative colitis (OR =1.43; 95% CI 0.65, 3.13) yielded similar positive yet heterogeneous results, with I^2 of 77% and 76%, respectively. The investigators noted that this "could not be explained by clinical or methodological differences between studies," and therefore suggested caution in interpretation of their results, but also noting that they "pooled data from nonrandomized studies because of the limitations that randomized trials have, such as generalizability of the results and capability to detect relatively rare events and events that occur far in the future and/or do not occur at a constant rate", and that "there is growing empirical evidence that systematic reviews of harm, such as ours, should consider both nonrandomized and randomized data." The first statement does not justify the pooling of poor quality, diverse observational studies, which is more likely to result in an effect measure that represents a precise estimate of the varying types of bias in the included studies, as opposed to the effect of the intervention of interest. Five of the included studies in Costa 2013 were reported only as abstracts, whereas the present systematic review excluded these studies. Whereas our systematic review considered only those studies with some form of adjustment for confounding in the design or analysis stage, or that provided adequate justification to not adjust for confounding variables, all comparative studies were pooled in Costa 2013 regardless of their methods. Costa 2013 also pooled case-control and cohort studies together, whereas the present study did not intend to do this. Another systematic review including observational studies, Chang 2013, aimed to "systematically review published studies directly comparing cyclosporine and infliximab in acute severe steroid-refractory UC and to perform meta-analyses of the relevant evidence."(61) This systematic review included six retrospective studies and assessed quality of included studies using the Newcastle Ottawa Scale. Results of all six included studies were pooled in meta-analysis. Although the overall Newcastle-Ottawa scores were presented for each study, there was no further information provided with respect to risk of bias, or confounding in particular, for the included studies. The only design feature noted for each study that the studies were retrospective and comparative. Pooled results of

the 3-month and 12-month colectomy endpoints were not statistically significant, with wide confidence intervals. Substantial heterogeneity was observed with I^2 of 68.8 and 77.6% in the primary analyses, respectively. The authors concluded that infliximab and cyclosporine were comparable. The apparent statistical heterogeneity was not discussed at any point. This is another example of unjustified and inappropriate pooling.

A systematic review of prospective observational registry studies in rheumatoid arthritis patients did not find an overall increased risk of malignancy with RR 0.95 (95% CI 0.85, 1.05) from seven studies. However, an increased risk of non-melanoma skin cancer was reported with RR 1.45 (95% CI 1.15, 1.76). The authors acknowledge the risk of bias and confounding of the included studies, and this must be considered in the interpretation of these results.{Mariette, 2011 #93}

A limitation of this study is the potential that some eligible studies could have been missed with the employed search strategy. A search filter for observational studies was used, but there is no validated search filter for observational studies. Reference lists from relevant systematic reviews, and studies included in this systematic review were reviewed in an attempt to identify all potentially relevant studies. It can be argued that with systematic reviews of observational studies, attempting to find every single study might not be the best approach;(78) because of the high risk of bias in many observational studies, a search strategy that is likely to encompass the more well-reported observational studies may be preferred.

Although the present study would not be expected to change clinical practice, it serves several functions: (1) the existence of a knowledge gap has been confirmed; (2) the available observational evidence for a class of drugs in a broad disease category has been described (3) A novel approach to synthesis of observational evidence involving careful consideration of study design features and clinical and methodological diversity has been presented; and (4) The need for a conservative approach in statistical synthesis of observational study data has been demonstrated.

CONCLUSIONS

Post-market observational evidence points towards no increased risk of malignancy with TNF-α inhibitors and no difference in efficacy between adalimumab and infliximab, but is of insufficient quality and quantity to determine whether real-world effectiveness and safety is consistent with pre-market RCTs. Owing to the risk of bias and diversity of available studies, questions regarding the real world and long term efficacy and safety of TNF-α inhibitors in IBD for the outcomes of response,

remission, mucosal healing, hospitalization, surgery, serious adverse events, discontinuation due to adverse events, and malignancy have not been adequately answered. Evidence from observational studies appears to be in alignment with evidence from randomized controlled trials, however the risk of bias of included observational studies precludes any firm conclusions from being drawn. Observational studies with rigorous control for confounding, sufficiently powered to detect clinically important differences, with long duration of follow-up, and independent from industry are needed to address this knowledge gap.

Chapter 5: Final remarks and recommendations

Post-market surveillance: considerations for TNF-α inhibitors in IBD

Post-market observational evidence is capable of addressing some of the knowledge gaps that are unobtainable by RCTs. In the case of TNF-α inhibitors in IBD, a question of particular importance that is difficult to address using RCT data is that of long-term efficacy and safety, and in particular, a potential association with risk of malignancy. Long term outcomes and rare adverse events are not possible to determine in pre-market RCTs which are typically of one years' duration at most and of inadequate sample size to detect rare adverse events. Because IBD is a lifelong condition for which there is no definitive cure, TNF-α inhibitors could be used for years or even decades. Despite the availability of TNF-α inhibitors for use in IBD for nearly 15 years, not a single post-market observational study included in the systematic review of post-market observational studies, described in Chapter 3 of this thesis, was deemed to be of high quality. The influence of industry in the post-market phase remains evident; the only large prospective registry study meeting eligibility criteria was industry-funded.(98)

In their review article, Giezen et al point out some challenges specific to post-market surveillance of biologic medications as compared to small-molecule drugs. Some examples of these specific issues include a "Complex production and purification process/(small) changes in manufacturing process can influence safety", "Potential for immunogenicity", "Limited predictability of preclinical to clinical data due to species specific action and immunogenicity of human proteins in animals", "Adverse events often related to exaggerated pharmacology" (e.g. "TNF-a has a role in the immune response to the mycobacteria responsible for tuberculosis"), and they note that there is "use primarily in the hospital setting therefore limited validity of use of large population databases that are often used for other medications."(130)

The availability of subsequent entry biologics, which have already received market authorization for use in other inflammatory conditions, will further increase post-market research demands for TNF-alpha inhibitors in IBD. Although requirements for market authorization of these subsequent entry biologics are more rigorous than for traditional generic medications, they are less stringent than for

new chemicals. Post-market surveillance of these medications will be of particular importance to ensure their safety.

The current system of post-market surveillance is in need of improvement

The current system of post-market surveillance of drugs in Canada relies heavily on passive reporting of adverse drug events by health professionals, patients, and manufacturers. It is well recognized that this is inadequate to ensure safety of currently marketed pharmaceuticals.(3) Given the inadequacy of spontaneous reporting of adverse drug reactions, it is not surprising that it often takes years to identify important safety concerns before the implicated drugs are eventually withdrawn from the market. A well-known example is that of rofecoxib (Vioxx®) which was available in Canada for 5 years before eventual market withdrawal in 2004 due to an identified increased risk of cardiovascular events. It was estimated that 88,000-140,000 cases of serious coronary heart disease, 44% resulting in death, occurred due to the sale of rofecoxib over 5 years in the US.(131) There is a median duration of 1271 days (IQR 706-2876) between date of notice of compliance and market withdrawal, according to a study of drugs approved between 1990 and 2009 and subsequently withdrawn from the Canadian market. There is no data regarding the average number of patients exposed to medications before market withdrawal.(42)

Other jurisdictions are working on improving their systems of post-market surveillance. Strategies in the EU, France, UK, USA and New Zealand represent a spectrum of approaches to post-market surveillance of pharmaceuticals, but their "relative similarity (as Western developed nations with well-established regulatory frameworks) allows for generalizability" to the Canadian system.(3) A summary of active post-market surveillance strategies in these five international jurisdictions is available in Appendix 4.1. The European Medicines agency currently requires submission of a risk-management plan, which must be submitted at the time of submission for market authorization. These risk management plans are "continually modified and updated throughout the lifetime of the medicine as new information becomes available."(132) Risk management plans, if executed, have the potential to improve safety of marketed medications. However, concerns with this approach are that they are the responsibility of industry to undertake, and they have shown to be difficult to enforce.(133)

RECOMMENDATIONS

1. **High quality post-market observational studies assessing safety and efficacy of TNF-α inhibitors in IBD are needed**

A large, prospective registry of IBD patients receiving pharmacologic treatments, assessing long-term efficacy and safety outcomes of importance to patients, should be established to address current knowledge gaps. Importantly, this registry should be independent from industry, of sufficient duration to allow for conclusions regarding long-term efficacy and safety, aim to be sufficiently powered to detect clinically meaningful differences in rare outcomes such as malignancy, and capture the data necessary to adequately control for confounding variables. Involvement of clinical experts free from conflict of interest would be imperative, to ensure collection of adequate data with respect to variables thought to be potential confounders, and to ensure assessment of the most clinically relevant outcomes. Studies using the registry data should account for pre-defined confounding variables for their outcomes of interest, and these pre-defined variables thought to potentially give rise to confounding should be addressed either in the design or analysis of the registry data.

2. **A mechanism for increasing funding of independent post-market surveillance research is needed**

In order to address the limitations with pre-market RCTs, post-market studies should be independent from industry, of sufficient duration to allow for conclusions on long-term efficacy and safety, and of sufficient sample size to detect rare adverse events of concern. Recognizing that observational studies are highly susceptible to bias, involvement of investigators with sufficient expertise and clinical experts free of conflict is imperative. Of particular importance to the validity of post-market studies is the potential for selection bias. Careful consideration is needed in determining important confounding variables to be considered and the outcomes of most clinical importance.

The establishment of the Drug Safety and Effectiveness Network is an important step towards improving post-market surveillance of pharmaceuticals in Canada. A branch of DSEN, The Canadian Network for Observational Drug Effect Studies (CNODES) aims specifically to address the need for post-market observational studies. DSEN's funding of 10 million dollars annually, which includes not only CNODES but the other networks under DSEN's umbrella, would not come close to addressing

the knowledge gaps for the large number of currently marketed products for which expertly designed, independent post-market studies are needed.

Knowing that independent post-market research is currently inadequately funded to address existing knowledge gaps, and that market authorization holders currently conduct post-market research on their own products, a policy change is needed. One solution would be to shift funding from industry to independent post-market research. This could be achieved by imposing a fee, determined perhaps as a % of revenue from a marketed medication as well on a gradient of the level of post-market surveillance expected to be required for a medication. This fee could be determined at the time of market authorization. Throughout the lifecycle of the product, the fee would be paid regularly into a pool that would essentially provide the funding for a much bigger version of DSEN. This larger DSEN would proactively determine the post-market surveillance needs of medications currently marketed in Canada as well as medications newly receiving market authorization, and conduct post-market research independently from industry. As new medications receive market authorization, a plan for post-market surveillance would be developed and carried out by DSEN. It would be expected that the market authorization holders would be able to scale back funding of their own post-market surveillance programs, in favor of funding this independent research.

OVERALL CONCLUSIONS:

This thesis provides a broad view of the available post-market evidence for TNF-α inhibitors in both Crohn's disease and ulcerative colitis. There is clear RCT evidence for the efficacy of TNF-α inhibitors in both forms of IBD according to a large number of systematic reviews, meta-analyses and network meta-analyses. The evident overlap of RCTs included within these systematic reviews points towards unnecessary duplication of research efforts. There is a large quantity of observational studies addressing questions of efficacy and safety of TNF-α inhibitors in IBD, however the ability to draw any conclusions from these studies is limited by the risk of bias of included studies. There is a clear need for high quality post-market observational studies assessing safety and efficacy of TNF-α inhibitors in IBD, and on a larger scale, a policy change resulting in increased funding of independent post-market surveillance research is required.

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Appendices

Appendix 2.1: Search strategy for overview of systematic reviews

Search Strategies for Medline, Embase and the Cochrane Library: Overview of systematic reviews

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Aril 28th 2014

1. Inflammatory Bowel Diseases/
2. Colitis, Ulcerative/
3. Crohn Disease/
4. (colitis or crohn* or IBD or IBDs or (inflammatory adj2 bowel disease*)).tw.
5. ((enteritis or enterocolitis or "entero-colitis") adj2 (granulomatous or regional)).tw.
6. (ileitis adj2 (regional or terminal)).tw.
7. (Ileocolitis or ileo-colitis).tw.
8. ((proctocolitis or procto-colitis) adj2 idiopathic).tw.
9. ((colorectitis or proctocolitis or procto-colitis) adj2 (ulcer* or mucosal)).tw.
10. or/1-9
11. Antibodies, Monoclonal/
12. Antibodies, Monoclonal, Humanized/
13. Biological Therapy/
14. ((monoclonal adj2 antibod*) or (mono-clonal adj2 antibod*) or (monoclonal adj2 anti-bod*) or (mono-clonal adj2 anti-bod*)).tw.
15. ((biologic* adj2 agent*) or (biologic* adj2 therap*) or (biologic* adj2 response adj2 modifier) or biotherap* or bio-therap*).tw.
16. Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
17. (anti-tnf* or anti tnf* or anti-tumor necrosis factor* or anti tumor necrosis factor* or anti-tumour necrosis factor* or anti tumour necrosis factor* or antitumour necrosis factor* or antitumor necrosis factor* or tnf-inhibitor* or (tumor-necrosis factor* adj2 inhibitor*) or (tumour-necrosis factor* adj2 inhibitor*) or (tnf* adj2 inhibitor*)).tw.
18. (infliximab or remicade or avakine or revellex or remsima or inflectra).tw.
19. (170277-31-3 or infliximab).rn.
20. (adalimumab or humira or trudexa).tw.
21. (331731-18-1 or adalimumab).rn.
22. (golimumab or simponi).tw.
23. (476181-74-5 or golimumab).rn.
24. (certolizumab or cimzia or czp).tw.
25. (428863-50-7 or certolizumab).rn.
26. or/11-25
27. 10 and 26
28. exp Animals/ not (exp Animals/ and Humans/)
29. 27 not 28
30. meta-analysis.pt.
31. meta-analysis/ or meta-analysis as topic/ or exp technology assessment, biomedical/
32. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.
33. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.
34. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.
35. (data synthes* or data extraction* or data abstraction*).tw.
36. (handsearch* or hand search*).tw.

37. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).tw.
38. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).tw.
39. (meta regression* or metaregression*).tw.
40. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
41. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
42. (cochrane or (health adj2 technology assessment) or evidence report).jw.
43. (cochrane or (health adj2 technology assessment) or evidence report).jw.
44. (comparative adj3 (efficacy or effectiveness)).tw.
45. (outcomes research or relative effectiveness).tw.
46. ((indirect or indirect treatment or mixed-treatment) adj comparison*).tw.
47. (Meta-review or metareview or meta review).tw.
48. ((umbrella adj2 review) or "review of reviews").tw.
49. or/30-48
50. (comment or editorial or interview or letter or news).pt.
51. 29 and 49
52. 51 not 50

Database: Embase Classic+Embase <1947 to present>
April 28th 2014

1. Inflammatory Bowel Diseases/
2. Ulcerative Colitis/
3. Crohn Disease/
4. (colitis or crohn* or IBD or IBDs or (inflammatory adj2 bowel disease*)).tw.
5. ((enteritis or enterocolitis or "entero-colitis") adj2 (granulomatous or regional)).tw.
6. (ileitis adj2 (regional or terminal)).tw.
7. (Ileocolitis or ileo-colitis).tw.
8. ((proctocolitis or procto-colitis) adj2 idiopathic).tw.
9. ((colorectitis or proctocolitis or procto-colitis) adj2 (ulcer* or mucosal)).tw.
10. or/1-9
11. Monoclonal Antibody/
12. infliximab/ or adalimumab/ or certolizumab pegol/ or golimumab/
13. Biological Therapy/
14. ((monoclonal adj2 antibod*) or (mono-clonal adj2 antibod*) or (monoclonal adj2 anti-bod*) or (mono-clonal adj2 anti-bod*)).tw.
15. ((biologic* adj2 agent*) or (biologic* adj2 therap*) or (biologic* adj2 response adj2 modifier) or biotherap* or bio-therap*).tw.
16. tumor necrosis factor alpha inhibitor/
17. (anti-tnf* or anti tnf* or anti-tumor necrosis factor* or anti tumor necrosis factor* or anti-tumour necrosis factor* or anti tumour necrosis factor* or antitumour necrosis factor* or antitumor necrosis factor* or tnf-inhibitor* or (tumor-necrosis factor* adj2 inhibitor*) or (tumour-necrosis factor* adj2 inhibitor*) or (tnf* adj2 inhibitor*)).tw.
18. (infliximab or remicade or avakine or revellex or inflectra or remsima).tw.
19. (170277-31-3 or infliximab).rn.
20. (adalimumab or humira or trudexa).tw.
21. (331731-18-1 or adalimumab).rn.
22. (golimumab or simponi).tw.
23. (476181-74-5 or golimumab).rn.
24. (certolizumab or cimzia or czp).tw.
25. (428863-50-7 or certolizumab).rn.

26. or/11-25

27. 10 and 26

28. exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/

29. exp humans/ or exp human experimentation/ or exp human experiment/

30. 28 not 29

31. 27 not 30

32. meta-analysis/ or systematic review/ or "meta analysis (topic)"/ or "systematic review (topic)"/

33. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.

34. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.

35. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.

36. (data synthes* or data extraction* or data abstraction*).tw.

37. (handsearch* or hand search*).tw.

38. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).tw.

39. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).tw.

40. (meta regression* or metaregression*).tw.

41. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

42. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.

43. (cochrane or (health adj2 technology assessment) or evidence report).jw.

44. (cochrane or (health adj2 technology assessment) or evidence report).jw.

45. (comparative adj3 (efficacy or effectiveness)).tw.

46. (outcomes research or relative effectiveness).tw.

47. ((indirect or indirect treatment or mixed-treatment) adj comparison*).tw.

48. (Meta-review or metareview or meta review).tw.

49. ((umbrella adj2 review) or "review of reviews").tw.

50. (editorial or letter).pt.

51. or/32-49

52. 31 and 51

53. 52 not 50

Cochrane Health Technology Assessment Database, Database of Abstracts of Reviews of Effects (DARE), and the Cochrane Database of Systematic Reviews
April 29th, 2014

#1 MeSH descriptor: [Inflammatory Bowel Diseases] this term only 252
#2 MeSH descriptor: [Crohn Disease] this term only 972
#3 MeSH descriptor: [Colitis, Ulcerative] this term only 911
#4 (colitis or crohn* or IBD or IBDs or (inflammatory near/2 (bowel next disease*))):ti,ab,kw 3285
#5 ((enteritis or enterocolitis or "entero-colitis") near/2 (granulomatous or regional)):ti,ab,kw 2
#6 (ileitis near/2 (regional or terminal)):ti,ab,kw 3
#7 (Ileocolitis or "ileo-colitis"):ti,ab,kw 21
#8 ((proctocolitis or "procto-colitis") near/2 idiopathic):ti,ab,kw 2
#9 ((colorectitis or proctocolitis or "procto-colitis") near/2 (ulcer* or mucosal)):ti,ab,kw 3
#10 {or #1-#9} 3289
#11 MeSH descriptor: [Antibodies, Monoclonal] this term only 3918
#12 MeSH descriptor: [Antibodies, Monoclonal, Humanized] this term only 2075
#13 MeSH descriptor: [Biological Therapy] this term only 34
#14 ((monoclonal near/2 antibod*) or (mono-clonal near/2 antibod*) or (monoclonal near/2 anti-bod*) or (mono-clonal near/2 anti-bod*)):ti,ab,kw 6123
#15 ((biologic* near/2 agent*) or (biologic* near/2 therap*) or (biologic* near/2 response near/2 modifier) or biotherap* or (bio next therap*)):ti,ab,kw 1460
#16 MeSH descriptor: [Tumor Necrosis Factor-alpha] this term only and with qualifier(s): [Antagonists & inhibitors - AI] 484
#17 ((anti next tnf*) or anti tnf* or (anti next "tumor necrosis factor*") or anti tumor necrosis factor* or (anti next "tumour necrosis

factor*") or anti tumour necrosis factor* or antitumour necrosis factor* or antitumor necrosis factor* or (tnf next inhibitor*) or ((tumor next "necrosis factor*") near/2 inhibitor*) or ((tumour next "necrosis factor*") near/2 inhibitor*) or (tnf* near/2 inhibitor*)):ti,ab,kw 1644
#18 (infliximab or remicade or avakine or revellex or inflectra or remsima):ti,ab,kw 732
#19 (adalimumab or humira or trudexa):ti,ab,kw 413
#20 (golimumab or simponi):ti,ab,kw 88
#21 (certolizumab or cimzia or czp):ti,ab,kw 74
#22 {or #11-#21} 8949
#23 #10 and #22 431

Appendix 2.2: Screening criteria for overview of systematic reviews

Screening criteria for first level (title and abstract) screening		
	Inclusion	Exclusion
Population	Adults (18 years or older) AND Crohn's Disease OR Ulcerative Colitis OR 'Inflammatory bowel disease' (encompasses Crohn's and Colitis) AND moderate to severe disease (see note below) AND Naïve to previous tnf-alpha/biologic therapy	Previous tnf-alpha/biologic therapy Pregnancy (studies include only pregnant women)
Intervention	Tnf-alpha inhibitors, one or many (infliximab, adalimumab, certolizumab, golimumab) AND initiated within the approved dosage range (See table)	
Comparison	Placebo OR 'traditional/usual care' (e.g. corticosteroids, immunosuppressants such as azathioprine or 6-MP, 5-ASA derivatives) OR Another tnf-alpha inhibitor OR TNF-alpha inhibitor monotherapy compared to combination therapy with that same tnf-alpha inhibitor (i.e. infliximab vs infliximab plus azathioprine)	Natalizumab or vedolizumab (biologics but not tnf-alpha inhibitors)
Outcome	Records will not be screened out based on outcome criteria until a later state	
Design	Systematic Review of RCT's +/- CCTS (and may also include trials of other design)	Narrative review/No systematic approach to literature searching

Notes:

Moderate to severe disease is traditionally defined by MAYO clinic (UC) and CDAI score (Crohn's), but other scales can be used. Any definition of moderate to severe disease will be accepted.

tnf-alpha inhibitors in Crohn's: infliximab (Remicade), adalimumab (Humira), certolizumab (Cimzia)

tnf-alpha inhibitors in Colitis: infliximab (Remicade), adalimumab (Humira), golimumab (Simponi)

Other tnf-alpha inhibitors may have been studied in Crohn's and Colitis, and these can be added to the above lists.

Vedolizumab and natalizumab are biologics but are NOT tnf-alpha inhibitors. Etanercept is also NOT included.

SECOND-level criteria for screening citations (full-text review)		
	Inclusion criteria	Exclusion criteria
Patient	-Adults (18 years or older) -AND Crohn's Disease OR Ulcerative Colitis OR 'Inflammatory bowel disease' (encompasses Crohn's and Colitis) -AND moderate to severe disease (see note below) -AND Naïve to previous tnf-alpha/biologic therapy	-Previous tnf-alpha/biologic therapy *(Exclude <u>only</u> SRs evaluating these patients exclusively)* -Pregnancy *(studies include only pregnant women)* -Patients in post-operative remission -Patients with planned surgery for ulcerative coliti or Crohn's (i.e studies evaluatig peri-operative tnf-alpha inhibitor use)
Intervention	tnf-alpha inhibitors, one or many (infliximab, adalimumab, certolizumab, golimumab), in combination with other treatment(s) or alone AND initiated within the approved dosage range **(See table below)**	
Comparison	-Placebo -'traditional/usual care' (e.g. corticosteroids, immunosuppressants such as azathioprine or 6-MP, 5-ASA derivatives) -Another tnf-alpha inhibitor -TNF-alpha inhibitor monotherapy compared to combination therapy with that same tnf-alpha inhibitor (i.e. infliximab vs infliximab plus azathioprine)	-Natalizumab or vedolizumab (biologics but not tnf-alpha inhibitors) -The same TNF-alpha inhibitor at a different dose or schedule or infusion rate
Outcome	Response, remission, mucosal healing (induction or maintenance), surgery, hospitalization, "serious adverse events", withdrawal/discontinuation of therapy due to adverse events, any malignancy ***NOTE:*** *Outcome will be the last item considered when determining study eligibility. Only if a study*	Studies assessing only post-operative complications, CRP levels, "immunogenicity", antibody levels, or other outcomes not listed in inclusion criteria

	fits all other criteria other than "outcome" should this be selected as the reason for exclusion.	
Design	Systematic Reviews (including network meta-analyses, meta-analyses) of RCTs/ CCTs (eligible systematic reviews may also include trials of other design) ***(SEE FULL DEFINITION OF SYSTEMATIC REVIEW FOR THE PURPOSE OF THIS OVERVIEW BELOW)***	Narrative review/No systematic approach to literature searching (i.e. no methods, or methods describe an search of the literature that is clearly not systematic) A systematic review where only observational studies (not RCTs or CCTs) are eligible

Notes:

Moderate to severe disease is traditionally defined by MAYO clinic (UC) and CDAI score (Crohn's), but other scales can be used. Any definition of moderate to severe disease is accepted.

tnf-alpha inhibitors used in Crohn's: **infliximab (Remicade), adalimumab (Humira), certolizumab (Cimzia)**

tnf-alpha inhibitors in Colitis: **infliximab (Remicade), adalimumab (Humira), golimumab (Simponi)**

Vedolizumab and natalizumab are biologics but are NOT tnf-alpha inhibitors. Etanercept is also NOT included.

Study Design - definition of systematic review (adapted from Cochrane):

In order to fulfill eligibility with respect to study design, studies must meet the following three criteria:

(1) a specific research question (i.e not just “to review the available studies on infliximab") OR specific eligibility criteria for inclusion of studies,

(2) a description of methods including process for selection of studies,* and

(3) a description of a systematic literature search to identify studies

*If there is no description of study selection (i.e. "a single reviewer reviewed titles and abstracts of all studies identified by the literature search", or "two independent reviewers..." but the results imply a systematic approach to study selection (i.e. describes number of studies for which title/abstract reviewed, and for which full-text are reviewed, or displays a prisma flow diagram) then they will be included.

*If a study does not describe a process for selection of studies but refers to standard methodology for systematic reviews (i.e. according to the Cochrane handbook, or according to PRISMA… even though PRISMA is a reporting guidelines) in their methodology they will be included.

Studies describing themselves as a "systematic review" but not meeting the above study design criteria are excluded.

Therapeutic doses of TNF-α inhibitors and countries with regulatory approval (as of April 3 2014)					
TNF-α inhibitor, generic name (brand name)	**Countries with regulatory approval for Crohn's or Colitis***	**Induction dose**	**Maintenance dose**	**Additional Comments**	**Dosing Source**
Infliximab (Remicade)	Canada, USA, EMA/UK, France (13 August 1999),	Intravenously: 5mg/kg at 0, 2, and 6 weeks	5mg/kg every 8 weeks	Consider increasing to 10mg in some situations	Canada
Adalimumab (Humira)	Canada, USA, EMA/UK, France (08 september 2003 for Crohn's, April 4 2012 for UC),	Subcutaneously: 160mg at week 0, 80mg at week 2	40mg every 2 weeks	"dose escalation may be considered" in patients experiencing flare (Crohn's)	Canada
Certolizumab (Cimzia)	USA (Crohn's), not Canada, not EMA/UK, not France (RA only)	Subcutaneously: 200mg at weeks 2 and 4 (Crohn's)	400mg every 4 weeks (Crohn's)		USA
Golimumab (Simponi)	USA (ulcerative colitis), EMA/UK (ulcerative colitis), France (UC, Sept 29 2013), not Canada	Subcutaneously: 200mg at week 0, 100mg at week 2 (Ulcerative colitis)	100mg every 2 weeks (Ulcerative Colitis)		USA
*Within EU, France, UK, Canada, US, or New Zealand. Medications approved under EMA's "centralised authorization procedure" will have regulatory approval in all EU countries plus Iceland, Liechtenstein and Norway. The TNF-α inhibitors are in this category.					

Source: Remicade and Humira, Canadian Product Monographs, Drugs@FDA. US Food and Drug Administration Website. Accessed April 3 2014. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, European Public assessment reports, available from: European Medicines Agency. Human Medicines. 2014. Accessed April 3 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124, MedSafe (New Zealand Medicines and Medical Devices Safety Authority). Medicines Data Sheets. Accessed April 3 2014. http://www.medsafe.govt.nz/profs/datasheet/datasheet.htm#S

Appendix 2.3: AMSTAR guidelines with notes

Obtained from: http://amstar.ca/Amstar_Checklist.php

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

□ Yes □ No □ Can't answer □ Not applicable

2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

□ Yes □ No □ Can't answer □ Not applicable

3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

□ Yes □ No □ Can't answer □ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

□ Yes □ No □ Can't answer □ Not applicable

5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

□ Yes □ No □ Can't answer □ Not applicable

6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

□ Yes □ No □ Can't answer □ Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

□ Yes □ No □ Can't answer □ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

□ Yes □ No □ Can't answer □ Not applicable

9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

□ Yes □ No □ Can't answer □ Not applicable

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

□ Yes □ No □ Can't answer □ Not applicable

11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

□ Yes □ No □ Can't answer □ Not applicable

Shea et al. BMC Medical Research Methodology 2007 7:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Appendix 2.4: Checklist of good research practices for conducting and reporting network-meta-analysis studies

Checklist item	Recommendation(s)
Search strategies	-Follow conventional guidelines for systematic literature searches; be explicit about search terms, literature, and time frames, and avoid use of ad hoc data -Consider iterative search methods to identify higher-order indirect comparisons that do not come up in the initial search focusing on lower-order indirect comparisons
Data collection	-Set forth evidence network demonstrating direct and indirect linkages between treatments, based on identifying study reports ---Follow conventional guidelines for data collection; use a pre-specified protocol and data extraction form -Include sufficient study detail in data extraction to permit assessment of comparability and homogeneity (e.g. patient and study characteristics, comparators, and outcome measures)
Statistical analysis plan	-Prepare statistical analysis plan prior to data analysis, but permit modifications during data analysis, if necessary -Provide step-by-step descriptions of all analyses, including explicit statements of all assumptions and procedures for checking them -Describe analytic features specific to network meta-analysis, including comparability and homogeneity, synthesis, sensitivity analysis, subgroup analysis and meta-regression, and special types of outcomes
Data analysis	-Follow conventional guidelines for statistical model diagnostics -Evaluate violations of similarity or consistency assumption in evidence network -If similarity or consistency is a problem, consider use of meta-regression models with treatment x covariate interactions to reduce bias
Reporting	-Follow PRISMA statement for reporting of meta-analysis -Explicitly state the study research questions (e.g., in introduction or objectives section of report) -Provide graphical depiction of evidence network -Indicate software package used in the analysis and provide code (at least in an online appendix)

Source: Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(4):429-37

Appendix 2.5: Records excluded from overview of systematic reviews at full-text review

Akobeng Anthony, K. Zachos, Mary. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews.* 2003.
Akobeng, A. K.. Review article: The evidence base for interventions used to maintain remission in Crohn's disease. *Alimentary Pharmacology and Therapeutics.* 2008. 27:11-18
Ali, T. Yun, L. Rubin, D. T.. Risk of post-operative complications associated with anti-TNF therapy in inflammatory bowel disease. *World Journal of Gastroenterology.* 2012. 18:197-204
Ardizzone, S. Cassinotti, A. De Franchis, R.. Immunosuppressive and biologic therapy for ulcerative colitis. *Expert Opinion on Emerging Drugs.* 2012. 17:449-467
Balzola, F. Cullen, G. Ho, G. T. Russell, R. K.. Meta-analysis: Rapid infliximab infusions are safe. *Inflammatory Bowel Disease Monitor.* 2013. 14:21
Bebb, J. R. Scott, B. B.. Systematic review: How effective are the usual treatments for Crohn's disease?. *Alimentary Pharmacology and Therapeutics.* 2004. 20:151-159
Bengi, G. Akpinar, H.. What is the importance of infliximab and cyclosporine in the treatment of corticosteroid-refractory severe ulcerative colitis?. *Turkish Journal of Gastroenterology.* 2012. 23:7-12
Bessissow, T. Renard, M. Hoffman, I. Vermeire, S. Rutgeerts, P. Van Assche, G.. Review article: Non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. *Alimentary Pharmacology and Therapeutics.* 2012. 36:312-323
Bewtra, M. **Lichtenstein, G. R.**. Infliximab use in Crohn's disease. *Expert Opinion on Biological Therapy.* 2005. 5:589-599
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Billioud, V. Sandborn, W. J. Peyrin-Biroulet, L.. Loss of response and need for adalimumab dose intensification in Crohn's disease: A systematic review. *American Journal of Gastroenterology.* 2011. 106:674-684
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Blonski, W. Buchner, A. M. Lichtenstein, G. R.. Treatment of ulcerative colitis. *Current Opinion in Gastroenterology.* 2014. 30:84-96
Blonski, W. Kundu, R. Lichtenstein, G. R.. Lymphoma risk in inflammatory bowel disease: Role of azathioprine/6- mercaptopurine and infliximab. *Practical Gastroenterology.* 2005. 29:17-32
Blonski, W. Mudireddy, P. R. Buchner, A. M. Lichtenstein, G. R.. Therapeutic options in steroid-refractory acute severe ulcerative colitis. *Journal of Clinical Outcomes Management.* 2012. 19:501-517

Blonski, W. Osterman, M. T. Lin, M. V. Brensinger, C. M.Kotlyar, D. Sonu, I. Lichtenstein, G.. Risk of postoperative infections in IBD patients treated with perioperative anti-TNF therapy: A meta-analysis. *Gastroenterology.* 2010. 1):S529

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Bressler, B. Sands, B. E.. Review article: Medical therapy for fistulizing Crohn's disease. *Alimentary Pharmacology and Therapeutics.* 2006. 24:1283-1293

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Brunasso, A. M. G. Puntoni, M. Gulia, A. Massone, C.. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: A systematic review. *Rheumatology.* 2011. 50:1700-1711

Bruzzese, V. Lorenzetti, R. Zullo, A. Hassan, C. Campo, S. M.. Anti-TNF therapy and tuberculosis risk in rheumatic diseases, psoriasis, and IBD: A pooled-data analysis of randomized controlled trials. *Annals of the Rheumatic Diseases.* 2013. 72:#pages#

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CADTH. Infliximab for Maintenance Therapy for Treatment of Crohn's Disease: A Review of the Clinical Effectiveness and Guidelines. *Canadian Agency for Drugs and Technologies in Health (CADTH) Health Technology Inquiry Service.* 2010. #volume#:#pages#

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Appendix 2.6: Calculation of risk difference from risk ratios or odds ratios

In order to allow comparison of pooled effect estimates of included studies, reported relative risks and odds ratios for induction and maintenance of remission outcomes were converted to a standardized risk difference.

Formulas

Where P= baseline prevalence, or prevalence without treatment

Converting Risk Ratio (relative risk) to Risk Difference:

(RR x P) – P = RD

Converting Odds Ratio to Risk Difference:

$Odds_2 = Risk_2 / (1 - Risk_2) = P / (1 - P)$

$Odds_1 = Odds\ Ratio \times Odds_2$

$Risk_1 = Odds_1 / (1 + Odds_1)$

$Risk_2 = P$

$Risk\ Difference = Risk_1 - Risk_2$

Alternatively,

Risk 1 = OR x Odds2 / (1+ (ORxOdds2))

Risk 2 = P

Risk difference = $Risk_1 - Risk_2$ (OR x Odds2 / (1+ (ORxOdds2))) - P

Plotting the results

The point estimate of the RD and extremes of the 95% confidence interval for the RD were calculated from the OR or RR using the above formulas. The standard error was then estimated using the following formula:

(Upper end of the 95% CI – point estimate for RD) / 1.96

Using the calculated standard error, the 'Generic Inverse Variance' method was used in RevMan to accurately represent the converted RDs and their 95% CIs in forest plots.

Determing 'P' for remission in Crohn's Disease

From Buresi 2013,(1) the pooled estimate for placebo rates in 15 included RCTs of induction therapy with monoclonal antibodies was 11% (8-13%) and for maintenance was 13%. It was noted that remission rates were lower than mucosal healing, possibly due to "irritable bowel syndrome-like symptoms leading to overestimates of activity indices."

From Su 2004,(2) placebo rates from RCTs of treatment for CD for remission were pooled. Analyses were not restricted to studies of TNF-alpha inhibitors, and "induction" and "maintenance" outcomes were not separated. Studies were stratified by duration: for 11 studies less than 2 months, the pooled placebo estimate was 12% (95% CI, 7% to 19%) and in 3 studies 4 months or longer the pooled estimate was 32% (95% CI, 23% to 42%).

From Tine 2008,(3) the pooled control rates of remission were 17% 17% (95% CI, 13 to 21%) in RCTs of biologics for Crohn's disease. It was noted that there was significant heterogeneity among studies ($p<0.0001$). Results were not reported separately for induction vs maintenance or stratified by study duration.

The estimates of 11% for induction and 13% for maintenance of remission were used because the study Buresi 2013 is the only to report induction and maintenance separately and specifically for a monoclonal antibody-receiving study population.

Determining 'P' for remission in ulcerative colitis

From Su 200,(4) the pooled remission rate in the placebo groups was **13%** (95% CI, 0% to 40%). There was significant heterogeneity among the studies, and there was no differentiation between induction and maintenance studies. The longest study duration was 12 weeks, and most studies were 8 weeks or less. Remission was defined as a UCDAI of 0 or as a UCDAI less than 3, with 6 studies studies using each definition.

The recent network meta-analysis, Stidham 2014, comments on the induction (ACT-1 and ULTRA-1) and maintenance (ACT-2 and ULTRA-2) studies for infliximab and adalimumab, nothing that "Heterogeneity in placebo remission rates between ACT-1 and 2 (14.9–16.5% at week 8 and 54), and ULTRA-1 and 2 (8.5–**9.3%**), suggest that variations in study conduct or design were present... Heterogeneity in placebo rates remains a prevalent issue in inflammatory bowel disease research with no clear consensus on a single mechanism but include selection of patients, clinical characteristics, timing of clinical evaluation and inter-observer variation as suggested by Renna et al. Others have proposed alternative endpoints in the evaluation of inflammatory bowel disease trials, but this has not been widely adopted."

From Stidham 2014, an overall placebo rate from 3 maintenance of remission RCTs was calculated by adding the total number of events and dividing by the total number of participants. These three studies encompassing one study for each anti-TNF: 65/537 = **12.1%.**

Because of the lack of available meta-analyses of placebo groups, a meta-analysis of the placebo rates in the above RCTs using the 'Generic Inverse Variance' method in Revman revealed a placebo group rate of 11% (95% CI 8%, 14%), similar to the results of the simple calculation from the same three maintenance of remission RCTs.

Because it is not expected that remission rates would decrease over time, the estimate of 13% was used for both induction and maintenance for ulcerative colitis rather than using 13% and 11%. This

estimate is within the 95% CI of the placebo prevalence estimate as determined by the meta-analysis of placebo rates from the three maintenance RCTs.

Also of note: Garud S1, Brown A, Cheifetz A, Levitan EB, Kelly CP. Dig Dis Sci. 2008 Apr;53(4):875-91. Epub 2007 Oct 13. Reports a meta-analysis of placebo response in ulcerative colitis RCTs. No maintenance trials are included, and this study does not differentiate anti-TNF studies from studies of other therapies in ulcerative colitis.

For hospitalization and surgery: Samuel S, Ingle SB, Dhillon S, Yadav S, Harmsen WS, et al. (2013) Cumulative Incidence and Risk Factors for Hospitalization and Surgery in a Population-based Cohort of Ulcerative Colitis. Inflammatory Bowel Diseases 19: 1858–1866. From R915.

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Appendix 2.7: Quality Assessment of included systematic reviews

Quality Assessment of included network meta-analyses of TNF-alpha inhibitors in ulcerative colitis and Crohn's Disease:

	Danese 2014	Stidham 2014 (UC)	Stidham 2014 (CD)	Thorlund 2014
Quality of the systematic review: Justification (AMSTAR items):	**High Quality**	**High Quality**	**High Quality**	**Acceptable**
Was an 'a priori' design provided?	Yes	Can't answer	Can't answer	Can't answer
Was there duplicate study selection and data extraction?	Can't answer. *There was duplicate data extraction, but no information about study selection.*	Yes	Yes	Can't Answer *Independent study selection, but not described if data extraction was independent or in duplicate*
Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes
Was the status of the publication (i.e. grey literature) used as an inclusion criterion?	Yes	No *Only published studies were eligible for inclusion*	No Restricted to full publications	Yes
Was a list of studies (included and excluded) provided?	No	No	No List of excluded studies not provided	Yes
Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes
Was the scientific quality of the included studies	Yes	Yes	Yes	No

assessed and documented?				
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	No	Yes	No (No description of assessment of quality or risk of bias of included studies)
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes
Was the likelihood of publication bias assessed?	Yes	Yes	Yes	No
Was the conflict of interest stated?	Yes	Yes	Yes	Yes
NMA quality:	**High Quality**	**High Quality**	**High Quality**	**Acceptable**
Comments re: NMA Quality	The probability of each treatment being best was not reported; there was no table of study characteristics to allow assessment of possible effect modifiers	No description or justification of model used was provided		No sensitivity analyses were described; there was inadequate justification of model choice and of prior distributions; the probability of each intervention being best was not reported

Quality assessment of systematic reviews +/- meta-analyses in Crohn's disease and ulcerative colitis:

	Nikfar 2014	Peyrin-	Rahimi 2007	Williams	Zhang 2013

		Biroulet 2008		2014	
Quality of the systematic review: Justification (AMSTAR items):	**Acceptable**	**Acceptable**	**Unacceptable**	**High Quality**	**Acceptable**
Was an 'a priori' design provided?	Can't answer. *No reference to a published protocol or registered proposal*	Can't answer	Can't answer	Can't answer	Can't answer
Was there duplicate study selection and data extraction?	No *Three independent reviewers for title and abstract review. Article does not specify number of reviewers for assessment of full text or data extraction*	Can't answer *Duplicate data extraction, not specified for study selection.*	No *Duplicate selection, extraction not described.*	No *Study selection not performed in duplicate at first level screening*	No *Data extraction not described.*
Was a comprehensive literature search performed?	Yes	Yes	Can't answer *Total number of citations retrieved not stated. Keywords provided, but search strategy for each database not provided. Does not mention working with an information specialist.*	Yes	No *Detailed search strategy not provided. Provided search terms did not suggest a comprehensive search.*

Was the status of the publication (i.e. grey literature) used as an inclusion criterion?	No Restricted to english language	Yes	Yes	Yes	Yes
Was a list of studies (included and excluded) provided?	Yes	No No list of excluded studies	No *Although some reasons for exclusion with references were given, it is not clear whether this is a comprehensive list of all studies retrieved for full-text review.*	No *A list of excluded studies was not provided.*	**No** *list of excluded studies was not provided***.**
Were the characteristics of the included studies provided?	Yes	No *Table of characteristics did not include patient characteritics*	No *No characteristics other than the drug name for each study.*	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	No *Quality assessment not reported*	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Can't answer. *Jadad scores ranging from 3 to 4. Some discussion of potential bias in the discussion section. No actual conclusions statement other than in the abstract.*	No *The only comment regarding quality of included studies was that they were all of high quality with Jadad 3 or higher.*	No	Yes	No *Jadad score for each study was presented in Table of Characteristics. Quality of included studies was not explicitly considered in conclusions.*

Were the methods used to combine the findings of studies appropriate?	Yes	Yes	No *Although statistically significant heterogeneity was found, there was no attempt to explain or explore this. Anti-TNFs were analyzed as a class. Separate pooled analyses by agent were not performed.*	Yes	Yes
Was the likelihood of publication bias assessed?	Yes	Yes	No	Yes	Yes
Was the conflict of interest stated?	Yes	Yes	No	Yes	Yes
Additional Comments:	Lack of clear inclusion and exclusion criteria (not stated in methods). Several grammatical errors (i.e. "Jada" scale). Search strategy was described but not provided in full. Excluded studies not provided in list form, but referenced with reason	Readability was not good. Referred to online figures, which included important outcome results and were difficult to navigate. Good handling of different maintenance trial designs.	The conclusions do not consider that results were very heterogeneous and that individual agents may have different effects. This was not brought up in the discussion.	General characteristics of included studies was provided. No information re: age, sex, or duration of disease of patients included in the trials.	All participants in 8 of 13 included RCTs received TNF-alpha inhibitors as induction therapy for 0-6 weeks which is a major limitation if short-term exposure can lead to adverse effects later on, and this is plausible. Follow-up was a

	for exclusion (although explanations were unclear, because of lack of clear inclusion and exclusion criteria to in methods).				maximum of 56 weeks therefore long-term risk of adverse effects cannot be inferred, 2 studies assessed CDP 571 which is not relevant to this overview.

	Akobeng 2009	Assassi 2009	Assassi 2010	Baggenstos 2013	Behm 2008
Quality of the systematic review: Justification (AMSTAR items):	**High Quality**	**High Quality**	**High Quality**	**Unacceptable**	**High Quality**
Was an 'a priori' design provided?	Can't answer *Link or reference to 'a priori' design was not provided, however, it is a cochrane review*	Can't answer.	Can't answer.	Can't answer.	Can't answer *Not reported. Cochrane review, however.*
Was there duplicate study selection and data extraction?	Yes	No *Independent study selection. All extracted data was checked by a second reviewer; not done independently*	Yes	No *Selection done partially in duplicate. Data extraction not described.*	*Yes*
Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	*Yes*

Was the status of the publication (i.e. grey literature) used as an inclusion criterion?	Yes	Yes	Yes	No *Restricted to english language.*	Yes
Was a list of studies (included and excluded) provided?	Yes	Yes	**No** *No list of excluded studies.*	No *List of excluded studies not provided.*	No *List of excluded studies not provided.*
Were the characteristics of the included studies provided?	Yes	*Yes*	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	No	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	*Yes*	Can't answer *The only explicit concluding statement related to the quality assessment of the included studies "All the included RCTs had a methodological quality score (Jadad scale) of 3 or more, which indicates higher quality and less potential for introducing bias."*	No	No *Not assessed.*	Yes
Were the methods used to combine the findings of studies appropriate?	Not applicable *It was determined to be*	Can't answer *Instances where RCTs were not pooled, it*	Can't answer *Both random and fixed effects reported for*	Can't answer. *Not applicable. Results were*	Yes

	inappropriate to combine the studies statistically.	*was not explicitly stated certain studies were not pooled, however a thorough description of each study was provided and it is implied that difference between them prohibited pooling of their results.*	*each outcome. Results were not pooled for some outcomes. Although it was stated in the methods that results would only be pooled if sufficiently similar, there was no explicit statement in the results re: the dissimilarity of studies that were not pooled. There was no pre-specified method of determining whether random or fixed effects model was most appropriate.*	*not pooled.*	
Was the likelihood of publication bias assessed?	No	No	No	No	No
Was the conflict of interest stated?	Yes	Yes	Yes	Yes	Yes
Additional Comments:					

Quality assessment of systematic reviews +/- meta-analyses in IBD (crohn's disease and ulcerative colitis)

	Chande 2013	Chang, 2013	Costa 2013	Da 2013	De cruz 2013
Quality of the	High	Acceptable	High quality	High	Unaccepta

systematic review: Justification (AMSTAR items):	Quality			Quality	ble
Was an 'a priori' design provided?	Can't answer *Protocol first published at the same time as the review, according to 'history' provided in this article.*	Can't answer	Can't answer *No mention of a protocol or proposal*	Can't answer	Can't answer
Was there duplicate study selection and data extraction?	Yes	Can't answer *Duplicate study selection; data extraction not described.*	Yes	Yes	No *Although it is noted that 4 authors screened titles and abstracts, it was not stated whether this was done independently. No statements were made re: data extraction or disagreements.*
Was a comprehensive literature search performed?	Yes	Can't answer Full search strategy not provided	Yes	Yes	Yes
Was the status of the publication (i.e. grey literature) used as an inclusion criterion?	Yes	No Restricted to published studies	Can't answer Although "no language restrictions"	No "All searches included	Can't answer Specific eligibility

			was specified, no explicit statement re: publication status was given.	literature published/ available online"	criteria was not presented.
Was a list of studies (included and excluded) provided?	Yes	No List of excluded studies not provided	No List of excluded studies was not provided.	No List of excluded studies not provided	No No list of included or excluded studies
Were the characteristics of the included studies provided?	Yes	Yes	Yes	No Basic design characteristics and results extracted, no patient characteristics or specific intervention characteristics reported.	No Studies narratively described, not in detail.
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	No
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	Yes	No formal assesment of quality. No distinct conclusions made with respect to efficacy of anti-tnf alpha therapies for mucosal healing

Were the methods used to combine the findings of studies appropriate?	yes	Can't answer *Although statistical heterogeneity was discussed, details re: study design characteristics and potential heterogeneity were not discussed.*	Yes	Yes	N/A Qualitatively described studies. No description of any attempt to perform a met-analysis
Was the likelihood of publication bias assessed?	Can't answer *Publication bias is part of GRADE level of evidence, but did not explicitly state that publication bias was assessed.*	Yes	Yes	Yes	No
Was the conflict of interest stated?	Yes	Yes	No No disclosure or conflict of interest statement.	Yes	No
Any additional comments?		Meta-analysis of <u>observational studies</u>	This quality assessment applies only to the quality of the systematic review of clinical trials. This systematic review analyzed observational studies separately.		

Quality assessment of systematic reviews +/- meta-analyses in ulcerative colitis

	Dretzke, 2011	Ehteshami-Afshar, S, 2011	Ford, 2011	Gisbert, 2007	Huang, 2011 (crohn's)
Quality of the systematic review: Justification (AMSTAR items):	High Quality	Unacceptable	High quality	Acceptable	Unacceptable
Was an 'a priori' design provided?	Can't answer	Can't answer	Can't answer	Can't answer	Can't answer
Was there duplicate study selection and data extraction?	Yes	Can't answer Three reviewers independently reviewed the title and abstract of each article". No comment re: data extraction.	Yes	Can't answer not described	Can't answer. Notes that there was duplicate extraction, but selection process was not described.
Was a comprehensive literature search performed?	Yes	Can't answer Full search was not provided. "all relevant MeSH terms were used."	Yes	Can't answer Full search strategy not provided, although appeared comprehensive	Yes
Was the status of the publication (i.e. grey literature) used as an inclusion criterion?	Yes	No. Studies published in languages other than english were excluded.	Yes	Yes	No. English language or studies that could be translated
Was a list of studies (included and excluded) provided?	No List of excluded studies not provided	No List of excluded studies not provided	No List of excluded studies not provided	No. List of excluded studies not provided.	No. List of included studies, although not entirely clear (not all included studies were

					used in analyses; no explanation given). No list of excluded studies.
Were the characteristics of the included studies provided?	Yes	No Inclusion criteria but not characteristics of patients in included studies not provided.	Yes	Yes	No. A table with minimal information on included studies was reported
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Quality assessment not explicitly related to conclusions	Yes	Yes	No. Although quality of 4 out of the 5 "included" studies was reported, they only noted that they all received a Jadad scoare of 5
Were the methods used to combine the findings of studies appropriate?	Can't answer Results were not pooled for any analyses; authors described reasons for not pooling results	Can't answer Little detail provided re: the analysis for colectomy. Statistically significant heterogeneity was found but reasons for this not explained.	Yes	Yes	yes

Was the likelihood of publication bias assessed?	no	Yes	Yes	No	Yes
Was the conflict of interest stated?	Yes	yes	Yes	Yes	No
Any additional comments?		included both UC and CD studies however these would be expected to be very heterogeneous. Subgroup analyses for Crohn's and UC not presented. No attempt to explain significant heterogeneity; studies combined using random-effects model. Unclear timing of endpoint assessment for colectomy.		Study selection and data extraction not described. Timing of outcome assessment not defined/reported.	Table of "results of included trials" was not clear and had minimal information. Study selection process not described, but basic eligibility criteria was provided, however it was very broad. Outcomes were not stated in methods section.

	Huang, 2011 (ulcerative colitis)	Hutfless, 2014	Kawalec, 2013	Lawson, 2009	Lv, 2014
Quality of the systematic review: Justification (AMSTAR items):	Acceptable	High quality	**High quality**	High Quality	High Quality
Was an 'a priori' design provided?	Cant' answer	Can't answer	Can't answer	Yes	Can't answer

Was there duplicate study selection and data extraction?	Can't answer Two authors independe ntly selected papers, but data extraction is not described.	Yes	Yes	Can't answer Study selection by two independent reviewers. It was noted that two reviewers separately extracted and recorded data, however not clear whether this was in duplicate or shared	**Yes**
Was a comprehensive literature search performed?	Can't answer Full search strategy not provided.	Yes	Yes	Yes	**Can't answer detailed search strategy not provided; list of keywords does not seem comprehensive**
Was the status of the publication (i.e. grey literature) used as an inclusion criterion?	Yes	No Restricted to english-language, peer reviewed publications	Can't answer "Articles published as full text were preferabl e". Justificati on given. Unpublish ed studies were "taken into considera tion".	yes	No **restricted to english language**
Was a list of studies (included and excluded) provided?	No A list of excluded studies	yes	No **Excluded studies not**	Yes	**Yes**

	was not provided.		**provided.**		
Were the characteristics of the included studies provided?	No Table of characteristics lacked intervention and comparison characteristics.	yes	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Although quality of studies was reported, an explicit link to conclusions was not made.	Yes	Can't answer It was noted that studies were mostly of high quality in the results.	No **It appears that a thorough assessment of risk of bias was performed, but there is no explicit statement to show that quality of included studies was considered in formulating conclusions**	Yes
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	yes	yes
Was the likelihood of publication bias assessed?	Yes	Yes	No	Yes	No However, it was stated that this was due to too few studies.
Was the conflict of interest stated?	No	Yes	No	Yes	yes

Any additional comments?	Pooled analyses included studies with both infliximab and adalimumab as interventions, and placebo or corticosteroids as control. Timing of outcome assessment not reported. Terminology used was different than in many other systematic reviews (i.e. "short-term relief" and "long-term relief" and outcomes were not well-defined in the methods. Inclusion and exclusion criteria was ambiguous ("baseline data that were not	Tables present grading of evidence for each intervention for each outcome.			Conclusions inconsistent with results

	similar to those in other papers").				

	McDonald, 2012	Mills, 2011	Neurath, 2012	Nikfar, 2011	Singh, 2011
Quality of the systematic review: Justification (AMSTAR items):	High Quality	Unacceptable	Unacceptable	Unacceptable	Acceptable
Was an 'a priori' design provided?	Yes	Can't answer	Can't answer	Can't answer	Yes
Was there duplicate study selection and data extraction?	Yes	No Information specialist screened titles and abstracts, and relevant full texts were reviewed by an author.	No Not specified. "titles and abstracts were reviewed. "	No Data extraction method not described	Yes
Was a comprehensive literature search performed?	Yes	Can't answer An information specialist performed the search, but full search strategy was not provided.	Can't answer keywords provided, but seems likely/possible that it was not comprehensive.	No only 3 search terms noted for literature search	No Relied on RCTs listed in previous systematic reviews, and updated with a comprehensive literature search. Probably ok.
Was the status of the publication (i.e. grey literature) used as an inclusion criterion?	Yes	No Published	No "published between 1992 and 2012" was specified	No Restricted to english-language only	Yes

Was a list of studies (included and excluded) provided?	yes	no No actual list of included studies	no Only noted that 251 articles were studied to construct this review. Not noted how many were actually 'included'.	no List of excluded studies not provided	no List of excluded studies not provided.
Were the characteristics of the included studies provided?	yes	no	No Studies qualitatively described in text. No actual list of included studies.	No Table of characteristics did not include any patient or intervention characteristics	No Table of characteristics includes only basic overall characteristics, not for each included study.
Was the scientific quality of the included studies assessed and documented?	Yes	No	No	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Can't answer Although there was no reported assessment of quality of included studies. a GRADE evaluation of evidence was performed.	No Conclusions do not explicitly state consideration of quality of studies. No actual list of included studies provided.	No Results of quality assessment were presented in a table, with total Jadad scores ranging from 0 to 5. There was no explicit statement in	Yes

				the article re: quality of included studies' impact on authors' conclusions.	
Were the methods used to combine the findings of studies appropriate?	Not applicable Studies not combined	No There was no description of a planned meta-analysis.	No Attempt to combine findings of studies not discussed	Yes	Yes
Was the likelihood of publication bias assessed?	No	No	No	Yes	No
Was the conflict of interest stated?	Yes	Yes	No	Yes	Yes
Any additional comments?					Subgroup analyses relevant to this overview were presented but details re: included studies were not provided.

Appendix 2.8: RCTs included within the systematic reviews

Ulcerative colitis RCTs:

Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462-76. [PMID: 16339095]
Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60:780-7. [PMID: 21209123]
Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142:257-65.e1-3. [PMID: 22062358]
Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical responseandremissioninpatientswithmoderate-to-severeulcerativecolitis.Gas- troenterology. 2014;146:85-95; quiz e14-5. [PMID: 23735746]
Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al; PURSUIT-Maintenance Study Group. Subcutaneous golimumab main- tains clinical response in patients with moderate-to-severe ulcerative colitis. Gas- troenterology. 2014;146:96-109.e1. [PMID: 23770005]
SuzukiY,MotoyaS,HanaiH,MatsumotoT,HibiT,RobinsonAM,etal. Efficacy and safety of adalimumab in Japanese patients with moderately to se- verely active ulcerative colitis. J Gastroenterol. 2014;49:283-94. [PMID: 24363029]
Probert CS, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomized controllled trial. Gut 2003;52:998-1002.
Sandborn WJ, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo of infliximab. Gastroenterology 2009;137(4):1250-60.
Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, Bala M, Johanns J, Olson A, Hanauer SB. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol 2007; 102(4):794-802.
Sands BE, Tremaine WJ, Sandborn WJ et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. Inflamm Bowel Dis 2001; 7: 83 – 8.
Jarnerot G, Hertervig E, Friis-Liby I et al. Infl iximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805– 11 .
Gustavsson A, Järnerot G, Hertervig E, et al. Clinical trial: colectomyafter rescue therapy in ulcerative colitis—3-year follow-up of the Swedish- Danish controlled infliximab study. Aliment Pharmacol Ther. 2010;32: 984–989.
Armuzzi A, De Pascalis B, Lupascu A, et al. Infliximab in the treatment of steroid-dependent ulcerative colitis. Eur Rev Med Pharmacol Sci. 2004;8: 231–233.
Armuzzi A, Lupascu A, De Pascalis B, Fedeli P, Vincenti F, Gasbarrini G, et al. Infliximab in the treatment of glucocorticoid-dependent ulcerative colitis: a 54 week randomized methylprednisolone-controlled trial [abstract]. Gastroenterology 2005;128(4 Suppl 2):A575.
Reinisch W, Sandborn WJ, Rutgeerts P, Blank M, Olson A, Johanns J, et al. Infliximab treatment for ulcerative colitis: Comparable clinical response, clinical remission, and mucosal healing in patients

with disease duration < 3 years vs>=3 years. Gastroenterology 2008;134(4, Supplement 1):A495.
Sandborn W, Lichtenstein G, Colombel J, Yan S, Sands B, Eisenberg D, et al. Infliximab therapy reduces hospitalizations in ulcerative colitis patients [abstract]. Am J Gastroenterol 2005;100(9 Suppl S):S312.
Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not steroid- refractory ulcerative colitis: a randomized pilot study. Eur J Gastroenterol Hepatol. 2004;16:1167–71.
Gavalas E, Kountouras J, Stergiopoulos C, Zavos C, Gisakis D et al, 2007. Efficacy and safety of infliximab in steroid-dependent ulcerative colitis patients. Hepatogastroenterology 2007;54:1074-79
Laharie D, Bourreille A, Branche J, Allez M, Bouhnik Y, et al. (2012) Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 380: 1909–1915.

Crohn's Disease RCTs:

Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997; 337: 1029– 35.
Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002; 359: 1541–9.
Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006; 130: 323–33.
Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial.(GAIN) Ann Intern Med 2007; 146: 829–38.
Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132: 52 –65.
Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007; 56: 1232–9.
Schreiber S, Rutgeerts P, Fedorak RN, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005; 129(3):807-18
Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease.(PRECISE 1) N Engl J Med 2007; 357: 228–38.
Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease.(PRECISE 2) N Engl J Med 2007; 357: 239–50.
Sandborn WJ, Schreiber S, Feagan BG, et al. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. Clin Gastroenterol Hepatol 2011; 9: 670–8.e3.
Winter TA, Wright J, Ghosh S, Jahnsen J, Innes A, Round P. Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. Aliment Pharmacol Ther. 2004 Dec;20(11-12):1337-46.
Rutgeerts P, D'Haens G, Targan S, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 1999; 117: 761-9.
Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350: 876-85.
Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulae in patients with Crohn's disease. N Engl J Med 1999; 340: 1398-405.
Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adali- mumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012; 142: 1102-11

Watanabe M, Hibi T, Lomax KG, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohns Colitis 2012; 6: 160-73.
Schreiber S, Lawrance IC, Thomsen OO/, Hanauer SB, Bloomfield R, Sandborn WJ. Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease – subgroup results from a placebo-controlled study. Aliment Pharmacol Ther 2011; 33: 185-93.
Riis A, Martinsen TC, Waldum HL, Fossmark R. Clinical experience with infliximab and adalimumab in a single-center cohort of patients with Crohn's disease. Scand J Gastroenterol 2012; 47: 649-57.
Van Assche G, Vermeire S, Ballet V, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. Gut 2012; 61: 229-34.
Colombel J - F, Schwartz DA, Sandborn WJ et al. Adalimumab for the treat- ment of fi stulas in patients with Crohn 's disease. Gut 2009; 58: 940 – 8.
Lemann M, MaryJ - Y, Duclos B et al. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. Gastroenterology 2006; 130: 1054–61.
Colombel JF, Sandborn WJ, Reinisch W et al. Infliximab, azathioprine, or combination therapy for Crohn 's disease. N Engl J Med 2010;362:1383–95.
Hibi T, Watanabe M, Camez A et al. Efficacy and safety of adalimumab for the treatment of Japanese patients with moderately to severely active Crohn's disease: results from a randomized controlled trial. Am J Gastroenterol 2008;103(Suppl 1s):S414 –5.
Schroder O, Blumenstein I, Stein J. Combining infliximab with methotrexate for the induction and maintenance of remission in refractory Crohn's disease: a controlled pilot study. Eur J Gastroenterol Hepatol 2006; 18(1):11-6. PMID: 16357613
D'Haens G, Baert F, van Assche G et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008; 371(9613):660-7. PMID: 18295023
Mantzaris GJ, Viazis N, Petraki K et al. A pilot study comparing hydrocortisone premedication to concomitant azathioprine treatment in preventing loss of response to infliximab. Eur J Gastroenterol Hepatol 2009; 21(9):1042-8. PMID: 20139856
Van Assche G, Magdelaine-Beuzelin C, D'Haens G et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008; 134(7):1861-8. PMID: 18440315
Feagan BG, Panaccione R, Sandborn WJ et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. Gastroenterology 2008; 135(5):1493-9. PMID: 18848553
Rutgeerts P, Diamond RH, Bala M et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc 2006; 63 (3):433-42; quiz 464.
Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005; 128(4):862-9.
Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol 2003; 98(10):2232-8. PMID: 14572573
Rutgeerts P, Feagan BG, Lichtenstein GR et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004; 126(2):402-13. PMID: 14762776
Colombel JF, Sandborn WJ, Rutgeerts P, Kamm MA, Yu AP, Wu EQ, Pollack PF, Lomax KG, Chao J, Mulani PM. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. J Gastroenterol. 2009 May;104(5):1170-9. doi: 10.1038/ajg.2009.59. Epub 2009 Apr 7.

Loftus EV, Feagan BG, Colombel JF et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reportedoutcomes of the CHARM trial. Am J Gastroenterol 2008; 103(12):3132-41. PMID: 18853973
Sands BE, Blank MA, Patel K, van Deventer SJ. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. Clin Gastroenterol Hepatol 2004; 2(10):912-20.
Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009; 136: 441–50.
Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2013; doi:10.1053/j.gastro.2013.10.052 [Epub ahead of print].
Feagan B, McDonald J, Panaccione R, Enns R, Bernstein C, Ponich T, et al.A randomized trial of methotrexate in combination with infliximab for the treatment of Crohn's disease. Gastroenterology 2008;135(1):294–5.
Mantzaris GJ, Ployzou P, Karagiannidis A, Christidou A, Koilakou S, Tsounis D, et al.A prospective, randomized trial of infliximab and azathioprine for the induction and maintenance of remission of steroid-dependent Crohn's disease. Gastroenterology 2004;126(4 Suppl 2):A54.
Costes L, Colombel Jf, Mary JY, Duclos B, Veyrac M, Dupas JL, et al. Long term follow-up of a cohort of steroid-dependent Crohn's disease patients included in a randomized trial evaluating short term infliximab combined with azathioprine. Gastroenterology 2008;134(4, Suppl. 1).
Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004;2(7):542-53.
Colombel Jf, Rutgeerts P, Yan S, Bala M, Bao W, Olson A, et al. Infliximab maintenance treatment results in lower hospitalization rate in Crohn's disease patients [abstract]. Gastroenterology 2002;122(4 Suppl 1):A613.
Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 2003;124(4):917-24.
Sandborn WJ, Colombel J-F, Rutgeerts P, Pollack PF, Chao J, Mulani P. Benefits of Dosage Adjustment with Adalimumab in Crohn's Disease: an Analysis of the CHARM trial [abstract]. Innsbruck, Austria: European Congress of the Crohn's and Colitis Organisation; 2007. Available: http://www.ecco-ibd.eu/publications/abstracts/abstract_detail.php?presentationNo=P079&year=2008&referer=abstract_search_result.php&navId=31 (accessed 2008 Nov 11).
Schreiber S, Reinisch W, Colombel Jf, Sandborn WJ, Hommes DW, Li J, et al. Early crohn's disease shows high levels of remission to therapy with adalimumab: Sub-analysis of charm. Gastroenterology 2007;132(4, Suppl. 2).

Appendix 3.1: Screening Criteria: Systematic review of observational post-market studies

First-level criteria for screening citations (title and abstract screening)

	Inclusion	Exclusion
Patient	Adults (18 years or older) AND Crohn's Disease OR Ulcerative Colitis OR 'Inflammatory bowel disease' (encompasses Crohn's and Colitis) AND moderate to severe disease (see note below) AND Naïve to previous tnf-alpha/biologic therapy (at least more than 50% of patients in the study)	-Pregnancy (studies including only pregnant women) -Studies that included children/pediatrics exclusively -Patients in post-operative remission (i.e. studies looking at preventing post-operative reccurrence) -Patients with planned surgery (i.e. peri-operative TNF-alpha inhibitor administration). *Note: patients undergoing seton placement are not considered peri-operative.* -Studies enrolling only patients who were previously intolerant or who lost response to another TNF-alpha inhibitor, and the study is not a continuation of a previous study. Studies with 50% or more of patients not naïve to TNF-alpha inhibitors, and results are not reported separately for TNF-alpha inhibitor naïve patients
Intervention	Tnf-alpha inhibitors, one or many (infliximab, adalimumab, certolizumab, golimumab), alone or in combination with immunosuppressants AND initiated within the approved dosage range (See table)	
Comparison	Any comparison or no	

	comparison	
Outcome	For the most part records will not be screened out based on outcome criteria until a later stage. See exclusion criteria for exception.	Articles where it is clear that the efficacy and safety endpoints of the current project would not be addressed in the article, such as a case series of infectious complications of TNF-alpha inhibitors, or a case control study looking at occurrence of an unrelated outcome.
Design	Post-market, observational studies: -An observational study is one in which the intervention is non-experimental, i.e. the intervention is not "manipulated" by the investigator. Observational studies are closely related ta type of "non-randomized" study, but there are some non-randomized studies that would not be observational (i.e. "controlled clinical trials" or CCTs). -Post-market status will be confirmed by determining the time of approval of a medication in a country in which the study was conducted, when it is unclear whether a study was done post-market. Anything conducted before 1996 could be eliminated immediately	-Case reports of a single patient -Case series less than 10 patients -Reviews, systematic reviews, meta-analyses, network meta-analyses -Commentaries or editorials -Pharmacokinetic studies -Open-label extensions of randomized controlled trials

Moderate to severe disease is traditionally defined by MAYO clinic (UC) and CDAI score (Crohn's), but other scales can be used. Any definition of moderate to severe disease will be accepted. If disease severity is not defined, because TNF-alpha inhibitors are used in moderate to severe disease in practice, it will be assumed.

Tnf-alpha inhibitors in Crohn's: infliximab (Remicade), adalimumab (Humira), certolizumab (Cimzia)

Tnf-alpha inhibitors in ulcerative colitis: infliximab (Remicade), adalimumab (Humira), golimumab (Simponi)

Other tnf-alpha inhibitors may have been studied in Crohn's and Colitis, and these can be added to the above lists.

Vedolizumab and natalizumab are biologics but are NOT tnf-alpha inhibitors. Etanercept is also NOT included.

Case-control studies looking at one of the outcomes of interest are eligible for inclusion; dependent on whether they looked at TNF-alpha as an exposure of interest and whether it satisfies above criteria (population, intervention)

Studies from administrative databases are tricky - it will likely be difficult to know whether at the 'beginning' of the study the patients were tnf-alpha inhibitor naïve. Err on the side of inclusion at first-pass review.

Also tricky are studies aiming to assess another intervention or answer another question but report data on infliximab use and an outcome of interest. E.g. a prospective cohort looking at efficacy and safety of azathioprine, but efficacy in patients receiving concomitant infliximab is reported and possibly compared to monotherapy with AZA. If it is clear that the TNF-alpha inhibitor is being analyzed solely as a 'covariate' in a model and data re: start date and disease severity at time of initiation of TNF-alpha inhibitor would not be available, then safe to exclude at first level.

Screening criteria for SECOND PASS (full-text) review

	Inclusion	Exclusion
Patient	Adults (18 years or older) AND Crohn's Disease OR Ulcerative Colitis OR 'Inflammatory bowel disease' (encompasses Crohn's and Colitis) AND moderate to severe disease (see note below) AND Naïve to previous tnf-alpha/biologic therapy (at least more than 50% of patients in the study)	Failure, intolerance or loss of response to previous tnf-alpha/biologic therapy Pregnancy (studies including only pregnant women) Studies that included children/pediatrics exclusively Patients in post-operative remission (i.e. studies looking at preventing post-operative reccurrence) Patients with planned surgery(i.e. peri-operative TNF-alpha inhibitor administration). Note: patients undergoing seton placement are not considered peri-operative. Studies enrolling only patients who were previously intolerant or who lost response to

		another TNF-alpha inhibitor, and the study is not a continuation of a previous study. Studies with 50% or more of patients not naïve to TNF-alpha inhibitors, and results are not reported separately for TNF-alpha inhibitor naïve patients
Intervention	Tnf-alpha inhibitors, one or many (infliximab, adalimumab, certolizumab, golimumab) alone or in combination with immunosuppressants AND initiated within the approved dosage range (See table)	
Comparison	Any comparison or no comparison	
Outcome	Induction of remission, induction of response, maintenance of remission, maintenance of response, mucosal healing, hospitalization, surgery any malignancy, any serious adverse event (as reported in each study), and withdrawal/discontinuation of therapy due to adverse events. As defined in the study, for all outcomes. Important note: Select "outcome" as reason for exclusion only if it is felt that the article meets all other eligibility criteria apart from not including any outcomes of interest.	
Design	Post-market, observational studies: -An observational study is one in which the intervention is	-Case reports of a single patient -Case series less than 10 patients -Reviews, systematic reviews,

	non-experimental, i.e. the intervention is not "manipulated" by the investigator. Observational studies are closely related ta type of "non-randomized" study, but there are some non-randomized studies that would not be observational (i.e. "controlled clinical trials" or CCTs). -Post-market status will be confirmed by determining the time of approval of a medication in a country in which the study was conducted, when it is unclear whether a study was done post-market. Anything conducted before 1996 could be eliminated immediately	meta-analyses, network meta-analyses -Commentaries or editorials -Pharmacokinetic studies -Open-label extensions of randomized controlled trials

Moderate to severe disease is traditionally defined by MAYO clinic (UC) and CDAI score (Crohn's), but other scales can be used. Any definition of moderate to severe disease will be accepted. If disease severity is not defined, because TNF-alpha inhibitors are used in moderate to severe disease in practice, it will be assumed.

Tnf-alpha inhibitors in Crohn's: infliximab (Remicade), adalimumab (Humira), certolizumab (Cimzia)

Tnf-alpha inhibitors in ulcerative colitis: infliximab (Remicade), adalimumab (Humira), golimumab (Simponi)

Other tnf-alpha inhibitors may have been studied in Crohn's and Colitis, and these can be added to the above lists.

Vedolizumab and natalizumab are biologics but are NOT tnf-alpha inhibitors. Etanercept is also NOT included.

Case-control studies looking at one of the outcomes of interest are eligible for inclusion; dependent on whether they looked at TNF-alpha as an exposure of interest and whether it satisfies above criteria (population, intervention)

Populations in observational studies are likely to be heterogeneous and may not be well-defined in the article. Judgement calls will have to be made re: inclusion. When in doubt, select 'unclear' or skip the article then discuss in general terms with a colleague and come back to it.

Studies from administrative databases are tricky - it will likely be difficult to know whether at the 'beginning' of the study the patients were tnf-alpha inhibitor naïve

Also tricky are studies aiming to assess another intervention or answer another question but report data on infliximab use and an outcome of interest. E.g. a prospective cohort looking at efficacy and safety of azathioprine, but efficacy in patients receiving concomitant infliximab is reported and possibly compared to monotherapy with AZA. If it is clear that the TNF-alpha inhibitor is being analyzed solely as a 'covariate' in a model and data re: start date and disease severity at time of initiation of TNF-alpha inhibitor would not be available, then safe to exclude at first level.

Therapeutic doses of TNF-α inhibitors and countries with regulatory approval (as of April 3 2014)

TNF-α inhibitor, generic name (brand name)	**Countries with regulatory approval for Crohn's or Colitis***	**Induction dose**	**Maintenance dose**	**Additional Comments**	**Dosing Source**
Infliximab (Remicade)	Canada, USA, EMA/UK, France (13 August 1999),	Intravenously: 5mg/kg at 0, 2, and 6 weeks	5mg/kg every 8 weeks	Consider increasing to 10mg in some situations	Canada
Adalimumab (Humira)	Canada, USA, EMA/UK, France (08 september 2003 for Crohn's, April 4 2012 for UC),	Subcutaneously: 160mg at week 0, 80mg at week 2	40mg every 2 weeks	"dose escalation may be considered" in patients experiencing flare (Crohn's)	Canada
Certolizumab (Cimzia)	USA (Crohn's), not Canada, not EMA/UK, not France (RA only)	Subcutaneously: 200mg at weeks 2 and 4 (Crohn's)	400mg every 4 weeks (Crohn's)		USA
Golimumab (Simponi)	USA (ulcerative colitis), EMA/UK (ulcerative colitis), France (UC, Sept 29 2013), not Canada	Subcutaneously: 200mg at week 0, 100mg at week 2 (Ulcerative colitis)	100mg every 2 weeks (Ulcerative Colitis)		USA

*Within EU, France, UK, Canada, US, or New Zealand. Medications approved under EMA's "centralised authorization procedure" will have regulatory approval in all EU countries plus Iceland, Liechtenstein and Norway. The TNF-α inhibitors are in this category.
Source: Remicade and Humira, Canadian Product Monographs, Drugs@FDA. US Food and Drug Administration Website. Accessed April 3 2014.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, European Public assessment reports, available from: European Medicines Agency. Human Medicines. 2014. Accessed April 3 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124, MedSafe (New Zealand Medicines and Medical Devices Safety Authority). Medicines Data Sheets. Accessed April 3 2014. http://www.medsafe.govt.nz/profs/datasheet/datasheet.htm#S

Appendix 3.2: Search strategy for systematic review of observational studies

Search strategies for Medline and Embase: Systematic review of post-market observational studies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
August 6th, 2014

1. Inflammatory Bowel Diseases/
2. Ulcerative Colitis/
3. Crohn Disease/
4. (colitis or crohn* or IBD or IBDs or (inflammatory adj2 bowel disease*)).tw.
5. ((enteritis or enterocolitis or "entero-colitis") adj2 (granulomatous or regional)).tw.
6. (ileitis adj2 (regional or terminal)).tw.
7. (Ileocolitis or ileo-colitis).tw.
8. ((proctocolitis or procto-colitis) adj2 idiopathic).tw.
9. ((colorectitis or proctocolitis or procto-colitis) adj2 (ulcer* or mucosal)).tw.
10. or/1-9
11. Monoclonal Antibody/
12. infliximab/ or adalimumab/ or certolizumab pegol/ or golimumab/
13. Biological Therapy/
14. ((monoclonal adj2 antibod*) or (mono-clonal adj2 antibod*) or (monoclonal adj2 anti-bod*) or (mono-clonal adj2 anti-bod*)).tw.
15. ((biologic* adj2 agent*) or (biologic* adj2 therap*) or (biologic* adj2 response adj2 modifier) or biotherap* or bio-therap*).tw.
16. or/11-25
17. or/32-36,39-52
18. Inflammatory Bowel Diseases/
19. Colitis, Ulcerative/
20. Crohn Disease/
21. (colitis or crohn* or IBD or IBDs or (inflammatory adj2 bowel disease*)).tw.
22. ((enteritis or enterocolitis or "entero-colitis") adj2 (granulomatous or regional)).tw.
23. (ileitis adj2 (regional or terminal)).tw.
24. (Ileocolitis or ileo-colitis).tw.
25. ((proctocolitis or procto-colitis) adj2 idiopathic).tw.
26. ((colorectitis or proctocolitis or procto-colitis) adj2 (ulcer* or mucosal)).tw.
27. or/18-26
28. Antibodies, Monoclonal/
29. Antibodies, Monoclonal, Humanized/
30. Biological Therapy/
31. ((monoclonal adj2 antibod*) or (mono-clonal adj2 antibod*) or (monoclonal adj2 anti-bod*) or (mono-clonal adj2 anti-bod*)).tw.
32. ((biologic* adj2 agent*) or (biologic* adj2 therap*) or (biologic* adj2 response adj2 modifier) or biotherap* or bio-therap*).tw.
33. Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
34. (anti-tnf* or anti tnf* or anti-tumor necrosis factor* or anti tumor necrosis factor* or anti-tumour necrosis factor* or anti tumour necrosis factor* or antitumour necrosis factor* or antitumor necrosis factor* or tnf-inhibitor* or (tumor-necrosis factor* adj2 inhibitor*) or (tumour-necrosis factor* adj2 inhibitor*) or (tnf* adj2 inhibitor*)).tw.

35. (infliximab or remicade or avakine or revellex or remsima or inflectra).tw.
36. (170277-31-3 or infliximab).rn.
37. (adalimumab or humira or trudexa).tw.
38. (331731-18-1 or adalimumab).rn.
39. (golimumab or simponi).tw.
40. (476181-74-5 or golimumab).rn.
41. (certolizumab or cimzia or czp).tw.
42. (428863-50-7 or certolizumab).rn.
43. or/28-42
44. 27 and 43
45. exp Animals/ not (exp Animals/ and Humans/)
46. 44 not 45
47. Epidemiologic studies/
48. exp case control studies/
49. exp cohort studies/
50. Case control.tw.
51. (cohort adj (study or studies)).tw.
52. Cohort analy$.tw.
53. (Follow up adj (study or studies)).tw.
54. (observational adj (study or studies)).tw.
55. Longitudinal.tw.
56. Retrospective.tw.
57. Cross sectional.tw.
58. Cross-sectional studies/
59. Registries/
60. (registry or registries).tw.
61. Product Surveillance, Postmarketing/
62. Pharmacovigilance/
63. pharmacovigilance.tw.
64. ((drug adj surveillance) or (medication adj surveillance)).tw.
65. (post-market* or postmarket* or post market*).tw.
66. adverse drug reaction reporting systems/ or clinical trials, phase iv as topic/
67. (pharmacosurveillance or pharmaco-surveillance or (pharmac* adj surveillance)).tw.
68. Observational Study/
69. or/47-68
70. 46 and 69

Embase Classic+Embase <1947 to present>
August 6th, 2014

1. Inflammatory Bowel Diseases/
2. Ulcerative Colitis/
3. Crohn Disease/
4. (colitis or crohn* or IBD or IBDs or (inflammatory adj2 bowel disease*)).tw.
5. ((enteritis or enterocolitis or "entero-colitis") adj2 (granulomatous or regional)).tw.
6. (ileitis adj2 (regional or terminal)).tw.
7. (Ileocolitis or ileo-colitis).tw.
8. ((proctocolitis or procto-colitis) adj2 idiopathic).tw.

9. ((colorectitis or proctocolitis or procto-colitis) adj2 (ulcer* or mucosal)).tw.
10. or/1-9
11. Monoclonal Antibody/
12. infliximab/ or adalimumab/ or certolizumab pegol/ or golimumab/
13. Biological Therapy/
14. ((monoclonal adj2 antibod*) or (mono-clonal adj2 antibod*) or (monoclonal adj2 anti-bod*) or (mono-clonal adj2 anti-bod*)).tw.
15. ((biologic* adj2 agent*) or (biologic* adj2 therap*) or (biologic* adj2 response adj2 modifier) or biotherap* or bio-therap*).tw.
16. tumor necrosis factor alpha inhibitor/
17. (anti-tnf* or anti tnf* or anti-tumor necrosis factor* or anti tumor necrosis factor* or anti-tumour necrosis factor* or anti tumour necrosis factor* or antitumour necrosis factor* or antitumor necrosis factor* or tnf-inhibitor* or (tumor-necrosis factor* adj2 inhibitor*) or (tumour-necrosis factor* adj2 inhibitor*) or (tnf* adj2 inhibitor*)).tw.
18. (infliximab or remicade or avakine or revellex or inflectra or remsima).tw.
19. (170277-31-3 or infliximab).rn.
20. (adalimumab or humira or trudexa).tw.
21. (331731-18-1 or adalimumab).rn.
22. (golimumab or simponi).tw.
23. (476181-74-5 or golimumab).rn.
24. (certolizumab or cimzia or czp).tw.
25. (428863-50-7 or certolizumab).rn.
26. or/11-25
27. 10 and 26
28. exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
29. exp humans/ or exp human experimentation/ or exp human experiment/
30. 28 not 29
31. 27 not 30
32. Clinical study/
33. case control study/
34. Family study/
35. Longitudinal study/
36. Retrospective study/
37. Prospective study/
38. Randomized controlled trials/
39. 37 not 38
40. Cohort analysis/
41. (Cohort adj (study or studies)).mp.
42. (Case control adj (study or studies)).tw.
43. (cross sectional adj (study or studies)).tw.
44. (follow up adj (study or studies)).tw.
45. (observational adj (study or studies)).tw.
46. (epidemiologic$ adj (study or studies)).tw.
47. register/
48. (registry or registries).tw.
49. postmarketing surveillance/
50. (post-market* or postmarket* or post market*).tw.
51. drug surveillance program/
52. (pharmacovigilance or (drug adj surveillance) or (medication adj surveillance)).tw.
53. (pharmacosurveillance or pharmaco-surveillance or (pharmac* adj surveillance)).tw.

54. or/32-36,39-53

55. 31 and 54

Appendix 3.3: SIGN50 methodology checklist for cohort studies

Obtained from: http://www.sign.ac.uk/methodology/checklists.html

SIGN	**Methodology Checklist 3: Cohort studies**	
Study identification (*Include author, title, year of publication, journal title, pages*)		
Guideline topic:	Key Question No:	Reviewer:
Before completing this checklist, consider: 1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. 2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..		
Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify): **Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.**		
SECTION 1: INTERNAL VALIDITY		
In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ Does not apply □

1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ No □ Can't say □ Does not apply □
ASSESSMENT		
1.7	The outcomes are clearly defined.	Yes □ No □ Can't say □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ No □ Can't say □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes □ No □ Can't say □ □
1.10	The method of assessment of exposure is reliable.	Yes □ No □ Can't say □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ No □ Can't say □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ No □ Can't say □ Does not apply □
CONFOUNDING		

1.13	The main potential confounders are identified and taken into account in the design and analysis	Yes □ No □ Can't say □	
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □ No □	
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes □ No □	
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

Appendix 3.4: SIGN50 Notes on cohort methodology checklist

Obtained from: **http://www.sign.ac.uk/methodology/checklists.html**

	Notes on Methodology Checklist 3: Cohort Studies		
The studies covered by this checklist are designed to answer questions of the type "What are the effects of this exposure?", It relates to studies that compare a group of people with a particular exposure with another group who either have not had the exposure, or have a different level of exposure. Cohort studies may be prospective (where the exposure is defined and subjects selected before outcomes occur), or retrospective (where exposure is assessed after the outcome is known, usually by the examination of medical records).			
Section 1	**Section 1** identifies the study, the reviewer, the guideline for which the paper is being considered as evidence, and the key question(s) it is expected to address. The reviewer is asked to consider a series of aspects of cohort study design and to make a judgement as to how well the current study meets this criterion. Each relates to an aspect of methodology that research has shown to be likely to influence the conclusions of a study. Because of the potential complexity and subtleties of the design of this type of study, there are comparatively few criteria that automatically rule out use of a study as evidence. It is more a matter of increasing confidence in the strength of association between exposure and outcome by identifying how many aspects of good study design are present, and how well they have been tackled. A study that fails to address or report on more than one or two of the questions addressed below should almost certainly be rejected. If you would like more information on cohort studies, their characteristics and weaknesses then please refer to Greenhalgh T. How to read a paper: the basics of evidence-based medicine. 3rd edition. Oxford: Blackwell;2006. Section 3.4 Page 49. **Retrospective studies or single cohort studies are generally regarded as a weaker design, and should not receive a rating higher than "+".** Definitions for terms marked with a * can be found in the Cochrane Handbook. *{Note that the "Response" column is for guidance only. You may opt for a different rating depending on how information is presented in any given review.}*		
Statement 1.1	**The study addresses an appropriate and clearly focused question**		
	What does this statement mean?	***When does this statement***	***Response:***

		apply?	
	Unless a clear and well defined question is specified in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question you are trying to answer on the basis of the conclusions.	Always applies	**Yes -** if elements of the research question are present in the text. **No** if there is no clear questioning the text. **Can't say -** if you think there is insufficient detail to allow an assessment to be made.
Statement 1.2	**The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	This relates to **selection bias**.* It is important that the two groups selected for comparison are as similar as possible in all characteristics except for their exposure status, or the presence of specific prognostic factors or prognostic markers relevant to the study in question.	Only when there is a comparison group	**YES** Where characteristics of the populations from which participants were selected are summarised (preferably in a table). **NO** Where there is no indication of how groups were selected, or what the relevant population characteristics were. **CAN'T SAY** Where source populations are identified, but no specific characteristics are tabulated. **NOT APPLICABLE** Where there is no comparison group.
Statement 1.3	**The study indicates how many of the people asked to take part did so, in each of the groups being studied.**		
	What does this statement mean?	***When does this statement apply?***	***Response:***

	This relates to **selection bias**.* The participation rate is defined as the number of study participants divided by the number of eligible subjects, and should be calculated separately for each branch of the study. A large difference in participation rate between the two arms of the study indicates that a significant degree of **selection bias*** may be present, and the study results should be treated with considerable caution.	Only in prospective, multiple cohort studies	**YES** Where the participation rate per group is clearly defined. **NO** Where authors do not indicate the actual participation rate. **NOT APPLICABLE** Where there is no comparison group.
Statement 1.4	**The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis?**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	If some of the eligible subjects, particularly those in the unexposed group, already have the outcome at the start of the trial the final result will be subject to **performance bias.*** A well conducted study will attempt to estimate the likelihood of this occurring, and take it into account in the analysis through the use of sensitivity studies or other methods.	Almost always applies	**YES** Where sensitivity analyses are carried out to assess the impact of this occurring. **NO** Where no mention is made of this possibility. **CAN'T SAY** where the possibility is acknowledged, but no estimate of actual impact is made. **NOT APPLICABLE** where the study relates to the long term effects of an existing condition.
Statement 1.5	**What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?**		
	What does this statement mean?	***when does this statement apply?***	***Response:***
	This question relates to the risk of **attrition bias**.*The number of	In prospective studies	**Percentage**

	patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop out rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher drop out rate is to be expected. A decision on whether to downgrade or reject a study because of a high drop out rate is a matter of judgement based on the reasons why people dropped out, and whether drop out rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study.		
Statement 1.6	**Comparison is made between full participants and those lost to follow-up, by exposure status.**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. This relates to the risk of **attrition bias**.* Any unexplained differences should lead to the study results being treated with caution.	Prospective, multiple cohors studies	**YES** Where there has been some follow-up of drop outs, with explanation provided. **NO** Where there is no indication that this factor has been considered. **CAN'T SAY** Where dropout rates are mentioned, but no follow-up information is provided. **NOT APPLICABLE** retrospective or single group studies.
Statement	**The outcomes are clearly defined**		

1.7			
	What does this statement mean?	***when does this statement apply?***	***Response:***
	This relates to the risk of **detection bias**.* Once enrolled in the study, participants should be followed until specified end points or outcomes are reached. In a study of the effect of exercise on the death rates from heart disease in middle aged men, for example, participants might be followed up until death, or until reaching a predefined age. **If outcomes and the criteria used for measuring them are not clearly defined, the study should be rejected.**	Always applies	**YES** Where endpoints or outcomes are clearly specified and used in the analysis. **NO** outcomes and measurement criteria are not discussed. **CAN'T SAY** Where definitions of outcomes and / or methods of measuring them are unclear.
Statement 1.8	**The assessment of outcome is made blind to exposure status**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	This relates to the risk of **detection bias.*** If the assessor is blinded to which participants received the exposure, and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done, or not done adequately.	In studies with more than one group	**YES** Where assessors are blinded to exposure status. **NO** Where assessors could have been blinded, but were not. **CAN'T SAY -I**f randomisation is mentioned, but method not specified. **NOT APPLICABLE** Where there is only one group being studied.
Statement 1.9	**Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.**		
	What does this statement	***When does this***	***Response:***

	mean?	***statement apply?***	
	This relates to the risk of **detection bias.*** Blinding is not possible in many cohort studies. In order to asses the extent of any bias that may be present, it may be helpful to compare process measures used on the participant groups - e.g. frequency of observations, who carried out the observations, the degree of detail and completeness of observations. If these process measures are comparable between the groups, the results may be regarded with more confidence.	Always applies	**YES** Where process measures are detailed across groups, and are the same or similar for each. **NO** Where there is no indication if or how measures were managed. **CAN'T SAY** Where there is insufficient information to decide how comparable measures were across groups.
Statement 1.10	**The measure of assessment of exposure is reliable.**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	This relates to the risk of **detection bias.*** A well conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study.	Always applies	**YES** Where measures used are clearly defined and have a known degree of accuracy. **NO** Where measures are not defined. **CAN'T SAY** Where it is unclear which measures were used, or how they were defined.
Statement 1.11	**Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.**		
	What does this statement	***When does this***	***Response:***

	mean?	***statement apply?***	
	This relates to the risk of **detection bias.*** The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected.** Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.	Whenever any kind of subjective measure is used.	**YES** Where clearly identified primary outcome measures are used in the analysis. If measures are subjective, justification for their use should be provided (eg validation of an assessment tool). **NO** Where outcome measures are not defined, or the analysis is based on secondary outcomes. **CAN'T SAY** Where subjective measures are described, but no indication given of how they were validated. **NOT APPLICABLE.** Where measures used are completely objective.

Appendix 3.5: SIGN50 methodology checklist for case-control studies

Obtained from: **http://www.sign.ac.uk/methodology/checklists.html**

SIGN	Methodology Checklist 4: Case-control studies	
Study identification (*Include author, title, year of publication, journal title, pages*)		
Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a case-control study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

SECTION 1: INTERNAL VALIDITY		
In an well conducted case control study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
SELECTION OF SUBJECTS		
1.2	The cases and controls are taken from comparable populations.	Yes ☐ No ☐ Can't say ☐
1.3	The same exclusion criteria are used for both cases and controls.	Yes ☐ No ☐ Can't say ☐

1.4	What percentage of each group (cases and controls) participated in the study?	Cases: Controls:
1.5	Comparison is made between participants and non-participants to establish their similarities or differences.	Yes ☐ No ☐ Can't say ☐
1.6	Cases are clearly defined and differentiated from controls.	Yes ☐ No ☐ Can't say ☐
1.7	It is clearly established that controls are non-cases.	Yes ☐ No ☐ Can't say ☐
ASSESSMENT		
1.8	Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
1.9	Exposure status is measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
CONFOUNDING		
1.10	The main potential confounders are identified and taken into account in the design and analysis.	Yes ☐ No ☐ Can't say ☐
STATISTICAL ANALYSIS		
1.11	Confidence intervals are provided.	Yes ☐ No ☐
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		

2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0 □	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes ☐	No ☐
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above..		

Appendix 3.6: SIGN50 Notes on case control studies methodology checklist

Obtained from: **http://www.sign.ac.uk/methodology/checklists.html**

	Notes on Methodology Checklist 4: Case Control Studies		
The studies covered by this checklist are designed to answer questions of the type "What are the factors that caused this event?", and involve comparison of individuals with an outcome with other individuals from the same population who do not have the outcome. These studies start after the outcome of an event, and can be used to assess multiple causes of a single event. They are generally used to assess the causes of a new problem, but may also be useful for the evaluation of population based interventions such as screening.			
Section 1	**SECTION 1** identifies the study, the reviewer, the guideline for which the paper is being considered as evidence, and the key question(s) it is expected to address. The reviewer is asked to consider a series of aspects of cohort study design and to make a judgement as to how well the current study meets this criterion. Each relates to an aspect of methodology that research has shown makes a significant difference to the conclusions of a study. Case-control studies need to be very carefully designed, and the complexity of their design is often not appreciated by investigators, leading to many poor quality studies being conducted. The questions in this checklist are designed to identify the main features that should be present in a well designed study. There are few criteria that should, alone and unsupported, lead to rejection of a study. However, a study that fails to address or report on more than one or two of the questions addressed below should almost certainly be rejected. If you would like more information on case-control studies, their characteristics and weaknesses then please refer to Greenhalgh T. How to read a paper: the basics of evidence-based medicine. 3rd edition. Oxford: Blackwell;2006. Section 3.5 Page 50. Definitions for terms marked with a * below can be found in the Cochrane Handbook. *{Note that the "Response" column is for guidance only. You may opt for a different rating depending on how information is presented in any given review.}*		
Statement 1.1	**The study addresses an appropriate and clearly focused question**		
	What does this statement mean?	***When does this statement apply?***	***Response:***

	Unless a clear and well defined question is specified in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question you are trying to answer on the basis of the conclusions.	Always applies	**YES** - if elements of the research question are present in the text. **NO** if there is no clear questioning the text. **CAN'T SAY** - if you think there is insufficient detail to allow an assessment to be made.
Statement 1.2	**The cases and controls are taken from comparable populations**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	Study participants may be selected from the target population (all individuals to which the results of the study could be applied), the source population (a defined subset of the target population from which participants are selected), or from a pool of eligible subjects (a clearly defined and counted group selected from the source population. **If the study does not include clear definitions of the source population it should be rejected.**	always applies	**YES** Where all populations are clearly defined. **NO** Where it is unclear on what bases the cases and controls were selected. **CAN'T SAY** Where there is some discussion of which populations cases and controls were selected from, but no clarity about how each group was selected.
Statement 1.3	**The same exclusion criteria are used for both cases and controls**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	All selection and exclusion criteria should be applied equally to cases and controls. Failure to do so may introduce a significant degree of bias into the results of the study.	Always applies	**YES** Where selection and exclusion criteria are explicitly stated for both cases and controls. **NO** Where there is evidence that selection and exclusion criteria

			were different for cases and controls. **CAN'T SAY** Where selection and / or exclusion criteria, or their application, are not clearly specified.
Statement 1.4	**What percentage of each group (cases and controls) participated in the study?**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	Differences between the eligible population and the participants are important, as they may influence the validity of the study. A participation rate can be calculated by dividing the number of study participants by the number of eligible subjects. It is more useful if calculated separately for cases and controls. If the participation rate is low, or there is a large difference between the two groups, the study results may well be invalid due to differences between participants and non-participants. In these circumstances, the study should be downgraded, and rejected if the differences are very large.	Always applies	Percentage cases: Percentage controls:
Statement 1.5	**Comparison is made between participants and non-participants to establish their similarities or differences**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	Even if participation rates are comparable and acceptable, it is still possible that the participants selected to act as cases or controls may differ from other members of the source population in some significant way. A well conducted case-control study will look at	Always applies	**YES** Where data is presented on the key characteristics of a sample of people from the source population that were not included in the study. **NO** Where no

	samples of the non-participants among the source population to ensure that the participants are a truly representative sample.		information on the characteristics of the source population is available. **CAN'T SAY** Where the issues is discussed, but detailed information is not provided.
Statement 1.6	**Cases are clearly defined and differentiated from controls**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	The method of selection of cases is of critical importance to the validity of the study. Investigators have to be certain that cases are truly cases, but must balance this with the need to ensure that the cases admitted into the study are representative of the eligible population. **The issues involved in case selection are complex, and should ideally be evaluated by someone with a good understanding of the design of case-control studies. If the study does not comment on how cases were selected, it is probably safest to reject it as a source of evidence.**	Always applies	**YES** Where methods used to define and identify cases are clearly described. **NO** Where there is no discussion of how cases were identified. **CAN'T SAY** Where the methods used to define or identify cases are mentioned, but no details or justification are provided.
Statement 1.7	**It is clearly established that controls are non-cases**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	Just as it is important to be sure that cases are true cases, it is important to be sure that controls do not have the outcome under investigation. Control subjects should be chosen so that information on exposure status can be obtained or assessed	Always applies	**YES** Where methods used to define and identify controls are clearly described. **NO** Where there is no discussion of how controls were identified.

	in a similar way to that used for the selection of cases. If the methods of control selection are not described, the study should be rejected. **If different methods of selection are used for cases and controls the study should be evaluated by someone with a good understanding of the design of case-control studies.**		**CAN'T SAY** Where the methods used to define or identify controls are mentioned, but no details or justification are provided.
Statement 1.8	**Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	If there is a possibility that case ascertainment can be influenced by knowledge of exposure status, assessment of any association is likely to be biased. A well conducted study should take this into account in the design of the study.	Nearly always applies	**YES** Where assessors are blinded to exposure status. **NO** Where no blinding of assessors takes place. **CAN'T SAY** Where it is not possible to fully blind assessors (eg where assessors talk directly to participant or if the study is retrospective ie database or chart). **NOT APPLICABLE.** Where studies are based on analysis of medical charts or databases.
Statement 1.9	**Exposure status is measured in a standard, valid and reliable way**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on**	Always applies	**YES** Where outcome measures are clearly identified and are either objective or use a validated evaluation

	secondary outcomes, the study should be rejected. Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.		tool. **NO** Where outcome measures are subjective, and are not based on a validated tool. **CAN'T SAY** Where outcome measures are not described in detail.
Statement 1.10	**The main potential confounders are identified and taken into account in the design and analysis**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The study should indicate which potential confounders have been considered, and how they have been allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected. **A study that does not address the possibility of confounding should be rejected.**	Always applies	**YES** Where confounders are discussed, identified, and allowed for in the analysis. **NO** Where confounding is not discussed **CAN'T SAY** Where confounding is mentioned, but not discussed in detail.
Statement 1.11	**Confidence intervals are provided**		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	Confidence limits are the preferred method for indicating the precision	Always applies	**YES**

	of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution.		**NO**
Section 2	**SECTION 2** relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system:		
Statement 2.1	How well was the study done to minimise the risk of bias or confounding?		
	++	High quality (++): Majority of criteria met. Little or no risk of bias. Results unlikely to be changed by further research.	
	+	Acceptable (+): Most criteria met. Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies.	
	0	Low quality (0): Either most criteria not met, or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies.	
Statement 2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?		
	What does this statement mean?		
	This is your clinical judgement of the study		
Statement 2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?		
	What does this statement mean?	***When does this statement apply?***	***Response:***
	Does this study make sense in the Scottish context.	Always.	**YES** **NO**
Statement 2.4	**Notes.** Summarise the author's conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. This section is very important and will appear on the evidence table. **PLEASE FILL IN**.		

Appendix 3.7: Studies excluded from post-market observational systematic review at full-text

Abiko, Y. Mizutani, T. Chiba, T.. Serial changes of serum cytokines in Crohn's disease following treatment with adalimumab. *Hepato-gastroenterology.* 2014. 61:357-362
Actis, G. C. Pellicano, R. Pinna-Pintor, M. Rizzetto, M.. Rescue with Infliximab and Surgical Outcomes for Refractory Ulcerative Colitis. *Journal of the American College of Surgeons.* 2007. 205:e3-e4
Actis, G. C. Rosina, F. Outpatient care for inflammatory bowel disease at a primary referral hospital in Turin. *Minerva Gastroenterologica e Dietologica.* 2010. 56:27-34
Afif, W. Leighton, J. A. Hanauer, S. B. Loftus, E. V., Jr. Faubion, W. A. Pardi, D. S. et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. *Inflammatory Bowel Diseases.* 2009. 15:1302-7
Ainsworth, M. A. Bendtzen, K. Brynskov, J.. Tumor necrosis factor-alpha binding capacity and anti-infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of infliximab in Crohn's disease. *American Journal of Gastroenterology.* 2008. 103:944-948
Alawneh, K. M. Ayesh, M. H. Khassawneh, B. Y. Saadeh, S. S. Smadi, M. Bashaireh, K.. Anti-TNF therapy in Jordan: A focus on severe infections and tuberculosis. *Biologics: Targets and Therapy.* 2014. 8:193-198
Alcain, G. Andrade, R. J. Queipo de Llano, M. P. Moreno, M. J. Garcia-Cortes, M. Franquelo, E.. Acute leukemia after infliximab therapy. *American Journal of Gastroenterology.* 2003. 98:2577
Algaba, A. Linares, P. M. Fernandez-Contreras, M. E. Figuerola, A. Calvet, X. Guerra, I. et al. The effects of infliximab or adalimumab on vascular endothelial growth factor and angiopoietin 1 angiogenic factor levels in inflammatory bowel disease: Serial observations in 37 patients. *Inflammatory Bowel Diseases.* 2014. 20:695-702
Alvarez, J. A. Bermejo, F. Algaba, A. Hernandez, M. P. Grau, M.. Surgical repair and biological therapy for fecal incontinence in Crohn's disease involving both sphincter defects and complex fistulas. *Journal of Crohn's and Colitis.* 2011. 5:598-607
Appau, K. A. Fazio, V. W. Shen, B. Church, J. M. Lashner, B. Remzi, F. et al. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. *Journal of Gastrointestinal Surgery.* 2008. 12:1738-1744
Ardizzone, S. Maconi, G. Colombo, E. Manzionna, G. Bollani, S. Bianchi Porro, G.. Perianal fistulae following infliximab treatment: clinical and endosonographic outcome. *Inflammatory Bowel Diseases.* 2004. 10:91-6
Armuzzi, A. Biancone, L. Daperno, M. Coli, A. Pugliese, D. Annese, et al. Adalimumab in active ulcerative colitis: A "real-life" observational study. *Digestive and Liver Disease.* 2013. 45:738-743
Arnott, I. D. McDonald, D. Williams, A. Ghosh, S.. Clinical use of Infliximab in Crohn's disease: the Edinburgh experience. *Alimentary Pharmacology & Therapeutics.* 2001. 15:1639-46
Arseneau, K. O. Stukenborg, G. J. Connors Jr, A. F. Cominelli, F.. The incidence of lymphoid and myeloid malignancies among hospitalized Crohn's disease patients. *Inflammatory Bowel Diseases.* 2001. 7:106-112
Atreya, R. Neumann, H. Neufert, C. Waldner, M. J. Billmeier, U. Zopf, Y.et al. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. *Nature Medicine.* 2014. 20:313-8
Baars, J. E. Looman, C. W. Steyerberg, E. W. Beukers, R. Tan, A. C. Weusten, B. L. et al. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study.[Erratum appears in Am J Gastroenterol. 2014 May;109(5):781-2]. *American Journal of Gastroenterology.* 2011. 106:319-28
Baert, F. Glorieus, E. Reenaers, C. D'Haens, G. Peeters, H. Franchimont, D. et al. Adalimumab dose escalation and dose de-escalation success rate and predictors in a large national cohort of Crohn's patients.

Journal of Crohn's and Colitis. 2013. 7:154-160

Baert, F. Moortgat, L. Van Assche, G. Caenepeel, P. Vergauwe, P. De Vos, M. et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology.* 2010. 138:463-8; quiz e10-1

Bafford, A. C. Powers, S. Ha, C. Kruse, D. Gorfine, S. R. Chessin, D. B. Bauer, J. J.. Immunosuppressive therapy does not increase operative morbidity in patients with Crohn's disease. *Journal of Clinical Gastroenterology.* 2013. 47:491-495

Bailey, R. A. Waters, H. C. Ernst, F. R. Johnson, B. H. McKenzie, R. S.. Infliximab dosing and administration patterns in patients with crohn's disease in a hospital outpatient setting. *American Journal of Pharmacy Benefits.* 2011. 3:e121-e126

Balzola, F. Bernstein, C. Ho, G. T. Lees, C.. Clinical outcome of newly diagnosed Crohn's disease: A comparative, retrospective study before and after infliximab availability: Commentary. *Inflammatory Bowel Disease Monitor.* 2010. 10:132-133

Balzola, F. Bernstein, C. Ho, G. T. Lees, C.. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy: Commentary. *Inflammatory Bowel Disease Monitor.* 2010. 11:81

Bastida Paz, G. Nos Mateu, P. Aguas Peris, M. Beltran Niclos, B. Rodriguez Soler, M. Ponce Garcia, J. et al. [Optimization of immunomodulatory treatment with azathioprine or 6-mercaptopurine in inflammatory bowel disease]. *Gastroenterologia y Hepatologia.* 2007. 30:511-6

Baumgart, D. C. Grittner, U. Steingraber, A. Azzaro, M. Philipp, S.. Frequency, phenotype, outcome, and therapeutic impact of skin reactions following initiation of adalimumab therapy: experience from a consecutive cohort of inflammatory bowel disease patients. *Inflammatory Bowel Diseases.* 2011. 17:2512-20

Beaugerie, L. Carrat, F. Colombel, J. F. Bouvier, A. M. Sokol, H. Babouri, A. et al. Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer. *Gut.* 2014. 63:1416-23

Beigel, F. Schnitzler, F. Paul Laubender, R. Pfennig, S. Weidinger, M. Goke, B. et al. Formation of antinuclear and double-strand DNA antibodies and frequency of lupus-like syndrome in anti-TNF-alpha antibody-treated patients with inflammatory bowel disease. *Inflammatory Bowel Diseases.* 2011. 17:91-98

Belhassan, M. Zeitoun, J. D. Lefevre, J. H. Charachon, A. Amiot, A. Le Baleur, Y. et al. Infliximab infusion time in patients with inflammatory bowel diseases: Is longer really safer?. *Clinics and Research in Hepatology and Gastroenterology.* 2013. 37:189-192

Bellizzi, A. Anzivino, E. Rodio, D. M. Cioccolo, S. Scrivo, R. Morreale, M. et al. Human Polyomavirus JC monitoring and noncoding control region analysis in dynamic cohorts of individuals affected by immune-mediated diseases under treatment with biologics: An observational study. *Virology Journal.* 2013. 10:#pages#

Biancone, L. Orlando, A. Kohn, A. Colombo, E. Sostegni, R. Angelucci, E. et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut.* 2006. 55:228-33

Blumenstein, I. Bock, H. Weber, C. Rambow, A. Tacke, W. Kihn, R. et al. Health care and cost of medication for inflammatory bowel disease in the Rhein-Main region, Germany: A multicenter, prospective, internet-based study. *Inflammatory Bowel Diseases.* 2008. 14:53-60

Bonnin, P. Coelho, J. Pocard, M. Levy, B. I. Marteau, P.. Anti-TNFalpha therapy early improves hemodynamics in local intestinal and extraintestinal circulations in active Crohn's disease. *Journal of Crohn's and Colitis.* 2013. 7:451-459

Bouguen, G. Siproudhis, L. Gizard, E. Wallenhorst, T. Billioud, V. Bretagne, J. F. et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clinical Gastroenterology & Hepatology.* 2013. 11:975-81.e1-4

Brackmann, S. Andersen, S. N. Aamodt, G. Langmark, F. Clausen, O. P. F. Aadland, E. et al. Relationship

between clinical parameters and the colitis-colorectal cancer interval in a cohort of patients with colorectal cancer in inflammatory bowel disease. *Scandinavian Journal of Gastroenterology.* 2009. 44:46-55

Bregnbak, D. Mortensen, C. Bendtsen, F.. Infliximab and complications after colectomy in patients with ulcerative colitis. *Journal of Crohn's & colitis.* 2012. 6:281-6

Bultman, E. De Haar, C. Van Liere-Baron, A. Verhoog, H. West, R. L. Kuipers, E. J. et al. Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. *Alimentary Pharmacology and Therapeutics.* 2012. 35:335-341

Burke, J. P. Kelleher, B. Ramadan, S. Quinlan, M. Sugrue, D. O'Donovan, M. A.. Pericarditis as a complication of infliximab therapy in Crohn's disease. *Inflammatory Bowel Diseases.* 2008. 14:428-9

Busquets, D. Aldeguer, X.. Clinical experience with adalimumab in anti-TNF-naive patients with ulcerative colitis. *Journal of Crohn's and Colitis.* 2013. 7:e195

Canedo, J. Lee, S. H. Pinto, R. Murad-Regadas, S. Rosen, L. Wexner, S. D.. Surgical resection in Crohn's disease: is immunosuppressive medication associated with higher postoperative infection rates?. *Colorectal Disease.* 2011. 13:1294-8

Cannom, R. R. Kaiser, A. M. Ault, G. T. Beart, R. W., Jr. Etzioni, D. A.. Inflammatory bowel disease in the United States from 1998 to 2005: has infliximab affected surgical rates?. *American Surgeon.* 2009. 75:976-80

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Carter, C. T. Waters, H. C. Smith, D. B. Effect of a continuous measure of adherence with infliximab maintenance treatment on inpatient outcomes in Crohn's disease. *Patient Preference and Adherence.* 2012. 6:417-426

Casellas, F. Robles, V. Borruel, N. Torrejon, A. Castells, I. Navarro, E. et al. Restoration of quality of life of patients with inflammatory bowel disease after one year with antiTNFalpha treatment. *Journal of Crohn's and Colitis.* 2012. 6:881-886

Casellas, F. Rodrigo, L. Nino, P. Pantiga, C. Riestra, S. Malagelada, J. R.. Sustained improvement of health-related quality of life in Crohn's disease patients treated with infliximab and azathioprine for 4 years. *Inflammatory Bowel Diseases.* 2007. 13:1395-1400

Chande, N. Abdelgadir, I. Gregor, J.. The safety and tolerability of methotrexate for treating patients with Crohn's disease. *Journal of Clinical Gastroenterology.* 2011. 45:599-601

Chaparro, M. Martinez-Montiel, P. Van Domselaar, M. Bermejo, F. Perez-Calle, J. L. Casis, B. Intensification of infliximab therapy in Crohn's disease: Efficacy and safety. *Journal of Crohn's and Colitis.* 2012. 6:62-67

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Appendix 3.8: Characteristics of included comparative studies not eligible for meta-analysis

Characteristics of included comparative studies not eligible for meta-analysis							
Study (author, year) **R# (temporary)** **Design**	**Methods**	**Participants** **(i.e. Disease (# UC and CD if IBD), age, sex)**	**Intervention(s) / comparator(s)**	**Relevant Outcomes**	**Total N, N receiving TNF-alpha inhibitor(s)**	**Length of follow-up**	**Comments**
Abraham, 2013 R474 WPC	Adj-A (See comment)	Crohn's Disease, ulcerative colitis	Infliximab / non-infliximab use	Hospitalization, surgery	20474, 35	1 year	Exposure status varied over time. Final model was not adjusted.
Aratari, 2008 R2290 C	N-Adj, C	Ulcerative Colitis	Infliximab / control (no infliximab)	Colectomy	52, 11	Median 26 months	Lists covariates considered as predictive factors of colectomy in a Kaplan-meier analysis, but it is not stated whether the association between infliximab and colectomy was "adjusted"

							for these covariates. An HR was not reported, only a p-value and an unadjusted OR.
Arijs, 2009 R2930 C	N-Adj, NC	Ulcerative Colitis	Infliximab / Infliximab + AZA or 6-MP	Response	24, 24	Not reported	"Aim was to identify mucosal gene signatures predictive or response to infliximab in patients with ulcerative colitis"
Armuzzi, 2013 R172 MV	Adj-A	**Ulcerative Colitis** Overall: Median age 36.5 55/126 male	Infliximab + azathioprine / infliximab monotherapy	Maintenance of remission, mucosal healing (at 12 months)	126, 126	12 months	
Baert, 2003 R3316 MV	Adj-A (see comment)	Crohn's disease	Infliximab / infliximab + immunosuppressive	Response	125, 125	Mean 10 months	Outcome data not extractable. No effect size reported for the comparison of combination therapy vs monotherapy, only p-value
Beigel, 2013 C	N-Adj, C	Crohn's disease, ulcerative colitis	Infliximab or adalimumab / thiopurines	Malignancy	666, 404	Median 68 weeks (infliximab), median 140 weeks	

						(thiopurines)	
Bhatia, 2007 R2326 C	N-Adj, C	Crohn's Disease	Infliximab / hydrocortisone continuous infusion	Response	33, 17	NR	Sixteen cases who received IFX were "matched" to sixteen who received IV hydrocortisone 300mg as a continuous infusion based on goals of therapy, but no other variables.
Biancone, 2011 R1601 MV	Adj-A	Crohn's disease, ulcerative colitis	TNF-alpha inhibitors / immunomodulators / no treatment	Cancer	198, 1222	Median 11 years (Crohn's disease), 7 years (ulcerative colitis)	Outcome data not extractable. Multivariate analysis for predictors of cancer assessed anti-TNF use. Only non-significant p-value was reported.
Bortlik, 2013 R2660 MV	Adj-A	Crohn's disease	Infliximab / Infliximab + thiopurines	Maintenance of response, surgery	84, 84	Median 25 months	Analyzed concomitant thiopurines as predictor of sustained response
Bouguen, 2010 R2894 C	N-Adj, NC	Ulcerative Colitis	Infliximab / Infliximab + AZA or 6-MP or MTX	Response	13, 13	Median 17 months	Ulcerative proctitis
Bountavong, 2014 R1092 C	N-Adj, NC	Crohn's Disease	Infliximab / adalimumab	Response	25, 25	12 months	Assessed anti-TNFs for any indication, reported response in subgroup of

							patients with CD and according to agent received
Castiglione, 2013 R2673 C	N-Adj, C	Crohn's Disease	TNF-alpha inhibitors (infliximab, adalimumab) / thiopurines	Remission, Mucosal healing	133, 66	2 years	Included only patients who received maintenance therapy for 2 years. Noted that groups were similar at baseline
Caviglia, 2007 R3047 C	N-Adj, NC	Crohn's Disease, Ulcerative Colitis	Infliximab / Infliximab + 6-MP or AZA	Response, malignancy	79	27 months (CD), 24.5 months (UC)	
Chaparro, 2011 R3303 MV	Adj-A	Crohn's disease	Infliximab / Infliximab + immunomodulators	Maintenance of response	309, 309	Median 41 months	"Immunomodulators" not defined
Chaparro, 2012 R1470 MV	Adj-A	Ulcerative Colitis *Overall* Male: 29/47 Mean age: 41	Infliximab + thiopurine / infliximab monotherapy	Surgery (colectomy)	47, 47	Median 58 weeks	
Colombel, 2003 R3170 C	N-Adj, NC	Crohn's Disease	Infliximab / infliximab + AZA or 6-MP or MTX	Response	26, 26	Median 21.5 months	Crohn's Disease with ileal pouch anastomosis. Likely a subgroup of patients included in Colombel 2004 (R3163)
Colombel, 2004 R3163 C	N-Adj, NC	Crohn's Disease	Infliximab / Infliximab + immunosuppressant (AZA or 6-MP or MTX)	Serious adverse events, malignancy	500, 500	Median 17 months	Aim was to evaluate the safety profile of infliximab in clinical

							practice in patients with CD. Reported the use of concomitant immunosuppressants in patients with SAEs and malignancy
Croft, 2013 R335 C	N-adj, C	**Crohn's disease**	Infliximab / cyclosporine	Colectomy, severe adverse events	83, 38	12 months	
de la Poza, 2012 R2792 C	N-adj, NC	Crohn's Disease	Infliximab / thiopurines / adalimumab / antibiotics / surgery	Response, Surgery	47, 34	NR	*Women with fistulising CD. Study calls itself a case series; no attempt made to compare treatment groups but outcomes reported separately by treatment received.*
Deepak, 2012 R1841 O	N-Adj, C (see comment)	Crohn's Disease, ulcerative colitis	TNF-alpha inhibitors / 5-ASA	Non-hodgkin's lymphoma, hepatosplenic T-cell lymphoma	66	NR	Analysis of FDA adverse reaction reporting database. N represents the number of cases of lymphoma in patients on a TNF-alpha inhibitor.
Desmond, 2012 R3302 C	N-Adj, NC	Ulcerative colitis	Infliximab / thiopurines / corticosteroids / no treatment	Hospitalization	424, 21	Median 14.2 months	
Din, 2008 R2283 C	Adj-M (see comment)	Crohn's Disease	Infliximab / azathioprine	Surgery	73, 146	2 years	Outcome data not extractable. Measure of association

							for relevant outcome (surgery) not reported, only that there was no significant difference. Disease progression according to Montreal scale was reported
Elder, 2012 R449 C	N-adj, NC	**Crohn's Disease**	Infliximab/adalimumab	Induction of response	35	Min-Max 10-13 weeks	Aim was to "assess the influence of anti-TNFs on the expression of apoptosis-related proteins…"
Eshuis, 2013 R 2683 MV	Adj, C	Crohn's Disease *Overall* Male: 168/469 Age: mean 33.2 years	Infliximab / Infliximab + thiopurine	Remission, surgery, malignancy	469, 469	*Overall* Median 4.5 years	
Farrell, 2000 R3223 C	N-Adj, C	Crohn's disease	Infliximab / infliximab + thiopurine	Response	100, 100	*NR*	
Ferrante, 2008 R3309 C	N-Adj, C	Ulcerative colitis	Infliximab / infliximab + immunosuppressive	Response, colectomy, serious adverse events, malignancy,	121, 121	Median 33 months	
Ferrante, 2007	N-Adj, C	Ulcerative colitis	Infliximab / infliximab +	Response,	100	Median 2.7	

R3311 C			immunosuppressive	colectomy		years	
Fidder, 2009 R2081 C	N-Adj, C	Crohn's Disease, Ulcerative Colitis P	Infliximab / control (no infliximab)	Serious adverse events, malignancy	1400, 734	*Infliximab* Median 58 weeks *Controls* Median 144 weeks	
Franchimont, 2005 R2443 C	N-Adj, NC	Crohn's Disease	Infliximab / corticosteroids	Remission	29, 20	4 weeks	Aim was to examine serum leptin levels in CD patients treated with infliximab
Gornet, 2003 R3175 C	N-Adj, NC	Ulcerative Colitis, Indeterminate Colitis	Infliximab / infliximab + AZA/6-MP/thioguanine or methotrexate	Response, colectomy	30, 30	Median 10 months	Pre-dates pivotal RCTs of infliximab in UC
Gustot, 2004 R2457 C	N-Adj, NC	Crohn's Disease	Infliximab / corticosteroids	Remission	30, 21	4 weeks	Aim was to "characterise the profiles of soluble cytokine receptors in quiescent and active CD"
Hamzaoglu, 2010 R2873 C	N-Adj, C	Crohn's Disease	Infliximab / Infliximab + immunosuppressants	Serious adverse events, malignancy	297, 297	Median 14.3 months	
Hayes, 2014 R1015 C	N-Adj, C	Ulcerative Colitis	Infliximab + concomitant immunosuppressants / infliximab monotherapy	Maintenance of remission	85, 85	1 year	

Haynes, 2013 R2735 WPC	Adj, C	Inflammatory Bowel Disease	TNF-alpha inhibitors/ no TNF-alpha inhibitors	Any lymphoma, any leukemia, any solid cancer, and nonmelanoma skin cancer	6357, 2657	NR	Medication exposure was a "time-updated variable". *"Medication exposure was treated as a time-updated variable such that patients could accrue follow-up time in one or both of the treatment arms sequentially and not simultaneously. However, once patients were treated with a TNF inhibitor, they could not accrue follow-up time in the comparator cohort."*
Herrinton, 2011 R1451 O	N-Adj, C	Crohn's disease, ulcerative colitis	Infliximab / infliximab + thiopurines thiopurines	Lymphoma	1122, 16023	Mean 5.8 years	Standardized incidence rate ratios for lymphoma risk associated with medications was reported (past use, current used, combination therapy, monotherapy)
Hlavaty, 2005 R2435 C	N-Adj, NC	Crohn's Disease	Infliximab / Infliximab + azathioprine or 6-MP	Response	287, 287	4 weeks for luminal Crohn's disease and 10	Aim was to study "whether polymorphisms in apoptosis genes predict

						weeks for fistulizing Crohn's disease	the response to infliximab…"
Hommes, 2002 R2586 C	N-Adj, NC	Crohn's Disease	Infliximab / Infliximab + MTX / Infliximab + AZA	Response	73, 73	Maximum 1 year	
Jewell, 2005 R3121 BA	N-Adj, C	Crohn's Disease, ulcerative colitis	Infliximab / pre-infliximab	Hospitalization, surgery	205, 205	6 months	Aim was to "quantify the impact of infliximab therapy on healthcare resource utilization" in the UK
Jurgens, 2011 R2850 C	N-Adj, NC	Crohn's Disease	Infliximab / Infliximab + concomitant immunomodulators (MTX, AZA)	Response, mucosal healing	718	Median 47 months	Aim was "to investigate whether CRP is helpful in optimizing therapy with infliximab in the individual patient with moderate to severe CD."
Kinney, 2003 R2535 C	N-Adj, C	Crohn's Disease	Infliximab / Infliximab + MTX / Infliximab + AZA or 6-MP	Remission, response	122, 122	Mean 52 weeks	
Kiss, 2011 R1401 MV	Adj-A (See comment)	Crohn's Disease	Adalimumab /adalimumab + azathioprine	Response, remission	201, 201	52 weeks	Outcome data not extractable. Concomitant azathioprine assessed as a predictor of outcome in multivariate analysis, but result was reported

							only for dose escalation outcome.
Kuzela, 2012 R1089 C	N-Adj, NC	Crohn's disease	Infliximab / adalimumab	Maintenance of remission, surgery, withdrawal due to adverse events	50, 50	1 year	Aim was to "evaluate mucosal lesions by capsule endoscopy" before and after treatment.
Laharie, 2005 R3314 C	N-Adj, NC (see comment)	Crohn's disease	Infliximab / Infliximab + immunosuppressive therapy	Response	44,44	At least 3 months	Association of immunosuppressive therapy with response is reported, however immunosuppression is categorized as naïve vs failure, and 'new or changed'
Lakatos, 2012 R2718 C	N-adj, NC	Crohn's Disease and Ulcerative Colitis	Infliximab / Infliximab + AZA / AZA / other treatments	Lymphoma	1420, 63	Median 13 years	Cohort of IBD patients, starting 1977. Rate of lymphoma calculated as patient-years exposure per medication class of medications utilized in IBD. No occurrences in either AZA or biologic exposed patients.
Lees, 2009 R2922	N-Adj, NC	Crohn's Disease and	Infliximab / Infliximab + immunosuppressant	Serious adverse events,	202, 202	Median 2.4 years	Reports 6 cases of malignancy

C		Ulcerative Colitis	s (AZA and/or 6-MP / and/or corticosteroids and/or methotrexate)	malignancy			and describes concomitant therapy for each case
Li, 2012 R1802 C	N-Adj, NC	Crohn's Disease	Adalimumab + thiopurine / adalimumab	Induction and maintenance of response, mucosal healing	48, 48	Median 25.1 months	
Lichtenstein, 2014 R714 C	N-adj, C	Crohn's disease	Infliximab/ non-infliximab treatment	Malignancy	3764, 6273	Mean 5.2 years	TREAT registry, malignancy
Lindsay, 2013 R216 BA	N-Adj, C	Crohn's disease	Infliximab / pre-infliximab	Surgery and hospitalization	380, 380	24 months	
Loomes, 2011 R2821 BA	N-Adj, C	Crohn's Disease	Infliximab / pre-infliximab	Hospitalization and surgery	66, 66	1 (n=66) or 2 (n=39) years	Patients responding to induction
Lynch, 2013 R500 C	N-adj, C	Crohn's disease, ulcerative colitis	Infliximab/cyclosporine	Induction of response, surgery	1836, 245	Median 9 days	
Magro, 2014 R670	N-adj, NC	Crohn's disease	Infliximab/infliximab +azathioprine	Induction of response	148, 148	14 weeks	Aim was to correlate CRP levels with outcome.
Marehbian, 2009 R2037 O	Adj-A (see comment)	Crohn's Disease	TNF-alpha inhibitors (infliximab or adalimumab) / no treatments, TNF-alpha inhbiitors + immunosuppressant	Solid tumor	292 person years, 8581	NR	Participants accumulated person-years in different treatment groups

			s / no treatment				throughout follow-up
Maser, 2006 R3088 C	N-Adj, NC (see comment)	Crohn's Disease	Infliximab / Infliximab + immunomodulator	Remission	105, 105	23 months	Reported that concomitant IM not associated with outcome, but no measures of association reported other than p-value.
Matsumoto, 2008 R3015 C	N-Adj, NC	Crohn's Disease	Infliximab / Infliximab + AZA	Induction of remission	138, 138	Not reported	Aim was to evaluate the efficacy of infliximab in patients with Crohn's disease of duration of less than 1 year. Reports results of two surveys; one surveys' results previously reported (Matsumoto 2005, R3116)
Miheller, 2009 R2035 MV	Adj-A	Crohn's Disease *Overall* Male: 180/363 Mean 33.5 years	Infliximab + azathioprine or methotrexate	Induction of response	363, 363	12 weeks	
Mocciaro, 2012 R1639 C	N-Adj, C	Ulcerative colitis	Infliximab / cyclosporine	Hospitalization, surgery (colectomy)	65, 30	*Cyclosporine* Mean 74.7 months *Infliximab*	*It is noted that groups were similar*

						Mean 33.6 months	
Moland er, 2013 R452 C	N-adj, NC	Crohn's disease, ulcerativ e colitis	Infliximab/adalimum ab	Maintena nce of remissio n	252, 252	Min 11 months	
Molnar, 2012 R2751 C	N-Adj, C	Crohn's Disease	Infliximab / Adalimumab	"Loss of response "	61, 61	NR	*Outcome definition of "loss of response" includes dose escalation; Also, more than 50% of ADA-treated patients were not IFX-naive so comparison may not be relevant.*
Moran, 2014 R725 MV	Adj-A	Crohn's disease Entire relevant cohort: Male 160/322 Age not reported as mean or median	"Anti-TNF" (infliximab or adalimumab) / "concomitant onset combination therapy"	Surgery	425 (releva nt cohort = 322), 322	Median 11.6 months	Comparison in multivariate analysis for 'concomitant onset combination therapy yes/no'.
O'Donn ell, 2010 R1383 C	N-Adj, NC	Ulcerati ve Colitis, Crohn's Disease	Infliximab + immunosuppressant / infliximab	Malignan cy	271, 271	Median 58.8 months	
Olsen, 2009 R2967 MV	Adj-A	Ulcerati ve Colitis *Overall* M: 40/59 Age: Median	Infliximab / Infliximab + immunosuppressive	Induction of remissio n, mucosal healing	59, 59	10 weeks	Aim was to "determine predictor factors for the clinical outcome of IFX induction therapy in

		38					UC." Multivariate analysis includes concomitant immunosuppressive as variable
Oltman, 2010 R1181 C	N-Adj, NC	Crohn's Disease	Infliximab, adalimumab	Mucosal healing	50, 50	1 year	
Ono, 2012 R1787 C	N-Adj, C	Crohn's Disease	Infliximab / infliximab + concomitant immunomodulators	Maintenance of response, surgery	185	Median 24 months	Methods described comparisons of efficacy between groups with and without combination therapy, however effect measures not reported, only a p-value for the outcome of sustained response
Park, 2013 R621 UV	N-adj, NC	Ulcerative Colitis	Infliximab/infliximab +thiopruine	Induction of response and remission, colectomy, malignancy	89, 89	Not reported	*case series with univariate analysis of concomitant AZA/6-MP as a predictor of response in univariate analysis
Parsi, 2002 R3319 MV	Adj-A	Crohn's disease	Infliximab / infliximab + immunosuppressive	Response	100, 100	Mean 9 months	
Parsi, 2004	N-Adj, NC	Crohn's Disease	Infliximab / Infliximab +	Response	60, 60	Mean 9 months	Reported that

R3160 C	(see comment)		immunosuppressant (AZA or 6-MP or MTX)				concomitant IM not associated with outcome, but no measures of association reported
Peyrin-Biroulet, 2011 R1365 MV	Adj-A	Crohn's disease	Infliximab*	Surgery	296, 176	Median 57 months (from diagnosis of CD)	*Reports duration of IFX use as a dichotomous variable as a covariate in multivariate analysis
Picco, 2009 R2097 C	N-Adj, NC	Crohn's Disease	Biologics (infliximab or adalimumab) / no biologic	Surgery	28, 159	NR	Aim was to assess whether thiopurines were associated with surgery
Reenaers, 2012 R595 WPC	Adj-A	Crohn's Disease	Adalimumab / Adalimumab + immunosuppressant	Response, withdrawal due to adversebraham events, hospitalization	207	Minimum 12 months	Exposure status varied over time; compared semesters with vs without concomitant IS
Rubenstein, 2002 R3205 BA	N-Adj, C	Crohn's Disease, ulcerative colitis	Infliximab / pre-infliximab	Hospitalization, surgery	79	1 year	
Rudolph, 2007 R3024 MV	Adj-A	Crohn's Disease *Overall* Male: 89 Mean age: 37	Infliximab / Infliximab + immunomodulator	Maintenance of response	127	Mean 29 months	Goal was "to evaluate the long-term durability of maintenance infliximab treatment beyond 12 months."
Samimi,	N-Adj,	Crohn's	Biologics (infliximab	Response	53, 32	180	Structuring

2010 R2891 C	C	Disease	or adalimumab) / AZA or 6-MP or corticosteroids	, relapse in responders, surgery		days	and penetrating disease
Sample, 2002 R2925 C	N-Adj, C	Crohn's Disease	Infliximab / Infliximab + (AZA or 6-MP or MTX)	Response	109, 109	Median 24 weeks	8/109 patients were enrolled in Accent trials
Saro, 2007 R2313 BA	N-Adj, C	Crohn's Disease	Infliximab (post) / no infliximab (pre-infliximab)	Hospitalization	34, 34	Mean 4.29 years	Before and after comparison
Satoh, 2012 R610 C	N-adj, C	Crohn's disease	Infliximab/thiopurines	Induction and maintenance of remission	46, 34	12 months	
Schmidt, 2007 R2361 C	N-Adj, NC	Crohn's Disease	Infliximab / cyclophosphamide	Remission	19, 10	Minimum 6 months	*Aim was to investigate cytokines' ability to predict long-term remission*
Schnitzler, 2009 R2946 C	N-Adj, C	Crohn's Disease	Infliximab / Infliximab + immunomodulator (AZA or 6-MP or methotrexate)	Mucosal healing	214, 214	Median 6.7 months	Reports association with concomitant immunomodulator at first infusion and mucosal healing. Subgroup of another included study: Schnitzler 2009 (R2082)
Sciaudone, 2010 R1187	N-Adj, C	Crohn's disease	Infliximab / surgery	Induction of response	25, 25	18.8 months	Comparative cohort study with no adjustment for

C							confounding. Compares IFX vs IFX + surgery vs surgery alone. "surgery" = seton placement.
Seow, 2009 R1899 C	N-Adj, NC	Ulcerative Colitis	Infliximab + immunosuppressants / infliximab	Remission, colectomy	115, 115	Median 10.7 months	Aim was to study relationship between trough serum concentrations of IFX and antibody formation on clinical outcomes
Siew, 2009 R2094 C	N-Adj, NC	Crohn's Disease	Infliximab / Adalimumab / thalidomide	Remission, response, surgery	34, 26	Median 110 weeks	*Crohn's patients with perianal fistulas. All patients receiving adalimumab had previously failed infliximab.*
Sjoberg, 2013 R438 C	N-adj, NC	**Ulcerative Colitis**	Infliximab / infliximab + thiopurines	Induction and maintenance of remission, colectomy, serious adverse events	211, 211	12 months	
Slattery, 2011 R1363 MV	Adj-A (see comment)	Crohn's disease	Infliximab / no infliximab	Surgery	NR, 722	NR	Infliximab use within 3 years of diagnosis was assessed as a predictor of

							surgery in multivariate analysis
Sokol, 2010 R2885 WPC	Adj-A	Crohn's Disease, ulcerative colitis	Infliximab / Infliximab + AZA or MTX	Surgery	121, 121	Minimum 12 months	"in each patient, IFX treatment was divided into semesters which were independently analysed regarding IBD activity." Semesters with vs without concomitant immunosuppression were compared.
Sprakes, 2011 R1499 MV	Adj-A	Crohn's disease *Overall* Male: 86/210	Infliximab + immunomodulator / infliximab monotherapy	Induction and maintenance of response	210, 210	Median 24 months	
Sprakes, 2010 R3304 BA	N-Ajd, C	Crohn's disease	Infliximab	Hopitalization, surgery	100	12 months	
Sulz, 2013 R326 MV	Adj-A	Crohn's disease, ulcerative colitis	Biologics (Infliximab or adalimumab) / no biologics	hospitalization	118, 1187	1 year	Multicenter, prospective, population-based study, assessing biologics as a y/n variable for predictor of outcome in multivariate analysis
Takagi, 2010 R1878 MV	Adj-A	Crohn's disease	Infliximab / no infliximab	Maintenance of remission, surgery	38, 224	Median 47 months	

Taxonera, 2009 R1189 BA	N-Adj, C	Crohn's disease	Infliximab / pre-infliximab	Hospitalization and surgery	153, 153	12 months	
Teshmia, 2009 R2007 C	N-Adj, NC	Crohn's Disease	Infliximab + immunosuppressants / infliximab	Induction and maintenance of resonse	117, 117	108 weeks	
Topstad, 2002 R2529 C	N-Adj, NC	Crohn's Disease	Infliximab / infliximab + immunosuppressant	Response	29, 29	Mean 10 months	
Tozar, 2012 R2753 C	N-Adj, NC	Crohn's Disease	Infliximab / Adalimumab	Clinical response and remission, radiological response	41, 41	Up to 3 years	All 9 ADA-treated patients had previously received infliximab
Tursi, 2014 R1108 C	N-Adj, C	Crohn's Disease	Infliximab / adalimumab	Response	22, 22	36 months	Published as a letter. Very little detail.
Ungar, 2014 R 1090 UV	N-Adj, NC	Crohn's disease, ulcerative colitis	Infliximab + immunomodulator / infliximab	Clinical response	125, 125	Median 11.5 months	Objective: "to characterise the temporal evoluation of antibodies to infliximab"
Vermeire, 2002 R3200 C	N-Adj, C (see comment)	Crohn's Disease *Overall* Male: 34/103 Age: mean 37 years	Infliximab / Infliximab + AZA or 6-MP or MTX	Response, remission	240, 240 (103 fistuliz ing)	4 weeks (luminal) or 10 weeks (fistulising)	Only fistulising subgroup received full induction regimen; In this subgroup specifically, it was not clear whether analyses adjusted for

							potential confounding variables but it was assumed no.
Waters, 2012 R2798 BA	N-Adj, C	Crohn's disease, ulcerative colitis	Infliximab / pre-infliximab	Hospitalization and surgery	268, 268	12 months	
Weiss, 2010 R1925 C	N-Adj, NC	Crohn's disease	Infliximab / AZA or 6-MP / steroids	Response	61, 199	Minimum 12 months	Aimed to determine relationship of genetic and other factors to outcome
Wenzl, 2004 R2502 C	N-Adj, C	Crohn's Disease	Infliximab / infliximab + azathioprine	Response	153, 153	Mean 29 months	*Questionnaire administered to treating physicians. Response was categorized according to physician's global response as no, poor, good, or excellent.*
Williet, 2012 R1712 UV	N-Adj, C	Ulcerative colitis	TNF-alpha inhibitors / cyclosporine / methotrexate / azathioprine	Surgery	46, 151	Median 58 months	Cohort of newly diagnosed ulcerative colitis patients. TNF-alpha inhibitors not included in multivariate analysis for predictors of surgery, only univariate
Yamada,	N-Adj,	Ulcerati	Infliximab /	Induction	33, 33	Maxim	

2014 R1006 UV	NC	ve Colitis	infliximab + thiopurines	and maintenance of remission, colectomy, mucosal healing		um 36 months	
Zelinkova, 2012 R2695 C	N-Adj, NC	Inflammatory Bowel Disease	TNF-alpha inhibitors / other therapies	Malignancy	843, 240	NR	Aim "to analyze sex differences in adverse drug reactions to the immune suppressive medication in inflammatory bowel disease patients."
Zorzi, 2012 R 1604 C	Adj-A	Crohn's Disease Adalimumab Male: 18/49 Mean 36 years Infliximab Male: 24/44 Mean 35 years	Infliximab / Adalimumab	Steroid-free remission	93, 93	76 weeks	Outcome data not extractable: only reported that infliximab vs adalimumab was not significant; did not give adjusted effect measure or even p-value

Participant characteristics reported by intervention group where available, otherwise for overall study population

Design: MV= relevant comparison made as a variable in multivariable analysis; UV= relevant comparison made as a variable in univariate analysis; C= cohort; BA= before/after comparison; WPC= other design with comparisons made within the same participant over time; o= other design

Methods: N-adj, NC = not adjusted for confounding, not aiming to compare interventions; N-adj, C = not adjusted for confounding, but aiming to compare two or more relevant interventions; Adj-A = Adjusted in the analysis; Adj-M = matched design

MTX= methotrexate; AZA= azathioprine; 6-MP= 6-mercaptopurine; NR= not reported

Appendix 3.9: Characteristics of included non-comparative studies

Study	Disease (CD, UC, or both)	Intervention(s)	Reporting relevant efficacy (E) or safety (S) outcomes, or both (E/S)	N receiving TNF-alpha inhibitor	Length of follow-up	Consecutive patient enrollment (Y/N/U) / Comments
Abidi, 2011 R1346	UC	Infliximab	E	29	NR	U
Abreu, 2006 R2383	CD	Infliximab	E	38	4 weeks	U
Alzafiri, 2011 R1354	CD	Infliximab	E	97	Median 62 months	U
Alzeni, 2005 R2438	CD	Infliximab	E, S	63	10 weeks	U
Antakia, 2013 R2732	CD	Infliximab	E, S	48	Median 20 months	Y
Ardizonne, 2002 R3208	CD	Infliximab	E, S	63	10 weeks	U
Arnott, 2003 R2525	CD	Infliximab	E	74	Up to 1 year	Y Aim was to identify markers of response to infliximab
Barreiro-de Acosta, 2012 R1585	UC	Infliximab	E, S	33	52 weeks	Y Pouchitis
Baudet, 2010 R1904	UC	Infliximab	E	43	Up to 12 months	Y
Baudet, 2010 R2874	UC	Infliximab	E	43	NR	U
Beigel, 2014 R1106	CD/UC	Adalimumab, infliximab	E	248	Median 11 and 22.5 months	Y Cohort study comparing patients receiving one or two agents.
Bjorkenstein, 2011	CD	Infliximab	E	71	3 months (n=19), 12	Y

R1352					months (n=52)	
Bjorkesten, 2013 R173	CD	Adalimumab, infliximab	E	42	Median 12.8 months	Y Aimed to determine role of endoscopy in predicting long-term response
Bor, 2013 R627	CD	Infliximab	E	53	1 year	U
Boschetti, 2011 R1319	IBD	Infliximab, adalimumab	E	25	2 weeks	Y
Bressler, 2009 R2220	UC	Infliximab	E	21	Median 155 days	Y
Bruining, 2011 R1390	CD	Infliximab	E	63	At least 6 months	Y
Cadahia, 2004 R2498	CD	Infliximab	E	25	10 weeks	Y
Calabrese, 2008 R3316	UC	Infliximab	E	16	48 weeks	U
Caprioli, 2012 R2723	CD, UC	Infliximab	E	16	6 weeks	U
Carter, 2011 R655	CD	Infliximab	E	638	12 months	Y
Carter, 2011 R2834	UC	Infliximab	E	402	14 months	Y Comparison non of relevance for this SR: persistent vs non-persistent infliximab use.
Caspersen, 2008 R2995	CD, UC	Infliximab	E,S	651	Median 29.1 months	U Aim was to describe the use of infliximab in a national Danish population-based IBD cohort during 1999-2005
Chaparro, 2012 R1575	CD	Adalimumab	E, S	380	Median 8 months	Y
Cohen, 2001 R2589	CD	Infliximab	E, S	129	1 year	Y
Cullen, 2009 R2086	CD	Infliximab	E	21	NR	Y Aiming to measuring effect of guideline adherence on

						outcome
Cullen, 2012 R2790	CD	Infliximab	E	13	Median 2.3 years	Y
De Vos, 2012 R1600	UC	Infliximab	E, S	53	10 weeks	U
Di Sabatino, 2008 R3018	CD	Infliximab	E	15	10 weeks	U
Diez, 2007 R2311	UC	Infliximab	E, S	19	At least 8 weeks	Y
Domenech, 2005 R 3312	CD	Infliximab	E	23	Median 33 weeks	Y
Doubremelle, 2003 R2567	CD	Infliximab	E, S	69	Median 8 months	Y
Duff, 2012 R2760	CD	Infliximab	E	52	Median 66 months	Y
Esters, 2002 R3210	CD	Infliximab	E	87	10 weeks	Y
Farrell, 2003 R2534	CD	Infliximab	E	53	Median 20 weeks	Y
Fortea-Ormaechea, 2911 R1392	CD	Adalimumab	E	174	Median 40 weeks	U
Ghazi, 2013 R2687	CD	Infliximab, adalimumab, or certolizumab	E	54	12 months	Y Early biologic therapy vs step-up therapy. Step-up therapy group may have also received biologics.
Gomez-Senent, 2013 R205	CD	Adalimumab, Infliximab	E	26	NR	Y
Gonzaga, 2009 R2022	CD	Infliximab	E/S	153	Median 49.4 months	Y
Gonzalez-Lama, 2008 R2226	UC	Infliximab	E,S	47	Mean 4.7 months	Y
Gonzalez-Lama, 2008 R2221	CD	Infliximab	E, S	169	Mean 28 months	Y
Hirai, 2013 R199	CD	Infliximab	E, S	122	Mean 544.1 days	Y
Holtman, 2003	CD	Infliximab	E, S	21	NR	U

R3192						
Hommes, 2002 R2578	CD	Infliximab	E, S	134	NR	Y
Hyder, 2006 R3084	CD	Infliximab	E, S	22	Median 21 months	Y
Izuel-Rami, 2004 R2480	CD	Infliximab	E, S	26	NR	Y
Juliao, 2013 R646	UC	Infliximab	E	28	Median 27.4 weeks	Y
Jurgens, 2010 R1914	UC	Infliximab	E, S	90	14 weeks	U
Kane, 2009 R3301	CD	Infliximab	E	571	1 year	Y
Karmiris, 2011 R2860	CD	Infliximab	E	59	Median 36 weeks	Y
Kashavarzian, 2007 R2337	CD	Infliximab	S	447	Median 2.2 years	Y
Kim, 2013 R637	CD	Infliximab	E, S	80	Mean 33.7 months	Y
Kim, 2009 R2006	CD	Infliximab	E, S	40	Median 26.5 months	U
Kotze, 2014 R889	CD	Adalimumab	E, S	50	1 year	Y
Kotze, 2014 R2627	CD	Adalimumab	E, S	50	1 year	Y
Koutroubakis, 2009 R2973	CD, UC	Infliximab	E	22	14 weeks	Y
Laharie, 2013 R178	UC	Infliximab	E	63	Median 27 months	Y
Laharie,2011 R1388	CD	Infliximab	S	65	52 weeks	Y Association of fecal calprotectin and response.
Lam, 2014 R643	CD	Infliximab	S	68	Minimum 12 months	Y
Lavagna, 2006 R3066	CD	Infliximab	E	60	Median 13.2 months	Y
Leblanc, 2011 R1339	UC	Infliximab	E, S	86	Median 22.6 months	Y
Lee, 2013 R757	UC	Infliximab	E, S	134	Mean 13.3 months	Y
Li, 2012 R108	UC	Infliximab	E, S	19	NR	U
Ljung, 2004 R2503	CD, UC	Infliximab	E, S	217	NR	Y

Loonkvist, 2009 R2943	CD	Infliximab	E, S	103	1-5 years	Y
Luna-Chadid, 2004 R2497	CD	Infliximab	E, S	108	At least 10 weeks	Y
Machkova, 2013 R130	CD	Infliximab, adalimumab	E	25	Median 32 weeks	U
Maillard, 2014 R1055	UC	Infliximab, adalimuamb	S	186	NR	N Subset of 'Swiss IBD cohort' where appropriateness of therapy was able to be assessed
Malickova, 2013 R188	CD, UC	Infliximab	E	30	14 weeks	N Participants "randomly selected"
Martorana, 2001 R3223	CD	Infliximab	E, S	30	24 weeks	U
Maser, 2008 R2237	UC	Infliximab	E, S	10	Median 7.8 months	U
Matsumoto, 2005 R3116	CD	Infliximab	E	97	2 weeks	U
Menosa, 2009 R2104	UC	Infliximab	E, S	16	Median 195 days	Y
Miheller, 2006 R3099	CD	Infliximab	E	27	42 days	U
Mocciaro, 2007 R3037	UC	Infliximab	E, S	21	12 weeks	U
Molnar, 2010 R2895	CD, UC	Infliximab	S	127	Mean 2.3 years	U
Molnar, 2011 R2862	UC	Infliximab	E, S	50	Mean 15 months	U
Molnar, 2014 R2641	CD	Infliximab	E	50	12 months	U
Monterubbianesi, 2014 R1048	UC	Infliximab	E, S	113	12 months	U
Mortensen, 2010 R1329	UC	Infliximab	E	56	Median 538 days	Y
Moss, 2008 R3010	CD	Infliximab	E,S	287	Median 35 months	Y Aim was "to investigate the

						long-term outcomes in patients who experience infusion reactions while receiving infliximab."
Nakahigashi, 2011 R1396	CD	Infliximab	E	50	60 weeks	Y
Nichita, 2010 R1872	CD	Adalimumab	E	12	52 weeks	Y 55 patients in entire study, 12 in relevant subgroup of TNF-alpha inhibitor naïve
Orlando, 2012 R2782	CD	Adalimumab	E, S	110	Mean 14.6 months	U
Oussalah, 2010 R1908	UC	Infliximab	E	191	Median 18 months	Y
Oussalah, 2010 R1141	CD	Infliximab + azathioprine	E	88	6 months	Y
Pallotta, 2008 R3023	CD	Infliximab	E	20	Mean 34.7 months	U
Parakkal, 2011 R3268	CD, UC	Infliximab, adalimumab	S	22	NR	N Case reports of hepatosplenic t-cell lymphoma with TNF-alpha inhibitors
Pedersen, 2010 R2886	CD	Infliximab	E	245	Median 37.5 months (132) and 38 months (113)	Y Surgery in patients with prolonged response vs non-responders.
Pelletier, 2009 R2980	CD	Infliximab	E	18	Median 18 months	U
Persoons, 2005 R2441	CD	Infliximab	E	100	9 months	Y
Peters, 2014 R1053	CD	Adalimumab	E, S	438	Median 2 years	Y Concomitant immunosuppressant during first 6 months assessed as variable in MVA for outcome of failure (not an

						outcome for this SR)
Portiz, 2002 R2579	CD	Infliximab	E, S	26	Mean 6.5 months	Y
Poupardin, 2006 R2410	CD	Infliximab	E, S	137	Mean 15.2 months	Y
Regueiro, 2003 R3179	CD	Infliximab	E, S	32	At least 4.5 months	Y
Regueiro, 2006 R3097	UC	Infliximab	E	12	26 weeks	Y
Riis, 2012 R1597	CD	Infliximab, adalimumab	E, S	83	Median 59 months	Y Although included patients receiving both infliximab and adalimumab, results were not reported separately by treatment
Rodrigo, 2004 R3315	CD	Infliximab	E	81	Mean 36 weeks	Y
Rostholder, 2012 R1503	UC	Infliximab	E	56	Median 38 months	Y
Russo, 2009 R2089	UC	Infliximab	E, S	38	Mean 15 months	N Web-based questionnaire to physicians from 6 centres
Ryan, 2004 R2485	CD	Infliximab	E	24	12-18 weeks	U
Sanchez, 2005 R2422	CD	Infliximab	E, S	35	NR	U
Savoye-Collet, 2011 R2837	CD	Infliximab or adalimumab	E	20	1 year	Y
Sazuka, 2012 R1800	CD	Infliximab	E	74	Median 85 weeks	Y
Schnitzler, 2009 R2082	CD	Infliximab	E, S	614	Median 55 months	Y
Schwartz, 2005 R2437	CD	Infliximab	E	21	Median 68 weeks	Y
Sciaudone, 2010 R2846	CD	Infliximab	E, S	12	Median 57.4 months	U
Seiderer, 2004 R2495	CD	Infliximab	S	100	Median 26 months after the last	U

					infusion	
Seminerio, 2014 R2717	CD	Infliximab	E, S	492	Median 6.3 years	Y
Serghini, 2009 R2014	CD	Infliximab	E, S	20	Mean 10 months	Y
Seydtaghia, 2011 R1455	CD, UC	Infliximab	E, S	62	Median 6 months	Y
Sood, 2013 R683	UC	Infliximab	E	28	Median 48 months	Y
Steenholdt, 2012 R1731	CD	Infliximab	E	124	NR	Y
Stein, 2010 R1162	CD	Infliximab	E	104	Minimum 3 years	Y
Stennholdt, 2013 R198	CD, UC	Infliximab	E	51	1 year	Y
Talbot, 2004 R2462	CD	Infliximab	E, S	21	Median 20 months	U
Tanaka, 2006 R3096	CD	Infliximab	E, S	110	16 weeks	Y
Taxonera, 2014 R2614	CD, UC	Infliximab	E, S	97	Mean 9 months	Y
Teisner, 2010 R1135	UC	Infliximab	E	52	Median 22 months	Y
Teriaky, 2014 R728	CD	Adalimumab	E/S	149	Median 15 months	Y Case series of ADA-treated patients
Theophile, 2011 R1412	CD	Infliximab, adalimumab	S	30	NR	N Case reports of lymphoma in patients receiving TNF-alpha inhibitors
Tielbeek, 2013 R483	CD	Infliximab or adalimumab	E	50	Median 112 weeks	N
Tourgeron, 2009 R2956	CD	Infliximab	E	23	Mean 4.6 years	Y Aim to assess the effectiveness of "combined therapy" consisting of abscess draining and seton placement

						+antibiotics followed by IFX induction.
Tsukamoto, 2013 R187	UC	Infliximab	E, S	13	30 weeks	U
Tursi, 2013 R2692	CD	Infliximab	E	40	Mean 36 months	U
Vadan, 2010 R1328	CD	Infliximab	E	30	48 weeks	U
Vries, 2008 R2227	CD, UC	Infliximab	S	147	Median 59 months	Y
Willert, 2008 R2920	UC	Infliximab	E,S	15	Median 25.8 months	Y
Witthoft, 2004 R2467	CD	Infliximab	E	147	NR	U
Wong, 2013 R669	CD	Adalimumab + 6-MP or AZA	E	12	12 weeks	Y
Wu, 2008 R2240	CD	Infliximab	E	262	24 months	Y Medical claims database
Yamada, 2010 R2879	CD	Infliximab	E	31	NR	N Randomly selected
Yanamoto, 2013 R748	UC	Infliximab	E, S	12	Median 16 months	Y
Zabana, 2010 R2910	CD, UC	Infliximab	S	152	Median 142 weeks	Y
Zborel, 2003 R2543	CD	Infliximab	E	19	NR	U
SR=systematic review; CD= Crohn's Disease; UC=ulcerative colitis						

Appendix 3.10: Quality assessment of observational studies

Quality assessment of truly comparative cohort studies									
	Andersen 2014	**Biancone 2011**	**Choi 2014**	**Gies 2010**	**Kestens 2013**	**Leombruno 2011**	**Osterman 2014**	**Patil 2013**	**Sussman 2012**
Population[a]	Probably Yes	Yes	Yes	Yes	Yes	Probably Yes	Probably Yes	Probably No	Probably Yes
Intervention[a]	Probably Yes	Probably Yes	Yes	Yes	Probably Yes	Probably Yes	Yes	Yes	Probably Yes
Comparator[a]	Probably Yes	Probably Yes	Yes	Yes	Probably Yes	Probably No	Yes	Probably No	Probably Yes
Outcome[a]	Yes	Yes	Yes	Yes	Probably Yes	Yes	Yes	Yes	Yes
Focused question?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Comparable source population?	Yes	Yes	Yes	Can't say	Yes	Yes	Yes	Yes	Yes
Response rate	Does not apply	No	Does not apply	No	Yes	Yes	Does not apply	Does not apply	Does not apply
Outcome at time of enrollment	Does not apply	No	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply
Percentage dropouts	0	18% in the treatment arm and 28% in the control.	NA	7.4% in the Infliximab maintenance arm	0%	10.5% of infliximab non-users and 8.9% of infliximab users lost to follow-up.	N/A	34.5% and 19.4%. No discussion of reasons for loss to follow-up. Possibly that they	N/A (database study), however out of 1533 eligible subjects, 1246 were

								stopped treatment. Unclear.	included after propensity-score matching.
Comparison between dropouts and participants	Does not apply	No	Does not apply	No	Does not apply	Yes	Does not apply	No	Yes
Defined outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blind exposure assessment	Does not apply	No	No	No	Does not apply	Does not apply	No	No	No
Acknowledgement that blinding could affect outcome assessment	No	No	No	No	No	No	Yes	No	No
Reliable method of assessment of exposure	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Can't say
Evidence used to determine that outcome assessment is valid/reliable	No	Yes	No	No	No	Yes	Does not apply	No	Can't say
Assessment of exposure more than once	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply	No	Does not apply
Confounding considered?[b]	Can't say	Yes	No	No	No	No	No	No	No

Confidence intervals provided?	Yes	No	No	No	No	Yes	Yes	Yes	No
Overall quality	Acceptable	Low quality/Unacceptable	Low quality/Unacceptable	Low quality/Unacceptable	Acceptable	Low quality/Unacceptable	Acceptable	Low quality/Unacceptable	Low quality/Unacceptable

[a]Assessment of study directness; not part of SIGN50 checklist

[b]For pre-defined important potential confounding variables, an assessment was made as to whether the variable did not give rise to confounding, was adequately adjusted for, was not adequately adjusted, or was not addressed. This was considered, and an overall assessment of adequacy of adjustment for confounding was made.

Quality assessment of case control studies							
	Ananthakrishnan 2009	**Baars 2011**	**Hutfless 2008**	**Long 2012**	**Long 2010**	**Singh 2011**	**Solem 2004**
Focused question	Yes	Yes	Yes	Yes	Yes	Yes	Yes
comparable populations	Yes	Yes	Yes	Yes	Yes	Yes	Yes
same exclusion criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Percentage participation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Comparison of participants to non-participants	Can't say	No	No	Can't say	Can't say	Can't say	Can't say
Cases clearly defined	Yes	Yes	Yes	Yes	Yes	Yes	Can't say
Controls established	Can't say	Yes	Yes	Yes	Can't say	Yes	Yes
Prevented exposure influencing case	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply	Does not apply

ascertainment							
Measurement of Exposure status	Can't say	Can't say	Can't say	Can't say	No	No	Can't say
Confounders accounted for	No	Yes	Can't say	No	No	No	No
Confidence intervals provided	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Overall quality	Low quality/unacceptable	Acceptable	Low quality/unacceptable	Low quality/unacceptable	Low quality/unacceptable	Low quality/unacceptable	Low quality/unacceptable

Appendix 4.1: Active pharmacosurveillance strategies in five international jurisdictions

Jurisdiction	Regulatory Agency	Related organizations	Risk Management Plans	Research Networks	Other strategies	Comments
EU	European Medicines Agency (EMA)	Committee for Medicinal Products for Human Use (pharmacovigilance section), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; EMA sponsored network of research centres)	Required; may include "specific obligations" or "follow-up measures" as a condition of market authorization. Industry developed and funded.	ENCePP -No public funding (industry-commissioned research) -university, hospital, and government-based centres -researchers have access to data to enable efficient research (e.g. ADR reporting, health care claims, pharmacy dispensing data, registries)	Increasing transparency through publication of 'European Public Assessment Reports' for drugs receiving market authorization	-Reactive approach to investigating drug safety issues (responds to ADR signals) -Lack of harmonization of EU and national legislation can make adherence to RMPs difficult (i.e. national database may be inaccessible to MAH). Still early in its development; adherence issues [Blake 2011, Frau 2010]
France	Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS)	Haute Autorité de Santé Commission de la Transparence (Transparency commission), the Surveillance du Risque, the Département du Bon Usage et de	Required; proposed by MAH at the time of market authorization. Coordinated and implemented by Regional Pharmacovigilance	Regional Pharmacovigilance centres -prospective monitoring of certain drugs is undertaken according to the	-Combination of voluntary and mandatory reporting -Feedback direction to health professionals from Regional	-Anticipatory approach to investigating drug safety issues

		l'Information sur les Médicaments, la Revue Prescrire, and Regional Pharmacovigilance Centres	Centres, funded by industry	National Pharmacovigilance committee of the AFSSaPS.	Pharmacovigilance Centres	
New Zealand	Medicines and Medical Devices Safety Authority (MedSafe)	The New Zealand Centre for Adverse Reactions Monitoring (a drug surveillance system)	Not required	National Pharmacovigilance Centre (University of Otago) conducts post-market studies commissioned by MedSafe (publicly funded) - Intensive Medicines Monitoring Programme (IMMP) conducts prospective observational cohort studies of drugs selected for intense monitoring.		-Anticipatory approach -high rate of spontaneous ADR reporting
UK	Medicine and Healthcare Products Regulatory Agency (MHRA)	UK Drug Safety Research Unit (DSRU), UK Medicines and Healthcare Regulatory Agency, The National Institute for Health and Clinical Excellence, (NICE; a national health technology assessment	Industry developed and funded in collaboration with MHRA.[Patient Safety Institute, 2012]	-VRMM works with external researchers to conduct independent research and submits reports to an “expert advisory group” (EAG)	-NICE reviews medications to make recommendations for funding, and may recommend further post-market research if evidence is insufficient to recommend	-Reactive approach -DSRU is industry-funded [Wiktorowicz, 2012]

		agency), Pharmacovigilance Risk Management Section of Vigilance and Risk Management of Medicines (VRMM) Division of MHRA			funding, or that a drug be funded 'only-in-research'. -Patient drug and disease registries	
US	FDA	FDA's Office of Surveillance and Epidemiology (OSE). Centers for Education and Research on Therapeutics (CERTs). Agency for Healthcare Research and Quality (and FDA) initiate projects from: Developing Evidence to Inform Decisions about Effectiveness (DEcIDE), and the U.S. Department of Veterans Affairs (VA)	Not required. FDA may mandate conduction of studies by MAH to address specific concerns, as determined by a "FDA advisory committee" including clinical experts	FDA commissions research through two networks: -DEcIDE: research commissioned by AHRQ and FDA, uses health care plan databases -CERTs: 14 university-based research centres and a coordinating office -Six FDA-supported Evidence-based Practice Centres (EPCs): conduct meta-analyses	FDA's Sentinel System -secure electronic database -enables efficient, complex observational analyses -signal generation for ADRs	-Reactive /anticipatory approach
Source of information for table (except where otherwise indicated): Wiktorowicz ME, Lexchin J, Moscou K, Silversides A, Eggertson L. (2010). Keeping an Eye on Prescription Drugs, Keeping Canadians Safe. Active Monitoring Systems for Drug Safety and Effectiveness in Canada and Internationally. Toronto: Health Council of Canada. www.healthcouncilcanada.ca.						