Supplemental Digital Content 1. Systematic literature review: Results and analysis

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Section 1. Dose escalation and switching

1A. Dose escalation and switching in ulcerative colitis

Table S1 presents data for dose escalation and switching with second-line anti-TNFα in patients with UC. A total of four studies reported data on either dose escalation or switching. Dose escalation for ADA ranged from 35% (Afif 2009[1]) to 46.2% (Oussalah 2008[2]).

Only one study reported data for switching in UC patients (Mocciaro 2012[3]). In this study, nine patients were switched to azathioprine in the INF treatment group and 13 patients started azathioprine in the cyclosporine treatment group. The rate of switching was 30% in the INF group as compared to 37.1% in the cyclosporine group. Actual rate of switching was calculated as patients responding to treatment*proportion of patients who continued the treatment*proportion of patients who switched (INF: 83.3% x 60% x 60%=30% and cyclosporine: 71.4% x 52% =37.1%).

In a study (Taxonera 2011[4]) assessing patients with active UC, treatment with ADA after failure of other therapies including INF resulted in dose escalation from 40 mg every other week to 40 mg weekly in 36.7% patients. The median time to dose escalation was 10 weeks (IQR: 8–23 weeks) (Taxonera 2011[4]). In another study with ADA, 35% patients had dose escalation of ADA between weeks eight and 16, from 40 mg every other week to 40 mg weekly due to incomplete response (Afif 2009[1]).

Table S1: Dose Escalation and Switching in UC

Study name	Countries	Treatment groups	No. of patients	Study duration	Dose escalation: n, %, rate	Switching: n (%)
Mocciaro 2012[3]	Italy	INF	30	Mean (SD) follow-up: 33.6 (15.5) months	NR	Actual rate of switching: responders*proportion continued treatment*proportion switched: 83.3% (25/30) x 60% (15/25) x 60% (9/15)=30% 15 patients (60%) continued the treatment every 8 weeks but only 9 of them were switched to azathioprine
Mocciaro 2012[3]	Italy	Cyclosporine	35	Mean (SD) follow-up: 74.7 (60.8) months	NR	Actual rate of switching: responders*proportion switched: 71.4% (25/35) x 52% (13/25)=37.1% 13 of 25 (52%) initial responders started azathioprine
Taxonera 2011[4]	Spain	ADA	30	Mean (SD) follow-up: 74.7 (60.8) months	11 (36.7) underwent dose escalation between weeks 4 and 12 from 40 mg every other week to 40 mg weekly.	NR
Afif 2009[1]	USA	ADA	20	Median (IQR) follow-up: 48 (16-104) weeks	7 (35)	NA
Oussalah 2008[2]	France	ADA	13	24 weeks	6 (46.2) had dose frequency increased to weekly	NR
				Mean (range) follow-up: 41.69 (10-100) weeks		

1B. Dose escalation and switching in Crohn's Disease

Table S2 presents data for dose escalation and switching with second-line anti-TNFα in patients with CD. A total of 17 studies reported data on either dose escalation or switching.

Dose escalation for ADA ranged from 14% (CARE Trial [Louis 2013][5]) to 72% (Cordero-Ruiz 2011[6]). A multinational study (Reenaers 2012[7]) reported dose escalation for semesters. A semester was defined as a six-month period with ADA. A flare semester was defined as deterioration in clinical symptoms requiring treatment modification (ADA reinduction, escalation to weekly ADA injection, initiation of corticosteroids or switch to another biologic), new perianal complication or abdominal surgery for active CD. A remission semester was a semester without a flare on ADA every other week or de-escalation from ADA. This study reported 81% dose escalation with ADA, which indicates that out of total 181 semesters, dose-escalation occurred in 104 semesters.

In the CARE Trial (Louis 2013)[5], dose escalation for ADA was required in 14% of the patients, with median time to dose escalation of 92 days (range: 70–137 days). In another study, 5.2% of patients (4 out of 76) had dose intensification (escalation of dose to INF 10 mg/kg in two patients and decreased interval of infusions to six weekly in the remaining two patients) (Bhalme 2013[8]). Discontinuation occurred in a total of 47.4% of patients. In the same study, 20% of patients in the ADA group required dose escalation due to LOR with a median time to LOR of 7.0 months (IQR: 4.0–12.0 months).

A study (Bultman 2012[9]) assessed the predictors for ADA dose escalation at initiation of ADA. In this study, a total of 122 (61%) CD patients received ADA for at least 3 months at the time of inclusion. Seventy-three patients (60%) had previously been treated with INF. The median length of follow-up after initiation of ADA was 51 weeks (range 12–111). Forty-six (38%) patients needed dose escalation during ADA treatment. The median time to dose escalation was 21 weeks after initiation of ADA (range 4–105). The cumulative probability of requiring dose escalation at 1 year of treatment was 39%. Median time to dose escalation was 79 weeks (95% CI: 58–100). Previous SNRs to INF more often required a dose escalation during ADA treatment than patients who previously responded to INF (57% versus. 15%, p=0.01). The cumulative probability of needing a dose escalation after 1 year was 60% in the previous SNRs to INF versus. 8% in the previous responders to INF (p=0.01). Hence this study concluded that more than one-third of patients treated with ADA required dose escalation within a median of 5 months of treatment. Higher BMI and previous non-response to INF treatment at start of ADA treatment were predictive of the need for dose escalation during ADA treatment.

In the WELCOME trial (Sandborn 2010)[10], switching was reported in 24.9% of patients in the CER every two weeks maintenance treatment group and 31.6% in the CER every four weeks maintenance treatment group. In a USA-based study, dose escalation was required in 50% of the population (59/118 patients) and occurred at a median of 4.2 months (range: 0.76 months to 3.0 years) after ADA initiation (Swoger 2010[11]). The cumulative probability of requiring a dose escalation was 54.0% at one year.

In another study in medical refractory CD patients, 59% required dose escalation to ADA 40 mg weekly treatment within six months of therapy (median time of escalation: 0.55 years [IQR: 0.22–1.5]) (Ho 2008[12]). Although ADA was efficacious in INF primary non-responders, many patients required escalation of dosing regimen. A study conducted in CD patients in Spain reported that 72% of patients required dose intensification (increase of ADA to a weekly dose), in order to maintain clinical response (Cordero-Ruiz 2011[6]).

Table S2: Dose Escalation and Switching in CD

Study name	Countries	Treatment groups	No. of patients	Study duration	Dose escalation: n, %, rate	Switching: n (%)
Bhalme 2013[8]	Netherlands and Germany	ADA	54	NR	11 (20)	NR
Bhalme 2013[8]	Netherlands and Germany	INF	76	NR	4 (5.2)	NR
CARE trial (Louis 2013)[5]	European countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, UK)	ADA	945	20 weeks	131 (14)	NR
Reenaers 2012[7]	Multinational (Belgium and UK)	Maintenance study: Patients treated 12 months with ADA	181	NR	Semesters: ADA monotherapy ADA dose escalation 104 (81) ADA+IS ADA dose escalation 53 (80), (p=0.95)	1 switch to IFX (0.01%)
Cohen 2012[13]	USA	ADA	75	NR	First dose escalation: 31 (41) Second dose escalation (80 mg/week): 10(32%)	NR
Bultman 2012[9]	Netherlands	ADA	122	Median (range) follow-up after initiation of ADA: 51 (12-111) weeks	46(38)	NR
ACCESS-trial (Panaccione 2011)[14]	Canada	ADA	304	24 weeks	120 (39), patients had their dosage increased to weekly ADA therapy	NR
Cordero-Ruiz 2011[6]	Spain	ADA	25	Follow-up: 12 months	18 (72), patients needed to increase ADA to weekly dose, in order to maintain clinical response	NR
Fortea-Ormaechea 2011[15]	Spain	ADA	174	Median (IQR) follow up: 36 (21-76) weeks	57 (32.8)	NR
WELCOME trial (Sandbo	Multinational (Austria, Belgium,	CER (every two weeks, maintenance)	161	26 weeks	NR	40 (24.9)

Study name	Countries	Treatment groups	No. of patients	Study duration	Dose escalation: n, %, rate	Switching: n (%)
rn 2010)[10]	Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK and USA)					
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK and USA)	CER (every four weeks, maintenance)	168	26 weeks	NR	53 (31.6)
Swoger 2010[11]	USA	ADA	118	Median (range) follow-up: 13.7 months (0.9 months to 4.3 years)	59 (50)	NR
Russo 2010[16]	England/Ireland	ADA	61	8 months	NR	NR
Echarri 2010[17]	Spain	NA	16	48 weeks	NR	2 (12.5); patients changed to a weekly dose of ADA during maintenance therapy
Lees 2009[18]	UK	ADA	30	Median (IQR) duration of follow-up from initiation of ADA: 0.92 years (0.37-1.84)	16 (53.3)	NR

Study name	Countries	Treatment groups	No. of patients	Study duration	Dose escalation: n, %, rate	Switching: n (%)
Ho 2009[19]	Scotland	ADA	98	NR	24.4%, 30.7% and 55.0% of patients required dose escalation to 40 mg weekly therapy at 6-months, 1-year and 2-year follow-up respectively. Two (28.6%) patients treated with the higher induction regimen (160/80 mg) required dose escalation over a median follow-up period of 0.56 years (0.24-0.72).	NA
West 2008[20]	Netherlands	ADA	30	NR	8 (27)	NA
Ho 2008[12]	UK	ADA	22	Median (IQR) follow-up: 1.0 (0.62-2.5) years	13 (59)	NR
Peyrin-Biroulet 2007[21]	France	ADA	24	52 weeks	6 (25)	NR

Section 2. Surgery

2A. Data on surgery in ulcerative colitis

Data for details of surgery for UC patients are presented in Table S3.

A study from the USA reported that from 2006 to 2010, 407 and 181 patients underwent initial subtotal colectomy with end ileostomy or total proctocolectomy with IPAA, respectively (Gu 2013[22]). Chaparro (2012)[23] reported a colectomy incidence of 20% per patient-year of follow-up. The cumulative incidence of colectomy was 27%, 29%, 29% and 35% at 12 weeks, 1 year, 2 years and 3 years of follow-up, respectively.

Table S3. Details of Surgery in Ulcerative Colitis

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
Gu 2013[22]	USA	Biologics: Anti-TNF-α therapy impact on outcomes after TPC/IPAA for UC	25	TPC/IPAA	Peripouch data and 30-day outcomes Laparoscopic surgery: 11 (44) J-pouch: 24 (96) Double-stapled anastomosis: 24 (96)	NR	Cumulative 1-year complication rate (Kaplan-Meier estimated 1-year cumulative rate of complications after TPC/IPAA) Anastomotic stricture: 2 (8) Pelvic sepsis: 8 (32) Fistula: 2(8) Pouch failure: 0 Pouchitis: 1 (4) Small-bowel obstruction: 3 (10)	Postoperative hospital stay: 7 (3-32) days	
Gu	USA	No	156	TPC/IPAA	Peripouch data and 30-day	NR	Cumulative 1-	Postoperative	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
2013[22]		Biologics: Anti-TNF-α therapy impact on outcomes after TPC/IPAA for UC			outcomes Laparoscopic surgery: 53 (34) J-pouch: 154 (99) Double-stapled anastomosis: 148 (95)		year complication rate (Kaplan-Meier estimated 1-year cumulative rate of complications after TPC/IPAA) Anastomotic stricture: 21 (13) Pelvic sepsis: 25 (16); *p*=0.012 Fistula: 9 (6) Pouch failure: 7 (4) Pouchitis: 15 (10) Small-bowel obstruction: 25 (16)	hospital stay: 6 (3-28) days	
Gu 2013[22]	USA	Biologics: Anti-TNF-α therapy impact on short-term outcomes after STC/EI for UC	142	STC/EI	Urgent surgery: 42 (30) Laparoscopic surgery: 73 (51)	NR	Perioperative and 30-day outcomes Pelvic abscess: 3 (2) (Colo)rectal stump leak: 16 (11) Wound infection: 21 (15) Urinary tract infection: 2 (1) Pneumonia: 2 (1)	Postoperative hospital stay: 5 (2-30) days	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
							Ileus: 17 (12) EPSBO: 6 (4) Postoperative hemorrhage: 3 (2) Stoma complications: 3 (2) Thromboembolic complications: 7 (5)		
Gu 2013[22]	USA	No Biologics: Anti-TNF-α impact therapy on short-term outcomes after STC/EI for UC	265	STC/EI	Urgent surgery: 96 (36) Laparoscopic surgery: 123 (46)	NR	Perioperative and 30-day outcomes Pelvic abscess: 12 (5) (Colo)rectal stump leak: 24 (9) Wound infection: 28 (11) Urinary tract infection: 8 (3) Pneumonia: 2 (1) Ileus: 34 (13) EPSBO: 12 (5) Postoperative hemorrhage: 9 (3) Stoma complications: 7 (3) Thromboembolic complications: 22 (8)	Postoperative hospital stay: 6 (2-42) days	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
Gu 2013[22]	USA	Biologics: Anti-TNF-α therapy use before colectomy on short- and long-term outcomes after CP/IPAA for UC in patients who underwent initial STC	88	CP/IPAA with initial STC	Peripouch data and 30-day outcomes Laparoscopic surgery: 21 (24) J-pouch: 88 (100) Double-stapled anastomosis: 85 (98)	NR	Cumulative 1-year complication rate (Kaplan-Meier estimated 1-year cumulative rate of complications after TPC/IPAA) Anastomotic stricture: 1 (1) Pelvic sepsis: 5 (6) Fistula: 2 (2) Pouch failure: 0 Pouchitis: 2 (2) Small-bowel obstruction: 9 (10)	Postoperative hospital stay: 6 (2-26) days	
Gu 2013[22]	USA	No Biologics: Anti-TNF-α therapy use before colectomy on short- and long-term outcomes after CP/IPAA for UC in patients who underwent initial STC	164	CP/IPAA with initial STC	Peripouch data and 30-day outcomes Laparoscopic surgery: 42 (26) J-pouch: 164 (100) Double-stapled anastomosis: 160 (98)	NR	Cumulative 1-year complication rate (Kaplan-Meier estimated 1-year cumulative rate of complications after TPC/IPAA) Anastomotic stricture: 8 (5) Pelvic sepsis: 16 (10) Fistula: 8 (5) Pouch failure: 6 (4)	Postoperative hospital stay: 6 (3-33) days	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
							Pouchitis: 6 (4) Small-bowel obstruction: 8 (5)		
Chaparro 2012[23]	Spain	Infliximab	47	Colectomy	Colectomy: 14 (30)	The incidence rate of colectomy was 20% per patient-year of follow-up. The cumulative incidence of colectomy was 27%, 29%, 29% and 35% at 12 weeks, 1 year, 2 years and 3 years of follow-up.	NR	NR	Patients underwent colectomy at a median of 8 weeks (range: 1–162) after the first infliximab infusion. In total, 37 patients avoided colectomy in the corticosteroid-refractory flare, and only four of these 37 patients underwent colectomy after a median of 90 weeks' follow-up.
Moccia ro 2012[3]	Italy	Cyclospori ne	35	Colectomy	3 months: 10 (28.5), *p*=0.25 12 months: 17 (48), *p*=0.01 2 years: 19 (54) 3 years: 20 (57) A the end of follow-up: 21 (60)	NR	NR	NR	
Moccia ro 2012[3]	Italy	Infliximab	30	Colectomy	3 months: 5 (17) 12 months: 5 (17) 2 years: 7 (23) 3 years: 8 (27) A the end of follow-up: 9 (30)	NR	NR	NR	
Waters	USA	Infliximab	86	NR	Pre- vs. Post-Infliximab: 21	NR	NR	NR	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
2012[24]					(24.4) vs. 11 (12.8), *p*=0.042				
Rostholder 2012[25]	USA	Infliximab	50 (maintenance cohort)	Colectomy	Patients with moderate UC who received maintenance IFX therapy required a colectomy during follow-up: % Overall: 27 Dose escalation group: 33 Non-dose escalation group: 21	NR	NR	NR	Mean time to colectomy was 17 months (SEM 6) in the cohort.
Laharie 2012[26]	Multinational (France, Spain, Belgium, and Finland)	Ciclosporin	58	Colectomy	10 (17)	NR	NR	NR	
Laharie 2012[26]	Multinational (France, Spain, Belgium, and Finland)	Infliximab	57	Colectomy	12 (21)	NR	NR	NR	
Taxonera 2011[4]	Spain	Adalimumab	30	Colectomy	6 (20)	NR	NR	NR	The probability of avoiding colectomy was 96.7%, 90%, 90%, 83.3%, 83.3% and 80% at 4, 12, 20, 30, 40 and 60 weeks, respectively.
Alzafiri	Canada	Infliximab	19	NR	NA	NR	NR	NR	2 (8%) UC patients

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
2011[27]									underwent surgery any time prior to infliximab
Oussalah 2010[28]	France	Infliximab	191	Colectomy	Colectomy: 36 (18.8); (95 % CI = 13.3-24.4 %) Colectomy rates according to mucosal healing: 1/30 (3%) patient who achieved mucosal healing and 13/33 (39%) without mucosal healing had a Colectomy during the follow-up *p*=0.004).	NR	NR	NR	
Herrlinger 2010[29]	Germany	Infliximab	24	Colectomy	Response only: 4 Failure: 10 total Colectomy: 14 (58.3)	NR	NR	NR	
Jurgens 2010[30]	Germany	Infliximab	90	Colectomy	6/90 (6.7)	NR	NR	NR	
Gies 2010[31]	Canada	Adalimumab (Maintenance)	20	Colectomy	Of the six ADA patients who lost response, two chose colectomy as therapy.	NR	NR	NR	
Gies 2010[31]	Canada	Infliximab (Maintenance)	18	Colectomy	Of the four IFX patients who lost response, one chose colectomy as therapy.	NR	NR	NR	
Ananthakrishnan 2009[32]	USA	Colectomy (Infliximab use Never: 13 (48.2) Ever: 14 (51.9)	27	NR	NR	NR	NR	Prior medical hospitalisation required for UC Never: 6 (22.2) Ever: 21 (77.8)	Among patients who required medical hospitalisation for management of disease, one-fifth (21/103, 20.4%) subsequently

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
									required colectomy, while only 6 out of 143 patients (4.2%) who had never required hospitalisation underwent colectomy. The median time to colectomy after hospitalisation was 2.0 months.
Ananthakrishnan 2009[32]	USA	No colectomy (Infliximab use Never: 170 (77.6) Ever: 49 (22.4))	219	NR	NR	NR	NR	Prior medical hospitalisation required for UC Never: 137 (62.6) Ever: 82 (37.4); *p*<0.001	
Ho 2009a[33]	UK	Corticosteroids	90	Colectomy	20 (22.2)	NR	NR	NR	
Ho 2009a[33]	UK	Infliximab	21	Colectomy	11 (52.4)	NR	NR	NR	
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium,	ACT 1 and 2 trial: Placebo	244	Colectomy	No. of UC related surgeries/procedures analysis Surgical procedures: 0: 197(81) 1: 34(14) 2: 8(3) >2: 5(2)	Kaplan Meir estimates for colectomy within 54 weeks: 36(17)	NR	No. of UC related surgeries/procedures analysis Hospitalisations: 0: 184(75) 1: 46(19) 2: 9(4) >2: 5(2)	The numbers of ulcerative colitis-related hospitalisations and surgeries/procedures through 54 weeks were

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
	Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)								expressed as events per 100 patient- years: n=34 Total duration of colectomy follow-up is the sum of the complete colectomy follow-up and incomplete colectomy follow-up, and is reported in patient-years(%): 202.5(87.8)
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 1 and 2 trial: 5 mg Infliximab	242	Colectomy	No. of UC related surgeries/procedures analysis Surgical procedures: 0: 207(86) 1: 28(12) 2: 3(1) >2: 4(2)	Kaplan Meir estimates for colectomy within 54 weeks: 28(12)	NR	No. of UC related surgeries/procedures analysis Hospitalisations: 0: 203(84) 1: 31(13) 2: 8(3) >2: 0(0)	The numbers of ulcerative colitis-related hospitalisations and surgeries/procedures through 54 weeks were expressed as events per 100 patient- years: n=22 Total duration of colectomy follow-up is the sum of the complete colectomy follow-up and incomplete colectomy follow-up, and is

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
									reported in patient-years(%): 223.1(94.6)
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 1 and 2 trial: 10 mg Infliximab	242	Colectomy	No. of UC related surgeries/procedures analysis Surgical procedures: 0: 214(88) 1: 18(7) 2: 7(3) >2: 3(1)	Kaplan Meir estimates for colectomy within 54 weeks: 18(8)	NR	No. of UC related surgeries/procedures analysis Hospitalisations: 0: 205(85) 1: 33(14) 2: 3(1) >2: 1(0.4)	The numbers of ulcerative colitis-related hospitalisations and surgeries/procedures through 54 weeks were expressed as events per 100 patient- years: n=19 Total duration of colectomy follow-up is the sum of the complete colectomy follow-up and incomplete colectomy follow-up, and is reported in patient-years(%): 220.8(92.4)
Aratari 2008[35]	Italy	Hydrocortisone	52	Colectomy	10 (19)	NR	NR	NR	The number of surgeries indicate overall number; 8 with steroid treatment and 2 with Infliximab
Maser 2008[36]	USA	Infliximab-salvage	10	Colectomy	For overall population: 8/19 (42) had a colectomy within 1 year	NR	NR	NR	In both groups, all patients who required

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
									colectomy or died had a Lichtiger score of greater than 10.
Maser 2008[36]	USA	Ciclosporine-salvage	9	Colectomy		NR	NR	NR	
Oussalah 2008[2]	France	Adalimumab	13	Colectomy	After a median duration of follow-up of 41 weeks, 6/13 (46.2) underwent colectomy	NR	NR	NR	The probability of remaining colectomy-free was 92.3% (±7.39%), 84.6% (±10.0%), 69.2% (±12.8%) and 49.5% (±14.9%) at 1, 3, 6 and 23 months respectively.
Regueiro 2006[37]	USA	Infliximab	12	Colectomy	9 (75)	NR	NR	NR	
Gornet 2003[38]	France	Infliximab	30	Colectomy	Colectomy: 8/30 (27) Probability of colectomy: The probability of colectomy was 7% (95% CI: 2% to 12%) at month 1, 17% (95% CI: 10% to 24%) at month 3, and 33% (95% CI: 23% to 43%) at month 12.	NR	NR	NR	Two variables were associated with a higher rate of colectomy: the severity of the attack (8/19 vs. 0/11; $p<0.02$), and the absence of concomitant use of antimetabolites (5/8 vs. 3/21; $p<0.001$).
Probert	Multinational (UK	Placebo group	20	Colectomy	One patient underwent colectomy because of toxic	NR	NR	NR	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD and UC	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Duration of hospitalisation (as reported)	Comments
2003[39]	and Germany)				exacerbation and spontaneous perforation.				
Probert 2003[39]	Multinational (UK and Germany)	Infliximab group	23	NR	NR	NR	NR	NR	
Su 2002[40]	USA	Infliximab	27	Proctocolectomy - 5	Five of the non-responders subsequently underwent total proctocolectomy 6 to 40 days (median, 10 days) after the last infliximab dose, and one of the partial responders had total proctocolectomy for a lack of sustained response 5 months after his second infliximab infusion.	NR	Central venous line sepsis and associated sub acute bacterial endocarditis: 1 patient Candidemia: 1 patient	NR	

2A. Data on surgery in Crohn's Disease

Table S4 presents details for the most common surgeries performed in CD patients.

The most common surgeries were colectomy, ileostomy, partial bowel resection, total colectomy and end-ileostomy. In one study (Patil 2013[41]), at one year follow-up, patients in the INF group had undergone a mean 0.61 (SD: 1.2) CD-related surgeries; whereas patients in the ADA/CER group had undergone a mean 0.41 (0.68) CD-related surgeries (p=0.44).

In a UK based study, the authors reported different types of surgeries. The proportions of patients undergoing colectomy, ileostomy or partial bowel resection were higher in the post-INF period than pre-INF period. During the 0 to 24 month period following initiation of INF, 13 patients (3.4%) underwent colectomy, 11 (2.9%) underwent ileostomy and 26 (6.8%) underwent partial bowel resection. However, patients who had recently undergone major surgery were less likely to be treated with INF; therefore, the number of procedures performed might have been low in the pre-INF group (Lindsay 2013[42]).

In the INF treated group, there were 79 (annual rate/100 person-years: 6.9) surgeries in the first year of follow-up; whereas in the ADA treated group, there were 52 (annual rate/100 person-years: 7.6) surgeries in the first year of follow-up (Osterman 2014[43]).

Table S4. Details of Surgery in Crohn's Disease

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
Patil 2013[41]	USA	Infliximab	31	NR	NR	Number of disease related surgeries at 1 year follow-up: Mean (SD): 0.61 (1.2), p=0.44	NR	Two patients were initiated on anti-TNF agents for postoperative prophylaxis
Patil 2013[41]	USA	Adalimumab/ Certolizumab	29	NR	NR	Number of disease related surgeries at 1 year follow-up: Mean (SD): 0.41 (0.68)	NR	Two patients were initiated on anti-TNF agents for postoperative prophylaxis
Bhalme 2013[8]	Multinational (Netherlands and Germany)	Adalimumab	54	NR	NR	NR	NR	Previous surgery: 22 (40.7)
Bhalme 2013[8]	Multinational (Netherlands and Germany)	Infliximab	76	NR	NR	NR	NR	Previous surgery: 54 (71.1)
CARE	Multinational	Adalimumab	945	NR	NR	NR	NR	Previous Crohn's disease

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
Trial (Louis 2013)[5]	(Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, UK)							related surgery: 518 (54.8)
Ghazi 2013[44]	USA	Step Up	39	NR	NR	Mean (SD) At 1 year, 0.28 (0.8) surgeries	NR	
Ghazi 2013[44]	USA	Early Bio	54	NR	NR	Mean (SD) At 1 year, 0.50 (0.8) surgeries; *p*=NS	NR	
Lindsay 2013[42]	UK	Infliximab	380	Colectomy, ileostomy, partial bowel resection	During the 0 to 24 month period following initiation of infliximab, 13 patients (3.4%) had a colectomy, 11 (2.9%) had an ileostomy and 26 (6.8%) had a partial bowel resection.	NR	NR	
Osterman 2014[43]	USA	Infliximab	1459 (Evaluable: 1445)	NR	122 (5.5)	Surgeries in first year of follow-up: 79 (6.9) After censoring follow-up 90 days after discontinuation of therapy: 77 (5.8)	NR	
Osterman	USA	Adalimumab	871 (Evaluable:	NR	91 (6.9)	Surgeries in first year of follow-up: 52 (7.6)	NR	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
2014[43]			865)			After censoring follow-up 90 days after discontinuation of therapy: 47 (7)		
Semineriro 2013[45]	USA	Infliximab	492	Intestinal operations	At least one Intestinal surgery: Prior to infliximab: 272/492 (55) While receiving infliximab: 65/492 (13) Following treatment with infliximab (>12 weeks off of the medication): 136/492 (28)	Median (range) number of intestinal surgeries: Prior to infliximab: 1 (0–9) During infliximab therapy: 0 (0–4) After infliximab therapy: 0 (0-6)	NR	
Sprakes 2012[46]	UK	Infliximab-Continuation	173	Intestinal resection	13 (7.5)	NR	NR	
Sakurab a 2013[47]	USA	Natalizumab	49	Colectomy - 1 patient who discontinued natalizumab after developing malignancy	14/25 (56) who discontinued natalizumab required surgical therapy	NR	NR	
Zorzi 2012[48]	Italy	Infliximab	44	NR	Induction: No response requiring urgent surgery after week 2 in 2 (4.5%) Maintenance: 3/5 patients with LOR required surgical resection due to refractory disease.	NR	NR	
Zorzi 2012[48]	Italy	Adalimumab	49	NR	Maintenance: 4/8 with LOR required elective surgery	NR	NR	
Reenaer s 2012[7]	Multinational (Belgium and UK)	Induction study	207	NR	NR	NR	NR	
Reenaer s	Multinational (Belgium and	Maintenance study:	181	NR	Semesters: Adalimumab monotherapy:	NR	NR	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
2012[7]	UK)	Patients treated 12 months with adalimumab			Surgery 12 (7) Adalimumab+IS: Surgery 6 (19), (p=0.06)			
Reenaers 2012[7]	Multinational (Belgium and UK)	Maintenance study: Patients treated with Adalimumab +IS during the 1st semester	45	NR	Abdominal surgery (n=3): 7%	NR	NR	
Waters 2012[24]	USA	Infliximab	182	NR	Pre- vs. Post-Infliximab: 54 (29.7) vs. 18 (9.9), p<0.0001	NR	NR	
Poza 2012[49]	Spain	One patient received more than one therapy:Antibiotics, Thiopurines, Infliximab, Adalimumab, Surgery, Second surgery	47 (Antibiotics - 28, Thiopurines- 38, Infliximab- 30, Adalimumab- 4, Surgery- 18, Second surgery- 4	Seton placement and drainage of associated abscesses, fistuloraphia or fistuloplastia, with advancement flaps, and ileostomy.	Surgical therapy was attempted in 18 patients. Five were treated with seton placement and drainage of associated abscesses, five patients with fistuloraphia or fistuloplastia, four with advancement flaps, and two with a definitive ileostomy.	NR	NR	
Cohen 2012[13]	USA	Adalimumab	75	NR	Out of 75, 31 patients who required dose escalation, of these 31, 19 (61%) required surgery Out of 75, 44 patients who did not require dose escalation, 29 (66%) required surgery	NR	NR	
Katz 2012[50]	Europe, USA, and Israel	Infliximab: 10 mg/kg/8w	112	NR	NR	NR	NR	Previous intestinal surgery: 10 mg/kg/8w: 41/112 (43)
Katz 2012[50]	Multinational (Europe, USA,	Infliximab: 5 mg/kg/4w	56	NR	NR	NR	NR	Previous intestinal surgery: 10 mg/kg/8w: 15/56 (32)

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
	and Israel)							
Bultman 2012[9]	Netherlands	Adalimumab	122	NR	NR	NR	NR	Previous resection: 52 (43%)
Sprakes 2012[46]	UK	Infliximab-Induction	210	Intestinal resection	7 (3.3)	NR	NR	Previous Crohn's-related surgery: 131 (62.4) Major abdominal surgery: 99 (47.1) Examination under anaesthesia: 43 (20.5) N1 surgical intervention: 70 (33.3)
Chaparro 2012[51]	Spain	Adalimumab	380 Anti-TNF naïve: 120 Anti-TNF experienced: 260	NR	NR	NR	NR	Previous surgery, n (%) Overall: 178 (47) Anti-TNF naïve: 39% Anti-TNF experienced: 51%
Chaparo 2012[52]	Spain	Infliximab	33	NR	Among 6/13 patients with partial response to intensified regimen Surgery: 2/6 (66.67)	NR	NR	Previous surgery: 19 (58)
Chaparro 2011[53]	Spain	Infliximab	309	NR	NR	NR	NR	Previous surgery: 87 (63)
Haveran 2011[54]	USA	Infliximab only; AZA/6-MP only; Both Infliximab/(AZA/6-MP)	22 (Infliximab only- 4; AZA/6-MP only- 8; Both Infliximab/(AZA/6-MP)- 9; lost to follow up-	NR	NR	NR	NR	Before institution of either AZA/6-MP or IFX Fistulising patient group: required an average of 3.9 surgical procedures per patient After treatment this fell to 0.5 per fistulising patient (although 6 patients had received stomas). In the remaining patients

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
			1)					with stricture and severe pouchitis (8 total), 4 operations were required before institution of AZA/6-MP (and one patient with IFX) therapy and no surgeries were required after therapy.
Leombruno 2011[55]	Canada	Infliximab users	338	NR	CD-related intra-abdominal surgery during the observation period: 34 (10.1)	NR	NR	
Leombruno 2011[55]	Canada	Infliximab non-users	670	NR	CD-related intra-abdominal surgery during the observation period: 112 (16.7)	NR	NR	
Cordero-Ruiz 2011[6]	Spain	Adalimumab	25	NR	2 (8)	NR	NR	Previous intestinal surgery: 8/25 (32%)
Sprakes 2011[56]	UK	Adalimumab	44	NR	7/9; among 9 non-responders 7 patients required surgery	NR	NR	20(45.5%) patients underwent previous CD-related surgery
Alzafiri 2011[27]	Canada	Infliximab	55	NR	5 (9.09)	NR	NR	17 (24%) CD patients underwent surgery any time prior to infliximab
Fortea-Ormaechea 2011[15]	Spain	Adalimumab	174	NR	NR	NR	NR	Previous surgery: Resections: 48 (27.6) Perianal: 17 (9.8) Combination of both: 22 (12.6) Not defined: 17 (9.8)
Billioud 2011[57]	France	Adalimumab	108	NR	NR	NR	NR	Previous surgery, n (%) Small intestine resection: 35 (32.4) Colonic resection: 29 (26.9) Perineal surgery: 21 (19.4)
Nugent 2010[58]	Canada	Infliximab	126	Thirty-eight percent of infliximab and	NR	NR	NR	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
				26 % of azathioprine subjects had gastrointestinal surgery before being prescribed infliximab or azathioprine, respectively (p=0.011).				
ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Placebo	261 (139 entered ADHERE)	NR	ADHERE: 1/261 (0.4) Overall in 2 years: 22/261 (8.4)	NR	NR	
ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Adalimumab eow	260 (144 entered ADHERE)	NR	ADHERE: 4/260 (1.5) Overall in 2 years: 14/260 (5.4)	NR	NR	
ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Adalimumab weekly	257 (184 entered ADHERE)	NR	ADHERE: 5/257 (2) Overall in 2 years: 14/257 (5.4)	NR	NR	
Allez 2010[60]	Multinational (France, Belgium, Switzerland, European centres (Leuven, Roma))	Certolizumab pegol/Adalimumab	40/27	NR	NR	NR	NR	Previously 31 (46%) patients underwent surgery.
Sprakes 2010[61]	UK	Infliximab	100	Intestinal resections and examinations under	60/100 patients had undergone at least one previous surgical intervention (either intestinal resection or	1 previous operation: 24 >1 previous operation: 36	NR	Number of acute surgical admissions Pre-infliximab: 34 Post-infliximab: 5

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
				anesthesia (EUAs)	EUA) at some point following their initial diagnosis, and prior to the commencement of infliximab therapy, with 36 (60%) of these having had more than one operation.			Mean length of stay per surgical admission (days) Pre-infliximab: 7 Post-infliximab: 9
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	Certolizumab (Induction)	539	NR	NR	NR	NR	Number of resections; 0: 294 (54.5) 1: 120 (22.3) 2: 77 (14.3) 3: 28 (5.2) >3: 20 (3.7)
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	Certolizumab (every 2 week, maintenance)	161	NR	NR	NR	NR	Number of resections; 0: 82 (50.9) 1: 41 (25.5) 2: 26 (16.1) 3: 8 (5.0) >3: 4 (2.5)
WELCOME trial (Sandborn	Multinational (Austria, Belgium, Canada,	Certolizumab (every 4 week, maintenance	168	NR	NR	NR	NR	Number of resections; 0: 96 (57.1) 1: 46 (27.4) 2: 14 (8.3)

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
2010)[10]	Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	)						3: 8 (4.8) >3: 4 (2.4)
Swoger 2010[11]	USA	Adalimumab	118	NR	34 (29) patients underwent 45 separate surgical interventions	1 year cumulative probability of surgery: 26.6% (95% CI: 16.9-35.7)	NR	25 (21%) reported total of 36 CR related intestinal complications.
Stein 2010[62]	USA	Infliximab	Prior Irregular (PI) Exposure, n=40	CD-related surgeries	NR	Rates of CD-related surgeries: 48.7% First year: 12.5% Second year: 20% Third year: 15%	NR	CD-related surgeries prior to infliximab initiation: 55%. CD-related medical hospitalisations prior to infliximab initiation: 37.5%.
Stein 2010[62]	USA	Infliximab	Scheduled Maintenance (SM), n=64		NR	Rates of CD-related surgeries: 21.8, *p*=0.004 First year: 9.3% Second year: 10.9% Third year: 1.6%	NR	CD-related surgeries prior to infliximab initiation: 60.9%. CD-related medical hospitalisations prior to infliximab initiation: 35.9%.
Echarri 2010[17]	Spain	Adalimumab	16	NR	NR	NR	NR	Two patients had undergone perianal surgery.
Hamzaoglu 2010[63]	USA	Infliximab without Immunosuppressants	160	NR	NR	NR	NR	In all, 152 patients (51%) had prior bowel resection for CD.
Taxonera 2009[64]	Spain	Infliximab	Luminal CD: 84	NR	NR	NR	NR	Overall, 21.6% of the patients had been hospitalised and undergone surgery during the pre-IFX period (34.8% fistulising and

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
								10.7% luminal).
Ho 2009[19]	Scotland	Adalimumab	98	Total colectomy, end-ileostomy	20 (20.4)	NR	NR	36 (36.7%) patients had previous surgical resections including 11 (11.2%) with total colectomy and end-ileostomy, 17 (17.3%) with more than two small bowel resections and 7 (7.3%) with multiple perianal abscess and fistulae requiring surgical treatment.
Ho 2008[12]	UK	Adalimumab	22	NR	6 (27)	NR	NR	Three patients had surgery (two colectomies, one small bowel resection) prior to initiation of adalimumab.
Schluender 2007[65]	USA	Study cohort	151	A complete mucosectomy and temporary diverting ileostomy were both performed in all patients.	Ileal pouch-anal anastomosis (IPAA): 112 (74) Subtotal colectomy (STC): 39 (36)	NR	Overall postoperative complications: 43/151 (28) Medical complications: Major: 8 patients (pneumonia - 3, deep vein thrombosis - 2, pancreatis -1, acute renal failure - 1, cerebrovascular accident - 1) Minor: 6 patients (dehydration - 3, superficial thrombophlebitis - 1, pyoderma gandrenosum - 1, urinary retention - 1) Surgical complications: Major: 14 (readmission for small bowel obstruction - 9, large peristomal abscess - 2,	Median length of stay after surgery was 6 (3-22) days Influence of Infliximab with Other Immunosuppressive Agents (1) Complications in the 6MP/Infliximab Patient Subsets (a) 6MP + Infliximab No of patients: 16 Overall complications: 6 (38) Medical complications: 2 (13) Major - 0 Minor - 2 Surgical complications: 4 (25) Major - 2 Minor - 2 Infectious complications: 2 (13) (b) 6MP - Infliximab No of patients: 59

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
							major bleeding requiring reoperation - 1, infected pyoderma gangrenosum requiring surgical debridement - 1, rectal stump leak - 1) Minor: 15 (superficial wound infection - 8, ileus - 5, minor bleeding requiring transfusion - 1) Infectious complications: 14 patients	Overall complications: 25 (42), *p*=1 Medical complications: 7 (12), *p*=1 Major - 2 Minor - 5 Surgical complications: 18 (31), *p*=0.76 Major - 9 Minor - 9 Infectious complications: 8 (14), *p*=1 (2) Complications in the CsA/Infliximab Patient Subsets (a) CsA + Infliximab No of patients: 5 Overall complications: 4 (80) Medical complications: 1 (20) Major - 0 Minor - 1 Surgical complications: 3 (60) Major - 1 Minor - 2 Infectious complications: 3 (60) (b) CsA - Infliximab No of patients: 56 Overall complications:16 (29), *p*=0.04 Medical complications: 5 (9), *p*=0.41 Major - 4 Minor - 1 Surgical complications: 11 (20),*p*=0.08 Major - 5

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
								Minor - 6 Infectious complications: 7 (13), *p*=0.03
Schluender 2007[65]	USA	With Infliximab	17	A complete mucosectomy and temporary diverting ileostomy were both performed in all patients.	IPAA: 15/17 (88) STC: 2/17 (12)	NR	Medical complications: 1/17 (6) Surgical complications: 5/17 (30) Infectious complications: 3/17 (18) Postoperative complications noted after initial subtotal colectomy (STC) or ileal pouch-anal anastomosis (IPAA): Initial STC: 1/2 (50) IPAA: 5/15 (33)	
Schluender 2007[65]	USA	Without Infliximab	134	A complete mucosectomy and temporary diverting ileostomy were both performed in all patients.	NR		Medical complications: 13/134 (10) Surgical complications: 24/134 (18) Infectious complications: 11/134 (8) Postoperative complications noted after initial subtotal colectomy (STC) or ileal pouch-anal anastomosis (IPAA): Initial STC: 7 (19) IPAA: 30 (31)	
Saro 2007[66]	Spain	Infliximab	34	NR	Pre- vs. Post-Infliximab, per year, Mean (CI); Overall surgeries: 0.335 (0.158–0.511) vs. 0.105	NR	NR	

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
					(0.011–0.198), *p*=0.004 Specific Perineal abscess drainage: 0.199 (0.041–0.356) vs. 0.012 (0–0.029), *p*=0.004 Terminal ileum resection: 0.039 (0–0.080) vs. 0.015 (0–0.046), *p*=0.249 Ileo-colic resection: 0.009 (0–0.018) vs. 0.004 (0–0.012), *p*=0.500 Abdominal-perineal resection of rectum-sigmoid: 0.009 (0–0.026) vs. 0.000 Laparotomy: 0.010 (0–0.023) vs. 0.000 Fistulectomy: 0.028 (0–0.073) vs. 0.015 (0–0.043), *p*=0.593 Partial colectomy: 0.003 (0–0.08) vs. 0.006 (0–0.017), *p*=0.655 Others: 0.039 vs. 0.052			
Jewell 2005[67]	UK	Infliximab	202	NR	NR	NR	NR	Number of patients who had resectional surgery prior to study period: 100 (49%)
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Placebo (Episodic strategy)	188	NR	14/188 (7.4)	NR	NR	Previous segmental resection: 95/188 (51)
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Infliximab 5 mg/kg (Scheduled strategy)	192	NR	5/193 (2.5), *p*=0.04 vs. placebo	NR	NR	Previous segmental resection: 100/192 (52)

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Infliximab 10 mg/kg (Scheduled strategy)	193	NR	6/192 (3.1), *p*=0.07 vs. placebo	NR	NR	Previous segmental resection: 96/193 (48)
ACCENT II Trial (Sands 2004)[69]	Multinational (North America, Europe, and Israel)	Placebo maintenance	Evaluable N=99 (Responders at the time of randomisation) (Total randomised N=143)	Major surgeries: Resection of the bowel Fistula resection or fistulotomy Ostomy placement or revision	NR	NR	NR	Previous segmental resection in responders: 54/99 (55) Previous segmental resection in overall non-responders (N=87): 47/87 (54) The most frequently occurring major surgeries were resection of the bowel (8), fistula-related surgeries (fistula resection or fistulotomy (3), and Ostomy placement or revision (5).
ACCENT II Trial (Sands 2004)[69]	Multinational (North America, Europe, and Israel)	Infliximab maintenance	Evaluable N=96 (Responders at the time of randomisation) (Total randomised N=139)	Major surgeries: Resection of the bowel Fistula resection or fistulotomy Ostomy placement or revision	NR	NR	NR	Previous segmental resection in responders: 55/96 (57) Previous segmental resection in overall non-responders (N=87): 47/87 (54) The most frequently occurring major surgeries were resection of the bowel (1), fistula-related surgeries (fistula resection or fistulotomy (2), and Ostomy placement or revision (0).
Vermeire 2002[70]	Belgium	Infliximab	Refractory CD, n=137	NR	NR	NR	NR	Previous abdominal surgery: 51 (37.2)

Study name	Countries	Treatment groups	No. of patients	Most common surgeries performed for CD	No of patients receiving surgery, and type of surgery n (%)	No. of surgeries in one year/ 5 years/ 10 years/ lifetime for CD and UC	Incidence of complications from the surgery types	Comments
Vermeire 2002[70]	Belgium	Infliximab	Fistulising CD, n=103	NR	NR	NR	NR	Previous abdominal surgery: 31 (30.1)
Arnott 2001[71]	UK	Infliximab	39	NR	Of the eight who did not respond, 3 had surgical resection	NR	NR	20 out of the 39 patients had undergone previous surgical resections
Arnott 2001[71]	UK	Infliximab	6	NR	When assessed at 4 weeks, of the two patients who did not respond 1 had surgery.	NR	NR	All 6 patients had undergone previous surgical resections

Section 3. Adverse events

3A. Data on adverse events in ulcerative colitis

Data for any AEs, serious AEs and withdrawals for UC patients are reported in Table S5.

The occurrence of any AEs was 7.1% (Gies 2010[31]) to 91% (ACT 1 [Sandborn 2009[34]]) in UC patients treated with infliximab and 4% (Gies 2010[31]) to 82.9% ULTRA 2 Trial [Sandborn 2013[72]]) in UC patients treated with adalimumab.

In ULTRA 2 Trial (Sandborn 2013[72] and Sandborn 2012[73]), 39.3% patients experienced AEs related to adalimumab. A total of 36.4% patients discontinued this study. A significantly high proportion of adalimumab treated patients experienced injection-site reactions compared to placebo (31 [12.1%] versus 10 [3.8%], p<0.001). In another study (Rostholder 2012[25]), a total of 10% patients experienced infusion reactions related to infliximab.

Table S5. Adverse events in ulcerative colitis

Study name	Countries	Treatment groups	No. of patients	Any adverse events (n, %)	Serious adverse events (n, %)	Adverse events related to treatment (n, %)	Total withdrawals (due to lack of tolerance to treatment/any adverse events/ serious adverse events related to inadequate treatment response)	Comments
ULTRA2 Trial (Sandborn 2013)[72]	Multinational (North America, Europe, Australia, New Zealand, and Israel)	Adalimumab	257	213 (82.9)	31 (12.1)	101 (39.3)	Discontinuation: 94 (36.4) Reasons for discontinuation: n (%) Lack of efficacy: 63 (24.4) Adverse events: 12 (4.6) Withdrew consent: 8 (3.1) Lost to follow-up: 1 (0.3) Protocol violation: 1 (0.3) Other: 9 (3.4)	
ULTRA2 Trial (Sandborn 2013)[72]	Multinational (North America, Europe, Australia, New Zealand, and Israel)	Placebo	260	218 (83.8)	32 (12.3)	86 (33.1)	Discontinuation: 115 (44.2) Reasons for discontinuation: n (%) Lack of efficacy: 70 (26.9) Adverse events: 25 (9.6) Withdrew consent: 4 (1.5) Protocol violation: 5 (1.9) Other: 11 (4.2)	

Chaparro 2012[23]	Spain	Infliximab	47	11 (23)	NR	NR	Of the 37 patients with an initial response to infliximab, 12 discontinued after a median of 10.5 months (range 1–20 months).	Seven patients discontinued infliximab after the second infusion. Patients who discontinued infliximab remained on thiopurines.
Mocciaro 2012[3]	Italy	Cyclosporine	35	1 (2.9)	0	NR	NR	
Mocciaro 2012[3]	Italy	Infliximab	30	6 (20)	0	NR	Total withdrawals: 6 due to adverse events	
Rostholder 2012[25]	USA	Infliximab	50 (maintenance cohort)	NR	NR	Infusion reactions: 5/50 (10) Mild: 4/5 Acute: 3/5	NR	
Laharie 2012[26]	Multinational (France, Spain, Belgium, and Finland)	Ciclosporin	58	NR	9 (16)	NR	NR	
Laharie 2012[26]	Multinational (France, Spain, Belgium, and Finland)	Infliximab	57	NR	14 (25)	NR	NR	
Oussalah 2010[28]	France	Infliximab	191	53 (27.8)	13 (6.8)	NR	Number of adverse events leading to infliximab withdrawal 6 (3.1)	
Herrlinger 2010[29]	Germany	Infliximab	24	8 (66.7)	2 (8.3)	NR	2 (8.3) adverse events were judged as severe (allergic reaction and viral pneumonia) and therapy with infliximab was stopped.	
Jurgens 2010[30]	Germany	Infliximab	90	9/90 (10)	NR	Side effects likely to be related to IFX treatment were arthralgia (n= 2), nausea and vomiting (n= 4), and viral respiratory infection (n = 3). Allergic infusion reaction: 9/90 (10)	In one case, delayed IFX-induced reaction was observed to appear as generalised exanthema. Therefore, IFX therapy was discontinued in this patient (after receiving a total number of nine IFX infusions).	

Taxonera 2011[4]	Spain	Adalimumab	30	6 (20)	NR	NR	15 (50)	
Tursi 2010[74]	Italy	Infliximab	23	2 (8.69)	NR	NR	NR	One patient (4.34%)affected by left-sided colitis experienced headache, not requiring suspension of the treatment; another-one patient affected by pancolitis developed sepsis by *Proteus* strain, requiring stopping treatment and colectomy.
Gies 2010[31]	Canada	Adalimumab (Induction)	25	1 (4)	NR	NR	NR	
Gies 2010[31]	Canada	Infliximab (Induction)	28	2 (7.1)	NR	1 (3.5)	NR	
Gies 2010[31]	Canada	Adalimumab (Maintenance)	20	NR	NR	NR	NR	
Gies 2010[31]	Canada	Infliximab (Maintenance)	18	3 (33.3)	NR	1 (5.5)	NR	
Afif 2009[1]	USA	Adalimumab	20	17 (85)	6 (30)	0 (0)	Nine patients with adverse events withdrew from the trial.	
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand,	ACT 1 trial: Placebo	121	103 (85.1)	31 (25.6)	Data was reported for adverse events occurring in >10% of any treatment group.	57	

	Switzerland, UK)						
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 1 trial: 5 mg Infliximab	121	106 (87.6)	26 (21.5)	Data was reported for adverse events occurring in >10% of any treatment group.	39
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 1 trial: 10 mg Infliximab	122	111 (91)	29 (23.8)	Data was reported for adverse events occurring in >10% of any treatment group.	39
Sandborn 2009[34]	Multinational (USA, Argentina, Australia,	ACT 2 trial: Placebo	123	90 (73.2)	24 (19.5)	Data was reported for adverse events occurring in >10% of any treatment group.	50

	Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)						
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 2 trial: 5 mg Infliximab	121	99 (81.8)	13 (10.7)	Data was reported for adverse events occurring in >10% of any treatment group.	24
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France,	ACT 2 trial: 10 mg Infliximab	120	96 (80)	11 (9.2)	Data was reported for adverse events occurring in >10% of any treatment group.	24

	Germany, Israel, Netherlands, New Zealand, Switzerland, UK)							
Maser 2008[36]	USA	Infliximab-salvage	10	NR	Sepsis and died: 1/10 (10)	NR	NR	Adverse events were attributed to acute salvage therapy if they occurred within 4 weeks of receiving the salvage drug and if they were thought to be caused by immune suppression or known metabolic toxicities of either cyclosporine or infliximab.
Maser 2008[36]	USA	Ciclosporine -salvage	9	Minor adverse events: 3/9 (33.33) Fatigue, leg cramps, weakness - 1 patient Fatigue and tingling in fingers - 1 patient Nonproductive cough for 3 weeks after cyclosporine salvage without evidence of infection - 1 patient	Herpetic esophagitis: 1/9 (11.1) Pancreatitis and bacteraemia: 1/9 (11.1)	NR	NR	
Oussalah 2008[2]	France	Adalimumab	13	5 (38.5) Adverse events Labial herpes and arthralgia: 1 Psoriasis de novo: 1 Erysipelas: 1 Urinary tract	0 (0)	NR	ADA Withdrawal due to adverse event (exacerbation of psoriasis): 1/13 (7.69)	

				infection: 1 Exacerbation of psoriasis: 1				
Gornet 2003[38]	France	Infliximab	30	9/30 (30) These patients experienced adverse events during the follow-up period	NR	NR	NR	Infection - 4 (13) Cutaneous herpes -2 (7) (1 case associated with keratitis) Oesophageal candidosis and a superinfection of colitis by cytomegalovirus - 1 (3) Bronchitis requiring a short hospitalization 4 months after the infliximab infusion - 1 (3) Minor adverse events possibly related to infliximab Headache: 1 (3) Delayed urticaria: 1 (3)
Probert 2003[39]	Multinational (UK and Germany)	Placebo group	20	NR	Two serious adverse events, which qualified as life threatening or severe, were recorded. One patient suffered septic complications. Another underwent colectomy because of toxic exacerbation and spontaneous perforation.	NR	NR	
Probert 2003[39]	Multinational (UK and Germany)	Infliximab group	23	NR	NR	NR	NR	All other serious adverse events were rated as mild and were not significantly different in frequency between infliximab and placebo treated patients.

								No significant infusion reactions were seen.
Steenholdt 2013[75]	Denmark	Infliximab: UC patients in remission	10	NR	NR	Infusion reaction to infliximab: 0 (0)	NR	
Steenholdt 2013[75]	Denmark	Infliximab: UC patients not in remission	12	NR	NR	Infusion reaction to infliximab: 3 (25)	NR	
Cottone 2011[76]	Italy	UC (Elderly patients treated with biologics)	37	Eleven severe infections (4 cases of pneumonia, 2 abscesses, 2 severe sepsis, 1 case of tuberculosis, 1 case of aspergillosis, and 1 case of interstitial pneumonia) and 3 cancers (rectal cancer, prostatic cancer, and basal cell carcinoma) were reported.	NR	NR	NR	
Cottone 2011[76]	Italy	UC (Adult matched control subjects treated with biologics)	74	Thirteen (7%) minor infections, no neoplasms, and 2 (1%) deaths (due to postoperative complications) were also observed.	NR	NR	NR	
Cottone 2011[76]	Italy	UC (Elderly control subjects not treated with biologics)	74	NR	NR	NR	NR	

3B. Data on adverse events in Crohn's Disease

Data for any AEs, serious AEs and withdrawals for CD patients are reported in Table S6.

The range of reported AE data was generally wide, reflecting significant variation in the nature and design of the various clinical studies (different sample sizes, study designs and follow-up periods) and in the time points of assessment (e.g. induction versus maintenance stages of treatment). The wide variation in AEs could also be due to the difference in type of AEs as reported in the studies.

Any AEs occurred in 7.69% (Tursi 2010[74]) to 94.6% (Rutgeerts 1999[77]) of CD patients treated with infliximab and in 0.5% (1 out of 181 patients; Reenaers 2012[7]) to 96.3% (251 out of 261 patients; CHARM trial [Colombel 2009[78]]) of CD patients treated with adalimumab. The lower limit, 0.5% (1 out of 181 patients) was a severe AE from a retrospective study evaluating adalimumab maintenance therapy for 12 months (Reenaers 2012[7]). The higher limit, 96.3% (251 out of 261 patients) was for any AEs from a RCT evaluating the safety profile of adalimumab induction therapy over 56 weeks (in this study, AEs occurred when patients switched to open-label therapy) (CHARM [Colombel 2009[78]]). If this study (Reenaers 2012[7]) is excluded from the qualitative reporting, the lower range changes to 12.6% with adalimumab therapy for any AEs (Chapparo 2012[51]).

In the CARE trial (Louis 2013[5]), 19.2% of patients experienced serious AEs, which may be attributable to the disease severity of included patients (moderate to severe). Among the serious AEs reported in this study, the most common serious infections were abscesses. A total of 47.3% of patients experienced AEs related to adalimumab. A total of 17% patients withdrew from the study. In the ACCESS-trial (Panaccione 2011[14]), a total of 47.4% patients experienced AEs related to adalimumab.

In the WELCOME trial (Sandborn 2010[10]), 7.4% patients experienced serious AEs with certolizumab induction therapy, 10.8% patients experienced AEs related to certolizumab maintenance therapy administered every two weeks and 12.8% patients experienced AEs related to certolizumab maintenance therapy administered every four weeks.

Table S6. Adverse events in Crohn's Disease

Study name	Countries	Treatment groups	No. of patients	Any adverse events (n, %)	Serious adverse events (n, %)	Adverse events related to treatment (n, %)	Total withdrawals (due to lack of tolerance to treatment/any adverse events/ serious adverse events related to inadequate treatment response)	Comments
CARE Trial (Louis 2013)[5]	Multinational (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, UK)	Adalimumab	945	754 (79.8)	181 (19.2)	447 (47.3)	160 (17) Reasons for discontinuation: n (%) Adverse events: 57 (6) Lack of efficacy: 54 (5.7) Protocol violations: 24 (2.5) Other reasons: 14 (1.5) Withdrew consent: 8 (0.8) Lost to follow-up: 2 (0.2) Administrative: 1 (0.1)	
Lindsay 2013[42]	UK	Infliximab	380	NR	10 (2.6)	NR	NR	25 infusion-related SAEs were experienced by 10 patients during the study. 6 cancer-related SAEs 8 infection-related SAEs
Seminerio 2013[45]	USA	Infliximab	492	Infectious adverse events with infliximab treatment, n (%) Major Septic shock: 3 (0.6) Septicemia: 6 (1) Abscess (abdominal or pelvic) 1 Abscess: 47 (10) 2 Abscesses: 8 (2) 3 Abscesses: 1 (0.2) Tuberculosis: 0 (0) Other mycobacterial infection: 1 (0.2)	NR	NR	NR	All adverse events were compiled over the entire study period but counted as an adverse event only when they occurred within 12 weeks of infliximab exposure (with the exceptions of malignancy and death, which were captured at any time during follow-up). Therefore, all adverse events noted were considered as being possibly associated with infliximab usage.

				Histoplasmosis: 3 (1) Other fungal infection: 10 (2) Minor Pneumonia: 15 (3) Hepatitis: 2 (0.4) Respiratory tract infection: 19 (4) Escherichia coli infection: 4 (1) Clostridium difficile infection: 4(1) Other bacterial infection: 28 (5) Herpes viral infection: 8 (2) Other viral infection: 8 (2) Candidiasis: 8 (2)				
Sakuraba 2013[47]	USA	Natalizumab	49	9 (18.4)	5 (10.2)	NR	25 (51)	No patient discontinued treatment because of infusion reactions. Adverse reactions to Natalizumab: Serious infections: 2/49 (4) Recurrence of herpes simplex virus meningitis: 1/49 (2) Sepsis: 1/49 (2) Mild immediate hypersensitivity infusion reactions: 4/49 (8)
Zorzi 2012[48]	Italy	Infliximab	44	NR	Induction: 13 (29.5) Maintenance: 5/33 (15.2)	NR	Induction, Total withdrawals: 10; No response: 2 Severe adverse events: 8 (18.2) Maintenance, Total withdrawals: 10; LOR: 5 (15.2) Severe adverse events: 5 (15.2)	
Zorzi 2012[48]	Italy	Adalimumab	49	One patient developed herpes zoster infection.	Induction: 0 (0) Maintenance:	NR	Induction, Total withdrawals: 0; Maintenance, Total withdrawals: 16 (32.7); LOR: 8 (24.2) Delayed hypersensitivity reaction:	

					1/33 (6.1)		1 (2) Herpes Zoster Infection: 1 (2) Dysplasia of uterine cervix: 1(2) Lost to follow-up, ectopic pregnancy, remission while on combined azathioprine, low compliance or pregnancy, patients decision: 5 (10.2)	
Reenaers 2012[7]	Multinational (Belgium and UK)	Induction study	207	0	NR	NR	NR	
Reenaers 2012[7]	Multinational (Belgium and UK)	Maintenance study: Patients treated 12 months with ADA	181	1 (0.5)	NR	NR	NR	
Reenaers 2012[7]	Multinational (Belgium and UK)	Maintenance study: Patients treated with ADA+IS during the 1st semester	45	1 (2)	NR	NR	NR	
Chaparro 2012[79]	Spain	Infliximab	15	2 (13.3)	NR	NR	NR	Adalimumab discontinuation in 3 patients due to AE
Sprakes 2012[46]	UK	Infliximab	210	59 (28.1)	NR	NR	During induction therapy Total withdrawals, n=37; Primary non-response: 18 Intolerable adverse events: 10 Other reasons: 9 During continuation therapy Total withdrawals, n=59; Secondary non-response: 32 Intolerable adverse events: 18 Malignancy: 3 Reactivation of varicella zoster: 2	Infections: 14 (6.7)

							Other reasons: 4	
Chaparro 2012[51]	Spain	Adalimumab	380 Anti-TNF naïve: 120 Anti-TNF experienced: 260	Overall: 48 (12.6) Anti-TNF naïve: 15/120 (12) Anti-TNF experienced: 33/260 (12.7)	NR	NR	Overall: 12 (5.5) Anti-TNF naïve: 9/120 (7) Anti-TNF experienced: 12/260 (4.6)	
Chaparo 2012[52]	Spain	Infliximab	33	Herpes zoster infection: 1/33 (3) Infusion reaction after 36 doses: 1/33 (3)	NR	NR	NR	
Barreiro-de-Acosta 2012[80]	Spain	Adalimumab	42	NR	NR	4 (9.4): 2 (4.7) due to advents related to adalimumab, 2 (4.7) due to absence of CD response after 10 weeks.	NR	
TREAT registry (Lichtenstein 2012)[81]	Multinational (USA and Canada)	Infliximab	3420	NR	NR	NR	1819 (53.2)	Of the 3,420 registry patients in the infliximab-treated group, 3,322 had data available for assessment of infusion reactions. Three percent (1,571 / 53,003) of infliximab infusions were associated with an infusion reaction; 0.047 % of reactions were serious. Number of patients (number of events) Neoplasia: 3,764 (139) Mortality: 3,764 (109) Serious infection:3,420 (333) Serious infection according to infliximab exposure within the previous 3 month: 2,942 (163)
TREAT registry (Lichte	Multinational (USA and Canada)	Other treatments only	2853	NR	NR	NR	1744 (61.1)	Number of patients (number of events) Neoplasia : 4,010 (113) Mortality: 4,113 (82)

nstein 2012)[81]								Serious infection: 4,557 (147) Serious infection according to infliximab exposure within the previous 3 months: 5,597 (317)
ACCESS-trial (Panaccione 2011)[14]	Canada	Adalimumab	304	242 (79.6)	44 (14.4)	144 (47.4)	Total withdrawals, n= 50: Adverse events: 33 (10.9) Withdrew consent: 6 Lost to follow-up: 2 Other reasons: 17	Infections: 90 (29.6)
Cordero-Ruiz 2011[6]	Spain	Adalimumab	25	5 (20)	2 (8)	NR	In 5 patients (20%) adverse events were observed, leading to drug withdrawal in 2 cases (8%). In 4 out of 25 patients (16%), ADA was suspended before the end of the follow-up period.	
Sprakes 2011[56]	UK	Adalimumab	44	9 (20.5)	NR	NR	Nine (20.5%) patients were classified as primary non-responders to adalimumab, and one patient had adalimumab therapy withdrawn during induction due to an adverse event (a hypersensitivity reaction).	
Alzafiri 2011[27]	Canada	Infliximab	71	NR	NR	NR	NR	
Fortea-Ormaechea 2011[15]	Spain	Adalimumab	174	32 (18.4)	7 (21)	NR	Drug discontinuation due to serious adverse events: 7 (21%), anaphylactic reaction: 2, psoriasis and loss of consciousness: 2	NR
Oussalah 2010[82]	France	Infliximab	48	NR	NR	NR	NR	3 of 48 developed infliximab intolerance, data already entered in first failure tab.
ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Placebo	261 (139 entered ADHERE)	NR	NR	NR	NR	Adverse events were reported in 94.1% (804) of patients, 25.6% (219) of patients experienced a serious adverse event and 20.4% (174) of patients discontinued from the study because of an adverse event.

ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Adalimumab eow	260 (144 entered ADHERE)	NR	NR	NR	NR	
ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Adalimumab weekly	257 (184 entered ADHERE)	NR	NR	NR	NR	
Allez 2010[60]	Multinational (France, Belgium, Switzerland, European centres (Leuven, Roma))	Certolizumab pegol/Adalimumab	40/27	16 (24)	5 (7)	NR	Total: 10 (15); Cardiac failure: 1 (1.5), Severe pulmonary infection: 1 (1.5), Perianal abscess: 1 (1.5), Inflammatory skin disorder: 4 (6), Immediate hypersensitivity: 1 (1.5), Delayed hypersensitivity: 1 (1.5), Cough: 1 (1.5), Diarrhea, Nausea: 1 (1.5)	Data reported for combined population receiving third line therapy (N=67).
Tursi 2010[74]	Italy	Infliximab	39	3 (7.69)	NR	NR	NR	Two patients (5.13% of overall treated patients) experienced mild side-effects (one headache and one somnolence) not requiring suspension of the treatment; one patient experienced severe side-effects (cholestasis) at 12th month of treatment, requiring stopping treatment.
Waugh 2010[83]	Canada	Infliximab	48 (patients who discontinued infliximab)	7/43 (16)	NR			
Sprakes 2010[61]	UK	Infliximab	100	NR	NR	NR	At 12 months: 10/100 (10) discontinued therapy due to intolerable adverse events	
CHOICE-trial (Lichtig	USA	Adalimumab	673	NR	88 (13.1)	NR	At baseline: Total withdrawals: 134 (19.9) Adverse event: 28 (4.2)	Infectious SAEs: 22 (3.3)

er 2010)[84]							SAEs: 23 (3.4) Withdrawal of consent: 33 (4.9) Lost to follow-up: 24 (3.6) Other: 38 (5.6)	
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	Certolizumab (Induction)	539	436 (80.9)	40 (7.4)	215 (39.9)	Total discontinuation, n=166 (30.8); Due to loss of efficacy: 121 (22.4) Withdrawal due to adverse events; 37 (6.9) Withdrawn consent: 5 (0.9) Other: 3 (0.6)	Infections: 142 (26.3)
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	Certolizumab (every 2 week, maintenance)	186	145 (78)	20 (10.8)	63 (33.9)	N=161 Total discontinuation, n=34 (21.1); Due to loss of efficacy: 13 (8.1) Withdrawal due to adverse events: 15 (9.3) Withdrawn consent: 4 (2.5) Lost to follow-up: 2 (1.2)	Infections: 81 (43.5)
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	Certolizumab (every 4 week, maintenance)	187	145 (77.5)	24 (12.8)	73 (39)	N=168Total discontinuation, n=20 (12.3); Due to loss of efficacy: 9 (5.4) Withdrawal due to adverse events: 9 (5.4) Withdrawn consent: 0 Other: 2 (2.1)	Infections: 78 (41.7)
Russo 2010[16]	Multinational (England/Ireland)	Adalimumab	61	14 (23)	NR	NR	NR	
Stein 2010[62]	USA	Infliximab	Prior Irregular (PI) Exposure, n = 40	NR	NR	NR	NR	Overall, 12 (8%) of 147 patients had 16 acute infusion reactions. Nine patients developed malignancies during follow-up.
Echarri 2010[17]	Spain	Adalimumab	16	5 (31.25)	NR	NR	1 (no response was achieved with the change of adalimumab to a weekly dose)	
Hamzaoglu 2010[6	USA	Infliximab without Immunosu	160	overall data mentioned in comments	16 (10)	NR	Overall in both the groups: Treatment aborted 33 (11)	Overall data: Any adverse events 99 (33) Serious adverse events 44 (14)

3]		ppressants						The rate of serious adverse events was further analyzed among patients on concomitant immunosuppressants with respect to concomitant 6-MP/AZA therapy (n = 61 patients), concomitant corticosteroids (n =50 patients), and concomitant 6-MP, AZA, and corticosteroid therapy. Infliximab + AZA/6MP: 14 adverse events Infliximab + Steroids: 10 adverse events Infliximab + AZA/6MP + Steroids: 4 adverse events
Hamzaoglu 2010[63]	USA	Infliximab with Immunosuppressants	137	NR	28 (20.4)	NR	Overall in both the groups: Treatment aborted 33 (11)	
CHARM Trial (Colombel 2009)[78]	Multinational (conducted at 92 sites in Europe, the United States, and Canada)	Placebo (Adalimumab induction only/reinitiation)	261	251 (96.3)	70 (26.8)	NR	Total withdrawals: 48; Lost to follow up: 2 Adverse events: 17 Lack of efficacy: 21 Other: 8	
CHARM Trial (Colombel 2009)[78]	Multinational (conducted at 92 sites in Europe, the United States, and Canada)	Adalimumab 40 mg every other week	260	249 (95.8)	45 (17.3)	NR	Total withdrawals: 56; Lost to follow up: 0 Adverse events: 20 Lack of efficacy: 29 Other: 7	
CHARM Trial (Colombel 2009)[78]	Multinational (conducted at 92 sites in Europe, the United States, and Canada)	Adalimumab 40 mg weekly	257	245 (95.3)	44 (17.1)	NR	Total withdrawals: 37; Lost to follow up: 0 Adverse events: 16 Lack of efficacy: 13 Other: 8	
Ho 2009[19]	Scotland	Adalimumab	98	29 (29.6)	8 (8.2)	NR	10 (10.5)	
West 2008[20]	Netherlands	Adalimumab	30	14 (47)	NR	NR	Six patients withdrew treatment due to adverse events.	
Ho	UK	Adalimuma	22	NR	3 (14)	NR	One case of early withdrawal due	A case of locally advanced nonsmall cell

2008[12]		b					to severe injection site pain.	lung cancer developed in a 70-year-old female (34 cigarette pack-years) with CD colitis
GAIN Trial (Sandborn 2007)[85]	Multinational (USA, Canada, Belgium, France)	Adalimumab	159	91 (57)	2 (1)	43 (27)	Total withdrawals: 4; Adverse event: 2 Withdrew consent: 1 Protocol violation: 1	
GAIN Trial (Sandborn 2007)[85]	Multinational (USA, Canada, Belgium, France)	Placebo	166	121 (73)	8 (5)	53 (32)	Total withdrawals: 10; Adverse event: 4 Withdrew consent: 1 Protocol violation: 5	
Peyrin-Biroulet 2007[21]	France	Adalimumab	24	13 (54.2)	0 (0)	NR	Patients discontinued adalimumab therapy: 6/24 (25) LOR: 5⁄6 (83.3) Intolerance 0⁄6 (0) Other (Pregnancy): 1/6 (16.7)	All patients were able to tolerate adalimumab, including six who previously experienced acute or delayed hypersensitivity reactions with infliximab.
Casellas 2007[86]	Spain	Infliximab	49	NR	NR	NR	At 4 year follow-up: 43 (87.8)	
Sands 2007[87]	USA	Placebo+Infliximab	27	Treatment-emergent AEs (adverse events that were newly acquired or that worsened during treatment with natalizumab or placebo): 27/27 (100) Headache: 6 (22) Fatigue: 2 (7) Exacerbation of Crohn's disease: 4 (15) Dizziness: 1 (4) Nasopharyngitis: 3 (11)	1 (4) Serious AE were not related to natalizumab or to infliximab	Serious adverse event was not considered related to study treatment.	4 (14.8) discontinued before completing the trial Out of these, 2/4: remained in the study and completed assessments through week 10, and 2/4: completely withdrew from the study before week 10 Out of these 2, Withdrawal due to AE: 1 patient Voluntary withdrawal: 1 patient	The total safety population comprised all patients who were randomized and had received at least 1 infusion of natalizumab or placebo (N = 79).

				Nausea: 3 (11) DNA antibody positive: 3 (11) Dyspepsia: 1 (4) Abdominal pain: 0 Antinuclear antibody positive: 1 (4) Arthralgia: 2 (7) Back pain: 2 (7) Insomnia: 1 (4) Pyrexia: 0 Upper respiratory tract infection: 1 (4) Note: A patient was counted only once for each type of adverse event AEs associated with infection: 8/27(30)			
Sands 2007[87]	USA	Natalizumab+Infliximab	52	Treatment-emergent AEs (adverse events that were newly acquired or that worsened during treatment with natalizumab or placebo): 48/52 (92) Within 120 minutes of receiving IFX, following reactions were experienced: Mild chest tightness: 1 (2) Mild chest pain: 1 (2)	1 (2) Serious AE were not related to natalizumab or to infliximab	Serious adverse event was not considered related to study treatment.	7 (13.5) discontinued before completing the trial Out of these, 5/7: remained in the study and completed assessments through week 10, and 2/7: completely withdrew from the study before week 10 Out of these 2, Voluntary withdrawal: 1 patient Lost to follow-up: 1 patient

Mild nausea: 1 (2)
Flushing: 3 (6)

There were no hypersensitivity-like reactions reported within 120 minutes of administration of natalizumab.
Headache: 12 (23)
Fatigue: 7 (13)
Exacerbation of Crohn's disease: 5 (10)
Dizziness: 5 (10)
Nasopharyngitis: 5 (10)
Nausea: 5 (10)
DNA antibody positive: 4 (8)
Dyspepsia: 4 (8)
Abdominal pain: 3 (6)
Antinuclear antibody positive: 3 (6)
Arthralgia: 3 (6)
Back pain: 3 (6)
Insomnia: 3 (6)
Pyrexia: 3 (6)
Upper respiratory tract infection:3 (6)

Note: A patient was counted only once for each type of adverse event

AEs associated with infection: 14/52 (27)

Saro 2007[66]	Spain	Infliximab	34	31 adverse events during treatment with infliximab, following 594 infusions of infliximab in the 34 patients.	NR	NR	For 3 patients the treatment with infliximab was discontinued because of adverse events.
Rutgeerts 2006[88]	Multinational (27 centres in 13 countries in North America, Europe, and Asia)	Placebo	37	Patients experiencing at least 1 Adverse event: 26 (70.3)	1 (2.7)	Patients experiencing at least 1 Drug-related adverse event: 19 (51.4) Adverse event possibly related to anti-TNF therapy:12 (32.4)	Withdrawal from the study due to adverse events: 3 (8.1)
Rutgeerts 2006[88]	Multinational (27 centres in 13 countries in North America, Europe, and Asia)	Onercept; 10 mg	44	Patients experiencing at least 1 Adverse event: 31 (70.5)	1 (2.3)	Patients experiencing at least 1 Drug-related adverse event: 25 (56.8) Adverse event possibly related to anti-TNF therapy: 11 (25.0)	Withdrawal from the study due to adverse events: 3 (7)
Rutgeerts 2006[88]	Multinational (27 centres in 13 countries in North America, Europe, and Asia)	Onercept; 25 mg	42	Patients experiencing at least 1 Adverse event: 28 (66.7)	1 (2.4)	Patients experiencing at least 1 Drug-related adverse event: 22 (52.4)	NR

						Adverse event possibly related to anti-TNF therapy: 14 (33.3)		
Rutgeerts 2006[88]	Multinational (27 centres in 13 countries in North America, Europe, and Asia)	Onercept; 35 mg	42	Patients experiencing at least 1 Adverse event: 30 (71.4)	3 (8.6)	Patients experiencing at least 1 Drug-related adverse event: 27 (64.3) Adverse event possibly related to anti-TNF therapy: 12 (28.6)	Withdrawal from the study due to adverse events: 2 (4.8)	
Rutgeerts 2006[88]	Multinational (27 centres in 13 countries in North America, Europe, and Asia)	Onercept; 50 mg	42	Patients experiencing at least 1 Adverse event: 32 (76.2)	NR	Patients experiencing at least 1 Drug-related adverse event: 25 (59.5) Adverse event possibly related to anti-TNF therapy: 16 (38.1)	Withdrawal from the study due to adverse events: 2 (4.8)	
Lemann 2006[89]	France	Failure Stratum (Placebo)	29	Refer comments	NR	NR	NR	The percent of patients who had at least 1 adverse event was 51% (29 of 57) in the infliximab group and 50% (28 of 56) in the placebo group. The frequency of infection was similar in the 2 treatment groups. Of note, 5 serious adverse events were probably or possibly related to

								azathioprine. One patient in the infliximab group had a severe reaction after the second and third infusions (2%).
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Placebo (Episodic strategy)	188	NR	55 (29)	NR	Maintenance treatment Discontinued treatment: 38 (20) Reason for discontinuation Noncompliance: 5 (3) Adverse event: 2 (1) Lack of efficacy: 23 (12) Other: 8 (4) Episodic retreatment (infliximab dosing during episodic retreatment was increased by 5 mg/kg above previous dose) Discontinued treatment: 36 (39) Reason for discontinuation Noncompliance: 10 (11) Adverse event: 3 (3) Lack of efficacy: 16 (17) Other: 7 (8)	
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Infliximab 5 mg/kg (Scheduled strategy)	193	NR	54 (28)	NR	Maintenance treatment Discontinued treatment: 49 (26) Reason for discontinuation Noncompliance: 2 (1) Adverse event: 23 (12) Lack of efficacy: 19 (10) Other: 5 (3) Episodic retreatment (infliximab dosing during episodic retreatment was increased by 5 mg/kg above previous dose) Discontinued treatment: 24 (41) Reason for discontinuation Noncompliance: 4 (7) Adverse event: 5 (9) Lack of efficacy: 9 (16) Other: 6 (10)	One patient assigned to group III (10 mg/kg maintenance dose) actually received 5 mg/kg and was analysed for safety as (group II) infliximab 5 mg/kg.
ACCENT I Trial (Rutgeerts 2004)[6	Multinational (North America, Europe, and Israel)	Infliximab 10 mg/kg (Scheduled strategy)	192	NR	43 (22)	NR	Maintenance treatment Discontinued treatment: 37 (19) Reason for discontinuation Noncompliance: 3 (2) Adverse event: 15 (8)	

8]							Lack of efficacy: 12 (6) Other: 7 (4) Episodic retreatment (infliximab dosing during episodic retreatment was increased by 5 mg/kg above previous dose) Discontinued treatment: 20 (39) Reason for discontinuation Noncompliance: 3 (6) Adverse event: 2 (4) Lack of efficacy: 6 (12) Other: 9 (18)	
ACCENT II Trial (Sands 2004)[69]	Multinational (North America, Europe, and Israel)	Placebo maintenance	144	132 (92)	33 (23)	NR	Adverse events leading to discontinuation of study agent: 12 (8)	
ACCENT II Trial (Sands 2004)[69]	Multinational (North America, Europe, and Israel)	Infliximab maintenance	138	123 (89)	19 (14)	NR	Adverse events leading to discontinuation of study agent: 5 (4)	
Rodrigo 2004[90]	Spain	Infliximab	81	NR	NR	NR	NR	Total 79 episodes of any adverse events No. of patients with adverse events not reported During maintenance treatment intermittent development of antinuclear antibodies (ANA) in 11 of 45 patients (25%) was observed, however, none of them presented a "lupus-like" reaction.
Arnott 2001[71]	UK	Infliximab	39	NR	NR	NR	NR	Other immediate adverse events consisted of short-lived headaches in three patients. This was associated with nausea in one. Adverse events occurring after hospital discharge were a perianal abscess 4 days post-infusion in one patient, and pulmonary infection in the first month post-infusion in two. One patient had a documented urinary tract infection.

Arnott 2001[71]	UK	Infliximab	6	1	NR	NR	NR	
Rutgeerts 1999[77]	Multinational (North America and Europe)	Infliximab	37	35 (94.6)	NR	NR	NR	
Rutgeerts 1999[77]	Multinational (North America and Europe)	Placebo	36	35 (97.2)	NR	NR	NR	
Targan 1997[91]	Multinational (North America and Europe)	Infliximab	102	76 (75)	NR	NR	The 102 patients refers to initial 83 patients + patients 19 non-responder patients in placebo receiving open label infliximab.	
Targan 1997[91]	Multinational (North America and Europe)	Placebo	25	15 (60)	NR	NR	NR	
Steenholdt 2013[75]	Denmark	Infliximab: CD patients in remission	8	NR	NR	Infusion reaction to infliximab: 0 (0)	NR	
Steenholdt 2013[75]	Denmark	Infliximab: CD patients not in remission	21	NR	NR	Infusion reaction to infliximab: 4 (19)	NR	
Pearce 2007[92]	Australia	Infliximab	CD (Luminal alone): 32	NR	NR	NR	NR	No serious adverse effects occurred in any patient with the induction therapy with infliximab. Adverse effects to the infliximab infusions occurred in three patients, one during a single induction dose and two during the three-dose induction course. These were all mild and transitory and required no specific treatment.

Section 4. Resource utilisation

4A.Data on resource utilisation in ulcerative colitis

Data for cost and resource utilisation for UC patients are presented in Table S7.

Resource utilisation (hospitalisations, surgical interventions, emergency room visits and radiology assessments) decreased significantly post-infliximab treatment compared to the pre-treatment period (Waters 2012[24]). The rates of hospitalisations in UC decreased from 15.1% (before infliximab treatment) to 3.5% (during infliximab treatment), p=0.0124 (Waters 2012[24]).

Patients persistent to infliximab maintenance therapy required lesser hospitalisation compared with patients without persistence (3.0% versus 20.4%; *p*<0.001). Hospitalised patients with persistent to infliximab maintenance therapy had significantly lower mean inpatient costs ($14,243 versus $32,745; *p*=0.046), with a trend toward shorter mean lengths of stay (6.67 versus 9.71 days; *p*=0.147) than patients without persistence (Carter 2011[93]).

Table S7. Cost and Resource Utilisation in Ulcerative Colitis

Study name	Countries	Treatment groups	No. of patients	Any adverse events (n, %)	Serious adverse events (n, %)	Adverse events related to treatment (n, %)	Total withdrawals (due to lack of tolerance to treatment/any adverse events/ serious adverse events related to inadequate treatment response)	Comments
ULTRA2 Trial (Sandborn 2013)[72]	Multinational (North America, Europe, Australia, New Zealand, and Israel)	Adalimumab	257	213 (82.9)	31 (12.1)	101 (39.3)	Discontinuation: 94 (36.4) Reasons for discontinuation: n (%) Lack of efficacy: 63 (24.4) Adverse events: 12 (4.6) Withdrew consent: 8 (3.1) Lost to follow-up: 1 (0.3) Protocol violation: 1 (0.3) Other: 9 (3.4)	
ULTRA2 Trial (Sandborn 2013)[72]	Multinational (North America, Europe, Australia, New Zealand, and Israel)	Placebo	260	218 (83.8)	32 (12.3)	86 (33.1)	Discontinuation: 115 (44.2) Reasons for discontinuation: n (%) Lack of efficacy: 70 (26.9) Adverse events: 25 (9.6) Withdrew consent: 4 (1.5) Protocol violation: 5 (1.9) Other: 11 (4.2)	

Chaparro 2012[23]	Spain	Infliximab	47	11 (23)	NR	NR	Of the 37 patients with an initial response to infliximab, 12 discontinued after a median of 10.5 months (range 1–20 months).	Seven patients discontinued infliximab after the second infusion. Patients who discontinued infliximab remained on thiopurines.
Mocciaro 2012[3]	Italy	Cyclosporine	35	1 (2.9)	0	NR	NR	
Mocciaro 2012[3]	Italy	Infliximab	30	6 (20)	0	NR	Total withdrawals: 6 due to adverse events	
Rostholder 2012[25]	USA	Infliximab	50 (maintenance cohort)	NR	NR	Infusion reactions: 5/50 (10) Mild: 4/5 Acute: 3/5	NR	
Laharie 2012[26]	Multinational (France, Spain, Belgium, and Finland)	Ciclosporin	58	NR	9 (16)	NR	NR	
Laharie 2012[26]	Multinational (France, Spain, Belgium, and Finland)	Infliximab	57	NR	14 (25)	NR	NR	
Oussalah 2010[28]	France	Infliximab	191	53 (27.8)	13 (6.8)	NR	Number of adverse events leading to infliximab withdrawal 6 (3.1)	
Herrlinger 2010[29]	Germany	Infliximab	24	8 (66.7)	2 (8.3)	NR	2 (8.3) adverse events were judged as severe (allergic reaction and viral pneumonia) and therapy with infliximab was stopped.	
Jurgens 2010[30]	Germany	Infliximab	90	9/90 (10)	NR	Side effects likely to be related to IFX treatment were arthralgia (n= 2), nausea and vomiting (n= 4), and viral respiratory infection (n = 3). Allergic infusion reaction: 9/90 (10)	In one case, delayed IFX-induced reaction was observed to appear as generalised exanthema. Therefore, IFX therapy was discontinued in this patient (after receiving a total number of nine IFX infusions).	

Taxonera 2011[4]	Spain	Adalimumab	30	6 (20)	NR	NR	15 (50)	
Tursi 2010[74]	Italy	Infliximab	23	2 (8.69)	NR	NR	NR	One patient (4.34%)affected by left-sided colitis experienced headache, not requiring suspension of the treatment; another-one patient affected by pancolitis developed sepsis by *Proteus* strain, requiring stopping treatment and colectomy.
Gies 2010[31]	Canada	Adalimumab (Induction)	25	1 (4)	NR	NR	NR	
Gies 2010[31]	Canada	Infliximab (Induction)	28	2 (7.1)	NR	1 (3.5)	NR	
Gies 2010[31]	Canada	Adalimumab (Maintenance)	20	NR	NR	NR	NR	
Gies 2010[31]	Canada	Infliximab (Maintenance)	18	3 (33.3)	NR	1 (5.5)	NR	
Afif 2009[1]	USA	Adalimumab	20	17 (85)	6 (30)	0 (0)	Nine patients with adverse events withdrew from the trial.	
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand,	ACT 1 trial: Placebo	121	103 (85.1)	31 (25.6)	Data was reported for adverse events occurring in >10% of any treatment group.	57	

	Switzerland, UK)						
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 1 trial: 5 mg Infliximab	121	106 (87.6)	26 (21.5)	Data was reported for adverse events occurring in >10% of any treatment group.	39
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 1 trial: 10 mg Infliximab	122	111 (91)	29 (23.8)	Data was reported for adverse events occurring in >10% of any treatment group.	39
Sandborn 2009[34]	Multinational (USA, Argentina, Australia,	ACT 2 trial: Placebo	123	90 (73.2)	24 (19.5)	Data was reported for adverse events occurring in >10% of any treatment group.	50

	Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)						
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Netherlands, New Zealand, Switzerland, UK)	ACT 2 trial: 5 mg Infliximab	121	99 (81.8)	13 (10.7)	Data was reported for adverse events occurring in >10% of any treatment group.	24
Sandborn 2009[34]	Multinational (USA, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France,	ACT 2 trial: 10 mg Infliximab	120	96 (80)	11 (9.2)	Data was reported for adverse events occurring in >10% of any treatment group.	24

	Germany, Israel, Netherlands, New Zealand, Switzerland, UK)							
Maser 2008[36]	USA	Infliximab-salvage	10	NR	Sepsis and died: 1/10 (10)	NR	NR	Adverse events were attributed to acute salvage therapy if they occurred within 4 weeks of receiving the salvage drug and if they were thought to be caused by immune suppression or known metabolic toxicities of either cyclosporine or infliximab.
Maser 2008[36]	USA	Ciclosporine -salvage	9	Minor adverse events: 3/9 (33.33) Fatigue, leg cramps, weakness - 1 patient Fatigue and tingling in fingers - 1 patient Nonproductive cough for 3 weeks after cyclosporine salvage without evidence of infection - 1 patient	Herpetic esophagitis: 1/9 (11.1) Pancreatitis and bacteraemia: 1/9 (11.1)	NR	NR	
Oussalah 2008[2]	France	Adalimumab	13	5 (38.5) Adverse events Labial herpes and arthralgia: 1 Psoriasis de novo: 1 Erysipelas: 1 Urinary tract	0 (0)	NR	ADA Withdrawal due to adverse event (exacerbation of psoriasis): 1/13 (7.69)	

				infection: 1 Exacerbation of psoriasis: 1				
Gornet 2003[38]	France	Infliximab	30	9/30 (30) These patients experienced adverse events during the follow-up period	NR	NR	NR	Infection - 4 (13) Cutaneous herpes -2 (7) (1 case associated with keratitis) Oesophageal candidosis and a superinfection of colitis by cytomegalovirus - 1 (3) Bronchitis requiring a short hospitalization 4 months after the infliximab infusion - 1 (3) Minor adverse events possibly related to infliximab Headache: 1 (3) Delayed urticaria: 1 (3)
Probert 2003[39]	Multinational (UK and Germany)	Placebo group	20	NR	Two serious adverse events, which qualified as life threatening or severe, were recorded. One patient suffered septic complications. Another underwent colectomy because of toxic exacerbation and spontaneous perforation.	NR	NR	
Probert 2003[39]	Multinational (UK and Germany)	Infliximab group	23	NR	NR	NR	NR	All other serious adverse events were rated as mild and were not significantly different in frequency between infliximab and placebo treated patients.

								No significant infusion reactions were seen.
Steenholdt 2013[75]	Denmark	Infliximab: UC patients in remission	10	NR	NR	Infusion reaction to infliximab: 0 (0)	NR	
Steenholdt 2013[75]	Denmark	Infliximab: UC patients not in remission	12	NR	NR	Infusion reaction to infliximab: 3 (25)	NR	
Cottone 2011[76]	Italy	UC (Elderly patients treated with biologics)	37	Eleven severe infections (4 cases of pneumonia, 2 abscesses, 2 severe sepsis, 1 case of tuberculosis, 1 case of aspergillosis, and 1 case of interstitial pneumonia) and 3 cancers (rectal cancer, prostatic cancer, and basal cell carcinoma) were reported.	NR	NR	NR	
Cottone 2011[76]	Italy	UC (Adult matched control subjects treated with biologics)	74	Thirteen (7%) minor infections, no neoplasms, and 2 (1%) deaths (due to postoperative complications) were also observed.	NR	NR	NR	
Cottone 2011[76]	Italy	UC (Elderly control subjects not treated with biologics)	74	NR	NR	NR	NR	

4B. Data on resource utilisation in Crohn's Disease

Data for cost and resource utilisation for CD patients are presented in Table S8.

Most of the studies reported data for direct costs. However, in the CARE trial (Louis 2013), indirect costs were reported as assessed by the WPAI scale. Costs of CD component for absenteeism, presenteeism and total work productivity impairment were €1180, €2408 and €2577, respectively. The estimated indirect cost savings were highest when adalimumab was administered as a first-line agent in infliximab-naïve patients. The cost-analysis in this study did not take into account medication cost for patients who required dosage increases, and also included the patients who were in employment throughout the study. Therefore, costs of unemployment may be underestimated.

For resource utilisation, a study reported significant difference in mean (SD) number of hospitalisations for step up and early bio group as 0.38 (0.8) and 0.81 (1.12), p=0.04, respectively (Ghazi 2013[44]). The early bio group had higher disease activity scores at baseline; therefore the higher hospitalisation rate may be associated with higher disease activity in this group.

Overall healthcare costs and resource utilisation (number of hospital visits, surgical procedures, length of hospital stay, drug treatment [days/year]) decreased significantly post-infliximab or post-adalimumab treatment compared to the pre-treatment period (Lindsay 2013[42], Water 2012[24], COMPAIRS [Sussman 2012], Carter 2011[94], Loomes 2011[95], Sprakes 2010[61], Taxonera 2009, Saro 2007[66], Jewell 2005[67]). However, after accounting for the costs of infliximab or adalimumab, the overall healthcare cost increased significantly (COMPAIRS [Sussman 2012], Loomes 2011[95], Sprakes 2010[61], Kane 2009[96], Saro 2007[66]). The overall healthcare cost was lower with adalimumab compared to infliximab (COMPAIRS [Sussman 2012]).

One study (Nugent 2010[58]) reported that, compared to therapies other than anti-TNFαs, physician visits with an associated diagnosis IBD and the frequency of hospital admissions were more common with infliximab than with azathioprine and steroids. The physician visits also included the obligatory visits for drug administration. Some of these obligatory visits would have contributed to the persistent increase in IBD-associated physician visits with infliximab.

LOR was also associated with an increase in cost; those who did not experience LOR incurred $24,532 as total costs, on average, whereas those who did experience LOR incurred 36% greater mean total costs ($33,289). The cost difference ($8,756) between the two groups was statistically significant, p<0.001 (Wu 2008[97]).

Table S8. Cost and Resource Use in Crohn's Disease Patients

Study name	Treatment groups	No. of patients	Direct costs (cost associated with treatment/management, concomitant medications, adverse events, office visits, hospitalisations related to "TNF failure patients"); p value	Indirect costs (productivity loss/ absenteeism) for anti-TNF inadequate responders/failure; p value	Overall total drug costs and total costs of patients initiating anti-TNFs	Resource utilisation	Comments
CARE Trial (Louis 2013)[5]	Adalimumab	945	NR	WPAI: Crohn's disease component Absenteeism: €1180 Presenteeism: €2408 Total work productivity impairment: €2577	NR	NR	
Ghazi 2013[44]	Step Up	39	NR	NR	NR	At 1 year, Mean (SD): 0.38 (0.8) hospitalisations	
Ghazi 2013[44]	Early Bio	54	NR	NR	NR	At 1 year, Mean (SD): 0.81 (1.12) hospitalisations; *p*= 0.04	
Lindsay 2013[42]	Infliximab	380	Pre- vs. Post-Infliximab elective procedures, annualised rates: £752.46 vs. £539.23 Pre- vs. Post-Infliximab all hospitalisations, annualised rates: £1908.85 vs. £1194.01, *p*<0.0001 Pre- vs. Post-Infliximab all non-elective/emergency hospitalisations, annualised rates: £1107.65 vs. £630.71, *p*<0.0001 Pre- vs. Post-Infliximab all outpatient consultations, annualised rates: £913.48 vs. £832.23, *p*<0.0001 Pre- vs. Post-Infliximab diagnostic tests consultations, annualised rates: £411 vs. £190.04,	NR	NR	Pre-infliximab (0-12 months) vs. Post-infliximab (0-24 months) Pre- vs. Post-Infliximab elective hospitalisation, Mean (SD): 0.18 (0.5) vs. 0.11 (0.26), *p*=0.0035 Pre- vs. Post-Infliximab non-elective hospitalisation, Mean (SD): 0.46 (0.79) vs. 0.29 (0.5), *p*< 0.0001 Pre- vs. Post-Infliximab total number of elective hospitalisation: 68 vs. 42.5 Pre- vs. Post-Infliximab number (%) of patients with at least one elective hospitalisation: 52 (13.7) vs. 35.5 (9.3)	

			p<0.0001 Mean cost of Infliximab over 24 months: £7128.02 Total cost of Infliximab over 24 months: £2708467.10			Pre- vs. Post-Infliximab Gastroenterologist consultation, Mean (SD): 4 (2.4) vs. 3.5 (2.3), *p*< 0.0001 Pre- vs. Post-Infliximab Gastrointestinal surgeon consultation, Mean (SD): 0.7 (1.4) vs. 0.5 (0.9), *p*= 0.0008 Pre- vs. Post-Infliximab Radiologist consultation, Mean (SD): 0.5 (0.8) vs. 0.2 (0.5), *p*< 0.0001 Pre- vs. Post-Infliximab Nurse (infliximab related) consultation, Mean (SD): 0 vs. 3.8 (2.7), *p*< 0.0001 Pre- vs. Post-Infliximab Nurse (non-infliximab related) consultation, Mean (SD): 1.7 (3.7) vs. 1.3 (2.7), p= 0.0007 Pre- vs. Post-Infliximab Dietician/nutritionist consultation, Mean (SD): 0.2 (0.7) vs. 0.1 (0.3), *p*= 0.0036
Osterman 2014[43]	Infliximab	1459	NR	NR	NR	Hospitalisation with CD as primary diagnosis: 245 (11.8) In first year of follow-up: 165 (8) Censoring follow-up 90 days after discontinuation of therapy: 163 (12.8) Hospitalisation with CD as primary or secondary diagnosis: 369 (19.5) In first year of follow-up: 284 (27.7) Censoring follow-up 90 days after discontinuation of therapy: 283 (23.5)
Osterman 2014[43]	Adalimumab	871	NR	NR	NR	Hospitalisation with CD as primary diagnosis: 185 (15.4) In first year of follow-up: 117 (9.7)

						Censoring follow-up 90 days after discontinuation of therapy: 101 (16) Hospitalisation with CD as primary or secondary diagnosis: 263 (24) In first year of follow-up: 178 (29.1) Censoring follow-up 90 days after discontinuation of therapy: 165 (27.8)	
Waters 2012[24]	Infliximab	182	Hospitalisation cost saving post-infliximab: $29061 Surgery related cost saving post-infliximab: $36936 Emergency room visit related cost addition post-infliximab: $194 Radiological assessment related cost saving post-infliximab: $6256 Colonoscopy related cost saving post-infliximab: $25518.96 to $47228.97 Esophagogastroduodenoscopy related cost saving post-infliximab: $11413.17 Sigmoidoscopy related cost saving post-infliximab: $185.83	NR	NR	Pre- vs. Post-Infliximab Hospitalisation: 19 (10.41) vs. 16 (8.8), *p*= Not significant Pre- vs. Post-Infliximab emergency room visit: 2 (1.1) vs. 4 (2.2), *p*= Not significant Pre- vs. Post-Infliximab radiology assessment: 42 (23.1) vs. 19 (10.4), *p*=0.006 Pre- vs. Post-Infliximab colonoscopy: 99 (54) vs. 32 (17.6), *p*= 0.0001 Pre- vs. Post-Infliximab esophagogastroduodenoscopy: 18 (9.9) vs. 9 (4.9), *p*=Not significant Pre- vs. Post-Infliximab Sigmoidoscopy: 1 (0.5) vs. 0 (0*), p*= Not significant	
COMPAIRS (Sussman 2012)[98]	Adalimumab	623	Pre- vs. Post-Adalimumab, Mean (SD) Index drug costs: NA vs. $10,709 ($4,979) Prescription drugs costs; Total prescription drug cost: $1,374 ($2,420) vs. $1,334 ($1,892) Total CD-related drug cost: $648 ($867) vs. $546 ($916) Medical service-related costs; Hospitalisation: $4,541 ($23,031) vs. $3,357 ($14,809)	NR	Pre- vs. Post-Adalimumab, Mean (SD) Total healthcare costs; Total healthcare costs: $11,640 ($27,088) vs. $18,885 ($21,049) Total healthcare costs, CD-related: $8,849 ($23,772) vs. $16,454 ($16,667) Post-Index Total healthcare costs excluding index drug, Mean (SD);	Pre- vs. Post-Adalimumab, Mean (SD) Hospitalisation; 6-Month rate, any cause, n (%): 138 (22) vs. 89 (14) 6-Month rate, CD-related, n (%): 125 (20) vs. 81 (13) Hospitalisation days, any cause: 1.79 (5.3) vs. 1.24 (5.3) Hospitalisation days, CD-related: 1.65 (5.2) vs. 1.2 (5.2)	Healthcare Utilisation; Adalimumab (n=296) vs. Infliximab (n=296), 12 months Post-Index Hospitalisation 12-Month rate, any cause (n, %): 76 (26%) vs. 74 (25%), Difference: 1.03, *p*= 0.8500 12-Month rate, CD-related (n, %): 68 (23%) vs. 65 (22%), Difference: 1.05, *p*= 0.7680

Hospitalisation, CD-related: $4,170 ($22,796) vs. $3,257 ($14,770) ER visit: $287 ($1,084) vs. $206 ($906) ER visit, CD-related: $227 ($1,014) vs. $136 ($852) Outpatient / office visit: $4,706 ($7,302) vs. $2,482 ($4,088) Outpatient / office visit, CD-related: $3,583 ($6,316) vs. $1,579 ($3,544) Other medical costs: $732 ($10,723) vs. $797 ($11,722) Other medical costs, CD-related: $220 ($1,503) vs. $227 ($1,992) Total medical service costs: $10,265 ($26,869) vs. $6,842 ($20,388) Total medical service costs, CD-related: $8,201 ($23,752) vs. $5,199 ($16,476)	Total healthcare costs $8,176 ($20,822) Total healthcare costs, CD-related $5,745 ($16,503)	Number of hospital visits, any cause: 0.3 (0.7) vs. 0.2 (0.6) Number of hospital visits, CD-related: 0.27 (0.6) vs. 0.19 (0.6) Emergency room visit; 6-Month rate, any cause, n (%): 134 (22) vs. 113 (18) 6-Month rate, CD-related, n (%): 89 (14) vs. 57 (9) Outpatient visits; Number of outpatient visits, any cause: 9.92 (7.1) vs. 8.84 (7.4) Number of outpatient visits, CD-related: 5.36 (4.2) vs. 4.28 (4.1)	Hospitalisation days, any cause, Mean (SD): 2.29 (6.2) vs. 2.75 (7.3), Difference: -0.46, *p*= 0.9398 Hospitalisation days, CD-related, Mean (SD): 2.14 (6.1) vs. 2.52 (7.2), Difference: -0.38, *p*= 0.9266 Number of hospital visits, any cause, Mean (SD): 0.4 (0.9) vs. 0.39 (0.8), Difference: 0.01, *p*= 0.8681 Number of hospital visits, CD-related, Mean (SD): 0.36 (0.8) vs. 0.33 (0.8), Difference: 0.03, *p*= 0.7641 Emergency room visit 12-Month rate, any cause (n, %): 87 (29%) vs. 73 (25%), Difference: 1.19, *p*= 0.1950 12-Month rate, CD-related (n, %): 44 (15%) vs. 40 (14%), Difference: 1.10, *p*= 0.6380 Outpatient visits Number of outpatient visits, any cause, Mean (SD): 18.07 (14.1) vs. 22.25 (13.7), Difference: -4.18, *p*<0.0001 Number of outpatient visits, CD-related, Mean (SD): 7.97 (7.2) vs. 12.23 (5.8), Difference: -4.26, *p*<0.0001	Healthcare costs ($); Adalimumab (n=296) vs.

Infliximab (n=296), 12 months Post-Index
Index drug costs, Mean (SD): $18,330 ($7,928) vs. $19,881 ($40,174), Difference: -$1,550, *p*= 0.0005*
Prescription drugs costs excluding index drug, Mean (SD)
Total prescription drug costs: $2,810 ($3,778) vs. $4,758 ($17,778), Difference: -$1,948, *p*= 0.3133
Total CD-related drug costs: $993 ($1,408) vs. $2,254 ($4,468), Difference: -$1,261, *p*= 0.2874
Medical service-related costs excluding index drug Mean (SD)
Hospitalisation: $6,655 ($20,020) vs. $8,569 ($38,009), Difference: -$1,914, *p*= 0.9784
Hospitalisation, CD-related: $6,164 ($19,613) vs. $8,111 ($37,846), Difference: -$1,947, *p*= 0.9037
ER visit: $407 ($1,396) vs. $330 ($869), Difference: $78, *p*= 0.4188
ER visit, CD-related: $242 ($1,243) vs. $178 ($712), Difference: $64, *p*= 0.7489
Outpatient / office visit: $5,443 ($8,998) vs. $9,172 ($11,676), Difference: -$3,729, *p*<0.0001*
Outpatient / office visit,

CD-related: $2,971 ($5,335) vs. $6,728 ($10,020), Difference: -$3,757, *p*<0.0001*

Other medical costs: $556 ($2,898) vs. $1,153 ($7,862), Difference: -$597, *p*= 0.2121

Other medical costs, CD-related: $378 ($2,841) vs. $549 ($2,867), Difference: -$171, *p*= 0.0666

Total medical service costs: $13,061 ($24,800) vs. $19,224 ($48,897), Difference: -$6,163, *p*<0.0001*

Total medical service cost, CD-related: $9,755 ($22,561) vs. $15,566 ($39,625), Difference: -$5,811, *p*<0.0001*

Total healthcare costs, Mean (SD)

Total healthcare costs: $34,202 ($26,680) vs. $43,863 ($74,009), Difference: -$9,662, *p*= 0.0035*

Total healthcare costs, CD-related: $29,078 ($23,680) vs. $37,701 ($56,314), Difference: -$8,623, p= 0.0011*

Total healthcare costs excluding index drug, Mean (SD)

Total healthcare costs $15,871 ($26,040) vs. $23,982 ($52,935), Difference: -$8,111, *p*<0.0001*

Total healthcare costs,

							CD-related $10,748 ($22,682) vs. $17,820 ($39,822), Difference: -$7,072, p<0.0001
COMPAIRS (Sussman 2012)[98]	Infliximab	623	Pre- vs. Post-Infliximab, Mean (SD) Index drug costs: NA vs. $12,401 ($20,834) Prescription drugs costs; Total prescription drug cost: $1,113 ($1,936) vs.$1,639 ($6,341) Total CD-related drug cost: $585 ($897) vs. $857 ($2,047) Medical service-related costs; Hospitalisation: $4,405 ($14,779) vs. $5,166 ($24,762) Hospitalisation, CD-related: $4,260 ($14,677) vs. $4,961 ($24,638) ER visit: $242 ($797) vs. $278 ($1,441) ER visit, CD-related: $165 ($593) vs. $182 ($1,330) Outpatient / office visit: $4,892 ($6,880) vs. $4,565 ($6,007) Outpatient / office visit, CD-related: $4,014 ($6,294) vs. $3,659 ($5,364) Other medical costs: $315 ($1,560) vs. $307 ($1,545) Other medical costs, CD-related: $248 ($1,522) vs. $257 ($1,503) Total medical service costs: $9,854 ($16,805) vs. $10,316 ($25,995) Total medical service costs, CD-related: $8,686 ($16,307) vs. $9,059 ($25,597)	NR	Pre- vs. Post-Infliximab, Mean (SD) Total healthcare costs; Total healthcare costs: $10,967 ($17,019) vs. $24,355 ($36,525) Total healthcare costs, CD-related: $9,271 ($16,323) vs.$22,316 ($32,578) Post-Index Total healthcare costs excluding index drug, Mean (SD); Total healthcare costs $11,955 ($27,032) Total healthcare costs, CD-related $9,916 ($25,672)	Pre- vs. Post-Infliximab, Mean (SD) Hospitalisation; 6-Month rate, any cause, n (%): 138 (22) vs. 102 (16) 6-Month rate, CD-related, n (%): 135 (22) vs. 94 (15) Hospitalisation days, any cause: 2.08 (7.6) vs. 1.78 (5.9) Hospitalisation days, CD-related: 2.04 (7.6) vs. 1.71 (5.9) Number of hospital visits, any cause: 0.33 (0.7) vs. 0.25 (0.7) Number of hospital visits, CD-related: 0.32 (0.7) vs.0.23 (0.6) Emergency room visit; 6-Month rate, any cause, n (%): 143 (23) vs. 120 (19) 6-Month rate, CD-related, n (%): 102 (16) vs. 62 (10) Outpatient visits; Number of outpatient visits, any cause: 9.66 (7.7) vs. 11.3 (7.3) Number of outpatient visits, CD-related: 5.48 (3.7) vs. 7.22 (3.9)	
TREAT registry (Lichtenstein	Infliximab	3420	NR	NR	NR	NR	Health resource utilisation in year before enrolment: Surgical admission: 596 (17.4)

2012)[81]							
TREAT registry (Lichtenstein 2012)[81]	Other treatments only	2853	NR	NR	NR	NR	Health resource utilisation in year before enrolment: Surgical admission: 387 (13.6)
Carter 2011[94]	Non-adherent (4-6 infusions)	172	PRE-INDEX : Hospitalisation costs among those hospitalised, $: Mean (SD): 20,515 (46,732) Median: 11,476 POST-INDEX : Hospitalisation costs, $: Mean (SD): 37,783 (44,986) Median: 28,864	NR	NR	Pre-index utilization of Crohn's disease-related healthcare services and inpatient costs: Outpatient services Emergency room visits Patients with ≥1 claim, n (%): 33 (19) Claims Mean (SD): 1.42 (0.87) Median: 1 Laboratory and pathology Patients with ≥1 claim, n (%): 137 (80) Claims Mean (SD): 11.30 (11.74) Median: 7 Radiology Patients with ≥1 claim, n (%): 7 3 (42) Claims Mean (SD): 2.38 (1.72) Median 2: Physician office visits Patients with ≥1 claim, n (%): 153 (89) Claims Mean (SD): 4.56 (3.28) Median 4: Surgical services Patients with ≥1 claim, n (%):

70 (41)
Claims
Mean (SD): 1.36 (0.87)
Median: 1

Ancillary/all other outpatient services
Patients with ≥1 claim, n (%): 134 (78)
Claims
Mean (SD): 8.32 (9.83)
Median: 5

Inpatient hospitalisations
Patients with ≥1 hospitalisation, n (%): 34 (20)

Hospital days among those hospitalised
Mean (SD): 9.35 (15.09)
Median: 6

POST-INDEX UTILIZATION OF CROHN'S DISEASE-RELATED HEALTHCARE SERVICES
Pharmacy services
Immunomodulators
Patients with ≥1 claim, n (%): 74 (43)
Claims
Mean (SD): 5.72 (3.68)
Median: 5

5-ASA
Patients with ≥1 claim, n (%): 59 (34)
Claims
Mean (SD): 3.98 (2.74)
Median: 3

Corticosteroids
Patients with ≥1 claim, n (%): 70 (41)

Claims
Mean (SD): 4.04 (3.39)
Median 3

<u>Outpatient services</u>
Emergency room visits
Patients with ≥1 claim, n (%): 30 (17)
Claims
Mean (SD): 1.33 (0.76)
Median: 1

Laboratory and pathology
Patients with ≥1 claim, n (%): 132 (77)
Claims
Mean (SD): 15.17 (17.26)
Median 11

Radiology
Patients with ≥1 claim, n (%): 52 (30)
Claims
Mean (SD): 3.00 (2.33)
Median: 2

Physician office visits
Patients with ≥1 claim, n (%): 158 (92)
Claims
Mean (SD): 5.96 (5.19)
Median: 5

Surgical services
Patients with ≥1 claim, n (%): 46 (27)
Claims
Mean (SD): 1.80 (1.11)
Median: 2

Ancillary/all other outpatient services
Patients with ≥1 claim, n (%):

						166 (97) Claims Mean (SD): 19.54 (12.53) Median: 18 POST-INDEX CROHN'S DISEASE-RELATED HOSPITALISATIONS, LENGTH OF STAY, AND INPATIENT COSTS AMONG CROHN'S DISEASE PATIENTS WITH A HOSPITALISATION Proportion of all patients with a hospitalisation, %: 12 Number of hospitalisations Mean (SD): 1.4 (0.6) Median: 1 Number of hospital days Mean (SD): 12.8 (13.0) Median: 8
Carter 2011[94]	Adherent (7-9 infusions)	466	PRE-INDEX : Hospitalisation costs among those hospitalised, $: Mean (SD): 17,270 (18,825) Median: 10,199 (*p*= 0.74) POST-INDEX : Hospitalisation costs, $: Mean (SD): 13,427 (11,085) Median: 9,352 (*p* value: 0.001)	NR	NR	PRE-INDEX UTILISATION OF CROHN'S DISEASE-RELATED HEALTHCARE SERVICES AND INPATIENT COSTS <u>Outpatient services</u> Emergency room visits Patients with ≥1 claim, n (%): 60 (13) (*p*= 0.05) Claims Mean (SD): 1.50 (0.98) Median: 1 (*p*= 0.77) Laboratory and pathology Patients with ≥1 claim, n (%): 373 (80) (*p*= 0.91) Claims Mean (SD): 11.99 (13.59) Median: 8 (*p* value: 0.63) Radiology Patients with ≥1 claim, n (%): 229 (49) (*p*= 0.13) Claims

Mean (SD): 2.42 (1.78)
Median: 2 (*p*= 0.92)

Physician office visits
Patients with ≥1 claim, n (%): 418 (90) (*p*= 0.79)
Claims
Mean (SD): 4.70 (3.47)
Median: 4 (*p*= 0.81)

Surgical services (P= 0.52)
Patients with ≥1 claim, n (%): 203 (44)
Claims
Mean (SD): 1.50 (0.98)
Median: 1 (*p*= 0.19)

Ancillary/all other outpatient services
Patients with ≥1 claim, n (%): 361 (78) *p*= 0.91)
Claims
Mean (SD): 7.41 (8.05)
Median: 5 (*p* value: 0.67)

<u>Inpatient hospitalisations</u>
Patients with ≥1 hospitalisation, n (%): 91 (20) *(p*= 0.95)

Hospital days among those hospitalised
Mean (SD): 8.13 (8.14)
Median: 6 (*p*= 0.64)

POST-INDEX UTILIZATION OF CROHN'S DISEASE-RELATED HEALTHCARE SERVICES
<u>Pharmacy services</u>
Immunomodulators
Patients with ≥1 claim, n (%): 217 (47) (*p*= 0.43)
Claims

Mean (SD): 6.61 (3.87)
Median: 6 (*p*= 0.09)

5-ASA
Patients with ≥1 claim, n (%):
174 (37) (*p*= 0.48)
Claims
Mean (SD): 5.13 (3.57)
Median: 4 (*p*= 0.05)

Corticosteroids
Patients with ≥1 claim, n (%):
189 (41) (*p*= 0.98)
Claims
Mean (SD): 3.02 (2.69)
Median: 2 (*p*= 0.02)

<u>Outpatient services</u>
Emergency room visits
Patients with ≥1 claim, n (%):
51 (11) (*p*= 0.03)
Claims
Mean (SD): 1.65 (1.07)
Median: 1 (*p*= 0.12)

Laboratory and pathology
Patients with ≥1 claim, n (%):
366 (79) (*p*= 0.63)
Claims
Mean (SD): 13.96 (18.02)
Median: 9 (*p*= 0.32)

Radiology
Patients with ≥1 claim, n (%):
123 (26) (*p*= 0.34)
Claims
Mean (SD): 2.20 (1.71)
Median: 2 (*p*= 0.04)

Physician office visits
Patients with ≥1 claim, n (%):
419 (90) (*p*= 0.46)
Claims

						Mean (SD): 6.03 (4.52) Median: 5 (*p*= 0.79) Surgical services Patients with ≥1 claim, n (%): 129 (28) (*p*= 0.81) Claims Mean (SD): 2.01 (1.95) Median: 1 (*p*= 0.41) Ancillary/all other outpatient services Patients with ≥1 claim, n (%): 451 (97) (*p*= 0.87) Claims Mean (SD): 23.93 (13.04) Median: 21 (*p*< 0.001) POST-INDEX CROHN'S DISEASE-RELATED HOSPITALISATIONS, LENGTH OF STAY, AND INPATIENT COSTS AMONG CROHN'S DISEASE PATIENTS WITH A HOSPITALISATION Proportion of all patients with a hospitalisation, %: 8 (*p*= 0.12) Number of hospitalisations Mean (SD): 1.2 (0.5) Median: 1 (*p*= 0.13) Number of hospital days Mean (SD): 5.9 (3.5) Median: 5 (*p*= 0.02)
Leombruno 2011[55]	Infliximab users	338	NR	NR	NR	No. of patients hospitalised at least once over the follow-up period: 115 (34) No. of patients CD-related hospital admission during the follow-up period of 671 patient years: 61 (18.0) Hospital admissions in which

						infection was listed as a primary or secondary diagnosis: 39 (11.5), experienced a total of 61 admissions. Total hospitalised days during the follow-up period of 671 patient years: 1888
Leombruno 2011[55]	Infliximab non-users	670	NR	NR	NR	No. of patients hospitalised at least once over the follow-up period: 273 (670) No. of patients CD-related hospital admission during the follow-up period of 1303 patient years: 133 (19.8) Hospital admissions in which infection was listed as a primary or secondary diagnosis: 84 (12.5), experienced a total of 147 admissions. Total hospitalised days during the follow-up period of 1303patient years: 5279
Loomes 2011[95]	One year before and after Infliximab	66	Stratified costs: Health care visit Inpatient: Pre- vs. Post-Infliximab Hospitalisation: $2715 vs. 968, *p*< 0.05 Outpatient: Pre- vs. Post-Infliximab Emergency room visit: $191 vs. 107, *p*= 0.12 Pre- vs. Post-Infliximab Outpatient visit: $285 vs. $478, *p*< 0.05 Endoscopy Outpatient: Pre- vs. Post-Infliximab Esophagogastroduodenoscopy: $6 vs. $0, *p*= 0.32 Pre- vs. Post-Infliximab	NR	Total direct cost; Pre- vs. Post-Infliximab: $3930 vs. $25346, *p*< 0.05	Health care visit Inpatient; Pre- vs. Post-Infliximab Hospitalisation: 47 vs. 25, *p*= 0.06 Pre- vs. Post-Infliximab Hospital day: 495 vs. 155, *p*< 0.05 Outpatient; Pre- vs. Post-Infliximab Emergency room visit: 52 vs. 29, *p*= 0.12 Pre- vs. Post-Infliximab Outpatient visit: 182 vs. 205, *p*< 0.05 Endoscopy Inpatient; Pre- vs. Post-Infliximab Esophagogastroduodenoscop

Colonoscopy: $426 vs. $242, $p<$ 0.05
Radiology
Outpatient:
Pre- vs. Post-Infliximab
Computed tomography scan: $114 vs. $75, $p=$ 0.32
Pre- vs. Post-Infliximab Magnetic resonance imaging: $38 vs. $53, $p=$ 0.58
Pre- vs. Post-Infliximab Other x-ray: $10 vs. $8, $p=$ 0.78
Therapeutic intervention
Inpatient:
Pre- vs. Post-Infliximab
Nonsurgical management: $926 vs. $380, $p=$ 0.05
Pre- vs. Post-Infliximab Minor surgery: $113 vs. 217, $p=$ 0.57
Pre- vs. Post-Infliximab Major surgery: $1504 vs. $263, $p<$ 0.05
Outpatient:
Pre- vs. Post-Infliximab Day surgery: $110 vs. $62, $p=$ 0.36
Pre- vs. Post-Infliximab
Transfusion: $36 vs. $26, $p=$ 0.71

y: 18 vs. 20, $p=$ 0.78
Pre- vs. Post-Infliximab
Colonoscopy: 46 vs. 24, $p<$ 0.05
Outpatient;
Pre- vs. Post-Infliximab
Esophagogastroduodenoscopy: 1 vs. 0, $p=$ 0.32
Pre- vs. Post-Infliximab
Colonoscopy: 58 vs. 33, $p<$ 0.05
Radiology
Inpatient;
Pre- vs. Post-Infliximab
Computed tomography scan: 19 vs. 10, $p=$ 0.29
Pre- vs. Post-Infliximab
Magnetic resonance imaging: 0 vs. 1, $p=$ 0.32
Pre- vs. Post-Infliximab Other x-ray: 24 vs. 13, $p=$ 0.29
Outpatient;
Pre- vs. Post-Infliximab
Computed tomography scan: 16 vs. 11, $p=$ 0.36
Pre- vs. Post-Infliximab
Magnetic resonance imaging: 5 vs. 7, $p=$ 0.58
Pre- vs. Post-Infliximab Other x-ray: 5 vs. 4, $p=$ 0.78
Therapeutic intervention
Inpatient;
Pre- vs. Post-Infliximab
Nonsurgical management: 22 vs. 11, $p=$ 0.10
Pre- vs. Post-Infliximab Minor surgery: 3 vs.3, $p=$ 1.00
Pre- vs. Post-Infliximab Major surgery: 10 vs. 2, $p<$ 0.05
Outpatient;
Pre- vs. Post-Infliximab Day surgery: 12 vs. 5, $p=$ 0.11
Pre- vs. Post-Infliximab

						Transfusion: 7 vs. 5, *p*= 0.71
Loomes 2011[95]	Two years before and after Infliximab	39	Stratified costs: Health care visit Inpatient: Pre- vs. Post-Infliximab Hospitalisation: $2881 vs. $1037, *p*= 0.06 Outpatient: Pre- vs. Post-Infliximab Emergency room visit: $118 vs. $131, *p*= 0.79 Pre- vs. Post-Infliximab Outpatient visit: $264 vs. $497, *p*< 0.05 Endoscopy Outpatient: Pre- vs. Post-Infliximab Esophagogastroduodenoscopy: $0 vs. $0 Pre- vs. Post-Infliximab Colonoscopy: $423 vs. $255, *p*< 0.16 Radiology Outpatient: Pre- vs. Post-Infliximab Computed tomography scan: $99 vs. $72, *p*= 0.47 Pre- vs. Post-Infliximab Magnetic resonance imaging: $45 vs. $32, *p*= 0.59 Pre- vs. Post-Infliximab Other x-ray: $14 vs. $7, *p*= 0.42 Therapeutic intervention Inpatient: Pre- vs. Post-Infliximab Nonsurgical management: $728 vs. $375, *p*= 0.22 Pre- vs. Post-Infliximab Minor surgery: $160 vs. $184, *p*=0.89 Pre- vs. Post-Infliximab Major surgery: $1895 vs. $351, *p*<0.05 Outpatient:	NR	Total direct cost; Pre- vs. Post-Infliximab: $3981 vs. $20098, *p*= 0.08	Health care visit Inpatient; Pre- vs. Post-Infliximab Hospitalisation: 26 vs. 14.5, *p*= 0.14 Pre- vs. Post-Infliximab Hospital day: 346 vs. 160, *p*= 0.10 Outpatient; Pre- vs. Post-Infliximab Emergency room visit: 38 vs. 42, *p*= 0.79 Pre- vs. Post-Infliximab Outpatient visit: 199 vs. 275, *p*< 0.05 Endoscopy Inpatient; Pre- vs. Post-Infliximab Esophagogastroduodenoscopy: 17 vs. 21, *p*= 0.60 Pre- vs. Post-Infliximab Colonoscopy: 26 vs. 41, *p*= 0.34 Outpatient; Pre- vs. Post-Infliximab Esophagogastroduodenoscopy: 0 vs. 0, *p*= NA Pre- vs. Post-Infliximab Colonoscopy: 68 vs. 41, *p*< 0.16 Radiology Inpatient; Pre- vs. Post-Infliximab Computed tomography scan: 9 vs. 12, *p*= 0.62 Pre- vs. Post-Infliximab Magnetic resonance imaging: 3 vs. 1, *p*= 0.53 Pre- vs. Post-Infliximab Other x-ray: 20 vs. 19, *p*= 0.94 Outpatient;

			Pre- vs. Post-Infliximab Day surgery: $108 vs. $86, *p*= 0.67 Pre- vs. Post-Infliximab Transfusion: $30 vs. $13, *p*= 0.59			Pre- vs. Post-Infliximab Computed tomography scan: 16 vs. 12, *p*= 0.5 Pre- vs. Post-Infliximab Magnetic resonance imaging: 7 vs. 5, *p*= 0.6 Pre- vs. Post-Infliximab Other x-ray: 8 vs. 4, *p*= 0.42 Therapeutic intervention Inpatient; Pre- vs. Post-Infliximab Nonsurgical management: 19 vs. 13, *p*= 0.45 Pre- vs. Post-Infliximab Minor surgery: 6 vs.3, *p*= 0.49 Pre- vs. Post-Infliximab Major surgery: 12 vs. 3, *p*< 0.05 Outpatient; Pre- vs. Post-Infliximab Day surgery: 16 vs. 9, *p*= 0.2 Pre- vs. Post-Infliximab Transfusion: 7 vs. 3, *p*= 0.59
Nugent 2010[58]	Infliximab	126	NR	NR	NR	Mean physician visits (compared in all 6-month time slots) Physician visits with an associated diagnosis of IBD were consistently more common in Infliximab than Azathioprine than in Steroids. All 6-month periods showed significant differences among the three cohorts for IBD-associated physician visits (*p*< 0.001). Frequency of hospital admissions Up until 6 months before their first prescription, with the exception of the 30 – 36-month time slot (*p*= 0.052), the three drug cohorts showed significant

						differences in the frequency of hospital admissions. The general pattern was Infliximab> Azathioprine> Steroids The groups then diff red significantly until 18 months after the first prescription (*p* values < 0.001 for 0 – 6 months, < 0.001 for 6 – 12 months, and 0.026 for 12 – 18 months). Overnights The first 12 – 18 months before the initial prescriptions and the 18 months after showed significant variation in overnights in hospital among the three drug cohorts (*p* values ≤ 0.02), with the Infliximab group having the greatest mean number of overnights in hospital throughout the 5 years before the initial prescription of Infliximab.
ADHERE (Panaccione 2010)[59]	Placebo	261 (139 entered ADHERE)	NR	NR	NR	All-cause hospitalisation Total number of hospitalised patients during ADHERE: 17/261 (6.5) Patients with new hospitalisations: 11/261 (4.2) 2-year overall number of patients hospitalised: 80/261 (30.6) CD-related hospitalisation Total number of hospitalised patients during ADHERE: 10/261 (3.8)

						Patients with new hospitalisations: 9/261 (3.4) 2-year overall number of patients hospitalised: 55/261 (21)
ADHERE (Panaccione 2010)[59]	Adalimumab eow	260 (144 entered ADHERE)	NR	NR	NR	All-cause hospitalisation Total number of hospitalised patients during ADHERE: 23/260 (8.8) Patients with new hospitalisations: 18/260 (6.9) 2-year overall number of patients hospitalised: 60/260 (23) CD-related hospitalisation Total number of hospitalised patients during ADHERE: 15/260 (5.7) Patients with new hospitalisations: 12/260 (4.6) 2-year overall number of patients hospitalised: 45/260 (17.3)
ADHERE (Panaccione 2010)[59]	Adalimumab weekly	257 (184 entered ADHERE)	NR	NR	NR	All-cause hospitalisation Total number of hospitalised patients during ADHERE: 33/257 (12.8) Patients with new hospitalisations: 25/257 (9.7) 2-year overall number of patients hospitalised: 69/257 (26.8) CD-related hospitalisation Total number of hospitalised patients during ADHERE: 16/257 (6.2) Patients with new hospitalisations: 12/257 (4.6) 2-year overall number of patients hospitalised: 41/257 (16)

Sprakes 2010[61]	Infliximab	100	NR	NR	Total Crohn's disease (CD)-related costs in 100 CD patients 12 months pre- and post-infliximab: Mean cost per person preinfliximab; Mean cost per person post-infliximab; Mean cost-saving per person post-infliximab; 95% CI; P-value Medication costs: £598.71; £448.45; £150.26; £54.59 to £245.93; 0.002 Radiology costs: £315.79; £89.46; £226.33; £170.48 to £282.18; <0.001 Endoscopy costs: £397.64; £77.86; £319.78; £227.26 to £412.30; <0.001 Surgery costs: £536.88; £124.06; £412.82; £116.00 to £709.64; 0.007 Outpatient visit costs: £479.30; £372.67; £106.63; £53.78 to £159.48; <0.001 Blood test costs: £48.52; £37.13; £11.39; £2.77 to £20.01; 0.01 Inpatient admission costs: £2588.36; £670.90; £1917.46; £1219.63 to £2615.29; <0.001 Day case infusion costs: £0; £393.86; -£393.86; -£453.18 to -£334.54; <0.001 Total costs: £4965.20; £2214.37; £2750.83; £1856.91 to £3660.93; <0.001 Mean costs at 12 months post-infliximab in responders were lower than in non-responders (£1656 vs.	Number of acute medical admissions Pre-infliximab: 56 Post-infliximab: 14 Mean length of stay per medical admission (days) Pre-infliximab: 5 Post-infliximab: 9	No statistically significant difference in costs post-infliximab was detected between the scheduled and episodic groups (£3339 vs. £2906, *p*= 0.44). There were a total of 518 (357 + 161) infliximab infusions administered to 100 patients during the 12 months of the study (mean: 5.2 infusions per patient). A total of 357 infusions were given to the scheduled group (mean: 6.3 infusions) compared with 161 (mean: 3.7) in the episodic group *p*< 0.001). The mean difference in costs of infliximab in the two groups of patients was statistically significant (£10 940 in scheduled vs. £6514 in episodic, *p*< 0.001). There were a total of 377 diagnostic tests performed in the 100 included patients in the year prior to infliximab therapy compared with 75 in the year following commencement of infliximab. All 100 patients had a

					£3608, *p*= 0.02)		chest X-ray (CXR) prior to commencement of infliximab, to exclude tuberculosis, and 67 plain X-rays were requested for other CD-related indications
Stein 2010[62]	Infliximab	Prior Irregular (PI) Exposure, n = 40	The excess costs per patient in the PI group (compared to the SM group) Excess Infusion-related costs attributed to the need for infliximab dose intensification in the PI group during the third year of treatment: $6,838 Excess Surgical cost: $3,740 Excess Medical hospitalisation cost: $886	NR	Total excess cost in the PI exposure cohort during the third year of infliximab maintenance therapy per patient, in spite of both cohorts being on SM therapy: $11,464.	Rate of hospitalisation: 47.5% First year: 20% Second year: 20% Third year: 7.5%	Difference in costs due to prior irregular exposure during the third year of infliximab treatment, when all patients in both groups were receiving regular maintenance therapy (i.e., infusion intervals of every 8 weeks or less) was calculated.
Stein 2010[62]	Infliximab	Scheduled Maintenance (SM), n = 64				Rate of hospitalisation: 26.5%, p=0.03 First year: 9.3% Second year: 10.9% Third year: 3.1%	
Taxonera 2009[64]	Infliximab	Luminal CD: 84	NR	NR	NR	<u>Pre-IFX</u> Hospital admission (%): 48.8 Hospital stay (d/y) (range): 11.23 (7.1-15.3) Surgery (%): 11.9 Surgery (interventions/y) (range): 0.13 (0.0-0.2) -Perianal surgery: 0.09 -Resections: 0.02 -Ostomy: 0.00 -Other surgery: 0.01 Clinical consultations (per year): 8.01 (6.2-9.8) -Gastroenterology: 6.81 -Surgery: 0.11 -Emergency: 0.42 -Other: 0.68 Diagnostic tests (per year)	

(range): 4.32 (3.6-5.1)
-Digestive tract: 2.06
-Other: 2.26
Laboratory tests (per year) (range): 11.09 (8.7-13.5)
Drug treatment (days treatment/y) (range): 564.38 (414.2-714.6)
-Immunomodulators: 152.96
-Corticosteroids: 86.64
-Antibiotics: 32.79
-Other treatments: 291.99
Parenteral nutrition (d/y): 3.92 (0.4-7.4)
Packed cells transfusion (per year): 0.01 (-0.01-0.04)
Day care hospitalisation (d/patient/y):
IFX administration: NA

Post-IFX

Hospital admission (%): 25.0; p= 0.002
Hospital stay (d/y) (range): 6.25 (1.8-10.7); *p*= 0.002
Surgery (%): 4.8; *p*= 0.000

Surgery (interventions/y) (range): 0.06 (0.0-0.1); *p*= 0.193
-Perianal surgery: 0.02; *p*= 0.107
-Resections: 0.01; *p*= 0.564
-Ostomy: 0.00; p= 1.000
-Other surgery: 0.02; *p*= 0.564

Clinical consultations (per year): 6.55 (5.6-7.5); *p*= 0.185
-Gastroenterology: 5.64; *p*= 0.546
-Surgery: 0.02; *p*= 0.257

						-Emergency: 0.17; *p*= 0.063 -Other: 0.71; p= 0.897 Diagnostic tests (per year) (range) 1.68 (1.1-2.2); *p*= 0.000 -Digestive tract: 0.84; *p*= 0.000 -Other: 0.83; *p*= 0.000 Laboratory tests (per year) (range): 16.04 (13.0-19.0); *p*= 0.001 Drug treatment (days treatment/y) (range): 573.92 (426.4-721.4); *p*= 0.698 -Immunomodulators: 184.20; *p*= 0.080 -Corticosteroids: 49.55; *p*= 0.004 -Antibiotics: 30.13; *p*= 0.375 -Other treatments: 310.04; *p*= 0.530 Parenteral nutrition (d/y): 0.40(-0.4-1.2); *p*= 0.008 Packed cells transfusion (per year): 0.00; *p*= 0.317 Day care hospitalisation (d/patient/y) IFX administration: 6.84 (6.4-7.3); *p*= 0.000
Taxonera 2009[64]	Infliximab	Fistulising CD: 69	NR	NR	NR	<u>Pre-IFX</u> Hospital admission (%): 62.3 Hospital stay (d/y) (range): 11.49 (7.9-15.1) Surgery (%): 37.7 Surgery (interventions/y) (range): 0.42 (0.3-0.6) -Perianal surgery: 0.36

-Resections: 0.01
-Ostomy: 0.01
-Other surgery: 0.03

Clinical consultations (per year): 7.38 (6.3-8.5)
-Gastroenterology: 5.65
-Surgery: 0.72
-Emergency: 0.41
-Other: 0.59

Diagnostic tests (per year) (range): 5.25 (4.3-6.2)
-Digestive tract: 3.00
-Other: 2.25

Laboratory tests (per year) (range): 17.13 (13.2-21.1)

Drug treatment (days treatment/y) (range): 627.19 (492.4-762)
-Immunomodulators: 183.67
-Corticosteroids: 76.71
-Antibiotics: 84.29
-Other treatments: 282.52

Parenteral nutrition (d/y): 6.56 (-3.4-16.5)
Packed cells transfusion (per year): 0.00
Day care hospitalisation (d/patient/y):
IFX administration NA

Post-IFX

Hospital admission (%): 37.7; *p*= 0.005
Hospital stay (d/y) (range): 6.33 (2.2-10.4); *p*= 0.002
Surgery (%): 17.4; *p*= 0.000

Surgery (interventions/y) (range): 0.20 (0.1-0.3); *p*= 0.014
-Perianal surgery: 0.16; *p*= 0.008
-Resections: 0.03; *p*= 0.564
-Ostomy: 0.01; *p*= 1.000
-Other surgery: 0.00; *p*= 0.157

Clinical consultations (per year): 7.42 (6.5-8.4); *p*= 0.971
-Gastroenterology: 6.07; *p*= 0.484
-Surgery: 0.46; *p*= 0.163
-Emergency: 0.07; *p*= 0.006
-Other: 0.81; *p*= 0.563

Diagnostic tests (per year) (range): 2.33 (1.1-3.3); *p*= 0.000
-Digestive tract: 0.154; *p*= 0.000
-Other: 0.80; *p*= 0.000

Laboratory tests (per year) (range): 19.00 (15.7-22.3); *p*= 0.216

Drug treatment (days treatment/y) (range): 736.12 (570.4-901.9); *p*= 0.266
-Immunomodulators: 262.94; p= 0.000
-Corticosteroids: 59.48; *p*= 0.077
-Antibiotics: 77.39; *p*= 0.137
-Other treatments: 336.30; *p*= 0.263

Parenteral nutrition (d/y): 1.84 (-1.6-5.3); *p*= 0.345
Packed cells transfusion (per

						year): 0.09 (-0.09-0.3); *p*= 0.317 Day care hospitalisation (d/patient/y) IFX administration: 7.22 (6.5-8.0); *p*= 0.000	
Kane 2009[96]	Adherent	375	NR	NR	CD-related health care cost (US $), mean (SD) Hospitalisation: 1,283 (4,214) Outpatient excluding infliximab cost: 2,335 (4,454) Emergency department visit: 94 (360) Total medical cost excluding infliximab cost: 5,285 (9,968) Outpatient infliximab cost: 28,699 (15,514)	Baseline Health care resource utilization, n (%) Hospitalisation: 206 (27.5) Outpatient visit: 724 (96.5) Emergency department visit: 210 (28.0) Ancillary care: 456 (60.8) CD-related health care resource utilization Any hospitalisation, %: 15.5 Hospital days, mean (SD): 1.1 (4.0)	
Kane 2009[96]	Non-adherent	196	NR	NR	CD-related health care cost (US $), mean (SD) Hospitalisation: 4,494 (10,694); *p*<0.001 Outpatient excluding infliximab cost: 3,931 (9,621); *p*=0.007 Emergency department visit: 91 (332); *p*=0.929 Total medical cost excluding infliximab cost: 10,243 (20,818); *p*<0.001 Outpatient infliximab cost: 18,751 (11,731); *p*<0.001	Baseline Health care resource utilisation, n (%) Hospitalisation: 120 (30.6); *p*= 0.264 Outpatient visit: 380 (96.9); *p*= 0.717 Emergency department visit: 130 (33.2); *p*= 0.070 Ancillary care: 186 (47.5); *p*< 0.001 CD-related health care resource utilisation Any hospitalisation, %: 29.1; *p*< 0.001 Hospital days, mean (SD): 3.1 (8.1); *p*< 0.001	
Wu 2008[97]	Infliximab	262	During the 6-month baseline period, patients who later lost treatment response and those who did not incurred similar total treatment costs (US $10,385 vs. $10,589, *p*> 0.05).	NR	Patients who did not experience LOR with infliximab treatment within 1 year incurred $19,506 in CD-related medical and pharmacy costs compared to	NR	CD related ED visit or hospitalisation: 40 patients

			During the 12-month follow-up period, those who did not experience loss of treatment response incurred $24,532 in total costs, on average; whereas those who did experience LOR incurred 36% greater mean total costs ($33,289). The cost difference ($8756) between the two groups was statistically significant ($p< 0.001$).		$27,250, or 40% greater CD-related costs for patients who experienced loss of treatment response. The $7744 difference was also statistically significant ($p< 0.001$). Based on these results, 88% of the total cost difference ($8756) was CD related.	
Ho 2008[12]	Adalimumab	22	Current local costing for financial year 2005–2006: Adalimumab 40 mg fortnightly treatment: £10 773 (£21 546 for adalimumab 40 mg ⁄ weekly); Infliximab at 5 mg ⁄ kg dosing regimen 8-weekly maintenance therapy: £7112	NR	NR	NR
Saro 2007[66]	Infliximab	34	Pre- vs. Post-Infliximab Hospital stay, Mean (CI) €: 2783 (1,041–5051) vs. 679 (57–1374), Cost saving: 2104 Pre- vs. Post-Infliximab surgery, Mean (CI) €: 139 (6–329) vs. 79 (0–239), Cost saving: 60 Pre- vs. Post-Infliximab Clinical consultations, Mean (CI) €: 390 (229–566) vs. 448 (350–568), Cost addition: 58 Pre- vs. Post-Infliximab Diagnostic tests and laboratory analyses, Mean (CI) €: 722 (450–1,005) vs. 807 (671–949), Cost addition:85 Pre- vs. Post-Infliximab Drug treatment in hospital, Mean (CI) €: 430 (200–795) vs. 585 (233–1118), Cost addition: 155 Pre- vs. Post-Infliximab, Infliximab treatment, Mean (CI) €: 0.00 vs.7996, Cost addition: 7996	NR	Pre- vs. Post-Infliximab Overall annual cost, Mean (CI) €: 4464 vs. 10594, Cost difference: 6130	Pre- vs. Post-Infliximab Hospital stay (days/year), Mean (CI): 8.59 (5.06–12.11) vs. 2.26 (0.54–3.99), $p< 0.001$ Pre- vs. Post-Infliximab Clinical consultations (per year), Mean (CI): 5.80 (4.57–7.03) vs. 6.67 (5.99–7.37), $p= 0.158$ Pre- vs. Post-Infliximab Diagnostic tests and laboratory analyses (per year), Mean (CI): 19.68 (15.08–24.29) vs. 26.59 (24.12–28.45), $p= 0.021$ Pre- vs. Post-Infliximab Drug treatment in hospital (days per year), Mean (CI): 598.39 (290.90–954.66) vs. 704.69 (408.32–1001.02) Pre- vs. Post-Infliximab, Infliximab (administrations per year), Mean (CI): 0 vs. 4.08 (3.35–4.81)

						Pre- vs. Post-Infliximab Day-care hospitalisation for Infliximab administration, Mean (CI): 0 vs. 4.40 (3.71–5.10)	
Ollendorf 2006[99]	Infliximab	2230	Infusion charges ($) Mean: $4,441 SD: $1,778 Minimum: $907 Maximum: $13,489 Median: $4,099 Infusion payments ($) Mean $2,793 SD $990 Minimum $588 Maximum $6,066 Median $2,628	NR	NR	Of the original total of 9724 infusions, 168 were not evaluable because of data quality issues, yielding cost evaluation for 9556 total infusions (4.29 infusions per patient on average). Number of submitted vials Mean: 4.79 SD: 1.74 Minimum: 2 Maximum: 10 Median: 5	Paid amounts were reduced by 37% on average in relation to charged amounts. Corresponding median amounts were $4099 and $2628, respectively. On a per-vial basis, charged and paid amounts averaged $927 and $583, respectively.
Jewell 2005[67]	Infliximab	205	Cost of 353 infliximab infusions: £562719	NR	Total reductions in direct costs were estimated at £591 006 (difference in cost for pre and post infliximab).	NR	Cost associated with 353 infusions during the treatment. Net decrease in direct cost was £28 287 or the equivalent of £137.98 per patient Reductions of £176677 came from fewer surgical procedures, examination under anaesthetics, diagnostic tests, blood transfusions and nutritional therapies.
ACCENT I Trial (Rutgeerts 2004)[68]	Placebo (Episodic strategy)	188	NA	NA	NA	NA	Significantly fewer Crohn's disease-related hospitalisations occurred in patients in the infliximab 5 and 10 mg/kg scheduled treatment strategy groups (23 and 24 per 100 patients, respectively) compared with patients in the episodic treatment

							strategy group (38 per 100 patients, *p*=0.047 and *p*=0.023, respectively, for each comparison).
ACCENT I Trial (Rutgeerts 2004)[68]	Infliximab 5 mg/kg (Scheduled strategy)	192	NA	NA	NA	NA	
ACCENT I Trial (Rutgeerts 2004)[68]	Infliximab 10 mg/kg (Scheduled strategy)	193	NA	NA	NA	NA	
ACCENT II Trial (Sands 2004)[69]	Placebo maintenance	143	NR	NR	NR	Hospitalisations (mean number per 100 patients with the total number in parentheses): 31 (45) Hospitalisation days (mean number of days hospitalised per patient): 2.4 All surgeries and procedures (mean number per 100 patients with the total number in parentheses): 118 (169) Inpatient surgeries and procedures (mean number per 100 patients with the total number in parentheses): 45 (65) Major surgeries (mean number per 100 patients with the total number in parentheses): 13 (18)	18.9% patients were hospitalised.
ACCENT II Trial (Sands	Infliximab maintenance	139	NR	NR	NR	Hospitalisations (mean number per 100 patients with the total number in	8.6% patients were hospitalised, *p*<0.05 vs. placebo maintenance.

2004)[69]	ance					parentheses): 14 (19), *p*<0.05 vs. placebo maintenance Hospitalisation days (mean number of days hospitalised per patient): 0.8, *p*=0.110 vs. placebo maintenance All surgeries and procedures (mean number per 100 patients with the total number in parentheses): 60 (83), *p*<0.01 vs. placebo maintenance Inpatient surgeries and procedures (mean number per 100 patients with the total number in parentheses): 10 (14) *p*<0.001 vs. placebo maintenance Major surgeries (mean number per 100 patients with the total number in parentheses): 2 (3), *p*<0.05 vs. placebo maintenance	
Arnott 2001[71]	Infliximab	39	The cost per vial of Infliximab (100 mg) the institution was £463.00. Therefore, the median cost per patient was £1389 (range, £926-£2315).	NR	NR	NR	
Abraham 2013[100]	Infliximab	CD: 8042	NR	NR	NR	<u>First-Year Hospitalisation Rate Reductions by Drug Therapy Durations</u> Duration of therapy: relative rate reduction in hospitalisations (compared with drug exposure)(%) (1) Immunomodulator therapy 1 month: 4.9 3 months: 13.9 6 months: 25.9 9 months: 36.2 12 months: 45.1	A 50% relative reduction in surgery was observed among patients receiving 7 months of infliximab or 5 months of dual therapy. Analysis of dose-response data revealed 73.1% and 92% reductions in risk of hospitalisation and surgery, respectively, after 9 months of dual therapy.

(2) Anti-TNF-α monotherapy
1 month: 1.3
3 months: 3.9
6 months: 37.9
9 months: 67.1
12 months: 82.6
(3) Dual therapy
1 month: 0.7
3 months: 2.1
6 months: 4.1
9 months: 86.1

Section 5. Quality of life

5A. Data on quality of life in ulcerative colitis

The QoL data for UC patients are presented in Table S9.

The most common scales used were IBDQ and the Cleveland Global Quality of Life (CGQL) scale.

In the ULTRA 2 trial (Sandborn 2013[72]), in the adalimumab treatment group, the mean (SD) baseline IBDQ score was 128 (29). At week 8, it decreased to 29 (36), at week 32 it decreased to 28 (41) and at week 52 it decreased to 27 (42). In a multinational study (Laharie 2012[26]), in the infliximab treatment group, the IBDQ median score increased by 100 points (75-112), between baseline and day 98.

Table S9. Quality of life in ulcerative colitis

Study name	Countries	Treatment groups	No. of patients	Name of QoL questionnaire	QoL questionnaire; Baseline Score, Mean (SD), Median, Range, p value	QoL questionnaire Score (at Endpoint); Mean (SD), Median, Range, p value	QoL questionnaire Score (change from baseline); Mean (SD), Median, Range; p value	Comments
ULTRA2 Trial (Sandborn 2013) [72]	Multinational (North America, Europe, Australia, New Zealand, and Israel)	Adalimumab	248	IBDQ	Mean (SD): 128 (29)	NR	Mean (SD) values At week 8: 29 (36), $p<0.05$ At week 32: 28 (41), $p<0.05$ At week 52: 27 (42), $p<0.05$	Among the 494 enrolled patients, 260 (52.6%) were observed to have achieved clinical remission during at least 1 visit during the 52 week clinical trial. Achievement of clinical remission at any time was associated with increases from baseline of 35.8 (SE=1.7) in the total IBDQ score, 5.0 (SE=0.4) in the Physical Component Summary (PCS) score of the SF-36, and 6.4 (SE=0.5) in

								the Mental Component Summary (MCS) score of the SF-36 and with reductions of 20.7 (SE=1.9) in WPAI total work productivity impairment (TWPI) score and 19.3 (SE=1.3) in total activity impairment (TAI) score (all $p<0.05$). Including the effect of current remission status, patients who achieved and sustained clinical remission for 6 months are estimated to experience increases of 49.6 (SE=2.3) in total IBDQ score, 7.9 (SE=0.5) in the PCS, and 8.2 (SE=0.7) in the MCS and decreases of 31.9 (SE=2.4) in TWPI score and 28.4 (SE=1.8) in TAI score compared to similar patients who did not achieve clinical remission (all $p<0.05$).
ULTRA2 Trial (Sandborn 2013) [72]	Multinational (North America, Europe, Australia, New Zealand, and Israel)	Placebo	246	IBDQ	Mean (SD): 123 (33)	NR	Mean (SD) values At week 8: 20 (36) At week 32: 20 (41) At week 52: 197 (41)	
Gu 2013	USA	Biologics: Anti-TNF-α	25	Cleveland Global Quality	NR	QoL: 8.0 (2.4) Quality of health: 7.8	NR	

[22]		therapy impact on outcomes after TPC/IPAA for UC		of Life (CGQL) Scale		(2.7) Quality of energy: 7.5 (2.7) CQGL: 0.8 (0.3)	
Gu 2013 [22]	USA	No Biologics: Anti-TNF-α therapy impact on outcomes after TPC/IPAA for UC	156	Cleveland Global Quality of Life (CGQL) Scale	NR	QoL: 8.0 (1.9) Quality of health: 8.0 (2.0) Quality of energy: 7.5 (2.2) CQGL: 0.8 (0.2)	NR
Gu 2013 [22]	USA	Biologics: Anti-TNF-α therapy impact on short-term outcomes after STC/EI for UC	142	Cleveland Global Quality of Life (CGQL) Scale	NR	NR	NR
Gu 2013 [22]	USA	No Biologics: Anti-TNF-α impact therapy on short-term outcomes after STC/EI for UC	265	Cleveland Global Quality of Life (CGQL) Scale	NR	NR	NR
Gu 2013 [22]	USA	Biologics: Anti-TNF-α therapy use before colectomy on short-	88	Cleveland Global Quality of Life (CGQL) Scale	NR	QoL: 7.8 (1.6) Quality of health: 8.0 (1.7) Quality of energy: 7.3 (1.9) CQGL: 0.8 (0.2)	NR

		and long-term outcomes after CP/IPAA for UC in patients who underwent initial STC						
Gu 2013 [22]	USA	No Biologics: Anti-TNF-α therapy use before colectomy on short- and long-term outcomes after CP/IPAA for UC in patients who underwent initial STC	164	Cleveland Global Quality of Life (CGQL) Scale	NR	QoL: 7.8 (1.8) Quality of health: 8.0 (2.0) 7.7 (1.9) Quality of energy: 6.9 (2.2) CQGL: 0.8 (0.2)	NR	
Laharie 2012 [26]	Multinational (France, Spain, Belgium, and Finland)	Ciclosporin	58	IBDQ	Median (IQR): 103 (89–118)	NR	Median score increased by 78 points (IQR 66–104; n=19) between baseline and day 98.	Responses to the inflammatory bowel disease questionnaire were available in only 36 patients evaluable at day 98.
Laharie 2012 [26]	Multinational (France, Spain,	Infliximab	57	IBDQ	Median (IQR): 96 (84–113)	NR	Median score increased by 100 points (75–112; 17) between baseline and day 98.	.

	Belgium, and Finland)							
Tursi 2010 [74]	Italy	Infliximab	23	IBDQ	Mean: 48	Mean: 198, $p<0.05$ vs. baseline	NR	The Mayo subscore for endoscopy decreased from mean value of 3 to mean value <1 (range 0-1) at the time of last endoscopic assessment ($p<0.05$).
Probert 2003 [39]	Multinational (UK and Germany)	Placebo group	20	IBDQ; EuroQol	Mean (SD) IBDQ: 114 (29) EuroQol: 49 (17)	Week 6 Mean (SD) IBDQ: 139 (43) EuroQol: 54 (23)	Improvement: Mean (SD) IBDQ: 25 (28) EuroQol: 4 (16)	
Probert 2003 [39]	Multinational (UK and Germany)	Infliximab group	23	IBDQ; EuroQol	Mean (SD) IBDQ: 127 (40) EuroQol: 52 (16)	Week 6 Mean (SD) IBDQ: 163 (40) EuroQol: 59 (19)	Improvement: Mean (SD) IBDQ: 36 (49) EuroQol: 7 (17)	
Casellas 2012 [101]	Spain	Infliximab/adalimumab: 7/4	UC: 11	IBDQ- 37	Median (IQR) Global IBDQ score: 144.0 (131.4-185.4)	Median (IQR) Global IBDQ score 235.0 (219.0–241.0); not significant Digestive symptoms: 52.0 (49.6–54.4); not significant Systemic symptoms: 44.8 (42.0–45.5); $p=0.056$ Emotional symptoms: 50.4 (44.8–54.4); not significant. Functional symptoms: 46.9 (45.5–49.0); $p=0.02$ Social affectation: 39.6 (39.6–40.8); $p=0.04$	NR	

5B. Data on quality of life in Crohn's Disease

The most common scale used was IBDQ. The other scales reported across studies were WPAI, SF-36, EQ-5D and MADRS.

In the CARE trial (Louis 2013[5]), mean baseline scores indicated severe productivity impairment and poor QoL. At week 20, 60% of infliximab-naïve and 47% of infliximab primary non-responders achieved clinically important improvements (≥9 points) on the SIBDQ and 51% and 43%, respectively, achieved the minimum clinically important difference (improvement ≥7 percentage points) for total work productivity impairment (non-responder imputation). At week 20, 64% of infliximab-naïve and 55% of infliximab primary non-responders achieved clinically important improvements in total activity impairment.

Table S10. Quality of Life in Crohn's Disease

Study name	Countries	Treatment groups	No. of patients	Name of QoL questionnaire	QoL questionnaire; Baseline Score, Mean (SD), Median, Range, p value	QoL questionnaire Score (at Endpoint); Mean (SD), Median, Range, p value	QoL questionnaire Score (change from baseline); Mean (SD), Median, Range; p value	Comments
Patil 2013 [41]	USA	Infliximab	30	SIBDQ	NR	At 2 months, N= 28: 53.75 (13.34); *p*= 0.02 At 9 months, N= 26: 54.67 (15.76); *p*= 0.045 At 12 months, N= 25: 54.92 (13.67); *p*= 0.026	NR	
Patil 2013 [41]	USA	Adalimumab/Certolizumab	28	SIBDQ	NR	At 2 months, N= 21: 44.3 (14.39) At 9 months, N= 15: 44.8 (11.16) At 12 months, N= 19: 50.55 (11.43)	NR	
CARE Trial (Louis 2013)[5]	Multinational (Austria, Belgium, Czech Republic, Denmark,	Adalimumab	945	Work productivity and activity impairment questionnaire (WPAI) SIBDQ	WPAI:CD component score; Mean (SD) Absenteeism (N= 468): 23.1 (34.4) Presenteeism (N= 484): 45.4 (27.2) Total work productivity impairment (N= 442): 51.9 (29.0) Total activity impairment	NR	Change from baseline to week 4 WPAI:CD component score Absenteeism (N= 353): −9.6 (30.0) Presenteeism (N= 395): −17.3 (27.1) Total work productivity impairment (N= 327): −18.4 (30.0) Total activity impairment (N= 856): −21.3 (27.0) SIBDQ total score (N= 880): 12.1 (22.0) Change from baseline to week 20	

	Finland, France, Germany, Greece, Ireland, Italy, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, UK)				(N= 907): 56.6 (25.8) SIBDQ total score (N= 910): 36.7 (10.3)		WPAI:CD component score Absenteeism (N= 328): −9.8 (31.7) Presenteeism (N= 360): −20.0 (30.9) Total work productivity impairment (N= 302): −21.4 (33.6) Total activity impairment (N= 747): −25.9 (29.7) SIBDQ total score (N= 763): 14.7 (12.9)
Ghazi 2013 [44]	USA	Step Up	39	Short Inflammatory Bowel Disease Questionnaire (SIBDQ)	Baseline SIBDQ: 52 (14)	Mean (SD) At 12 months, QoL: 58 (12)	Mean (SD) At 12 months, QoL: 4.8 (10)
Ghazi 2013 [44]	USA	Early Bio	54	Short Inflammatory Bowel Disease Questionnaire (SIBDQ)	Baseline SIBDQ: 43 (14); p= 0.003	Mean (SD) At 12 months, QoL: 53 (13)	Mean (SD) At 12 months, QoL: 9.9 (13)
Zorzi 2012 [48]	Italy	Infliximab	44	IBDQ	NR	Induction: Significant improvement in IBDQ was found at week 6 compared to baseline in 16 patients, $p<0.0001$ Maintenance: No significant improvement in IBDQ was found at week 6 and 54 compared to baseline in 10 patients.	NR

Zorzi 2012 [48]	Italy	Adalimumab	49	IBDQ	NR	Induction: Significant improvement in IBDQ was found at week 4 compared to baseline in 34 patients, $p<0.01$ Maintenance: Significant improvement in IBDQ was found at each scheduled visit compared to baseline in 10 patients, $p<0.002$.	NR	
ACCESS-trial (Panaccione 2011)[14]	Canada	Adalimumab	304	SIBDQ, WPAI	SIBDQ; Mean (SD): 36 (10) WPAI component scores Absenteeism; Mean (SD): 16 (28) Presenteeism; Mean (SD): 50 (25) TWPI; Mean (SD): 57 (25) TAI; Mean (SD): 63 (24)	SIBDQ; Week 4, n= 301: 46 Week 8, n= 303: 47 Week 12, n= 303: 48 Week 24, n= 303: 49 WPAI component scores, Mean TWAI; Week 4, n= 182: 33 Week 8, n= 204: 33 Week 12, n= 214: 29 Week 24, n= 222: 29 TAI; Week 4, n= 297: 39 Week 8, n= 302: 39 Week 12, n= 303: 35 Week 24, n= 303: 33	NR	*SIBDQ, TWPI, TAI changes at all visits vs. baseline was significant *Absenteeism and presenteeism score changes given for TNF-naïve and infliximab-experienced subgroups but not overall.
ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Placebo	261 (139 entered ADHERE)	IBDQ	Median: 125	Represented graphically	NR	
ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Adalimumab eow	260 (144 entered ADHERE)	IBDQ	Median: 124	Represented graphically	NR	

ADHERE (Panaccione 2010)[59]	Multinational (Europe, USA, Canada)	Adalimumab weekly	257 (184 entered ADHERE)	IBDQ	Median: 122	Represented graphically	NR	
Tursi 2010 [74]	Italy	Infliximab	39	IBDQ	Mean: 48	Mean: 198, p<0.005 vs. baseline	NR	
CHOICE-trial (Lichtiger 2010)[84]	USA	Adalimumab	673	SIBDQ, WPAI, TAI, TWPI	SIBDQ; Mean (SD): 37.4 (11) WPAI component scores Absenteeism; Mean: 14.8 (25.1) Presenteeism; Mean: 44.3 (27) TWPI; Mean (SD): 49.4 (29.3) TAI; Mean (SD): 57.9 (26.3)	WPAI component scores, Mean Absenteeism; Week 4: 6, p<0.05 Week 8: 8, p<0.05 Week 12: 7, p<0.05 Week 24: 9, p<0.05 Presenteeism; Week 4: 29, p<0.05 Week 8: 28, p<0.05 Week 12: 28, p<0.05 Week 24: 25, p<0.05 TWAI; Week 4: 31,p<0.05 Week 8: 31, p<0.05 Week 12: 31, p<0.05 Week 24: 28, p<0.05 TAI; Week 4: 39, p<0.05 Week 8: 38, p<0.05 Week 12: 38, p<0.05 Week 24: 34, p<0.05	SIBDQ; Week 4, n=645: 9.1 (10.5), p<0.001 Week 8, n=611: 9.1 (11.7), p<0.001 Week 12, n=503: 9.5 (11.7), p<0.001 Week 24, n=290: 11.9 (12.6), p<0.001 WPAI component scores, Mean (SD) Absenteeism; Week 4, n=339: -8.3 (24.1), p<0.05 Week 8, n=321: -6.5 (26.3), p<0.05 Week 12, n=259: -7.5 (24.5), p<0.05 Week 24, n=141: -7.2 (31.0), p<0.05 Presenteeism; Week 4, n=358: -15.2 (27.4), p<0.05 Week 8, n=337: -15.2 (29.7), p<0.05 Week 12, n=272: -15.7 (29.3), p<0.05 Week 24, n=146: -18 (29.7), p< 0.05 TWPI; Week 4, n=333: -17.9 (30.8), p<0.05 Week 8, n=317: -17.5 (32.0), p<0.05 Week 12, n=256: -17.3 (31.4), p<0.05 Week 24, n=136: -19.4 (34.5), p<0.05 TAI Week 4, n=642: -18.8 (28.0), p<0.05 Week 8, n=606: -19.2 (30.0), p<0.05 Week 12, n=505: -0.5 (30.0), p<0.05 Week 24, n=287: -23.9 (32.3), p<0.05	*The 9-point threshold, which correlates with a 100-point change on the CDAI, was met or surpassed in the all adalimumab patients *At all scheduled visits, the mean changes in work productivity component (absenteeism, Presenteeism and TWPI) scores represented statistically significant improvements compared with baseline *SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TAI, total activity impairment; TWPI, total work productivity

								impairment; WPAI, Work Productivity and Activity Impairment Questionnaire
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	Certolizumab (every 2 week, maintenance)	161	IBDQ, WPAI-CD	Dimensions of IBDQ, Mean (SD); Total IBDQ score: 120.4 (29.4) Bowel symptoms: 38.7 (9.5) Systemic symptoms: 15.8 (4.9) Emotional function: 46.2 (13.4) Social function: 19.7 (7.3) WPAI:CD scores, Mean (SD) Absenteeism, n= 89: 25.4 (34.1) Presenteeism, n= 83: 48.1 (23.8) Overall work impairment, n= 77: 53.7 (24.0) Daily activity impairment, n= 159: 62.0 (24.9)	Dimensions of IBDQ, Mean (SD); Total IBDQ score Week 6, n= 160: 167.8 (28.3) Week 16, n= 116: 163.4 (32.3) Week 26, n= 71: 171.7 (30.3) Bowel symptoms Week 6, n= 161: 53.4 (8.3) Week 16, n= 116: 51.1 (10.4) Week 26, n= 71: 54.3 (9.9) Systemic symptoms Week 6, n= 161: 23.9 (5.3) Week 16, n= 116: 22.6 (6.2) Week 26, n= 71: 23.6 (5.9) Emotional function Week 6, n= 161: 62.1 (12.8) Week 16, n= 116: 61.5 (13.4) Week 26, n= 71: 64.4 (12.2) Social function Week 6, n= 161: 28.4 (6.4) Week 16, n= 116: 28.2 (6.8) Week 26, n= 71: 29.5 (6.3) WPAI:CD scores, Mean (SD); Absenteeism Week 6, n= 87: 6.3 (20.4) Week 16, n= 69: 11.9 (27.0) Week 26, n= 34: 16.5 (32.7) Presenteeism Week 6, n= 90: 22.2 (19.7) Week 16, n= 67: 27.6 (24.2) Week 26, n= 33: 26.4 (22.8) Overall work impairment Week 6, n= 84: 23.2 (21.2) Week 16, n= 64: 29.7 (25.9) Week 26, n= 29: 27.4 (24.0)	Dimensions of IBDQ, Mean (SD); Total IBDQ score Week 6, n= 160: 47.9 (30.0) Week 16, n= 116: 41.0 (35.6) Week 26, n= 71: 52.0 (37.6) Bowel symptoms Week 6, n= 160: 14.9 (9.4) Week 16, n= 116: 12.0 (11.9) Week 26, n= 71: 15.9 (12.9) Systemic symptoms Week 6, n= 161: 8.1 (5.6) Week 16, n= 116: 6.4 (6.5) Week 26, n= 71: 8.0 (6.9) Emotional function Week 6, n= 160: 16.0 (12.9) Week 16, n= 116: 15.0 (14.1) Week 26, n= 71: 19.0 (15.0) Social function Week 6, n= 160: 8.8 (6.8) Week 16, n= 116: 7.5 (7.3) Week 26, n= 71: 9.2 (7.3)	

						Daily activity impairment Week 6, n= 159: 33.6 (24.8) Week 16, n= 114: 35.3 (29.1) Week 26, n= 69: 30.4 (25.6)	
WELCOME trial (Sandborn 2010)[10]	Multinational (Austria, Belgium, Canada, Denmark, France, Germany, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, the UK, and USA)	Certolizumab (every 4 week, maintenance)	168	IBDQ, WPAI-CD	Dimensions of IBDQ, Mean (SD); Total IBDQ score: 118.0 (28.6) Bowel symptoms: 38.1 (8.8) Systemic symptoms: 14.8 (5.2) Emotional function: 45.9 (12.4) Social function: 19.3 (7.6) WPAI:CD scores, Mean (SD) Absenteeism, n= 80: 22.7 (33.3) Presenteeism, n= 79: 42.9 (23.3) Overall work impairment, n= 71: 46.2 (26.2) Daily activity impairment, n= 167: 64.2 (24.6)	Dimensions of IBDQ, Mean (SD); Total IBDQ score Week 6, n= 166: 163.9 (31.0) Week 16, n= 120: 159.4 (31.8) Week 26, n= 75: 167.8 (34.5) Bowel symptoms Week 6, n= 166: 53.0 (8.7) Week 16, n= 120: 50.7 (10.5) Week 26, n= 75: 53.9 (11.3) Systemic symptoms Week 6, n= 166: 22.8 (5.5) Week 16, n= 120: 21.9 (5.6) Week 26, n= 75: 23.9 (5.8) Emotional function Week 6, n= 166: 60.7 (13.6) Week 16, n= 120: 59.9 (13.1) Week 26, n= 75: 61.8 (14.2) Social function Week 6, n= 166: 27.4 (6.9) Week 16, n= 120: 26.9 (7.2) Week 26, n= 75: 28.2 (6.9) WPAI:CD scores, Mean (SD); Absenteeism Week 6, n= 87: 11.2 (26.7) Week 16, n= 60: 9.6 (22.6) Week 26, n= 32: 12.4 (26.6) Presenteeism Week 6, n= 84: 25.5 (22.9) Week 16, n= 61: 27.4 (24.6) Week 26, n= 36: 26.4 (25.1) Overall work impairment Week 6, n= 82: 27.6 (24.4) Week 16, n= 58: 31.0 (26.2) Week 26, n= 30: 30.3 (27.2) Daily activity impairment Week 6, n= 162: 35.4 (25.3)	Dimensions of IBDQ, Mean (SD); Total IBDQ score Week 6, n= 166: 45.4 (29.2) Week 16, n= 120: 41.9 (33.3) Week 26, n= 75: 47.3 (32.5) Bowel symptoms Week 6, n= 166: 14.8 (9.6) Week 16, n= 120: 12.8 (10.7) Week 26, n= 75: 15.4 (10.2) Systemic symptoms Week 6, n= 166: 8.0 (5.6) Week 16, n= 120: 7.2 (6.3) Week 26, n= 75: 8.8 (6.6) Emotional function Week 6, n= 166: 14.7 (11.9) Week 16, n= 120: 14.0 (13.4) Week 26, n= 75: 14.7 (13.1) Social function Week 6, n= 166: 8.0 (6.6) Week 16, n= 120: 7.9 (7.4) Week 26, n= 75: 8.4 (6.9)

						Week 16, n= 117: 42.8 (28.0) Week 26, n= 75: 35.5 (27.8)		
Banovic 2009 [102]	France	Infliximab	22	MADRS, MOS-SF36	NR	MADRS, Mean (SD): 10.95 (9.47) MOS-SF36; PF Physical Functioning: 83.64 (19.89) RP Role Physical: 59.09 (37.44) BP Bodily Pain: 65.05 (28.87) GH General Health: 41.59 (19.33) VT Vitality: 38.41 (21.90) SF Social Functioning: 60.80 (25.67) RE Role Emotional: 60.61 (43.20) MH Mental Health: 53.45 (25.37) HT Health Transition: 3.13 (1.01)	NR	MADRS, scale for depression assessment: Montgomery and Asberg Depression Rating Scale MOS-SF36: QOL assessment scale
Banovic 2009 [102]	France	Conventional therapy	29	MADRS, MOS-SF36	NR	MADRS, Mean (SD): 7.38 (6.55) MOS-SF36; PF Physical Functioning: 81.72 (20.06) RP Role Physical: 66.38 (36.76) BP Bodily Pain: 67.10 (23.19) GH General Health: 51.62 (22.70) VT Vitality: 46.21 (21.03) SF Social Functioning: 67.67 (23.27) RE Role Emotional: 66.67 (37.80) MH Mental Health: 57.10 (21.64) HT Health Transition: 2.78 (1.13)	NR	MADRS, scale for depression assessment: Montgomery and Asberg Depression Rating Scale MOS-SF36: QOL assessment scale
GAIN Trial (Sandborn 2007)[85]	Multinational (USA, Canada, Belgium, France)	Placebo	166	IBDQ	NR	Week 4: 139	Week 4: 15	
GAIN Trial (Sandbor	Multinational (USA, Canada,	Adalimumab	159	IBDQ	NR	Week 4: 150, *p*< 0.001	Week 4: 30	Rate difference in IBDQ between the two groups at week 4 was 14.1

n 2007)[85]	Belgium , France)							percentage points (CI, 7.92 to 20.41).
Caselas 2007 [86]	Spain	Infliximab	49	IBDQ-36, EuroQol-5D	5 Dimensions of IBDQ-36, Median (IQR); Digestive symptoms: 6.5 (5.6-6.7) Systemic symptoms: 6.1 (5.5-6.7) Emotional affectation: 6.0 (5.4-6.7) Functional affectation: 6.0 (5.1-6.4) Social affectation: 6.0 (5.7-6.7) EuroQol-5D Preference value: 1.0 (0.8–1.0) Visual analog scale: 65 (60–80)	5 Dimensions of IBDQ-36, Median (IQR); Digestive symptoms 12 months: 6.3 (6.0–6.6) 24 months: 6.6 (6.1–6.8) 36 months: 6.5 (6.3–6.8) 48 months: 6.5 (6.4–6.8) Systemic symptoms 12 months: 6.5 (6.0–7.0) 24 months: 6.8 (6.2–7.0) 36 months: 6.6 (6.1–7.0) 48 months: 6.8 (6.4–7.0) Emotional affectation 12 months:6.4 (6.0–6.8) 24 months: 6.4 (6.0–7.0) 36 months: 6.6 (6.3–7.0) 48 months: 6.7 (6.6–7.0) Functional affectation 12 months: 6.1 (5.4–7.0) 24 months: 6.2 (5.3–7.0) 36 months: 6.5 (5.3–7.0) 48 months: 6.1 (6.0–6.5) Social affectation 12 months: 6.2 (6.0–7.0) 24 months: 6.5 (6.0–7.0) 36 months: 6.8 (5.9–7.0) 48 months: 6.9 (6.8–7.0) EuroQol-5D, Median (IQR); Preference value 12 months: 1.0 (1.0–1.0) 24 months: 1.0 (1.0–1.0) 36 months: 1.0 (0.9–1.0) 48 months: 1.0 (0.8–1.0) Visual analog scale 12 months: 70 (60–80) 24 months: 70 (60–80) 36 months: 70 (60–82)	NR	As per IBDQ-36, at inclusion 49% of patients corresponded to good-excellent category and that proportion ranged from 54%-60% throughout the study. According to EuroQol-5D score, majority of patients reported having no problems on the mobility (96%), self-care (100%), usual activities (98%), and pain/discomfort (94%) dimensions during remission.

					48 months: 77 (60–90)			
Sands 2007 [87]	USA	Placebo +Infliximab	27	Inflammatory Bowel Disease Questionnaire (IBDQ)	138.4	The Subject Global Assessment scores: Week 6: 50.6 mm Week 10: 60.2 mm	Mean increase in IBDQ score: Week 6: 9.1 Week 10: 17.3	HRQoL was assessed in weeks 0, 6, and 10 and as part of any early-discontinuation visits before week 10.
Sands 2007 [87]	USA	Natalizumab+Infliximab	52	Inflammatory Bowel Disease Questionnaire (IBDQ)	133.1	The Subject Global Assessment scores: Week 6: 62.3 mm, *p*=0.018 Week 10: 66.9 mm, *p*=0.174	Mean increase in IBDQ score: Week 6: 12.3 *p*=0.605 Week 10: 18.7, *p*=0.811	
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Placebo (Episodic strategy)	188	IBDQ SF-36 PCS SF-36 MCS	IBDQ (N= 188) Median (IQR): 126 (110-114) (N= 335, all patients randomised as week 2 responders): 129, 130 (27) SF-36 PCS, Median, mean (SD) (N= 573, all randomised patients): 34, 34 (8) (N= 335, all patients randomised as week 2 responders): 34, 34 (8) SF-36 MCS, Median, mean (SD) (N= 573, all randomised patients): 38, 39 (11) (N= 335, all patients randomised as week 2 responders): 39, 39 (11)	NR	At week 10, (N= 107) IBDQ: 28.9 SF-36 PCS: 4.9 SF-36 MCS: 3.8 At week 30, (N= 109) IBDQ: 14.0 SF-36 PCS: 3.1 SF-36 MCS: 2.9 At week 54, (N= 108) IBDQ: 8.9 SF-36 PCS: 2.5 SF-36 MCS:2.0	Data presented graphically. The improvement observed in average IBDQ was not significantly better (*p*=0.208) in the infliximab 5 mg/kg scheduled treatment strategy group but was significantly better in the infliximab 10 mg/kg (p=0.001) and combined scheduled treatment strategy groups (*p*=0.008) when compared with that of the episodic treatment strategy group. There was a significantly higher proportion of patients with IBDQ

								scores exceeding 170 in the combined scheduled strategy group at weeks 14, 22, and 46 (p=0.028, p =0.012, and p=0.049, respectively) than in the episodic strategy group.
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Infliximab 5 mg/kg (Scheduled strategy)	192	IBDQ SF-36 PCS SF-36 MCS	IBDQ (N= 192) Median (IQR): 126 (109-146) (N= 335, all patients randomised as week 2 responders): 129, 130 (27) SF-36 PCS, Median, mean (SD) (N= 573, all randomised patients): 34, 34 (8) (N= 335, all patients randomised as week 2 responders): 34, 34 (8) SF-36 MCS, Median, mean (SD) (N= 573, all randomised patients): 38, 39 (11) (N= 335, all patients randomised as week 2 responders): 39, 39 (11)	NR	At week 10, (N= 220, combined maintenance groups) IBDQ: 37.8, p< 0.05 vs. episodic group SF-36 PCS: 8.6 , p< 0.001 vs. episodic group SF-36 MCS: 6.5, p≥ 0.05 vs. episodic group At week 30, (N= 107) IBDQ: 27.1, p< 0.05 vs. episodic group SF-36 PCS: 7.3, p< 0.01 vs. episodic group SF-36 MCS: 4.6, p≥ 0.05 vs. episodic group At week 54, (N= 111) IBDQ: 22.1, p< 0.05 vs. episodic group SF-36 PCS: 6.1, p< 0.05 vs. episodic group SF-36 MCS: 5.1, p≥ 0.05 vs. episodic group	Data presented graphically. The improvement observed in average IBDQ was not significantly better (p=0.208) in the infliximab 5 mg/kg scheduled treatment strategy group but was significantly better in the infliximab 10 mg/kg (p=0.001) and combined scheduled treatment strategy groups (p=0.008) when compared with that of the episodic treatment strategy group. There was a significantly higher proportion of patients with IBDQ scores exceeding 170 in the combined

								scheduled strategy group at weeks 14, 22, and 46 (p=0.028, p=0.012, and p=0.049, respectively) than in the episodic strategy group.
ACCENT I Trial (Rutgeerts 2004)[68]	Multinational (North America, Europe, and Israel)	Infliximab 10 mg/kg (Scheduled strategy)	193	IBDQ SF-36 PCS SF-36 MCS	IBDQ (N= 193) Median (IQR): 131 (109-152) (N= 335, all patients randomised as week 2 responders): 129, 130 (27) SF-36 PCS, Median, mean (SD) (N= 573, all randomised patients): 34, 34 (8) (N= 335, all patients randomised as week 2 responders): 34, 34 (8) SF-36 MCS, Median, mean (SD) (N= 573, all randomised patients): 38, 39 (11) (N= 335, all patients randomised as week 2 responders): 39, 39 (11)	NR	At week 10, (N= 220, combined maintenance groups) IBDQ: 37.8, p< 0.05 vs. episodic group SF-36 PCS: 8.6 , p< 0.001 vs. episodic group SF-36 MCS: 6.5, p≥ 0.05 vs. episodic group At week 30, (N= 111) IBDQ: 31.7, p< 0.01 vs. episodic group SF-36 PCS: 7.3, p< 0.05 vs. episodic group SF-36 MCS: 4.9, p≥ 0.05 vs. episodic group At week 54, (N= 109) IBDQ: 30.2, p< 0.001 vs. episodic group SF-36 PCS: 7.2, p< 0.01 vs. episodic group SF-36 MCS: 5.8, p< 0.05 vs. episodic group	Data presented graphically. The improvement observed in average IBDQ was not significantly better (p=0.208) in the infliximab 5 mg/kg scheduled treatment strategy group but was significantly better in the infliximab 10 mg/kg (p=0.001) and combined scheduled treatment strategy groups (p=0.008) when compared with that of the episodic treatment strategy group. There was a significantly higher proportion of patients with IBDQ scores exceeding 170 in the combined scheduled strategy group at weeks 14, 22, and 46 (p=

								0.028, *p*= 0.012, and *p*=0.049, respectively) than in the episodic strategy group.
ACCENT II Trial (Sands 2004)[69]	Multinational (North America, Europe, and Israel)	Placebo maintenance	Evaluable N=99 (Responders at the time of randomisation) (Total randomised N=143)	IBDQ	Median (IQR): 168 (145-193)	NR	Median increase from baseline in IBDQ score At week 30: 4 At week 54: 5	Median (IQR) IBDQ score at baseline for overall non-responders (N=87): 161 (136-176)
ACCENT II Trial (Sands 2004)[69]	Multinational (North America, Europe, and Israel)	Infliximab maintenance	Evaluable N=96 (Responders at the time of randomisation) (Total randomised N=139)	IBDQ	Median (IQR): 155 (135-187)	NR	Median increase from baseline in IBDQ score At week 30: 14, *p*=0.002 vs. placebo maintenance At week 54: 10, *p*=0.03 vs. placebo maintenance	Median (IQR) IBDQ score at baseline for overall non-responders (N=87): 161 (136-176)
Balkom 2002 [103]	The Netherlands	Infliximab	23	IBDQ	Mean IBDQ: 117.5 (17.7) Bowel: 39.1 (6.0) Systemic: 14.8 (4.9) Emotional: 47.5 (9.2) Social: 16.1 (6.7)	Mean IBDQ (at 4 weeks): 168.7 (31.8)	The IBDQ in the active Crohn's disease group improved significantly 4 weeks after the single infusion from 117.5 (17.7) to 168.7 (31.8) (p< 0.0001, increase of 51.2; 95% confidence	

							interval (CI), 36.7–65.7). The percentage of improvement was higher in the active disease group than in the fistulising group: Total IBDQ (46% vs. 25%, respectively; *p*< 0.05), Bowel (43% vs. 19%, respectively; *p*<0.05), Systemic (84% vs. 33%, respectively; p<0.01), Social (84% vs. 33%, respectively; *p*=0.018), Emotional (84% vs. 33%, respectively; *p*< 0.05),	
Balkom 2002 [103]	The Netherlands	Infliximab	33	IBDQ	Mean IBDQ: 151.8 (33.9) Bowel: 51.5 (10.7) Systemic: 20.5 (6.0) Emotional: 56.8 (14.3) Social: 22.9 (8.0)	Mean IBDQ (at 2 weeks): 164.0 (29.2); (at 10 weeks): 179.6 (25.5)	In the fistulising group, the total IBDQ score improved 2 weeks after infusion from 151.8 (33.9) to 164.0 (29.2) *p*= 0.002, increase of 12.2; 95% CI, 4.8–19.7).	
Rutgeerts 1999 [77]	Multinational (North America and Europe)	Infliximab	37	IBDQ	NR	NR	NR	Infliximab-retreatment demonstrated continued/improved suppression of disease activity at levels associated with disease remission.
Rutgeerts 1999 [77]	Multinational (North America and Europe)	Placebo	36	IBDQ	NR	NR	NR	Placebo-retreatment had a gradual loss of the initial treatment benefit throughout the study period, returning to values associated with active disease.
Targan 1997 [91]	Multinational (North America and Europe)	Infliximab 5mg/kg	27	IBDQ	Mean (SD): 122 (29) All Infliximab groups, n= 83: 118 (27)	Mean (SD), *p* value for change from baseline; At week 4: 168 (36), *p*< 0.0001 All Infliximab groups, n= 83, At week 4: 154 (38), *p*= 0.001	46	

Targan 1997 [91]	Multinational (North America and Europe)	Infliximab 10mg/kg	28	IBDQ	Mean (SD): 116 (23) All Infliximab groups, n= 83: 118 (27)	Mean (SD), p value for change from baseline; At week 4: 146 (41), *p*= 0.002 All Infliximab groups, n= 83, At week 4: 154 (39), *p*= 0.001	30
Targan 1997 [91]	Multinational (North America and Europe)	Infliximab 20mg/kg	28	IBDQ	Mean (SD): 118 (28) All Infliximab groups, n= 83: 118 (27)	Mean (SD), p value for change from baseline; At week 4: 149 (35), *p*= 0.03 All Infliximab groups, n= 83, At week 4: 154 (40), *p*= 0.001	32
Targan 1997 [91]	Multinational (North America and Europe)	Placebo	25	IBDQ	Mean (SD): 128 (29)	Mean (SD), At week 4: 133 (28)	5, *p*= 0.001 compared to the overall Infliximab group
Caselas 2012 [101]	Spain	Infliximab/adalimumab: 17/26	CD: 43	IBDQ- 36	Median (IQR) Global IBDQ score: 201.6 (180.9-232.2)	Median (IQR) Global IBDQ score: 228.0 (206.0–240.0) Digestive symptoms: 52.0. (45.6–54.4) Systemic symptoms: 42.0 (37.8–44.8) Emotional symptoms: 50.4 (45.6–54.4) Functional symptoms: 44.8 (39.9–47.6) Social affectation 39.6: (36.0–40.2)	Normalisation of HRQOL was achieved in all 11 UC patients and in 29 out of 43 CD patients (67%). In our sample population, restoration of health was significantly more frequent in UC than in CD (*p*<0.05).

Section 6. Identified studies

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