Year : 2019

An economic evaluation of inflammatory bowel disease using real world data in Switzerland

Pillai Nadia

Pillai Nadia, 2019, An economic evaluation of inflammatory bowel disease using real world data in Switzerland

Originally published at : Thesis, University of Lausanne

Posted at the University of Lausanne Open Archive http://serval.unil.ch
Document URN : urn:nbn:ch:serval-BIB_B152A30AEB333

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Centre universitaire de médecine générale et santé publique (Unisanté)

An economic evaluation of inflammatory bowel disease using real world data in Switzerland

Thèse de doctorat ès sciences de la vie (PhD)

présentée à la

Faculté de biologie et de médecine
de l'Université de Lausanne

par

Nadia PILLAI

Master of Public Health, Imperial College London, UK

Jury

Président	Prof. Olivier Bonny
Directrice de thèse	PD Dr. Valérie Pittet
Co-directeur	Prof. Mark Dusheiko
Expert	Prof. Pierre Michetti
Expert	Dr. Keith Bodger
Experte	Dr. Isabelle Durand-Zaleski

Lausanne 2019

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Ecole Doctorale
Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président·e	Monsieur	Prof.	Dario	**Diviani**
Directeur·trice de thèse	Madame	Dre	Valérie	**Pittet**
Co-directeur·trice	Monsieur	Prof.	Mark	**Dusheiko**
Expert·e·s	Madame	Dre	Isabelle	**Durand-Zaleski**
	Monsieur	Dr	Keith	**Bodger**
	Monsieur	Prof.	Pierre	**Michetti**

le Conseil de Faculté autorise l'impression de la thèse de

Madame Nadia Pillai

Master en santé publique, Imperial College London, Royaume-Uni

intitulée

An economic evaluation of inflammatory bowel disease using real world data in Switzerland

Lausanne, le 25 octobre 2019

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Dario Diviani

This thesis is dedicated to my parents
for always inspiring me

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

This PhD thesis is a result of the support, collaboration, and expertise of several people - you have all helped shape this work and my development as a researcher in numerous ways and, for that, I would like to thank you all.

To my supervisors, Valérie Pittet and Mark Dusheiko, I am truly grateful to have worked with you both over the past three years. Your advice and mentorship have helped me to develop as a scientist and researcher. Thank you for giving me the opportunity to work on this important topic and for all the insightful discussions we have had. I would also like to acknowledge Bernard Burnand and Joachim Marti for supporting me at the IUMSP/Unisanté and for overseeing the development of this PhD.

I am also grateful for the scientific contributions that I have received from all my collaborators. In particular, to Matthias Schwenkglenks, Judith Lupatsch, and Simone Sutherland from the Institute for Pharmaceutical Medicine (ECPM) - thank you for collaborating on the cost-effectiveness analysis and hosting me at your offices. Aside from providing valuable expertise to develop the economic model, I am so grateful for your moral support during some of the more stressful final months of my PhD. In addition, I would like to acknowledge Michel Maillard, Alain Schoepfer, and Pierre Michetti for their clinical expertise; and the Swiss IBD Cohort Study and the Helsana group, in particular Caroline Bähler-Baumgartner, Beat Brüngger, and Eva Blozik, for providing data used in this work. Finally, thank you to my thesis committee, Pierre Michetti, Keith Bodger, and Isabelle Durand-Zaleski, for taking the time to provide expert review on this thesis, and to Olivier Bonny, for presiding over the thesis process.

My biggest gratitude goes to my family who were always there to listen to my grumbles and cheer me on when I thought I was winning. To my parents, for giving me the opportunities to accomplish everything I set out to do. You taught me to persevere, always provided strong advice, and gave me the confidence to pursue this PhD. I am glad you didn't leave me on the side of the road when I was a kid and I hope that it has (so far) been worth it for you too. To my sister and brother-in-law, for always having my back, and for making sure there was enough food, wine, and Kirschstängeli along the way. To my partner, for celebrating every milestone with me, for keeping me grounded, for being patient, and for always remaining optimistic and encouraging. Thank you for staying interested as you read my drafts, listened to my presentations, and let me talk for hours about my work. Finally, I am eternally grateful for my friends and family all over the world for the fun holidays, visits to Lausanne, hikes, braais, banter, and general distractions over the years. *Thank you all for always lifting me up.*

ABBREVIATIONS

Anti-TNF	Anti-tumour necrosis factor
CD	Crohn's disease
CDAI	Crohn's disease activity index
CHF	Swiss francs
CI	Confidence interval
CPI	Consumer Price Index
DRG	Diagnosis-related group
EIM	Extra-intestinal manifestations
EMA	European Medicines Agency
FDA	Food and drug administration
FOPH	Federal Office of Public Health
GLM	Generalised linear model
GP	General practitioner
HTA	Health technology assessments
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
IQR	Inter-quartile range
MTWAI	Modified Truelove and Witts Activity Index
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PICOS	population, intervention, comparator, outcomes, study design
PPP	Purchasing power parity
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RCT	Randomised controlled trials
RWD	Real world data
SD	Standard deviation
SE	Standard error
SF-36	Short-Form 36
SF-6D	Short-Form 6 Dimensions
SIBDCS	Swiss IBD Cohort Study
UC	Ulcerative colitis
WTP	Willingness-to-pay threshold

LIST OF TABLES

Supplementary Files

LIST OF FIGURES

Supplementary Files

SUMMARY

Inflammatory bowel disease (IBD), consisting primarily of Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition of the gastrointestinal tract placing a large health and economic burden on health systems worldwide. Increased availability of biologic agents have shown promise to improve health outcomes and reduce the need for steroids and surgery; however, the long-term clinical and cost implications of their use needs to be determined. This thesis aimed to evaluate the costs and cost-effectiveness associated with novel pharmaceuticals for the treatment of adults diagnosed with IBD in Switzerland. Studies in this thesis draw on statistical and econometric methods to evaluate real world data obtained from the Swiss IBD Cohort Study (SIBDCS) and reimbursement claims.

In Switzerland, the economic burden of CD and UC was demonstrated with mean health care costs estimated at CHF 10,553 for CD and CHF 6,334 for UC per patient per year. Between 2006 and 2016, expenditures rose by 7% for CD and 10% for UC per year, on average, due to a rapid uptake of biologic agents. Moreover, expenditures on inpatient and outpatient events, and indirect costs associated with work absenteeism remained stable during this period. This study points to an important shift in the clinical management of IBD towards greater use of pharmaceuticals.

Early aggressive treatment with biologic agents has been suggested as a novel strategy to help achieve long-term mucosal healing and modify the natural course of CD. This thesis showed that CD patients treated with biologics within 2 years of diagnosis (early biologic treatment) did not experience significant improvements in disease progression or surgery rates over 10 years when compared to similar patients who did not receive biologics or received biologics >2 years after diagnosis (late/no biologic treatment). Moreover, early compared to late or no biologic treatment was associated with high lifetime costs (CHF 384,607 versus CHF 340,800) and minor improvements in quality-adjusted life years (QALYs: 16.84 versus 16.75) and was therefore not cost-effective with incremental cost-effectiveness ratios (ICERs) above acceptable thresholds from the Swiss health system (CHF 887,450 per QALY) and societal perspectives (CHF 449,130 per QALY). However, in a subgroup of patients known to receive biologic treatments during the course of their disease, earlier initiation improved clinical outcomes and was cost-effective compared to late initiation. In addition, future price reductions from biosimilars may help contain rising costs in IBD and improve the cost-effectiveness of early biologic treatment approaches.

This thesis highlights the need to identify characteristics influencing disease prognosis for IBD patients in order to stratify patients and target aggressive treatment strategies to those likely to benefit. Moreover, closer monitoring of patients' response to treatments will help timely decision-making and improve the efficiency of patient care. More generally, this work contributes to the ongoing development of methods to use real world data to evaluate long-term health outcomes and cost-effectiveness and highlights the importance of continuous evaluation of the cost-effectiveness of novel pharmaceuticals to ensure value for money in the health system.

CHAPTER 1

General introduction and outline of the thesis

BACKGROUND AND MOTIVATION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD), which cause inflammation in the gastrointestinal tract and extra-intestinal complications[1]. IBD follows a course of exacerbation and remission of inflammation and is characterised by chronic abdominal pain, diarrhoea and weight loss. CD can affect all segments of the gastrointestinal tract, from the mouth to perianal area, and most commonly affects the terminal ileum and colon[2]. It is a progressive disease leading to severe bowel damage caused by strictures, fistulae, and abscesses. In contrast to CD, UC often presents as continuous inflammation affecting the colon and rectum[3]. IBD places a large health and financial burden on the health system due to loss of quality of life, and high costs of clinical management associated with surgical interventions, hospitalisations, long-term pharmaceutical treatments, and routine specialist visits[4]. In Europe, 2.5 - 3 million people are affected with IBD contributing an overall direct health care cost of 4.6 - 5.6 billion euros per year[5]. In Switzerland, estimates suggest that between 12,000 – 16,000 people are affected with IBD, representing 0.2% of the population[6 7]. The rising prevalence and high cost of IBD management presents an important challenge for patients, public health and health systems requiring infrastructure for long-term chronic disease management and efficient allocation of resources[8].

Clinical management of IBD

The clinical management of IBD is based on several aspects including disease severity and location (for both CD and UC), and disease behaviour (for CD)[9 10]. The treatment landscape for IBD is complex with multiple pharmaceutical and surgical interventions to induce and maintain remission and manage disease complications and extra-intestinal manifestations (EIMs)[9 11 12]. The current standard of care recommends a step-up treatment approach using conventional pharmaceutical therapies, such as aminosalicylates, corticosteroids, immunomodulators, and biologic treatments. In this approach, treatments are intensified in response to treatment failure and increased disease severity. Biologic therapies are often reserved for patients who are refractory to conventional therapies, steroid-dependent, or presenting with moderate to severe inflammation or complications[9 12]. Intestinal resection surgery is an additional option for both diseases to remove affected tissues and treat disease complications. While the surgical removal of the colon and rectum could in principle offer a cure for UC, surgical treatment for CD is not curative since inflammations are not limited to the colon or rectum[10 11].

Over the past two decades, the management of IBD has been revolutionised by increased availability and uptake of biologic agents and, more recently, biosimilars. Biologic agents were found to increase remission rates, reduce the need for steroid treatment, and repair structural damage to the intestinal lining[13]. These treatments target pro-inflammatory molecules responsible for the inflammation in the gastrointestinal tract[14]. There are currently several biologic agents available on the market and approved for IBD. In Switzerland, this includes anti-tumour necrosis factor (TNF) agents (infliximab, adalimumab, golimumab and certolizumab pegol), anti-alpha-4-beta-7 integrin (vedolizumab) and, most recently, an anti-interleukin 12/23 agent (ustekinumab). As patents for older biologic agents expire, biosimilars have arrived on the market offering more therapeutic options for IBD as well as potential cost savings[15]. This rapidly changing treatment landscape calls for increased scrutiny into the added value to patients especially given high costs of novel therapeutics.

Increasingly, debate about when to start biologic therapy has created a shift towards early aggressive treatment in a top-down treatment strategy. It is hoped that this would change the natural history of the disease by preventing disease progression in the long-term[13]. This is particularly relevant in CD where patients are at risk of developing severe and disabling disease over time[16]. Recent evidence from randomised controlled trials (RCTs) and population-based cohort studies have shown favourable outcomes for patients treated with biologics early[17-19]. However, due to the strong immunosuppressive capacity of biologic agents, frequent monitoring and follow-up of patients is needed in order to manage drug response, potential complications, and side effects[20]. Thus, the long-term clinical and cost-effectiveness of early biologic use needs to be confirmed before widespread adoption in clinical practice is advocated.

Economic burden of IBD

The economic burden of IBD has been demonstrated in Europe and North America[21-24]. Health care costs are driven by the need for surgical interventions and long-term pharmaceutical use, which has been exacerbated by increased adoption of biologic agents[25]. Moreover, IBD patients require frequent clinical follow-up with specialist nurses and clinicians to monitor the relapsing and remitting phases of the disease, disease severity, and development of complications and EIMs. In addition, patients are

often diagnosed in early adult life during their peak economic productivity[26]. Disease and treatment-related morbidity, and frequent health care visits can affect patients' quality of life leading to disruption in education and employment as well as long-term dependence on the health and social system contributing to a high societal burden of the disease[24 27]. Given the chronic, dynamic, and resource intensive management of IBD, a clear understanding of the optimal treatment strategies to manage the disease is required to reduce the burden placed on both the health system and patients[27].

Economic models to evaluate the cost-effectiveness of new treatments and treatment strategies are essential to guide political and clinical decision-making on the reimbursement and use of new treatments[22]. Published cost-effectiveness studies in IBD often rely on modelling techniques using data from a variety of sources, including RCTs, in order to assess the efficacy of new treatments. Often assumptions are made in order to fill gaps associated with the paucity of data[28]. Although, evidence from RCTs offer a high degree of internal validity, they are often criticized for having low external validity given the large heterogeneity of patients and treatment practices in real world settings[29 30]. Real world data (RWD), such as those from cohort studies, patient registries, and electronic medical records, have higher external validity and allow evaluation of specific outcomes, treatment patterns, safety, and comparative effectiveness of treatments. Increasingly, health care payers are demanding post-marketing real world effectiveness and cost-effectiveness evidence of new products in order to supplement RCT data[31]. Although the use of RWD poses several potential benefits for decision-making, specific methods are needed to deal with biases associated with their use, such as confounding by indication and missing data[32].

The Swiss health system

Switzerland has achieved universal health coverage through its mandatory statutory health insurance system. Non-profit private health insurance companies compete to provide health insurance to all residents in the country. In addition, optional complementary and voluntary health insurance packages are offered for services not included in the mandatory package, thereby increasing coverage and access to health care services and providers[33]. The system is decentralised with the 26 cantons (administrative geographic unit in Switzerland) responsible for the overall implementation and coordination of health care services, provider supervision, and financing. The system is publicly

financed through (1) canton level tax-based contributions provided to inpatient acute care hospitals, (2) mandatory health insurance premiums paid by all residents to private insurance companies, and (3) social insurance contributions for accident, disability, old-age, and military[33]. The Swiss health system is considered to be one of the highest performing and most responsive health systems in the world[34]. However, it is also very expensive compared to other Organisation for Economic Co-operation and Development (OECD) countries with rising health insurance premiums and a high burden of out-of-pocket expenditures due to co-payments and additional voluntary health insurance[34].

Cantons and private insurance companies are responsible for the reimbursement of health care services. Traditionally, the Federal Office of Public Health (FOPH) approves the reimbursement of pharmaceuticals through the statutory health insurance package on the basis of clinical effectiveness, appropriateness, and cost-effectiveness. For expensive medications, such as biologic agents, additional authorisations are required from patient's health insurers to use such treatments. This can lead to inequality and delays in access to innovative treatments, as well as inconsistent decisions. As costs in the Swiss health system continue to rise, the FOPH has expressed the internal motivation to strengthen the use of health technology assessments and cost-effectiveness analyses in order to aid reimbursement decisions for new and previously approved treatments[35].

THESIS AIMS AND OVERVIEW

The aim of this thesis was to evaluate the costs and cost-effectiveness of novel pharmaceutical therapies for the treatment of adults diagnosed with IBD in Switzerland. This was addressed in four original studies, which are presented in this thesis.

Primary data sources

This thesis used data from the Swiss IBD Cohort Study (SIBDCS), a national prospective cohort running in Switzerland since 2006[36]. The SIBDCS was initiated with the aim of understanding the manifestation, clinical management, and socio-economic impact of IBD in Switzerland. Adult and paediatric IBD patients are enrolled in the cohort through their physicians during routine clinical visits. Participating centres include large academic and non-academic centres across the German and French-speaking regions of Switzerland. While the cohort does not capture all IBD patients in Switzerland, it has enrolled

a selection of patients from across the largest cantons in Switzerland. Data collection is conducted annually using two questionnaires completed by patients and their treating physicians. Physicians record information on clinical characteristics of patient's diagnosis, including disease phenotype, activity, and complications, and treatment and health care utilisation. In addition, patient questionnaires capture additional data on clinical characteristics and health care utilisation, as well as information on IBD family history, and quality of life. To date, more than 3500 patients are enrolled in the SIBDCS, 56% are diagnosed with CD and 44% with UC, and the mean follow-up time is 6 years[36]. For this thesis, anonymised patient-level data reported by both patients and physicians, and collected between 2006 and 2018, were extracted. This included data on socio-demographic characteristics, disease history, treatment and health care utilisation, and quality of life. Patients were included in this study if they had a confirmed diagnosis of CD or UC, were aged ≥18 years at enrolment, and had received some pharmaceutical or surgical interventions for their disease.

In addition, reimbursement claims data were obtained from the Helsana Group, a leading private health insurance company in Switzerland covering statutory health insurance for up to 15% of the Swiss population across all cantons[37]. Due to the absence of diagnostic information in the outpatient setting in Switzerland, IBD patients in the insurance database were identified based on pharmaceutical use (using the WHO Anatomical therapeutic chemical classification system) and specialist consultation visits with gastroenterologists[38]. This approach was evaluated by the Helsana Group and showed high sensitivity when compared with inpatient data, where diagnostic information was known[38]. In total, 8434 suspected IBD patients were identified in the insurance data. For this thesis, anonymised, patient-level data on inpatient and outpatient events were extracted between 2012 and 2014. Data on inpatient events included the dates of hospital admission and discharge, canton of service providers, codes for inpatient procedures using diagnosis-related groups (DRGs), and the total amount reimbursed. Data on outpatient events included the date of visits, facility type, provider specialisation, codes for outpatient events using TARMED (a national administrative coding system), and the total amount reimbursed. The insurance data were used in this thesis to generate unit cost estimates for inpatient and outpatient procedures, which were linked to resource utilisation data reported in the SIBDCS.

Ethical approval and data confidentiality

The work conducted in this thesis was exempted from ethical approval by the ethics committee in the Canton of Vaud (Commission cantonale d'éthique de la recherche sur l'être humain Ref. AP/CCG/cc).

Ethical approval to conduct the SIBDCS was obtained by Principal Investigators from regional Swiss Ethics Committees where patients were enrolled (Commission d'éthique du Canton de Vaud/Protocol no. 33/06). Written informed consent was obtained from all patients enrolled in the cohort study. Permission to use data from the SIBDCS in this thesis was obtained from the Swiss IBD Cohort Scientific Committee in 2016 (approval number: 2016-20). Anonymised extracts of patient-level data were provided by the Swiss IBD Cohort Datacenter at the Centre universitaire de médecine générale et santé publique (Unisanté).

Data from the Helsana Group was obtained through contractual agreement between the Helsana Versicherungen AG and the Institut Universitaire de Médecine Sociale et Préventive (now Unisanté). Anonymised data extracts were obtained from the Helsana Group through a secured file transfer program and were only used for the purposes of this thesis.

Brief summary of methods for cost-effectiveness analyses

This thesis uses cost-effectiveness analysis in order to systematically evaluate the value for money of alternative treatment strategies. In cost-effectiveness analyses, improvements in health outcomes and overall treatment costs between two or more interventions are compared over time[29]. Cost-effectiveness analyses are increasingly used to aid reimbursement decisions for novel pharmaceuticals and health care technologies. One approach to cost-effectiveness modelling includes using Markov models in order to represent clinical events that occur repeatedly over time[39]. Patients in a Markovmodel transition between mutually exclusive and collectively exhaustive health states defined to reflect clinically and economically important events based on the natural history of the disease. Transition probabilities are assigned to each pathway of the decision tree, which represent the probability (or risk) that the patient experiences a health state over time. Data on health state risks are usually obtained from a variety of sources including RCTs, registries, or pooled estimates obtained through meta-analyses. In addition, data on health care costs, indirect non-health care costs, and an effectiveness measure, usually

represented by health-related quality of life, are attributed to each health state. During each period (cycle) that the model is run, a weighted expected value of costs and quality of life is calculated based on the transition probabilities for each health state[40]. The model is run over several cycles, usually defined to reflect an average patient's life expectancy from disease diagnosis, in order to estimate the overall costs and effectiveness of each intervention.

The incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) was the primary outcome measure for this economic evaluation. The QALY is a standardised, generic measure of health status, which is often used in cost-effectiveness studies to represent the effectiveness of interventions. QALYs are calculated by multiplying gains in length of life and quality of life (also known as utilities) over time[29]. Utilities represent patient's preferences for different health states and are obtained using standardised questionnaires (e.g., the EQ-5D and SF-6D)[40]. They are traditionally measured on a scale from 0 to 1, where 1 represents perfect health and 0 represents death. The use of standardised effectiveness measures, such as the QALY, facilitates comparisons between cost-effectiveness results across different interventions and disease areas and enables decisions about resource allocation in the health system that reflect societal preferences[29].

Thesis outline

This thesis is organised in six chapters. The first study, in **Chapter 2**, is a systematic review of the literature, which was conducted with the aim of summarising existing evidence on the cost-effectiveness of pharmaceutical and surgical interventions for patients diagnosed with CD and UC[41]. In addition, this review helped to understand the quality of existing cost-effectiveness studies and the knowledge gaps that remain. The second study, presented in **Chapter 3**, aimed to evaluate the evolution of direct and indirect costs and health care utilisation for CD and UC in response to increased availability of biologic agents over 10 years[42]. Two subsequent studies presented in this thesis evaluated the clinical outcomes **(Chapter 4)** and cost-effectiveness **(Chapter 5)** of early biologic use compared to the current standard of care for CD patients. These studies were motivated by recent literature and ongoing clinical debate suggesting early biologic treatment as a novel approach for the management of patients with CD in order to prevent long-term disease progression. In **Chapter 4**, a retrospective analysis was conducted to evaluate the risks of key clinical outcomes over 10 years for CD patients who received biologic

treatment within 2 years of diagnosis (early biologic use) compared to patients who received biologics more than two years after diagnosis or those who did not receive any biologic treatments (late/no biologic use). In **Chapter 5**, results from this analysis, as well as additional data on costs and quality of life, were used to develop and parameterise a Markov model to evaluate the cost-effectiveness of early compared to late/no biologic treatment over patients' lifetime from the Swiss health system and societal perspectives. Finally, in **Chapter 6**, a general discussion and conclusions from this work is presented.

REFERENCES

1. Hanauer SB. Inflammatory Bowel Disease. *New England Journal of Medicine* 1996;334(13):841-48.
2. Torres J, Mehandru S, Colombel J-F, et al. Crohn's disease. *The Lancet* 2017;389(10080):1741-55. doi: 10.1016/s0140-6736(16)31711-1
3. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *The Lancet* 2017;389(10080):1756-70. doi: 10.1016/s0140-6736(16)32126-2
4. Stone CD. The economic burden of inflammatory bowel disease: Clear problem, unclear solution. *Digestive Diseases and Sciences* 2012;57(12):3042-44.
5. Burisch J, et al. The burden of inflammatory bowel disease in Europe. *Journal of Crohn's and Colitis* 2013;7:322-37.
6. Biétry F, Pitzurra R, Schwenkglenks M, et al. Helsana-Arzneimittelreport für die Schweiz 2014: Auswertungsergebnisse der Helsana Arzneimitteldaten aus den Jahren 2010 bis 2013: Helsana-Gruppe, 2014.
7. Juillerat P, Pittet V, Bulliard JL, et al. Prevalence of Inflammatory Bowel Disease in the Canton of Vaud (Switzerland): A population-based cohort study. *J Crohns Colitis* 2008;2(2):131-41. doi: 10.1016/j.crohns.2007.10.006 [published Online First: 2008/06/01]
8. M'Koma AE. Inflammatory bowel disease: An expanding global health problem. *Clinical Medicine Insights: Gastroenterology* 2013;6:33-47.
9. Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017;11(1):3-25. doi: 10.1093/ecco-jcc/jjw168 [published Online First: 2016/09/24]
10. Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017;11(6):649-70. doi: 10.1093/ecco-jcc/jjx008 [published Online First: 2017/02/06]
11. Gionchetti P, Dignass A, Danese S, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. *J Crohns Colitis* 2017;11(2):135-49. doi: 10.1093/ecco-jcc/jjw169 [published Online First: 2016/09/24]
12. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis* 2017;11(7):769-84. doi: 10.1093/ecco-jcc/jjx009 [published Online First: 2017/05/18]
13. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017;66(12):2179-87. doi: 10.1136/gutjnl-2017-314519 [published Online First: 2017/09/07]

14. Park KT. Utilisation trends of Anti-TNF agents and health outcomes in adults and children with inflammatory bowel diseases: A single-center experience. *Inflammatory Bowel Diseases* 2014;20(7):1242-49.
15. Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: from theory to practice. *Nat Rev Gastroenterol Hepatol* 2017;14(1):22-31. doi: 10.1038/nrgastro.2016.155
16. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;105(2):289-97. doi: 10.1038/ajg.2009.579 [published Online First: 2009/10/29]
17. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *The Lancet* 2008;371(9613):660-67. doi: 10.1016/s0140-6736(08)60304-9
18. Ma C, Beilman CL, Huang VW, et al. Anti-TNF Therapy Within 2 Years of Crohn's Disease Diagnosis Improves Patient Outcomes: A Retrospective Cohort Study. *Inflamm Bowel Dis* 2016;22(4):870-9. doi: 10.1097/MIB.0000000000000679 [published Online First: 2016/01/29]
19. Tsui JJ, Huynh HQ. Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? *Ann Gastroenterol* 2018;31(4):413-24. doi: 10.20524/aog.2018.0253 [published Online First: 2018/07/12]
20. Stallmach A, Hagel S, Bruns T. Adverse effects of biologics used for treating IBD. *Best Pract Res Clin Gastroenterol* 2010;24(2):167-82. doi: 10.1016/j.bpg.2010.01.002 [published Online First: 2010/03/17]
21. Kappelman MDea, et al. Direct health care costs of Crohn's Disease and Ulcerative Colitis in United States children and adults. *Gastroenterology* 2008;235(6):1907-13.
22. Burisch J, Vardi H, Pedersen N, et al. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom Study. *Inflammatory Bowel Diseases* 2015;21(1):121-31.
23. Odes S. How expensive is inflammatory bowel disease? A critical analysis. *World Journal of Gastroenterology* 2008;14(43):6641-47.
24. Kaplan G. The global burden of IBD: from 2015 to 2025. *Nature Review Gastroenterology and Hepatology* 2015;12:720-27.
25. van der Valk ME, Mangen MJ, Severs M, et al. Evolution of Costs of Inflammatory Bowel Disease over Two Years of Follow-Up. *PLoS One* 2016;11(4):e0142481. doi: 10.1371/journal.pone.0142481 [published Online First: 2016/04/23]
26. Molodecky NA ea. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142(1):46-57.
27. Mehta F. Economic implications of inflammatory bowel disease and its management. *American Journal Managing Care* 2016;22(3):S51-S60.
28. Bodger K. Cost Effectiveness of Treatments for Inflammatory Bowel Disease. *Pharmacoeconomics* 2011;29(5):387-401.
29. Drummond M, Sculpher M, Claxton K, et al. Methods for the economic evaluation of health care programmes: Fourth Edition. New York: Oxford University Press 2015.

30. Dreyer NA, Garner S. Registries for robust evidence. *JAMA* 2009;302(1):790-91.
31. Makady A, Ham RT, de Boer A, et al. Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies. *Value Health* 2017;20(4):520-32. doi: 10.1016/j.jval.2016.12.003 [published Online First: 2017/04/15]
32. Blommestein HM, Franken MG, Uyl-de Groot CA. A Practical Guide for Using Registry Data to Inform Decisions About the Cost Effectiveness of New Cancer Drugs: Lessons Learned from the PHAROS Registry. *Pharmacoeconomics* 2015;33:551-60.
33. Sturny I. The Swiss health care sytem [Available from: https://international.commonwealthfund.org/countries/switzerland/ accessed 15 August 2019.
34. OECD/WHO. OECD reviews of health systems: Switzerland 2011 Paris: OECD Publishing; 2011 [
35. BAG. Unwirksame und ineffiziente medizinische Leistungen sollen reduziert werden. In: Bundeskanzlei S, ed. Bern, 2016.
36. Pittet V, Michetti P, Mueller C, et al. Cohort Profile Update: The Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *International Journal ofEpidemiology* 2019:1-8. doi: 10.1093/ije/dyy298
37. Bähler C, Schoepfer AM, Vavricka SR, et al. Chronic comorbidities associated with inflammatory bowel disease: prevalence and impact on healthcare costs in Switzerland. *Eur J Gastroenterol Hepatol* 2017;29(8):916-25. doi: 10.1097/MEG.0000000000000891 [published Online First: 2017/05/05]
38. Bahler C, Vavricka SR, Schoepfer AM, et al. Trends in prevalence, mortality, health care utilization and health care costs of Swiss IBD patients: a claims data based study of the years 2010, 2012 and 2014. *BMC Gastroenterol* 2017;17(1):138. doi: 10.1186/s12876-017-0681-y [published Online First: 2017/12/05]
39. Kuntz KM, Weinstein MC. Modelling in economic evaluation. In: Drummond M, McGuire A, eds. Economic evaluation in health care: Merging theory with practice. Oxford: Oxford University Press 2001:141-71.
40. Briggs A, Schulpher M, Claxton K. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press 2006.
41. Pillai N, Dusheiko M, Burnand B, et al. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *Plos ONE* 2017;12(10):e0185500. doi: https://doi.org/10.1371/journal.pone.0185500
42. Pillai N, Dusheiko M, Maillard MH, et al. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. *J Crohns Colitis* 2019;13(6):744-54. doi: 10.1093/ecco-jcc/jjz003 [published Online First: 2019/03/28]

CHAPTER 2

A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease

Nadia Pillai, Mark Dusheiko, Bernard Burnand, Valérie Pittet

This study was published in PloSOne.

Citation:

Pillai N, Dusheiko M, Burnand B, Pittet V (2017). A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. PLoS ONE 12(10): e0185500. https://doi.org/10.1371/journal.pone.0185500

ABSTRACT

Background

Inflammatory bowel disease (IBD) is a chronic disease placing a large health and economic burden on health systems worldwide. The treatment landscape is complex with multiple strategies to induce and maintain remission while avoiding long-term complications. The extent to which rising treatment costs, due to expensive biologic agents, are offset by improved outcomes and fewer hospitalisations and surgeries needs to be evaluated. This systematic review aimed to assess the cost-effectiveness of treatment strategies for IBD.

Methods

A systematic literature search was performed in March 2017 to identify economic evaluations of pharmacological and surgical interventions for adults diagnosed with Crohn's disease (CD) or ulcerative colitis (UC). Costs and incremental cost-effectiveness ratios (ICERs) were adjusted to reflect 2015 purchasing power parity (PPP). Risk of bias assessments and a narrative synthesis of individual study findings are presented.

Results

Forty-nine articles were included; 24 on CD and 25 on UC. Infliximab and adalimumab induction and maintenance treatments were cost-effective compared to standard care in patients with moderate or severe CD; however, in patients with conventional-drug refractory CD, fistulising CD, and for maintenance of surgically-induced remission ICERs were above acceptable cost-effectiveness thresholds. In mild UC, induction of remission using high dose mesalazine was dominant compared to standard dose. In UC refractory to conventional treatments, infliximab and adalimumab induction and maintenance treatment were not cost-effective compared to standard care; however, ICERs for treatment with vedolizumab and surgery were favourable.

Conclusions

We found that, in general, while biologic agents helped improve outcomes, they incurred high costs and therefore were not cost-effective, particularly for use as maintenance therapy. The cost-effectiveness

of biologic agents may improve as market prices fall and with the introduction of biosimilars. Future research should identify optimal treatment strategies reflecting routine clinical practice, incorporate indirect costs and evaluate lifetime costs and benefits.

INTRODUCTION

Inflammatory bowel disease (IBD) refers mainly to Crohn's disease (CD) and ulcerative colitis (UC), which are chronic, autoimmune conditions causing inflammation in the gastrointestinal tract and extra-intestinal complications. IBD follows a course of exacerbation and remission of inflammation with symptoms characterised by chronic abdominal pain, diarrhoea and weight loss[1].

The clinical management of IBD aims to induce and maintain remission in patients with active disease[2]. Treatment strategies are complex, consisting of pharmacological treatment and surgery depending on disease location, severity and patients' treatment history[3]. The traditional step-up approach consists of first-line therapy with "conventional" or standard of care treatments such as aminosalicylates, corticosteroids, and immunomodulators (e.g. azathiopurine, 6-mercaptopurine)[4]. More recently, biologic agents are being used to induce remission in patients with moderate to severe disease and disease which responds poorly or is refractory to conventional medicines[5 6]. Anti-tumour necrosis factor (TNF) agents, infliximab, adalimumab, and golimumab are approved for use in CD and UC by the European Medicine's Agency (EMA) and the USA Food and Drug Administration (FDA); certolizumab pegol is approved only for CD in Switzerland, the USA and Russia[7]. In addition, two anti-integrin molecules are available: vedolizumab, approved in the USA and Europe for CD and UC, and natalizumab, approved in the USA for CD only. These agents provide promising alternatives to conventional medications as they are associated with reduced dependence on corticosteroids as well as longer duration of remission and improved overall quality of life[8].

IBD is among the top five most expensive gastrointestinal disorders to treat; it incurs wider social costs and reduces patients' quality of life[9]. Within Europe, estimates from 2013 suggest that 2.5 - 3 million people are affected with IBD contributing an overall direct health care cost of 4.6 - 5.6 billion Euros per year[10]. These figures are higher in the USA, which has an estimated prevalence of 214 per 100,000 individuals for CD and UC each[6 11]. The increasing prevalence, and high morbidity and costs of IBD represent an important challenge, requiring resources and infrastructure for efficient long-term chronic disease management[11 12].

The economic burden of IBD is changing whereby costs are increasingly driven by biologic agents and less by hospitalisations and surgery[13]. Despite the high costs of biologic agents, increasing use of these agents is seen due to their efficacy[14]. Given the uncertainties around the optimal use of biologic agents in IBD, increased scrutiny on the cost-effectiveness of different treatment strategies is required to aid cost-containment discussions while still ensuring patients' receive the best available treatments. Economic evaluations aim to compare alternative strategies by relating the improvement in health outcomes to the overall treatment costs across health states and over time in order to inform decision-making on the optimal use of available resources[15].

We conducted a systematic literature review of the cost-effectiveness of pharmacological or surgical interventions in adults diagnosed with CD or UC across different health systems and a spectrum of clinical presentations. The objective of this review was to provide an understanding of the cost-effective treatment strategies, particularly the biologic agents, and identify gaps in the literature and requirements for future economic models in IBD.

METHODS

Literature search

An extensive literature search was performed on 16 November 2016 and updated on 21 March 2017 in key databases: Ovid Medline (1946 to present), Embase (1974 to Nov 14, 2011), Database of Abstracts of Reviews of Effects (DARE, 1994 to March 2015), National Health Service Economic Evaluation Database (NHS EED, 1994 to March 2015), and Health Technology Assessment (HTA). Search terms used were: Crohn's disease, ulcerative colitis, inflammatory bowel disease, cost effectiveness, cost utility, cost benefit, health economic, economic evaluation (see Supplementary Files *Table A1* for detailed search strategy). Searches were limited to articles published in English and no date limits were applied. Attempts were made to identify full texts for any conference abstracts, however, where none were available, the abstracts were excluded due to insufficient information reported. In addition, a manual search of references from identified literature was performed. All references were downloaded to EndNote X8 and duplicates were removed.

Study selection

Title, abstract and full-text screening was conducted by NP. Studies were included in the review according to the PICOS (population, intervention, comparator, outcomes and study design) criteria. Full economic evaluations (cost-effectiveness, cost-benefit and cost-utility analyses) were included in the review if they included adults (aged ≥18), diagnosed with CD or UC, and compared surgical or pharmacological interventions. Models from drug manufacturers reported in HTA submissions were also included provided sufficient detail was available. Studies were excluded from the review if they were partial economic evaluations, if they did not specifically evaluate treatments for IBD or if they were a letter, comment piece or editorial.

Data extraction and interpretation

Data extraction was conducted based on guidance from the Cochrane Handbook[16]. Data extracted included disease indication, year and setting, intervention and comparator, perspective, study design, type of decision analysis (e.g. Markov model or decision tree analysis), time horizon, source and year of costs, currency, discount rate, source of outcomes and benefits, sensitivity analysis, and study results. To aid comparisons, costs were inflated to 2015 prices in US Dollars, using the OECD consumer price index (CPI)[17], and then converted to 2015 purchasing power parity (PPP) using OECD rates[18]. Where the year of cost data collection was not reported the year of publication was used instead.

The overall cost-effectiveness result, normally expressed in terms of an incremental cost-effectiveness ratio (ICER), represents the additional cost per unit of effectiveness (often the quality-adjusted life year (QALY)) achieved from adopting one intervention relative to an alternative. The ICER was recalculated to reflect 2015 PPP costs per unit of effectiveness, using the following formula:

$$ICER = \frac{\text{PPP Cost of intervention 1} - \text{PPP Cost of intervention 2}}{\text{Effectiveness of intervention 1} - \text{Effectiveness of intervention 2}}$$

When interpreting the ICER, interventions were said to be dominant (or dominated) if the costs of intervention 1 were lower (or higher) and its effectiveness better (or worse) than intervention 2. When both the costs and effectiveness of intervention 1 were higher (or lower) a threshold at which the cost of obtaining an additional unit of effectiveness (or savings for the loss of effectiveness) is acceptable was normally used. In the UK, the National Institute for Clinical Excellence (NICE) recommends a

technology or drug as cost-effective if it has an ICER between 20'000 GBP to 30'000 GBP per QALY gained (29'069.77 – 43'604.65 in 2015 PPP), reflecting the opportunity cost incurred of obtaining an additional QALY had the money been spent elsewhere in the health system[19]. In the USA, a threshold of 100'000 USD to 150'000 USD has been informally accepted by decision-makers and researchers based on estimated values of an additional statistical life year[20]. These thresholds are still contested and subject to change[21-23], therefore, in this study, conclusions drawn with respect to cost-effectiveness reflect the setting of the original study.

Risk of bias

As recommended by available guidelines, bias assessments were performed using the Drummond et al. (2006) checklist[24] for economic evaluations and the checklist from Philips et al. (2004) for model-based economic evaluations[25 26].

Study synthesis

This systematic review presents a narrative summary discussing studies on CD and UC by clinical presentation (mild, moderate, severe, disease refractory to conventional treatments, fistulising CD, and surgically-induced remission) and treatment aims (induction, maintenance and both induction and maintenance). A descriptive analysis of the studies is presented followed by the results of cost-effectiveness for individual studies. Based on recommendations from guidelines for systematic reviews in economic evaluations, no attempts were made to quantitatively pool study results[26].

RESULTS

Study selection

The literature search revealed 803 records of which 49 full text articles were retained after removing duplicates and applying the inclusion and exclusion criteria (See *Figure 1*). Of the included studies, 24 focus on CD and 25 on UC.

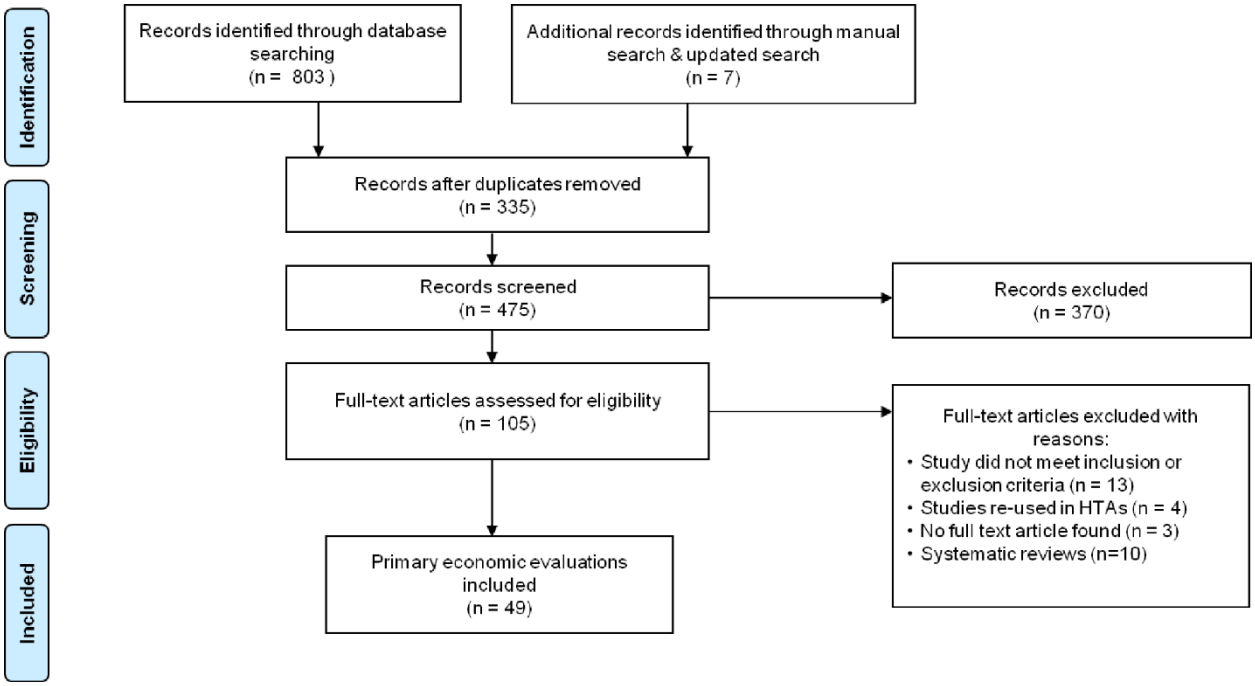


Figure 1 Flow chart of study inclusion based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Descriptive analysis

An increasing number of economic evaluations in IBD have been published over the past 20 years (*Figure 2*). The oldest study identified on CD was published in 1997, while, the majority were published from 2000, following the market approval of infliximab. A large increase in economic evaluations on UC was seen in 2016; however, the first publication identified was in 2007. This reflects both the increasing number of novel pharmacological agents for IBD as well as the uptake of economic evaluations in healthcare.

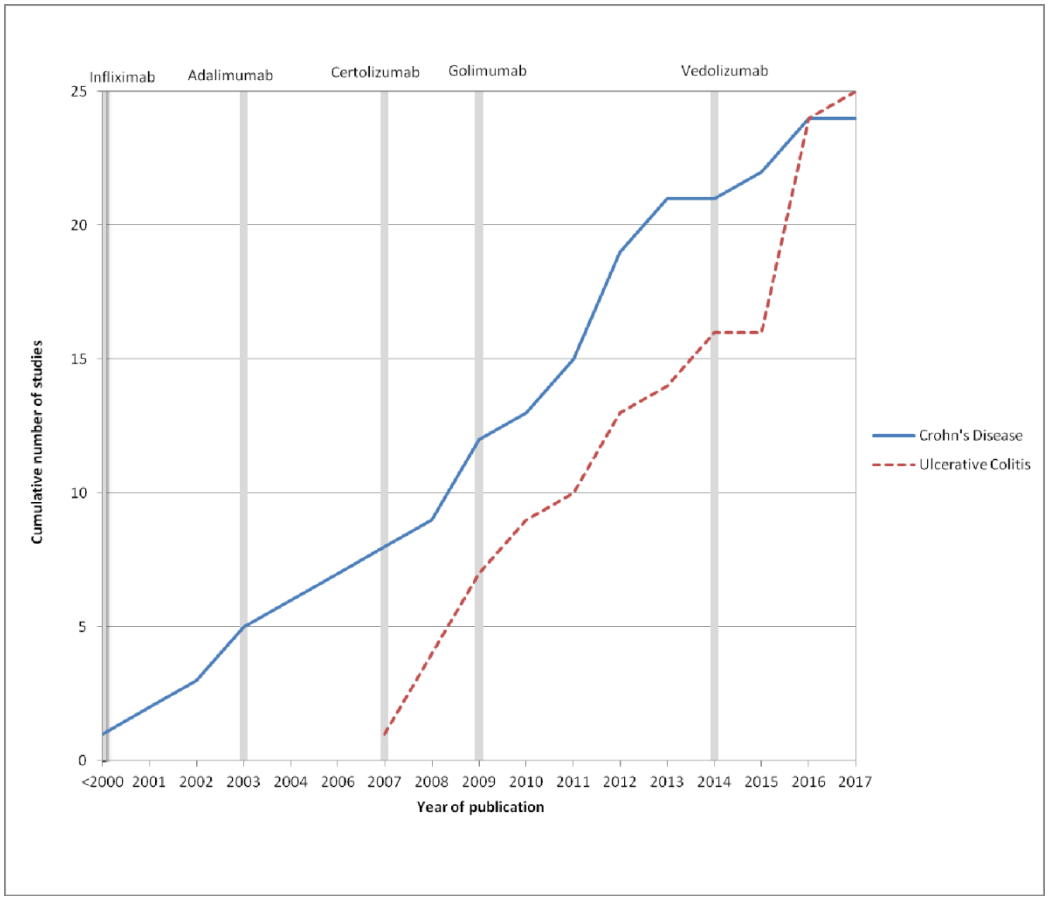


Figure 2 Frequency of published economic evaluations on Crohn's Disease and Ulcerative Colitis over time; grey bars indicate year of market approval by the European Medicines Agency (EMA)

Heterogeneous methods were used to generate cost-effectiveness results across studies (*Table 1*). For example, a time horizon of one year or less was used in more than 50% of the studies on CD but in only 36% of studies on UC. Only 21% and 24% of studies on CD and UC, respectively, used the recommended lifetime time horizon. Secondly, studies mostly adopted the health system perspective, particularly the third party payer and the publically funded health system, reflecting the USA and UK health systems, where the majority of studies were conducted. Two studies on CD and three studies on UC reported adopting a societal perspective (i.e. incorporating indirect costs to the patient in the model); however, in three of these studies no evidence of indirect costs were found in the publications [28-30]. Studies also differed in the type of decision analysis used (e.g. static decision analytic models versus Markov models). Finally, most studies used QALYs as the main effectiveness measure, creating a cost-utility analysis; while, two studies on CD and two studies on UC undertook a cost-effectiveness analysis, using outcomes such as number of patients in remission[31,32], number of surgeries[32], time spent in remission[33] and the probability of achieving mucosal healing (MH)[34].

Table 1 Key characteristics of published economic evaluations in Crohn's Disease and Ulcerative Colitis

Characteristics	Crohn's Disease (N, %)	Ulcerative Colitis (N, %)
Time horizon		
Lifetime	5 (21%)	6 (24%)
10 years	1 (4%)	5 (20%)
5 years	3 (13%)	4 (16%)
2 years	1 (4%)	1 (4%)
1 year	13 (54%)	6 (24%)
32 weeks	0	1 (4%)
12 weeks	0	1 (4%)
Not stated	0	1 (4%)
Other	1 (4%)	0
Setting		
USA	10 (42%)	4 (16%)
UK	8 (33%)	11 (44%)
Canada	2 (8%)	2 (8%)
Other	4 (17%)	8 (32%)
Study design		
Cost-effectiveness analysis	2 (8%)	2 (8%)
Cost-utility analysis	22 (92%)	23 (92%)
Type of decision analysis		
Decision analytic model	8 (33%)	7 (28%)
Markov model	12 (50%)	16 (64%)
Monte Carlo simulation	2 (8%)	0
Markov cohort model	1 (4%)	2 (8%)
Cohort model not clearly defined	1 (4%)	0
Perspective		
Third party payer	11 (46%)	6 (24%)
Publically-funded health system	8 (33%)	16 (64%)
Societal	2 (8%)	3 (12%)
Not clear	3 (13%)	0

Crohn's Disease

The results of the 24 studies on CD are summarised in *Table 2* (see Supplementary Files *Table A2* for descriptive information about studies).

Table 2 Summary of cost-effectiveness results adjusted to 2015 PPP for studies on Crohn's Disease

Reference (year, country)	Clinical presentation	Interventions/Comparators*	Inflated cost (2015 PPP)	Outcome (QALY unless otherwise stated)	ICER (PPP per outcome gained)†
Trallori et al. (1997, unclear) [30]	Patients in remission	Maintenance therapy with mesalazine	8'578'448.72	1713.6	8'471.74
		No maintenance treatment	8'417'485.58	1694.6	Reference
Arsenau et al. (2001, USA) [35]	Initial treatment of perianal fistula	6MP /metronidazole combination	4'118.09	0.76	Reference
		Initial infliximab induction infusions plus combination with 6MP/metronidazole if treatment failure	14'234.03	0.78	505'796.84
		Initial infliximab induction infusions with episodic reinfusion if treatment failure	14'389.13	0.78	513'552.06
		6MP/metronidazole followed by infliximab induction infusions with episodic reinfusion if treatment failure	9'482.71	0.77	536'461.97
Marshall et al. (2002, Canada) [36]	Active disease refractory to conventional therapies	Strategy A: "usual care" immunosuppressants, intravenous corticosteroids and surgery	10'278.04	0.6281	Strategy A vs. Strategy B: 187'890.19
		Strategy B: Single infliximab infusion at week 0	13'133.97	0.6433	Strategy C vs. Strategy B: 487'393.91
		Strategy C: Single infliximab infusion at week 0 plus reinfusion for patients who relapse	14'206.24	0.6455	Strategy D vs. Strategy C: 719'047.53
		Strategy D: Single infliximab infusion at week 0 plus maintenance infliximab for patients who respond and usual care for patients who do not respond	22'331.48	0.6568	-
Clark et al. (2003, UK) Schering-Plough model [37‡]	Chronic active disease refractory to	Single infliximab infusion			9'738.37
		Episodic infliximab infusions *(timing not stated)*			15'116.28

	conventional therapies	Maintenance infliximab infusions *(timing not stated)*			122'674.42
		Placebo			Reference
Clark et al. (2003, UK) Schering-Plough model [37‡]	Fistulising Crohn's disease	Initial infliximab induction infusions			178'779.07
		Initial infliximab induction infusions plus retreatment if fistula reopens			139'534.88
		Initial infliximab induction infusions plus maintenance treatment for patients achieving 100% fistula closure			170'058.14
		Placebo			Reference
Clark et al. (2003, UK) Primary economic evaluation [37‡]	Chronic active disease refractory to conventional therapies	Infliximab 5mg/kg single infusion			135'529.07
		Infliximab 5mg/kg episodic infusions (three re-treatments)			90'139.53
		Infliximab (5, 10 and 20mg/kg doses) single infusion			196'704.94
		Infliximab (all doses) episodic (three re-treatments)			105'030.52
		Placebo			Reference
Jaisson-Hot et al. (2004, France) [38§]	Moderate to severe active ileocolonic disease refractory to conventional therapies	Strategy 1a: Initial infliximab infusion plus re-treatment when patients relapse or do not respond	173'478.98	30.78	60'550.01
		Strategy 1b: Initial infliximab infusion plus maintenance infliximab infusions every 8 weeks	994'937.83	30.78	768'704.19
		Strategy 2: Surgery	103'240.97	29.62	Reference
Priest et al. (2006, NZ) [39**]	Moderate to severe CD indicated for immuno-suppressive therapy	Azathioprine maintenance therapy	1'220'732.02	877.6	Azathioprine dominant
		Methotrexate maintenance therapy	1'493'388.54	633.4	Reference

Kaplan et al. (2007, USA) [32]	Moderate to severe disease after loss of response during maintenance infliximab treatment	Infliximab dose escalation to 10mg/kg every 8 weeks	33'349.18	0.79	403'359.61
		Discontinue infliximab and switch to adalimumab induction and maintenance therapy	21'248.39	0.76	
Lindsay et al. (2008, UK) [40]	Moderate to severe active luminal disease	Infliximab initial infusions and maintenance treatment	58'626.42	2.145	48'751.83
		Standard care (immunomodulators and/or corticosteroids)	49'558.58	1.959	
Lindsay et al. (2008, UK) [40]	Fistulising Crohn's Disease	Infliximab initial infusions and maintenance therapy	69'773.24	2.449	55'265.19
		Standard care (immunomodulators and/or corticosteroids)	58'609.67	2.247	
Bodger et al. (2009, UK) [41]	Moderate to severe active disease	Infliximab infusions for induction of remission followed by maintenance treatment for 1 year	91'568.88	14.568	34'664.32
		Infliximab infusions for induction of remission followed by maintenance treatment for 2 years	105'941.90	14.901	38'753.63
		Adalimumab injection for induction of remission followed by maintenance treatment for 1 year	85'019.15	14.682	12'462.49
		Adalimumab injection for induction of remission followed by maintenance treatment for 2 year	96'590.34	15.156	18'443.45
		Standard care (5ASA, immunosuppressive agents, corticosteroids, antibiotics, symptomatic therapies, topical therapies and surgery)	79'124.39	14.209	Reference
Loftus et al. (2009, UK) [42]	Severe active disease	Adalimumab induction and maintenance therapy injection	19'798.38	0.8516	29'215.03
		Non-biologic therapy (based on the CLASSIC I trial: placebo and conventional medications)	16'359.77	0.7339	Reference

	Moderate to severe active disease	Adalimumab induction and maintenance therapy injection	17'640.61	0.8647	61'323.23
		Non-biologic therapy (based on the CLASSIC I trial: placebo and conventional medications)	12'096.99	0.7743	Reference
Yu et al. (2009, USA) [43]	Moderate to severe active disease	Adalimumab induction and maintenance injections	40'198.41	0.865	Adalimumab dominant
		Infliximab induction and maintenance infusions	45'902.58	0.851	
Bakhshai et al. (2010, USA) [33§]	Moderate to severe active disease eligible for second line biologic therapy	Natalizumab induction and maintenance infusion	74'316.05	4.5 months in remission	Reference
		Infliximab induction and maintenance infusions	67'487.91	2.4 months in remission	Dominated by adalimumab
		Adalimumab induction and maintenance injection	67'168.35	2.88 months in remission	4412.16 per month of remission
Dretzke et al. (2011, UK) [44]	Severe active disease refractory to conventional therapies	Standard care	24'406.85	0.8119	Dominated
		Infliximab induction infusions	21'925.23	0.8943	Reference
		Infliximab maintenance infusions	34'828.20	0.8957	9'216'407.48
	Severe active disease refractory to conventional therapies	Standard care	24'417.76	0.8118	Dominated
		Adalimumab induction infusions	12'832.02	0.8942	Reference
		Adalimumab maintenance infusions	25'556.69	0.8956	9'089'051.59
	Moderate active disease refractory to conventional therapies	Standard care	12'035.13	0.8926	Reference
		Infliximab induction infusions	17'416.83	0.924	171'391.59
		Infliximab maintenance infusions	30'476.26	0.9245	578'091.91
	Moderate active disease	Standard care	12'035.13	0.8922	Dominated
		Adalimumab induction infusions	8'338.17	0.9231	Reference

	refractory to conventional therapies	Adalimumab maintenance infusions	21'208.39	0.9236	25'740'443.62
Ananthakrishnan et al. (2011, USA) [45]	Patients in surgically-induced remission after first ileocecal resection	Antibiotics arm: Metronidazole given post-operatively. No treatment given if patients experience adverse events on metronidazole unless disease recurred in which case they received infliximab	3'086.90	0.8209	Reference
		Azathioprine arm: Azathioprine given post-operatively. No treatment given if patients experience adverse events on azathioprine unless disease recurred in which case they received infliximab induction and maintenance infusions	3'497.76	0.814	Dominated
		No treatment arm: No treatment given post-operatively. Patients who develop clinical recurrence receive infliximab induction and maintenance infusions	4'265.14	0.805	Dominated
		Tailored infliximab arm: No treatment post-operatively. Patients receive colonoscopy at 6 months; those at no or mild endoscopic recurrence risk received no treatment and those at high endoscopic recurrence risk receive infliximab induction and maintenance infusions	8'728.10	0.8206	Dominated

		Upfront infliximab arm: Infliximab standard dose maintenance infusions given post-operatively. Patients who do not respond to infliximab receive stop treatment and receive no alternative treatment but switch to azathioprine if disease recurs. Patients who develop disease recurrence while on infliximab receive increased infliximab dose (10mg/kg every 8 weeks).	24'070.22	0.828	2'955'396.77
Ananthakrishnan et al. (2012, USA) [46]	Moderate to severe disease who lose response to two prior TNF-antagonists	Natalizumab induction and maintenance infusion	56'348.98	0.71	600'858.73
		Certolizumab pegol induction and maintenance injection	50'340.40	0.7	
Blackhouse et al. (2012, Canada) [47]	Moderate to severe disease refractory to conventional therapies	Infliximab induction and maintenance infusions	47'928.87	2.721	197'402.17
		Adalimumab induction and maintenance injection	40'304.06	2.701	172'218.88
		Usual care: Immunosuppressants and corticosteroids	15'160.10	2.555	Reference
		Infliximab strategy vs. Adalimumab strategy			360355.43**
Doherty et al. (2012, USA) [28]	Patients achieving surgically-induced remission after intestinal resection	Infliximab induction and maintenance infusions	27'311.46	0.87	839'477.61
		Once daily continuous oral azathioprine	7'273.78	0.86	257'332.31
		Once daily continuous oral mesalazine	6'417.28	0.85	Dominated
		No treatment	2'127.14	0.84	Reference
Tang et al. (2012, USA) [48]	Moderate to severe disease refractory to conventional	Infliximab induction and maintenance infusions	24'658.25	0.796	Dominant
		Adalimumab induction and maintenance injection	29'957.07	0.799	Dominated

	therapies and naive to biologic agents	Certolizumab pegol induction and maintenance injection	31'692.91	0.8	Dominated
		Natalizumab induction and maintenance infusion	33'988.52	0.79	Dominated
Marchetti et al. (2013, Italy) [49§]	Moderate to severe newly diagnosed active disease	Top-down arm: Initial induction infusion with infliximab plus azathioprine, followed by infliximab re-treatment and continued azathioprine if symptom exacerbation occurred and finally methylprednisolone added if necessary	20'174.41	3.9	Top-down strategy dominant
		Step up arm: Induction treatment with methylprednisolone, followed by re-treatment with methylprednisolone plus azathioprine if relapse occurred and finally infliximab plus azathioprine added if necessary	21'240.29	3.76	
Saito et al. (2013, UK) [50]	Moderate to severe disease refractory to conventional therapies and naive to biologic therapy	Infliximab induction and maintenance infusions plus azathioprine	14'717.04	0.668	4'528.59
		Infliximab induction and maintenance infusions monotherapy	11'981.77	0.064	
Erim et al. (2015, USA) [51]	Moderate to severe active disease that failed to respond to infliximab and conventional therapies	Adalimumab and vedolizumab without prior dose increase: Adalimumab induction injections followed by maintenance injections for responders and switch to vedolizumab maintenance infusion for non-responders or patients who lose response	42'065.42	0.83	Reference
		Adalimumab only without dose increase: Adalimumab induction injections and maintenance injections for primary responders	44'229.01	0.81	Dominated

		Adalimumab and vedolizumab with prior dose increase: Adalimumab induction injections followed by maintenance injections for primary responders. For patients who do not respond or lose response receive adalimumab maintenance dose intensification (weekly) or switch to vedolizumab induction and maintenance infusion	45'642.71	0.83	621'851.83
		Adalimumab only with dose increase: Adalimumab induction injection followed by adalimumab maintenance therapy every other week for responders and maintenance therapy weekly for non-responders	48'302.89	0.82	Dominated
Taleban et al. (2016, USA) [52]	Medically refractory disease with extensive colitis and no perianal or small bowel inflammation	Total colectomy with ileal pouch anal anastomosis (IPAA)	172'469.72	10.93	Reference
		Total colectomy with permanent end ileostomy (EI)	123'559.09	10.24	70'884.96
Rafia et al. (2016, UK) Takeda submission [53]	Moderate to severe active disease after failure of initial therapy	*Mixed population:*			
		Vedolizumab induction and maintenance infusion			Reference
		Conventional therapy (5ASA, immunomodulators, and corticosteroids)			95'213.02
		Anti-TNF failed population:			
		Vedolizumab induction and maintenance infusion			Reference
		Conventional therapy (5ASA, immunomodulators, and corticosteroids)			149'021.70
		Anti-TNF naive population:			
		Vedolizumab induction and maintenance infusion			Reference

		Conventional therapy (5ASA, immunomodulators, and corticosteroids)			34'387.06
		Infliximab induction and maintenance infusion			40'232.77
		Adalimumab induction and maintenance injection			1'147'866.07

* Conventional therapy/standard of care is defined as drug treatment with aminosalicylates, methotrexate, corticosteroids, azathioprine, metronidazole or surgery; standard dosing approved by FDA and EMA applies unless otherwise specified.
† Unless otherwise stated, the ICER reports the cost per QALY gained
‡ When only ICERs were reported these were converted to 2015 PPP values using the PPP exchange rate for the original currency
§ Year of cost data collection not reported therefore year of publication used to complete PPP conversion
** The indication in this study is “moderate to severe IBD” however, efficacy data was extracted from studies on CD therefore it is assumed that this model reflects the cost-effectiveness for patients with CD. This lack of clarity is captured in the risk of bias assessment.

Moderate or severe CD

Priest et al. (2006) showed that maintenance therapy using azathioprine was dominant compared to methotrexate for patients with moderate to severe CD due to lower costs of treatment, fewer adverse events, more patients in remission and increased QALYs[39]. In addition, using first-line infliximab plus azathioprine to induce remission (a top-down strategy) in newly diagnosed patients with moderate to severe CD was dominant compared to the standard step-up approach[49].

Compared to standard care, adalimumab induction and maintenance therapy was cost-effective for severe CD (29'215.03 PPP/QALY) but not for moderate CD (61'323.23 PPP/QALY) in the UK[42]. Additionally, in a lifetime model, infliximab and adalimumab induction and maintenance therapy were cost-effective compared to standard care when maintenance therapy was administered for one or two years only[41]. In these studies, induction and maintenance treatment using adalimumab was cheaper and produced better outcomes compared to infliximab infusions[33 41 43].

In a study performed in the USA, for patients who lost response to initial infliximab infusions, switching to adalimumab induction and maintenance therapy was associated with reduced costs and QALYs compared to increasing the infliximab dose to 10mg/kg; however, neither strategy was cost-effective (403'359.61 PPP/QALY)[32]. Alternatively, certolizumab pegol was shown to be a cost-effective third-line biologic agents when compared to natalizumab for induction and maintenance of remission in patients who fail anti-TNF treatment[46].

CD refractory to conventional therapies

For patients with CD refractory to conventional treatments, infliximab induction and maintenance therapy was not cost-effective compared to continued treatment with standard care; ICERs ranged from 122'674.42 PPP/QALY to 768'704.19 PPP/QALY in European and Canadian healthcare settings[36-38 47]. Adalimumab induction and maintenance treatment was also not cost-effective at 172'218.88 PPP/QALY[47]. However, when considering induction doses only, infliximab and adalimumab were dominant compared to standard care for patients with severe disease and adalimumab was cost-effective for patients with moderate disease[44]. ICERs for maintenance treatment strategies, as opposed

to induction only and episodic re-treatment (i.e. induce remission, stop treatment and then re-treat when disease recurs), were very high for both infliximab[36-38 44] and adalimumab[44].

Comparing biologic agents to each other, infliximab induction and maintenance infusions were dominant when compared to adalimumab, certolizumab pegol and natalizumab for patients naive to biologic treatment and refractory to conventional therapies[48] and cost-effective compared to vedolizumab[53]. For patients who failed to respond to infliximab, adalimumab and standard care induction treatments, evidence suggested switching to vedolizumab may be less costly and improve outcomes compared to increasing the dose of adalimumab; however, at current prices, this was not cost-effective in the USA at 621'851.83 PPP/QALY[51]. Similarly, in an anti-TNF naive population in the UK, vedolizumab was not cost-effective compared to standard care, infliximab and adalimumab; however, the gross assumptions made in this model still need to be validated[53].

Fistulising CD

For patients with fistulising CD, the ICER for infliximab induction and maintenance infusions compared to standard care was 55'265.19 PPP/QALY in a UK study[40] and 513'552.06 PPP/QALY in the USA[35], which is above accepted cost-effectiveness thresholds. Although still not cost-effective, a single infliximab infusion followed by re-treatment if the fistula recurs, was associated with fewer costs per QALY compared to maintenance infliximab infusions (139'534.88 PPP/QALY versus 170'058.14 PPP/QALY)[37].

Surgical and post-surgical interventions

Only one study evaluated the cost-effectiveness of surgery[52]. Total colectomy with permanent end ileostomy was found to be cost-effective compared to total colectomy with ileal pouch-anal anastomosis (IPAA), despite increased QALYs from IPAA, in male patients with isolated medically refractory colonic CD[52]. To maintain remission post-operatively, maintenance treatment with daily azathioprine was cost-effective compared to infliximab maintenance infusions, mesalazine maintenance treatment and no maintenance therapy over a 1 year time horizon[28]. Alternatively, immediate use of antibiotics was the most cost-effective strategy compared to (a) no post-operative treatment, (b) treatment with

azathioprine, (c) infliximab infusions for patients at risk of endoscopic recurrence given 6 months after surgery, and (d) immediate post-surgical infliximab infusions[45].

Ulcerative Colitis

The results of the 24 studies on UC are summarised in *Table 3* (see Supplementary Files *Table A3* for descriptive information about studies).

Table 3 Summary of cost-effectiveness results adjusted to 2015 PPP for studies on Ulcerative Colitis

Reference (year, country)	Clinical presentation	Interventions & comparators*	Cost (2015 PPP)	Outcome (QALY unless otherwise stated)	ICER (PPP per outcome gained)†
Panes et al. (2007, Spain) [31]	Active and steroid-dependent moderate to severe disease	Induction treatment with prednisone followed by 5-ASA maintenance therapy for patients in remission or azathioprine for non-responders	11'236.97	38.50% achieved remission	44'320.62 per remission achieved
		Induction treatment with prednisolone followed by 5-ASA maintenance therapy for patients in remission or granulocyte, monocyte adsorption (GMA)-apheresis for non-responders	21'209.11	61% achieved remission	Reference
Buckland et al. (2008, UK) [54]	First line treatment for moderately active disease	Induction therapy using high dose mesalazine (4.8g/day)	4'236.30	0.1394	High dose dominant
		Induction therapy using standard dose mesalazine (2.4g/day)	4'399.92	0.1378	Reference
Tsai et al. (2008, UK) [55]	Moderate-severe chronic disease refractory to conventional therapies responding to initial infliximab induction infusions	Maintenance infliximab infusions	120'915.32	4.591	49'922.73
		Standard care	83'323.50	3.838	Reference
		Maintenance infliximab infusions	98'016.73	4.154	35'799.74

	Moderate-severe chronic disease refractory to conventional therapies in remission after initial infliximab induction infusions	Standard care	84'162.23	3.767	Reference
Yen et al. (2008, USA) [56]	Mild to moderate disease in remission	No maintenance 5ASA: 5-ASA 4.8g/day given during a flare and stopped once remission achieved	4'145.68	1.75	291'540.46
		Maintenance 5ASA: 5-ASA 2.4g/day given for maintenance treatment and escalated to 4.8g/day after first flare to induce and maintain remission	9'976.49	1.77	Reference
Connolly et al. (2009a, UK) [57]	Mild to moderate disease in remission	Once daily 2g mesalazine maintenance therapy	2'011.20	0.935	Once daily mesalazine is dominant
		Twice daily 1g mesalazine maintenance therapy	2'396.16	0.931	Reference
Connolly et al. (2009b, UK) [58]	Mild to moderate active disease	Induction treatment with 1g/100ml topical mesalazine plus 4g oral mesalazine combination	4'316.14	0.56	Combination therapy dominant
		Induction treatment with 4g oral mesalazine monotherapy	5'692.92	0.55	Reference
Xie et al. (2009, Canada) [59]	Moderate to severe disease	Strategy A: Standard care (5-ASA or immunosuppressants)	21'506.13	2.015	Reference

	refractory to conventional therapies	Strategy B: Infliximab induction infusions followed by infliximab maintenance infusions if patient responds. If no response or response lost during maintenance therapy, then switch to adalimumab induction and maintenance injections. If still no response or if response is lost switch to surgery.	73'337.79	2.178	317'985.64
		Strategy C: Infliximab induction infusions followed by infliximab maintenance infusions if patient responds. If no response, escalate dose to 10mg/kg infliximab maintenance infusions. If still no response or response is lost switch to adalimumab induction and maintenance injections	89'746.54	2.149	509'256.80
Brereton et al. (2010, UK) [60]	Newly diagnosed or relapsing active mild to moderate disease	5 year model: Induction and maintenance treatment with MMX mesalazine (1200mg tablets once a day)	9'582.42	3.445	1'248.48
		5 year model: Induction and maintenance treatment with Mesalazine (400mg tablets two to three times a day)	9'568.69	3.434	Reference
	Newly diagnosed or relapsing active mild to moderate disease	Lifetime model: Induction and maintenance treatment with MMX Mesalazine (1200mg tablets once a day)	37'196.70	14.861	12'897.00
		Lifetime model: Induction and maintenance treatment with Mesalazine (400mg tablets two to three times a day)	36'693.72	14.822	Reference
Punekar et al. (2010, UK) [61]	Patients hospitalised with acute severe exacerbations refractory to intravenous (IV) hydrocortisone	IV cyclosporine plus IV hydrocortisone. If patient responds, switch to oral cyclosporine plus oral prednisolone and azathioprine. For non-responders, switch to surgery	32'970.62	0.7	Reference
		Colectomy: 71% of patients receive illeostomy and 29% of patients receive ileal pouch anal anastomosis (IPAA)	31'051.18	0.58	15'995.29

		Standard care: Continue IV hydrocortisone for 7 days. If patient responds, switch to oral prednisolone and azathioprine. For non-responders, switch to surgery.	33'702.01	0.68	Dominated
		Infliximab induction infusions plus IV hydrocortisone. If patient responds, receive two more infliximab infusions plus prednisolone and azathioprine. For non-responders, switch to surgery	36'109.03	0.8	31'384.13
Prenzler et al. (2011, Germany) [62]	Newly diagnosed or relapsing mild to moderate active disease	MMX mesalazine (2400mg/day) induction and maintenance therapy for patients who respond. For non-responders, increase dose to 4800mg/day and if still no response add oral corticosteroids. If still no response or relapse, patient receives immunosuppressants and/or IV steroids and surgery if medical treatment continues to fail.	6'902.31	3.32	MMX is dominant
		Mesalazine (2400mg/day) induction and maintenance therapy for patients who respond. For non-responders, increase dose to 4800mg/day and if still no response add oral corticosteroids. If still no response or relapse, patient receives immunosuppressants and/or IV steroids and surgery if medical treatment continues to fail.	7'774.18	3.309	Reference
Connolly et al. (2012, Netherlands) [63]	Mild to moderately active disease	Induction treatment with 1g topical mesalazine combined with 4g oral mesalazine	2'989.80	0.56	Combination therapy is dominant
		Induction treatment with 4g oral mesalazine and placebo enema monotherapy	3'989.56	0.55	Reference
	Mild to moderate disease in remission	Maintenance treatment with once daily 2g mesalazine	1'751.61	0.931	Once daily mesalazine is dominant

		Maintenance treatment with twice daily 1g mesalazine	2'034.74	0.927	Reference
Park et al. (2012, USA) [29]	Hospitalised patients with severe pancolitis	Standard medical therapy: IV methylprednisolone followed by mesalazine maintenance treatment for responders; if response lost during maintenance therapy switch to azathioprine. For methylprednisolone non-responders switch to infliximab induction infusions and maintenance infusions for responders. For infliximab non-responders, switch to tacrolimus. If all medical therapies fail, switch to colectomy with IPAA.	261'132.75	20.78	1'631'495.11
		Early colectomy with IPAA: Subtotal colectomy and laparoscopic IPAA given after initial hospitalisation followed by medical treatment for patients with acute or chronic pouchitis.	163'243.05	20.72	Reference
Saini et al. (2012, USA) [64]	Recently diagnosed, mild to moderate 5-ASA responsive disease in remission	Inflammation-targeted treatment: patients receive predictive stool testing every 3 months and those with positive test treated with 3-month course of 5-ASA	25'186.38	4.5	Reference
		Symptom-targeted treatment: 5-ASA used for symptomatic disease flares	26'931.90	4.5	623'401.80
		Continuous maintenance treatment: 5-ASA maintenance therapy for all patients in remission	28'305.12	4.5	Dominated
Chaudhary et al. (2013, Netherlands) [65]	Patients hospitalised with acute severe exacerbations refractory to IV steroids	Infliximab induction infusions followed by infliximab plus azathioprine and oral steroids for responders. Maintenance treatment continued with azathioprine and oral steroids for responders. Non-responders or patients who lose response switch to surgery.	23'113.73	0.8	Reference

		IV cyclosporine followed by oral cyclosporine plus azathioprine and oral steroids for responders. Maintenance treatment continued with azathioprine and oral steroids for responders. Non-responders or patients who lose response switch to surgery.	20'027.74	0.7	30'859.85
		Surgery with no concomitant medication use	18'937.22	0.58	18'984.14
Connolly et al. (2014, Netherlands) [66]	Mild to moderate active disease	Induction therapy with once daily mesalazine	4'001.12	0.57	Once daily mesalazine is dominant
		Induction therapy with twice daily mesalazine	4'583.78	0.56	Reference
Essat et al. (2014, UK) Takeda submission [67]‡	Moderate to severe disease refractory or inadequately responding to conventional therapy and anti-TNF alpha agents	*Whole population (patients who received anti-TNF inhibitor and those who did not):*			
		Conventional therapies: Combination of aminosalicylates, immunomodulators and corticosteroids			49'122.75
		Surgery: 40% of patients have illeostomy and 60% have subtotal proctocolectomy			Dominated
		Vedolizumab: Induction infusions of vedolizumab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy			Reference
	Moderate to severe disease refractory or inadequately responding to conventional	*Anti-TNF alpha naive patients:*			
		Conventional therapies (combination of aminosalicylates, immunomodulators and corticosteroids)			7'172.86
		Surgery: 40% of patients have illeostomy and 60% have subtotal proctocolectomy			Dominated

	therapy and anti-TNF alpha agents	Infliximab: Induction infusions of infliximab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy			Dominated
		Adalimumab: Induction injections of adalimumab followed by maintenance injections for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy			9'787.08
		Golimumab: Induction injections of golimumab followed by maintenance injections for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy			Dominated
		Vedolizumab: Induction infusions of vedolizumab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy			Reference
	Moderate to severe disease refractory or inadequately responding to conventional	*Patients who failed TNF-alpha inhibitors:*			
		Conventional therapies: Combination of aminosalicylates, immunomodulators and corticosteroids			95'892.42
		Surgery: 40% of patients have illeostomy and 60% have subtotal proctocolectomy			Dominated

	therapy and anti-TNF alpha agents	Vedolizumab: Induction infusions of vedolizumab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy			Reference
Archer et al. (2016, UK) MSD Submission [68]	Moderate to severe disease refractory or inadequately responding to conventional therapy	Infliximab induction infusions followed by maintenance infusions for responders. For non-responders, switch to relapse management with IV steroids. For patients who fail IV steroids switch to colectomy.	64'509.13	5.7	57'765.06
		Golimumab induction injections followed by maintenance injections for responders. For non-responders, switch to relapse management with IV steroids. For patients who fail IV steroids switch to colectomy.	45'608.55	5.54	40'518.32
		Adalimumab induction injections followed by maintenance injections for responders. For non-responders, switch to relapse management with IV steroids. For patients who fail IV steroids switch to colectomy.	46'651.89	5.49	Dominated
		Immediate colectomy	22'918.28	4.98	Reference
Archer et al. (2016, UK) Abbvie Submission [68]	Moderate to severe disease refractory or inadequately responding to conventional therapy	Adalimumab induction and maintenance injections for patients who respond. For non-responders, dose escalation to 40mg every week and switch to conventional therapies if still no response. For non-responders to conventional treatments, switch to surgery.	112'700.41	5.73	50'730.06
		Conventional therapies: Anti-inflammatory drugs or immunosuppressants). For non-responders, switch to colectomy	75'160.16	4.99	Reference

Beilman et al. (2016, Canada) [69]	Moderate to severe active corticosteroid-dependent and/or intolerant to thiopurine treatment	No adalimumab: Patients receive no treatment and remain in chronically unwell state to avoid colectomy	89'881.15	3.154	59'398.07
		Adalimumab therapy: Adalimumab induction injections and maintenance injections for responders. For non-responders, switch to steroid therapy.	99'147.25	3.321	Reference
Stawowczyk et al. (2016, Poland) [70]	Moderate to severe disease refractory or not responding conventional therapies and contraindicated for cyclosporine	Public payer perspective: Golimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and, if failure persists, switch to colectomy. Maintenance treatment with golimumab restricted to 1 year.	53'374.23	19.241	222'355.35
		Public payer perspective: Standard care alone induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	26'024.52	19.118	Reference
	Moderate to severe active disease refractory or not responding conventional medical therapies and contraindicated for cyclosporine	Societal perspective: Golimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and colectomy if failure persists. Maintenance treatment with golimumab restricted to 1 year.	173'211.58	19.241	212'762.53
		Societal perspective: Standard care alone, induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	147'041.79	19.118	Reference

Stawowczyk et al. (2016, Poland) [71]	Moderate to severe active disease refractory to conventional medical therapies	Public payer perspective: Adalimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and colectomy if failure persists. Maintenance treatment with golimumab restricted to 1 year.	27'464.00	15.204	101'409.52
		Public payer perspective: Standard care alone induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	13'266.67	15.064	Reference
		Societal perspective: Adalimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and colectomy if failure persists. Maintenance treatment with golimumab restricted to 1 year.	125'020.00	15.204	95'190.48
		Societal perspective: Standard care alone induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	111'693.33	15.064	Reference
Stawowczyk et al. (2016, Poland) [72]	Moderate to severe refractory, intolerant or inadequately responding to conventional medical therapies	Infliximab and standard care combination: Infliximab plus standard care induction infusions followed by maintenance therapy for responders. For non-responders, switch to adalimumab induction injections and maintenance injections for responders. For non-responders to adalimumab, switch to conventional therapy alone or colectomy.	56'425.63	14.296	229'015.09
		Standard care alone: Standard care induction and maintenance treatment. If disease remains active, switch to colectomy.	16'806.02	14.123	Reference

Tappenden et al. (2016, UK) [73]	Moderate to severe refractory or intolerant to conventional medical therapies	*Patients in whom surgery is an option:*			
		Colectomy	83'011.66	14.71	Reference
		Adalimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	134'578.97	10.82	Dominated
		Infliximab induction infusions followed by maintenance infusions for responders. For non-responders, switch to conventional therapy.	142'505.70	10.81	Dominated
		Golimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	132'904.51	10.63	Dominated
		Conventional treatment for induction and maintenance phases (includes 5-ASA, azathioprine, 6-mercaptopurine, prednisolone)	108'610.90	10.47	Dominated
	Moderate to severe refractory or intolerant to conventional medical therapies	*Patients in whom surgery is not an option:*			
		Adalimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	134'578.97	10.82	74'194.48
		Infliximab induction infusions followed by maintenance infusions for responders. For non-responders, switch to conventional therapy.	142'505.70	10.81	Extendedly dominated
		Golimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	132'904.51	10.63	Extendedly dominated
		Conventional treatment for induction and maintenance phases (includes 5-ASA, azathioprine, 6-mercaptopurine, prednisolone)	108'610.90	10.47	Reference

Yokomizo et al. (2016, USA) [34‡]	Moderate to severe active disease naive to biologic agents	Infliximab 5mg/kg induction and maintenance infusions			99290.01 per MH achieved
		Infliximab 10mg/kg induction and maintenance infusions			123801.38 per MH achieved
		Adalimumab induction and maintenance injections			316757.65 per MH achieved
		Vedolizumab induction and maintenance infusions			302331.36 per MH achieved
Wilson et al. (2017, UK) [74]	Moderate to severe active disease refractory, inadequately responding or lost response to conventional medical therapies and who are anti-TNF naive	Vedolizumab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to another combination of conventional therapies or surgery.	202'422.62	14.077	Reference
		Infliximab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to another combination of conventional therapies or surgery.	209'156.89	13.788	Dominated
		Adalimumab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to another combination of conventional therapies or surgery.	197'686.20	13.972	65'565.01

		Golimumab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to another combination of conventional therapies or surgery.	203'018.58	13.809	Dominated

*Conventional therapy/standard of care is defined as drug treatment with aminosalicylates, methotrexate, corticosteroids, azathioprine, metronidazole or surgery; standard dosing approved by FDA and EMA applies unless otherwise specified.
†Unless otherwise stated, the ICER reports the cost per QALY gained
‡ When only ICERs were reported these were converted to 2015 PPP values using the PPP exchange rate for the original currency

Mild UC

The cost-effectiveness of high dose MMX™ mesalazine, once daily 2g mesalazine and concomitant oral and topical mesalazine compared to standard oral mesalazine for induction and maintenance of remission was demonstrated across various time horizons in different health systems; ICERs were dominant in five European studies[57 58 62 63 66]. In contrast, in the USA high dose (4.8g/day) maintenance mesalazine was not cost-effective, despite increased QALYs and decreased risk of flares[56]. Interestingly, an inflammation-targeted re-treatment strategy was shown to dominate maintenance treatment with mesalazine even when costs of a predictive stool test every 3-months is taken into account[64].

Moderate or severe UC

Only one study evaluated moderate to severe UC eligible for treatment with conventional medications and found high dose mesalazine was dominant when administered over a short 12 week time horizon due to lower costs compared to standard dose mesalazine (5'878.12 PPP/QALY versus 6'105.16 PPP/QALY)[54].

In addition, colectomy soon after diagnosis of severe UC was more cost-effective than first-line medical therapy (methylprednisolone and azathioprine, followed by infliximab induction and maintenance therapy); however, this study used single-centre cost values potentially reducing the generalisability of these results[29].

UC refractory to conventional therapies

Compared to standard care, infliximab induction and maintenance therapy was either dominated[67 73 74] or had very high ICERs[68 72] in studies reflecting European health systems. On the other hand, infliximab was cost-effective for patients hospitalised with acute severe exacerbations and refractory to IV steroids compared to continued IV cyclosporine (30'859.85 PPP/QALY) and surgery (18'984.14 PPP/QALY)[65]. These results support the findings from a similar modelling study based in the UK[61].

Moreover, induction and maintenance treatment with adalimumab produced high ICERs, ranging from 74,194.48 PPP/QALY in the UK to 317,985.64 PPP/QALY in Canada, compared to standard care[59 71 73]. However, adalimumab was cost-effective in a Canadian setting when compared to a strategy without adalimumab, including scenarios with no treatment, treatment with steroids and colectomy[69]. Alternatively, in a lifetime model based in the UK, surgery dominated anti-TNF agents and conventional therapies in a subgroup of patients where surgery was acceptable and feasible[73]. When surgery was not feasible, adalimumab dominated infliximab and golimumab but overall conventional therapies were the most cost-effective treatment option.

Recent studies in the UK point to the cost-effectiveness of vedolizumab in an anti-TNF alpha naive population when compared to infliximab, golimumab, adalimumab and conventional therapies; ICERs for each agent ranged from dominance to 9'787 PPP/QALY[67 74]. Vedolizumab was associated with the highest QALYs compared to anti-TNF alpha agents over the patient's lifetime[74]. Findings from the USA contradicted this, suggesting that vedolizumab would only be cost-effective as a first-line treatment if drug costs fell below 2'500 USD[34].

Risk of bias assessments

On average, 67% and 71% of criteria were fulfilled from the Drummond et al. (1996) checklist and 49% and 55% of criteria were fulfilled from the Phillips et al. (2004) checklist for CD and UC, respectively, representing fair quality (see Supplementary Files *Table A4* and *Table A5*). Studies failed to report details on the methods of synthesis of effectiveness data, the population from which utility values were acquired, and disaggregated cost and resource use data. In addition, only 57% of CD studies and 29% of UC studies declared that there were no potential conflicts of interest from researchers and funding sources. This likely reflects the growing demand for the pharmaceutical industry to show not only the clinical effectiveness but also the cost-effectiveness of their products [75].

DISCUSSION

This review found that, in general, biologic agents help to improve outcomes in terms of QALYs and remission rates; however, at current prices they did not provide good value for money in the majority of clinical situations when compared to conventional therapies. In particular, when administered to

maintain remission and when compared to current conventional therapies, biologic agents were not cost-effective in both CD and UC. Moreover, the cost-effectiveness of biologic agents compared to each other remains inconclusive, reflecting a major gap in the literature. Importantly, evidence from CD illustrates the potential for biologic agents to be cost-effective if initiated early (as a top-down strategy) and when the patient's lifetime clinical management is considered. In addition, in UC, high dose mesalazine for mild disease and early surgical intervention for severe and refractory disease showed greater cost-effectiveness compared to the standard of care and biologic agents, respectively. These findings, however, should be reviewed within the context of the methodologies used and the health systems represented in the studies.

ICERs for induction and maintenance treatment with infliximab and adalimumab compared to conventional therapies were well above acceptable cost-effectiveness thresholds in CD and UC refractory to conventional therapies[28 35-38 45 47 53 59 67 68 73]. In clinical practice maintenance treatment with biologic agents is preferred to intermittent re-treatment strategies due to the potential development of anti-drug antibodies[76]. Several authors extrapolated the costs and effects of maintenance treatment with biologic agents over a long time horizon, which could explain the high costs incurred over time. In contrast, both infliximab and adalimumab were cost-effective for patients with moderate to severe CD when maintenance treatment was limited to one year[40 41]. Interestingly, when treatment with adalimumab and infliximab was modelled over the patients' lifetime rather than one or two years, the ICERs were no longer cost-effective[41]. This suggests an opportunity for the cost-effectiveness of biologic agents if short maintenance therapy schedules are defined and adhered to. Alternatively, maintenance therapy with gradual dose intensification or concomitant treatment with immunomodulators have been suggested to reduce the risk of immunogenicity for both CD and UC; however, the clinical- and cost-effectiveness of these strategies need to be validated[77-79].

The cost-effectiveness of front-line induction therapy using infliximab in newly diagnosed CD patients was an important finding[49]. Current treatment guidelines reserve biologic agents as second-line treatment for moderate to severe disease or when conventional treatments fail[5 6]. However, early management of CD with infliximab reduced the rate of relapse and hospitalisation compared to patients who received upfront steroids[49]. It has been argued that early intervention with biologic agents in

patients who are at high risk of complications may provide long-lasting benefit and help to alter the clinical course of the disease[76]. Stratifying patients based on their risk of complications soon after diagnosis may be one way to ensure the value for money of biologic agents is captured[80].

Recent economic evaluations have compared a broader scope of interventions, including newer biologic agents and surgery. For example, in UC refractory to conventional treatments, one study showed vedolizumab was cost-effective compared to anti-TNF agents[74], while another study found surgery was cost-effective compared to conventional and anti-TNF agents[73]. Such evidence was limited in literature on CD, where only one study, submitted by the manufacturers of vedolizumab, compared adalimumab, infliximab and conventional treatments to vedolizumab[53]. Importantly, this study had a high risk of bias due to the assumptions made in the modelling and because the choice of comparators was not comprehensive. Models which incrementally compare treatment strategies are useful for decision-making since they are in line with routine clinical practice where a broad choice of interventions exists.

An important opportunity for the cost-effectiveness of biologic agents is falling drug prices over time due to the increasing number of biologic agents available on the market and in the development pipeline. Moreover, as patents for older biologic agents expire, biologically similar (biosimilar) versions are entering the market, creating an important opportunity for increasing access and reducing costs. Biosimilars to infliximab have been available for IBD since 2013, in Europe, and 2016, in the USA and several biosimilars to adalimumab are in the pipeline[5]. While biosimilars are not identical in molecular structure to their reference products, they have been shown to have similar safety and efficacy profiles[81]. In addition, biosimilars show promise in reducing costs, with initial research suggesting they enter the market at up to 30% lower cost compared to their reference products[82].

Future research is needed to address the gaps identified in the published literature. Firstly, indirect costs (i.e. non-medical costs incurred by the patient due to their disease such as absence from work) were not taken into account in the majority of studies. Indirect costs have been shown to exceed direct costs because IBD is often diagnosed in adolescence and early adulthood and therefore impacts patients' during their peak productive years[83]. Secondly, studies relied on utility scores from a few

studies associated with a high degree of uncertainty[84-86]. When using secondary data sources, there is a risk of introducing bias when specific disease states used in the economic model do not match those for which the utilities were derived. Moreover, evidence suggests, utility scores vary across geographies due to cultural differences[87]. In several studies the utility scores were found to impact the overall cost-effectiveness results significantly; therefore, these should be accurately captured with large samples from the countries evaluated. Future economic models could also help to identify optimal strategies for the use of biologic agents, including the impact of early adoption, risk stratification and the impact of switching between different agents over time[80].

This study has several strengths including that a broad inclusion criteria allowed for an overall understanding of the commonly evaluated treatments in IBD and their cost-effectiveness across different clinical presentations and health systems. In addition, by inflating and converting costs to a common currency we were able to make more reliable comparisons of results between studies. The review methods were documented a priori and approved by all co-authors in order to limit bias in the selection of studies. This systematic literature review incorporates evidence from newer biologic agents and the large number of studies on UC published in 2016, which the latest review did not capture[88]. In addition, this review differs from previous literature reviews which focus only on biologic agents[88] or were less systematic and focused on specific agents and/or diseases[89 90]. One limitation of the review methods is that one reviewer conducted the literature search, study selection, data extraction and risk of bias assessments, which may have introduced bias into the selection and critical appraisal of studies.

Economic evaluations in IBD have become increasingly popular over the last decade due to the growth of therapeutic options from novel and efficacious biologic agents. While the need for and benefit of systematic reviews in economic evaluations has been contested by some authors[91], this review shows that it is an effective tool to gain an understanding of drivers of treatment costs and benefits across countries. The main limitation to systematic reviews of economic evaluations is the lack of consensus around acceptable cost-effectiveness thresholds. Previous reviews used different thresholds including 35'000 Euros/QALY (38'290 USD)[88] and 100'000 USD/QALY[89]. This study found that studies generally concluded that treatments were cost-effective when ICERs were below 50'000 PPP/QALY. Systematic reviews in health economics could become more effective as a decision-making tool for clinicians and

policy makers if consensus on methods of synthesis, taking into account variation in costs across countries and health systems, can be established.

The results of this review have major implications for future research in this field. Biologic agents were associated with ICERs above 100'000 PPP/QALY in the majority of studies for CD and UC; however, their use consistently demonstrated improvements in quality of life and remission rates. In the future, cost-effectiveness of biologic agents may improve as the market price falls and with the introduction of biosimilars[82]. Future economic models need to strengthen existing literature by more accurately reflecting real world treatment pathways, ensuring the chronic and dynamic nature of IBD is captured and accounting for indirect, as well as direct costs, incurred by the health system and the patients.

REFERENCES

1. Hanauer SB. Inflammatory Bowel Disease. *New England Journal of Medicine* 1996;334(13):841-48.
2. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010;4(1):28-62. doi: 10.1016/j.crohns.2009.12.002
3. Bodger K. Cost Effectiveness of Treatments for Inflammatory Bowel Disease. *Pharmacoeconomics* 2011;29(5):387-401.
4. Hanauer SB. Top-down versus step-up approaches to chronic inflammatory bowel disease: presumed innocent or presumed guilty. *Nat Clin Pract Gastroenterol Hepatol* 2005;2(11):493. doi: 10.1038/ncpgasthep0318
5. Torres J, Mehandru S, Colombel J-F, et al. Crohn's disease. *The Lancet* 2017;389(10080):1741-55. doi: 10.1016/s0140-6736(16)31711-1
6. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *The Lancet* 2017;389(10080):1756-70. doi: 10.1016/s0140-6736(16)32126-2
7. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol* 2015;12(9):537-45. doi: 10.1038/nrgastro.2015.135
8. Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. *Therapeutic Advances in Gastroenterology* 2015;8(2):66-82. doi: 10.1177/1756283X14558193
9. Stone CD. The economic burden of inflammatory bowel disease: Clear problem, unclear solution. *Digestive Diseases and Sciences* 2012;57(12):3042-44.
10. Burisch J, et al. The burden of inflammatory bowel disease in Europe. *Journal of Crohn's and Colitis* 2013;7:322-37.
11. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142(1):46-54 e42; quiz e30. doi: 10.1053/j.gastro.2011.10.001
12. M'Koma AE. Inflammatory bowel disease: An expanding global health problem. *Clinical Medicine Insights: Gastroenterology* 2013;6:33-47.
13. Odes S, Greenberg D. A medicoeconomic review of early intervention with biologic agents in the treatment of inflammatory bowel diseases. *Clinicoeconomics & Outcomes Research* 2014;6:431-43.
14. Stone CD. The economic burden of inflammatory bowel disease: clear problem, unclear solution. *Dig Dis Sci* 2012;57(12):3042-4. doi: 10.1007/s10620-012-2417-8
15. Drummond M, Sculpher M, Claxton K, et al. Methods for the economic evaluation of health care programmes: Fourth Edition. New York: Oxford University Press 2015.
16. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011.
17. OECD. Inflation (CPI) (indicator) 2017 [accessed 01 February 2017 2017.

18. OECD. Purchasing power parities (PPP) (indicator) 2017 [accessed 01 February 2017) 2017.
19. NICE. Guide to the methods of technology appraisal 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword
20. Ubel PA, Hirth RA, Chernew ME, et al. What Is the Price of Life and Why Doesn't It Increase at the Rate of Inflation? *Arch Intern Med* 2003;163(14):1637-41.
21. Marseille E, Larson B, Kazi DS, et al. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bull World Health Organ* 2015;93(2):118-24. doi: 10.2471/BLT.14.138206
22. Claxton K, Sculpher M, Palmer S, et al. Causes for concern: is NICE failing to uphold its responsibilities to all NHS patients? *Health Econ* 2015;24(1):1-7. doi: 10.1002/hec.3130
23. Goldman D, Lakdawalla D, Philipson T. The economic value of medical innovation. ed. Washington, DC: Milken Institute, 2012.
24. Drummond M JT. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;313:275-83.
25. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment* 2004;8(36)
26. University of York Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. In: Centre for Reviews and Dissemination UoY, ed. York: University of York, 2009.
27. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Plos Medicine* 2009;6(7):1- 6. doi: 10.1371/
28. Doherty GA, Miksad RA, Cheifetz AS, et al. Comparative cost-effectiveness of strategies to prevent postoperative clinical recurrence of Crohn's disease. *Inflammatory Bowel Diseases* 2012;18(9):1608-16.
29. Park KT, Tsai R, Perez F, et al. Cost-effectiveness of early colectomy with ileal pouch-anal anastamosis versus standard medical therapy in severe ulcerative colitis. *Annals of Surgery* 2012;256(1):117-24.
30. Trallori G, Messori A. Drug treatments for maintaining remission in Crohn's disease: A lifetime cost-utility analysis. *PharmacoEconomics* 1997;11(5):444-53.
31. Panes J, Guilera M, Ginard D, et al. Treatment cost of ulcerative colitis. Is apheresis with Adacolumn cost-effective? *Digestive and Liver Disease* 2007;39(7):617-25.
32. Kaplan GG, Hur C, Korzenik J, et al. Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: A cost-effectiveness analysis. *Alimentary Pharmacology and Therapeutics* 2007;26(11-12):1509-20.
33. Bakhshai J, Bleu-Laine R, Jung M, et al. The cost effectiveness and budget impact of natalizumab for formulary inclusion. *Journal of Medical Economics* 2010;13(1):63-9.
34. Yokomizo L, Limketkai B, Park KT. Cost-effectiveness of adalimumab, infliximab or vedolizumab as first-line biological therapy in moderate-to-severe ulcerative colitis. *BMJ Open Gastroenterology* 2016;3(1):e000093.

35. Arseneau KO, Cohn SM, Cominelli F, et al. Cost-utility of initial medical management for Crohn's disease perianal fistulae. *Gastroenterology* 2001;120(7):1640-56.
36. Marshall J, Blackhouse G, Goeree R, et al. Infliximab for the treatment of Crohn's disease: a systematic review and cost-utility analysis. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 2002.
37. Clark W, Raftery J, Song F, et al. Systemic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease. *Health Technology Assessment* 2003;7(3)
38. Jaisson-Hot I, Flourie B, Descos L, et al. Management for severe Crohn's disease: A lifetime cost-utility analysis. *International Journal of Technology Assessment in Health Care* 2004;20(3):274-79.
39. Priest VL, Begg EJ, Gardiner SJ, et al. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. *Pharmacoeconomics* 2006;24(8):767-81.
40. Lindsay J, Punekar YS, Morris J, et al. Health-economic analysis: Cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease - Modelling outcomes in active luminal and fistulizing disease in adults. *Alimentary Pharmacology and Therapeutics* 2008;28(1):76-87.
41. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Alimentary Pharmacology and Therapeutics* 2009;30(3):265-74.
42. Loftus EV, Johnson SJ, Yu AP, et al. Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease. *European Journal of Gastroenterology and Hepatology* 2009;21(11):1302-09.
43. Yu AP, Johnson S, Wang ST, et al. Cost utility of adalimumab versus infliximab maintenance therapies in the United States for moderately to severely active Crohn's disease. *Pharmacoeconomics* 2009;27(7):609-21.
44. Dretzke J, Edlin R, Round J, et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. *Health Technology Assessment* 2011;15(6):1-244.
45. Ananthakrishnan AN, Hur C, Juillerat P, et al. Strategies for the prevention of postoperative recurrence in crohn's disease: Results of a decision analysis. *American Journal of Gastroenterology* 2011;106(11):2009-17.
46. Ananthakrishnan AN, Hur C, Korzenik JR. Certolizumab Pegol Compared to Natalizumab in Patients with Moderate to Severe Crohn's Disease: Results of a Decision Analysis. *Digestive Diseases and Sciences* 2012:1-9.
47. Blackhouse G, Assasi N, Xie F, et al. Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-alpha drugs for refractory Crohn's disease. *Journal of Crohn's and Colitis* 2012;6(1):77-85.
48. Tang DH, Armstrong EP, Lee JK. Cost-utility analysis of biologic treatments for moderate-to-severe crohn's disease. *Pharmacotherapy* 2012;32(6):515-26.

49. Marchetti M, Liberato NL, Di Sabatino A, et al. Cost-effectiveness analysis of top-down versus step-up strategies in patients with newly diagnosed active luminal Crohn's disease. *European Journal of Health Economics* 2013;14(6):853-61.
50. Saito S, Shimizu U, Nan Z, et al. Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis. *Journal of Crohn's & colitis* 2013;7(2):167-74.
51. Erim D, Mahendraratnam N, Okafor P, et al. The value of vedolizumab as rescue therapy in moderate-severe Crohn's disease patients with adalimumab non-response in the USA. *Journal of Crohns Colitis* 2015;9(8):669-75.
52. Taleban S, Van Oijen MGH, Vasiliauskas EA, et al. Colectomy with Permanent End Ileostomy Is More Cost-Effective than Ileal Pouch-Anal Anastomosis for Crohn's Colitis. *Digestive Diseases and Sciences* 2016;61(2):550-59.
53. Rafia R, Scope A, Harnan S, et al. Vedolizumab for Treating Moderately to Severely Active Crohn's Disease After Prior Therapy: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics* 2016;34(12):1241-53. doi: 10.1007/s40273-016-0436-6
54. Buckland A, Bodger K. The cost-utility of high dose oral mesalazine for moderately active ulcerative colitis. *Alimentary Pharmacology & Therapeutics* 2008;28(11-12):1287-96.
55. Tsai HH, Black C. A review of the cost-effectiveness of vedolizumab for treating moderate- to severely active ulcerative colitis. *Expert Review of Pharmacoeconomics and Outcomes Research* 2016:1-5.
56. Yen EF, Kane SV, Ladabaum U. Cost-effectiveness of 5-aminosalicylic acid therapy for maintenance of remission in ulcerative colitis. *American Journal of Gastroenterology* 2008;103(12):3094-105.
57. Connolly MP, Nielsen SK, Currie CJ, et al. An economic evaluation comparing once daily with twice daily mesalazine for maintaining remission based on results from a randomised controlled clinical trial. *Journal of Crohn's and Colitis* 2009;3(1):32-37.
58. Connolly MP, Nielsen SK, Currie CJ, et al. An economic evaluation comparing concomitant oral and topical mesalazine versus oral mesalazine alone in mild-to-moderately active ulcerative colitis based on results from randomised controlled trial. *Journal of Crohn's and Colitis* 2009;3(3):168-74.
59. Xie F, Blackhouse G, Assasi N, et al. Cost-utility analysis of infliximab and adalimumab for refractory ulcerative colitis. *Cost Effectiveness & Resource Allocation* 2009;7:20.
60. Brereton N, Bodger K, Kamm MA, et al. A cost-effectiveness analysis of MMX mesalazine compared with mesalazine in the treatment of mild-to-moderate ulcerative colitis from a UK perspective. *Journal of Medical Economics* 2010;13(1):148-61.
61. Punekar YS, Hawkins N. Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. *European Journal of Health Economics* 2010;11(1):67-76.

62. Prenzler A, Yen L, Mittendorf T, et al. Cost effectiveness of ulcerative colitis treatment in Germany: a comparison of two oral formulations of mesalazine. *BMC Health Services Research* 2011;11:157.
63. Connolly MP, Boersma C, Oldenburg B. The economics of mesalazine in active ulcerative colitis and maintenance in the Netherlands. *Netherlands Journal of Medicine* 2012;70(6):272-77.
64. Saini SD, Waljee AK, Higgins PD. Cost utility of inflammation-targeted therapy for patients with ulcerative colitis. *Clinical Gastroenterology and Hepatology* 2012;10(10):1143-51.
65. Chaudhary MA, Fan T. Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis in the Netherlands. *Biologics in Therapy* 2013;3(1):45-60.
66. Connolly MP, Kuyvenhoven JP, Postma MJ, et al. Cost and quality-adjusted life year differences in the treatment of active ulcerative colitis using once-daily 4g or twice-daily 2g mesalazine dosing. *Journal of Crohn's and Colitis* 2014;8(5):357-62.
67. Essat M, Tappenden P, Ren S, et al. Vedolizumab for the treatment of adults with moderately to severely active ulcerative colitis: A single technology appraisal. In: NICE, ed., 2014.
68. Archer R, Tappenden P, Ren S, et al. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model. *Health Technol Assess* 2016;20(39):1-326. doi: 10.3310/hta20390
69. Beilman CL, Thanh NX, Ung V, et al. Real-Life Treatment Paradigms Show Adalimumab Is Cost-Effective for the Management of Ulcerative Colitis. *Canadian Journal of Gastroenterology & Hepatology* 2016;2016:5315798.
70. Stawowczyk E, Kawalec P, Pilc A. Cost-Effectiveness Analysis of 1-Year Treatment with Golimumab/Standard Care and Standard Care Alone for Ulcerative Colitis in Poland. *PLoS ONE* 2016;11(8):e0160444.
71. Stawowczyk E, Kawalec P, Pilc A. Cost-utility analysis of 1-year treatment with adalimumab/standard care and standard care alone for ulcerative colitis in Poland. *European Journal of Clinical Pharmacology* 2016;72(11):1319-25.
72. Stawowczyk E, Kawalec P, Pilc A. Cost-Utility Analysis of Infliximab with Standard Care versus Standard Care Alone for Induction and Maintenance Treatment of Patients with Ulcerative Colitis in Poland. *Pharmacotherapy* 2016;36(5):472-81.
73. Tappenden P, Ren S, Archer R, et al. A Model-Based Economic Evaluation of Biologic and Non-Biologic Options for the Treatment of Adults with Moderately-to-Severely Active Ulcerative Colitis after the Failure of Conventional Therapy. *Pharmacoeconomics* 2016;34(10):1023-38.
74. Wilson MR, Bergman A, Chevrou-Severac H, et al. Cost-effectiveness of vedolizumab compared with infliximab, adalimumab, and golimumab in patients with ulcerative colitis in the United Kingdom. *Eur J Health Econ* 2017 doi: 10.1007/s10198-017-0879-5
75. Ramsey S, Willke R, Briggs A, et al. Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report. *Value in Health* 2005;8(5):521-33.

76. Moss A. Optimizing the use of biological therapy in patients with inflammatory bowel disease. *Gastroenterol Rep* 2015;3(1):63-8. doi: 10.1093/gastro/gou087
77. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol* 2011;106(4):674-84. doi: 10.1038/ajg.2011.60
78. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;146(2):392-400 e3. doi: 10.1053/j.gastro.2013.10.052
79. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *The new england journal o f medicine* 2010;362:1383-95.
80. Panaccione R, Gosh S. Optimal use of biologics in the management of Crohn's disease. *Therapeutic Advances in Gastroenterology* 2010;3(3):179-89. doi: 10.1177/
81. Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *The Lancet* 2017;389(10086):2304-16. doi: 10.1016/s0140-6736(17)30068-5
82. Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: from theory to practice. *Nat Rev Gastroenterol Hepatol* 2017;14(1):22-31. doi: 10.1038/nrgastro.2016.155
83. Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015;12(12):720-7. doi: 10.1038/nrgastro.2015.150
84. Gregor J, McDonald J, Klar N, et al. An evaluation of utility measurement in Crohn's disease. *Inflammatory Bowel Disease* 1997;3(4):265-76.
85. Poole CD, Connolly MP, Nielsen SK, et al. A comparison of physician-rated disease severity and patient reported outcomes in mild to moderately active ulcerative colitis. *J Crohns Colitis* 2010;4(3):275-82. doi: 10.1016/j.crohns.2009.11.010
86. Woehl A, Hawthorne AB, Morgan CL, et al. Pg113 the Epidemiology and Health Care Resource Use in Patients with Crohn's Disease: A Population Based UK Study. *Value in Health* 2007;10(6):A355. doi: 10.1016/s1098-3015(10)65262-x
87. Knies S, Evers SM, Candel MJ, et al. Utilities of the EQ-5D: Transferable or Not? *Pharmacoeconomics* 2009;27(9):767-79.
88. Huoponen S, Blom M. A systematic review of the cost-effectiveness of biologics for the treatment of inflammatory bowel diseases. *PLoS ONE* 2015;10 (12) (no pagination)(e0145087)
89. Tang DH, Harrington AR, Lee JK, et al. A systematic review of economic studies on biological agents used to treat Crohn's disease. *Inflammatory Bowel Diseases* 2013;19(12):2673-94.
90. Schneider Y, Saumoy M, Cohen-Mekelburg S, et al. The cost-effectiveness of vedolizumab for inflammatory bowel disease: A review of the current literature. *Gastroenterology and Hepatology* 2016;12(10):617-21.
91. Anderson R. Systematic reviews of economic evaluations: utility or futility? *Health Econ* 2010;19(3):350-64. doi: 10.1002/hec.1486

92. Tsai HH, Punekar YS, Morris J, et al. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 2008;28(10):1230-39.

CHAPTER 3

The evolution of health care utilisation and costs for inflammatory bowel disease over ten years

Nadia Pillai, Mark Dusheiko, Michel H. Maillard, Gerhard Rogler, Beat Brüngger, Caroline Bähler, Valérie E. H. Pittet, On behalf of the Swiss IBD Cohort study group

This study was published in the Journal of Crohn's and Colitis.

Citation:

Pillai N, Dusheiko M, Maillard MH, Rogler G, Brüngger B, Bähler C, Pittet V (2019). The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. Journal of Crohn's and Colitis;13(6):744-54. doi: 10.1093/ecco-jcc/jjz003

ABSTRACT

Background

Inflammatory bowel disease (IBD) places an economic strain on health systems due to expensive pharmaceutical therapy, risk of hospitalisation and surgery, and long-term monitoring. The evolving treatment guidelines advocate rapid scale-up to biologic agents in order to improve health outcomes and quality of life. This study evaluated changes in health care utilisation and expenditures for IBD in Switzerland over time.

Methods

We extracted clinical, patient and resource consumption data from the Swiss IBD Cohort Study between 2006 and 2016. Average unit costs for IBD-related events were derived from Swiss claims data and pharmaceutical price lists. We used multivariate regression, controlling for patient-level characteristics, to estimate trends and determinants of direct and indirect costs and resource utilisation.

Results

We included 2,365 adults diagnosed with Crohn's disease (CD; N=1,353) and ulcerative colitis (UC; N=1,012). From 2006 to 2016, mean health care expenditures per patient per year were 9,504 euros (70% drugs, 23% inpatient, 7% outpatient) for CD and 5,704 euros (68% drugs, 22% inpatient, 10% outpatient) for UC. Healthcare costs increased by 7% (CD) and 10% (UC) per year, largely due to rising pharmaceutical expenditures driven by increased biologic agent use. Inpatient, outpatient and indirect costs fluctuated and did not offset increased pharmaceutical costs. Disease characteristics were important predictors of costs.

Conclusions

Increased expenditure for IBD was marked by a shift towards greater pharmaceutical management over the past decade. This study highlights the need to identify cost-effective treatment strategies in the face of increased uptake and expenditures associated with innovative treatments.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), known as inflammatory bowel disease (IBD), are chronic conditions causing inflammation in the gastrointestinal tract and extra-intestinal complications. With a growing worldwide prevalence, IBD poses a global public health challenge due to severe morbidity and high health care utilisation[1]. The estimated prevalence of IBD in many high-income countries is greater than 0.3% of the population[2]. In Western Europe, the prevalence of CD and UC ranged between 28 to 322 and 43 to 505 per 100,000 persons, respectively[2]. IBD follows a course of exacerbation and remission of inflammation, and is characterised by chronic abdominal pain, diarrhoea and weight loss[3 4]. In addition, IBD patients often experience extra-intestinal manifestations (EIMs) commonly involving inflammation of the joints, skin and eyes[5].

While treatment for IBD is not curative, clinical management aims to induce and maintain remission using pharmaceutical agents and surgery. This creates a large health and economic burden due to long-term medical monitoring, high rates of productivity loss and expensive clinical care[6 7]. According to a large cohort study across European countries, total direct health care costs within the first year of diagnosis was 5,942 euros and 2,753 euros per patient for CD and UC, respectively[8]. Previous literature suggested that these costs were driven by surgeries and increasing use of biologic agents[9]. The evolving treatment landscape for IBD advocates early use of and rapid scale-up to biologic agents in order to reduce surgery rates and improve health outcomes and quality of life. Consequently, concerns have been raised about the overall impact on health care costs, particularly because the cost-effectiveness of long-term biologic agent use remains inconclusive when compared with conventional therapies due to high drug costs[10].

In Switzerland, total health care costs for IBD patients increased by 6% per year compared to 2.4% in non-IBD equivalent individuals largely due to increased outpatient management[11]. With a rising prevalence, estimated between 0.2% and 0.4%, increased costs of IBD management will have major implications for health financing and clinical practice in Switzerland[11 12]. As approaches to contain the growth in health expenditures are considered, it becomes increasingly important to understand what drives costs in the health system and where efficiency gains can be made[13 14].

This study aimed to evaluate annual patient-level changes in health care utilisation and direct and indirect costs of IBD in Switzerland, associated with therapeutic advancements and disease progression. We first described trends in health care utilisation and expenditures for inpatient, outpatient, and pharmaceutical care, and indirect costs associated with productivity loss due to work absenteeism, for CD and UC patients between 2006 and 2016. Second, we evaluated how patient demographic, socio-economic, and clinical characteristics affected costs in an explanatory model.

METHODS

Study design and population

We conducted a retrospective costing study from the societal perspective, including both direct health care costs paid by all third parties and indirect costs due to work absenteeism. Adult patients (≥18 years) diagnosed with CD or UC, enrolled in the Swiss IBD Cohort Study (SIBDCS) from 2006 to 2016, were included in this study. We excluded patients with indeterminate IBD, those who had a change of diagnosis during follow-up, and those who failed to return at least one patient questionnaire.

Cohort data

The SIBDCS is a national prospective cohort recruiting patients from academic and non-academic centres across Switzerland since 2006[15]. The cohort is dynamic with continual enrolment of patients by their treating physicians. Data were collected annually through paper-based questionnaires completed by physicians and patients. Physician-reported data were validated to ensure accuracy and completeness. We extracted physician-reported data on patient demographics, disease characteristics, and IBD-related pharmaceutical use, surgical procedures, hospitalisations and imaging scans (see Supplementary Files *Table B1* and *Table B2* for a full list of procedures and drugs considered). In addition, we used patient-reported data on employment status, days absent from work per year, general IBD-related hospitalisations and outpatient consultation visits to ambulatory outpatients, general practitioners (GP), and gastroenterologists. The frequency of outpatient consultations was based on a 3-month recall, which was scaled up by a factor of four to extrapolate to annual consultation rates.

Patient characteristics included age, gender, canton (region) of treatment, smoking history (current, former, and non-smoker), education attainment (less than the obligatory level of school, basic and obligatory school, vocational apprenticeship, upper secondary school, and tertiary education), and employment status (full-time, part-time, student, unemployed, and retired).

Clinical characteristics included diagnosis (CD and UC), disease severity (remission, mild, moderate, and severe), disease location (L1 ileal, L2 colonic, L3 ileocolonic, L4 isolated upper disease, L1+L4, L2+L4, L3+L4, pancolitis, left-sided colitis, and proctitis), disease behaviour (B1 non-penetrating, non-stricturing disease, B2 stricturing disease, B3 penetrating disease, and B1p/B2p/B3p representing perianal involvement), disease duration (time from diagnosis to year of event), and binary variables for the presence/absence of fistula, abscess, fissure, stenosis, EIMs (including peripheral arthritis/arthralgia, uveitis/iritis, pyoderma gangrenosum, eythema nodosum, aphthous oral ulcers/stomatitis, ankylosing spondylitis, sacroilitis, and primary sclerosing cholangitis), and other major complications (including colorectal cancer, colon dysplasia, intestinal lymphoma, osteopenia/osteoporosis, anaemia, deep venous thrombosis, pulmonary embolism, nephrolithiasis, gallstone, malabsorption syndrome, massive haemorrhage, perforation/peritonitis, and pouchitis). Disease severity was defined based on the Crohn's Disease Activity Index (CDAI) and, for UC, the modified Truelove and Witts Activity Index (MTWAI).

Indirect cost data

We used the human capital approach to calculate indirect costs from productivity loss[16]. This assumed that the monetary value of an individual's contribution to an employer is equal to their wage rate and therefore absence from work results in lost salary. We extracted patient-reported IBD-related absence from employment (full-time and part-time) and education from the SIBDCS (recorded from 2007 onwards). National median salaries by age group and gender, obtained from the Swiss Federal Office for Statistics[17], were multiplied by days absent from work/education to derive an estimate of indirect costs.

Direct cost data

Direct costs included all IBD-related health care costs for inpatient, outpatient, and pharmaceutical interventions. Unit cost estimates for inpatient and outpatient events were derived from anonymised insurance claims data from 2012 to 2014 provided by the Helsana Group. The Helsana Group provides mandatory health insurance for up to 15% of the Swiss population across all cantons[11]. IBD patients in the insurance database were identified based on pharmaceutical use and consultations with gastroenterologists[11].

The costs of inpatient events were derived from Swiss-Diagnosis Related Group (DRG) codes. DRG cost weights are standardised nationally and multiplied by a hospital-specific base rate. DRG codes in Switzerland are not procedure-specific and represent a bundle of care provided during a hospitalisation, incorporating the costs of resources used, including all surgical and medical interventions, health worker time, average length of stay, and excess bed days[18]. Unit costs for surgical interventions are not available in Switzerland; thus unit costs used in this study reflect the total average cost of an inpatient stay when a given surgery was performed. To capture IBD-related hospitalisations, we used DRG codes for diseases of the digestive system (Major Diagnostic Category 6).

The costs of outpatient events were derived from a nationwide tariff system (TARMED)[19]. TARMED contains more than 4000 levels of detailed outpatient activities and associated nationally standardised cost weights. This was used to derive unit costs for IBD-specific general consultations, specialist visits, imaging scans, examinations, and parenteral drug administration.

Pharmaceutical costs were derived from publicly available national price lists in Switzerland from 2017[20]. Dose recommendations from Swiss guidelines were used to calculate an average drug cost per dose[21]. We assumed costs for 1 gastroenterologist consultation for any new prescription and drug administration costs (including infusion costs and nurse time) for infliximab and vedolizumab infusions.

Statistical methods and analysis

We used Poisson regression models to derive average unit cost estimates of inpatient and outpatient procedures adjusted for age (in 10-year groups), gender, and canton of the health care provider. The

Poisson model was used instead of crude mean costs because health care in Switzerland is decentralised and cost variations exist between cantons. This model accounted for the non-negative and skewed characteristics of cost data and proportionally adjusted for the effect of covariates[22]. Adjusted average unit cost estimates were used to cost-weight the resource utilisation reported in the SIBDCS by age-gender-canton groups.

All unit costs are reported in Supplementary Files *Table B1* and *Table B2*. Costs were inflated to 2017 prices using the consumer price index (CPI)[23]. Therefore, the analysis reflected changes in the quantity, intensity, and composition of health care utilisation and productivity loss, and not changes in prices and wage rates, which were held constant over time.

Trends in expenditures over time

We analysed mean expenditures (total direct and indirect costs) for the study population between 2006 and 2016 using fixed effects linear regression models with binary variables representing the year in which an event occurred. This model adjusted for time-invariant individual fixed effects, which controlled for variations in costs due to changes in the composition of the cohort population related to continuous enrolment and attrition[24]. Total direct costs were broken down by health care sector (drug, inpatient, and outpatient). We report the mean costs per patient per year and annual growth rates with 95% confidence intervals (CI).

Multivariate regression analysis

Using a two-part model, we evaluated drivers of direct and indirect expenditures controlling for the year in which events occurred, time followed up in the SIBDCS (cohort wave), disease duration, and patient and clinical characteristics described previously. This model accounted for zero costs associated with non-use of health care, and estimated the expected mean adjusted costs for the full sample[22]. The first part estimated the probability of a non-zero health care cost in logistic regression models, and the second part estimated the mean expected costs conditional on having a positive cost, using generalised linear regression models (GLM) with a gamma distribution and log-link[25]. GLM gamma models are frequently used for health care costs because they take into account skewness and heteroscedasticity and constrain predicted average costs to be positive on the log scale, without associated

retransformation biases[26 27]. The expected mean costs by sector of clinically and statistically important covariates with 95% CI are reported; standard errors were clustered due to the panel data structure. Expected costs were calculated by multiplying the probability of a non-zero cost (first part) by the expected costs conditional on having a non-zero cost (second part), after adjusting for the same covariates in both parts[26]. Full model results are available in the Supplementary Files (*Table B3* and *Table B4*).

Changes in the utilisation of biologic agents, outpatient consultations, hospitalisations, and surgical interventions (binary variables) over time were evaluated using random effects logistic regression models adjusting for patient and clinical characteristics. The expected probabilities of experiencing an event with 95% CI are reported.

Statistical analyses were performed in Stata Version 14 (College Station, TX). Descriptive statistics for the study population included the mean and standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. Costs were converted from Swiss francs (CHF) to euros using the average exchange rate for 2017 of 1 CHF = 0.90 euros[28].

RESULTS

Descriptive characteristics of the study population

In total, 2365 adults were included in this analysis, 1353 (57%) with CD and 1012 (43%) with UC. The majority of CD patients were female (54%) compared to 48% of UC patients (*Table 4*). On average, patients were enrolled in the cohort at age 42 and received their diagnosis 11 (CD) and 9 (UC) years before enrolment. Enrolment in the SIBDCS is continuous, with patient numbers increasing from 989 to 1792 from 2006 to 2016. On average, patients were followed up for 9 years.

Table 4 Descriptive socio-demographic and clinical characteristics of the study population

	Crohn's disease (N=1353)	**Ulcerative Colitis (N=1012)**
Female gender (N, %)	736 (54%)	482 (48%)
Age at enrolment (Mean, SD)	41 (15)	43 (14)
Smoking status at enrolment (N, %)		
Current smoker	621 (46%)	222 (22%)
Former smoker	85 (6%)	28 (3%)
Non-smoker	621 (46%)	736 (73%)
Missing	26 (2%)	26 (3%)
Provider canton by language (N, %)		
German	904 (67%)	717 (71%)
French	449 (33%)	295 (29%)
Education attainment (N, %)		
No education	26 (2%)	14 (1%)
Basic & obligatory school	176 (13%)	116 (11%)
Vocational apprenticeship with diploma	574 (42%)	391 (39%)
Upper secondary school	160 (12%)	115 (11%)
Tertiary education	396 (29%)	362 (36%)
Missing	21 (2%)	14 (1%)
Employment status at enrolment (N, %)		
Full-time employment	726 (54%)	554 (55%)
Part-time employment	258 (19%)	202 (20%)
Education	31 (2%)	27 (3%)
Unemployed	151 (11%)	115 (11%)
Retired	186 (14%)	114 (11%)
Missing	1 (0.1%)	0
Disease duration at enrolment (Mean, SD)	11 (10.3)	9 (9.1)
Montreal classification at enrolment (N, %)		
Non-stricturing, non-penetrating (B1)	739 (54.6%)	
Stricturing (B2)	308 (22.8%)	
Penetrating (B3)	306 (22.6%)	
Perianal involvement (B1p/B2p/B3p)	351 (25.9%)	
Disease location at diagnosis (N, %)		
Ileal (L1)	321 (24%)	
Colonic (L2)	303 (22%)	
Ileocolonic (L3)	610 (45%)	
Upper gastrointestinal disease (L4)	13 (1%)	
L1+L4	14 (1%)	
L2+L4	10 (1%)	
L3+L4	37 (3%)	
Pancolitis		391 (39%)
Left-sided colitis		366 (36%)
Proctitis		229 (23%)
Missing	45 (3%)	26 (3%)

Disease activity at enrolment* (N, %)		
Remission	1,271 (94%)	541 (53%)
Mild	56 (4%)	110 (11%)
Moderate	25 (2%)	145 (14%)
Severe	1 (0.1%)	216 (21%)
Total years of follow-up in SIBDCS (Mean, SD)	9 (2.6)	9 (2.5)
Highest level of treatment received at enrolment§		
Biologic agent	531 (39%)	165 (16%)
Immunosuppressant	478 (35%)	328 (32%)
No treatment	144 (11%)	76 (8%)
Aminosalicylates	87 (6%)	293 (29%)
Topical steroids	56 (4%)	46 (5%)
Systemic steroids	46 (3%)	89 (9%)
Other (bile acid preparations, probiotics, bisphosphonates)	6 (0.44%)	9 (1%)
Antibiotic	5 (0.37%)	6 (1%)
Highest level of treatment received during whole follow-up§		
Biologic agent	783 (58%)	308 (30%)
Immunosuppressant	360 (27%)	303 (30%)
No treatment	77 (6%)	42 (4%)
Aminosalicylates	46 (3%)	205 (20%)
Topical steroids	40 (3%)	42 (4%)
Systemic steroids	34 (3%)	85 (8%)
Antibiotic	9 (1%)	19 (2%)
Other (bile acid preparations, probiotics, bisphosphonates)	4 (0.30%)	8 (1%)

*Crohn's disease activity index (CDAI): remission <150; mild ≥150 & <200; moderate ≥220 & <450; severe ≥450; Modified Truelove and Witts activity index (MTWAI): remission <3; mild <4 & ≥3; moderate ≥4 & <6; severe ≥6

§Highest level of treatment received during follow-up in the SIBDCS is defined based on the step-up treatment protocol.

Patients had 5 (CD, 95% CI: 4.8, 5.5; UC, 95% CI: 3.9, 4.6) outpatient consultations per year on average; consisting of 2 gastroenterologist visits, 2 GP visits and 1 ambulatory outpatient visit (*Table 5*). Inpatient events were rare but resulted in an average length of stay of 13 days.

Table 5 Mean frequency of healthcare utilisation per patient per year from 2006-2016

	Crohn's disease (N=1353)	Ulcerative Colitis (N=1012)
Overall outpatient consultations (mean, 95% CI)	5.16 (4.82, 5.50)	4.23 (3.91, 4.55)
Ambulatory outpatient visits	1.04 (0.93, 1.15)	0.93 (0.80, 1.05)
General practitioner visits	1.67 (1.48, 1.86)	1.29 (1.12, 1.46)
Gastroenterologist visits	2.45 (2.28, 2.62)	2.02 (1.86, 2.17)
Diagnostic scans (mean, 95% CI)	0.63 (0.61, 0.66)	0.60 (0.57, 0.63)
Inpatient events (mean, 95% CI)	0.13 (0.11, 0.14)	0.07 (0.06, 0.08)
Surgical procedures	0.08 (0.07, 0.09)	0.02 (0.02, 0.03)
General hospitalisation for flare management	0.04 (0.04, 0.05)	0.04 (0.04, 0.05)
Duration of general hospitalisations for those hospitalised (days)	12.77 (10.48, 15.1)	13.57 (0.38, 0.63)

Trends in expenditures over time

Mean total direct expenditures per patient per year were 9,504 euros (95% CI: 9,047 euros, 9,961 euros; median: 8,230 euros) for CD and 5,704 euros (95% CI: 5,303 euros, 6,106 euros; median: 4,578 euros) for UC (*Table 6*).

Table 6 Mean and median costs (euros) per patient per year and annual growth rates (%) from 2006/7-2016 by sector

	Crohn's disease (N=1353)		Ulcerative colitis (N=1012)	
	Mean (median) cost (euros) per patient per year	**Mean annual growth rates (95% CI)**	**Mean (median) cost (euros) per patient per year**	**Mean annual growth rate (95% CI)**
Total direct costs	9504 (8230)	7% (5%, 9%)	5704 (4578))	10% (7%, 14%)
Drugs costs	6618 (6678)	11% (9%, 14%)	3895 (3670)	11% (8%, 14%)
Inpatient costs	2188 (499)	-0.52% (-7%, 6%)	1242 (241)	10% (-8%, 28%)
Outpatient costs§	698 (517)	24% (16%, 33%)	567 (383)	33% (17%, 49%)
Indirect costs*	1339 (686)	-9% (-39%, 21%)	707 (170)	-28% (-58%, 2%)‡

Adjusted mean annual growth rates were estimated from linear fixed effects regression models on the original cost scale.

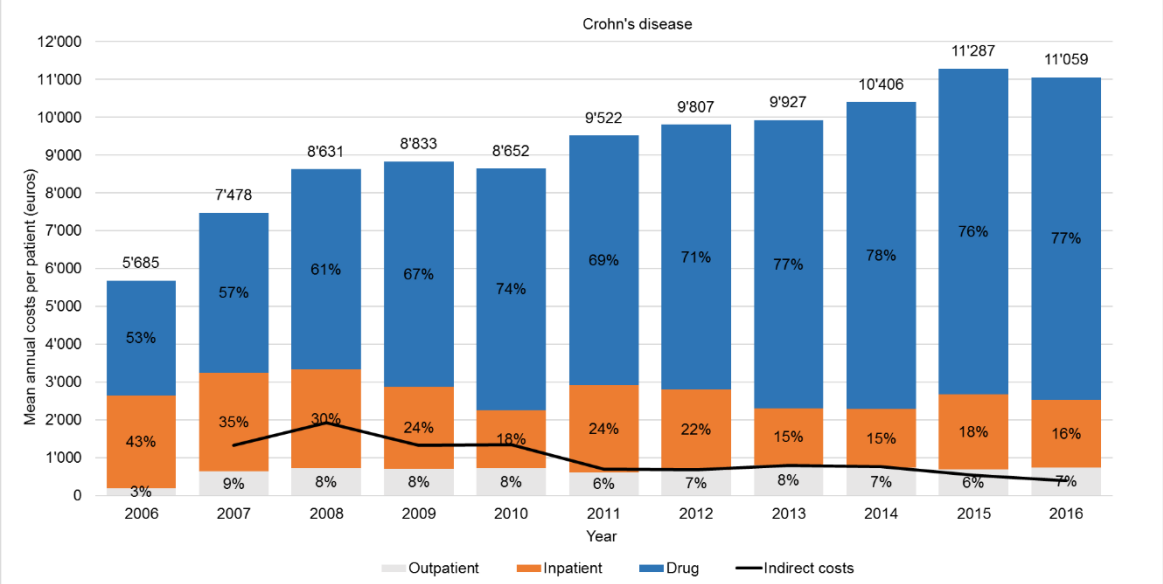
§Patient-reported data on outpatient consultations were routinely collected from 2007 onwards; however, retrospective data was available for some patients from 2006. Hence, the average growth rate is affected by a small sample of observations in 2006. After excluding 2006, the mean annual growth rate for outpatient costs (i.e., from 2007-2016) was 2% for CD and UC. Cost estimates for drugs and inpatient events were captured from 2006 using patients' medical records.

*Data collection on patient-reported absenteeism began from 2007 onwards. Indirect costs are based on a smaller sample of individuals reporting to be in employment or studying.

‡The large decline in indirect costs over time for UC may be due to missing observations in 2007 and 2015/16; analysing estimates from 2008-2014, suggests an annual decline of 5% on average.

Total health care expenditures nearly doubled between 2006 and 2016, increasing from 5,685 euros to 11,059 euros per CD patient and from 2,807 euros to 6,041 euros per UC patient (*Figure 3*). This was largely due to an average annual increase in pharmaceutical expenditures of 11% (CD 95% CI: 9%, 14%; UC 95% CI: 8%, 14%; *Table 6*) representing an absolute increase in drug costs of 5,500 euros for CD and 3,000 euros for UC over 10 years. Drug expenditures accounted for almost 80% of total health care expenditures in 2016 compared to 53% (CD) and 66% (UC) in 2006 (*Figure 3*). This was marked by an increase in crude mean expenditures for biologic agents over time, accounting for 90% (CD) and 73% (UC) of total drug costs in 2016 (*Figure 4*).

A



B

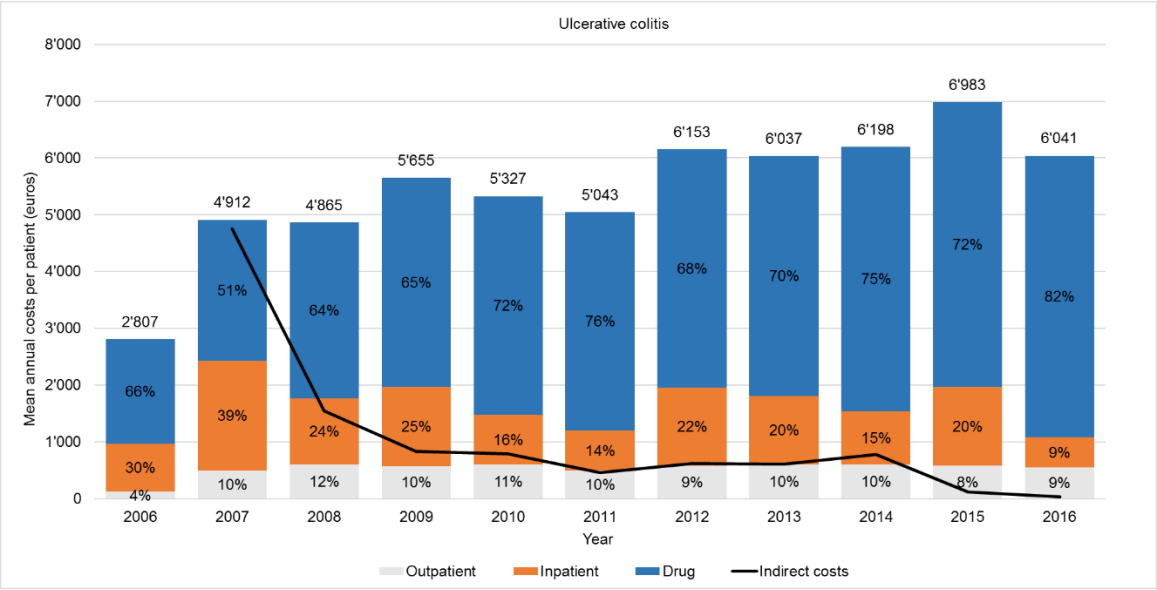


Figure 3 Mean annual direct and indirect costs (euros) per patient and proportion of expenditures by healthcare sector (outpatient, inpatient, and drugs) estimated using fixed effects regression models for Crohn's disease (A) and ulcerative colitis (B) [NB: Incomplete patient records created uncertainty in indirect cost estimates in 2007 & 2015/2016 for UC patients. Indirect costs are based on a smaller sample of individuals reporting to be in employment or studying.]

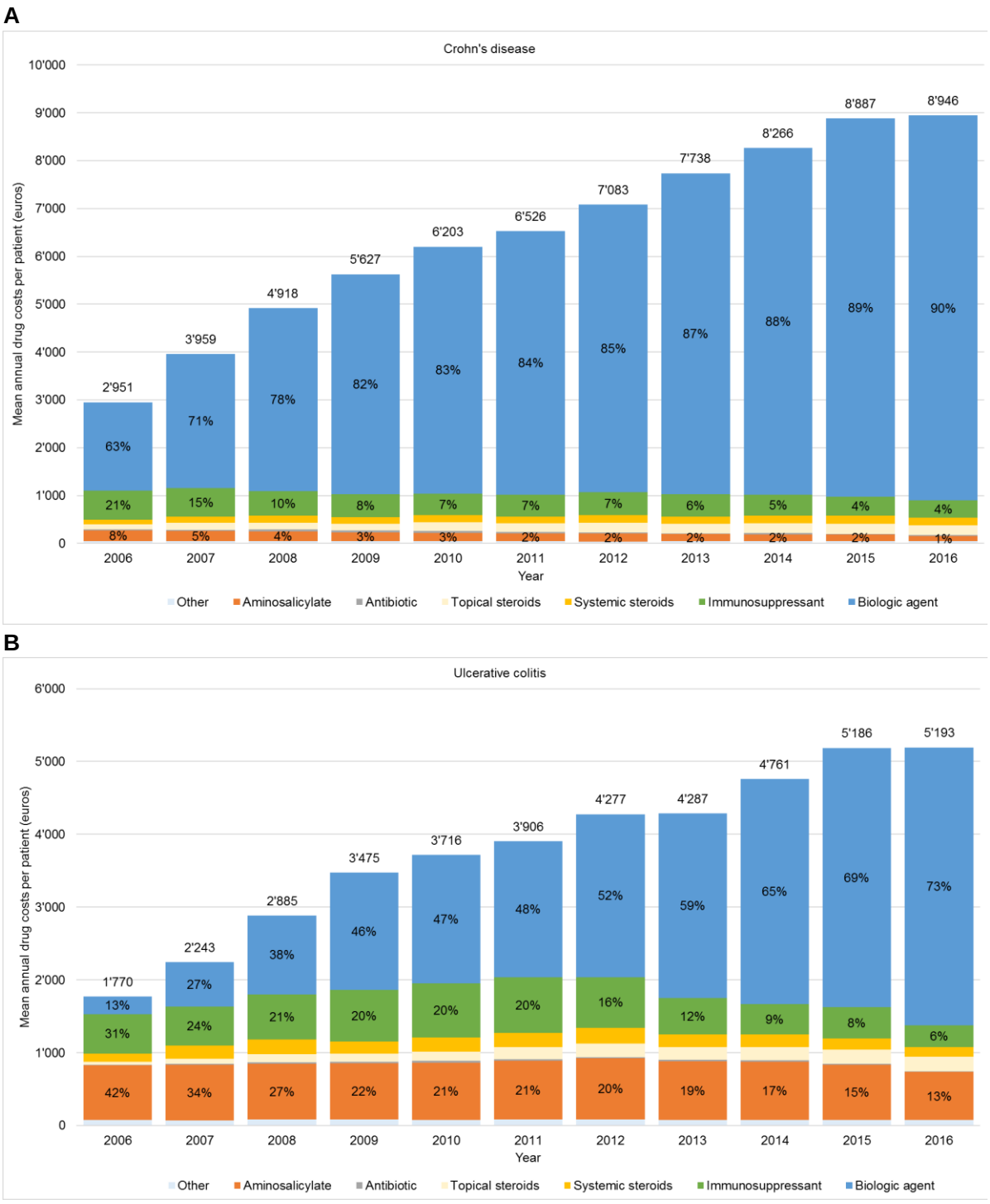


Figure 4 Crude mean drug costs (euros) per patient per year and proportion of total by drug class for Crohn's disease (A) and ulcerative colitis (B)

Outpatient costs grew by 24% for CD (95% CI: 16%, 33%) and 33% for UC (95% CI: 17%, 49%) per year (*Table 6*); however, their contribution to total expenditures was small (*Figure 3*). Note, this annual growth declined to 2% on average after excluding 2006 (i.e. from 2007-2016) due to low reporting of outpatient consultations in 2006. In addition, mean inpatient expenditures fluctuated per year,

declining by 0.52% (95% CI: -7%, 6%) for CD and increasing by 10% (95% CI: -8%, 28%) for UC on average (*Table 6*). This reflected a growth in crude rates of hospitalisations for flare management whereas surgery rates declined over time (see Supplementary Files *Figure B1*).

Indirect costs declined significantly by 9% (95% CI: -39%, 21%) for CD and 28% (95% CI: -58%, 2%) for UC per year on average (*Figure 3*). Mean indirect costs per patient per year from 2007-2016 were 1339 euros (95% CI: 882 euros, 1796 euros; median: 686 euros) and 707 euros (95% CI: 515 euros, 900 euros; median 170 euros) for CD and UC, respectively (*Table 6*).

Multivariate regression analysis of expenditures

After controlling for patient and disease characteristics, mean total direct expenditures per patient increased annually and was more than 20% greater than the predicted overall mean cost (i.e., the global average cost per patient per year from 2006-2016) in 2016 representing an absolute difference of 4,000 euros for CD and 1,400 euros for UC (*Figure 5*). This effect was driven by a year-on-year growth in drug costs of 10% on average. In addition, utilisation of biologic agents grew, with the predicted adjusted probability of biologic treatment increasing from 30% to 60% for CD and 10% to 35% for UC from 2006 to 2016 (see Supplementary Files *Figure B2*).

Inpatient costs fluctuated around the overall mean for CD and remained stable for UC (*Figure 5*), reflecting a rise in general hospitalisations and relatively constant rates of surgeries after controlling for patient and clinical characteristics (see Supplementary Files *Figure B2*). Moreover, despite the declining probability of outpatient consultations over time (see Supplementary Files *Figure B2*) no clear trends were observed for mean outpatient costs, potentially due to rising costs of outpatient activities performed during consultations (see Supplementary File *Table B3* and *Table B4*). Finally, mean annual indirect costs increased for CD and declined for UC; however, these trends had large uncertainty due to a low frequency of reported absenteeism (*Figure 5*).

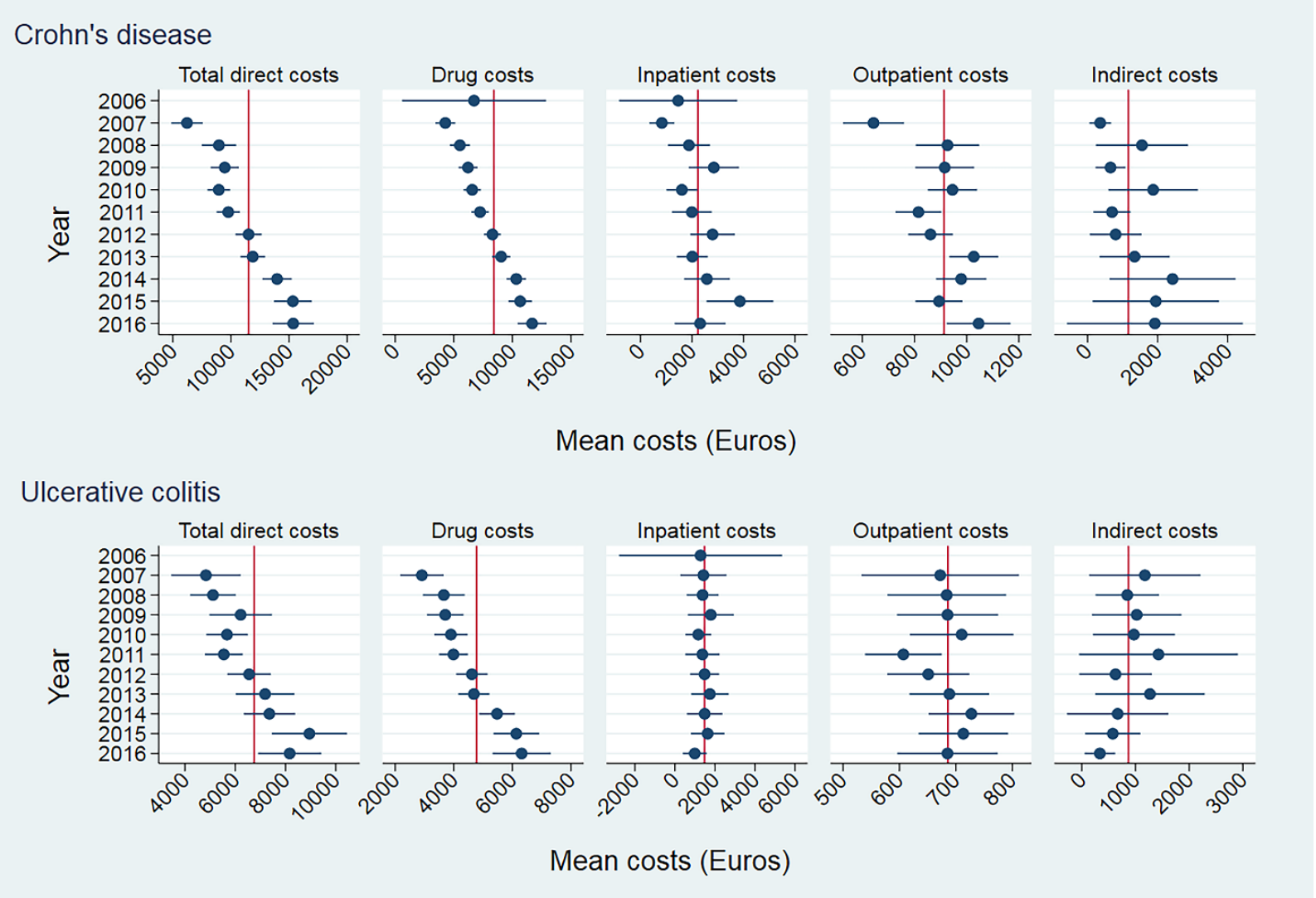


Figure 5 Adjusted mean expected costs (euros) with 95% CI per patient per year by sector for Crohn's disease and ulcerative colitis [NB: red line represents the overall mean annual costs per patient per year from 2006-2016 after controlling for patient and clinical characteristics; some estimates dropped due to small sample sizes in the model; total direct costs is the sum of drug, inpatient and outpatient costs]

Figure 6 shows the effects of key patient characteristics on costs. For both diseases, males had higher than average total direct costs compared to females. Moreover, total direct, drug, and outpatient costs declined with age, whereas inpatient costs remained stable around the overall mean and indirect costs increased. In addition, individuals who completed upper secondary and tertiary education had lower total health care costs compared to those with lower education attainment. Note, CD patients reporting less than the obligatory level of school had lower than average costs in all sectors; however, this effect was based on a small sample size.

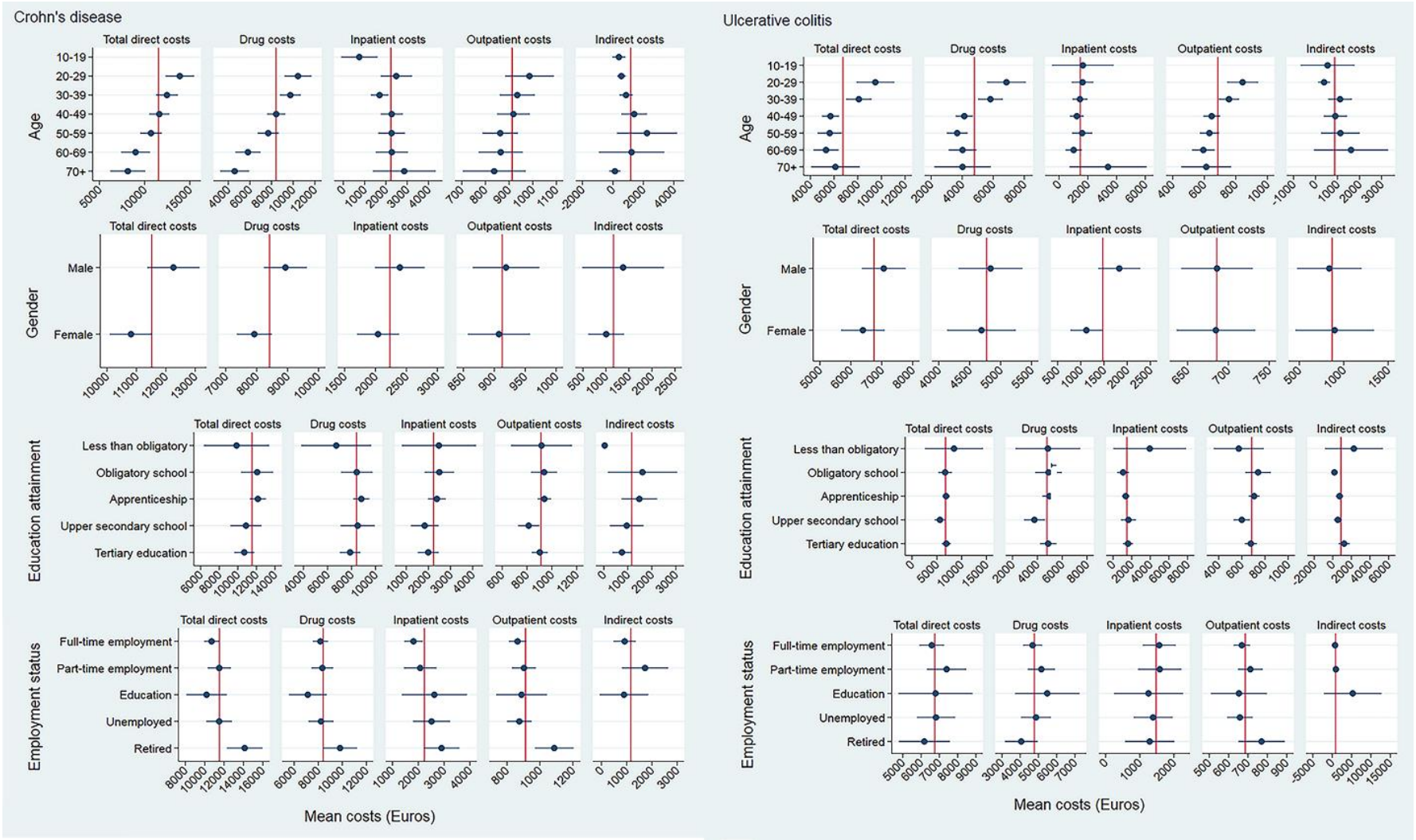


Figure 6 Adjusted mean expected costs (euros) with 95% CI per patient per year by age, gender, education attainment and employment status in each sector for Crohn's disease and ulcerative colitis [NB: red line represents the overall mean annual costs per patient per year from 2006-2016 after controlling for patient and clinical characteristics; some estimates dropped due to small sample sizes in the model; total direct costs is the sum of drug, inpatient and outpatient costs]

Total health care costs increased with greater disease severity, extension, and complexity (*Figure 7*). Total direct costs for patients with moderate disease were 22% (CD) and 70% (UC) higher compared to patients in remission. Moreover, health care expenditures were significantly higher when patients had complications. For example, drug costs were 25% (CD) and 36% (UC) higher than average when EIMs were present, and fistula and other major complications were associated with higher than average drug, inpatient, and outpatient costs. Interestingly, although the presence of fistulas in UC is rare, these were shown to increase outpatient and inpatient costs when present. In addition, CD with stricturing (B2) and penetrating (B3) disease behaviour incurred higher health care and indirect costs compared to a non-stricturing, non-penetrating (B1) disease behaviour. Furthermore, perianal involvement increased drug expenditures and indirect costs by more than 20% compared to disease without perianal involvement.

Finally, disease duration significantly influenced costs for both diseases (*Figure 7*). For CD patients, drug, inpatient, and indirect costs were highest for individuals in the early years of diagnosis and declined with longer disease duration. A similar pattern was observed for UC patients; however, inpatient costs increased with disease duration.

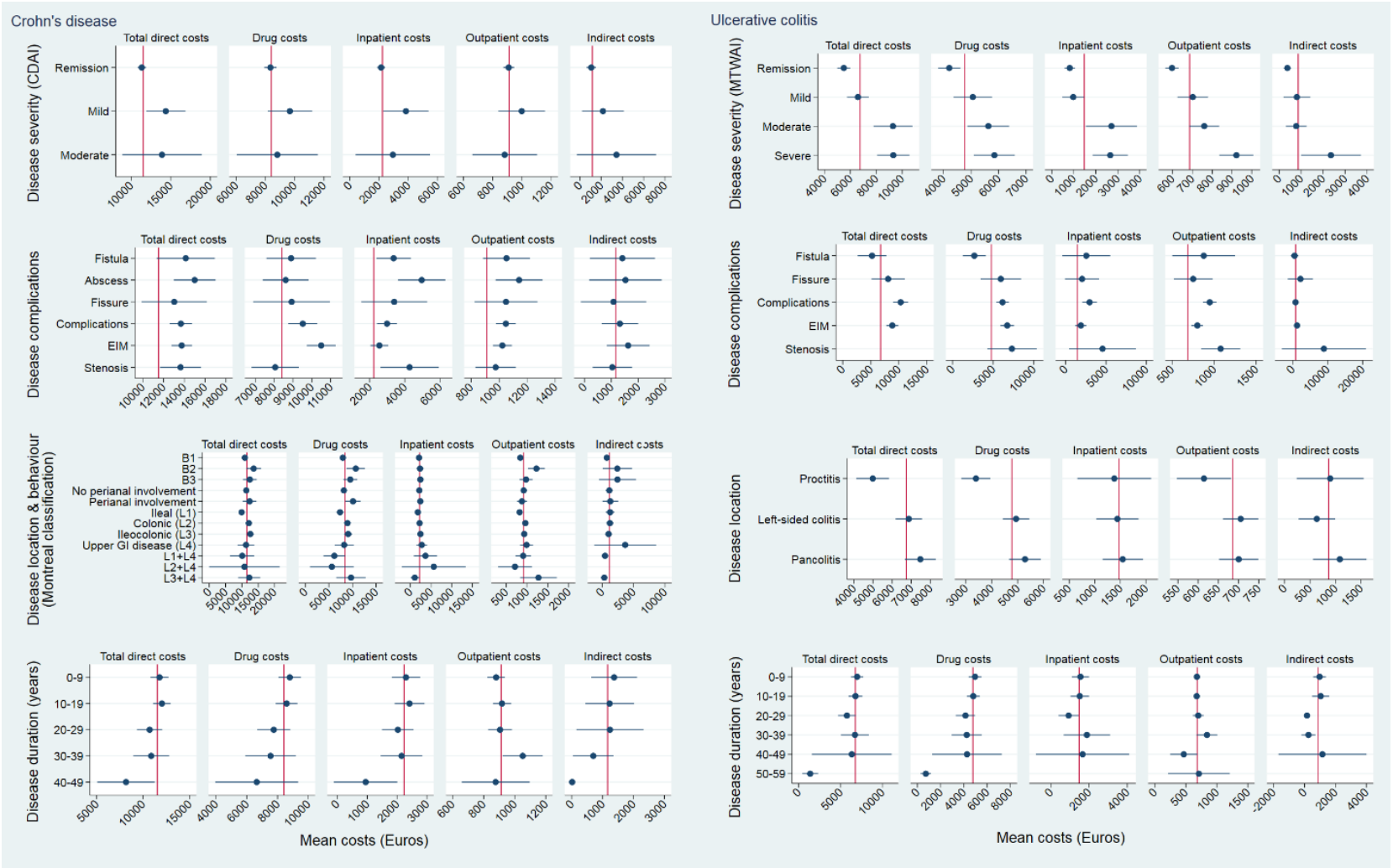


Figure 7 Adjusted mean expected costs (euros) with 95% CI per patient per year by disease severity, complications, location and behaviour, and disease duration in each sector for Crohn's disease and ulcerative colitis [NB: red line represents the overall mean annual costs per patient per year from 2006-2016 after controlling for patient and clinical characteristics; some estimates dropped due to small sample sizes in the model; total direct costs is the sum of drug, inpatient and outpatient costs; disease behaviour classified according to Montreal classification: non-stricturing, non-penetrating (B1), stricturing (B2), penetrating (B3)]

DISCUSSION

This study provides a detailed description of the evolution of patient-level costs for IBD across the different sectors of the health system, as well as the impact on lost productivity in Switzerland over the past decade. We found that the management of IBD was associated with increased health care expenditures, primarily due to rising pharmaceutical costs associated with increased uptake of biologic agents since 2006. This effect remained after controlling for patient and disease characteristics, suggesting changes in clinical management over time independent of disease progression. Importantly, inpatient, outpatient, and indirect costs fluctuated during the study period and did not offset rising drug costs. Disease characteristics were important drivers of health care costs whereby greater complexity associated with severe disease, extensive disease locations, EIMs, and complications increased costs. EIMs were associated with high drug costs, highlighting the importance of an interdisciplinary approach to IBD management[29]. Early detection of these complications and risk-stratification could help to manage patients more efficiently from a health and cost perspective.

The observed increase in pharmaceutical management for IBD is consistent with several studies from different settings[6 9 30-32] and contrasts with older literature, which found that inpatient care drove total expenditures[33-35]. Although we cannot discern a causal relationship from these observational studies, the change coincided with greater uptake of biologic agents and supports clinical trial evidence showing associated reductions in hospitalisations and surgical interventions[36]. In contrast, our study showed mean inpatient expenditures remained stable over time, suggesting no direct substitution between inpatient and outpatient/pharmaceutical care in Switzerland. Of note, this pattern has been observed previously in Switzerland[37]. Despite stable surgery rates, inpatient costs in this study were influenced by a rise in general hospitalisations over time. This could be associated with the observed decline in outpatient consultations, adverse events of pharmaceuticals, or changing hospital admission thresholds due to health care reforms[38]. Unfortunately, this could not be evaluated in our study.

Cost-of-illness studies notoriously vary in methodology, creating inconsistencies in the results and impeding comparability across studies and settings. Literature reviews found that per patient annual costs for UC and CD varied between 6,217-11,477 USD (5,290–9,800 euros) and 11,034-18,932 USD (9,390-16,100 euros) in the USA and 8,949–10,395 euros and 2,898–6,742 euros in European

countries, respectively[39 40]. In addition, a European population-based cohort study found average health care costs for CD and UC were 5,942 euros and 2,753 euros, respectively, per patient 1 year after diagnosis[8]. These results were supported by studies in The Netherlands and Germany using patient-reported costs measured over 3 months and 4 weeks[6 9 41]. The higher magnitude of costs reported in our study could be explained by: methodological differences such as a longer observation period and including data up to 2016; systemic differences between health systems, resulting in differential access to treatments and specialist care; and generally higher health care costs in Switzerland compared to other European countries.

Previous work in Switzerland, using the same claims data, found mean health care costs for IBD patients in 2014 were 11,069 euros; higher than estimated in our study[11]. This variation could be due to different observation periods and inclusion of different cost items (e.g., specialist or paramedical visits, home care and rehabilitation) based on data availability. In addition, this study included health care events not specifically related to IBD, which could lead to an overestimation of resource utilisation and costs. We addressed this constraint by evaluating resource utilisation recorded in the SIBDCS for known IBD patients and related events.

IBD places a large burden on societies, particularly due to early disease onset during peak employment years[36]. We found indirect costs from productivity losses reduced significantly during the study period, suggesting that changing disease management may positively impact the wider societal costs of IBD. However, after controlling for patient and disease characteristics these trends were less marked, especially for CD. Previous studies found that indirect costs contributed 33-68% of total IBD-related costs, significantly more than estimated in our study[39 42]. Our findings are consistent with work in the UK, which used similar methods[35], and could be underestimated because other productivity losses associated with IBD, such as presenteeism and early retirement, were not evaluated. Furthermore, our estimates have large uncertainty due to low rates of absenteeism, and could be biased due to self-reporting and recall bias. Estimating indirect costs is often neglected due to data collection difficulties; thus, our study addresses an important gap in the literature that should be explored further using objective methods.

This study points to an important shift in the clinical management of IBD towards greater use of pharmaceuticals and outpatient care. Increasing outpatient and pharmaceutical costs are not unique to Switzerland or IBD and requires health systems to identify economically efficient reimbursement models and care pathways in order to contain costs. The availability of biosimilars presents an important opportunity in IBD. These treatments were shown to be clinically equivalent in terms of tolerability and efficacy and are expected to reduce costs significantly compared to reference products [43 44]. Lower prices could lead to reduced expenditures on pharmaceuticals; however, they could also increase access to efficacious treatments, creating uncertainty about the long-term budget impact of IBD.

The SIBDCS provides a rich panel dataset, which allowed us to evaluate the changes in the economic burden of IBD over the past decade and identify important predictors of costs, controlling for individual-level characteristics. Recruitment from large university hospitals and private clinics ensured that a representative sample of patients from German- and French-speaking regions of Switzerland were captured. Annual prospective data collection helped to avoid recall bias, ensured low attrition (15% withdrew or were lost to follow-up), and allowed verification of records across patient and physician questionnaires. Data are potentially biased towards patients with more severe or complex disease, since those with mild disease or in remission may not seek care or complete questionnaires regularly. In addition, the timing of returning completed patient questionnaires varied, resulting in incomplete records, particularly affecting indirect cost estimates in 2016.

We derived unit costs from insurance claims data of a suspected IBD population, identified based on medication use and gastroenterologist visits. This may poorly capture individuals with mild disease or in long-term remission. However, since pharmaceutical therapy is the mainstay in IBD, even to maintain remission, this is likely to be a very small proportion of the population. In addition, this method was frequently used in studies using claims data and showed high sensitivity; thus, it currently represents the best approach where cost data are not routinely collected [11 45]. Detailed data from more than 8000 suspected-IBD patients allowed a large sample from which to calculate average unit costs with adjustments for regional, age, and gender variations. By using the gastroenterology-specific codes for inpatient and outpatient claims, we ensured that unit costs reflected only those for an IBD-related event. Unit costs for surgical procedures were estimated based on DRG claims, which captured all resources

consumed during a hospitalisation. However, due to a lack of detailed procedure information, assumptions were made to assign unit costs to specific surgical procedures, resulting in wide variation around unit costs. Internal validation suggests that this is indicative of the heterogeneity of hospital costs between patients and regions in Switzerland, and likely does not affect average total expenditures reported in this study.

In conclusion, we found a large increase in total health care expenditures for IBD over the past decade, with a marked rise in costs due to pharmaceuticals, driven by greater uptake of biologic agents. This study calls for economically sustainable health-financing mechanisms to cope with an outpatient care model. We provide important evidence towards understanding patient and clinical characteristics that drive costs in IBD. Future research evaluating how rising health care costs associated with changing disease management affect health outcomes and quality of care for IBD patients is needed, in order to aid decision making on the cost-efficiency of innovative therapies.

REFERENCES

1. Longobardi T, Bernstein CN. Utilization of health-care resources by patients with IBD in Manitoba: a profile of time since diagnosis. *Am J Gastroenterol* 2007;102(8):1683-91. doi: 10.1111/j.1572-0241.2007.01232.x
2. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet* 2017;390(10114):2769-78. doi: 10.1016/s0140-6736(17)32448-0
3. Torres J, Mehandru S, Colombel J-F, et al. Crohn's disease. *The Lancet* 2017;389(10080):1741-55. doi: 10.1016/s0140-6736(16)31711-1
4. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *The Lancet* 2017;389(10080):1756-70. doi: 10.1016/s0140-6736(16)32126-2
5. Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal Manifestations of Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2015;21(8):1982-92. doi: 10.1097/MIB.0000000000000392
6. van der Valk ME, Mangen MJ, Severs M, et al. Evolution of Costs of Inflammatory Bowel Disease over Two Years of Follow-Up. *PLoS One* 2016;11(4):e0142481. doi: 10.1371/journal.pone.0142481
7. Longobardi, T. Work losses related to inflammatory bowel disease in the United States results from the National Health Interview Survey. *The American Journal of Gastroenterology* 2003;98(5):1064-72. doi: 10.1016/s0002-9270(02)06007-0
8. Burisch J, Vardi H, Pedersen N, et al. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom Study. *Inflamm Bowel Dis* 2015;21(1):121-31. doi: 10.1097/MIB.0000000000000250
9. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut* 2014;63(1):72-9. doi: 10.1136/gutjnl-2012-303376
10. Pillai N, Dusheiko M, Burnand B, et al. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *PLoS One* 2017;12(10):e0185500. doi: 10.1371/journal.pone.0185500 [published Online First: 2017/10/04]
11. Bähler C, Vavricka SR, Schoepfer AM, et al. Trends in prevalence, mortality, health care utilization and health care costs of Swiss IBD patients: a claims data based study of the years 2010, 2012 and 2014. *BMC Gastroenterology* 2017;17(1):138. doi: 10.1186/s12876-017-0681-y
12. Juillerat P, Pittet V, Bulliard J-L, et al. Prevalence of Inflammatory Bowel Disease in the Canton of Vaud (Switzerland): A population-based cohort study. *Journal of Crohn's and Colitis* 2008;2(2):131-41. doi: 10.1016/j.crohns.2007.10.006
13. Bundesamt für Gesundheit. Krankenversicherung: Kostendämpfung (Health insurance: Cost containment) 2018 [Available from:

https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/kostendaempfung-kv.html accessed 15 August 2018.

14. Federal Office of Public Health (FOPH). Re-evaluation of compulsory health insurance benefits: HTA 2018 [Available from: https://www.bag.admin.ch/bag/en/home/versicherungen/krankenversicherung/krankenversicherung-bezeichnung-der-leistungen/re-evaluation-hta.html accessed 29 May 2018.
15. Pittet V, Juillerat P, Mottet C, et al. Cohort profile: the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *Int J Epidemiol* 2009;38(4):922-31. doi: 10.1093/ije/dyn180 [published Online First: 2008/09/11]
16. Pritchard C, Sculpher M. Productivity costs: Principles and practice in economic evaluation. London: Office of Health Economics, 2000.
17. Federal Statistical Office. Gross monthly wage by age and gender, 2016 [Available from: https://www.bfs.admin.ch/bfs/en/home/statistics/work-income/wages-income-employment-labour-costs/wage-levels-switzerland/categories-persons.html accessed 29 May 2018.
18. SwissDRG 6.0: Abrechnungsversion (2017/2017): Definitionshandbuch. SwissDRG: Definitionshandbuch [Available from: https://www.swissdrg.org/de/akutsomatik/archiv-swissdrg-system/swissdrg-system-602017 accessed 29 May 2018.
19. FMH. TARMED – umfassender Einzelleistungstarif [Available from: https://www.fmh.ch/ambulante_tarife/tarmed-tarif.html accessed 29 May 2018.
20. Bundesamt für Gesundheit. Spezialitätenliste (SL) 2017 [Available from: http://www.xn--spezialittenliste-yqb.ch/ accessed 12 June 2018.
21. Compendium.ch. [Available from: http://compendium.ch/home/de accessed 15 June 2018.
22. Jones A. Models For Health Care. *University of York: HEDG Working Paper 10/01* 2010
23. OECD. Inflation (CPI) 2018 [Available from: https://data.oecd.org/price/inflation-cpi.htm#indicator-chart accessed 29 May 2018.
24. Lechner M, Rodriguez-Planas N, Kranz D. Difference-in-Difference Estimation by FE and OLS when there is Panel Non-Response. *Journal of Applied Statistics* 2015;43(11):2044-52.
25. Belotti F, Deb P, Manning WG, et al. twopm: Two-part models. *The Stata Journal* 2015;15(1):3-20.
26. Deb P, Norton EC. Modeling Health Care Expenditures and Use. *Annual Review of Public Health* 2018;39:489-505. doi: 10.1146/annurev-publhealth-040617-013517
27. Mihaylova B, Briggs A, O'Hagan A, et al. Review of statistical methods for analysing healthcare resources and costs. *Health Econ* 2011;20(8):897-916. doi: 10.1002/hec.1653
28. European Central Bank. 2017 [Available from: https://www.ecb.europa.eu/stats/policy_and_exchange_rates/euro_reference_exchange_rates/html/eurofxref-graph-chf.en.html accessed 9 July 2018.
29. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011;106(1):110-9. doi: 10.1038/ajg.2010.343

30. Parragi L, Fournier N, Zeitz J, et al. Colectomy Rates in Ulcerative Colitis Are Low and Decreasing: 10-year-follow-up Data from the Swiss IBD Cohort Study. *J Crohns Colitis* 2018 doi: 10.1093/ecco-jcc/jjy040
31. Targownik LE, Singh H, Nugent Z, et al. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. *American Journal of Gastroenterology* 2012;107(8):1228-35. doi: 10.1038/ajg.2012.127
32. Ma C, Moran GW, Benchimol EI, et al. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. *Am J Gastroenterol* 2017;112(12):1840-48. doi: 10.1038/ajg.2017.394
33. Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology* 2006;131(3):719-28. doi: 10.1053/j.gastro.2006.05.052 [published Online First: 2006/09/06]
34. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology* 2008;135(6):1907-13. doi: 10.1053/j.gastro.2008.09.012
35. Bassi A, Dodd S, Williamson P, et al. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut* 2004;53(10):1471-8. doi: 10.1136/gut.2004.041616
36. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology* 2008;135(5):1493-9. doi: 10.1053/j.gastro.2008.07.069
37. Schleiniger R. Health care costs in Switzerland: Quantity or price driven? *Health Policy* 2014;117:83-89.
38. Wild V, Carina F, Frouzakis R, et al. Assessing the impact of DRGs on patient care and professional practice in Switzerland (IDoC) - a potential model for monitoring and evaluating healthcare reform. *Swiss Med Wkly* 2015;145:w14034. doi: 10.4414/smw.2015.14034
39. Cohen RD, Yu AP, Wu EQ, et al. Systematic review: the costs of ulcerative colitis in Western countries. *Alimentary Pharmacology and Therapeutics* 2010;31(7):693-707. doi: 10.1111/j.1365-2036.2010.04234.x
40. Yu AP, Cabanilla LA, Wu EQ, et al. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Current Medical Research and Opinion* 2008;24(2):319-28. doi: 10.1185/030079908X260790 [published Online First: 2007/12/11]
41. Stark R, König H-H, Leidl R. Costs of Inflammatory Bowel Disease in Germany. *Pharmacoeconomics* 2006;24(8):797-814.
42. Kawalec P. Indirect costs of inflammatory bowel diseases: Crohn's disease and ulcerative colitis. A systematic review. *Arch Med Sci* 2016;12(2):295-302. doi: 10.5114/aoms.2016.59254
43. Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: from theory to practice. *Nature Reviews Gastroenterology & Hepatology* 2017;14(1):22-31. doi: 10.1038/nrgastro.2016.155 [published Online First: 2016/11/04]
44. The Lancet Gastroenterology & Hepatology. Bullying biosimilars: cheaper drugs stymied in USA. *The Lancet Gastroenterology & Hepatology* 2018;3(6) doi: 10.1016/s2468-1253(18)30126-2

45. Bähler C, Schoepfer AM, Vavricka SR, et al. Chronic comorbidities associated with inflammatory bowel disease: prevalence and impact on healthcare costs in Switzerland. *European Journal of Gastroenterolgy and Hepatology* 2017;29(8):916-25. doi: 10.1097/MEG.0000000000000891

CHAPTER 4

Clinical outcomes over 10 years for patients with Crohn's disease receiving early compared to late or no biologic therapy

Nadia Pillai

Working paper

ABSTRACT

Background

A clear understanding of the long-term clinical benefits of early treatment with biologic agents to manage Crohn's disease (CD) is needed before widespread adoption of this treatment approach is advocated in routine clinical practice. This study aimed to evaluate the clinical outcomes for adults diagnosed with CD receiving biologics within 2 years of diagnosis (early biologic initiation group) compared to patients receiving biologics >2 years after diagnosis or not receiving any biologic treatment (late/no biologic initiation group).

Methods

A retrospective analysis was conducted using 10 years of follow-up data from the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). We used propensity score methods to match patients in the early and late/no biologic initiation groups on key baseline patient and clinical characteristics. Kaplan-Meier and parametric time-to-event models were used to evaluate the risks of intestinal resection surgery, fistula, stricture, and disease flares for each treatment group. In addition, a subgroup analysis was performed stratifying patients known to receive biologic treatments into early (≤2 years after diagnosis) and late (>2 years after diagnosis) biologic treatment groups.

Results

In total, 411 patients were matched in the early biologic (N=230) and late/no biologic (N=181) initiation groups. Two years after diagnosis, patients in the early biologic group had a 12% lower risk of intestinal resection surgery, a 9% higher risk of disease flares and fistula, and a 5% higher risk of stricture compared to patients in the late/no biologic group. After 10 years, the overall difference in risks were not statistically significant between the two groups. In the subgroup analysis, patients who received biologics early had a lower overall risk of stricture ($p<0.01$), disease flares ($p<0.01$), and intestinal resection surgery ($p=0.72$), and a higher risk of fistula ($p=0.74$) 10 years after diagnosis when compared to a group of similar patients who received biologics late.

Conclusions

This study found no significant differences in the long-term cumulative probabilities of intestinal resection surgery, fistula, stricture, and disease flares amongst CD patients who received early biologic treatment compared to similar patients who received late or no biologic therapy. However, in a subgroup of patients known to receive biologic treatments, early initiation was associated with significantly lower overall risks of strictures and disease flares. These results signal a need for more individualised care in CD in order to target aggressive treatment approaches to patients who show early signs of a complicated disease course.

INTRODUCTION

Crohn's disease (CD) is a chronic progressive condition causing inflammation along the gastrointestinal tract and severe complications. Treatment of CD aims to induce and maintain remission using pharmaceutical therapies and surgery[1]. The current standard of care involves stepping up pharmaceutical treatments using aminosalicylates, corticosteroids, immunosuppressants, and biologic agents[2]. While this approach can effectively induce remission for most patients, it does not alter the natural course of the disease in the long-term[3]. As a result, increasingly the clinical management of CD has shifted towards earlier use of immunosuppressants and biologic agents, in a top-down/early treatment strategy[3]. This is hoped to reduce disease progression, repair structural damage, and induce deep remission[4]. However, due to a lack of long-term clinical evidence widespread adoption of this approach is limited.

The impact of earlier use of immunosuppressants and biologic therapies on the natural history of CD remains unclear. Population-based cohort studies exploring this question suggested that disease progression rates have remained stable over time. Specifically, studies reported that 5 years after diagnosis at least 14% of CD patients initially diagnosed with non-penetrating and non-stricturing disease progressed to more complicated disease phenotypes, and more than 20% required surgery or hospitalisation[5 6]. Promising evidence from randomised controlled trials (RCTs) showed that patients receiving combination immunosuppressant and biologic treatment within two years of diagnosis had higher response and remission rates after one year of treatment. Follow-up was, however, not sufficient to observe changes in the long-term outcomes for these groups. Alternatively, cohort studies in Canada, Switzerland and Korea reported improved response[7], and reduced rates of strictures and intestinal surgery[8-10] for patients treated with anti-tumour necrosis factor (TNF) agents within two years of diagnosis. However, these studies were limited by small sample sizes and selection bias associated with observational data. In addition, the evidence remains inconclusive with several RCTs and observational studies reporting no major reductions in complication rates or surgery when biologics were used early on in the disease course either in combination with immunosuppressants or as monotherapy[8 10-15].

In Switzerland, increased adoption of biologic therapies has led to a rise in health care expenditures for CD[16]. Understanding the optimal use of biologic treatments will help contain costs in the health care system and ensure efficient patient management. This study aimed to evaluate the impact of early biologic use on clinical outcomes for adults diagnosed with CD using real world data collected over 10 years from the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). We evaluated key clinical outcomes, which reflected disease severity and progression, and impacted patient's quality of life and the costs of disease management[17].

METHODS

Study design and data

A retrospective analysis was conducted using data from the SIBDCS. Patients were included in this study if they were aged ≥18 years at the time of enrolment in the SIBDCS and had a confirmed diagnosis of CD and no change in diagnosis during follow-up. Patients eligible for inclusion were stratified into treatment groups based on the time from diagnosis to biologic initiation using commonly accepted definitions[18]. Patients who started biologic therapy ≤2 years after diagnosis were stratified into the early biologic initiation group while those who received biologics >2 years after diagnosis and those who did not receive any biologic treatment during follow-up in the SIBDCS were included in the late/no biologic initiation group. Biologic agents included all those approved in Switzerland up to 2018: anti-TNF-alpha (infliximab, adalimumab, golimumab and certolizumab pegol), anti-interleukin-12/23 (ustekinumab), and anti-integrin (vedolizumab) agents.

All data used in this study were extracted from the SIBDCS, described in detail elsewhere[19]. The SIBDCS is a prospective, national cohort recruiting IBD patients from across Switzerland since 2006. For this study, we extracted annual follow-up data reported by physicians on age, gender, smoking history, canton (administrative geographic unit in Switzerland) of treating physician, disease location, severity, and duration, disease complications (fistula, stricture, abscess, fissures, and other major complications), extra-intestinal manifestations (EIMs), and surgical interventions (intestinal resection surgeries, fistula or abscess-related surgeries, and other abdominal surgeries).

Defining key clinical outcomes

Four clinical outcomes were evaluated in this study: disease flares with no complications (disease flares), fistula, stricture, and intestinal resection surgery. These outcomes were chosen because they indicate progression towards a severe/complicated disease course, and influenced patients quality of life and the costs of disease management (see Chapter 5; *Table 10*). Outcomes were recorded in annual questionnaires completed by physicians and captured all events that occurred since the last report to the SIBDCS.

Disease flares were defined as an active inflammation and/or the initiation of a new corticosteroid prescription and no indication of stricture, fistula or surgery at the same time. Fistula and stricture were diagnosed using imaging scans and included any active perianal or non-perianal indication or any surgery related to the complication. Intestinal resection surgeries included ileal resection, small bowel resection, ileo-ceacal resection, right and left colectomy, ileostomy, and colostomy.

Statistical methods and analysis

All statistical analyses were performed in Stata Version 15 (College Station, Texas). Descriptive statistics are summarized using the mean and standard deviation (SD) for continuous normally-distributed variables, the median and inter-quartile range (IQR) for continuous non-normally distributed variables, and frequency and percentages for categorical variables. Differences between the treatment and control groups were assessed using the Student's t-test for continuous normally distributed data, Wilcoxon rank-sum test for continuous non-normally distributed data, and the Chi-squared test for categorical data.

Propensity score matching

Patients in the early and late/no biologic initiation groups were matched using propensity score methods to reduce bias associated with non-random treatment allocation and to ensure that patients in each group were comparable based on baseline characteristics. We used a logistic regression model to estimate the probability (propensity score) of receiving the treatment (early biologic use) adjusting for baseline characteristics measured at diagnosis or enrolment (Supplementary Files *Table C1*)[20].

Baseline characteristics were determined based on their association with receiving the treatment and their potential influence on future disease course. Characteristics recorded at diagnosis included gender, age (continuous variable), smoking status (current, former, and non-smoker), and disease location (ileal, colonic, ileocolonic and upper gastrointestinal disease). Characteristics captured at enrolment were year of enrolment (2006-2018), canton of treating physician, disease duration (measured from date of diagnosis to date of enrolment), disease activity (measured using the Crohn's Disease Activity Index), disease complications (stricture, fistula, abscess, fissure, and other major complications), EIMs, and prior surgical interventions (intestinal resection surgeries, fistula or abscess related surgeries, and other abdominal surgeries).

A three-nearest neighbour matching approach was used where one "treated" (early biologic initiation) patient was matched to three "untreated" (late/no biologic initiation) patients based on the closest probability score. A common support was imposed, which removed individuals in the early biologic initiation group with probability scores higher than the maximum probability score for the late/no biologic initiation group.

Time-to-event analysis

Kaplan-Meier and parametric time-to-event models were used to evaluate the risks of each clinical outcome (surgery, fistula, stricture, and disease flares) over time. We assessed the risk of all outcomes from the time of diagnosis to the time when the event occurred or the date of administrative censoring (right censoring). Left truncation/delayed entry was accounted for since all events were observed prospectively from enrolment in the SIBDCS. Given the panel structure of the data and the non-absorbing nature of the events, analyses for disease flares, fistula, and stricture accounted for the presence of repeated events at the patient level. For the intestinal resection surgery outcome, single event models were used due to a small sample of repeated events in our study population.

Kaplan-Meier time-to-event curves measured the absolute cumulative probability of each outcome for a given point in time measured from disease diagnosis and for each treatment group[21]. The overall difference in time-to-event curves between the two treatment groups 10 years after diagnosis was compared using the non-parametric log-rank test of equality.

We derived parametric survival models to calculate the predicted annual probability (hazard rates) of each event. Separate models were used for each treatment group and clinical outcome in order to avoid making strict assumptions on the proportionality of treatment effects over time[22]. Repeated event shared frailty parametric models were estimated, which accounted for patient-level unobserved heterogeneity and dependence between event failures for disease flares, fistula, and stricture[22]. Standard single event models were used for intestinal resection surgery. Parametric models tested included the Weibull, lognormal, loglogistic, Gompertz, and exponential distributions. Appropriate models were chosen based on visual inspection of the fit of predicted survival curves on non-parametric Kaplan-Meier curves (Supplementary Files *Figure C2*) and the Akaike Information Criteria (Supplementary Files *Table C3*).

The annual probabilities for each outcome were derived from time-to-event functions using the following formula:

$$1 - \frac{S(t+1)}{S(t)}$$

Where, *S(t)* represents the survival function at time point *t* (i.e., the probability of surviving past time *t*) and *S(t+1)* represents the survival function in the next period.

Subgroup analysis

A subgroup analysis was performed comparing health outcomes for the subset of the population followed in the SIBDCS who were known to receive biologic therapies. In this analysis, we excluded patients who did not receive at least one dose of any biologic therapy during follow-up in the SIBDCS. Remaining patients were stratified based on the time to biologic initiation where those starting biologics within 2 years of diagnosis were in the early biologic initiation group and those starting biologic treatment >2 years after diagnosis were in the late biologic initiation group. We used propensity score methods, as described previously, in order to ensure that baseline characteristics for this subgroup were balanced (Supplementary Files *Table C4*). Clinical outcomes were evaluated using time-to-event analysis as described previously (Supplementary Files *Table C6* and *Figure C4*).

RESULTS

Descriptive characteristics of the study population

In total, 1493 patients were eligible for inclusion in this study, of which 411 patients were matched in the early biologic initiation group (N=230) and the late/no biologic initiation group (N=181). Descriptive characteristics before and after propensity score matching are outlined in Supplementary Files *Table C2*. Balance diagnostics indicated sufficient overlap on propensity scores between the two groups after performing the matching (Supplementary Files *Figure C1*).

On average, 50% of the study population were female with a mean age at diagnosis of 33 years (*Table 7*). Mean disease duration at enrolment was 1.4 years (IQR 0.6 - 3.1 years) in the early biologic initiation group and 2.1 years (IQR 0.5 - 1.9 years) in the late/no biologic initiation group, after matching ($p<0.01$). The difference in the rates of treatment complications and surgery were not statistically significant between treatment groups after matching. More than 20% of patients in each group had fistulising or stricturing disease and at least one diagnosed EIM. The proportion of patients with an EIM was 9 percentage points higher in the early biologic initiation group compared to the late/no biologic initiation group ($p=0.06$). In addition, 17% of patients had intestinal resection ($p=0.49$) or fistula-related ($p=0.29$) surgery prior to enrolment.

Table 7 Description of patient and clinical characteristics after propensity score matching

	Late/no biologic use N=181	Early biologic use[§] N=230	p-value
Sex, female (N, %)	94 (52%)	117 (51%)	0.83
Mean (median, IQR) age at diagnosis, years	33.4 (27, 21-42)	32.8 (28, 22-40)	0.77
Smoking status at diagnosis (N, %)			0.71
Non-smoker	62 (34%)	86 (37%)	
Smoker	78 (43%)	90 (39%)	
Unknown	41 (23%)	54 (23%)	
Mean (median, IQR) disease duration at enrolment, years	2.1 (1,4, 0.6-3.1)	1.4 (1.0, 0.5-1.9)	<0.01
Disease location at diagnosis (N, %)			0.18
Ileal (L1)	61 (34%)	65 (28%)	
Colonic (L2)	37 (20%)	45 (20%)	
Ileocolonic (L3)	81 (45%)	113 (49%)	
Isolated upper disease (L4) only	1 (1%)	7 (3%)	
Complications at enrolment (N, %)			
Stricture	44 (24%)	44 (19%)	0.20
Fistula	34 (19%)	58 (25%)	0.12
Abscess	26 (14%)	37 (16%)	0.63
Fissure	13 (7%)	20 (9%)	0.58
Extra-intestinal manifestation (EIM)	46 (25%)	78 (34%)	0.06
Surgeries at enrolment (N, %)	59 (33%)	76 (33%)	0.92
Intestinal resection surgery	33 (18%)	36 (16%)	0.49
Fistula-related surgery	21 (12%)	35 (15%)	0.29
Other abdominal surgery	15 (8%)	28 (12%)	0.20
Mean (median, IQR) total follow-up in SIBDCS, years*	5.1 (5, 3-8)	4.3 (4, 2-7)	<0.01

[§]Early biologic use: patients receiving biologic treatment ≤2 years after diagnosis; late/no biologic use: patients receiving biologic treatment >2 years after diagnosis and patients who did not have any record of biologic therapy during follow-up in the SIBDCS
IQR: interquartile range
*Not included in propensity score matching logistic regression model

In the late/no biologic group, 51% of patients received at least one dose of biologic therapy, while the remaining 49% did not receive any biologic therapy during follow-up in the SIBDCS (*Figure 8B*). The use of conventional therapies such as aminosalicylates, corticosteroids and immunosuppressants was higher in the late/no biologic initiation group compared to the early biologic initiation group both at enrolment (*Figure 8A*) and during follow-up (*Figure 8B*). The mean time from diagnosis to initiation of biologic treatment was 0.7 years (IQR 0.25 - 1.17 years) and 4.3 years (IQR 2.8 - 5.1 years) for the

early and late/no biologic initiation groups, respectively ($p<0.01$). Patients in the early biologic group received biologic therapy for significantly longer (mean 4.6, IQR 2.4 - 6.4 years), compared to biologic users in the late/no biologic group (mean 3.5, IQR 1.5 - 5.3 years; $p<0.001$).

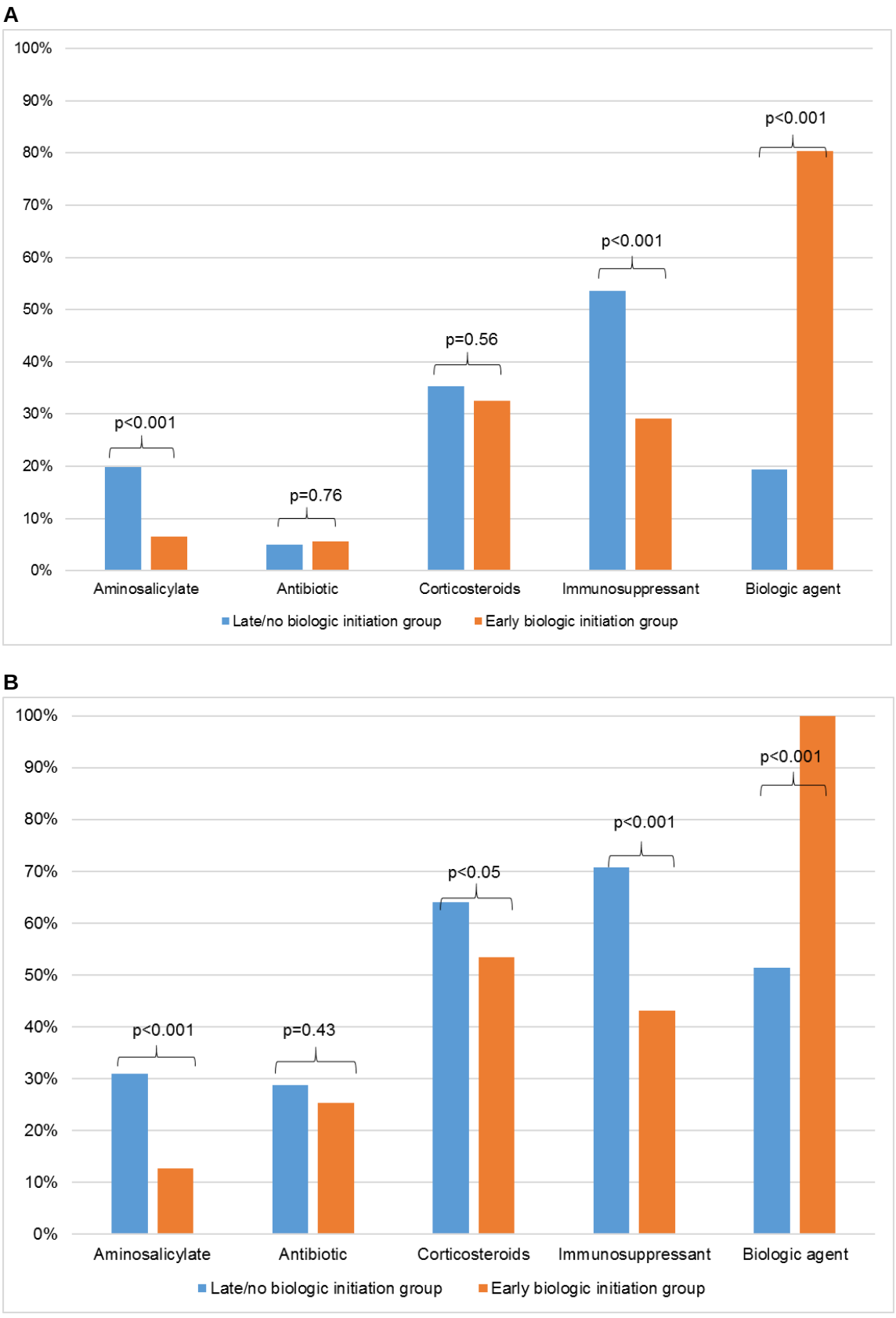


Figure 8 Proportion (%) of patients in the early and late/no biologic initiation groups receiving at least one dose of treatment by drug class at enrolment (A) and at the end of follow-up (B) in the Swiss IBD Cohort Study (SIBDCS)

Clinical outcomes: Time-to-event analysis

In Kaplan-Meier analysis, the overall cumulative probability of surgery, fistula, stricture, and disease flares were not statistically significantly different in the early biologic group compared to the late/no biologic group after 10 years.

The cumulative risk of surgery was 12% lower for the early biologic group compared to the late/no biologic group 2 years after diagnosis (*Figure 9A*). This difference decreased over time with comparable rates in each group after 4 years.

The cumulative probability of fistula was 4%, 10% and 17% higher for the early biologic group 1 year, 2 years and 5 years after diagnosis, respectively, compared to the late/no biologic group (*Figure 9B*). After 8 years, the risk of fistula for the late/no biologic group increased leading to a reduction in the differences in the overall cumulative probability of fistula between the two groups (*Figure 9B*).

Kaplan-Meier curves for stricture and disease flares indicated similar patterns between the two treatment groups over 10 years. The cumulative absolute risks of stricture and disease flares increased at a faster rate for the early biologic initiation group in the first 2 years of diagnosis but this slowed down in later years relative to the late/no biologic initiation group (*Figure 9C and Figure 9D*). After 8 years, the risks of stricture appeared to stabilise for the early biologic initiation group and increased for the late/no biologic group.

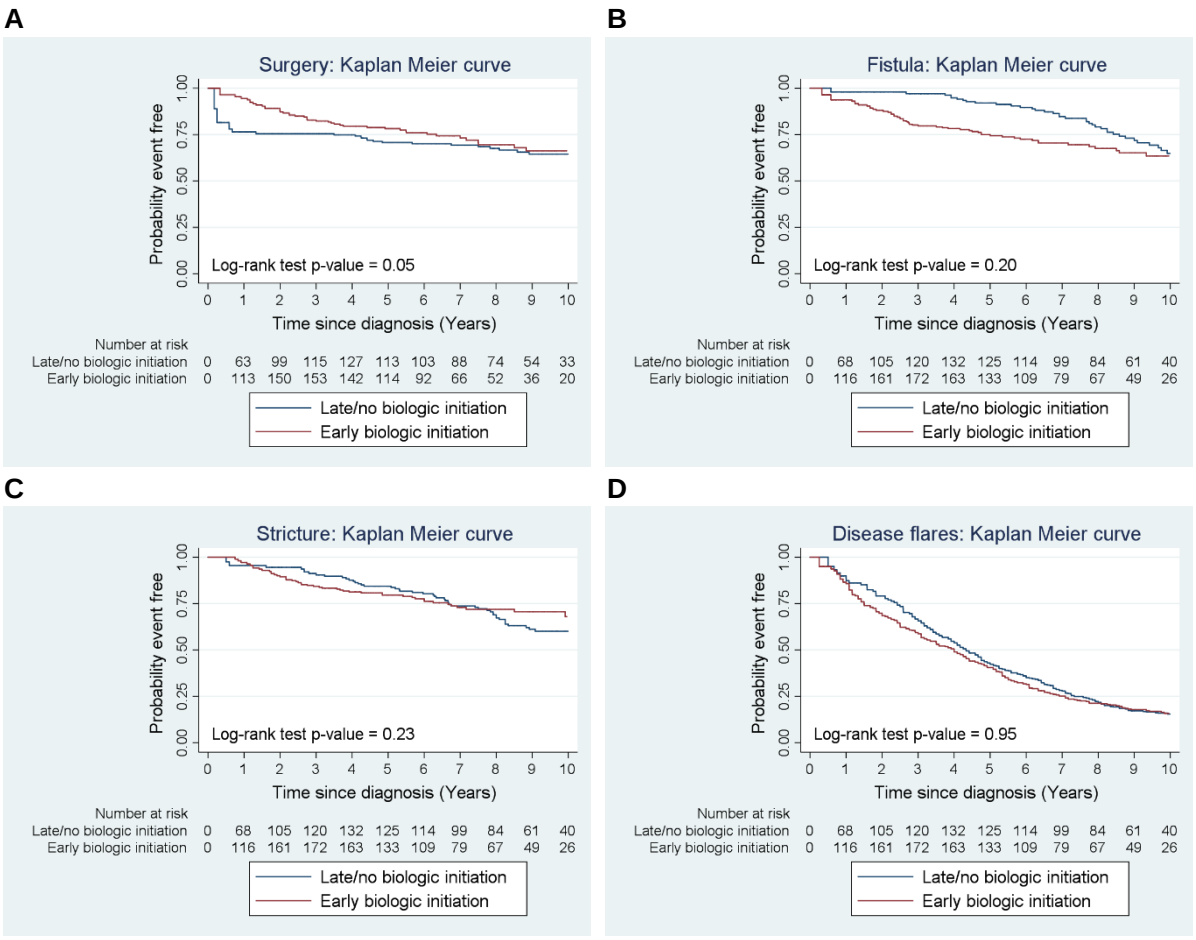


Figure 9 Kaplan-Meier time-to-event curves for (A) surgery, (B) fistula, (C) stricture, and (D) disease flares. [Due to left truncation (i.e., delayed entry), there were no subjects considered at risk at 0 years since diagnosis because patients were only observed from the point of enrolment in the SIBDCS. Enrolment in the cohort was continuous, hence numbers at risk increase over time in the initial years. In addition, Kaplan-Meier curves for fistula, stricture and disease flares account for multiple event failures.]

The parametric time-to-event analysis reflects the observed patterns of the Kaplan-Meier analysis. With the exception of surgery (*Figure 10A*), the annual predicted probability of fistula (*Figure 10B*), stricture (*Figure 10C*), and disease flares (*Figure 10D*), was higher for the early biologic group in the early years and remained constant or declined over time compared to the late/no biologic group where the probabilities increased.

The early biologic group had a 0.09 probability of fistula in the first year after diagnosis, which declined to 0.04 five years after diagnosis. Conversely, the probability of fistula increased from 0.002 in the first year after diagnosis to 0.03 five years after diagnosis for the late/no biologic group.

The predicted annual probability of stricture and disease flares remained constant over time and was higher for the early biologic group in the first year after diagnosis at 0.05 and 0.18, respectively, relative to the late/no biologic group. In contrast, the probabilities increased over time for the late/no biologic group and were higher than those for the early biologic group five years after diagnosis.

The predicted annual probability of intestinal resection surgery one year after diagnosis was 0.07 for the early biologic group and 0.20 for late/no biologic group; this decreased over time for both groups to similar levels after 4 years (*Figure 10A*).

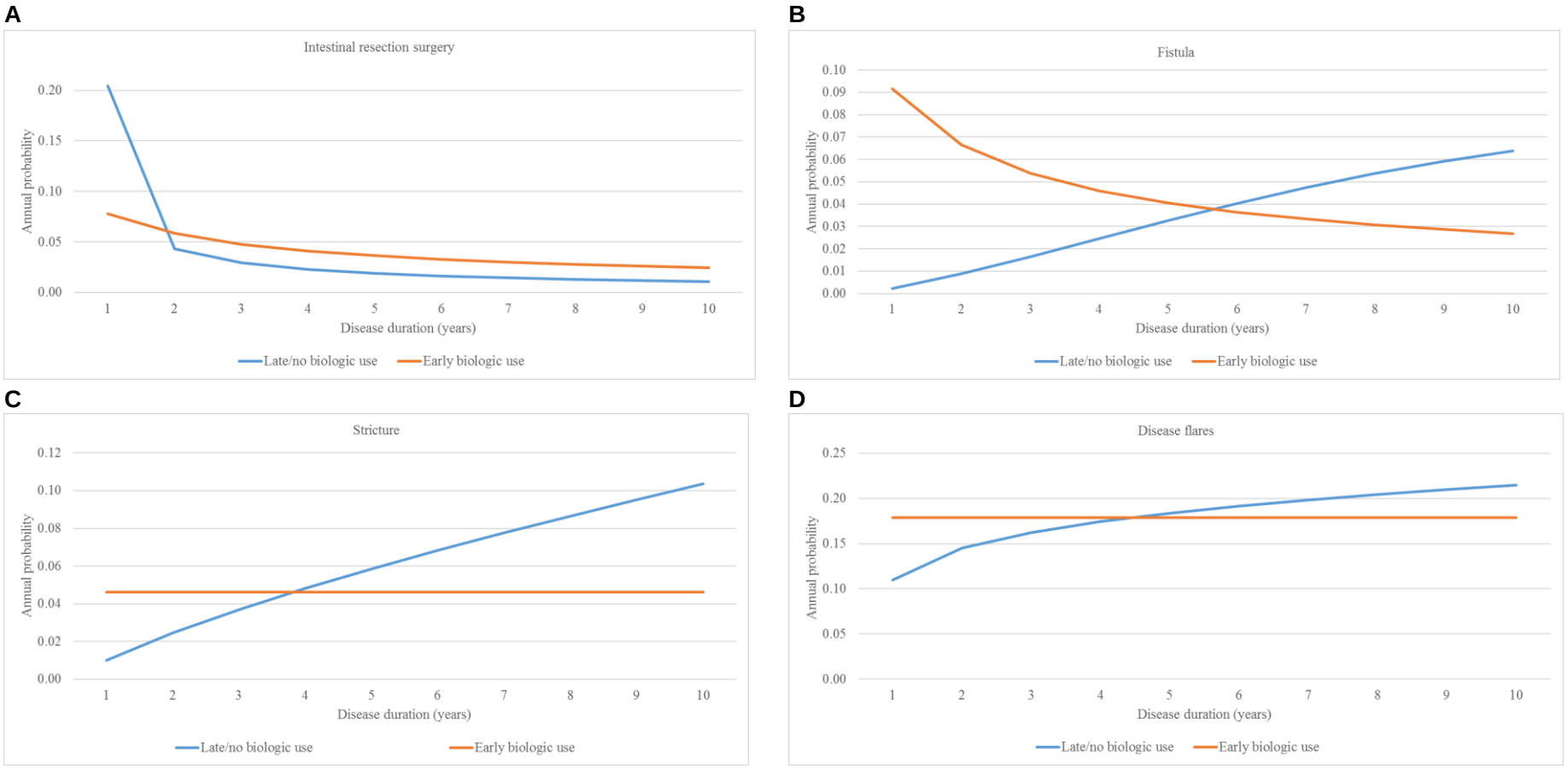


Figure 10 Annual probabilities of (A) intestinal resection surgery, (B) fistula, (C) stricture, and (D) disease flares over 10 years derived from parametric time-to-event analyses

Subgroup analysis

For the subgroup analysis, patients that did not receive at least one dose of biologic treatment during follow-up in the SIBDCS were excluded (N=483). Balance diagnostics (Supplementary Files *Figure C3*) and descriptive statistics (Supplementary Files *Table C5*) after propensity score matching indicated comparability between the remaining patients after stratification into early (N=225) and late (N=112) biologic initiation groups.

The cumulative absolute risks of stricture and disease flares were significantly lower (p<0.01) over 10 years for the early biologic initiation group compared to the late biologic initiation group (*Figure 11C and Figure 11D*). Specifically, 10 years after diagnosis, patients in the early biologic group had a 17% and 8% lower risk of stricture and disease flares, respectively, compared to patients in the late biologic group. In parametric models, the early biologic group had a constant annual probability of stricture and disease flares of 0.05 and 0.18, respectively, relative to an increasing probability over time for both events in the late biologic group (Supplementary Files *Figure C5C and Figure C5D*).

The cumulative probability of intestinal resection surgery was initially lower for the early biologic initiation group but reached similar levels as the late biologic group after 3 years (p=0.72; *Figure 11A*). The probability of surgery was 10%, 8%, and 5% lower for the early biologic group 1, 2, and 5 years after diagnosis, respectively, compared to patients in the late biologic group (*Figure 11A*). In parametric models, the predicted annual probability of surgery in the first year after diagnosis was 0.05 for the early biologic group compared to 0.10 for the late biologic group; this declined to 0.04 for both groups after 3 years (Supplementary Files *Figure C5A*).

The cumulative absolute probability of fistula was higher for the early biologic group in the first five years after diagnosis although this difference was not statistically significant (p=0.74; *Figure 11B*). Over time, the risk of fistula appeared to increase for the late biologic group. This corresponded to a declining predicted annual probability of fistula for the early biologic group, while the probability increased over time for the late biologic group (Supplementary Files *Figure C5B*).

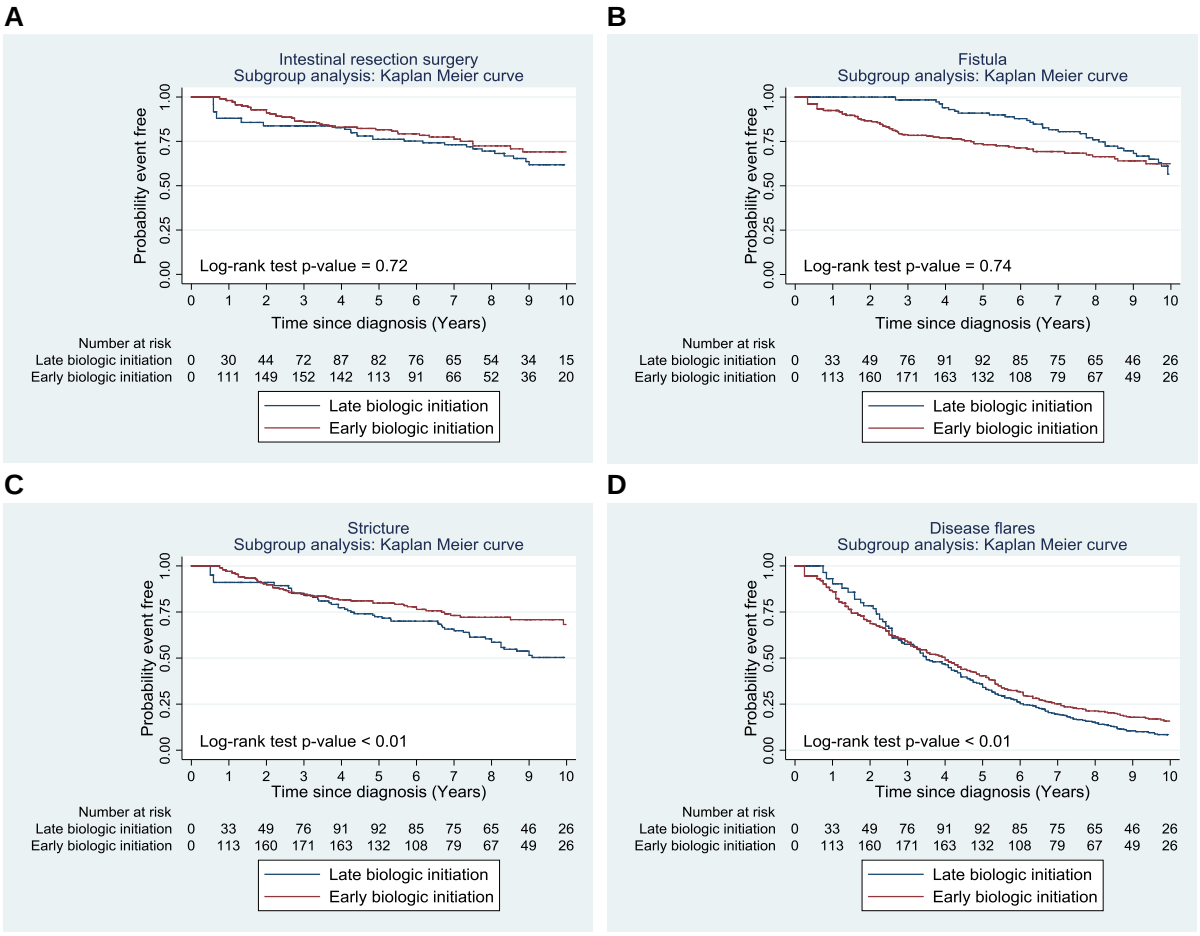


Figure 11 Subgroup analysis: Kaplan-Meier time-to-event curves for (A) surgery, (B) fistula, (C) stricture, and (D) disease flares. [Due to left truncation (i.e., delayed entry), there were no subjects considered at risk at 0 years since diagnosis because patients were only observed from the point of enrolment in the SIBDCS. Enrolment in the cohort was continuous, hence numbers at risk increase over time in the initial years. In addition, Kaplan-Meier curves for fistula, stricture and disease flares account for multiple event failures.]

DISCUSSION

This study showed no significant differences in the 10-year cumulative probabilities of intestinal resection surgery, fistula, stricture, and disease flares amongst CD patients treated with biologic agents within 2 years of diagnosis compared to similar patients treated more than 2 years after diagnosis or patients not receiving biologic therapy. However, annual probabilities, according to fitted parametric models, indicated a stable or decreasing probability of fistula, stricture, and disease flares over time for the early biologic treatment group. In contrast, we observed increasing probabilities of fistula, stricture, and disease flares for the late/no biologic treatment group, despite initially lower probabilities in the early years of diagnosis. Moreover, our findings indicated a reduced risk of intestinal resection surgery two years after diagnosis amongst patients treated with biologics early; however, these risks were comparable between the two treatment groups after 4 years. Amongst the subgroup of patients known to receive biologic treatments, patients who received biologics early had significantly lower risks of stricture and disease flares, higher risks of fistula, and similar risks of intestinal resection surgery after 10 years compared to patients who received biologics late. These results signal a need for more individualised care in CD in order to target aggressive treatment approaches to patients who show early signs of a complicated disease course. Previous literature found that young age at diagnosis, upper gastrointestinal, stricturing or penetrating disease, and smoking were important factors associated with a poor disease course[23]. Further research into genetic and phenotypic markers of poor disease prognosis would help to optimise treatment strategies further[24]. In addition, these results support a rapid step-up treatment approach, which was shown to improve remission rates when patients were monitored closely and treatment escalation decisions were based on known biomarkers of inflammation as opposed to clinical symptoms alone[25].

Previous literature using data from the SIBDCS found a significant reduction in risks of strictures and non-significant reductions in the risks of intestinal and perianal surgery for patients treated with anti-TNF agents within two years of diagnosis compared to those treated after two years[8 10]. Methodological considerations might explain the difference between our results compared to previous work. For example, we included non-biologic users in this study since several CD patients respond to conventional pharmaceutical treatments and do not require more aggressive therapies during the course of their disease[6 26]. This ensured that a representative sample of patients were captured for this analysis. Our

subgroup analysis included a subset of patients who were known to receive biologic treatment. These results were consistent with previous studies showing lower probabilities of stricture and intestinal surgery for patients treated with biologics early. In addition, we used propensity score methods to ensure patients were comparable in terms of baseline disease characteristics that might influence their health outcomes and the likelihood of receiving biologic treatment. Previous studies used covariate adjustment and stratified patients based on the presence of disease complications resulting in small subgroups and potentially reducing the precision in the analysis.

In RCTs, the clinical benefits of early combined immunosuppression using immunosuppressants and biologic agents were inconclusive when compared to the standard step-up regimen in CD[4 13 14 27 28]. Studies supporting early combination therapy observed favourable outcomes in the initial weeks of treatment, however, these effects were not sustained up to two years after diagnosis[4 27 28]. Notably, a large RCT conducted in Belgium and Canada, found no significant differences in corticosteroid-free remission rates over 2 years for patients receiving early combination therapy but significantly lower rates of surgery and overall complications after 2 years of follow-up[13]. Similarly, our analysis showed lower annual risks of surgery in the first two years after diagnosis for patients receiving early biologic therapy; however, after four years, probabilities were comparable between the treatment groups. This suggests that early biologic use may have delayed surgery in the short-term but did not reduce the overall long-term surgery risk. Previous RCTs cannot be directly compared to our results since we did not evaluate combination immunosuppressant and biologic therapy. Nevertheless, this work highlights the importance of real-world longitudinal studies to evaluate the risk of key clinical outcomes, which might develop and worsen over a long period.

Population-based cohort studies can help shed light on the changes in disease progression associated with therapeutic advancements. For example, despite an overall increase in the use of immunosuppressants and biologic agents from 1991 to 2011, disease progression was reported to remain stable during this period in a population-based cohort study in the Netherlands[12]. These results were supported by a large European population-based cohort study that found early use of immunosuppressants and biologic agents did not improve surgery and disease progression rates in both Eastern and Western European countries[5]. Similarly, in the SIBDCS, despite greater use of biologic

agents between 2006 and 2016, no changes in the rates of inpatient events were observed[16]. This suggests that early aggressive treatment with biologic agents might not have the expected impact on disease progression and may not change the natural history of CD in the long-term. Cohort studies across Europe and the USA specifically evaluating early compared to late treatment in CD support our findings showing no significant improvements in clinical outcomes for patients receiving early aggressive treatment with biologic therapies[11 12 14]. In contrast, one study in Canada reported that patients treated with anti-TNF agents within 2 years of diagnosis had improved response and lower surgery rates after 7 years[7]. Of note, this study only included patients who received and responded to treatment with biologic agents and therefore results might not generalise to the wider CD population.

Using 10-year follow-up data, this study demonstrated the uptake of novel treatment approaches in real world clinical practice and their impact on clinical outcomes and disease progression. We used propensity score matching to ensure patients were comparable in each treatment group and reduce the risk of selection bias. We included a rich selection of patient and disease characteristics that might influence treatment decisions and outcomes. However, some bias may have remained due to unobserved factors that were not captured in the SIBDCS. Importantly, our findings were qualitatively similar when we conducted the analyses on the late or no biologic treatment group and in the subgroup analysis of late biologic users only, suggesting that our results are not indicative of selection bias due to unobserved patient characteristics. Finally, since this was an observational study, treatment regimens varied between health care facilities and patients. As a result, the impact of specific treatments and treatment sequences, such as combination therapies, on health outcomes could not be discerned.

In conclusion, this study showed that the long-term overall risks of key clinical outcomes for CD patients did not significantly improve despite early aggressive treatment with biologic agents when compared to similar patients who did not receive biologic therapies and those who received biologics later in the disease course. However, amongst the subgroup of patients known to receive biologic treatments, patients who received biologics early had significantly lower risks of stricture and disease flares after 10 years compared to patients who received biologics late. Future research should explore targeted treatment approaches based on patients' risk of severe or complicated disease. Early identification of patients who might have lower response to conventional pharmaceuticals and are at risk of experiencing

severe or complicated disease would ensure rapid access to the treatments they need. This would help improve the efficiency of disease management from a clinical perspective and reduce the financial burden of CD on health systems.

REFERENCES

1. Berg DR, Colombel JF, Ungaro R. The Role of Early Biologic Therapy in Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2019 doi: 10.1093/ibd/izz059 [published Online First: 2019/04/02]
2. Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017;11(1):3-25. doi: 10.1093/ecco-jcc/jjw168 [published Online First: 2016/09/24]
3. Hanauer SB. Positioning biologic agents in the treatment of Crohn's disease. *Inflammatory bowel diseases* 2009;15(10):1570-82. doi: 10.1002/ibd.20918 [published Online First: 2009/03/25]
4. Colombel JF, Reinisch W, Mantzaris GJ, et al. Randomised clinical trial: deep remission in biologic and immunomodulator naive patients with Crohn's disease - a SONIC post hoc analysis. *Alimentary pharmacology & therapeutics* 2015;41(8):734-46. doi: 10.1111/apt.13139 [published Online First: 2015/03/03]
5. Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut* 2018 doi: 10.1136/gutjnl-2017-315568 [published Online First: 2018/01/25]
6. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. *The American journal of gastroenterology* 2010;105(2):289-97. doi: 10.1038/ajg.2009.579 [published Online First: 2009/10/29]
7. Ma C, Beilman CL, Huang VW, et al. Anti-TNF Therapy Within 2 Years of Crohn's Disease Diagnosis Improves Patient Outcomes: A Retrospective Cohort Study. *Inflammatory bowel diseases* 2016;22(4):870-9. doi: 10.1097/mib.0000000000000679 [published Online First: 2016/01/29]
8. Frei R, Fournier N, Zeitz J, et al. Early initiation of anti-TNF is associated with favourable long-term outcome in Crohn's Disease: 10-year-follow-up data from the Swiss IBD Cohort Study. *Journal of Crohn's & colitis* 2019 doi: 10.1093/ecco-jcc/jjz057 [published Online First: 2019/03/12]
9. Oh EH, Oh K, Han M, et al. Early anti-TNF/immunomodulator therapy is associated with better long-term clinical outcomes in Asian patients with Crohn's disease with poor prognostic factors. *PloS one* 2017;12(5):e0177479. doi: 10.1371/journal.pone.0177479 [published Online First: 2017/05/26]
10. Safroneeva E, Vavricka SR, Fournier N, et al. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. *Alimentary pharmacology & therapeutics* 2015;42(8):977-89. doi: 10.1111/apt.13363 [published Online First: 2015/08/15]
11. Ghazi LJ, Patil SA, Rustgi A, et al. Step up versus early biologic therapy for Crohn's disease in clinical practice. *Inflammatory bowel diseases* 2013;19(7):1397-403. doi: 10.1097/MIB.0b013e318281337d [published Online First: 2013/04/20]
12. Jeuring SF, van den Heuvel TR, Liu LY, et al. Improvements in the Long-Term Outcome of Crohn's Disease Over the Past Two Decades and the Relation to Changes in Medical Management: Results from the Population-Based IBDSL Cohort. *The American journal of*

gastroenterology 2017;112(2):325-36. doi: 10.1038/ajg.2016.524 [published Online First: 2016/12/07]

13. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *The Lancet* 2015;386(10006):1825-34. doi: 10.1016/s0140-6736(15)00068-9
14. Tsui JJ, Huynh HQ. Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? *Annals of gastroenterology* 2018;31(4):413-24. doi: 10.20524/aog.2018.0253 [published Online First: 2018/07/12]
15. Kim NH, Jung YS, Moon CM, et al. Long-term clinical outcomes of korean patient with Crohn's disease following early use of infliximab. *Intestinal research* 2014;12(4):281-6. doi: 10.5217/ir.2014.12.4.281 [published Online First: 2014/11/07]
16. Pillai N, Dusheiko M, Maillard MH, et al. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. *Journal of Crohn's & colitis* 2019 doi: 10.1093/ecco-jcc/jjz003 [published Online First: 2019/03/28]
17. Torres J, Mehandru S, Colombel J-F, et al. Crohn's disease. *The Lancet* 2017;389(10080):1741-55. doi: 10.1016/s0140-6736(16)31711-1
18. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017;66(12):2179-87. doi: 10.1136/gutjnl-2017-314519 [published Online First: 2017/09/07]
19. Pittet V, Juillerat P, Mottet C, et al. Cohort profile: the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *Int J Epidemiol* 2009;38(4):922-31. doi: 10.1093/ije/dyn180 [published Online First: 2008/09/11]
20. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. Boston College Department of Economics: Statistical Software Components S432001, 2003.
21. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014;33(7):1242-58. doi: 10.1002/sim.5984 [published Online First: 2013/10/15]
22. Gutierrez RG. Parametric frailty and shared frailty survival models. *The Stata Journal* 2002;2(1):22-44.
23. Flamant M, Roblin X. Inflammatory bowel disease: towards a personalized medicine. *Therapeutic advances in gastroenterology* 2018;11:1756283X17745029. doi: 10.1177/1756283X17745029 [published Online First: 2018/02/01]
24. Lee JC, Biasci D, Roberts R, et al. Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn's disease. *Nature genetics* 2017;49(2):262-68. doi: 10.1038/ng.3755 [published Online First: 2017/01/10]
25. Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet (London, England)* 2017;390:2779-89. doi: 10.1016/S0140-6736(17)32641-7

26. D'Haens GR. Top-down therapy for Crohn's disease: Rationale and evidence. *Acta clinica Belgica* 2009;64(6):540-6. doi: 10.1179/acb.2009.092 [published Online First: 2010/01/28]
27. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: An open randomised trial. *The Lancet* 2008;371(9613):660-67. doi: 10.1016/s0140-6736(08)60304-9
28. Fan R, Zhong J, Wang Z-T, et al. Evaluation of top-down treatmetn of early Crohn's disease by double balloon enteroscopy. *World journal of gastroenterology* 2014;20(39):14479-87. doi: 10.3748/wjg.v20

CHAPTER 5

Evaluating the cost-effectiveness of early compared to late or no biologic treatment to manage Crohn's disease using real world data

Nadia Pillai, Judith E. Lupatsch, Mark Dusheiko, Matthias Schwenkglenks, Michel Maillard, C. Simone Sutherland, Valérie E. H. Pittet, On behalf of the Swiss IBD Cohort study group

This study was published in the Journal of Crohn's and Colitis.

Citation:

Pillai N, Lupatsch JE, Dusheiko M, Schwenkglenks M, Maillard MH, Sutherland CS, Pittet V (2019). Evaluating the cost-effectiveness of early compared to late or no biologic treatment to manage Crohn's disease using real world data. Journal of Crohn's and Colitis. doi: 10.1093/ecco-jcc/jjz169

ABSTRACT

Background

We evaluated the cost-effectiveness of early (≤2 years after diagnosis) compared to late or no biologic initiation (starting biologics >2 years after diagnosis or no biologic use) for adults with Crohn's disease in Switzerland.

Methods

We developed a Markov cohort model over the patient's lifetime from the health system and societal perspectives. Transition probabilities, quality of life, and costs were estimated using real world data. Propensity score matching was used to ensure comparability between patients in the early (intervention) and late/no (comparator) biologic initiation strategies. The incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained is reported in Swiss francs (CHF). Sensitivity and scenario analyses were performed.

Results

Total costs and QALYs were higher for the intervention (CHF 384,607; 16.84 QALYs) compared to comparator (CHF 340,800; 16.75 QALYs) strategy, resulting in high ICERs (health system: CHF 887,450 per QALY; societal: CHF 449,130 per QALY). In probabilistic sensitivity analysis, assuming a threshold of CHF 100,000 per QALY, the probability that the intervention strategy was cost-effective was 0.1 and 0.25 from the health system and societal perspectives, respectively. In addition, ICERs improved when we assumed a 30% reduction in biologic prices (health system: CHF 134,502 per QALY; societal: intervention dominant).

Conclusions

Early biologic use was not cost-effective considering a threshold of CHF 100,000 per QALY compared to late/no biologic use. However, early identification of patients likely to need biologics and future drug price reductions through increased availability of biosimilars may improve the cost-effectiveness of an early treatment approach.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) causing inflammation in the gastrointestinal tract. It is characterised by active and remitting phases, severe symptoms, and extra-intestinal complications. Patients are at risk of developing bowel complications, including strictures and fistulae, and often require surgical interventions and long-term pharmaceutical treatment to manage the disease[1]. The prevalence of CD varies significantly in Europe with estimates between 1.5 and 213 per 100,000 persons[2]. In Switzerland, uptake of novel biologic treatments to manage the disease was associated with a marked increase in health care expenditures placing significant financial pressure on the health system[3]. In addition, the rising prevalence of CD[4] highlights the need to identify clinically- and cost-efficient treatment strategies.

The primary aim of CD clinical management is to induce and maintain remission. Pharmaceutical treatments include aminosalicylates, corticosteroids, immunosuppressants, and biologic agents. The current standard of care involves stepping-up therapy and reserving more aggressive treatments, such as biologic agents, for patients with severe and refractory disease[5]. Treatment with biologic agents have helped increase remission rates and reduce the need for surgery and hospitalisation, sparking debate about the optimal timing of treatment initiation[6 7]. Some have advocated for early biologic treatment, within 2 years of diagnosis, with the hope that this would shift disease management from symptom control towards long-term mucosal healing and modification of the disease course[8-10]. However, few studies have evaluated the long-term clinical efficacy or cost-effectiveness of this approach[11 12].

A randomised controlled trial (RCT) found increased corticosteroid-free remission and reduced surgical resection rates after one year in patients receiving early treatment with immunosuppressants and biologic agents compared to the standard step-up approach[6]. Based on this trial, early combination therapy was reported to be cost-effective compared to the standard of care from the Italian health system perspective over five years[13]. These studies are limited in scope, however, since only induction of remission was evaluated and follow-up was short. Another analysis, using seven years of follow-up data from a retrospective cohort study in Canada[14], demonstrated that early treatment with biologic agents was cost-saving and improved health outcomes over patients' lifetime due to high response rates[15]. However, several RCTs and observational studies found conflicting evidence, suggesting no health

gains from early biologic and combination therapy[12 16]. Existing evidence needs to be validated in order to inform health care planning and decision-making.

This study aimed to evaluate the cost-effectiveness of early initiation (≤2 years after diagnosis) of biologic treatment compared to late or no biologic use (starting biologic therapy >2 years after diagnosis or continuing non-biologic therapy) for CD patients using real world data in Switzerland.

METHODS

Overview of modelling approach

A Markov cohort model was developed to compare the cost-effectiveness of early biologic treatment (intervention) to late/no biologic treatment (comparator) for recently diagnosed adult (≥18 years) CD patients. The analysis was conducted from the Swiss health system perspective, considering all direct health care costs irrespective of payer (cantons/regions, health insurers, and patients' out-of-pocket co-payments), and from a societal perspective, including direct and indirect costs associated with productivity losses from work absenteeism. The model was run over the patients' lifetime based on the mean age at diagnosis and life expectancy in Switzerland[17]. The model was parameterised using transition probabilities, costs and utilities estimated from the Swiss IBD Cohort Study (SIBDCS) and insurance claims data. Costs and utilities occurring after the first year were discounted by 3%. One-way and probabilistic sensitivity analysis (PSA) were performed to evaluate the impact of parameter uncertainty on results. The model was built and analysed using TreeAge Pro 2018 (Williamstown, MA). Statistical analyses to derive parameters for the model were performed in Stata Version 15 (College Station, TX).

The primary outcome of the model was the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained, reported in Swiss francs (CHF). The ICER measured the additional costs required to achieve one unit of additional effect and was calculated by dividing the difference in costs by the difference in effects between the two strategies. Effects are expressed as QALYs reflecting individuals' length of life and health-related quality of life[18]. The ICER was compared to a willingness-to-pay (WTP) threshold, which captured the assumed value of an additional QALY, to draw conclusions

about cost-effectiveness[18]. There is no commonly accepted WTP threshold in Switzerland, therefore, based on previous literature[19], we tentatively used a threshold of CHF 100,000 (€89,500) per QALY.

Data source and patient population

The SIBDCS is a prospective, national cohort recruiting adult and paediatric IBD patients from academic and non-academic centres across Switzerland. The cohort is described in detail elsewhere[20]. For this study, we conducted a retrospective analysis of annual patient-level data extracted from questionnaires completed by patients and their treating physicians between 2006 and 2018. Physician-reported data included information on patient demographics, disease and treatment characteristics, and health care utilisation. Patient-reported data included outpatient consultation visits, days of work missed due to IBD, and health-related quality of life.

We used propensity score matching to ensure patients in the intervention and comparator groups were similar based on baseline characteristics that might influence treatment assignment and health outcomes[21]. This reduced the effects of selection bias associated with observational data. We used a logistic regression model, adjusting for treatment group and key characteristics measured at diagnosis or enrolment, to estimate the probability (propensity score) of receiving the intervention (Supplementary Files *Table C1*). A "three-nearest neighbour" approach was used where one patient in the intervention group was matched to three patients in the comparator group based on the closest probability score. A common support was imposed to exclude patients in the intervention group with probability scores higher than the maximum score in the comparator group. Characteristics adjusted for in the model and measured at diagnosis were: gender, age, smoking status (current, former, and non-smoker), and disease location (ileal, colonic, ileocolonic and upper gastrointestinal disease). Characteristics captured at enrolment were: year of enrolment (2006-2018), canton (administrative geographic unit in Switzerland) of treating physician, disease duration (measured from date of diagnosis to date of enrolment), disease activity (measured using the Crohn's Disease Activity Index), disease complications (stricture, fistula, abscess, fissure, and other major complications), extra-intestinal manifestations (EIMs), and prior surgical interventions (intestinal resection surgeries, fistula or abscess related surgeries, and other abdominal surgeries).

In total, 411 patients were matched in the intervention (N=230) and comparator (N=181) groups; 50% were female with a mean age at diagnosis of 33 years (Supplementary Files *Table C2*). Key clinical characteristics such as age at diagnosis, disease location, and disease complications were balanced between the groups, resulting in significant overlap in propensity scores after matching (Supplementary Files *Figure C3*). In the comparator group, 51% of patients received a biologic treatment more than two years after diagnosis, while the remaining 49% did not receive any biologics during follow-up (Supplementary Files *Table C2*). Biologic treatments included all those approved in Switzerland in 2018: infliximab, adalimumab, golimumab, certolizumab pegol, vedolizumab, and ustekinumab. All subsequent analyses including estimation of health state risks, costs, and utilities, were performed using the matched sample.

Model structure and assumptions

The Markov model reflects patients moving between active and remitting phases of the disease in annual periods (cycles). Costs and QALYs in the first and last cycle were multiplied by 0.5 (half-cycle correction) to adjust for overestimation from annual state transitions. Active disease states were split into four mutually exclusive and exhaustive groups: disease flares with no complications (disease flares), fistula, stricture, and intestinal resection surgery (surgery); defined in *Table 8*.

Table 8 Definition of health states in the Markov model

Disease flares with no complications (disease flares)	Active inflammation and/or initiation of new corticosteroid prescription and no indication of stricture, fistula or surgery at the same time
Fistula	Active perianal and non-perianal fistula observed through imaging scans and/or fistula-related surgeries (fistulectomy, fistula plug, fibrin glue instillation)
Stricture	Active stricture observed through imaging scans
Intestinal resection surgery	Intestinal resection surgeries including: ileal resection, small bowel resection, ileocecal resection, right & left colectomy, ileostomy and colostomy
Remission	Clinical remission defined based on a Crohn's Disease Activity Index score <150 and the absence of disease flares, surgical interventions, fistula or stricture

Patients entered the model at diagnosis in the disease flares state based on data from the SIBDCS. After each cycle of the model patients transition to other active health states, remission, or death (*Figure 12*). Patients could remain in the previous health state over multiple cycles of the model or transition to death from any state where they then remain. Patients are assumed to be in one health state at a time.

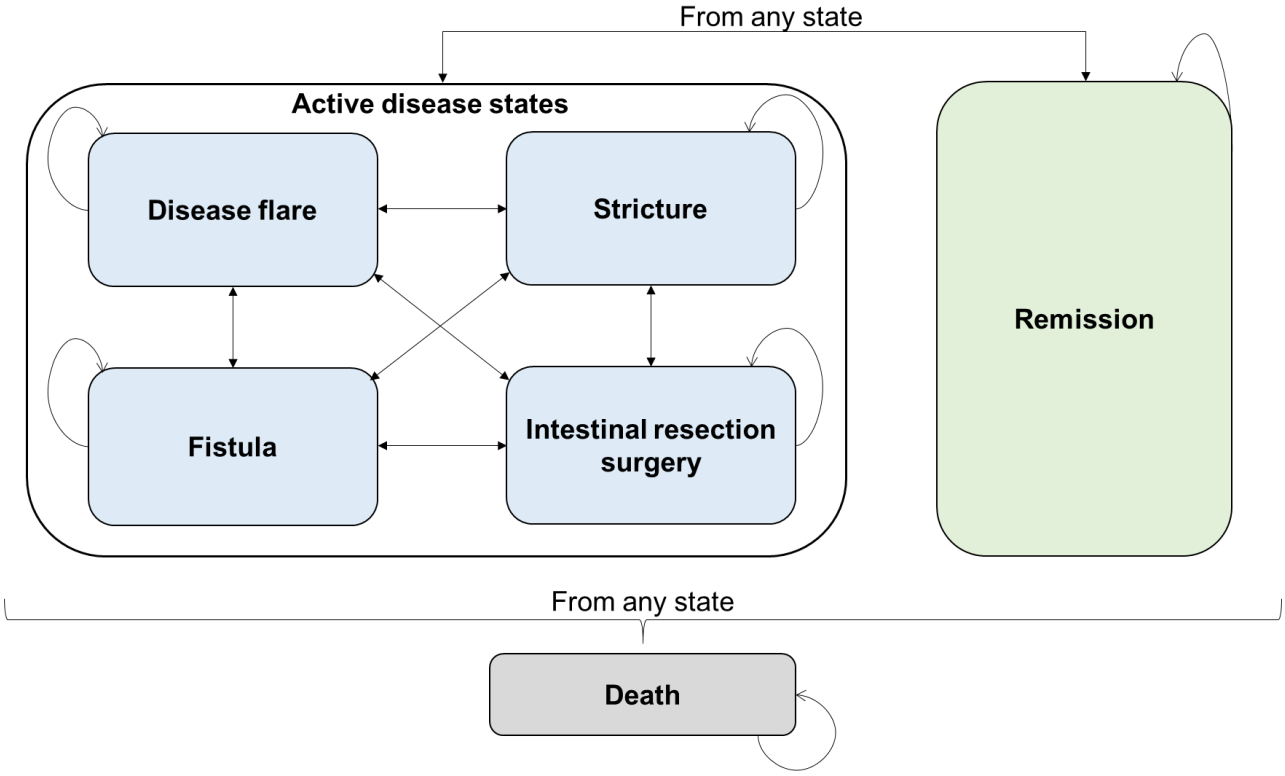


Figure 12 Graphical representation of Crohn's disease Markov model structure and movements between health states

Model parameterisation

Transition probabilities

Parametric time-to-event analysis was used to estimate time-to-event curves for each health state, from which time-varying annual transition probabilities were calculated (Supplementary Files *Figure D2*). Separate time-to-event curves were estimated for the intervention and comparator groups allowing for time-dependent treatment effects. The analysis period was defined from the time of diagnosis to event/failure or administrative censoring. Events were observed prospectively from enrolment in the SIBDCS; thus, delayed entry/left truncation was accounted for. Due to the recurrent nature of events, unconditional shared frailty models were used to predict the risks of disease flares, fistula, stricture, and remission. These models accounted for unobserved heterogeneity and dependence between event

failures for each individual[22 23]. Single event models were used to parameterise the risk of surgery since repeated event models did not fit the data well due to a paucity of multiple surgeries in this sample.

Parametric models were used to extrapolate time-to-event curves over patients' lifetime (Supplementary Files *Table D2*). Models tested included the Weibull, lognormal, loglogistic, Gompertz, and exponential distributions. Appropriate models were chosen based on visual inspection of the fit of predicted time-to-event curves on non-parametric Kaplan-Meier curves (Supplementary Files *Figure D1*) and the Akaike Information Criteria (Supplementary Files *Table D1*).

Transition probabilities did not consider disease history thereby assuming that the probability of recurrent events was independent of previous health states (Supplementary Files *Table D3*). This assumption was made due to a small sample to parameterise conditional probabilities and increased model complexity required to capture disease history. Correlations between events were not considered, thus events were assumed to occur independently. The complement of probabilities in each cycle was used to parametrise the probability of remaining in the same health state such that transition probabilities summed to 1.

Mortality rates

Mortality rates were obtained from the general Swiss population in 2017 in 10-year age groups[24] (Supplementary Files *Table D4*). These were increased by 39% to reflect the CD-specific mortality risk using evidence from a meta-analysis of population-based studies across Europe and the USA[25].

Direct and indirect costs

Methods used to derive unit costs for health care utilisation are described in detail elsewhere[3]. In brief, unit costs for IBD-related inpatient (surgical interventions and hospitalisations) and outpatient (consultation visits, biologic agent infusion-related costs, and imaging scans such as endoscopy) events recorded in the SIBDCS were estimated from reimbursement claims data obtained from the Helsana Group (Supplementary Files *Table D6*). This is a leading health insurance company in Switzerland providing statutory health insurance to 15% of the population[4]. Unit costs estimated from this data were used to cost-weight the health care utilisation reported in the SIBDCS. Pharmaceutical

costs were derived from public price lists[26] using recommended dosing schedules[27]. All costs were inflated to 2017 values using the consumer price index in Switzerland[28]. Indirect costs were calculated using 2017 national median salaries in Switzerland[29] and patient-reported days absent from work extracted from the SIBDCS. Swiss national labour participation rates in 2017 were used to adjust indirect costs by age[30] (Supplementary Files *Table D5*). Costs are reported in CHF and converted to euros (€) using the average exchange rate in 2017 of CHF 1 = €0.89[31].

For the cost-effectiveness model, mean annual per patient costs were estimated from generalised linear regression models with a gamma distribution and log link function. We used separate regression models for each treatment group including the presence of all health states and disease duration as covariates. Mean direct costs for the first eight years after diagnosis were predicted for each health state (*Table 9*). This allowed costs to vary over time due to patients switching treatments. After eight years, costs in each health state were held constant for the remainder of the time that the model was run, assuming that a stable treatment pattern was reached and that drug prices remained constant over time. Mean annual per patient indirect costs were estimated for active disease states combined and remission, and were assumed to remain constant over time (*Table 10*)

Table 9 Mean total direct costs (CHF) per patient per year by health state for the comparator (late/no biologic use) and intervention (early biologic use) groups

Disease duration (years)	Disease flare		Fistula		Stricture		Surgery		Remission	
	Late/no biologic	Early biologic	Late/no biologic	Early biologic	Late/no biologic	Early biologic	Late/no biologic	Early biologic	Late/no biologic	Early biologic
0	6,219	15,775	15,618	19,062	6,253	21,610	26,494	32,233	2,709	17,817
1	6,846	15,548	16,520	19,114	6,789	20,603	27,517	32,854	3,112	17,043
2	7,536	15,325	17,474	19,165	7,371	19,644	28,579	33,487	3,576	16,302
3	8,296	15,105	18,484	19,217	8,004	18,729	29,682	34,132	4,109	15,593
4	9,133	14,888	19,551	19,269	8,690	17,857	30,828	34,789	4,721	14,915
5	10,054	14,675	20,680	19,321	9,435	17,025	32,017	35,459	5,425	14,266
6	11,069	14,464	21,875	19,374	10,244	16,232	33,253	36,143	6,233	13,646
7	12,185	14,256	23,138	19,426	11,123	15,476	34,537	36,839	7,162	13,053
8*	13,414	14,052	24,474	19,479	12,077	14,756	35,870	37,548	8,230	12,485
*Costs after 8 years were held constant for the remainder of the time that the model was run Average exchange rate in 2017: CHF 1 = € 0.89[35]										

Quality-adjusted life years

Patient-reported quality of life was measured annually using the Short Form 36 (SF-36) questionnaire in the SIBDCS[32]. To generate utilities, patients' responses to each item in the SF-36 were mapped to the SF-6D using published algorithms[32]. Utility valuations from the SF-6D were obtained from a sample of the general population in the UK[33].

Mean utilities (*Table 10*) for each health state were estimated from a linear regression model adjusting for treatment group, health state, disease duration, and the gap (in years) between the date of SF-36 record and the health event (used to adjust for the effects of any delay between the measurement of patient-reported quality of life and the physician-reported health event in the SIBDCS). Utilities were multiplied by patients' length of life per model cycle to calculate QALYs for each health state[18]. Utilities were assumed to be the same for a given health state irrespective of treatment group and were held constant over time. Thus, any differences in QALYs reflect variations in the risks of health outcomes between the treatment groups.

One-way and probabilistic sensitivity analysis

In one-way sensitivity analysis all parameters (transition probabilities, costs, and utilities) were varied independently using the 95% confidence intervals (CI) (*Table 10*). Standard errors (SE) for transition probabilities and costs were assumed to be 20% of the mean. The mean annual probability for each health state was calculated by averaging annual transition probabilities over the time horizon of the model. This ensured that transition probabilities did not sum to greater than 1 when varied over wide ranges. For indirect costs, ±20% of the mean was used because the lower bound of the 95% CIs was negative.

In PSA, joint parameter uncertainty was assessed using 10,000 Monte Carlo simulations. Parameters were varied around the mean and SEs using recommended distributions[18] (*Table 10*). Specifically, beta distributions were used for utilities and transition probabilities to ensure that sampled values were bounded between zero and one. Gamma distributions were used for costs to account for its non-negative and skewed properties. Transition probabilities were normalised so that they summed to one when varied over wide ranges.

Table 10 Parameters used in the base case analysis and ranges and distributions used to vary parameters in sensitivity and scenario analyses

	Base case analysis	One-way sensitivity analysis	Probabilistic sensitivity analysis
Direct and indirect costs	**Mean cost (CHF) per patient per year**	**95% CI (lower, upper)**	**Gamma distribution (Mean[a], SE[‡] in CHF)**
Late/no biologic use (comparator): Disease flares	See *Table 9*	8064, 13921	10,992 (2198)
Late/no biologic use (comparator): Fistula		16435, 26594	21,515 (4303)
Late/no biologic use (comparator): Stricture		7481, 12756	10,119 (2024)
Late/no biologic use (comparator): Surgery		27291, 38227	32,759 (6552)
Late/no biologic use (comparator): Remission		5190, 7584	6387 (1277)
Late/no biologic use (comparator): Indirect costs active health states[§]	7019	5616, 8423*	7019 (1404)
Late/no biologic use (comparator): Indirect costs remission[§]	220	176, 264*	220 (44)
Early biologic use (intervention): Disease flares	See *Table 9*	13220, 16442	14,831 (2966)
Early biologic use (intervention): Fistula		16159, 22415	19,287 (3857)
Early biologic use (intervention): Stricture		15001, 20476	17,739 (3548)
Early biologic use (intervention): Surgery		30697, 39417	35,057 (7011)
Early biologic use (intervention): Remission		14064, 15566	14,815 (2963)
Early biologic use (intervention): Indirect costs active health states[§]	2560	2048; 3072*	2560 (512)
Early biologic use (intervention): Indirect costs remission[§]	730	584, 876*	730 (146)
Utilities	**Mean utility per patient per year**	**95% CI**	**Beta distribution (Mean, SE)**
Disease flares	0.66	0.63, 0.68	0.66 (0.14)
Fistula	0.67	0.61, 0.74	0.67 (0.17)
Stricture	0.68	0.64, 0.72	0.68 (0.13)
Surgery	0.64	0.60, 0.68	0.64 (0.14)
Remission	0.71	0.69, 0.73	0.71 (0.14)
Transition probabilities	**Annual transition probability**	**95% CI**	**Beta distribution (Mean[b], SE[‡])**
Late/no biologic use (comparator): Disease flares	See Supplementary Files *Figure D2*	0.15, 0.35	0.25 (0.05)
Late/no biologic use (comparator): Fistula		0.03, 0.08	0.06 (0.02)
Late/no biologic use (comparator): Stricture		0.12, 0.28	0.20 (0.04)
Late/no biologic use (comparator): Surgery		0.007, 0.02	0.01 (0.002)
Late/no biologic use (comparator): Remission		0.19, 0.45	0.32 (0.06)
Early biologic use (intervention): Disease flares		0.11, 0.25	0.18 (0.04)
Early biologic use (intervention): Fistula		0.01, 0.03	0.02 (0.004)
Early biologic use (intervention): Stricture		0.03, 0.06	0.05 (0.01)
Early biologic use (intervention): Surgery		0.01, 0.03	0.02 (0.004)
Early biologic use (intervention): Remission		0.22, 0.51	0.36 (0.07)
Mortality rates	See Supplementary Files *Table D4*		
Other parameters			
Crohn's disease standardised mortality rate[25]	1.39	1.3, 1.49	N/A

[‡]Standard error (SE) defined as 20% of mean

[§]Mean indirect costs were adjusted for the labour participation rates in Switzerland (see Supplementary Files *Table D5*)
[a]The mean cost value used in PSA reflect the mean cost averaged over disease duration
[b]The mean transition probability per health state was calculated by averaging annual transition probabilities over 50 years
*Mean ± 20% used because 95% CI was negative
Average exchange rate in 2017: CHF 1 = € 0.89[35]

Scenario and subgroup analyses

Several scenarios were analysed to assess variations in the base case results based on methodological assumptions. This included choosing alternative discount rates (0%, 2% and 5%), shorter time horizons (1 year and 10 years), varying utility estimates using values from published literature, and using a fixed overall mean direct cost per health state. In addition, we evaluated the impact of a 30% reduction on the price of biologic agents based on the estimated price difference between biosimilars and branded biologics in the EU[34].

We also tested the influence of alternative derivations for transition probabilities. First, to account for disease history, we generated subgroup-specific transition probabilities from patients who experienced a previous remission or active event (Supplementary Files *Table D7* and *Table D8*). Second, we used the complement of all probabilities in each cycle to parameterise the probability of remission (Supplementary Files *Table D9*). Finally, we derived transition probabilities from Kaplan-Meier curves (instead of parametric models) over a 10 year time horizon (Supplementary Files *Table D10*).

A subgroup analysis was performed including only patients who were known to receive biologic treatment during follow-up in the SIBDCS. Thus, patients who did not receive any biologic treatment were excluded since they may have a different, and potentially milder, disease course to those who required biologic treatment. Propensity score matching was performed stratifying patients into early (≤2 years after diagnosis) and late (>2 years after diagnosis) biologic initiation groups (Supplementary Files *Table C4* and *Figure C3*). Transition probabilities, costs, and QALYs were estimated after propensity score matching as described previously. Descriptive characteristics of the subgroup are summarised in Supplementary Files *Table C5*.

Model validation

The model structure, assumptions and input parameters were evaluated by clinical experts in Switzerland and were considered to reflect the natural history of the disease. Additional model checks included comparing life expectancy estimates from the model to Swiss life tables for consistency. In addition, we performed quality control of inputted formulae and parameters. Finally, the plausibility of model structure, inputs and results were compared to previous literature and are discussed.

RESULTS

Base case cost-effectiveness analysis

From the health system and societal perspectives, the intervention strategy cost CHF 86,562 (€77,464) and CHF 43,808 (€39,204) more, respectively, compared to the comparator strategy over each patient's lifetime (*Table 11*). Despite incurring 0.1 more QALYs and CHF 42,754 (€38,261) lower indirect costs in the intervention strategy, ICERs were above the WTP threshold from both perspectives (health system: CHF 887,450/€794,180 per QALY; societal: CHF 449,130/€402,000 per QALY). This was driven by higher costs of inducing and maintaining remission, and managing disease flares and strictures in the intervention strategy (*Table 9*). In addition, patients in the intervention group received biologic therapies for significantly longer (Mean: 5 years, SD: 2.7) compared to biologic users in the comparator group (Mean: 3.5 years, SD: 2.7; $p<0.001$), contributing to higher health care costs. The QALY improvements reflected a lower lifetime risk of disease flares and strictures, and a higher probability of being in remission for patients in the intervention strategy (Supplementary Files *Figure D2*).

Table 11 Cost-effectiveness results for the base case analysis

	Late/no biologic use (comparator)		Early biologic use (intervention)		Incremental difference
	Undiscounted	**Discounted**	**Undiscounted**	**Discounted**	**Discounted**
Direct costs	CHF 520,826 (€ 466,087)	CHF 270,667 (€ 242,220)	CHF 645,439 (€ 577,603)	CHF 357,229 (€ 319,684)	CHF 86,562 (€ 77,464)
Indirect costs	CHF 112,599 (€ 100,765)	CHF 70,132 (€ 62,761)	CHF 42,015 (€ 37,599)	CHF 27,379 (€ 24,501)	CHF -42,754 (€ -38,261)
Total costs	CHF 633,425 (€ 566,852)	340,799 (€ 304,981)	CHF 687,455 (€ 615,203)	CHF 384,607 (€ 344,185)	CHF 43,808 € 39,204
Quality-adjusted life years (QALYs)	30.79	16.75	31.01	16.84	0.10
Incremental cost-effectiveness ratios (costs per QALY)					
Swiss health system perspective					CHF 887,450 (€ 794,180)
Societal perspective					CHF 449,130 (€ 401,926)
Average exchange rate in 2017: CHF 1 = € 0.89[35]					

Sensitivity analysis

In one-way sensitivity analysis, the ICER from the health system perspective was most sensitive to changes in utility values for stricture, the probability of disease flares in the intervention and comparator groups, and the probability of remission in the comparator group (*Figure 13*). The intervention was dominated (higher costs and lower QALYs) at the upper utility value for stricture and at the lower bound for the probability of remission in the intervention group. None of the parameters led to the ICER being cost-effective at a WTP of CHF 100,000 per QALY when varied over its 95% CI. Similar results were found from the societal perspective (Supplementary Files *Figure D3*). The intervention was dominant (CostΔ: CHF -1621, QALYΔ: 0.25) from the societal perspective when the probability of remission in the comparator group was reduced.

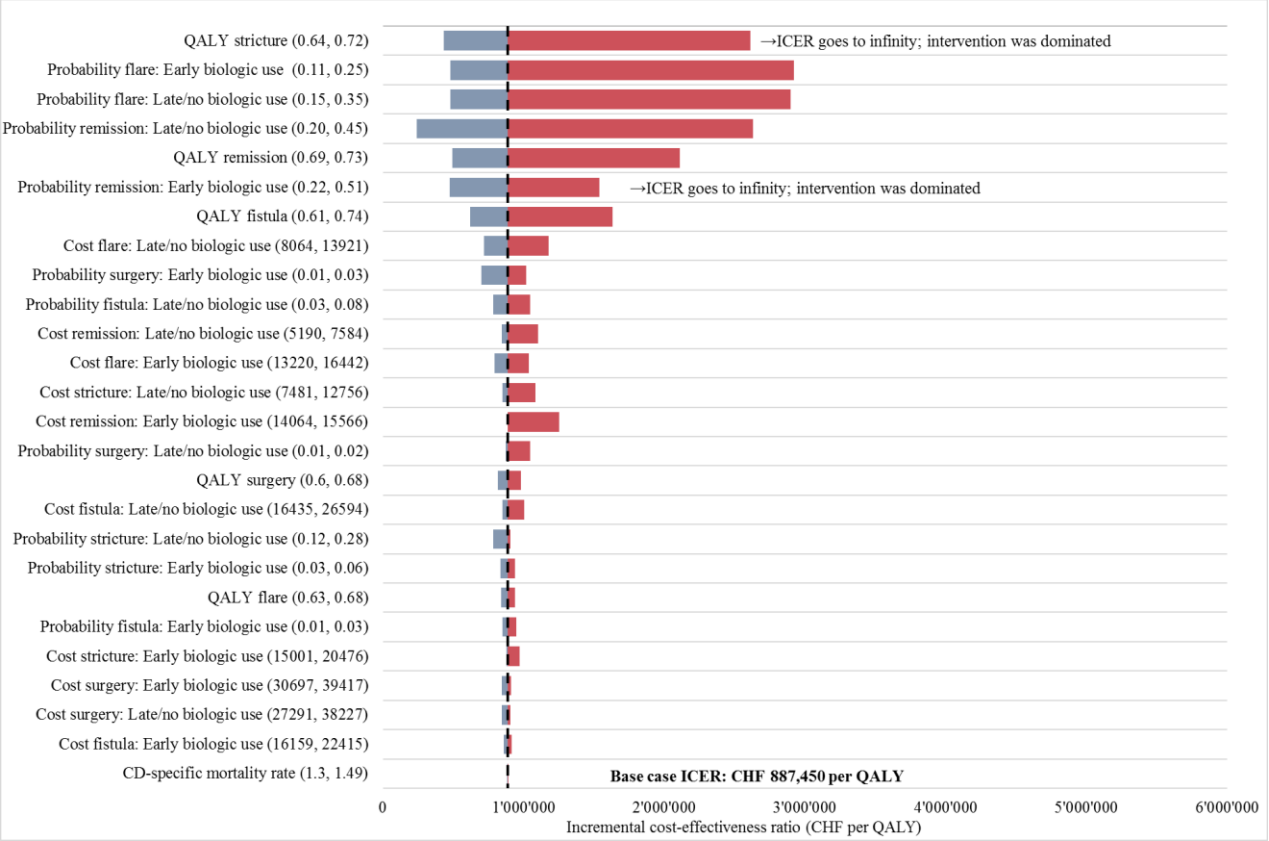


Figure 13 Tornado diagram showing the influence of varying each parameter individually on the ICER from the health system perspective; blue bars indicate ICER was reduced and red bars indicate ICER increased

In PSA, the intervention strategy had a 0.10 and 0.25 probability of being below the WTP threshold from the health system and societal perspectives, respectively (*Figure 14*). The majority of simulations were clustered above the WTP threshold (Supplementary Files *Figure D4*).

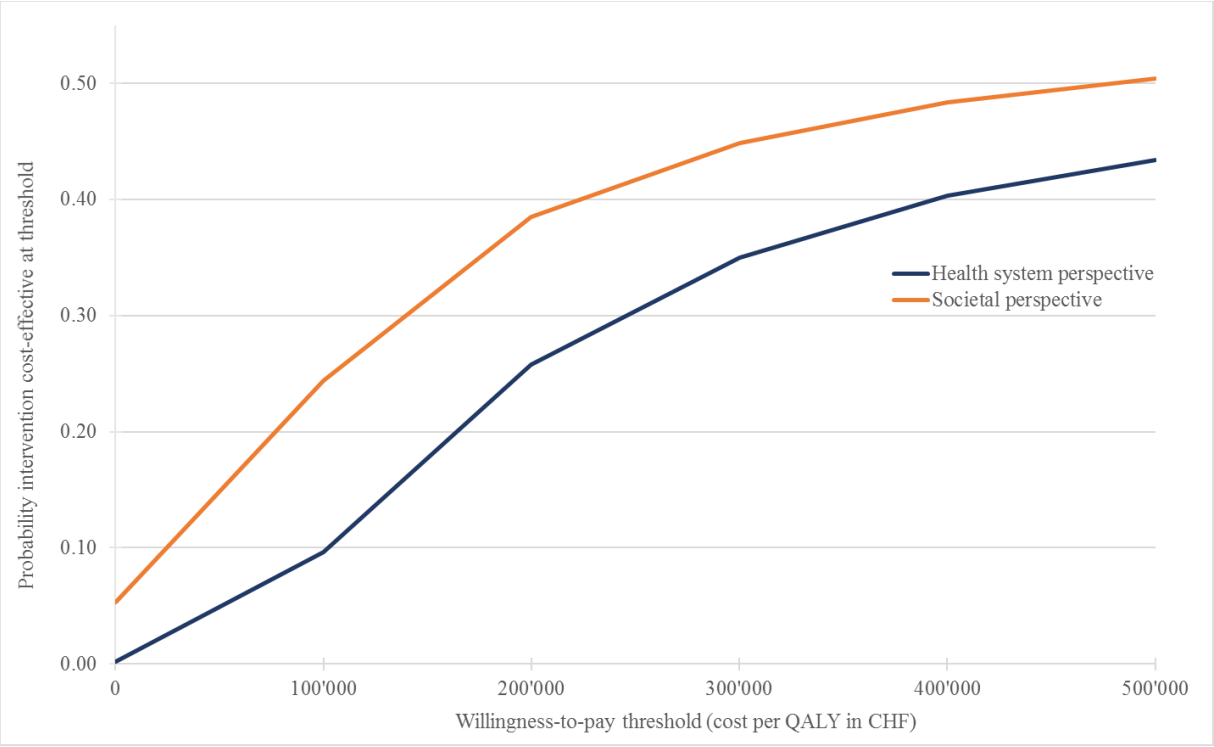


Figure 14 Cost-effectiveness acceptability curve from probabilistic sensitivity analysis after 10'000 Monte Carlo simulations showing the probability that the intervention strategy is cost-effective at different willingness to pay thresholds

Scenario analyses

ICERs were high when the model was evaluated over shorter time horizons and when using transition probabilities from Kaplan-Meier curves due to negligible differences in QALYs and high costs (*Table 12*). ICERs remained above the WTP threshold when using alternative transition probabilities and when utility estimates were varied for remission (CHF 169,160 per QALY), fistula (CHF 311,015 per QALY), and surgery (CHF 1,160,000 per QALY) (*Table 12*).

Assuming a 30% reduction in the price of biologics reduced the ICER from the health system perspective (CHF 134,502 per QALY). Moreover, from the societal perspective, costs were lower and QALYs were higher (dominance) for the intervention group (*Table 12*).

In the subgroup analysis considering only patients who were known to receive biologic treatments, early biologic initiation was cost saving and improved QALYs from the health system and societal perspectives. This was driven by lower health care costs for the early biologic initiation group and

reduced risks of disease flares, fistulae and strictures over patient's lifetime compared to the late biologic group (Supplementary Files *Figure C5*).

Table 12 Results of scenario analyses used to test the impact of methodological uncertainty on base case results

Description of scenario	Incremental direct costs (CHF)	Incremental total costs (CHF)	Incremental QALYs	ICER in CHF Health system perspective	ICER in CHF Societal perspective
Base case analysis	**86,562**	**43,808**	**0.10**	**887,450**	**449,130**
Discount rate: 2%	96,114	46,192	0.13	755,770	363,216
Discount rate: 5%	72,844	40,427	0.06	1,225,429	680,083
Time horizon: 1 year	8211	4633	-0.0001	Intervention dominated[a]	Intervention dominated[a]
Time horizon: 10 years	59,229	44,917	0.002	>35 million	>30 million
Subgroup analysis: Biologic users only (see Supplementary Files *Table C5*)	-24,636	-64,097	0.19	Intervention dominant[b]	Intervention dominant[b]
Transition probabilities					
Probability of remission parameterised using the complement of row probabilities	93,288	40,559	0.15	615,409	267,564
Transition probability from remission to any active disease derived from time-to-event model for the subgroup of the population who experienced at least 1 remission event	88,790	24,831	0.12	744,585	208,235
Transition probability from a given active state to remission derived from time-to-event model for the subgroup of patients who experienced at least 1 of the relevant active events (disease flare, surgery, stricture, and fistula)	83,874	17,750	0.10	808,273	171,051
Transition probabilities derived from Kaplan-Meier curves for a time horizon of 10 years; removing the need for extrapolation of health outcomes	59,487	44,072	0.003	17,527,352	12,985,400
Utilities					
Fistula: 0.4[*]	86,562	43,808	0.28	311,014	81,213
Remission: 0.83[*]	86,562	43,808	0.51	169,159	44,172
Disease flares: 0.62[‡]	86,562	43,808	0.11	821,207	214,438
Surgery: 0.54[‡]	86,562	43,808	0.07	1,157,638	302,288
Costs					

Mean overall annual per patient direct costs fixed for each health state	142,383	78,425	0.10	1,459,745	804,032
Assume price of biologic agents reduced by 30%[§]	13,119	-29,634	0.10	134'502	Intervention dominant[b]
[*]Lindsay J, et al. (2008)[35] [‡]Gregor et al. (1997)[36] [§]IMS Institute for healthcare informatics (2016)[34] [a]Dominated: Intervention had higher costs and lower QALYs [b]Dominant: Intervention had lower costs and higher QALYs Average exchange rate in 2017: CHF 1 = € 0.89; Source: https://www.ecb.europa.eu/stats/policy_and_exchange_rates/euro_reference_exchange_rates/html/eurofxref-graph-chf.en.html					

DISCUSSION

Early treatment with biologic agents was associated with a significant cost burden and did not sufficiently improve health outcomes over a patient's lifetime compared to similar patients who started biologics >2 years after diagnosis or who did not receive any biologic treatment. ICERs were considerably above CHF 100,000 per QALY from the Swiss health system and societal perspectives. Early biologic users received biologic therapies for significantly longer compared to patients in the comparator group, contributing to high costs, which were not fully offset by QALY improvements despite reduced risks of disease flares and strictures. Moreover, 50% of patients in the comparator group in the base case analysis did not progress to biologic therapies despite .having similar observable baseline characteristics to patients who received biologic treatments early. Thus, widespread adoption of an early biologic treatment strategy could lead to overtreatment of these patients who may respond to conventional pharmaceuticals, incurring unnecessary costs. These results suggest that a rapid step-up treatment approach may be more appropriate from a cost-effectiveness perspective given the heterogeneity of disease presentation and prognosis.

We identified several scenarios that might influence the cost-effectiveness of early biologic treatment. First, the comparator group had a higher burden of work absenteeism during active disease states. This indicates some societal gains from early biologic use although broader societal costs such as the need for invalidity benefits, and informal or formal care should also be considered. Moreover, a 30% reduction in the price of biologic therapies improved the ICER in favour of early biologic treatment, providing an opportunity for biosimilars, which were estimated to be significantly cheaper than their branded reference products in Europe[37 38]. The overall cost-effectiveness of biosimilars, however, will depend on how utilisation changes in response to price reductions with the potential for increased access as prices fall[39]. Finally, in the subgroup analysis considering only patients who were known to receive biologic treatments, starting treatment within 2 years of diagnosis (early) was associated with reduced costs and improved health outcomes compared to starting biologics >2 years after diagnosis (late). However, this subgroup analysis assumed perfect knowledge of which patients will require biologic treatment during the disease course. Thus, a better understanding of the characteristics of patients likely to benefit from and respond to aggressive biologic treatment approaches could help target early treatment strategies to the appropriate patients.

Previous studies found that early compared to late biologic treatment was cost-saving and improved QALYs for moderate to severe CD over the lifetime in Canada[15] and 5 years in Italy[13]. These studies were similar to our subgroup analysis since they included only patients who received biologic treatments. The results underscore the need to target early biologic treatment towards high-risk patients with poor outcomes. A systematic review showed that biologics were not cost-effective for maintenance of remission in several studies in Europe and North America[11]. This may explain our results since patients remained on biologic therapies for several years and those in the intervention strategy received treatment for even longer. Clear guidelines about when to withdraw biologic treatments might help optimise disease management further from a clinical and cost perspective[40].

Our study differed from previous literature in the estimation of utilities, some of which used older sources of health-related quality of life data that might not reflect the benefits of current treatments[11 15 35]. Quality of life data was limited by missing information and a delay between the time of the event and response to questionnaires in the SIBDCS. We estimated higher mean utilities for patients with fistula, surgery and disease flares, and lower utilities for remission compared to previous literature[35]. This could be because patients in our study were recently diagnosed and might experience lower quality of life as they initially manage their diagnosis. Sensitivity and scenario analysis confirmed the importance of utility values on overall results. Future cost-effectiveness analyses will benefit from rigorous evaluation of patients' utilities over the course of the disease.

The main strength of this work is the use of long-term follow-up data reflecting real world clinical practice and treatment patterns. This allowed us to capture the dynamic and progressive nature of CD with health states to reflect the development of important disease complications. We used propensity score matching to reduce the risk of confounding and selection bias. Moreover, data used to parameterise the model were collected from the SIBDCS, reducing bias associated with pooling estimates from studies using heterogeneous methodologies and patient populations.

The model structure and parameterisation required assumptions, which may limit the generalisability of the results. Specifically, the risks of health outcomes were extrapolated using parametric time-to-event

models. These predictions may have been affected by fewer patients in later years of follow-up. Long-term monitoring of health outcomes is required to evaluate the natural history of the disease as novel treatments are adopted. In addition, we could not evaluate transition specific probabilities or capture disease history due to small sample sizes and few event failures within these subgroups. However, preliminary analyses indicated no significant differences in results when alternative probabilities were used. Finally, some selection bias may have persisted despite propensity score matching due to unobserved factors. To manage this, we evaluated the impact of additional socio-demographic and clinical characteristics on the propensity score estimates based on feedback from clinical experts (e.g., education, employment status, diagnostic delay, and laboratory values). These did not significantly influence treatment assignment and were therefore excluded from the propensity score model.

In conclusion, this study found that early biologic treatment was not cost-effective compared to biologic use more than 2 years after diagnosis or no biologic use in the Swiss CD population assuming a WTP threshold of CHF 100,000 per QALY. However, there may exist a subgroup of patients for whom biologic treatment is necessary and where early initiation would be more cost-effective. In addition, price reductions from biosimilar agents would improve the cost-effectiveness of early initiation. Future work should identify characteristics that help early stratification of patients that are more likely to benefit from biologic treatments in order to utilise these therapies effectively.

REFERENCES

1. Rogler G, Biedermann L, Scharl M. New insights into the pathophysiology of inflammatory bowel disease: microbiota, epigenetics and common signalling pathways. *Swiss Med Wkly* 2018;148:w14599. doi: 10.4414/smw.2018.14599 [published Online First: 2018/03/23]
2. Burisch J, Jess T, Martinato M, et al. The burden of inflammatory bowel disease in Europe. *Journal of Crohn's & colitis* 2013;7(4):322-37. doi: 10.1016/j.crohns.2013.01.010 [published Online First: 2013/02/12]
3. Pillai N, Dusheiko M, Maillard MH, et al. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. *Journal of Crohn's & colitis* 2019 doi: 10.1093/ecco-jcc/jjz003 [published Online First: 2019/03/28]
4. Bahler C, Vavricka SR, Schoepfer AM, et al. Trends in prevalence, mortality, health care utilization and health care costs of Swiss IBD patients: a claims data based study of the years 2010, 2012 and 2014. *BMC Gastroenterol* 2017;17(1):138. doi: 10.1186/s12876-017-0681-y [published Online First: 2017/12/05]
5. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *Journal of Crohn's & colitis* 2010;4(1):28-62. doi: 10.1016/j.crohns.2009.12.002 [published Online First: 2010/12/03]
6. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: An open randomised trial. *Lancet (London, England)* 2008;371:660-67.
7. Mao EJ, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. *Alimentary pharmacology & therapeutics* 2017;45(1):3-13. doi: 10.1111/apt.13847 [published Online First: 2016/11/20]
8. Berg DR, Colombel JF, Ungaro R. The Role of Early Biologic Therapy in Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2019 doi: 10.1093/ibd/izz059 [published Online First: 2019/04/02]
9. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017;66(12):2179-87. doi: 10.1136/gutjnl-2017-314519 [published Online First: 2017/09/07]
10. Le Berre C, Danese S, Peyrin-Biroulet L. Timely Use of Biologics in Early Crohn's Disease: The Return of "Hit Hard and Early"? *Digestive diseases and sciences* 2019 doi: 10.1007/s10620-019-05504-x [published Online First: 2019/02/07]
11. Pillai N, Dusheiko M, Burnand B, et al. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *PLoS One* 2017;12(10):e0185500. doi: 10.1371/journal.pone.0185500 [published Online First: 2017/10/04]

12. Tsui JJ, Huynh HQ. Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? *Annals of gastroenterology* 2018;31(4):413-24. doi: 10.20524/aog.2018.0253 [published Online First: 2018/07/12]
13. Marchetti M, Liberato NL, Di Sabatino A, et al. Cost-effectiveness analysis of top-down versus step-up strategies in patients with newly diagnosed active luminal Crohn's disease. *Eur J Health Econ* 2013;14(6):853-61. doi: 10.1007/s10198-012-0430-7 [published Online First: 2012/09/15]
14. An V, Cohen L, Lawrence M, et al. Early surgery in Crohn's disease a benefit in selected cases. *World journal of gastrointestinal surgery* 2016;8(7):492-500. doi: 10.4240/wjgs.v8.i7.492 [published Online First: 2016/07/28]
15. Beilman CL, Kirwin E, Ma C, et al. Early Initiation of Tumor Necrosis Factor Antagonist-Based Therapy for Patients With Crohn's Disease Reduces Costs Compared With Late Initiation. *Clin Gastroenterol Hepatol* 2018 doi: 10.1016/j.cgh.2018.07.032 [published Online First: 2018/07/30]
16. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet (London, England)* 2015;386(10006):1825-34. doi: 10.1016/s0140-6736(15)00068-9 [published Online First: 2015/09/08]
17. The World Bank. Life expectancy at birth, total (years) 2017 [Available from: https://data.worldbank.org/indicator/SP.DYN.LE00.IN accessed 18 Feb 2019.
18. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford, UK: Oxford University Press 2006.
19. Ademi Z, Pfeil AM, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. *Swiss Medical Weekly* 2017;147(w14533) doi: 10.4414/smw.2107.14533
20. Pittet V, Michetti P, Mueller C, et al. Cohort Profile Update: The Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *International Journal of Epidemiology* 2019:1-8. doi: 10.1093/ije/dyy298/5303219
21. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. Boston College Department of Economics: Statistical Software Components S432001, 2003.
22. Cleves M, Gutierrez R, Gould W, et al. An introduction to survival analysis using Stata. 3 ed. College Station, Texas: Stata Press 2010.
23. Gutierrez R. Parametric frailty and shared frailty survival models. *The Stata Journal* 2002;2(1):22-44.
24. Swiss Federal Office of Statistics. Deaths by institutional units, sex, nationality (category), marital status and age class 2017 [Available from: https://www.pxweb.bfs.admin.ch/pxweb/en/px-x-0102020206_102/px-x-0102020206_102/px-x-0102020206_102.px/?rxid=f40d14c2-5353-4268-a894-b6f6464a5d3e accessed 11 Feb 2019.

25. Duricova D, Pedersen N, Elkjaer M, et al. Overall and cause-specific mortality in Crohn's disease: a meta-analysis of population-based studies. *Inflammatory bowel diseases* 2010;16(2):347-53. doi: 10.1002/ibd.21007 [published Online First: 2009/07/03]
26. Bundesamt für Gesundheit. Spezialitätenliste (SL) [Available from: http://www.xn--spezialittenliste-yqb.ch/ accessed 11 Feb 2019.
27. Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *Journal of Crohn's & colitis* 2017;11(1):3-25. doi: 10.1093/ecco-jcc/jjw168 [published Online First: 2016/09/24]
28. OECD. Inflation (CPI) 2018 [Available from: https://data.oecd.org/price/inflation-cpi.htm#indicator-chart accessed 29 May 2018.
29. Federal Statistical Office. Gross monthly wage by age and gender, 2016 [Available from: https://www.bfs.admin.ch/bfs/en/home/statistics/work-income/wages-income-employment-labour-costs/wage-levels-switzerland/categories-persons.html accessed 29 May 2018.
30. Organisation for economic cooperation and development (OECD). Labour force statistics by sex and age - indicators, 2017.
31. European Central Bank. Swiss franc (CHF) 2019 [Available from: https://www.ecb.europa.eu/stats/policy_and_exchange_rates/euro_reference_exchange_rates/html/eurofxref-graph-chf.en.html accessed 2 July 2019.
32. Brazier JE, Robinson AM, Deverill M. The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics* 2002;21:271-92.
33. Kharroubi SA, Brazier JE, Roberts J, et al. Modelling SF-6D health state preference data using a nonparametric Bayesian method. *J Health Econ* 2007;26(3):597-612. doi: 10.1016/j.jhealeco.2006.09.002 [published Online First: 2006/10/31]
34. IMS Institute for healthcare informatics. Delivering on the potential of biosimilar medicines: The role of functioning competitive markets. Parsippany, NJ, 2016.
35. Lindsay J, Punekar YS, Morris J, et al. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease--modelling outcomes in active luminal and fistulizing disease in adults. *Alimentary pharmacology & therapeutics* 2008;28(1):76-87. doi: 10.1111/j.1365-2036.2008.03709.x [published Online First: 2008/04/16]
36. Gregor J, McDonald J, Klar N, et al. An evaluation of utlity measurement in Crohn's disease. *Inflammatory bowel diseases* 1997;3(4):265-76.
37. Zheng MK, Shih DQ, Chen GC. Insights on the use of biosimilars in the treatment of inflammatory bowel disease. *World journal of gastroenterology* 2017;23(11):1932-43. doi: 10.3748/wjg.v23.i11.1932 [published Online First: 2017/04/05]
38. NHS England. NHS set to save £150 million by switching to new versions of most costly drug, 2018.
39. Mulcahy AW, Hlavka JP, Case S. Biosimilar cost savings in the United States. *Rand Health Quarterly* 2018;7(4):3. [published Online First: 30 March 2018]

40. Bolin K, Hertervig E, Louis E. The cost-effectiveness of biological therapy cycles in the management of Crohn's disease. *Journal of Crohn's & Colitis* 2019 doi: 10.1093/ecco-jcc/jjz063 [published Online First: 2019/03/21]

CHAPTER 6

General discussion and conclusions

Widespread availability and uptake of expensive biologic treatments to manage inflammatory bowel disease (IBD) places a significant financial burden on health systems worldwide[1]. In Switzerland, political motivation to contain increasing health care costs is high with a focus on using cost-effectiveness analyses to systematically evaluate new and existing pharmaceuticals and technologies. This thesis evaluated the cost and cost-effectiveness of novel treatment approaches for Crohn's disease (CD) and ulcerative colitis (UC) in Switzerland. Analyses were conducted using real world data from the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) and reimbursement claims data from a leading private health insurance company in Switzerland. The studies presented in this thesis provide important insights into the impact of changing treatment patterns in routine clinical practice on health care utilisation, expenditures, and outcomes for patients with IBD.

SUMMARY OF THESIS FINDINGS

In **Chapter 2**, the systematic literature review showed that although biologic agents have helped to improve quality-adjusted life years (QALYs) and remission rates for CD and UC, high drug prices led to incremental cost-effectiveness ratios (ICERs) above acceptable willingness-to-pay thresholds in the majority of clinical situations[2]. We found that studies relied on data from randomised controlled trials (RCTs), which were conducted over short time periods and for specific subgroups of IBD patients. In addition, they did not capture the chronic and dynamic nature of IBD or reflect real world treatment pathways. Based on these studies, it was evident that comprehensive cost-effectiveness evaluations were needed in order to identify optimal treatment strategies in the face of rising health care costs.

Pillai et al. (2019) evaluated the impact of therapeutic advances and disease progression on trends in health care utilisation and expenditures for IBD in Switzerland over 10 years **(Chapter 3)**[3]. We observed a dramatic rise in the uptake of biologic treatments to manage IBD from 2006 to 2016 leading to a significant increase in overall health care expenditures of 7% for CD and 10% for UC per year, on average[3]. Pharmaceutical expenditures accounted for almost 80% of total health care spending for CD and UC in 2016 compared to 53% (CD) and 66% (UC) in 2006. Importantly, rising pharmaceutical expenditures were not offset by changes to utilisation and expenditures for inpatient and outpatient care after controlling for disease severity and patient characteristics[3]. In addition, indirect costs from productivity losses remained stable for CD and declined moderately for UC. The observed increase in

pharmaceutical expenditures for IBD is supported by literature from other countries and contrasts with early literature, which reported inpatient care as the main driver of costs in IBD. This research demonstrated the need for future studies to understand the impact of changing clinical management on health outcomes, quality of life, and productivity loss in order to ensure value for money from novel therapies in Switzerland.

Recent literature has suggested that earlier initiation of treatment with biologic agents for patients with CD might reduce the risks of disease complications and surgery in the long-term[4 5]. The observed increase in biologic treatment adoption between 2006 and 2016 in Switzerland **(Chapter 3)** might indicate a lower threshold for utilising biologics, which could also lead to patients receiving biologics earlier on in the disease course. This topic was evaluated in two studies presented in this thesis looking at the clinical outcomes **(Chapter 4)** and cost-effectiveness **(Chapter 5)** of early biologic treatment compared to late or no biologic treatment in CD patients.

In **Chapter 4**, we conducted a retrospective analysis of clinical outcomes over 10 years using data collected in the SIBDCS. Patients who received biologic treatments within 2 years of diagnosis (early biologic treatment) were compared to similar patients who received biologics more than 2 years after diagnosis or who did not receive any biologic treatments (late/no biologic treatment). Propensity score matching was used to ensure patients were similar in each treatment group and to reduce the risk of selection bias associated with observational data. This study found no significant differences in the cumulative probability of intestinal resection surgery, fistula, stricture, and disease flares between the early biologic treatment group and the late/no biologic treatment group after 10 years of follow-up. However, annual trends in the predicted probability of fistula, stricture, and disease flares indicated an initially higher risk of each outcome for the early biologic group, which remained stable or declined over time. Conversely, annual predicted probabilities increased over time for the late/no biologic group in the first 10 years after diagnosis. In addition, in a subgroup analysis of patients known to receive biologic treatments, early initiation significantly reduced the cumulative risks of strictures and disease flares over time, but the risk of fistula was higher compared to late biologic initiation.

In the cost-effectiveness analysis, clinical outcomes presented in Chapter 4, quality of life, direct health care costs, and indirect costs associated with productivity loss were extrapolated and modelled over the patient's lifetime for the early compared to the late/no biologic treatment groups **(Chapter 5)**. Results showed that patients receiving biologic treatments early had higher lifetime QALYs (16.84 QALYs), due to lower overall risks of stricture and disease flares over the lifetime, compared to those in the late/no biologic treatment group (16.75 QALYs). However, QALY gains were not sufficient to offset the high health care costs of early biologic treatment, which were greater than CHF 300,000 per patient due to the high costs of inducing and maintaining remission and managing disease complications over patients' lifetime. Thus, early biologic use was not cost-effective from the Swiss health system (CHF 887,450 per QALY) and societal (CHF 449,130 per QALY) perspectives assuming a societal willingness-to-pay threshold of CHF 100,000 per QALY **(Chapter 5)**. In probabilistic sensitivity analyses, taking into account uncertainty in the model input parameters, early biologic use had a low probability of being cost-effective of 0.1 from the Swiss health system and 0.25 from the societal perspectives. Early biologic use was, however, associated with a reduced burden of work absenteeism indicating some societal gains from early treatment. In addition, simulating a reduction in drug prices based on cost savings from biosimilars and evaluating only the subgroup of patients known to progress to biologics improved the cost-effectiveness of early biologic treatment.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

As patents for biologic agents expire, increased availability and uptake of biosimilars will provide an opportunity for reduced drug prices, which might help to manage rising health care costs in IBD and increase access to treatments[6]. However, increased access might significantly influence health care budgets despite reduced drug prices as utilisation volumes grow. To manage drug utilisation and avoid unnecessary treatment and costs, it is important to understand clinical factors that indicate a need for biologic treatment. Moreover, clear guidelines on the duration of treatment with biologic agents are currently lacking[7]. Our systematic literature review identified several studies across different geographies reporting that maintenance treatment with biologic agents was not cost-effective compared to conventional pharmaceuticals for both CD and UC **(Chapter 2)**[2]. However, data from the SIBDCS showed that CD patients treated with biologics remained on these therapies for 4 years, on average **(Chapter 4)**. Moreover, those who received biologics early on in the disease course continued therapy

for significantly longer than those who stepped up therapy in the conventional approach contributing to higher overall health care costs **(Chapter 5)**. Future research should explore the clinical effectiveness and cost implications of different treatment durations and withdrawal strategies.

With the rising use of biologic agents, therapeutic drug monitoring has gained attention in recent literature as a means to reduce treatment costs in IBD and manage the risks of inefficient and inappropriate disease management[8-10]. Closely monitoring drug concentration and anti-drug antibody levels following biologic initiation can increase drug efficacy, reduce the risks of toxicity, and improve patient outcomes through quicker decision making[11]. Two types of monitoring are discussed in the literature. Proactive drug monitoring closely follows patients during maintenance phases of IBD in order to adjust drug doses and minimise the risk of treatment failure. Alternatively, reactive drug monitoring, during active phases of the disease, helps to guide decision making following loss of response to biologic treatment and poor disease control[11 12]. Reactive drug monitoring was shown to be cost-effective compared to clinically-driven treatment optimisation for patients on biologic treatments[13 14]. A recent systematic review of the literature found no clear evidence that proactive or reactive drug monitoring improved remission rates in IBD when compared to drug optimisation based on symptoms or biomarkers[9]. However, proactive drug monitoring was reported to decrease drug discontinuation and relapse rates[9 15]. Given the lack of evidence, long-term studies are needed to assess the role of therapeutic drug monitoring in IBD. In particular, we need an understanding of the optimal drug concentration levels to achieve, when to perform therapeutic drug monitoring (during active or remission phases), and the costs and outcomes related to long-term continuous monitoring. Importantly, for therapeutic drug monitoring to be effective, clear treatment protocols should be established to guide decision-making in the case of suboptimal drug response or treatment failure.

In **Chapters 4 and 5**, we observed a large proportion of CD patients that did not progress to biologic therapies and did not experience worse clinical outcomes despite similar baseline characteristics to patients receiving biologic treatments early. This suggests that widespread adoption of an early biologic treatment strategy could lead to overtreatment of patients that respond to conventional pharmaceuticals, incurring unnecessary costs. Importantly, when only patients who were known to receive biologic treatments were included in subgroup analyses, retrospective analyses indicated that

early biologic use improved clinical outcomes **(Chapter 4)** and was cost-effective **(Chapter 5)** compared to later treatment initiation. This was due to lower health care and societal costs and reduced overall risks of strictures and disease flares. This indicates scope for future research to identify factors associated with the need for biologic treatment in order to allow for early detection and treatment of patients who might benefit from aggressive therapies. Studies suggested that a young age at diagnosis of <40 years, extra-intestinal manifestations (EIMs), initial steroid treatment, smoking, and perianal disease were strongly associated with a future need for biologic treatments and poor disease prognosis[16-18]. Future research identifying genetic and phenotypic markers of a complicated disease course will help to prioritise patients for early treatment strategies[19]. In addition, faster escalation of treatments based on closer monitoring of known biomarkers of inflammation (such as C-reactive protein and faecal calprotectin) was shown to improve remission rates and was cost-effective for patients with CD compared to the conventional step-up approach where treatments were escalated based on clinical symptoms using disease activity scores[20 21]. Thus, closer monitoring of disease progression and treatment response combined with predictive tools to help target aggressive treatment strategies to the appropriate patients has the potential to improve the efficiency of CD management.

We found a significant rise in the utilisation of biologic therapies to manage UC patients in Switzerland, raising questions about the appropriate integration of these treatments in routine care **(Chapter 3)**[3]. Little evidence currently exists about the clinical benefits of early biologic treatments for patients with UC. Since several UC patients respond to first line therapies, biologic agents are often reserved for patients with severe disease[17]. A cohort study reported similar rates of colectomy and hospitalisation amongst patients with mild to moderate UC receiving anti-TNF treatment within three years of diagnosis compared to patients who received treatment later[22]. This study may be limited by selection effects given that UC patients in the early treatment group had more severe disease compared to those in the late group and were therefore more likely to need colectomy. Since UC presents primarily as a mucosal disease and rarely exhibits progressive characteristics through strictures and fistula, an early treatment approach may be less relevant relative to CD where patients are at high risk of disease progression[17 23]. Nevertheless, given the risks associated with surgery, such as post-operative complications and reduced quality of life, understanding the role of biologic treatments in delaying total colectomy will help to improve the management of UC.

IMPLICATIONS FOR HEALTH POLICY

The comprehensive statutory health insurance system in Switzerland ensures universal access to high quality care for all residents in the country. However, spiralling health care costs resulting in annual increases in health insurance premiums are of great concern to the population and policy-makers[24]. Due to an aging population and increasing burden of chronic disease, political motivation to contain costs in the health system are at the forefront of the new health agenda[25]. This thesis is timely given ongoing discussions to increase and formalise the use of health technology assessments (HTA) and cost-effectiveness analyses to manage efficiency in the health system[24 26]. The evidence reported in this study can contribute to reimbursement decisions by public health policy makers, health insurance companies, and clinicians in Switzerland about the use of biologic agents in the IBD population. More generally, it confirms the need to continuously assess the cost-effectiveness of health care technologies in order to strike a balance between providing clinically effective interventions and ensuring economic efficiency.

The incidence and prevalence of IBD is rising worldwide, including an increasing burden of the disease observed in low- and middle-income countries[27 28]. This represents a global public health challenge with decisions to be made about optimal care pathways and resource allocation. The results presented in this thesis are consistent with previous literature across high-income countries reporting a growing economic burden of IBD due to the increased use of biologic agents[29 30]. This thesis showed that there might be subgroups of patients for whom biologic treatment is clinically effective and where early aggressive treatment with biologics might be more cost-effective. Since drug prices and health system structures vary across countries, applying cost-effectiveness results to different countries is often limited. However, rising health care costs and an increasing burden of chronic diseases are challenges faced by health systems worldwide. This calls for innovative treatment strategies and financially sustainable health financing mechanisms to contain the costs of IBD care and ensure access to appropriate and effective treatments for patients who need them.

USING REAL WORLD DATA IN ECONOMIC EVALUATIONS

The importance of real world data (RWD) to inform the clinical- and cost-effectiveness of novel pharmaceuticals after regulatory approval and market authorisation is recognised by reimbursement agencies worldwide[31-34]. This includes using data from clinical registries, cohort studies, electronic medical records, and administrative data to complement evidence from RCTs by evaluating the effectiveness of treatments in diverse, real life patient settings. The analyses presented in this thesis demonstrated the statistical implications and feasibility of using RWD to evaluate health care utilisation, changing health care costs, and cost-effectiveness. Specifically, cost data from reimbursement claims were linked to patient- and physician-reported health care and treatment utilisation data collected in the SIBDCS in order to understand changing treatment patterns in IBD and the cost-effectiveness of novel treatment strategies. The work benefited from the rich and broad scope of data collected in the SIBDCS including detailed clinical data on the timing of disease diagnosis, health outcomes, health care and treatment utilisation, and patient-reported quality of life. In addition, there was sufficient variation in the adoption of new treatments over time and across providers participating in the SIBDCS, which could be exploited in these analyses by identifying clinically similar patients following distinct treatment pathways.

In this thesis, statistical approaches including propensity score matching and panel data regression analyses were used to manage biases associated with RWD. Propensity score methods are often limited by the potential for unobserved confounding variables that may influence the outcome, the choice of matching approach, and the numbers of patients dropped in the treatment due to non-matching (common support). In order to minimise the effects of these limitations, a broad selection of patient and clinical variables, which captured disease severity and the potential for future complications, were included in our propensity score model **(Chapter 4 and 5)**. In addition, subgroup and sensitivity analyses were conducted using different patient groups and matching approaches. In these analyses, qualitatively similar trends in clinical outcomes were observed, suggesting a low risk that results were influenced by unobserved patient factors or the chosen matching approach. Finally, there were few patients dropped due to a lack of common support, highlighting the variability in treatment strategies captured in the SIBDCS. An additional consideration for this work was to ensure that there was sufficient data and patient numbers to extrapolate observed clinical outcomes over patients' lifetime in the cost-effectiveness analysis **(Chapter 5)**. This required assumptions that treatment patterns remained stable and health outcomes consistently followed the observed trends over time. Moreover, due to low patient

numbers, the influence of patient's event history on future health outcomes could not be explicitly captured in the cost-effectiveness study. The impact of these uncertainties on the cost-effectiveness results were tested in sensitivity analyses and found to not significantly influence overall results. Future studies with longer follow-up data could be informative to validate these results.

QALYs are often used in cost-effectiveness studies to capture patients' health-related quality of life. In this thesis, QALYs were based on patient-reported data from the Short-Form 36 (SF-36) questionnaire, which evaluated health status on 8 dimensions capturing the physical, emotional, and social aspects of functioning[35]. These measures fail to capture broader aspects of health care that may be of value to patients such as the perceived appropriateness of care, attitudes towards treatments, satisfaction with health care professionals and the care pathway, and non-health related measures of well-being (e.g., productivity losses and the impact on families/caregivers). Moreover, there is typically wide variation around preference-based scores for health states generated from the SF-36[36]. However, cost-effectiveness studies recommend treatment strategies based on the average patient experience. Heterogeneity at the individual patient level can have consequences for the cost-effectiveness of interventions and health care services, particularly if they affect adherence rates and outcomes[37-40]. Integrating data on patients' experience with different treatments over the course of their disease can help to shed light on patient's values and preferences. Recent examples include the use of discrete choice experiments, whereby patient preferences for interventions are elicited by presenting a series of competing scenarios[37 41 42]. As novel methods are applied, it will be important to develop standardised guidelines on how to incorporate this evidence into cost-effectiveness models to aid evaluation of health care interventions.

CONCLUSIONS

The studies reported in this thesis indicated that, in general, while biologic agents have helped improve outcomes for some patients, high drug prices contributed to a growing economic burden of CD and UC. In Switzerland, increasing health care expenditures for IBD over 10 years was marked by a shift towards greater pharmaceutical management over the past decade driven by greater uptake of biologic agents. While the costs of biologic treatments are high, inefficient treatment strategies can have significant

health and cost implications. Closer monitoring of patients' response to treatments will help timely decision-making and improve patient care.

Further examination of an early biologic treatment approach for CD patients indicated no significant improvements in long-term disease progression or surgery rates compared to late or no biologic treatment over 10 years. Consequently, due to high treatment costs and small lifetime improvements in QALYs, early biologic treatment was not cost-effective for CD patients compared to late or no biologic treatment based on current thresholds and prices in Switzerland. This thesis identified a subgroup of patients for whom biologic treatment is necessary and where earlier initiation would be both clinically- and cost-effective. Future studies characterising clinical, serological and genetic factors influencing disease prognosis will help to stratify patients and target aggressive treatment strategies to those likely to benefit. In addition, future price reductions from biosimilar agents may help improve the cost-effectiveness of early biologic initiation.

Finally, this thesis demonstrated the feasibility and importance of using real world data to evaluate the cost and health implications of the changing treatment landscape for chronic diseases. Continuous re-evaluation of the cost-effectiveness of novel treatments and treatment approaches will help to manage costs and improve health care efficiency as the burden of chronic disease rises.

REFERENCES

1. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol* 2015;12(9):537-45. doi: 10.1038/nrgastro.2015.135 [published Online First: 2015/08/19]
2. Pillai N, Dusheiko M, Burnand B, et al. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *Plos One* 2017;12(10) doi: 10.1371/journal.pone.0185500
3. Pillai N, Dusheiko M, Maillard MH, et al. The Evolution of Health Care Utilisation and Costs for Inflammatory Bowel Disease Over Ten Years. *J Crohns Colitis* 2019;13(6):744-54. doi: 10.1093/ecco-jcc/jjz003 [published Online First: 2019/03/28]
4. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017;66(12):2179-87. doi: 10.1136/gutjnl-2017-314519 [published Online First: 2017/09/07]
5. Tsui JJ, Huynh HQ. Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? *Ann Gastroenterol* 2018;31(4):413-24. doi: 10.20524/aog.2018.0253 [published Online First: 2018/07/12]
6. IMS Institute for healthcare informatics. Delivering on the potential of biosimilar medicines: The role of functioning competitive markets. Parsippany, NJ, 2016.
7. Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017;11(1):3-25. doi: 10.1093/ecco-jcc/jjw168 [published Online First: 2016/09/24]
8. Steenholdt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 2014;63(6):919-27. doi: 10.1136/gutjnl-2013-305279 [published Online First: 2013/07/24]
9. Ricciuto A, Dhaliwal J, Walters TD, et al. Clinical Outcomes With Therapeutic Drug Monitoring in Inflammatory Bowel Disease: A Systematic Review With Meta-Analysis. *J Crohns Colitis* 2018;12(11):1302-15. doi: 10.1093/ecco-jcc/jjy109 [published Online First: 2018/08/15]
10. Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *The Lancet* 2017;390(10114):2779-89. doi: 10.1016/s0140-6736(17)32641-7
11. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology* 2017;153(3):827-34. doi: 10.1053/j.gastro.2017.07.032 [published Online First: 2017/08/07]
12. Steenholdt C. Proactive and Reactive Therapeutic Drug Monitoring of Biologic Therapies in Inflammatory Bowel Disease Are Complementary, Not Mutually Exclusive. *Clin Gastroenterol Hepatol* 2018;16(4):597-98. doi: 10.1016/j.cgh.2017.11.033 [published Online First: 2018/03/21]

13. Martelli L, Olivera P, Roblin X, et al. Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: a systematic review. *J Gastroenterol* 2017;52(1):19-25. doi: 10.1007/s00535-016-1266-1 [published Online First: 2016/09/26]
14. Guidi L, Pugliese D, Panici Tonucci T, et al. Therapeutic drug monitoring is more cost-effective than a clinically-based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multi-centre study. *J Crohns Colitis* 2018 doi: 10.1093/ecco-jcc/jjy076 [published Online First: 2018/06/04]
15. Papamichael K, Cheifetz AS. Therapeutic drug monitoring in inflammatory bowel disease: for every patient and every drug? *Curr Opin Gastroenterol* 2019 doi: 10.1097/MOG.0000000000000536 [published Online First: 2019/04/12]
16. Flamant M, Roblin X. Inflammatory bowel disease: towards a personalized medicine. *Therapeutic advances in gastroenterology* 2018;11:1756283X17745029. doi: 10.1177/1756283X17745029 [published Online First: 2018/02/01]
17. Berg DR, Colombel JF, Ungaro R. The Role of Early Biologic Therapy in Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2019 doi: 10.1093/ibd/izz059 [published Online First: 2019/04/02]
18. Dias CC, Rodrigues PP, da Costa-Pereira A, et al. Clinical prognostic factors for disabling Crohn's disease: a systematic review and meta-analysis. *World J Gastroenterol* 2013;19(24):3866-71. doi: 10.3748/wjg.v19.i24.3866 [published Online First: 2013/07/11]
19. Lee JC, Biasci D, Roberts R, et al. Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn's disease. *Nature genetics* 2017;49(2):262-68. doi: 10.1038/ng.3755 [published Online First: 2017/01/10]
20. Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet (London, England)* 2017;390:2779-89. doi: 10.1016/S0140-6736(17)32641-7
21. Panaccione R, Colombel JF, Travis SPL, et al. Tight control for Crohn's disease with adalimumab-based treatment is cost-effective: an economic assessment of the CALM trial. *Gut* 2019 doi: 10.1136/gutjnl-2019-318256 [published Online First: 2019/07/10]
22. Ma C, Beilman CL, Huang VW, et al. Similar Clinical and Surgical Outcomes Achieved with Early Compared to Late Anti-TNF Induction in Mild-to-Moderate Ulcerative Colitis: A Retrospective Cohort Study. *Canadian Journal of Gastroenterology and Hepatology* 2016;2016:1-9. doi: 10.1155/2016/2079582
23. Torres J, Billioud V, Sachar DB, et al. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis* 2012;18(7):1356-63. doi: 10.1002/ibd.22839 [published Online First: 2011/12/14]
24. Bundesamt für Gesundheit (BAG). Unwirksame und ineffiziente medizinische Leistungen sollen reduziert werden 2016 [Available from: https://www.admin.ch/gov/de/start/dokumentation/medienmitteilungen.msg-id-61615.html accessed 4 July 2019.
25. Federal Office of Public Health (FOPH). Health 2020, 2013.

26. Swiss HTA. HTA in Switzerland 2017 [Available from: www.swisshta.org/index.php/HTA_in_Switzerland.html accessed 4 July 2019.
27. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142(1):46-54 e42; quiz e30. doi: 10.1053/j.gastro.2011.10.001 [published Online First: 2011/10/18]
28. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet* 2017;390(10114):2769-78. doi: 10.1016/s0140-6736(17)32448-0
29. Burisch J, Jess T, Martinato M, et al. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis* 2013;7(4):322-37. doi: 10.1016/j.crohns.2013.01.010
30. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology* 2008;135(6):1907-13. doi: 10.1053/j.gastro.2008.09.012
31. Garrison LP, Neumann PJ, Marshall D, et al. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World DataTask Force Report. *Value in Health* 2007;10(5):326-35.
32. Makady A, Ham RT, de Boer A, et al. Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies. *Value Health* 2017;20(4):520-32. doi: 10.1016/j.jval.2016.12.003 [published Online First: 2017/04/15]
33. NICE: National Institute for Health and Care Excellence. Consultation on the data and analytics statement of intent 2019 [Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/how-we-develop-nice-guidelines/consultation-data-and-analytics-statement-of-intent accessed 1 July 2019.
34. U.S. Department of Health and Human Services Food and Drug Administration. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics: Guidance for Industry 2019 [Available from: https://www.fda.gov/media/124795/download accessed 1 July 2019.
35. Ware JE, Snow KK, Kosinski M, et al. SF 36 Health Survey: Manual and Interpretation Guide. In: Trust TMO, ed. Boston, 1993.
36. Brazier J, Roberts J, Deveritt M. The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics* 2002;21:271-92.
37. Tinelli M, Ryan M, Bond C. What, who and when? Incorporating a discrete choice experiment into an economic evaluation. *Health Econ Rev* 2016;6(1):31. doi: 10.1186/s13561-016-0108-4 [published Online First: 2016/07/31]
38. Basu A, Meltzer D. Value of information on preference heterogeneity and individualized care. *Med Decis Making* 2007;27(2):112-27. doi: 10.1177/0272989X06297393 [published Online First: 2007/04/06]
39. Brazier JE, Dixon S, Ratcliffe J. The Role of Patient Preferences in Cost-Effectiveness Analysis. *Pharmacoeconomics* 2009;27(9):705-12.

40. Ioannidis JP, Garber AM. Individualized cost-effectiveness analysis. *PLoS Med* 2011;8(7):e1001058. doi: 10.1371/journal.pmed.1001058 [published Online First: 2011/07/19]
41. Tang D, Armstrong E, Lee J. Cost-Utility Analysis of Biologic Treatments for Moderate-to-Severe Crohn's Disease. *Pharmacotherapy* 2012;32(6):515-26.
42. Ryan M, Watson V. Counting the cost of fast access: using discrete choice experiments to elicit preferences in general practice. *British Journal of General Practice* 2006

SUPPLEMENTARY FILES

SUPPLEMENTARY FILES A: CHAPTER 2

Full literature search strategy

Table A1 Full search strategy in Ovid MEDLINE, Embase, and York Centers for Reviews and Dissemination

Search in Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid EDLINE(R) 1946 to Present

Number	Search terms	Results
1	crohn* disease.ti,ab,kw.	39445
2	ulcerative colitis.ti,ab,kw.	33430
3	inflammatory bowel disease*.ti,ab,jw.	39791
4	1 or 2 or 3	81955
5	cost effectiveness*.ti,ab,kw.	48099
6	cost utility.ti,ab,kw.	3569
7	cost benefit.ti,ab,kw.	8698
8	health economic*.ti,ab,kw.	6165
9	economic evaluation*.ti,ab,kw.	9451
10	5 or 6 or 7 or 8 or 9	65240
11	4 and 10	280
12	limit 11 to English language	259

Search in Embase 1974-November 9 2016

Number	Search terms	Results
1	crohn* disease.ti,ab,kw.	60956
2	ulcerative colitis.ti,ab,kw.	49359
3	inflammatory bowel disease*.ti,ab,jw.	60016
4	1 or 2 or 3	118867
5	cost effectiveness*.ti,ab,kw.	66971
6	cost utility.ti,ab,kw.	5770
7	cost benefit.ti,ab,kw.	13108
8	health economic*.ti,ab,kw.	9738
9	economic evaluation*.ti,ab,kw.	13216
10	5 or 6 or 7 or 8 or 9	91499
11	4 and 10	552
12	limit 11 to English language	519

Search in York Centers for Reviews and Dissemination (CRD) databases: DARE, NHS EED, HTA

Number	Search	Results
1	(cost benefit) OR (cost effectiveness) OR (cost utility) IN DARE, NHSEED, HTA	19213
2	(crohn* disease) OR (ulcerative colitis) OR (inflammatory bowel disease) IN DARE, NHSEED, HTA	584
3	(economic evaluation) IN DARE, NHSEED, HTA	18503
4	#1 OR #3	22049
5	#2 AND #4	152

Descriptive information of included studies

Table A2 Descriptive data and original costs extracted from studies on Crohn's Disease

Reference (year, country)	Model type	Perspective	Time horizon	Interventions/Comparators*	Original cost (currency)	ICER (cost per outcome gained)§
Trallori et al. (1997, unclear) [30]	None	Societal	Lifetime	Maintenance therapy with mesalazine	5077899 (USD)	5015 USD
				No maintenance treatment	4982619 (USD)	
Arsenau et al. (2001, USA) [35]	Markov model	Third party payer	1 year	6MP /metronidazole combination	2894 (USD)	Reference
				Initial infliximab infusions plus combination with 6MP/metronidazole if treatment failure	10003 (USD)	355450
				Initial infliximab infusion with episodic reinfusion if treatment failure	10112 (USD)	360900
				6MP/metronidazole followed by infliximab with episodic reinfusion if treatment failure	6664 (USD)	377000
Marshall et al. (2002, Canada) [36]	Markov model	Publically-funded health system	1 year	Strategy A: "usual care" immunosuppressants, intravenous corticosteroids and surgery	9940 (CAD)	Strategy A vs. Strategy B: 181201 CAD
				Strategy B: Single infliximab infusion	12702 (CAD)	Strategy C vs. Strategy B: 480111 CAD
				Strategy C: Single infliximab infusion plus reinfusion for patients who relapse	13739 (CAD)	Strategy D vs. Strategy C: 696078 CAD
				Strategy D: Single infliximab infusion plus maintenance infliximab for patients who respond and usual care for patients who do not respond	21597 (CAD)	
Clark et al. (2003, UK) Schering-Plough model [37]	Markov model	Publically-funded health system	Lifetime	Episodic infliximab treatment		10400 GBP
				Single infliximab treatment		6700 GBP
				Maintenance infliximab treatment		84400 GBP

				Placebo		Reference
Clark et al. (2003, UK) Schering-Plough model [37]	Markov model	Publically-funded health system		Initial treatment with infliximab		12300 GBP
				Initial treatment with infliximab plus retreatment if fistula reopens		96000 GBP
				Initial treatment with infliximab plus maintenance treatment for patients achieving 100% fistula closure		117000 GBP
				Placebo		Reference
Clark et al. (2003, UK) Primary economic evaluation [37]	Markov model	Publically-funded health system	Other	Infliximab (5mg/kg) single dose		93244 GBP
				Infliximab (5mg/kg) episodic dose		62016 GBP
				Infliximab (all doses) single dose		135333 GBP
				Infliximab (all doses) episodic		72261 GBP
				Placebo		Reference
Jaisson-Hot et al. (2004, France) [38]	Markov model	Third party payer	Lifetime	Strategy 1a: Initial infliximab infusion plus re-treatment when patients relapse or do not respond	119801.60 (Euros)	63700.82 Euros
				Strategy 1b: Initial infliximab infusion plus maintenance infliximab infusions every 8 weeks	687086.96 (Euros)	784057 Euros
				Strategy 2: Surgery	71296.44 (Euros)	Reference
Priest et al. (2006, NZ) [39‡]	Decision analytic model	Third party payer	1 year	Azathioprine maintenance therapy	972891 (USD)	Azathioprine dominant
				Methotrexate maintenance therapy	1190191 (USD)	
Kaplan et al. (2007, USA) [32]	Decision analytic model	Not clear	1 year	Infliximab dose escalation to 10mg/kg every 8 weeks	28367 (USD)	332032 USD

				Discontinue infliximab and switch to adalimumab induction and maintenance therapy	18074 (USD)	
Lindsay et al. (2008, UK) [40]	Markov model	Publically-funded health system	5 years	Infliximab initial infusions and maintenance treatment	31499 (GBP)	26128 GBP
				Standard care (immunomodulators and/or corticosteroids)	26627 (GBP)	
Lindsay et al. (2008, UK) [40]	Markov model	Publically-funded health system	5 years	Infliximab initial infusions and maintenance therapy	37488 (GBP)	29752 GBP
				Standard care (immunomodulators and/or corticosteroids)	31490 (GBP)	
Bodger et al. (2009, UK) [41]	Markov model	Publically-funded health system	Lifetime	Infliximab infusions for induction of remission followed by maintenance treatment for 1 year	50330 (GBP)	19050 GBP
				Infliximab infusions for induction of remission followed by maintenance treatment for 2 years	58230 (GBP	21300 GBP
				Adalimumab injection for induction of remission followed by maintenance treatment for 1 year	46730 (GBP)	7190 GBP
				Adalimumab injection for induction of remission followed by maintenance treatment for 2 year	53090 (GBP)	10310 GBP
				Standard care (5ASA, immunosuppressive agents, corticosteroids, antibiotics, symptomatic therapies, topical therapies and surgery)	43490 (GBP)	Reference
Loftus et al. (2009, UK) [42]	Decision analytic model	Publically-funded health system	1 year	Adalimumab maintenance therapy injection	10882 (GBP)	16064 GBP

				Non-biologic therapy (based on the CLASSIC I trial: placebo and conventional medications)	8992 (GBP)	Reference
				Adalimumab maintenance therapy injection	9696 (GBP)	33731 GBP
				Non-biologic therapy (based on the CLASSIC I trial: placebo and conventional medications)	6649 (GBP)	
Yu et al. (2009, USA) [43]	Decision analytic model	Third party payer	1 year	Adalimumab maintenance therapy injection	34193 (USD)	Adalimumab dominant
				Infliximab maintenance therapy infusion	39045 (USD)	
Bakhshai et al. (2010, USA) [33]	Decision analytic model	Third party payer	2 years	Natalizumab induction and maintenance infusion	68372 (USD)	Reference
				Infliximab induction and maintenance infusions	62090 (USD)	Dominated by adalimumab
				Adalimumab induction and maintenance injection	61796 (USD)	4059.26 per month of remission
Dretzke et al. (2011, UK) [44]	Markov model	Publically-funded health system	1 year	Standard care	13415 (GBP)	Dominated
				Infliximab induction infusions	12051 (GBP)	Reference
				Infliximab maintenance infusions	19143 (GBP)	5.03 million GBP
				Standard care	13421 (GBP)	Dominated
				Adalimumab induction infusions	7053 (GBP)	Reference
				Adalimumab maintenance infusions	14047 (GBP)	4.98 million GBP
				Standard care	6615 (GBP)	Reference
				Infliximab induction infusions	9573 (GBP)	94321 GBP
				Infliximab maintenance infusions	16751 (GBP)	13.9 million GBP
				Standard care	6615 (GBP)	Dominated
				Adalimumab induction infusions	4583 (GBP)	Reference
				Adalimumab maintenance infusions	11657 (GBP)	13.9 million GBP
Ananthakrishnan et al. (2011, USA) [45]	Decision analytic model	Third party payer	1 year	Antibiotics arm: Metronidazole given post-operatively. No treatment given if patients experience adverse events on metronidazole	2840 (USD)	Reference

				unless disease recurred in which case they received infliximab		
				Azathioprine arm: Azathioprine given post-operatively. No treatment given if patients experience adverse events on azathioprine unless disease recurred in which case they received infliximab induction and maintenance infusions	3218 (USD)	Dominated
				No treatment arm: No treatment given post-operatively. Patients who develop clinical recurrence receive infliximab induction and maintenance infusions	3924 (USD)	Dominated
				Tailored infliximab arm: No treatment post-operatively. Patients receive colonoscopy at 6 months; those at no or mild endoscopic recurrence risk received no treatment and those at high endoscopic recurrence risk receive infliximab induction and maintenance infusions	8030 (USD)	Dominated
				Upfront infliximab arm: Infliximab standard dose maintenance infusions given post-operatively. Patients who do not respond to infliximab receive stop treatment and receive no alternative treatment but switch to azathioprine if disease recurs. Patients who develop disease recurrence while on infliximab receive increased infliximab dose (10mg/kg every 8 weeks).	22145 (USD)	2757857 USD
Ananthakrishnan et al. (2012, USA) [46]	Decision analytic model	Third party payer	1 year	Natalizumab induction and maintenance infusion	51842 (USD)	381,678 USD
				Certolizumab pegol induction and maintenance injection	46314 (USD)	

Blackhouse et al. (2012, Canada) [47]	Markov model	Publically-funded health system	5 years	Infliximab induction and maintenance infusions	54084 (CAD)	222955 CAD
				Adalimumab induction and maintenance injection	45480 (CAD)	193305 CAD
				Usual care: Immunosuppressants and corticosteroids	17107 (CAD)	Reference
				Infliximab strategy vs. Adalimumab strategy		451165 CAD
Doherty et al. (2012, USA) [28]	Monte Carlo simulation	Societal	1 year	Infliximab induction and maintenance infusions	25127 (USD)	831912 USD
				Once daily continuous oral azathioprine	6692 (USD)	299188 USD
				Once daily continuous oral mesalazine	5904 (USD)	Dominated
				No treatment	1957 (USD)	Reference
Tang et al. (2012, USA) [48]	Monte Carlo simulation	Third party payer	1 year	Infliximab induction and maintenance infusions	22686 (USD)	Dominant strategy
				Adalimumab induction and maintenance injection	27561 (USD)	Dominated
				Certolizumab pegol induction and maintenance injection	29158 (USD)	Dominated
				Natalizumab induction and maintenance infusion	31270 (USD)	Dominated
Marchetti et al. (2013, Italy) [49]	Markov model	Third party payer	5 years	Top-down arm: Initial induction infusion with infliximab plus azathioprine, followed by infliximab re-treatment and continued azathioprine if symptom exacerbation occurred and finally methylprednisolone added if necessary	14631 (Euros)	Top-down strategy dominant
				Step up arm: Induction treatment with methylprednisolone, followed by re-treatment with methylprednisolone plus azathioprine if relapse occurred and finally infliximab plus azathioprine added if necessary	15404 (Euros)	

Saito et al. (2013, UK) [50]	Decision analytic model	Publically-funded health system	1 year	Infliximab induction and maintenance infusions plus azathioprine	8573.04 (GBP)	24917 GBP
				Infliximab induction and maintenance infusions monotherapy	6979.68 (GBP)	
Erim et al. (2015, USA) [51]	Markov cohort model	Third party payer	1 year	Adalimumab plus vedolizumab without prior dose increase: Adalimumab induction injections followed by maintenance injections for responders and switch to vedolizumab maintenance infusion for non-responders or patients who lose response	42015 (USD)	Reference
				Adalimumab strategy without dose increase: Adalimumab induction injections and maintenance injections for primary responders	44176 (USD)	Dominated
				Adalimumab plus vedolizumab with prior dose increase: Adalimumab induction injections followed by maintenance injections for primary responders. For patients who do not respond or lose response receive adalimumab maintenance dose intensification (weekly) or switch to vedolizumab induction and maintenance infusion	45588 (USD)	611974 USD
				Adalimumab with dose increase: Adalimumab induction injection followed by adalimumab maintenance therapy every other week for responders and maintenance therapy weekly for non-responders	48245 (USD)	Dominated
Taleban et al. (2016, USA) [52]	Markov model	Third party payer	Lifetime	Total colectomy with ileal pouch anal anastomosis (IPAA)	172263 (USD)	70715 USD
				Total colectomy with permanent end ileostomy (EI)	123411 (USD)	

Rafia et al. (2016, UK) Takeda submission [53]	Markov model	Publically-funded health system	10 year	Mixed population:		
				Vedolizumab induction and maintenance infusion		Reference
				Conventional therapy (5ASA, immunomodulators, and corticosteroids)		62903 GBP
				Anti-TNF failed population:		
				Vedolizumab induction and maintenance infusion		Reference
				Conventional therapy (5ASA, immunomodulators, and corticosteroids)		98452 GBP
				Anti-TNF naive population:		
				Vedolizumab induction and maintenance infusion		Reference
				Conventional therapy (5ASA, immunomodulators, and corticosteroids)		22718 GBP
				Infliximab induction and maintenance infusion		26580 GBP
				Adalimumab induction and maintenance injection		758344 GBP

[*]Conventional therapy/standard of care defined as drug treatment with aminosalicylates, methotrexate, corticosteroids, azathioprine, metronidazole or surgery; standard dosing approved by FDA and EMA applies unless otherwise specified.
[§]Unless otherwise stated, the ICER reports the cost per QALY gained
[‡]The indication in this study is "moderate to severe IBD" however, efficacy data was extracted from studies on CD therefore it is assumed that this model reflects the cost-effectiveness for patients with CD. This lack of clarity is captured in the risk of bias assessment.

Table A3 Descriptive data and original costs extracted from studies on Ulcerative Colitis

Reference (year, country)	Model type	Perspective	Time horizon	Interventions & comparators*	Cost (currency)	ICER (cost per outcome gained)§
Panes et al. (2007, Spain) [31]	Decision analytic model	Third party payer	1 year	Induction treatment with prednisone followed by 5-ASA maintenance therapy for patients in remission or azathioprine for non-responders	6059 (Euros)	23898 Euros
				Induction treatment with prednisolone followed by 5-ASA maintenance therapy for patients in remission or granulocyte manocyte adsorptive (GMA)-apheresis for non-responders	11436 (Euros)	
Buckland et al. (2008, UK) [54]	Decision analytic model	Publically-funded health system	12 weeks	Induction therapy using high dose mesalazine (4.8g/day)	2382 (GBP)	High dose dominant
				Induction therapy using standard dose mesalazine (2.4g/day)	2474 (GBP)	
Tsai et al. (2008, UK) [92]	Markov model	Publically-funded health system	10 years	Patients responding to initial infliximab infusions: Maintenance infliximab infusions	66460 (GBP)	27424 GBP
				Standard care	45798 (GBP)	
				Patients in remission after initial infliximab infusions: Maintenance infliximab infusions	53874 (GBP)	19696 GBP
				Standard care	46259 (GBP)	
Yen et al. (2008, USA) [56]	Markov model	Third party payer	2 years	No maintenance 5ASA: 5-ASA 4.8g/day given during a flare and stopped once remission achieved	3304 (USD)	224000 USD
				Maintenance 5ASA: 5-ASA 2.4g/day given for maintenance treatment and escalated to 4.8g/day after first flare to induce and maintain remission	7951 (USD)	

Connolly et al. (2009a, UK) [57]	Decision analytic model	Publically-funded health system	1 year	Once daily mesalazine maintenance therapy	815 (GBP)	Once daily mesalazine is dominant
				Twice daily mesalazine maintenance therapy	971 (GBP)	
Connolly et al. (2009b, UK) [58]	Markov model	Publically-funded health system	Not stated	Induction treatment with topical mesalazine plus oral mesalazine combination	1812 (GBP)	Combination therapy dominant
				Induction treatment with oral mesalazine monotherapy	2390 (GBP)	
Xie et al. (2009, Canada) [59]	Markov model	Publically-funded health system	5 years	Strategy A: Standard care (5-ASA or immunosuppressants)	24268 (CAD)	Reference
				Strategy B: Infliximab induction infusions followed by infliximab maintenance infusions if patient responds. If no response or response lost during maintenance therapy, then switch to adalimumab induction and maintenance injections. If still no response or if response is lost switch to surgery.	82756 (CAD)	358088 CAD
				Strategy C: Infliximab induction infusions followed by infliximab maintenance infusions if patient responds. If no response, escalate dose to 10mg/kg infliximab maintenance infusions. If still no response or response is lost switch to adalimumab induction and maintenance injections	101272 (CAD)	575540 CAD
Brereton et al. (2010, UK) [60]	Markov cohort model	Publically-funded health system	5 years	5 year model: Induction and maintenance treatment with MMX mesalazine (1200mg tablets once a day)	5582 (GBP)	749 GBP
				5 year model: Induction and maintenance treatment with Mesalazine (400mg tablets two to three times a day)	5574 (GBP)	

				Lifetime model: Induction and maintenance treatment with MMX Mesalazine (1200mg tablets once a day)	21668 (GBP)	7600 GBP
				Lifetime model: Induction and maintenance treatment with Mesalazine (400mg tablets two to three times a day)	21375 (GBP)	
Punekar et al. (2010, UK) [61]	Decision analytic model	Publically-funded health system	1 year	Cyclosporine: IV cyclosporine plus IV hydrocortisone. If patient responds, switch to oral cyclosporine plus oral prednisolone and azathioprine. For non-responders, switch to surgery	18122 (GBP)	Reference
				Colectomy: 71% of patients receive illeostomy and 29% of patients receive ileal pouch anal anastomosis (IPAA)	17067 (GBP)	9,032 GBP
				Standard care: Continue IV hydrocortisone for 7 days. If patient responds, switch to oral prednisolone and azathioprine. For non-responders, switch to surgery.	18524 (GBP)	Dominated
				Infliximab: Infliximab induction infusions plus IV hydrocortisone. If patient responds, receive two more infliximab infusions plus prednisolone and azathioprine. For non-responders, switch to surgery	19847 (GBP)	18388 GBP
Prenzler et al. (2011, Germany) [62]	Markov model	Third party payer	5 years	MMX mesalazine (2400mg/day) induction and maintenance therapy for patients who respond. For non-responders, increase dose to 4800mg/day and if still no response add oral corticosteroids. If still no response or relapse, patient receives immunosuppressants and/or IV steroids and surgery if medical treatment continues to fail.	4940 (Euros)	MMX is dominant
				Mesalazine (2400mg/day) induction and maintenance therapy for patients who	5564 (Euros)	

				respond. For non-responders, increase dose to 4800mg/day and if still no response add oral corticosteroids. If still no response or relapse, patient receives immunosuppressants and/or IV steroids and surgery if medical treatment continues to fail.		
Connolly et al. (2012, Netherlands) [63]	Decision analytic model	Publically-funded health system	1 year	Induction treatment with topical mesalazine combined with oral mesalazine	2207 (Euros)	Combination therapy is dominant
				Induction treatment with oral mesalazine monotherapy	2945 (Euros)	
				Maintenance treatment with once daily mesalazine	1293 (Euros)	Once daily mesalazine is dominant
				Maintenance treatment with twice daily mesalazine	1502 (Euros)	
Park et al. (2012, USA) [29]	Markov model	Societal	Lifetime	Standard medical therapy: IV methylprednisolone followed by mesalazine maintenance treatment for responders; if response lost during maintenance therapy switch to azathioprine. For methylprednisolone non-responders switch to infliximab induction infusions and maintenance infusions for responders. For infliximab non-responders, switch to tacrolimus. If all medical therapies fail, switch to colectomy with IPAA.	236370 (USD)	1476783 USD
				Early colectomy with IPAA: Subtotal colectomy and laparoscopic IPAA given after initial hospitalisation followed by medical treatment for patients with acute or chronic pouchitis.	147763 (USD)	

Saini et al. (2012, USA) [64]	Markov cohort model	Third party payer	5 years	Inflammation-targeted treatment: Patients receive predictive stool testing every 3 months and those with positive test treated with 3-month course of 5-ASA	22798 (USD)	Reference
				Symptom-targeted treatment: 5-ASA used for symptomatic disease flares	24378 (USD)	575894 USD
				Continuous maintenance treatment: 5-ASA maintenance therapy for all patients in remission	25621 (USD)	Dominated
Chaudhary et al. (2013, Netherlands) [65]	Markov model	Third party payer	1 year	Infliximab induction infusions followed by infliximab plus azathioprine and oral steroids for responders. Maintenance treatment continued with azathioprine and oral steroids for responders.Non-responders or patients who lose response switch to surgery.	17062 (Euros)	Reference
				IV cyclosporine followed by oral cyclosporine plus azathioprine and oral steroids for responders. Maintenance treatment continued with azathioprine and oral steroids for responders. Non-responders or patients who lose response switch to surgery.	14784 (Euros)	24277 Euro
				Surgery with no concomitant medication use	13979 (Euros)	14639 Euro
Connolly et al. (2014, Netherlands) [66]	Markov model	Publically-funded health system	32 weeks	Induction therapy with once daily mesalazine	3097 (Euros)	Once daily mesalazine is dominant
				Induction therapy with twice daily mesalazine	3548 (Euros)	
Essat et al. (2014, UK) Takeda submission [67]	Markov model	Publically-funded health system	10 years	*Whole population (patients who received anti-TNF inhibitor and those who did not):*		
				Conventional therapies: Combination of aminosalicylates, immunomodulators and corticosteroids	Unknown	33297 GBP

				Surgery: 40% of patients have illeostomy and 60% have subtotal proctocolectomy		Dominated
				Vedolizumab: Induction infusions of vedolizumab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy		Reference
				Anti-TNF alpha naive patients:		
				Conventional therapies (combination of aminosalicylates, immunomodulators and corticosteroids)	Unknown	4862 GBP
				Surgery: 40% of patients have illeostomy and 60% have subtotal proctocolectomy		Dominated
				Infliximab: Induction infusions of infliximab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy		Dominated
				Adalimumab: Induction injections of adalimumab followed by maintenance injections for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy		66634 GBP
				Golimumab: Induction injections of golimumab followed by maintenance injections for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy		Dominated

				Vedolizumab: Induction infusions of vedolizumab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy		Reference
				Patients who failed TNF-alpha inhibitors:		
				Conventional therapies: Combination of aminosalicylates, immunomodulators and corticosteroids	Unknown	64999 GBP
				Surgery: 40% of patients have illeostomy and 60% have subtotal proctocolectomy		Dominated
				Vedolizumab: Induction infusions of vedolizumab followed by maintenance infusions for responders. For non-responders switch to surgery. For patients who discontinue biologic treatment switch to conventional therapy		Reference
Archer et al. (2016, UK) MSD Submission [68]	Markov model	Publically-funded health system	10 years	Infliximab induction infusions followed by maintenance infusions for responders. For non-responders, switch to relapse management with IV steroids. For patients who fail IV steroids switch to colectomy.	44382.28 (GBP)	80316 GBP
				Golimumab induction injections followed by maintenance injections for responders. For non-responders, switch to relapse management with IV steroids. For patients who fail IV steroids switch to colectomy.	31378.68 (GBP)	27994 GBP
				Adalimumab induction injections followed by maintenance injections for responders. For non-responders, switch to relapse management with IV steroids. For patients who fail IV steroids switch to colectomy.	32096.50 (GBP)	Dominated

				Immediate colectomy	15767.78 (GBP)	Reference
Archer et al. (2016, UK) Abbvie Submission [68]	Markov model	Publically-funded health system	10 years	Adalimumab induction and maintenance injections for patients who respond. For non-responders, dose escalation to 40mg every week and switch to conventional therapies if still no response. For non-responders to conventional treatments, switch to surgery.	76392 (GBP)	34417 GBP
				Conventional therapies: Anti-inflammatory drugs or immunosuppressants). For non-responders, switch to colectomy	50946 (GBP)	
Beilman et al. (2016, Canada) [69]	Markov model	Publically-funded health system	10 years	No adalimumab: Patients receive no treatment and remain in chronically unwell state to avoid colectomy	97000 (CAD)	59000 CAD
				Adalimumab therapy: Adalimumab induction injections and maintenance injections for responders. For non-responders, switch to steroid therapy.	107000 (CAD)	
Stawowczyk et al. (2016, Poland) [70]	Markov model	Societal	Lifetime	Public payer perspective: Golimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and colectomy if failure persists. Maintenance treatment with golimumab restricted to 1 year.	93321 (PLN)	391252 PLN
				Public payer perspective: Standard care alone induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	45502 (PLN)	
				Societal perspective: Golimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and colectomy if	302848 (PLN)	374377 PLN

				failure persists. Maintenance treatment with golimumab restricted to 1 year.		
				Societal perspective: Standard care alone induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	257092 (PLN)	
Stawowczyk et al. (2016, Poland) [71]	Markov model	Societal	Lifetime	Public payer perspective: Adalimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and colectomy if failure persists. Maintenance treatment with golimumab restricted to 1 year.	20598 (Euros)	76120 Euros
				Public payer perspective: Standard care alone induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	9950 (Euros)	
				Societal perspective: Adalimumab and standard care combination induction treatment followed by maintenance treatment for responders. For non-responders, switch to standard care alone and colectomy if failure persists. Maintenance treatment with golimumab restricted to 1 year.	93765 (Euros)	71457 Euros
				Societal perspective: Standard care alone induction and maintenance treatment regardless of response. If disease remains active, switch to colectomy.	83770 (Euros)	
Stawowczyk et al. (2016, Poland) [72]	Markov model	Societal	Lifetime	Infliximab and standard care combination: Infliximab plus standard care induction infusions followed by maintenance therapy for responders. For non-responders, switch to adalimumab induction injections and	99522 (PLN)	402420 PLN

				maintenance injections for responders. For non-responders to adalimumab, switch to conventional therapy alone or colectomy.		
				Standard care alone: Standard care induction and maintenance treatment. If disease remains active, switch to colectomy.	29642 (PLN)	
Tappenden et al. (2016, UK) [73]	Markov model	Publically-funded health system	Lifetime	*Patients in whom surgery is an option:*		
				Colectomy	56268 (GBP)	Reference
				Adalimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	91222 (GBP)	Dominated
				Infliximab induction infusions followed by maintenance infusions for responders. For non-responders, switch to conventional therapy.	96595 (GBP)	Dominated
				Golimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	90087 (GBP)	Dominated
				Conventional treatment for induction and maintenance phases (includes 5-asas, azathioprine, 6-mercaptopurine, prednisolone)	73620 (GBP)	Dominated
				Patients in whom surgery is not an option:		
				Adalimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	91222 (GBP)	50728 GBP
				Infliximab induction infusions followed by maintenance infusions for responders. For	96595 (GBP)	Extendedly dominated

				non-responders, switch to conventional therapy.		
				Golimumab induction injections followed by maintenance injections for responders. For non-responders, switch to conventional therapy.	90087 (GBP)	Extendedly dominated
				Conventional treatment for induction and maintenance phases (includes 5-asas, azathioprine, 6-mercaptopurine, prednisolone)	73620 (GBP)	Reference
Yokomizo et al. (2016, USA) [34]	Decision analytic model	Third party payer	1 year	Infliximab 5mg/kg induction and maintenance infusions	Unknown	99171 USD per MH achieved
				Infliximab 10mg/kg induction and maintenance infusions		123653 USD per MH achieved
				Adalimumab induction and maintenance injections		316378 USD per MH achieved
				Vedolizumab induction and maintenance infusions		301969 USD per MH achieved
Wilson et al. (2017, UK) [74]	Markov model	Publically funded health system	Lifetime	Vedolizumab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to another combination of conventional therapies or surgery.	199431.15 GBP	Reference
				Infliximab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to	206065.90 GBP	Dominated

				another combination of conventional therapies or surgery.		
				Adalimumab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to another combination of conventional therapies or surgery.	194764.73 GBP	22775 GBP
				Golimumab induction infusions followed by maintenance infusions for responders. For non-responders, patients who lose response, or patients who discontinue due to adverse events, switch to conventional therapy. If no response to conventional therapy, switch to another combination of conventional therapies or surgery.	200018.31 GBP	Dominated

*Conventional therapy/standard of care defined as drug treatment with aminosalicylates, methotrexate, corticosteroids, azathioprine, metronidazole or surgery; standard dosing approved by FDA and EMA applies unless otherwise specified.
§Unless otherwise stated, the ICER reports the cost per QALY gained

Risk of bias assessments

Table A4 Risk of bias assessment for studies on Crohn's Disease using Drummond et al. (1996) and Phillips et al. (2004) checklists

	Reference	Tralori (1997)	Arsenau et al. (2001)	Marshall (2002)	Clark et al (2003): Manufacturer's active model	Clark et al (2003): (Manufacturers fistulising model	Clark et al. (2003) : Original model	Jaisson-Hot et al. (2004)	Priest et al. (2006)	Kaplan et al. (2007)	Lindsay et al. (2008)	Bodger et al. (2009)	Loftus et al. (2009)	Yu et al. (2009)	Bakhshai et al. (2010)	Ananthakrishnan et al. (2011)	Dretzke et al. (2011)	Ananthakrishnan et al. (2012)	Blackhouse et al. (2012)	Doherty et al. (2012)	Tang et al. (2012)	Marchetti et al. (2013)	Saito et al. (2013)	Erim et al. (2015)	Rafia (2016)	Taleban et al. (2016)
	Drummond et al. (1996) checklist																									
	Study design																									
1	The research question is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	The economic importance of the research question is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	The viewpoint(s) of the analysis are clearly stated and justified.	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

4	The rationale for choosing alternative programmes or interventions compared is stated.	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	The alternatives being compared are clearly described.	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	The form of economic evaluation used is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Data collection																									
8	The source(s) of effectiveness estimates used are stated.	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Details of the design and results of effectiveness study are given (if based on a single study).	N	NA	N	NA	NA	N	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA	NA
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	N	Y	NA	N	N	NA	NA	N	N	N	Y	N	Y	N	N	Y	N	N	N	N	NA	N	N	Y	N

11	The primary outcome measure(s) for the economic evaluation are clearly stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Methods to value benefits are stated.	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
13	Details of the subjects from whom valuations were obtained were given.	N	Y	N	Y	N	N	Y	Y	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
14	Productivity changes (if included) are reported separately.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA	NA	NA	NA	N	NA	NA	NA	NA	NA	NA	NA
15	The relevance of productivity changes to the study question is discussed.	N	Y	Y	N	N	N	Y	N	N	Y	N	Y	Y	N	N	N	N	Y	N	N	Y	N	Y	N	N
16	Quantities of resource use are reported separately from their unit costs.	N	Y	N	N	N	N	N	N	N	Y	N	N	Y	N	N	Y	N	Y	N	N	Y	N	N	N	N
17	Methods for the estimation of quantities and unit costs are described.	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
18	Currency and price data are recorded.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19	Details of currency of price adjustments for inflation or currency conversion are given.	N	N	N	N	N	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	Y	Y	Y	NA
20	Details of any model used are given.	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

21	The choice of model used and the key parameters on which it is based are justified.	N	Y	Y	N	N	N	N	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Analysis and interpretation of results																									
22	Time horizon of costs and benefits is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
23	The discount rate(s) is stated.	Y	Y	NA	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y
24	The choice of discount rate(s) is justified.	Y	N	Y	N	N	N	N	Y	N	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N	N	Y	Y	N
25	An explanation is given if costs and benefits are not discounted.	NA	NA	Y	NA	NA	N	NA	Y	N	NA	NA	NA	Y	N	N	NA	N	NA	Y	Y	NA	N	Y	NA	NA
26	Details of statistical tests and confidence intervals are given for stochastic data.	NA	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
27	The approach to sensitivity analysis is given.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
28	The choice of variables for sensitivity analysis is justified.	N	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	N	N	Y	N	N	N	N	N	N	N	N	Y
29	The ranges over which the variables are varied are justified.	N	N	Y	Y	Y	N	Y	N	Y	N	N	Y	Y	N	N	Y	N	N	Y	N	N	N	Y	N	N
30	Relevant alternatives are compared.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	N	Y	Y
31	Incremental analysis is reported.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y

32	Major outcomes are presented in a disaggregated as well as aggregated form.	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	NA	Y
33	The answer to the study question is given.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
34	Conclusions follow from the data reported.	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
35	Conclusions are accompanied by the appropriate caveats.	Y	Y	Y	NA	NA	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
	Phillips et al. (2004) Checklist																									
	Statement of decision problem/objective																									
1	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Is the primary decision-maker specified?	N	N	Y	N	N	N	N	Y	N	N	N	Y	N	N	N	Y	N	Y	N	N	N	Y	N	Y	N
	Statement of scope/perspective																									
4	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

5	Are the model inputs consistent with the stated perspective?	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
6	Has the scope of the model been stated and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Rationale for structure																									
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
9	Are the sources of data used to develop the structure of the model specified?	N	Y	Y	N	N	N	Y	Y	N	N	Y	N	N	N	N	Y	N	N	N	Y	Y	N	N	Y	Y
10	Are the causal relationships described by the model structure justified appropriately?	N	N	Y	N	N	N	N	N	N	Y	Y	NA	N	N	Y	Y	Y	Y	Y	Y	N	Y	N	NA	N
	Structural assumptions																									
11	Are the structural assumptions transparent and justified?	N	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	N	Y	Y
12	Are the structural assumptions reasonable given the	NA	Y	Y	N	N	Y	N	N	N	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	N	N	N	N	N	Y

	overall objective, perspective and scope of the model?																									
	Strategies/comparators																									
13	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14	Have all feasible and practical options been evaluated?	Y	Y	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	Y	N	N	N	N	N	Y	Y
15	Is there justification for the exclusion of feasible options?	NA	NA	N	N	N	N	N	N	N	N	Y	N	N	N	N	NA	Y	NA	N	N	N	N	N	NA	NA
	Model type																									
16	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Not clear	N	N	N	Y	N	Y	N	N	Y	N	Y	Y	Y
	Time horizon																									
17	Is the time horizon of the model sufficient to reflect all important differences between options?	Y	N	N	Y	N	N	Y	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	Y	Y
18	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Y	Y	Y	N	N	N	N	Y	Y	N	Y	Y	Y	N	N	Y	N	N	N	N	Y	Y	Y	Y	N

	Disease states/pathways																								
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
	Cycle length																									
20	Is the cycle length defined and justified in terms of the natural history of disease?	N	Y	Y	N	N	N	Y	N	N	Y	Y	NA	NA	NA	N	Y	N	Y	N	N	Y	N	Y	Y	Y
	Data identification																									
21	Are the data identification methods transparent and appropriate given the objectives of the model?	N	N	Y	N	N	N	N	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	N	N	N	N
22	Where choices have been made between data sources, are these justified appropriately?	N	N	N	N	NA	N	N	N	N	N	Y	NA	N	N	N	Y	N	N	N	N	NA	N	N	NA	N
23	Has particular attention been paid to identifying data for the important parameters in the model?	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y

24	Has the quality of the data been assessed appropriately?	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N
25	Where expert opinion has been used, are the methods described and justified?	Y	N	Y	N	NA	NA	N	N	NA	NA	NA	NA	NA	NA	NA	Y	NA	N	N	NA	NA	N	NA	NA	Y
	Data modelling																									
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Baseline data																									
27	Is the choice of baseline data described and justified?	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
28	Are transition probabilities calculated appropriately?	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
29	Has a half-cycle correction been applied to both cost and outcome? If not, has this omission been justified?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y
	Treatment effects																									
30	If relative treatment effects have been derived from trial data, have they been synthesised using	NA	Y	Y	N	N	N	NA	N	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	NA	N	N	Y	N

	appropriate techniques?																								
31	Have the methods and assumptions used to extrapolate shortterm results to final outcomes been documented and justified?	NA	N	N	N	NA	N	N	NA	N	N	Y	Y	N	Y	N	N	N	N	N	N	N	N	N	N
32	Have alternative assumptions been explored through sensitivity analysis?	Y	N	N	Y	N	Y	N	N	Y	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N
33	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? Have alternative assumptions been explored through sensitivity analysis?	N	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
	Costs																								
34	Are the costs incorporated into the model justified?	N	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
35	Has the source for all costs been described?	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
36	Have discount rates been described and	Y	Y	NA	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Y

	justified given the target decision-maker?																								
	Quality of life weights (utilities)																								
37	Are the utilities incorporated into the model appropriate?	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
38	Is the source for the utility weights referenced?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
39	Are the methods of derivation for the utility weights justified?	N	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	NA	N	Y	N	Y	Y	N	Y	Y	N	Y	N
	Data incorporation																									
40	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	N	Y	N	N	N	N	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
41	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	N	Y	N	N	N	N	N	N	Y	N	Y	N	N	N	Y	Y	N	Y	Y	N	N	Y	N	N	Y
42	Is the process of data incorporation transparent?	N	Y	Y	N	N	N	N	N	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	NA	Y
43	If data have been incorporated as distributions, has the choice of distribution for each parameter	NA	NA	Y	NA	NA	NA	NA	NA	NA	NA	N	Y	Y	NA	NA	NA	NA	NA	NA	Y	Y	N	NA	NA	NA

	been described and justified?																								
44	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	NA	N	NA	NA	NA	NA	NA	NA	NA	N	N	N	NA	NA	NA	NA	NA	NA	Y	Y	N	NA	NA	NA
	Assessment of uncertainty																									
45	Have the four principal types of uncertainty been addressed?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N
46	If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	NA	N	N	N	N	N	N	N
	Methodological																									
47	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	Y	Y	N	N	N	N	NA	N
	Structural																									
48	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	NA	N
	Heterogeneity		N																							

49	Has heterogeneity been dealt with by running the model separately for different subgroups?	N		N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Parameter																								
50	Are the methods of assessment of parameter uncertainty appropriate?	N	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	NA	N	Y	N	Y	Y	Y	Y	Y	Y	NA	Y
51	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	N	Y	Y	N	N	N	N	N	N	N	N	N	Y	NA	N	Y	N	N	Y	N	N	N	Y	NA	Y
	Internal consistency																								
52	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	Y	N	N	N	Y	N
	External consistency																								
53	Are any counterintuitive results from the model explained and justified?	N	NA	Y	N	N	N	N	Y	NA	NA	Y	N	Y	N	Y	Y	NA	Y	Y	Y	NA	Y	NA	NA	NA
54	If the model has been calibrated against independent data, have any differences been	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	explained and justified?																									
55	Have the results of the model been compared with those of previous models and any differences in results explained?	N	N	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	N

Table A5 Risk of bias assessment for studies on Ulcerative Colitis using Drummond et al. (1996) and Phillips et al. (2004) checklists

	Reference	Panes et al. (2007)	Buckland & Bodger (2008)	Yen et al. (2008)	Tsai et al. (2008)	Connolly et al. (a) (2009)	Connolly et al. (b) (2009)	Xie et al. (2009)	Brereton et al. (2010)	Punekar et al. (2010)	Prenzler et al. (2011)	Connolly et al. (2012)	Park et al. (2012)	Saini et al. (2012)	Chaudhary & Fan (2013)	Connolly et al. (2014)	Essat (2014)	Archer et al. (2014): MSD model	Archer et al. (2014) : AbbVie model	Beilman et al. (2016)	Stawowczyk et al. (2016): Golimumab	Stawowczyk et al. (2016): Adalimumab	Stawowczyk et al. (2016): Infliximab	Yokomizo et al. (2016)	Tappenden et al. (2016)	Wilson et al. (2017)
	Drummond et al. (1996) checklist																									
	Study design																									
1	The research question is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	The economic importance of the research question is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	The viewpoint(s) of the analysis are clearly stated and justified.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	The rationale for choosing alternative programmes or interventions compared is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	The alternatives being compared are clearly described.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

6	The form of economic evaluation used is stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Data collection																										
8	The source(s) of effectiveness estimates used are stated.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
9	Details of the design and results of effectiveness study are given (if based on a single study).	NA	NA	N	NA	Y	N	NA	NA	NA	NA	N	NA	NA	NA	Y	Y	NA	NA	NA	NA	Y	Y	Y	NA	NA	
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	N	Y	N	N	NA	NA	Y	N	Y	N	NA	Y	N	N	NA	NA	Y	Y	N	N	NA	NA	NA	Y	Y	
11	The primary outcome measure(s) for the economic evaluation are clearly stated.	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
12	Methods to value benefits are stated.	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	
13	Details of the subjects from whom valuations were obtained were given.	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
14	Productivity changes (if included) are reported separately.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	Y	NA	NA	NA	
15	The relevance of productivity changes to the study question is discussed.	N	N	N	Y	Y	N	N	N	Y	N	Y	N	N	Y	N	N	N	N	Y	Y	Y	N	N	N	N	

16	Quantities of resource use are reported separately from their unit costs.	Y	N	N	Y	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	Y
17	Methods for the estimation of quantities and unit costs are described.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
18	Currency and price data are recorded.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19	Details of currency of price adjustments for inflation or currency conversion are given.	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	N	N	N	N	Y	Y	Y	N	Y	Y
20	Details of any model used are given.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
21	The choice of model used and the key parameters on which it is based are justified.	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Analysis and interpretation of results																									
22	Time horizon of costs and benefits is stated.	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
23	The discount rate(s) is stated.	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
24	The choice of discount rate(s) is justified.	Y	N	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y
25	An explanation is given if costs and benefits are not discounted.	Y	N	Y	NA	N	N	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA	NA	NA	NA	NA	N	NA	NA
26	Details of statistical tests and confidence intervals are given for stochastic data.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
27	The approach to sensitivity analysis is given.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
28	The choice of variables for sensitivity analysis is justified.	N	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	Y	N	N	N	Y	N	N	N	N	N	N	Y	N

29	The ranges over which the variables are varied are justified.	N	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	Y	Y
30	Relevant alternatives are compared.	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	N	N	N	N	N	Y	Y
31	Incremental analysis is reported.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
32	Major outcomes are presented in a disaggregated as well as aggregated form.	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
33	The answer to the study question is given.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
34	Conclusions follow from the data reported.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	Y	Y	Y	Y	Y	Y	Y
35	Conclusions are accompanied by the appropriate caveats.	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	Y	Y	Y	Y	Y	Y	Y
	Phillips et al. (2004) Checklist																									
	Statement of decision problem/objective																									
1	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Is the primary decision-maker specified?	N	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	Y	N	N	N	N	N	Y	Y
	Statement of scope/perspective																									
4	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Are the model inputs consistent with the stated perspective?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

6	Has the scope of the model been stated and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	Rationale for structure																										
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
9	Are the sources of data used to develop the structure of the model specified?	N	N	Y	N	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	N	N	N	N	Y	Y	Y
10	Are the causal relationships described by the model structure justified appropriately?	N	N	N	N	Y	N	Y	Y	N	Y	N	N	Y	N	N	NA	N	N	N	Y	Y	Y	N	Y	Y	Y
	Structural assumptions																										
11	Are the structural assumptions transparent and justified?	N	N	Y	N	N	N	Y	N	N	N	N	N	Y	Y	N	Y	N	N	N	Y	Y	Y	N	Y	N	Y
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	N	N	Y	N	N	N	Y	NA	N	NA	NA	N	Y	Y	NA	Y	N	N	N	N	N	Y	N	Y	Y	Y
	Strategies/comparators																										
13	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14	Have all feasible and practical options been evaluated?	N	N	Y	N	Y	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	N	N	N	N	N	N	Y	Y	Y

15	Is there justification for the exclusion of feasible options?	N	N	NA	N	Y	Y	NA	Y	NA	Y	NA	NA	Y	NA	Y	NA	N	N	N	N	N	N	N	Y	NA
	Model type																									
16	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y
	Time horizon																									
17	Is the time horizon of the model sufficient to reflect all important differences between options?	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y	Y	Y	N	Y	Y
18	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	N	N	N	N	N	N	Y	Y	Y	N	Y	Y
	Disease states/pathways																									
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Cycle length																									
20	Is the cycle length defined and justified in terms of the natural history of disease?	NA	NA	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
	Data identification																									

21	Are the data identification methods transparent and appropriate given the objectives of the model?	N	N	Y	N	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	N	N	N	Y	N	Y	Y	Y
22	Where choices have been made between data sources, are these justified appropriately?	N	N	Y	N	NA	NA	N	NA	N	Y	NA	N	N	N	NA	NA	N	NA	NA	NA	NA	N	NA	NA	NA
23	Has particular attention been paid to identifying data for the important parameters in the model?	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	NA	N	Y	Y	Y	Y	Y	Y
24	Has the quality of the data been assessed appropriately?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N
25	Where expert opinion has been used, are the methods described and justified?	N	Y	N	NA	NA	NA	NA	NA	N	NA	NA	N	NA	NA	NA	NA	N	NA	Y	N	N	N	NA	N	N
	Data modelling																									
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Baseline data																									
27	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
28	Are transition probabilities calculated appropriately?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
29	Has a half-cycle correction been applied to both cost and outcome? If not, has this omission been justified?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Treatment effects																									

30	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
31	Have the methods and assumptions used to extrapolate shortterm results to final outcomes been documented and justified?	NA	NA	Y	Y	NA	NA	N	N	N	N	NA	N	N	NA	N	N	N	N	N	N	NA	N	Y	N	N
32	Have alternative assumptions been explored through sensitivity analysis?	Y	Y	Y	Y	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
33	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? Have alternative assumptions been explored through sensitivity analysis?	NA	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y
	Costs																									
34	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
35	Has the source for all costs been described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
36	Have discount rates been described and justified given the target decision-maker?	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
	Quality of life weights (utilities)																									
37	Are the utilities incorporated into the model appropriate?	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	NA	Y	N

38	Is the source for the utility weights referenced?	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA	Y	Y
39	Are the methods of derivation for the utility weights justified?	NA	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Y	N	N	N	N	N	Y	Y	Y	NA	Y	N
	Data incorporation																									
40	Have all data incorporated into the model been described and referenced in sufficient detail?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y
41	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	N	N	Y	N	N	N	Y	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	Y	Y	Y
42	Is the process of data incorporation transparent?	N	N	Y	N	N	N	Y	Y	Y	N	N	N	N	Y	N	NA	N	N	N	Y	Y	Y	Y	Y	Y
43	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	NA	NA	NA	NA	N	NA	Y	NA	N	NA	NA	N	NA	NA	N	NA	NA	NA	NA	NA	NA	NA	NA	N	NA
44	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	NA	NA	NA	Y	NA	Y	NA	N	NA	NA	N	NA	NA	N	NA	NA	NA	NA	NA	NA	NA	NA	N	NA
	Assessment of uncertainty																									
45	Have the four principal types of uncertainty been addressed?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
46	If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Methodological																									

47	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	N	N	Y	Y	Y	Y	Y	N	N	N	Y	N	N	Y	N	Y	N	N	N	N	N	N	N	N	N
	Structural																									
48	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	Y	N	N	Y	Y	Y	N	N	N	N	N	N	Y	N	N	Y	Y	Y	Y	N	Y	Y
	Heterogeneity																									
49	Has heterogeneity been dealt with by running the model separately for different subgroups?	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	Y	N
	Parameter																									
50	Are the methods of assessment of parameter uncertainty appropriate?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
51	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	NA	N	N	Y	Y	Y	Y	Y	Y	Y
	Internal consistency																									
52	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y
	External consistency																									

53	Are any counterintuitive results from the model explained and justified?	NA	NA	NA	NA	NA	NA	Y	Y	NA	NA	NA	NA	Y	NA	Y	NA	NA	NA	N	NA	NA	NA	Y	NA	NA
54	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	NA	NA	NA	NA	NA	NA
55	Have the results of the model been compared with those of previous models and any differences in results explained?	Y	N	N	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	NA	NA	NA	N	Y	Y	Y	N	Y	Y

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Table A6 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	29
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16 (CD); 20-27 (UC)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	S3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	30
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	31
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A
Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Plos Med 6(7): e1000097. Doi:10.1371/journal.pmed1000097			

SUPPLEMENTARY FILES B: CHAPTER 3

Unit cost estimates

Table B1 Inpatient stays, surgical procedures and outpatient imaging scans and consultations considered in the cost analysis with mean (min-max) unit costs (euros) derived from reimbursement claims data and inflated to 2017 prices

	Mean (Min, Max) cost per procedure (euros)
Inpatient procedures	
Adhesiolysis	18,483 (10,971, 29,285)
Appendectomy	13,074 (7386, 21,210)
Cholecystecomy	22,466 (6916, 33,921)
Colostomy	20,688 (12,565, 29,521)
Fistulectomy, fistula plug	11,667 (7227, 19,806)
General hospitalisation (per day)	1375 (337, 3491)
Hemicolectomy	19,911 (15,004, 35,245)
Ileal resection	18,128 (4904, 33,705)
Ileo-cecal resection	24,000 (6394, 50,461)
Ileostomy	21,197 (14,582, 26,963)
Proctectomy	24,102 (19,261, 35,329)
Seton placement, abscess drainage	10,197 (5787, 17,185)
Sigmoid resection	18,537 (11,592, 30,402)
Subtotal colectomy	22,542 (5908, 34,009)
Total proctocolectomy	20,178 (13,294, 31,857)
Outpatient procedures	
CT scan	404 (311, 488)
Colonoscopy	437 (219, 548)
MRI scan	531 (388, 668)
Ultrasonography	84 (65, 109)
Sigmoidoscopy	181 (143, 224)
Endoscopy	307 (226, 398)
GP consultation	50 (41, 71)
Gastroenterologist consultation	66 (49, 93)
Ambulatory outpatient visit	89 (71, 129)
Biologic agent infusion	86 (61, 113)

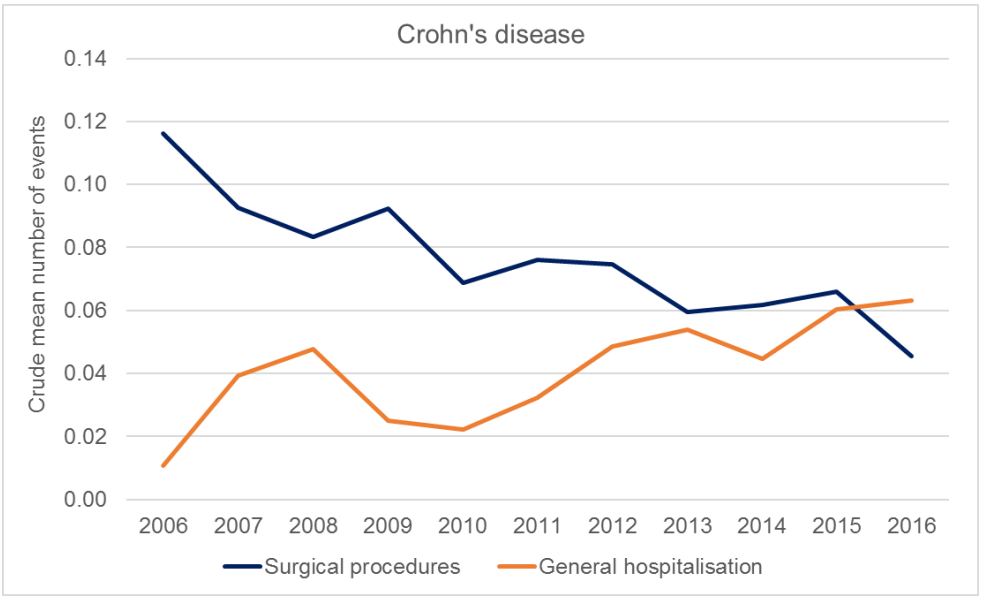
Table B2 All pharmaceuticals considered in the cost analysis with mean unit costs (euros) per dose obtained from 2017 public price lists in Switzerland and dose recommendations based on Swiss clinical guidelines

Drug name	Mean cost per dose (euros)[‡]	Recommended dose[§]
Sulfasalazine	3.00	6g/day
Oral 5-ASA	6.00	4g/day
Topical 5-ASA	3.00	1g/day
6-Mercaptopurine	7.00	1-1.5mg/kg/day
Azathioprine	2.00	2-2.5mg/kg/day
Cyclosporine	28.00	4-8 mg/kg/day
Methotrexate	53.00	25mg per week (induction dose); 15mg per week (maintenance dose)
Tacrolimus	42.00	0.025mg/kg 2x per day
Metronidazole	3.00	750-1500mg/day
Ciprofloxacin	5.00	1000mg/day
Clarithromycin	4.00	500mg/day
Prednisolone	2.00	0.5-0.75 mg/kg/day
Methylprednisone	8.00	1mg/kg/day
Deflazacort	2.00	1mg/kg/day for up to 2 months
Budesonide	6.00	9mg/day
Certolizumab pegol	1208.00	400mg at weeks 0, 2 and 4; 400mg every 4 weeks
Infliximab	2191.00	5mg/kg at weeks 0, 2 and 6; 5mg/kg every 8 weeks
Ustekinumab	34,586.00 (520mg) 5986.00 (90mg)	520mg at week 0; then 90mg at week 8; then 90mg every 8 weeks
Vedolizumab	2627.00	300mg at weeks 0, 2 and 6; 300mg every 8 weeks
Adalimumab	2632.00 (160mg) 1316.00 (80mg) 658.00 (40mg)	160 mg at week 0; 80mg at week 2; then 40mg at week 4; continue 40mg every 2 weeks
Golimumab	4792.00 (200mg) 2396.00 (100mg) 1198.00 (50mg)	200mg at week 0; 100mg at week 2; 50 mg every 4 weeks for those <80kg and 100mg for those >80kg
Ursodeoxycholic acid	7.00	1350mg (based on data from SIBDCS) per day
Bisphosphonates	1.00	3 mg (based on data from SIBDCS) per day
Mutaflor	2.00	2 tablets per day
Cholestyramine	3.00	3g per day

Source: [‡]Bundesamt für Gesundheit. Spezialitätenliste (SL) [Available from: http://www.xn--spezialittenliste-yqb.ch/; accessed 12 June 2018]. [§]Compendium.ch. [Available from: http://compendium.ch/home/de; accessed 15 June 2018]

Resource utilisation

A



B

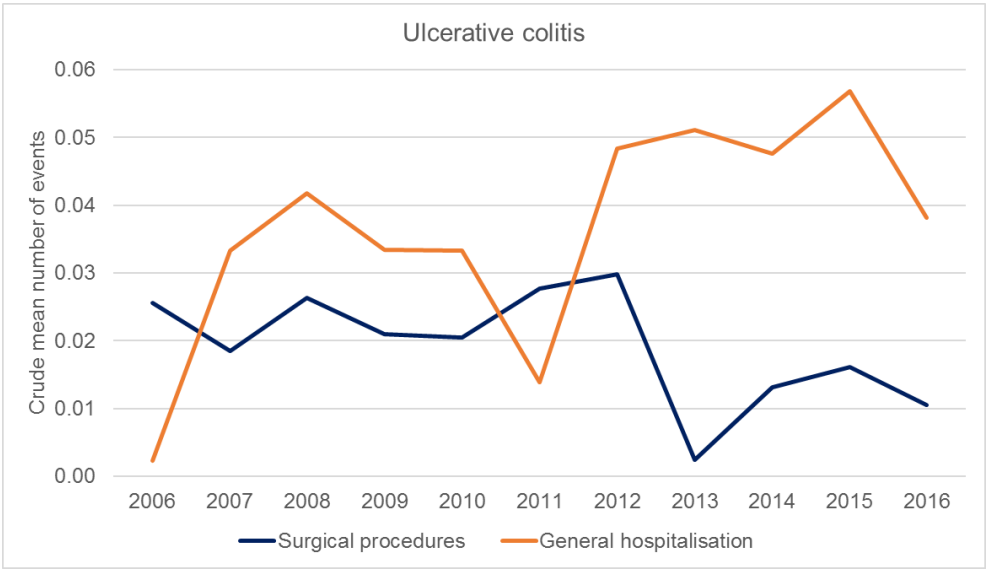


Figure B1 Crude mean number of surgical procedures and hospitalisations for Crohn's disease (A) and ulcerative colitis (B)

The predicted adjusted probability of surgical procedures and general hospitalisations over time for Crohn's disease and ulcerative colitis were estimated using logit random effects regression model adjusting for patient and clinical characteristics (*Figure B2*). Covariates included visit year, cohort wave, age (in groups of 10), gender, canton, smoking status, education attainment, employment status, disease activity (remission, mild, moderate, severe), disease location, disease behaviour, disease duration and the presence of disease complications (fistula, abscess, fissure, complications, EIM, and stenosis).

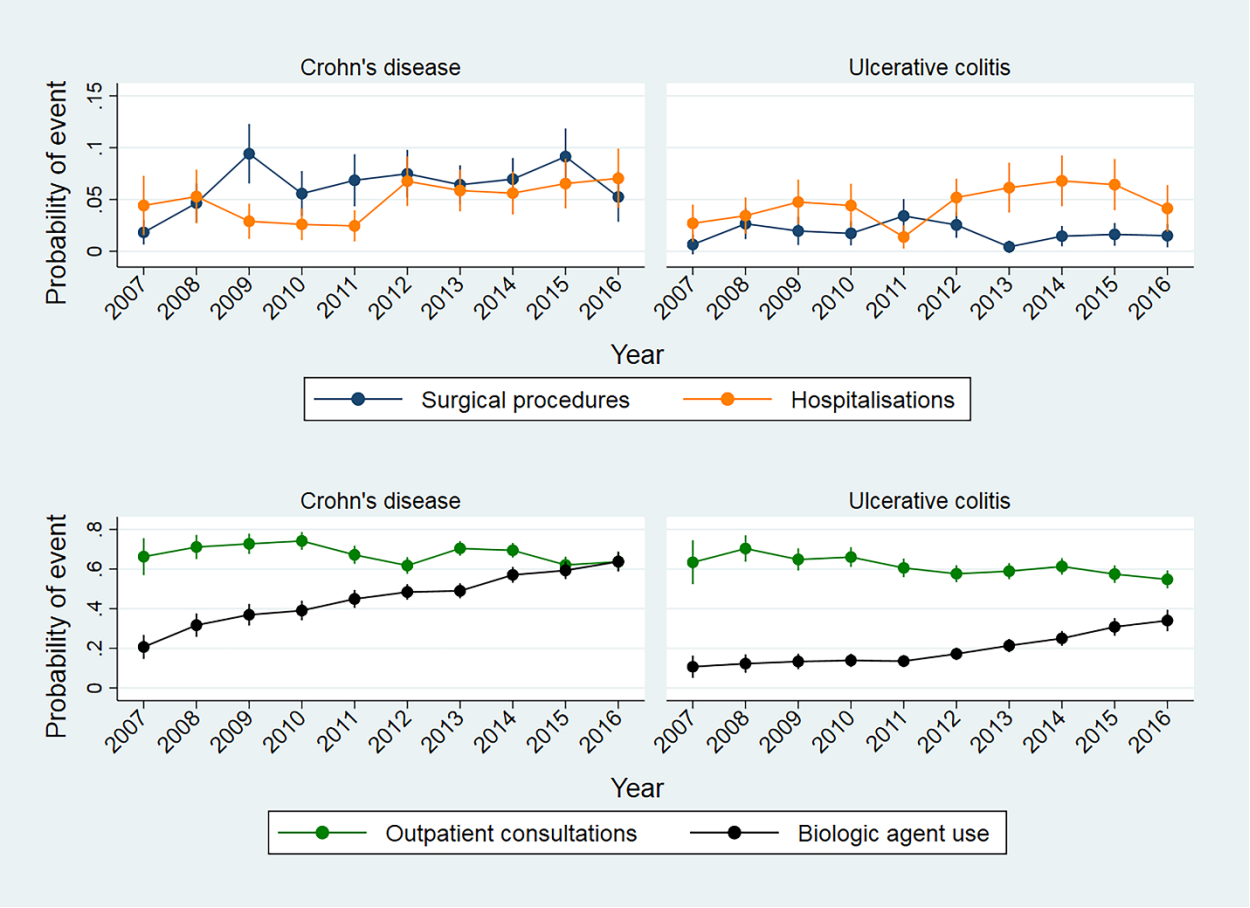


Figure B2 Adjusted predicted probability of surgical procedure, general hospitalisations, outpatient consultations and biologic agent use over time with 95% CI for Crohn's disease and ulcerative colitis

Two-part model results

Table B3 Results (coefficients and 95% CI) of the two-part model by sector for Crohn's disease

	Total direct costs [b, 95% CI]		**Inpatient costs [b, 95% CI]**		**Drug costs [b, 95% CI]**		**Outpatient costs [b, 95% CI]**		**Indirect costs [b, 95% CI]**	
	Logit	GLM	Logit	GLM	Logit	GLM	Logit	GLM	Logit	GLM
Visit year										
2006	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]		
2007	1.345* [0.13,2.56]	-0.103 [-0.79,0.59]	-0.441 [-2.36,1.48]	-0.421 [-1.33,0.48]	-1.353 [-3.49,0.78]	0.467 [-0.22,1.16]	1.355* [0.15,2.56]	0.843** [0.32,1.36]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
2008	0.626 [-0.21,1.46]	0.282 [-0.38,0.94]	-0.238 [-2.16,1.68]	-0.182 [-1.08,0.72]	-0.482 [-2.60,1.63]	0.599 [-0.03,1.23]	0.675 [-0.16,1.51]	1.227*** [0.73,1.73]	0.385 [-0.34,1.11]	1.163* [0.14,2.18]
2009	0.771 [-0.01,1.55]	0.331 [-0.33,0.99]	-0.102 [-2.02,1.82]	-0.073 [-0.98,0.83]	-0.126 [-2.25,1.99]	0.754* [0.14,1.37]	0.823* [0.04,1.60]	1.211*** [0.71,1.71]	0.628 [-0.11,1.37]	0.125 [-0.79,1.04]
2010	1.239** [0.47,2.01]	0.264 [-0.40,0.93]	0.030 [-1.91,1.97]	-0.025 [-0.93,0.88]	-0.604 [-2.70,1.50]	0.533 [-0.08,1.15]	1.237** [0.46,2.01]	1.231*** [0.73,1.73]	0.810* [0.09,1.53]	1.046* [0.17,1.93]
2011	0.730* [0.08,1.38]	0.364 [-0.30,1.03]	-0.271 [-2.20,1.65]	0.091 [-0.82,1.00]	-0.534 [-2.66,1.59]	0.696* [0.06,1.33]	0.721* [0.07,1.37]	1.098*** [0.59,1.60]	0.419 [-0.36,1.20]	0.338 [-0.61,1.28]
2012	0.633* [0.05,1.21]	0.532 [-0.13,1.20]	-0.251 [-2.18,1.67]	0.226 [-0.68,1.13]	0.021 [-2.09,2.13]	0.632* [0.02,1.25]	0.597* [0.02,1.17]	1.157*** [0.66,1.66]	-0.097 [-0.86,0.66]	0.872 [-0.11,1.85]
2013	0.376 [-0.15,0.90]	0.573 [-0.09,1.24]	-0.573 [-2.49,1.35]	0.339 [-0.57,1.25]	-0.074 [-2.19,2.04]	0.369 [-0.26,1.00]	0.292 [-0.22,0.81]	1.347*** [0.84,1.85]	0.556 [-0.22,1.34]	0.893 [-0.03,1.82]
2014	0.292 [-0.14,0.73]	0.739* [0.07,1.41]	-0.454 [-2.39,1.48]	0.462 [-0.45,1.38]	-0.181 [-2.29,1.93]	0.694* [0.04,1.35]	0.274 [-0.16,0.71]	1.300*** [0.79,1.81]	0.943* [0.16,1.72]	1.213** [0.29,2.13]
2015	0.268 [-0.20,0.74]	0.833* [0.16,1.51]	-0.660 [-2.58,1.27]	0.512 [-0.40,1.43]	0.106 [-2.00,2.21]	0.896** [0.25,1.54]	0.264 [-0.20,0.73]	1.210*** [0.70,1.72]	0.690 [-0.13,1.51]	1.171* [0.07,2.28]
2016	0.000 [0.00,0.00]	0.850* [0.17,1.53]	-0.770 [-2.72,1.18]	0.615 [-0.30,1.53]	-0.158 [-2.29,1.97]	0.568 [-0.11,1.24]	0.000 [0.00,0.00]	1.382*** [0.87,1.89]	0.333 [-0.55,1.22]	1.416 [-0.03,2.87]
Cohort wave										
1	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
2	0.451	-0.152	1.132***	0.525***	-1.186***	-0.358*	0.441	-0.282**	-1.518***	-1.087**

	[-0.47,1.38]	[-0.41,0.11]	[0.68,1.58]	[0.34,0.71]	[-1.69,-0.69]	[-0.68,-0.04]	[-0.49,1.37]	[-0.48,-0.08]	[-2.07,-0.96]	[-1.74,-0.44]
3	0.938* [0.03,1.84]	-0.096 [-0.34,0.15]	1.433*** [0.92,1.94]	0.561*** [0.36,0.76]	-0.875*** [-1.36,-0.39]	-0.374* [-0.69,-0.06]	0.865 [-0.04,1.77]	-0.572*** [-0.76,-0.39]	-1.885*** [-2.47,-1.30]	-0.867* [-1.54,-0.19]
4	0.790 [-0.08,1.66]	-0.048 [-0.29,0.20]	1.598*** [1.04,2.15]	0.593*** [0.39,0.80]	-0.965*** [-1.47,-0.46]	-0.325* [-0.63,-0.02]	0.742 [-0.13,1.61]	-0.532*** [-0.74,-0.33]	-1.741*** [-2.34,-1.14]	-0.405 [-1.08,0.27]
5	0.193 [-0.69,1.07]	-0.054 [-0.30,0.19]	1.201*** [0.65,1.75]	0.551*** [0.34,0.76]	-0.874** [-1.42,-0.33]	-0.168 [-0.50,0.16]	0.209 [-0.68,1.10]	-0.656*** [-0.86,-0.46]	-2.026*** [-2.68,-1.37]	-1.398** [-2.29,-0.51]
6	0.548 [-0.37,1.47]	-0.130 [-0.39,0.13]	1.496*** [0.91,2.08]	0.503*** [0.28,0.72]	-1.053*** [-1.61,-0.50]	-0.334 [-0.67,0.00]	0.559 [-0.37,1.49]	-0.617*** [-0.83,-0.41]	-2.097*** [-2.78,-1.41]	-0.843* [-1.68,-0.00]
7	0.813 [-0.11,1.73]	-0.176 [-0.45,0.09]	1.488*** [0.88,2.09]	0.430*** [0.21,0.66]	-1.117*** [-1.67,-0.56]	-0.033 [-0.41,0.34]	0.806 [-0.12,1.73]	-0.718*** [-0.92,-0.51]	-2.462*** [-3.27,-1.66]	-0.696 [-1.72,0.33]
8	0.471 [-0.44,1.38]	-0.179 [-0.46,0.10]	1.704*** [1.07,2.34]	0.409*** [0.17,0.65]	-1.092*** [-1.66,-0.52]	-0.088 [-0.52,0.34]	0.495 [-0.43,1.42]	-0.721*** [-0.94,-0.50]	-2.532*** [-3.32,-1.75]	-1.296* [-2.52,-0.07]
9	0.538 [-0.39,1.47]	-0.264 [-0.55,0.02]	1.549*** [0.87,2.23]	0.346** [0.09,0.60]	-1.068*** [-1.67,-0.47]	-0.275 [-0.73,0.18]	0.517 [-0.42,1.46]	-0.785*** [-1.02,-0.55]	-2.754*** [-3.65,-1.86]	-1.123 [-2.56,0.32]
10	0.661 [-0.35,1.67]	-0.322* [-0.62,-0.03]	1.926*** [1.15,2.70]	0.383** [0.12,0.65]	-1.454*** [-2.18,-0.73]	-0.660** [-1.08,-0.24]	0.674 [-0.34,1.69]	-0.810*** [-1.06,-0.56]	-2.945*** [-4.15,-1.74]	-2.300* [-4.10,-0.50]
11	0.901 [-0.22,2.03]	-0.132 [-0.46,0.19]	2.251*** [1.35,3.16]	0.435** [0.14,0.73]	-1.486*** [-2.31,-0.66]	0.535 [-0.20,1.27]	0.928 [-0.20,2.06]	-0.764*** [-1.03,-0.50]	-1.416** [-2.48,-0.35]	-2.233** [-3.79,-0.68]
Age (years)										
10-19	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
20-29	0.438 [-0.60,1.48]	0.210 [-0.27,0.69]	1.078* [0.05,2.11]	-0.132 [-0.63,0.36]	1.179 [-0.27,2.63]	0.680* [0.01,1.35]	0.363 [-0.69,1.42]	0.239 [-0.24,0.72]	-0.312 [-1.63,1.01]	0.666 [-0.65,1.99]
30-39	1.648** [0.55,2.74]	0.212 [-0.27,0.70]	1.873*** [0.94,2.80]	-0.085 [-0.61,0.44]	0.971 [-0.54,2.49]	0.279 [-0.34,0.90]	1.593** [0.50,2.69]	0.259 [-0.22,0.74]	-0.724 [-2.20,0.75]	1.198 [-0.11,2.51]
40-49	0.924 [-0.15,2.00]	0.010 [-0.48,0.50]	1.080* [0.18,1.98]	-0.323 [-0.86,0.21]	0.825 [-0.68,2.33]	0.772* [0.13,1.42]	0.867 [-0.21,1.94]	0.098 [-0.38,0.57]	-0.328 [-1.76,1.10]	0.974 [-0.46,2.41]
50-59	0.582 [-0.49,1.66]	0.047 [-0.45,0.55]	1.104* [0.14,2.07]	-0.352 [-0.89,0.19]	1.175 [-0.34,2.69]	0.770* [0.14,1.40]	0.381 [-0.78,1.54]	0.100 [-0.38,0.58]	-0.807 [-2.29,0.67]	2.701*** [1.13,4.27]
60-69	-0.145 [-0.99,0.70]	0.001 [-0.53,0.54]	0.190 [-0.58,0.96]	-0.445 [-1.02,0.13]	1.172 [-0.34,2.68]	0.784* [0.07,1.50]	-0.167 [-1.01,0.68]	0.126 [-0.37,0.62]	-1.031 [-2.66,0.60]	2.637* [0.50,4.78]

70+	0.000 [0.00,0.00]	-0.118 [-0.72,0.48]	0.000 [0.00,0.00]	-0.561 [-1.20,0.07]	0.615 [-1.01,2.24]	1.037** [0.25,1.82]	0.000 [0.00,0.00]	0.216 [-0.31,0.74]	-0.439 [-3.93,3.06]	-0.820 [-3.07,1.43]
Gender										
Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Female	0.549 [-0.52,1.62]	-0.142 [-0.84,0.56]	0.978 [-0.10,2.06]	-0.658 [-1.56,0.24]	0.410 [-1.71,2.53]	0.224 [-0.38,0.83]	0.547 [-0.53,1.63]	0.174 [-0.43,0.77]	1.312 [-0.67,3.30]	-1.063 [-2.38,0.25]
Canton of treatment										
AG	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
BE	-0.332 [-1.91,1.25]	-0.007 [-0.43,0.42]	-0.760 [-2.34,0.82]	0.107 [-0.33,0.54]	0.218 [-0.54,0.97]	-0.086 [-0.60,0.43]	-0.381 [-1.97,1.21]	0.190 [-0.15,0.53]	-0.538 [-1.58,0.50]	0.841 [-0.04,1.72]
BL	0.000 [0.00,0.00]	-0.684 [-1.45,0.08]	0.000 [0.00,0.00]	-0.612 [-1.45,0.22]	-0.431 [-2.02,1.16]	0.051 [-1.14,1.24]	0.000 [0.00,0.00]	-0.390 [-0.97,0.19]	-0.782 [-2.87,1.31]	-0.448 [-2.26,1.36]
BS	-0.230 [-1.89,1.43]	0.242 [-0.19,0.67]	-0.563 [-2.18,1.05]	0.311 [-0.13,0.75]	0.376 [-0.44,1.19]	0.279 [-0.24,0.80]	-0.256 [-1.92,1.41]	0.142 [-0.20,0.49]	-0.445 [-1.53,0.64]	1.659*** [0.67,2.64]
FR	0.000 [0.00,0.00]	0.002 [-0.51,0.52]	0.000 [0.00,0.00]	0.301 [-0.27,0.87]	0.000 [0.00,0.00]		0.000 [0.00,0.00]	0.574** [0.23,0.92]		
GE	-1.702* [-3.34,-0.06]	-0.025 [-0.47,0.42]	-2.100* [-3.74,-0.46]	-0.014 [-0.48,0.45]	0.357 [-0.44,1.15]	0.200 [-0.35,0.75]	-1.821* [-3.51,-0.14]	0.128 [-0.23,0.49]	-0.437 [-1.46,0.58]	1.563** [0.52,2.60]
GR	0.000 [0.00,0.00]	-0.195 [-1.01,0.62]	0.000 [0.00,0.00]	-0.216 [-1.16,0.73]	1.286* [0.00,2.57]	-0.785* [-1.43,-0.14]	0.000 [0.00,0.00]	0.507* [0.10,0.91]	1.897* [0.20,3.59]	0.824 [-0.65,2.29]
JU	0.459 [-1.52,2.44]	-0.243 [-0.77,0.28]	-0.240 [-2.15,1.67]	-0.144 [-0.67,0.38]	0.217 [-0.87,1.30]	-0.429 [-1.37,0.51]	0.434 [-1.55,2.42]	0.120 [-0.27,0.51]	-0.350 [-1.51,0.81]	1.252 [-0.10,2.61]
LU	-0.560 [-2.83,1.71]	-0.359 [-0.92,0.20]	-0.791 [-3.00,1.42]	-0.362 [-0.98,0.25]	0.335 [-0.69,1.36]	-0.241 [-0.92,0.44]	-0.614 [-2.89,1.66]	0.096 [-0.36,0.55]	-1.286 [-2.65,0.08]	-0.198 [-2.66,2.26]
NE	0.693 [-1.79,3.18]	-0.009 [-0.61,0.59]	0.509 [-1.48,2.50]	-0.203 [-0.83,0.42]	0.753 [-0.20,1.70]	0.268 [-0.40,0.94]	0.658 [-1.83,3.14]	0.057 [-0.38,0.50]	0.219 [-1.21,1.65]	0.731 [-0.69,2.15]
NW	-1.972* [-3.66,-0.28]	-1.113*** [-1.62,-0.60]	-2.252* [-3.99,-0.52]	-1.301*** [-1.87,-0.74]	0.259 [-0.76,1.28]	-0.249 [-0.88,0.38]	-2.002* [-3.71,-0.30]	-0.536** [-0.92,-0.15]	-0.919 [-2.22,0.39]	0.696 [-0.78,2.17]

SG	-0.758 [-2.36,0.84]	-0.129 [-0.56,0.30]	-1.160 [-2.75,0.43]	-0.053 [-0.50,0.39]	0.185 [-0.58,0.95]	0.124 [-0.41,0.66]	-0.797 [-2.40,0.81]	-0.089 [-0.43,0.25]	-0.629 [-1.62,0.36]	0.432 [-0.54,1.40]
SH	0.000 [0.00,0.00]	0.488* [0.04,0.93]	0.000 [0.00,0.00]	0.711** [0.26,1.16]	0.000 [0.00,0.00]		0.000 [0.00,0.00]	0.350 [-0.01,0.71]	0.000 [0.00,0.00]	
SO	0.244 [-1.63,2.12]	-0.325 [-0.91,0.26]	-0.507 [-2.32,1.31]	-0.247 [-0.87,0.38]	0.056 [-0.98,1.09]	0.364 [-0.35,1.08]	0.222 [-1.66,2.10]	-0.129 [-0.53,0.27]	-0.919 [-2.50,0.67]	0.372 [-2.14,2.88]
SZ	0.298 [-2.24,2.83]	-0.418 [-1.16,0.32]	-0.365 [-2.45,1.72]	-0.204 [-0.98,0.57]	-1.287 [-3.18,0.60]	-0.651 [-1.45,0.15]	0.252 [-2.30,2.80]	0.032 [-0.42,0.49]	0.000 [0.00,0.00]	
UR	0.000 [0.00,0.00]	-3.080*** [-3.59,-2.57]	0.000 [0.00,0.00]	-2.762*** [-3.26,-2.26]	0.000 [0.00,0.00]		0.000 [0.00,0.00]	-0.606** [-1.05,-0.16]	0.000 [0.00,0.00]	
VD	-0.731 [-2.31,0.85]	-0.052 [-0.47,0.37]	-0.946 [-2.53,0.64]	0.053 [-0.38,0.48]	0.092 [-0.68,0.87]	-0.178 [-0.69,0.33]	-0.794 [-2.38,0.80]	0.176 [-0.16,0.51]	-0.545 [-1.52,0.43]	1.126** [0.28,1.98]
ZH	-0.593 [-2.20,1.02]	0.070 [-0.35,0.49]	-1.212 [-2.82,0.39]	0.203 [-0.23,0.63]	0.366 [-0.40,1.13]	-0.048 [-0.55,0.46]	-0.612 [-2.23,1.00]	0.148 [-0.19,0.49]	-0.338 [-1.33,0.65]	1.020* [0.17,1.87]
Smoking status										
Smoker	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Former smoker	0.045 [-0.43,0.52]	0.007 [-0.11,0.12]	0.247 [-0.18,0.67]	-0.100 [-0.22,0.02]	0.225 [-0.05,0.50]	0.123 [-0.05,0.30]	-0.010 [-0.50,0.47]	-0.015 [-0.11,0.08]	0.095 [-0.29,0.48]	-0.141 [-0.91,0.63]
Non-smoker	0.053 [-0.40,0.51]	-0.027 [-0.14,0.08]	-0.108 [-0.49,0.27]	-0.099 [-0.22,0.02]	0.233 [-0.02,0.49]	0.135 [-0.04,0.31]	0.048 [-0.41,0.51]	0.010 [-0.07,0.09]	-0.124 [-0.49,0.24]	-0.008 [-0.58,0.57]
Unknown	0.000 [0.00,0.00]	0.139 [-0.25,0.53]	0.574 [-0.81,1.96]	-0.131 [-0.63,0.37]	0.943* [0.14,1.75]	0.495* [0.02,0.97]	0.000 [0.00,0.00]	0.124 [-0.20,0.44]	0.749 [-0.45,1.94]	-0.277 [-1.95,1.39]
Age X gender interaction										
10-19 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
10-19 x Female	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
20-29 x Male	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]
20-29 x Female	0.050 [-1.34,1.44]	0.155 [-0.55,0.86]	-0.519 [-1.92,0.88]	0.678 [-0.22,1.57]	-0.185 [-2.34,1.97]	-0.558 [-1.22,0.11]	0.041 [-1.36,1.45]	-0.172 [-0.80,0.46]	-0.719 [-2.69,1.25]	0.228 [-1.29,1.74]
30-39 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
30-39 x Female	-1.490* [-2.79,-0.19]	-0.087 [-0.80,0.63]	-1.846** [-3.08,-0.61]	0.441 [-0.47,1.36]	-0.361 [-2.54,1.82]	-0.094 [-0.74,0.55]	-1.525* [-2.83,-0.22]	-0.341 [-0.96,0.27]	-0.761 [-2.86,1.34]	0.671 [-0.65,1.99]
40-49 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
40-49 x Female	-0.534 [-1.88,0.81]	0.182 [-0.54,0.91]	-0.751 [-2.03,0.53]	0.650 [-0.27,1.57]	-0.064 [-2.23,2.10]	-0.490 [-1.22,0.24]	-0.518 [-1.87,0.83]	-0.058 [-0.67,0.55]	-0.921 [-3.02,1.18]	1.410 [-0.26,3.08]
50-59 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
50-59 x Female	-0.393 [-1.78,1.00]	-0.030 [-0.76,0.70]	-1.304 [-2.65,0.04]	0.577 [-0.36,1.51]	-0.919 [-3.11,1.27]	-0.424 [-1.10,0.25]	-0.242 [-1.67,1.19]	-0.152 [-0.77,0.46]	-0.702 [-2.81,1.41]	-0.431 [-2.20,1.33]
60-69 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
60-69 x Female	-0.391 [-1.62,0.83]	-0.209 [-0.98,0.56]	-0.998 [-2.18,0.18]	0.392 [-0.58,1.36]	-0.937 [-3.13,1.26]	-0.431 [-1.16,0.30]	-0.454 [-1.68,0.77]	-0.118 [-0.75,0.51]	-1.964 [-4.73,0.80]	-1.591 [-4.39,1.21]
70+ x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
70+ x Female	0.000 [0.00,0.00]	-0.217 [-1.03,0.60]	0.000 [0.00,0.00]	0.050 [-0.97,1.07]	-0.113 [-2.39,2.16]	-0.226 [-1.13,0.68]	0.000 [0.00,0.00]	-0.415 [-1.07,0.24]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Disease severity (CDAI)										
Remission	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Mild	0.462 [-0.68,1.60]	0.221* [0.05,0.39]	0.001 [-0.60,0.60]	0.148 [-0.00,0.30]	0.507* [0.07,0.95]	0.214 [-0.06,0.48]	0.510 [-0.62,1.64]	0.075 [-0.08,0.23]	0.820** [0.25,1.39]	0.099 [-0.65,0.84]
Moderate	-0.700	0.244	-1.127*	0.202	-0.066	0.368	-0.661	0.008	1.500**	0.118

	[-1.97,0.57]	[-0.10,0.59]	[-2.08,-0.18]	[-0.06,0.46]	[-0.84,0.71]	[-0.27,1.01]	[-1.95,0.62]	[-0.23,0.24]	[0.59,2.41]	[-0.70,0.94]
Disease location										
Ileal (L1)	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Colonic (L2)	0.594* [0.13,1.06]	0.175** [0.05,0.30]	0.384 [-0.00,0.77]	0.160* [0.02,0.30]	0.147 [-0.11,0.41]	0.108 [-0.07,0.29]	0.536* [0.06,1.01]	0.133** [0.05,0.22]	-0.090 [-0.48,0.30]	0.041 [-0.41,0.49]
Ileocolonic (L3)	0.249 [-0.26,0.76]	0.225*** [0.10,0.35]	0.256 [-0.17,0.68]	0.187** [0.05,0.32]	0.295* [0.02,0.58]	0.084 [-0.13,0.30]	0.229 [-0.28,0.73]	0.116* [0.02,0.21]	-0.305 [-0.67,0.06]	0.016 [-0.53,0.56]
Isolated upper disease (L4)	0.250 [-0.77,1.27]	0.115 [-0.13,0.36]	-0.339 [-1.33,0.65]	0.150 [-0.09,0.39]	0.541 [-0.01,1.09]	0.025 [-0.29,0.34]	0.231 [-0.80,1.26]	0.173* [0.01,0.34]	0.229 [-0.91,1.36]	0.898 [-0.12,1.92]
L1+L4	0.941 [-0.37,2.25]	-0.016 [-0.39,0.36]	0.686 [-0.34,1.72]	-0.233 [-0.62,0.15]	0.376 [-0.40,1.15]	0.419 [-0.13,0.97]	0.936 [-0.40,2.27]	0.063 [-0.15,0.27]	-0.443 [-1.43,0.54]	-0.699 [-1.65,0.25]
L2+L4	-0.325 [-2.22,1.57]	0.103 [-0.89,1.10]	0.262 [-1.73,2.25]	-0.293 [-1.11,0.52]	0.509 [-0.89,1.91]	0.759 [-0.18,1.70]	-0.384 [-2.25,1.49]	-0.123 [-0.68,0.44]	0.000 [0.00,0.00]	
L3+L4	-0.749 [-1.78,0.28]	0.266 [-0.01,0.55]	-0.495 [-1.74,0.75]	0.335* [0.04,0.63]	-0.368 [-1.30,0.56]	-0.221 [-0.86,0.42]	-0.774 [-1.81,0.26]	0.495** [0.16,0.83]	-0.589 [-1.97,0.80]	-0.877 [-1.91,0.16]
Disease complications[a]										
Fistula	-0.786 [-2.14,0.57]	0.308** [0.11,0.51]	-0.154 [-0.88,0.57]	0.083 [-0.07,0.24]	0.556** [0.15,0.96]	0.134 [-0.03,0.30]	-0.838 [-2.04,0.37]	0.232** [0.09,0.38]	0.224 [-0.52,0.97]	0.089 [-0.79,0.97]
Abscess	1.937 [-0.11,3.98]	0.249*** [0.11,0.39]	0.277 [-0.42,0.97]	0.003 [-0.13,0.14]	1.393*** [1.00,1.78]	-0.072 [-0.26,0.11]	1.249 [-0.22,2.72]	0.211** [0.06,0.36]	0.297 [-0.31,0.91]	0.097 [-0.67,0.87]
Fissure	0.708 [-1.37,2.79]	0.106 [-0.13,0.34]	0.367 [-0.66,1.39]	0.034 [-0.19,0.26]	0.265 [-0.29,0.82]	0.249 [-0.14,0.64]	0.622 [-1.38,2.62]	0.124 [-0.09,0.34]	0.319 [-0.60,1.24]	-0.318 [-1.31,0.67]
Other major complications	0.921*** [0.44,1.40]	0.201*** [0.11,0.29]	0.662*** [0.33,1.00]	0.115** [0.03,0.20]	0.376*** [0.16,0.60]	0.162 [-0.01,0.33]	0.932*** [0.46,1.40]	0.158*** [0.08,0.23]	0.236 [-0.11,0.58]	-0.001 [-0.40,0.40]
EIM	0.416* [0.04,0.79]	0.252*** [0.17,0.34]	0.420** [0.12,0.72]	0.299*** [0.21,0.39]	0.108 [-0.12,0.33]	0.132 [-0.03,0.30]	0.429* [0.05,0.80]	0.155*** [0.08,0.23]	0.280 [-0.04,0.60]	0.333 [-0.05,0.72]

Stenosis	1.360** [0.50,2.22]	0.176* [0.00,0.35]	0.534 [-0.31,1.38]	-0.095 [-0.28,0.09]	0.608* [0.10,1.12]	0.477*** [0.20,0.75]	1.375** [0.52,2.23]	0.045 [-0.14,0.23]	-0.034 [-0.79,0.72]	-0.167 [-1.00,0.67]
Education attainment										
Less than obligatory	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Basic & obligatory school	-0.250 [-1.68,1.18]	0.210 [-0.17,0.59]	-0.022 [-1.51,1.47]	0.227 [-0.23,0.68]	-0.013 [-0.64,0.61]	0.018 [-0.51,0.54]	0.124 [-1.36,1.61]	0.018 [-0.26,0.30]	0.411 [-1.70,2.52]	3.388*** [1.69,5.09]
Apprentice-ship & Vocational	-0.549 [-1.89,0.79]	0.228 [-0.14,0.59]	-0.420 [-1.85,1.01]	0.298 [-0.14,0.73]	-0.053 [-0.66,0.55]	0.002 [-0.54,0.55]	-0.184 [-1.59,1.22]	0.031 [-0.24,0.30]	0.428 [-1.63,2.49]	3.290*** [1.93,4.65]
Upper Secondary	-0.979 [-2.39,0.43]	0.138 [-0.25,0.53]	-1.119 [-2.62,0.39]	0.336 [-0.12,0.79]	-0.404 [-1.06,0.26]	0.006 [-0.57,0.58]	-0.606 [-2.08,0.86]	-0.092 [-0.38,0.19]	0.244 [-1.87,2.36]	2.994*** [1.49,4.50]
Tertiary education	-0.634 [-2.02,0.75]	0.103 [-0.27,0.47]	-0.617 [-2.07,0.84]	0.203 [-0.24,0.64]	-0.214 [-0.84,0.41]	-0.056 [-0.60,0.49]	-0.330 [-1.77,1.11]	-0.002 [-0.28,0.27]	0.482 [-1.59,2.55]	2.579*** [1.22,3.93]
Employment status										
Full-time employment	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Part-time employment	-0.138 [-0.62,0.35]	0.077 [-0.04,0.20]	-0.044 [-0.48,0.39]	0.023 [-0.10,0.15]	0.043 [-0.28,0.37]	0.101 [-0.14,0.35]	-0.144 [-0.63,0.34]	0.050 [-0.05,0.15]	0.217 [-0.16,0.59]	0.466 [-0.01,0.94]
Education	0.355 [-0.90,1.61]	-0.062 [-0.27,0.14]	-0.004 [-0.94,0.93]	-0.136 [-0.35,0.08]	0.373 [-0.10,0.84]	0.088 [-0.25,0.42]	0.333 [-0.93,1.60]	0.017 [-0.16,0.19]	-0.410 [-1.01,0.19]	0.296 [-0.65,1.24]
Unemployed	-0.523 [-1.08,0.03]	0.096 [-0.04,0.23]	-0.213 [-0.72,0.29]	0.025 [-0.12,0.17]	0.197 [-0.15,0.54]	0.176 [-0.06,0.41]	-0.580* [-1.13,-0.03]	0.041 [-0.06,0.15]		
Retired	-0.086 [-0.71,0.54]	0.280*** [0.12,0.44]	-0.083 [-0.60,0.43]	0.189* [0.02,0.36]	0.661*** [0.31,1.01]	-0.019 [-0.22,0.19]	-0.155 [-0.77,0.46]	0.236*** [0.11,0.36]		
Disease duration										
0-9 years	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]

10-19 years	-0.238 [-0.65,0.17]	0.032 [-0.08,0.14]	-0.244 [-0.62,0.14]	-0.004 [-0.12,0.11]	0.197 [-0.08,0.48]	-0.098 [-0.28,0.08]	-0.250 [-0.66,0.16]	0.054 [-0.03,0.14]	-0.279 [-0.67,0.11]	0.098 [-0.39,0.58]
20-29 years	0.153 [-0.40,0.71]	-0.101 [-0.26,0.06]	-0.475 [-0.95,0.00]	-0.084 [-0.26,0.09]	0.061 [-0.28,0.40]	-0.173 [-0.39,0.04]	0.091 [-0.46,0.64]	0.024 [-0.09,0.13]	-0.416 [-0.95,0.12]	0.211 [-0.58,1.01]
30-39 years	0.320 [-0.42,1.06]	-0.091 [-0.29,0.11]	-0.255 [-0.86,0.35]	-0.132 [-0.37,0.11]	0.350 [-0.06,0.76]	-0.326* [-0.59,-0.06]	0.324 [-0.42,1.06]	0.166* [0.02,0.31]	-0.043 [-0.77,0.69]	-0.643 [-1.70,0.41]
40-49 years	0.427 [-0.65,1.51]	-0.381 [-0.77,0.01]	-0.318 [-1.29,0.65]	-0.253 [-0.66,0.16]	-0.490 [-1.62,0.64]	-0.499 [-1.18,0.19]	0.277 [-0.79,1.35]	-0.014 [-0.27,0.24]	0.824 [-1.43,3.08]	-5.166*** [-6.62,-3.71]
50+ years	0.000 [0.00,0.00]	-1.828*** [-2.77,-0.89]	0.000 [0.00,0.00]	-1.950** [-3.18,-0.72]	0.000 [0.00,0.00]		0.000 [0.00,0.00]	-0.301 [-0.74,0.14]		
Disease behaviour										
B1	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
B2	0.238 [-0.97,1.44]	0.211* [0.02,0.40]	0.435 [-0.47,1.34]	0.264** [0.07,0.46]	0.352 [-0.21,0.91]	-0.166 [-0.49,0.16]	0.258 [-0.93,1.45]	0.369*** [0.18,0.56]	0.689 [-0.12,1.50]	0.651 [-0.29,1.59]
B3	-0.010 [-1.59,1.57]	0.131 [-0.05,0.31]	0.259 [-0.54,1.06]	0.159 [-0.00,0.32]	0.325 [-0.15,0.80]	-0.109 [-0.36,0.14]	0.085 [-1.38,1.55]	0.148 [-0.03,0.33]	0.383 [-0.43,1.20]	0.897 [-0.26,2.05]
Perianal involvement[a]	1.436* [0.07,2.80]	0.046 [-0.15,0.24]	0.509 [-0.30,1.32]	0.176* [0.01,0.35]	0.214 [-0.23,0.66]	-0.054 [-0.26,0.15]	1.447* [0.22,2.68]	-0.089 [-0.24,0.07]	0.353 [-0.44,1.15]	-0.137 [-1.09,0.82]
_cons	1.751 [-0.64,4.14]	8.304*** [7.37,9.24]	1.376 [-1.54,4.29]	8.127*** [6.96,9.29]	-3.403* [-6.03,-0.78]	8.516*** [7.45,9.58]	1.609 [-0.87,4.09]	5.531*** [4.76,6.30]	-0.942 [-3.53,1.65]	3.550** [1.32,5.78]
N	4967	4858	5028	4600	5107	542	4967	4853	3261	279

[a]*Reference level is non-present (binary variables)*
* p<.05; ** p<.01; *** p<.001

Table B4 Results (coefficients and 95% CI) of the two-part model by sector for ulcerative colitis

	Total direct costs [b, 95% CI]		**Inpatient costs [b, 95% CI]**		**Drug costs [b, 95% CI]**		**Outpatient costs [b, 95% CI]**		**Indirect costs [b, 95% CI]**	
	Logit	GLM	Logit	GLM	Logit	GLM	Logit	GLM	Logit	GLM
Visit year										
2006	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]		
2007	1.297* [0.09,2.50]	0.500 [-0.36,1.36]	2.102*** [1.10,3.10]	0.087 [-0.80,0.98]	-0.867 [-4.56,2.82]	0.844 [-0.27,1.96]	1.320* [0.11,2.53]	0.913*** [0.43,1.40]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
2008	3.084*** [1.74,4.42]	0.522 [-0.31,1.36]	1.621*** [0.93,2.32]	0.336 [-0.54,1.21]	-0.237 [-3.93,3.46]	0.274 [-0.88,1.43]	3.110*** [1.77,4.45]	0.892*** [0.42,1.37]	0.115 [-0.27,0.50]	-0.515 [-1.22,0.19]
2009	1.015** [0.31,1.72]	0.764 [-0.10,1.63]	1.419*** [0.81,2.03]	0.361 [-0.53,1.25]	-0.145 [-3.81,3.52]	0.456 [-0.69,1.60]	1.077** [0.38,1.78]	0.944*** [0.46,1.42]	0.291 [-0.12,0.70]	-0.602 [-1.39,0.19]
2010	1.457*** [0.76,2.16]	0.654 [-0.19,1.50]	1.312*** [0.76,1.86]	0.419 [-0.49,1.33]	-0.195 [-3.90,3.51]	0.067 [-1.08,1.21]	1.462*** [0.77,2.15]	0.962*** [0.48,1.45]	0.100 [-0.34,0.54]	-0.355 [-1.11,0.40]
2011	2.217*** [1.48,2.95]	0.613 [-0.23,1.46]	2.002*** [1.46,2.54]	0.405 [-0.50,1.31]	-0.506 [-4.21,3.20]	0.493 [-0.67,1.66]	2.274*** [1.54,3.01]	0.784** [0.30,1.27]	-0.077 [-0.55,0.40]	0.326 [-0.69,1.34]
2012	1.561*** [0.99,2.14]	0.795 [-0.05,1.64]	1.672*** [1.21,2.13]	0.566 [-0.34,1.47]	0.079 [-3.61,3.77]	0.082 [-1.01,1.17]	1.597*** [1.02,2.17]	0.871*** [0.38,1.36]	-0.170 [-0.64,0.30]	-0.334 [-1.46,0.80]
2013	0.884*** [0.43,1.34]	0.916* [0.07,1.76]	1.166*** [0.79,1.54]	0.613 [-0.30,1.52]	-0.107 [-3.83,3.62]	0.399 [-0.74,1.54]	0.894*** [0.44,1.35]	0.959*** [0.47,1.45]	0.114 [-0.35,0.58]	-0.108 [-1.11,0.90]
2014	0.736*** [0.33,1.14]	0.948* [0.10,1.80]	0.915*** [0.58,1.25]	0.791 [-0.13,1.71]	0.187 [-3.53,3.91]	-0.002 [-1.12,1.12]	0.765*** [0.36,1.17]	1.022*** [0.53,1.51]	-0.026 [-0.49,0.44]	-0.519 [-2.14,1.10]
2015	0.715*** [0.35,1.08]	1.146** [0.28,2.01]	0.783*** [0.51,1.05]	0.917 [-0.01,1.85]	0.226 [-3.49,3.95]	0.062 [-1.01,1.13]	0.687*** [0.32,1.05]	1.008*** [0.52,1.50]	-0.023 [-0.50,0.45]	-0.672 [-1.58,0.23]
2016	0.000 [0.00,0.00]	1.114* [0.25,1.98]	0.000 [0.00,0.00]	1.056* [0.11,2.00]	-0.187 [-3.92,3.55]	-0.103 [-1.24,1.03]	0.000 [0.00,0.00]	1.033*** [0.53,1.53]	0.215 [-0.27,0.70]	-1.594** [-2.56,-0.63]
Cohort wave										
1	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
2	0.338 [-0.86,1.54]	-0.269 [-0.65,0.11]	0.461 [-0.15,1.07]	0.506*** [0.25,0.76]	-0.906** [-1.51,-0.31]	-0.708** [-1.23,-0.19]	0.340 [-0.86,1.54]	-0.329*** [-0.52,-0.14]	-0.774*** [-1.11,-0.44]	0.140 [-0.47,0.75]

3	-0.078 [-1.06,0.90]	-0.252 [-0.62,0.11]	0.763* [0.09,1.44]	0.588*** [0.30,0.87]	-0.968** [-1.58,-0.36]	-0.892** [-1.49,-0.29]	-0.088 [-1.07,0.90]	-0.428*** [-0.60,-0.25]	-0.993*** [-1.35,-0.63]	-0.458 [-1.06,0.14]
4	0.379 [-0.69,1.45]	-0.318 [-0.71,0.08]	0.913* [0.18,1.65]	0.636*** [0.32,0.95]	-1.659*** [-2.32,-1.00]	-0.407 [-1.19,0.38]	0.323 [-0.74,1.39]	-0.598*** [-0.79,-0.41]	-1.311*** [-1.70,-0.92]	-0.916* [-1.74,-0.10]
5	0.423 [-0.64,1.48]	-0.354 [-0.74,0.03]	0.907* [0.14,1.68]	0.598*** [0.28,0.92]	-1.595*** [-2.28,-0.91]	-0.616* [-1.22,-0.01]	0.383 [-0.64,1.40]	-0.687*** [-0.88,-0.49]	-1.319*** [-1.73,-0.91]	-0.613 [-1.35,0.12]
6	-0.027 [-1.07,1.02]	-0.240 [-0.64,0.16]	0.750 [-0.05,1.55]	0.635*** [0.31,0.96]	-1.604*** [-2.32,-0.88]	-0.056 [-0.72,0.61]	-0.068 [-1.12,0.98]	-0.709*** [-0.90,-0.52]	-1.871*** [-2.40,-1.34]	0.584 [-0.76,1.93]
7	0.117 [-0.92,1.16]	-0.273 [-0.68,0.13]	0.817* [0.05,1.59]	0.520** [0.19,0.85]	-1.429*** [-2.11,-0.75]	-0.091 [-0.77,0.59]	0.121 [-0.93,1.17]	-0.685*** [-0.88,-0.49]	-1.382*** [-1.83,-0.93]	-0.254 [-1.37,0.86]
8	0.467 [-0.60,1.54]	-0.359 [-0.77,0.05]	1.031* [0.22,1.84]	0.538** [0.19,0.88]	-1.240** [-1.99,-0.49]	-0.562 [-1.22,0.09]	0.460 [-0.63,1.55]	-0.606*** [-0.82,-0.39]	-1.228*** [-1.69,-0.77]	0.347 [-0.76,1.46]
9	0.625 [-0.47,1.72]	-0.355 [-0.80,0.09]	1.192** [0.32,2.06]	0.432* [0.07,0.80]	-1.626*** [-2.41,-0.84]	-0.090 [-0.89,0.71]	0.567 [-0.54,1.68]	-0.741*** [-0.96,-0.52]	-1.312*** [-1.78,-0.84]	0.129 [-1.51,1.77]
10	0.559 [-0.58,1.70]	-0.531* [-0.98,-0.08]	1.300** [0.39,2.21]	0.379 [-0.02,0.78]	-1.814*** [-2.68,-0.95]	-0.580 [-1.43,0.27]	0.598 [-0.55,1.74]	-0.725*** [-0.98,-0.47]	-1.277*** [-1.82,-0.74]	0.810 [-0.51,2.13]
11	1.202 [-0.04,2.44]	-0.478* [-0.95,-0.01]	1.843*** [0.86,2.83]	0.405 [-0.04,0.85]	-1.409** [-2.40,-0.42]	-0.732 [-1.61,0.15]	1.225 [-0.02,2.47]	-0.786*** [-1.07,-0.51]	-1.382*** [-1.98,-0.79]	0.481 [-1.10,2.06]
Age (years)										
10-19	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
20-29	1.444* [0.21,2.67]	-0.733** [-1.25,-0.22]	1.596** [0.48,2.71]	-0.832** [-1.35,-0.31]	-0.511 [-2.04,1.02]	0.221 [-0.61,1.05]	1.447* [0.21,2.68]	-0.730** [-1.20,-0.26]	-0.738 [-1.87,0.40]	0.433 [-1.71,2.58]
30-39	1.365** [0.51,2.22]	-0.996*** [-1.54,-0.45]	1.213** [0.37,2.06]	-1.054*** [-1.59,-0.52]	-1.091 [-2.60,0.41]	0.353 [-0.64,1.35]	1.353** [0.50,2.21]	-0.872*** [-1.36,-0.39]	-0.805 [-1.94,0.33]	1.398 [-0.72,3.51]
40-49	0.696 [-0.09,1.48]	-1.248*** [-1.78,-0.71]	0.577 [-0.23,1.38]	-1.271*** [-1.79,-0.75]	-1.111 [-2.64,0.42]	0.263 [-0.75,1.28]	0.616 [-0.17,1.40]	-0.990*** [-1.48,-0.50]	-1.112 [-2.26,0.03]	1.352 [-0.98,3.68]
50-59	0.866* [0.06,1.67]	-1.287*** [-1.83,-0.74]	0.602 [-0.26,1.47]	-1.443*** [-1.97,-0.92]	-0.996 [-2.54,0.55]	0.324 [-0.74,1.39]	0.801 [-0.02,1.62]	-1.033*** [-1.53,-0.54]	-0.911 [-2.07,0.24]	1.806 [-0.27,3.89]
60-69	0.756 [-0.06,1.57]	-1.259*** [-1.83,-0.68]	0.583 [-0.27,1.44]	-1.225*** [-1.79,-0.66]	-0.745 [-2.35,0.86]	-0.329 [-1.33,0.67]	0.769 [-0.05,1.58]	-0.998*** [-1.50,-0.49]	-0.975 [-2.18,0.23]	2.112* [0.04,4.19]
70+	0.000 [0.00,0.00]	-1.435*** [-2.10,-0.77]	0.000 [0.00,0.00]	-1.901*** [-2.50,-1.30]	-0.444 [-2.11,1.22]	0.916 [-0.25,2.09]	0.000 [0.00,0.00]	-1.249*** [-1.80,-0.70]	0.000 [0.00,0.00]	

Gender										
Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Female	0.041 [-1.02,1.10]	-1.829*** [-2.41,-1.25]	-0.471 [-1.49,0.55]	-2.270*** [-2.77,-1.77]	-0.559 [-2.65,1.53]	-1.585** [-2.65,-0.52]	0.047 [-1.01,1.11]	-0.332 [-1.21,0.54]	-0.402 [-1.78,0.97]	-1.628 [-4.06,0.81]
Canton										
AG	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
AR	0.000 [0.00,0.00]	0.529* [0.12,0.94]	0.000 [0.00,0.00]	0.717** [0.28,1.15]	0.000 [0.00,0.00]		0.000 [0.00,0.00]	0.593*** [0.29,0.89]	0.000 [0.00,0.00]	
BE	0.276 [-0.95,1.51]	0.109 [-0.29,0.51]	-0.260 [-1.33,0.81]	0.031 [-0.39,0.45]	-0.002 [-0.88,0.87]	0.958** [0.32,1.59]	0.336 [-0.87,1.54]	0.272 [-0.00,0.54]	-0.012 [-0.45,0.43]	-0.197 [-0.96,0.56]
BL	0.527 [-1.12,2.17]	-0.458 [-1.26,0.35]	-0.488 [-1.98,1.00]	-0.366 [-1.23,0.50]	-1.207 [-3.31,0.90]	-0.093 [-1.14,0.96]	0.648 [-0.96,2.26]	-0.109 [-0.59,0.37]	-0.281 [-1.03,0.47]	-0.079 [-2.02,1.86]
BS	0.132 [-1.00,1.26]	-0.024 [-0.44,0.39]	-0.026 [-1.05,1.00]	-0.269 [-0.72,0.18]	0.879* [0.05,1.71]	1.144*** [0.48,1.81]	0.243 [-0.83,1.32]	0.052 [-0.25,0.35]	-0.033 [-0.57,0.51]	-0.759 [-1.81,0.29]
GE	-1.177* [-2.29,-0.07]	-0.105 [-0.58,0.37]	-1.205* [-2.29,-0.12]	-0.300 [-0.78,0.19]	0.210 [-0.67,1.09]	0.829* [0.01,1.64]	-1.025 [-2.10,0.05]	0.019 [-0.29,0.32]	-0.188 [-0.65,0.27]	-0.094 [-1.08,0.89]
GR	0.000 [0.00,0.00]	0.223 [-0.43,0.87]	0.339 [-2.00,2.68]	0.325 [-0.37,1.02]	0.377 [-0.54,1.30]	0.467 [-0.63,1.57]	0.000 [0.00,0.00]	0.500 [-0.18,1.18]	-0.262 [-1.16,0.64]	-5.046*** [-7.09,-3.01]
JU	-0.272 [-1.44,0.90]	-0.607** [-1.03,-0.18]	-0.534 [-1.72,0.66]	-0.681** [-1.14,-0.22]	-0.294 [-1.47,0.88]	0.315 [-0.53,1.16]	-0.242 [-1.33,0.85]	-0.024 [-0.37,0.32]	-0.566 [-1.33,0.20]	0.358 [-0.74,1.45]
LU	-1.121 [-2.30,0.06]	-0.150 [-0.70,0.40]	-1.160* [-2.28,-0.04]	-0.328 [-0.89,0.23]	0.242 [-0.85,1.34]	0.897* [0.14,1.65]	-0.994 [-2.12,0.13]	0.134 [-0.20,0.47]	-0.498 [-1.21,0.21]	0.005 [-1.43,1.44]
NE	0.076 [-1.65,1.81]	-0.692 [-1.39,0.00]	-0.523 [-1.90,0.85]	-0.843* [-1.61,-0.07]	0.813 [-0.32,1.94]	0.025 [-0.84,0.89]	0.194 [-1.51,1.90]	-0.189 [-0.66,0.29]	0.017 [-0.62,0.65]	-0.438 [-2.34,1.47]
NW	-0.859 [-2.12,0.41]	-0.169 [-0.67,0.34]	-0.506 [-1.78,0.76]	-0.484 [-1.01,0.04]	0.813 [-0.12,1.74]	0.818 [-0.08,1.72]	-0.765 [-1.98,0.45]	0.131 [-0.23,0.49]	-0.094 [-0.87,0.68]	-0.075 [-1.58,1.43]
SG	-0.647 [-1.72,0.42]	-0.175 [-0.56,0.21]	-0.620 [-1.63,0.39]	-0.277 [-0.69,0.13]	0.298 [-0.52,1.12]	0.611* [0.05,1.18]	-0.554 [-1.57,0.47]	-0.053 [-0.32,0.22]	-0.179 [-0.57,0.22]	-0.037 [-0.85,0.77]
SH	-1.135* [-2.17,-0.10]	-0.250 [-0.68,0.18]	-1.028* [-2.04,-0.01]	-0.081 [-0.54,0.38]	0.000 [0.00,0.00]		-0.962 [-1.95,0.02]	-0.287 [-0.57,0.00]	0.922*** [0.46,1.38]	-3.166*** [-4.83,-1.50]

SO	-1.086* [-2.17,-0.00]	-0.186 [-0.80,0.43]	-1.453** [-2.53,-0.37]	-0.203 [-0.89,0.48]	0.411 [-0.72,1.54]	0.511 [-0.26,1.28]	-1.099* [-2.14,-0.06]	-0.096 [-0.49,0.30]	0.114 [-0.53,0.76]	0.471 [-0.66,1.60]
SZ	0.000 [0.00,0.00]	-0.208 [-0.72,0.31]	1.233 [-0.93,3.39]	-0.344 [-0.97,0.28]	-0.048 [-1.32,1.23]	1.114 [-1.17,3.40]	0.000 [0.00,0.00]	0.541** [0.20,0.89]	0.000 [0.00,0.00]	
TG	0.000 [0.00,0.00]	0.391 [-0.01,0.80]	0.000 [0.00,0.00]	-1.240*** [-1.67,-0.81]	1.626*** [0.73,2.52]	1.394*** [0.65,2.14]	0.000 [0.00,0.00]	0.623*** [0.33,0.92]	0.063 [-0.48,0.61]	0.353 [-0.76,1.46]
UR	-2.475*** [-3.63,-1.32]	-0.222 [-0.65,0.21]	-1.927*** [-3.03,-0.82]	-0.198 [-0.65,0.25]	0.000 [0.00,0.00]		-2.390*** [-3.49,-1.29]	0.108 [-0.18,0.40]	0.000 [0.00,0.00]	
VD	-0.783 [-1.79,0.22]	-0.079 [-0.48,0.32]	-0.838 [-1.77,0.10]	-0.073 [-0.50,0.35]	-0.050 [-0.89,0.79]	0.332 [-0.36,1.02]	-0.685 [-1.63,0.26]	0.132 [-0.13,0.40]	-0.213 [-0.64,0.22]	-0.047 [-0.81,0.72]
ZG	0.000 [0.00,0.00]	-1.483*** [-1.90,-1.07]	0.000 [0.00,0.00]	-1.437*** [-1.87,-1.00]	0.000 [0.00,0.00]		0.000 [0.00,0.00]	-1.047*** [-1.35,-0.74]	0.000 [0.00,0.00]	
ZH	-0.286 [-1.34,0.76]	-0.074 [-0.45,0.30]	-0.451 [-1.43,0.53]	-0.132 [-0.53,0.27]	0.072 [-0.76,0.90]	0.855** [0.23,1.48]	-0.163 [-1.16,0.83]	0.077 [-0.19,0.34]	-0.327 [-0.77,0.11]	0.139 [-0.82,1.09]
Smoking status										
Smoker	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Former smoker	0.863* [0.09,1.64]	0.042 [-0.15,0.23]	0.729* [0.07,1.39]	0.067 [-0.12,0.25]	0.288 [-0.19,0.77]	-0.395 [-0.91,0.11]	0.852* [0.08,1.63]	0.113 [-0.03,0.25]	0.261 [-0.03,0.55]	0.709 [-0.40,1.81]
Non-smoker	-0.007 [-0.51,0.49]	0.095 [-0.08,0.27]	0.044 [-0.41,0.50]	0.070 [-0.11,0.25]	0.212 [-0.17,0.59]	-0.076 [-0.50,0.35]	-0.038 [-0.54,0.46]	0.045 [-0.07,0.16]	-0.063 [-0.31,0.18]	0.221 [-0.82,1.26]
Unknown	-0.507 [-1.69,0.67]	-0.331 [-0.72,0.06]	-0.727 [-1.75,0.29]	-0.328 [-0.71,0.06]	-0.293 [-1.25,0.66]	0.188 [-0.44,0.82]	-0.648 [-1.79,0.49]	-0.078 [-0.31,0.15]	-0.704* [-1.35,-0.05]	2.289*** [0.99,3.59]
Age X Gender interaction										
10-19 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
10-19 x Female	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
20-29 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]

20-29 x Female	-0.740 [-2.47,0.99]	1.613*** [0.98,2.24]	-0.116 [-1.68,1.45]	2.171*** [1.58,2.77]	0.038 [-2.18,2.26]	0.958 [-0.15,2.06]	-0.719 [-2.44,1.00]	0.283 [-0.61,1.18]	0.441 [-1.02,1.90]	1.026 [-1.67,3.72]
30-39 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
30-39 x Female	-0.204 [-1.45,1.05]	1.830*** [1.19,2.47]	0.154 [-1.03,1.34]	2.333*** [1.77,2.89]	0.533 [-1.63,2.69]	1.293* [0.09,2.49]	-0.203 [-1.45,1.05]	0.341 [-0.55,1.23]	0.704 [-0.70,2.10]	1.251 [-1.26,3.76]
40-49 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
40-49 x Female	0.054 [-1.16,1.27]	1.665*** [1.03,2.30]	0.502 [-0.70,1.70]	2.141*** [1.57,2.71]	0.344 [-1.80,2.49]	1.300* [0.07,2.53]	0.117 [-1.10,1.33]	0.317 [-0.57,1.21]	0.835 [-0.59,2.26]	1.743 [-0.95,4.44]
50-59 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
50-59 x Female	-0.679 [-1.96,0.60]	1.754*** [1.07,2.44]	-0.027 [-1.28,1.22]	2.316*** [1.70,2.93]	0.496 [-1.69,2.68]	1.441* [0.17,2.72]	-0.686 [-1.96,0.59]	0.390 [-0.51,1.29]	0.465 [-0.94,1.87]	0.799 [-1.54,3.14]
60-69 x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
60-69 x Female	-0.491 [-1.84,0.85]	1.554*** [0.86,2.24]	0.077 [-1.21,1.36]	2.009*** [1.35,2.66]	-0.255 [-2.61,2.10]	2.028** [0.81,3.24]	-0.474 [-1.82,0.87]	0.156 [-0.75,1.06]	0.992 [-0.54,2.52]	0.593 [-1.80,2.99]
70+ x Male	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	
70+ x Female	0.000 [0.00,0.00]	2.282*** [1.42,3.15]	0.000 [0.00,0.00]	3.392*** [2.53,4.26]	0.607 [-1.68,2.89]	0.449 [-0.99,1.88]	0.000 [0.00,0.00]	0.803 [-0.20,1.80]	0.000 [0.00,0.00]	
Disease severity (MTWAI)										
Remission	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Mild	-0.166 [-0.64,0.31]	0.190** [0.05,0.33]	-0.136 [-0.56,0.29]	0.197** [0.05,0.35]	0.037 [-0.44,0.51]	0.142 [-0.24,0.53]	-0.157 [-0.63,0.32]	0.172** [0.05,0.29]	0.214 [-0.04,0.47]	0.374 [-0.25,1.00]
Moderate	-0.156 [-0.60,0.29]	0.534*** [0.36,0.71]	-0.306 [-0.76,0.15]	0.319*** [0.17,0.47]	0.539** [0.14,0.94]	0.724*** [0.38,1.07]	-0.207 [-0.67,0.26]	0.254*** [0.15,0.36]	0.316** [0.08,0.55]	0.162 [-0.43,0.75]
Severe	0.206 [-0.39,0.80]	0.518*** [0.36,0.67]	-0.097 [-0.57,0.38]	0.337*** [0.19,0.48]	1.069*** [0.72,1.42]	0.262 [-0.02,0.55]	0.181 [-0.40,0.77]	0.427*** [0.32,0.53]	0.605*** [0.41,0.80]	0.803* [0.16,1.45]

Disease location										
Proctitis	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Left-sided colitis	0.452 [-0.04,0.94]	0.296** [0.11,0.49]	0.431 [-0.03,0.89]	0.338*** [0.16,0.52]	0.154 [-0.25,0.56]	-0.088 [-0.54,0.36]	0.443 [-0.04,0.93]	0.113 [-0.01,0.23]	-0.046 [-0.29,0.20]	-0.272 [-1.12,0.57]
Pancolitis	0.309 [-0.20,0.82]	0.387*** [0.20,0.58]	0.037 [-0.44,0.52]	0.439*** [0.25,0.63]	0.262 [-0.14,0.66]	-0.107 [-0.55,0.33]	0.297 [-0.21,0.80]	0.113 [-0.01,0.24]	0.163 [-0.08,0.40]	-0.072 [-0.83,0.68]
Disease complications[a]										
Fistula	-0.134 [-2.42,2.15]	-0.250 [-0.72,0.22]	0.832 [-1.30,2.96]	-0.633* [-1.15,-0.12]	0.750 [-0.52,2.02]	-0.041 [-0.70,0.62]	-0.059 [-2.34,2.23]	0.250 [-0.16,0.66]	0.140 [-0.54,0.82]	-0.668 [-2.31,0.98]
Abscess	0.000 [0.00,0.00]	0.193 [-0.56,0.94]	0.000 [0.00,0.00]	-0.157 [-0.99,0.67]	0.668 [-0.79,2.13]	0.662 [-0.62,1.95]	0.000 [0.00,0.00]	0.073 [-0.71,0.86]	0.084 [-0.75,0.92]	0.000 [0.00,0.00]
Fissure	1.104 [-0.54,2.75]	0.147 [-0.23,0.52]	0.051 [-1.21,1.31]	0.217 [-0.19,0.63]	0.255 [-0.77,1.27]	0.120 [-0.53,0.77]	1.136 [-0.50,2.77]	0.053 [-0.25,0.36]	0.180 [-0.58,0.94]	0.696 [-0.43,1.82]
Other major complications	1.166*** [0.63,1.70]	0.480*** [0.35,0.61]	0.896*** [0.49,1.31]	0.243*** [0.12,0.37]	0.872*** [0.56,1.18]	0.242* [0.00,0.48]	1.098*** [0.57,1.62]	0.355*** [0.26,0.45]	0.291** [0.08,0.50]	-0.537 [-1.11,0.04]
EIM	0.550* [0.00,1.10]	0.311*** [0.18,0.44]	0.675** [0.23,1.12]	0.372*** [0.25,0.49]	0.287 [-0.04,0.61]	0.091 [-0.20,0.38]	0.588* [0.05,1.13]	0.164*** [0.07,0.25]	0.253* [0.06,0.45]	0.112 [-0.36,0.58]
Stenosis	0.000 [0.00,0.00]	0.622*** [0.28,0.96]	0.287 [-1.28,1.86]	0.409* [0.00,0.81]	1.310** [0.40,2.22]	0.146 [-0.51,0.81]	0.487 [-1.64,2.62]	0.436*** [0.23,0.64]	0.750* [0.12,1.38]	1.344** [0.33,2.36]
Education attainment										
Less than obligatory	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Basic & obligatory school	-0.045 [-1.47,1.38]	-0.236 [-0.95,0.48]	0.033 [-1.41,1.47]	0.009 [-0.57,0.58]	-0.825 [-1.72,0.07]	-0.622 [-1.51,0.26]	-0.102 [-1.49,1.29]	0.258 [-0.15,0.66]	0.014 [-0.61,0.64]	-2.618*** [-3.99,-1.25]
Vocational apprentice-	-0.883 [-2.14,0.38]	-0.175 [-0.87,0.52]	-0.676 [-1.96,0.61]	0.070 [-0.47,0.61]	-0.514 [-1.29,0.26]	-0.653 [-1.49,0.18]	-0.875 [-2.12,0.37]	0.243 [-0.14,0.63]	0.583* [0.10,1.06]	-2.115*** [-3.17,-1.06]

ship w/ diploma										
Upper Secondary	-0.762 [-2.04,0.51]	-0.381 [-1.09,0.33]	-0.823 [-2.15,0.51]	-0.194 [-0.77,0.38]	-0.214 [-1.05,0.62]	-0.700 [-1.58,0.18]	-0.749 [-2.00,0.51]	0.073 [-0.32,0.47]	0.560 [-0.01,1.13]	-2.368*** [-3.73,-1.01]
Tertiary education	-0.968 [-2.25,0.31]	-0.163 [-0.87,0.54]	-0.792 [-2.11,0.52]	0.062 [-0.49,0.61]	-0.639 [-1.44,0.16]	-0.376 [-1.24,0.49]	-0.969 [-2.23,0.29]	0.207 [-0.18,0.59]	0.527* [0.02,1.03]	-1.514** [-2.63,-0.40]
Employment status										
Full-time employment	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
Part-time employment	0.140 [-0.35,0.63]	0.110 [-0.06,0.28]	0.186 [-0.30,0.67]	0.083 [-0.10,0.26]	0.153 [-0.20,0.51]	-0.116 [-0.48,0.25]	0.106 [-0.38,0.59]	0.059 [-0.05,0.17]	-0.000 [-0.21,0.21]	0.244 [-0.31,0.80]
Education	0.385 [-0.95,1.72]	0.015 [-0.29,0.32]	-0.215 [-1.23,0.80]	0.179 [-0.14,0.50]	-0.159 [-0.88,0.56]	-0.089 [-0.69,0.52]	0.383 [-0.94,1.71]	-0.039 [-0.26,0.18]	-0.042 [-0.42,0.33]	2.029*** [0.91,3.15]
Un-employed	-0.119 [-0.62,0.38]	0.041 [-0.14,0.22]	0.011 [-0.47,0.50]	0.038 [-0.17,0.24]	-0.183 [-0.63,0.27]	0.032 [-0.28,0.35]	-0.168 [-0.66,0.33]	-0.006 [-0.13,0.12]		
Retired	-0.423 [-0.97,0.13]	-0.038 [-0.29,0.21]	-0.525 [-1.06,0.01]	-0.088 [-0.33,0.15]	-0.204 [-0.72,0.31]	-0.024 [-0.53,0.48]	-0.426 [-0.98,0.13]	0.167* [0.00,0.33]		
Disease duration										
0-9 years	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]	0.000 [0.00,0.00]
10-19 years	-0.731*** [-1.16,-0.30]	0.011 [-0.15,0.17]	-0.717*** [-1.11,-0.32]	0.031 [-0.12,0.18]	0.125 [-0.21,0.46]	-0.128 [-0.43,0.17]	-0.712** [-1.15,-0.27]	0.033 [-0.06,0.13]	-0.028 [-0.24,0.18]	0.114 [-0.32,0.54]
20-29 years	-0.548 [-1.12,0.03]	-0.166 [-0.38,0.05]	-0.644* [-1.18,-0.11]	-0.127 [-0.36,0.11]	-0.071 [-0.58,0.43]	-0.450 [-0.96,0.05]	-0.528 [-1.11,0.06]	0.057 [-0.09,0.20]	-0.228 [-0.57,0.11]	-1.411** [-2.34,-0.49]
30-39 years	-0.084 [-0.87,0.70]	-0.034 [-0.31,0.24]	-0.441 [-1.22,0.34]	-0.122 [-0.44,0.20]	0.711* [0.12,1.30]	-0.379 [-0.94,0.18]	-0.133 [-0.93,0.66]	0.220* [0.01,0.43]	0.013 [-0.45,0.48]	-1.340 [-2.98,0.30]
40-49 years	0.458 [-1.38,2.30]	-0.110 [-0.87,0.65]	-0.137 [-1.38,1.11]	-0.141 [-0.85,0.57]	1.104 [-0.02,2.23]	-0.800 [-2.09,0.49]	-0.004 [-1.44,1.43]	-0.373 [-0.84,0.10]	0.622 [-0.75,2.00]	-0.715 [-2.53,1.10]
50+ years	-0.582	-1.599***	-2.739***	-1.404***	0.000		-0.646	0.079		

	[-1.75,0.59]	[-2.30,-0.90]	[-3.91,-1.57]	[-1.89,-0.92]	[0.00,0.00]		[-1.82,0.53]	[-0.62,0.78]		
_cons	1.870	9.082***	0.901	8.106***	-1.030	9.834***	1.843	6.464***	-0.341	9.922***
	[-0.21,3.95]	[7.86,10.31]	[-1.04,2.85]	[6.91,9.30]	[-5.10,3.04]	[8.05,11.62]	[-0.21,3.89]	[5.65,7.28]	[-1.68,1.00]	[7.46,12.38]
N	4816	4667	4928	4458	4952	291	4854	4661	3281	198

[a]*Reference level is non-present (binary variables)*

* p<.05; ** p<.01; *** p<.001

SUPPLEMENTARY FILES C: CHAPTER 4

Propensity score matching: Extended methods and results

Propensity score matching was performed using the user-written command *psmatch2* in Stata 15 (College Station, Texas)[18]. Characteristics and results of the propensity score logistic regression model are outlined in *Table C1*.

In total, 1493 patients were eligible for inclusion in this study, of which 411 patients were matched in the treatment (N=230) and control (N=181) groups. In propensity score matching, six patients in the treatment group were dropped due to a lack of common support and no match was identified for nine patients. Enrolment in the SIBDCS after 2011, disease duration (p<0.001), and the presence of EIMs (p<0.001) were significant predictors of early biologic use (Supplementary Files *Table C2*). Balance diagnostics indicated sufficient overlap on propensity scores between the treatment and control groups after matching (Supplementary Files *Figure C1*).

Table C1 Results of logistic regression model to determine the probability of receiving the intervention (early biologic treatment) required for propensity score matching

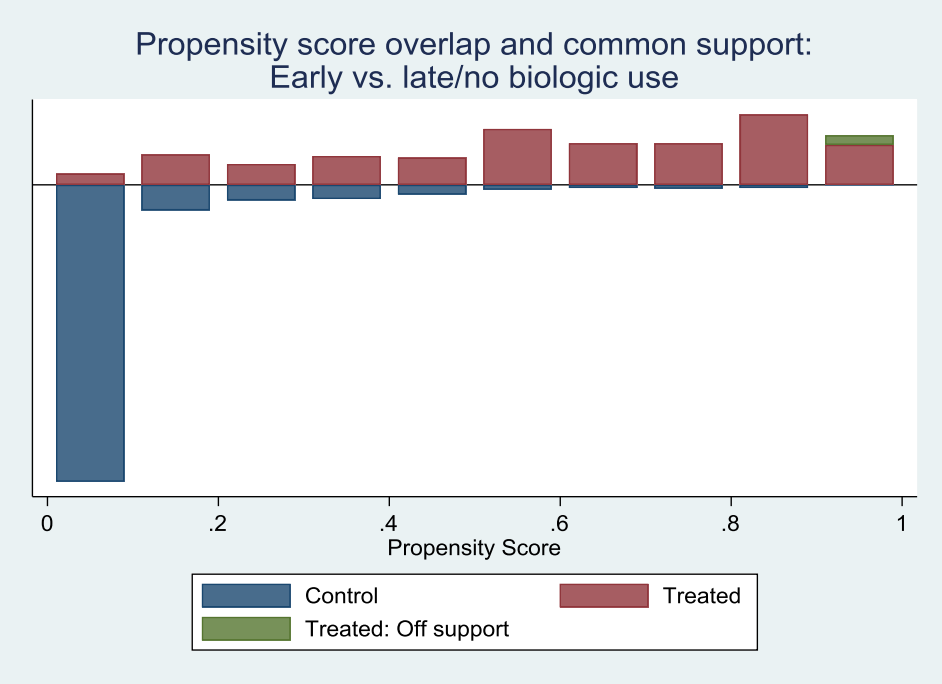
Covariates	**Coefficient [95% CI]**
Gender	
Male	0.000 [0.00,0.00]
Female	-0.264 [-0.69,0.16]
Year enrolment in SIBDCS	
2006	0.000 [0.00,0.00]
2007	0.486 [-0.82,1.80]
2008	1.281 [-0.03,2.59]
2009	1.005 [-0.39,2.40]
2010	0.725 [-0.71,2.16]
2011	1.612* [0.20,3.03]
2012	2.062** [0.62,3.51]
2013	2.275** [0.85,3.70]
2014	2.662*** [1.32,4.01]
2015	4.008*** [2.51,5.50]

2016	4.040*** [1.94,6.14]
2017	0.000 [0.00,0.00]
Canton	
AG	0.000 [0.00,0.00]
AR	0.000 [0.00,0.00]
BE	0.092 [-1.44,1.62]
BL	0.000 [0.00,0.00]
BS	0.733 [-0.84,2.30]
FR	0.000 [0.00,0.00]
GE	-0.956 [-2.68,0.76]
GR	-1.189 [-3.87,1.49]
JU	0.632 [-1.35,2.61]
LU	-0.070 [-1.86,1.72]
NE	-0.765 [-2.45,0.92]
NW	-1.144 [-3.21,0.92]
SG	-0.472 [-2.05,1.11]
SH	0.000 [0.00,0.00]
SO	0.513 [-2.30,3.33]
SZ	-2.247* [-4.45,-0.04]
TG	0.000 [0.00,0.00]
UR	0.000 [0.00,0.00]
VD	0.022 [-1.51,1.56]
ZH	0.354 [-1.24,1.95]
Age at diagnosis	-0.011 [-0.03,0.00]
Disease location at diagnosis	
L1-ileal	0.000 [0.00,0.00]

L2-colonic	-0.110 [-0.79,0.57]
L3 – ileocolonic	0.256 [-0.25,0.76]
L4 – isolated upper disease	1.873* [0.08,3.66]
L1+L4	-0.409 [-2.04,1.22]
L2+L4	0.882 [-0.78,2.54]
L3+L4	1.264* [0.21,2.32]
Smoking status at diagnosis	
Non-smoker	0.000 [0.00,0.00]
Smoker	0.409 [-0.08,0.89]
Unknown	0.160 [-0.42,0.74]
Disease duration at enrolment	-0.847*** [-1.00,-0.69]
Presence of disease complications and surgery at enrolment	
Stricture	0.096 [-0.47,0.66]
Fistula	0.588 [-0.02,1.19]
Abscess	0.324 [-0.35,0.99]
Fissure	0.173 [-0.62,0.97]
Any surgery	0.277 [-0.22,0.77]
Extra-intestinal manifestations (EIM)[a]	1.189*** [0.69,1.68]
Other major complications[b]	-0.699 [-2.29,0.89]
Disease activity at enrolment (CDAI score)[c]	
Remission	0.000 [0.00,0.00]
Mild	0.143 [-0.98,1.27]
Moderate	0.630 [-0.60,1.86]
_cons	-1.093 [-3.11,0.92]
N	1405
[a]*EIMs:* peripheral arthritis/arthralgia, uveitis/iritis, pyoderma gangrenosum, erythema nodosum, aphthous oral ulcers/stomatitis, ankylosing spondylitis, sacroilitis, and primary sclerosing	

cholangitis
[b]Other major complications: colorectal cancer, colon dysplasia, intestinal lymphoma, osteopenia/osteoporosis, anaemia, deep venous thrombosis, pulmonary embolism, nephrolithiasis, gallstone, malabsorption syndrome, massive haemorrhage, perforation/peritonitis, and pouchitis
[c]Crohn's disease activity index (CDAI) categories: remission <150; mild >=150 &< 200; moderate >=220 & <450; severe >=450
significance level at *p<0.05; **p<0.01; ***p<0.001

A



B

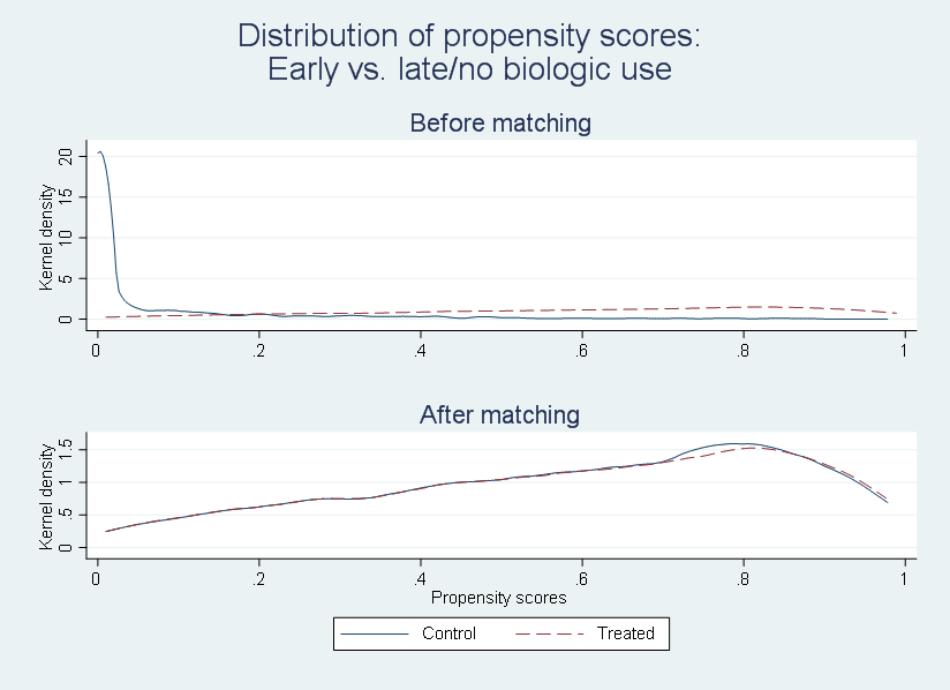


Figure C1 Propensity score balance graphs (A) indicates the overlap in the estimated propensity scores for the treatment (red) and control (blue) groups. This shows that propensity score matching is feasible since propensity scores for patients in the control groups overlapped with those in the treated group. The proportion of patients in the treatment group whose propensity scores were above the maximum value for the control group is in green (common support). The density plot (B) outlines the distribution of propensity scores for the treatment and control groups in the full sample (before matching) and in the matched sample (after matching). This shows significant overlap in propensity scores after matching

Descriptive characteristics of the population before and after propensity score matching

Table C2 Descriptive characteristics of the study population before and after propensity score matching

	Full cohort (N=1493)			Matched sample (N=411)		
	Late/no biologic use (comparator) N=1248[a]	**Early biologic use (intervention) N=245**	**p-value**	**Late/no biologic use (comparator) N=181[a]**	**Early biologic use (intervention) N=230**	**p-value**
Female (N, %)	660 (53%)	123 (50%)	0.44	94 (52%)	117 (51%)	0.83
Mean (median, IQR) age at diagnosis, years	29.0 (25.6, 19.7-35.4)	32.4 (27.9, 22.1-39.3)	<0.01	33.4 (27, 21-42)	32.8 (28, 22-40)	0.77
Mean (median, IQR) Disease duration at enrolment, years	11.9 (9.2, 4.1-17.6)	1.4 (0.9, 0.5-1.9)	<0.001	2.1 (1.4, 0.6-3.1)	1.4 (1.0, 0.5-1.9)	<0.01
Disease location at diagnosis (N, %)			<0.01			0.18
Ileal (L1)	303 (24%)	69 (28%)		62 (34%)	65 (28%)	
Colonic (L2)	283 (23%)	45 (18%)		37 (20%)	45 (20%)	
Ileocolonic (L3)	616 (49%)	120 (49%)		81 (45%)	113 (49%)	
Upper gastrointestinal involvement only (L4)	5 (0.4%)	8 (3%)		1 (1%)	7 (3%)	
Missing	41 (3%)	3 (1%)		0	0	
Complications and surgery prior to enrolment (N, %)						
Stricture	457 (37%)	48 (20%)	<0.01	44 (24%)	44 (19%)	0.20
Fistula	395 (32%)	66 (27%)	0.14	34 (19%)	58 (25%)	0.12
Abscess	265 (21%)	42 (17%)	0.15	26 (14%)	37 (16%)	0.63
Fissure	101 (8%)	21 (9%)	0.80	13 (7%)	20 (9%)	0.58
Extra-intestinal manifestations (EIM)	320 (26%)	85 (35%)	<0.01	46 (25%)	78 (34%)	0.06
Surgery	672 (54%)	82 (33%)	<0.01	59 (33%)	76 (33%)	0.92
Treatment use during follow-up (N, %)*						
Aminosalicylates	351 (28%)	29 (12%)	<0.001	56 (31%)	29 (13%)	<0.001
Antibiotic	377 (30%)	62 (25%)	0.13	52 (29%)	58 (25%)	0.43
Corticosteroids	759 (61%)	127 (52%)	<0.01	116 (64%)	123 (53%)	<0.05
Immunosuppressant	800 (64%)	104 (42%)	<0.001	128 (71%)	99 (43%)	<0.001
Biologic agent	765 (61%)	245 (100%)	<0.001	93 (51%)	230 (100%)	<0.001
Other[§]	149 (12%)	18 (7%)	<0.01	15 (8%)	18 (8%)	0.87
Mean (median, IQR) total follow-up in SIBDCS, years (Mean, SD)*	5.9 (6, 3-9)	4.2 (3, 2-6)	p<0.001	5.1 (5, 3-8)	4.3 (4, 2-7)	<0.01

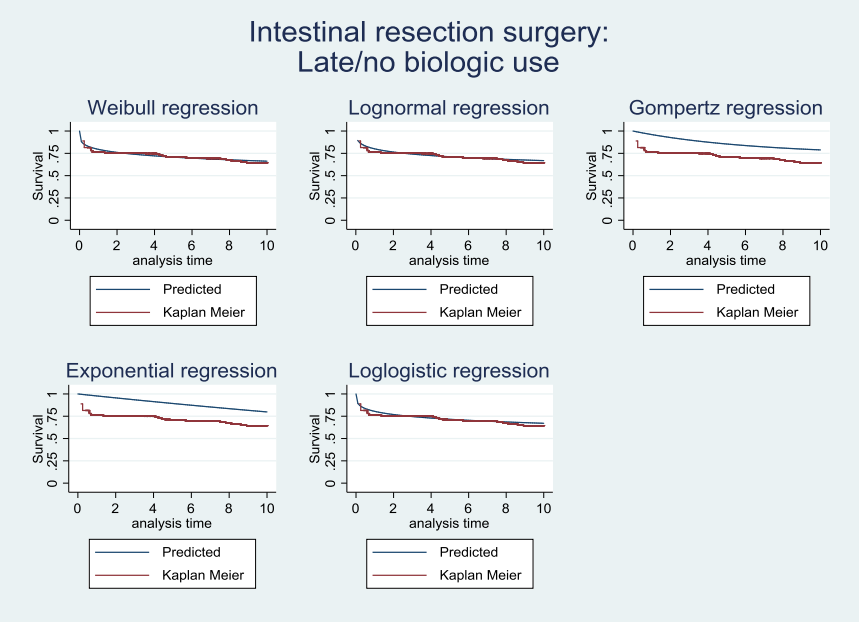
[§]Other drugs: Bisphosphonates, Cholestyramine, Mutaflor, Usodeoxcholic acid

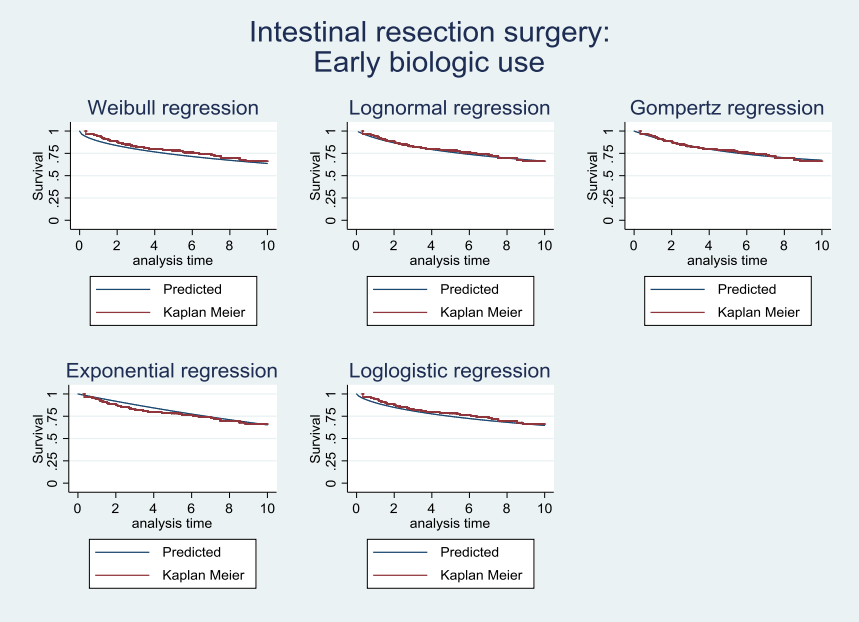
*Not included in propensity score matching logistic regression model
[a]Number of patients not receiving biologic treatments (included in the late/no biologic group):
Before matching N = 483
After matching N = 88
IQR: Inter-quartile range

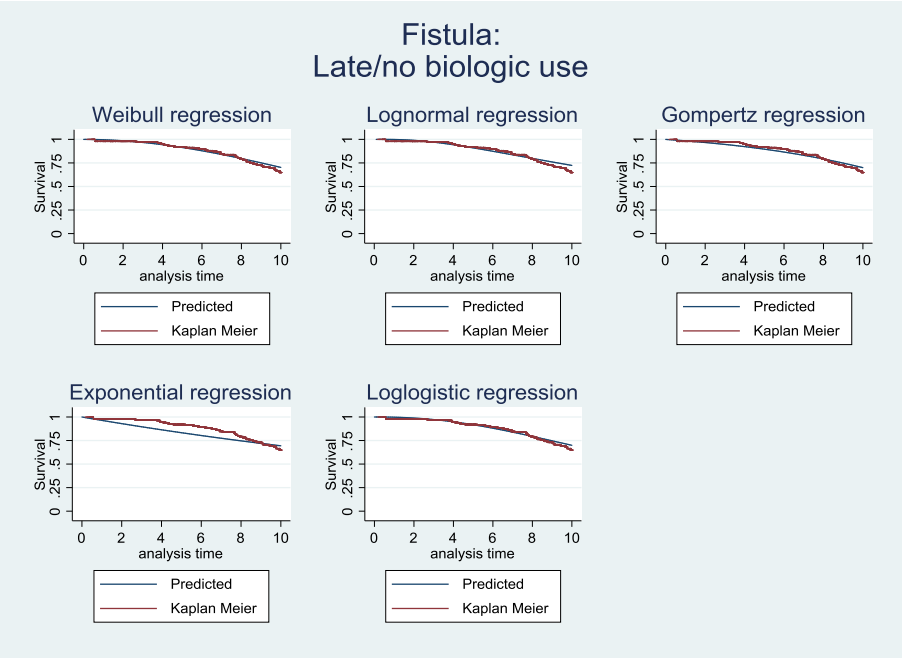
Parametric time-to-event analysis

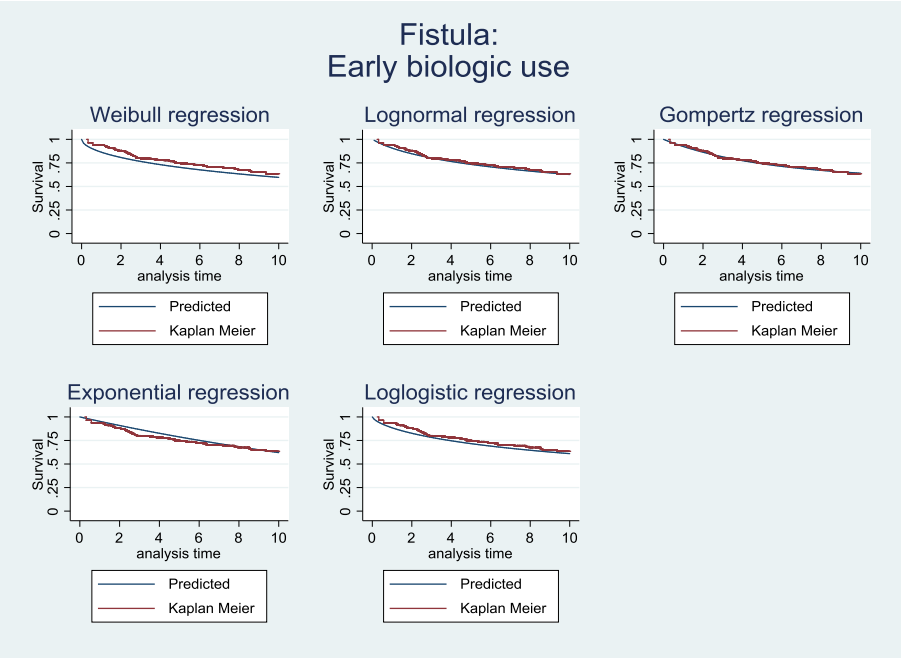
To calculate predicted annual probabilities for each event, we derived parametric survival models. Parametric models tested included the Weibull, lognormal, loglogistic, Gompertz, and Exponential distributions. Appropriate models were chosen based on visual inspection of the fit of predicted survival curves on non-parametric Kaplan-Meier curves (Supplementary Files *Figure C2*) and the Akaike Information Criteria (Supplementary Files *Table C3*).

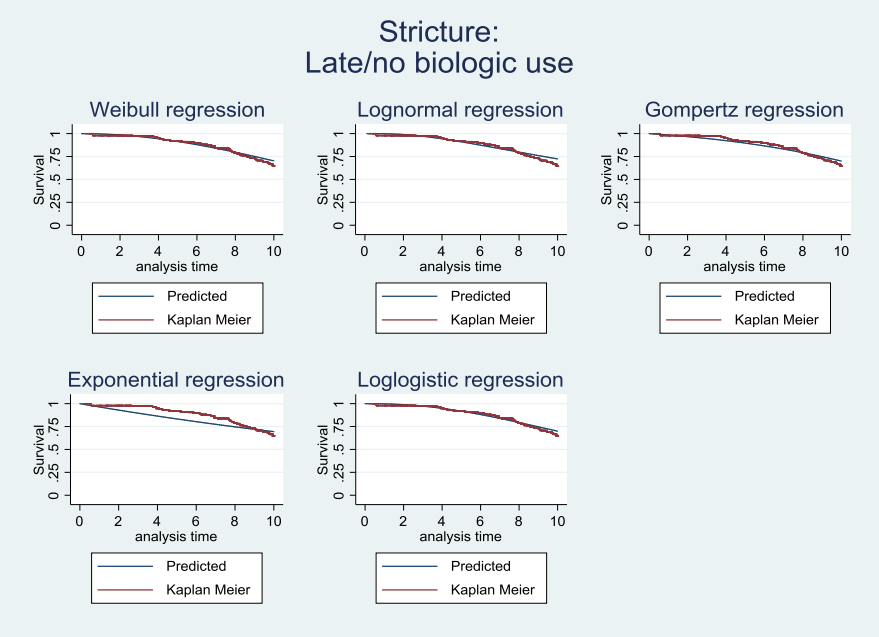
Figure C2 Predicted parametric time-to-event curves (blue) fitted against Kaplan-Meier curves (red) for each treatment group and clinical outcome. Used to visually assess goodness-of-fit of predicted time-to-event functions

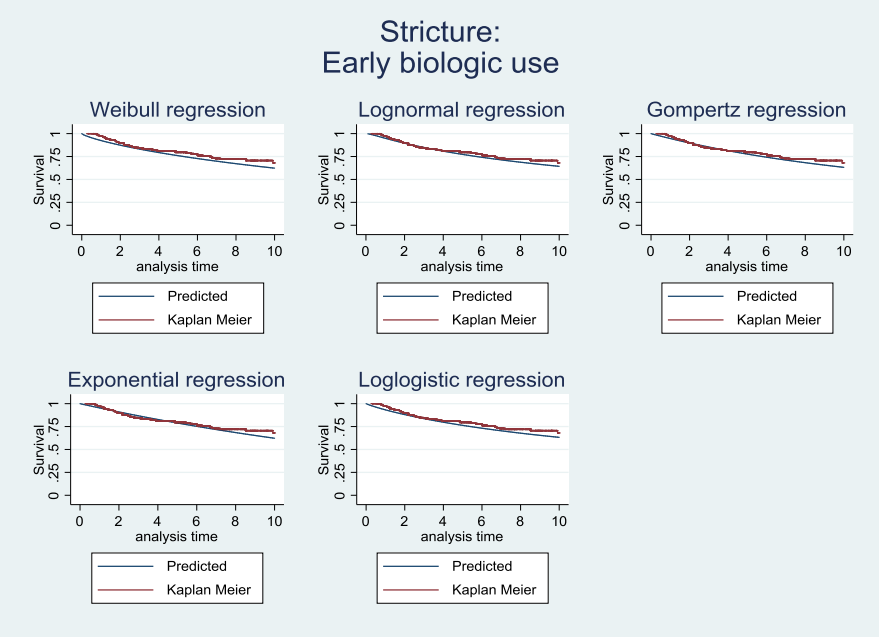


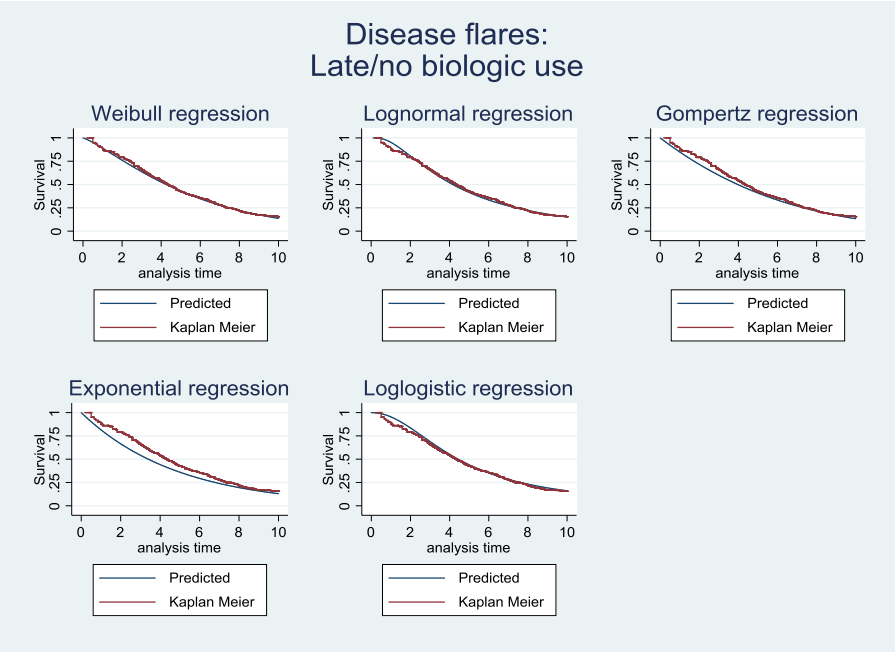



Fistula:
Late/no biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier


Fistula:
Early biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier


Stricture:
Late/no biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier


Stricture:
Early biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier


Disease flares:
Late/no biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier

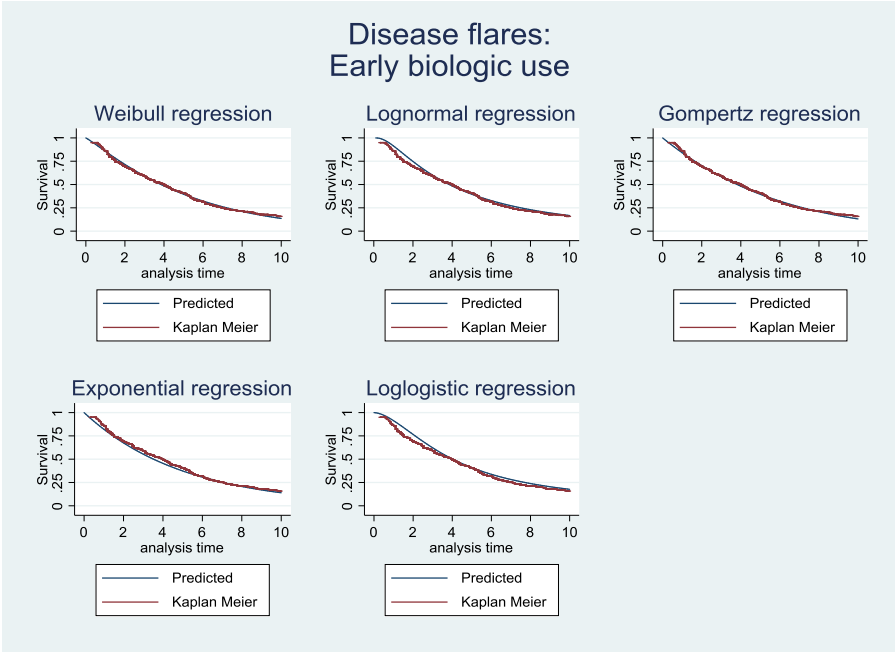

Disease flares:
Early biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier

Table C3 Akaike Information Criteria (AIC) for parametric time-to-event models

	Late/no biologic use				**Early biologic use**			
	Surgery	**Stricture**	**Fistula**	**Disease flares**	**Surgery**	**Stricture**	**Fistula**	**Disease flares**
Weibull	**154.4**	**212.1**	142.1	**395.9**	257.4	283.5	271.8	532.0
Lognormal	154.7	223.3	145.3	403.2	**257.0**	283.4	**271.4**	540.3
Gompertz	159.7	208.0	143.3	396.8	257.1	284.2	271.5	531.6
Exponential	160.5	220.8	147.5	397.9	259.7	**282.7**	274.6	**531.0**
Loglogistic	154.6	216.8	**141.7**	403.3	257.2	283.8	271.5	541.3
**Distribution chosen based on AIC and best fit on Kaplan-Meier curves are in bold*								

Subgroup analysis: Extended methods and results

Subgroup analysis: Methodology

A subgroup analysis was conducted to compare the cost-effectiveness of early vs. late biologic initiation in the population of patients who received biologic therapies during follow-up in the SIBDCS. This excluded patients who did not receive at least one dose of any biologic treatment during follow-up in the SIBDCS (N=483). Remaining patients were stratified in treatment groups based on the time to initiation of biologic treatment: early initiation was defined as starting biologic therapy within 2 years of diagnosis (N=245); and late initiation was defined as starting biologic therapy more than 2 years after diagnosis (N=765). Propensity score matching was performed for this group using key baseline characteristics as described for the base case analysis (*Table C4*). All subsequent analyses to derive transition probabilities, costs and utility estimates were performed on this matched subgroup. Propensity score matching results and descriptive statistics are outlined below.

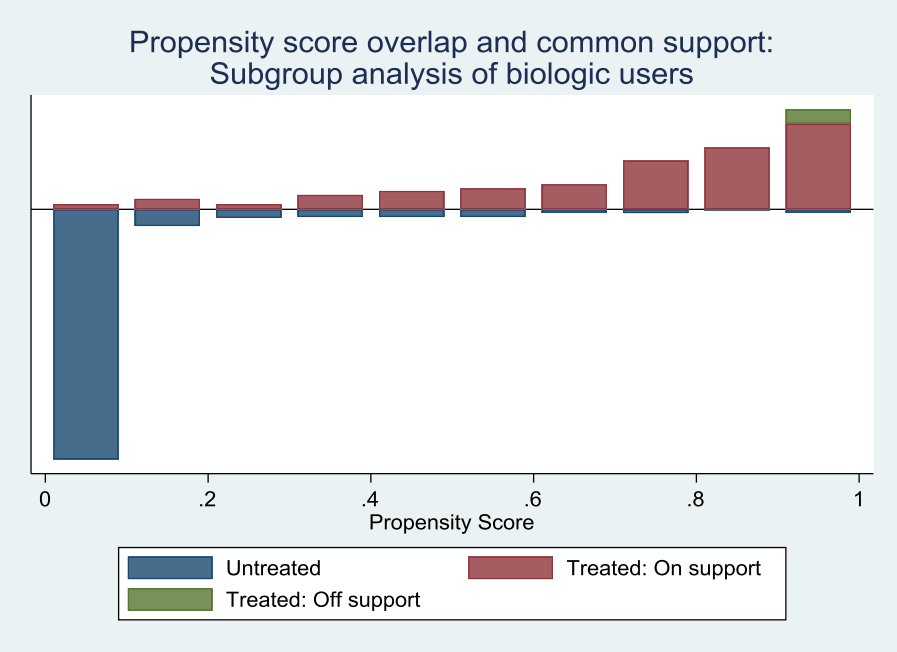
Table C4 Subgroup analysis: Logistic regression model to derive propensity score to match early biologic initiation group (treatment) to the late biologic initiation group (control) in the subgroup analysis

Covariates	**Beta (95% CI)**
Gender	
Male	Ref
Female	-0.384 (-0.92, 0.15)
Year enrolment in SIBDCS	
2006	Ref
2007	0.99 (-0.59, 2.58)
2008	2.05* (0.44, 3.65)
2009	1.4 (-0.22, 3.02)
2010	1.48 (-0.27, 3.22)
2011	2.24* (0.49, 3.98)
2012	2.85** (1.06, 4.64)
2013	3.19*** (1.47, 4.91)
2014	2.91*** (1.24, 4.58)
2015	4.59*** (2.69, 6.50)
2016	5.54*** (2.44, 8.63)
2017	0.000
Canton	
AG	Ref
AR	0.000
BE	-0.18 (-2.09, 1.73)
BL	0.00

BS	0.48 (-1.52, 2.48)
FR	0.00
GE	-0.48 (-2.55, 1.60)
GR	-1.64 (-4.26, 0.99)
JU	1.26 (-1.11, 3.63)
LU	-0.32 (-2.69, 2.04)
NE	-0.52 (-2.81, 1.76)
NW	-1.41 (-4.11, 1.30)
SG	-1.14 (-3.17, 0.89)
SH	0.000
SO	1.16 (-1.45, 3.77)
SZ	-1.64 (-4.41, 1.14)
TG	0.000
UR	0.000
VD	0.01 (-1.94, 1.96)
ZH	0.11 (-1.86, 2.08)
Age at diagnosis	0.004 (-0.02, 0.03)
Disease location at diagnosis	
L1-ileal	Ref
L2-colonic	-0.27 (-1.1, 0.52)
L3 – ileocolonic	0.15 (-0.46, 0.76)
L4 – isolated upper disease	1.61 (-1.38, 4.60)
L1+L4	0.40 (-1.78, 2.58)
L2+L4	4.28*** (2.52, 6.04)
L3+L4	0.86 (-0.42, 2.15)
Smoking status at diagnosis	
Non-smoker	0.000
Smoker	0.40 (-0.17, 0.98)
Unknown	0.11 (-0.58, 0.81)
Disease duration at enrolment	-1.02*** (-1.23, -0.82)
Presence of disease complications and surgery at enrolment	
Stricture	-0.34 (-1.00, 0.33)
Fistula	0.42 (-0.25, 1.09)
Abscess	0.85 (-0.04, 1.73)
Fissure	0.04 (-0.89, 0.98)
Any surgery	0.11 (-0.55, 0.77)
Extra-intestinal manifestations (EIM)[a]	1.04** (0.40, 1.68)
Other major complications[b]	-1.75 (-4.15, 0.65)
Disease activity at enrolment (CDAI score)[c]	
Remission	Ref
Mild	-0.16 (-1.35, 1.03)
Moderate	-0.03 (-1.34, 1.28)
_cons	**-0.45 (-2.96, 2.05)**
N	**959**

[a]*EIMs:* peripheral arthritis/arthralgia, uveitis/iritis, pyoderma gangrenosum, erythema nodosum, aphthous oral ulcers/stomatitis, ankylosing spondylitis, sacroilitis, and primary sclerosing cholangitis [b]Other major complications: colorectal cancer, colon dysplasia, intestinal lymphoma, osteopenia/osteoporosis, anaemia, deep venous thrombosis, pulmonary embolism, nephrolithiasis, gallstone, malabsorption syndrome, massive haemorrhage, perforation/peritonitis, and pouchitis [c]Crohn's disease activity index (CDAI) categories: remission <150; mild >=150 &< 200; moderate >=220 & <450; severe >=450 significance level at *p<0.05; **p<0.01; ***p<0.001	

A



B

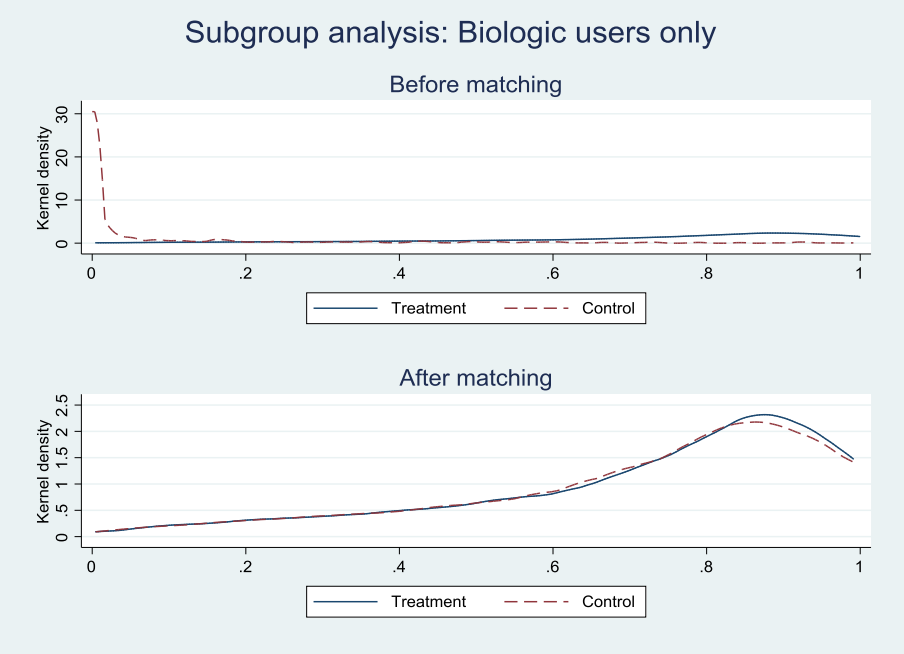


Figure C3 Subgroup analysis: Propensity score balance graphs for (A) indicates the overlap in the estimated propensity scores for the early biologic initiation (red) and late biologic initiation (blue) groups. This shows that propensity score matching is feasible since propensity scores for patients in the control groups overlapped with those in the treated group. The proportion of patients in the early biologic initiation group whose propensity scores were above the maximum value for the control group is in green (common support). (B) Outlines the distribution of propensity scores for the early biologic initiation and late biologic initiation groups in the full sample (before matching) and in the matched sample (after matching). This shows significant overlap in propensity scores after matching

Subgroup analysis: Descriptive characteristics of the sample

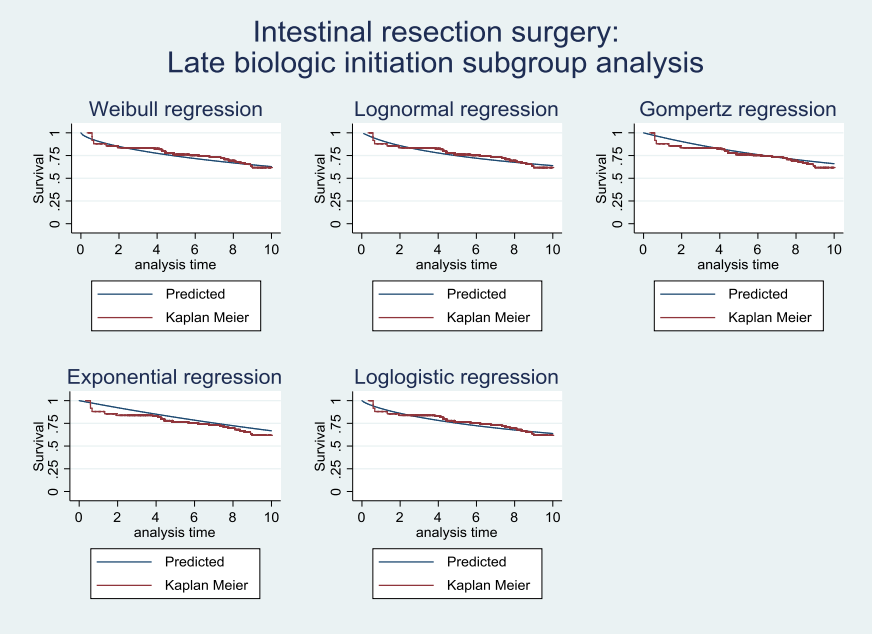
Table C5 Subgroup analysis: Descriptive characteristics of the population

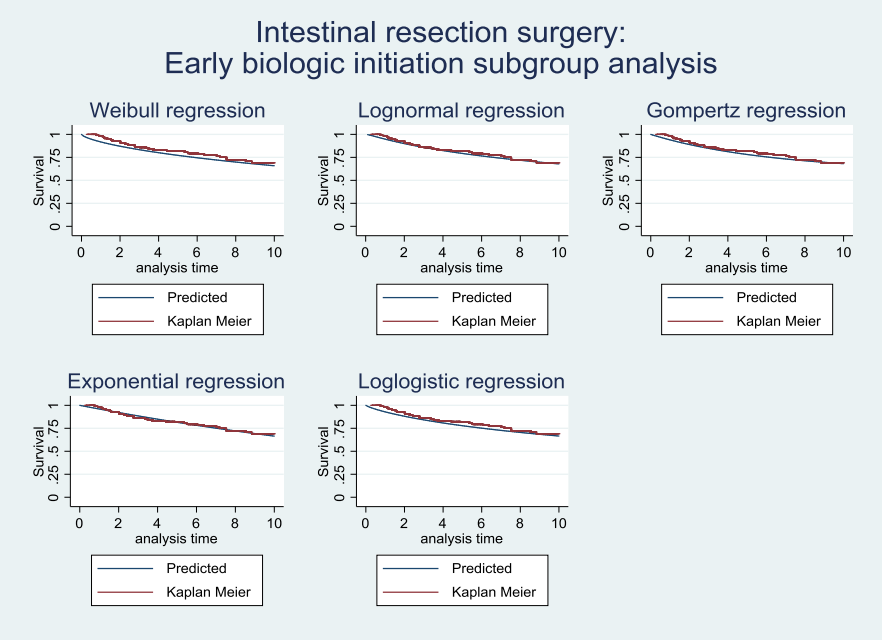
	Unmatched (N=1010)			Matched (N=337)		
	Late biologic use (Control) N=765	**Early biologic use (Treatment) N=245**	**p-value**	**Late biologic use (Control) N=112**	**Early biologic use (Treatment) N=225**	**p-value**
Female (N, %)	396 (52%)	123 (50%)	0.45	54 (48.2 %)	113 (50.2%)	0.73
Mean (median, IQR) age at diagnosis, years	26.9 (24.3, 18.7-32.8)	32.4 (27.9, 22.1-39.3)	<0.001	30.4 (26.3, 20.8-37.0)	32.5 (27.9, 22.1-38.7)	0.19
Smoking status at diagnosis (N, %)			<0.024			0.71
Non-smoker	272 (36%)	92 (38%)		38 (34%)	84 (37%)	
Smoker	320 (42%)	95 (39%)		48 (43%)	86 (38%)	
Unknown	173 (23%)	58 (24%)		26 (23%)	55 (24%)	
Mean (median, IQR) disease duration at enrolment, years	12.2 (9.8, 5.2-17.6)	1.43 (0.9, 0.5-1.9)	<0.001	2.4 (2.4, 0.8-3.2)	1.4 (1.0, 0.5-1.9)	<0.001
Disease location at diagnosis (N, %)			<0.001			0.48
Ileal (L1)	174 (23%)	69 (28%)		35 (31%)	63 (28%)	
Colonic (L2)	178 (23%)	45 (18%)		25 (22%)	43 (19%)	
Ileocolonic (L3)	384 (50%)	120 (49%)		51 (46%)	112 (50%)	
Isolated upper disease (L4) only	3 (0.4%)	8 (3%)		1 (1%)	7 (3%)	
Missing	26 (3.4%)	3 (1.2%)				
Complications at enrolment (N, %)						
Stricture	306	48	<0.001	28 (25%)	44 (20%)	0.25
Fistula	269	66	<0.001	25 (22%)	59 (26%)	0.44
Abscess	179	42	<0.01	14 (13%)	36 (16%)	0.40
Fissure	65	21	0.78	10 (9%)	20 (9%)	0.99
Extra-intestinal manifestations (EIM)	223	85	<0.01	31 (28%)	75 (33%)	0.29
Any surgery	433	82	<0.001	34 (30%)	77 (34%)	0.48
Mean (median, IQR) total follow-up in SIBDCS, years (Mean, SD)*	6.1 (7, 3-9)	4.2 (3, 2-6)	p<0.001	5.7 (6, 3-8)	4.4 (4, 2-7)	<0.001

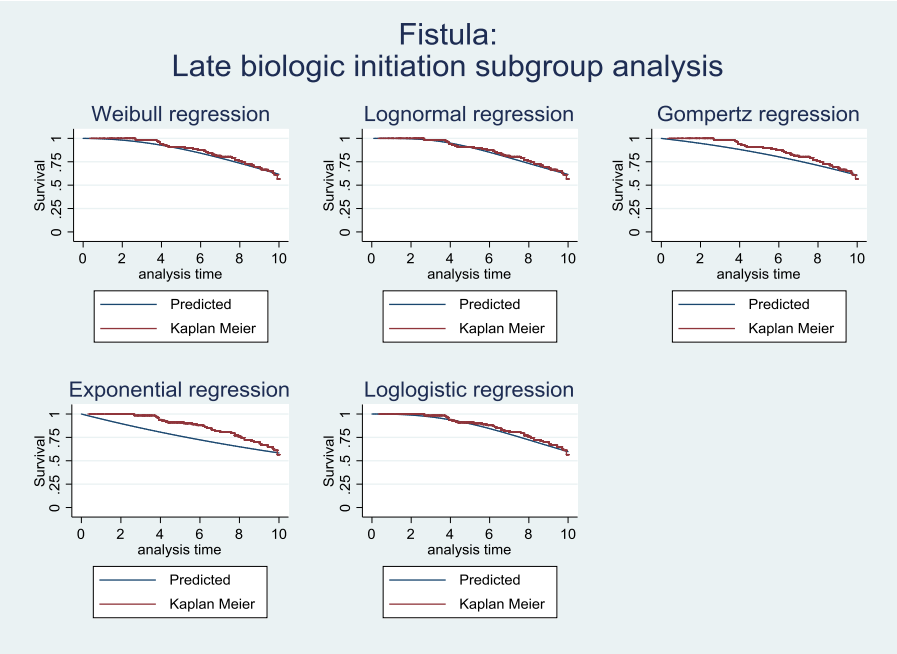
IQR: inter-quartile range
*Not included in propensity score matching logistic regression model

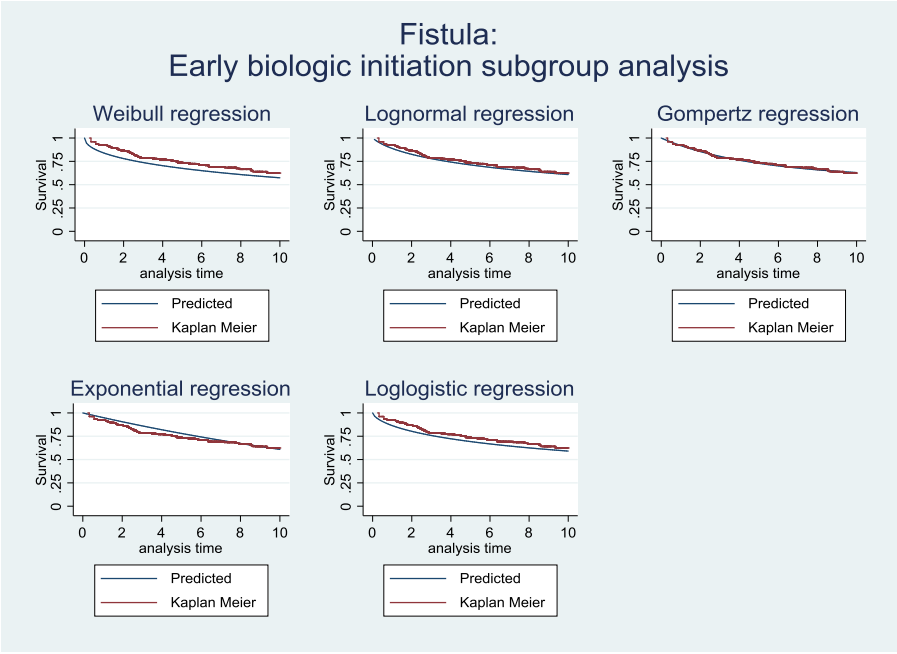
Subgroup analysis: Parametric time-to-event analysis

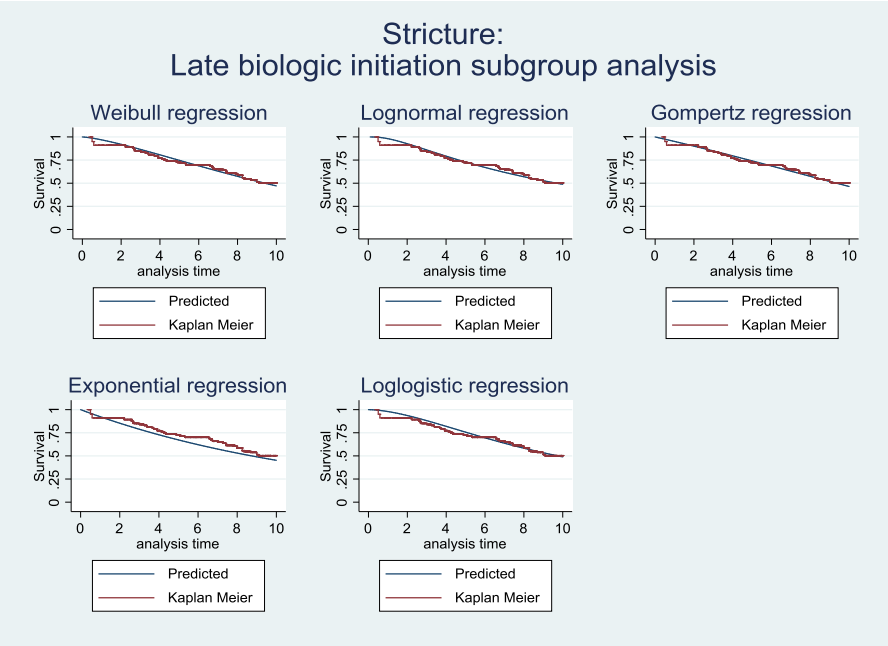
Figure C4 Subgroup analysis: Predicted parametric time-to-event curves (blue) fitted against Kaplan-Meier curves (red) for each treatment group and clinical outcome. Used to visually assess goodness-of-fit of predicted time-to-event functions

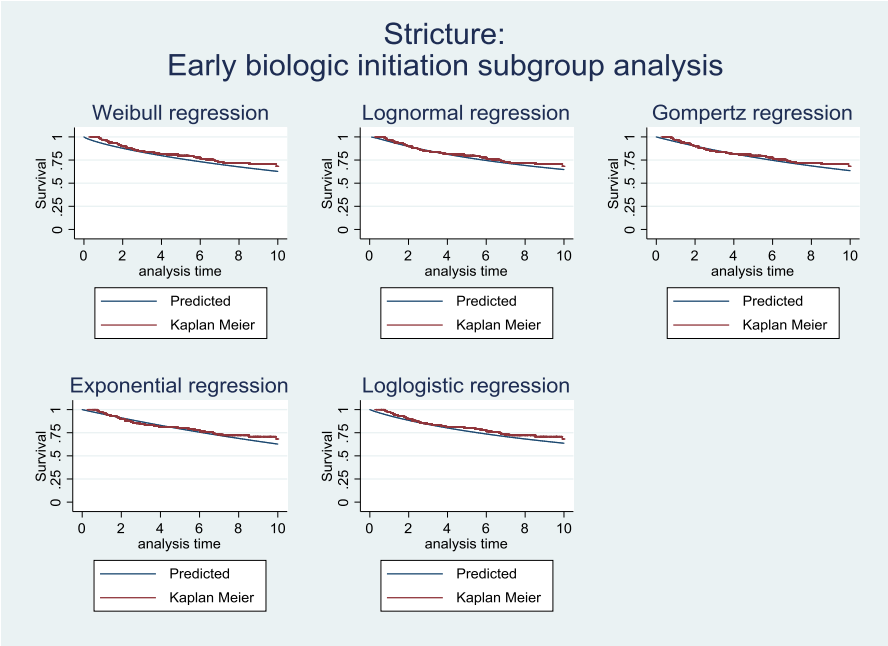


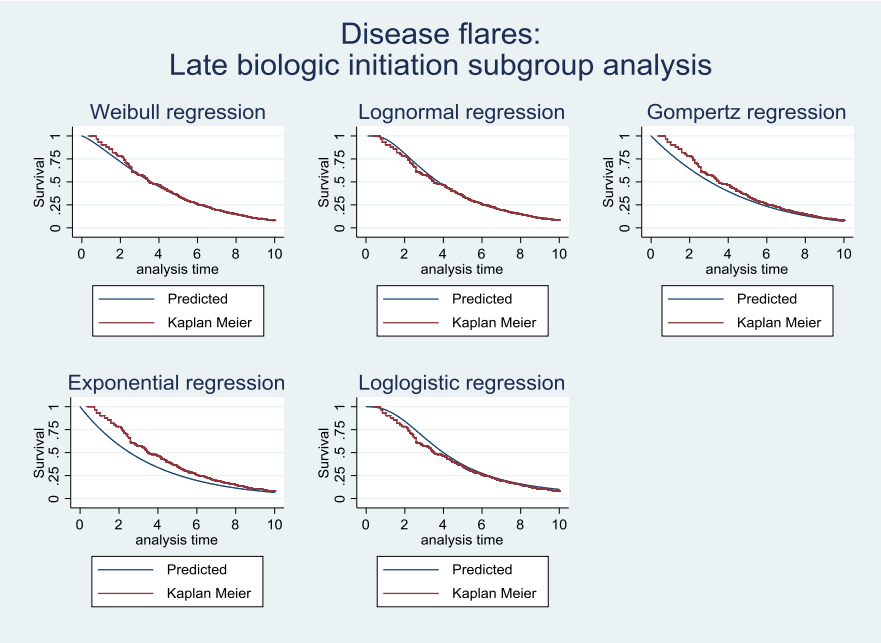



Fistula:
Late biologic initiation subgroup analysis
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier


Fistula:
Early biologic initiation subgroup analysis
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier


Stricture:
Late biologic initiation subgroup analysis
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier


Stricture:
Early biologic initiation subgroup analysis
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 2 4 6 8 10
analysis time
Predicted
Kaplan Meier



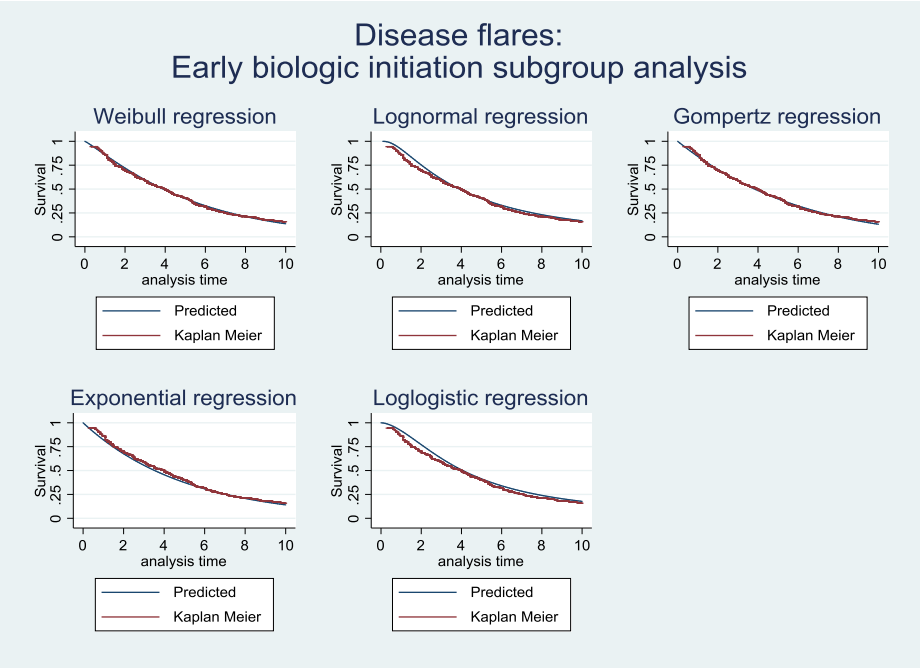


Table C6 **Subgroup analysis:** ***Akaike Information Criteria (AIC) for parametric time-to-event models***

	Late biologic initiation group				Early biologic initiation group			
	Surgery	**Fistula**	**Stricture**	**Flare**	**Surgery**	**Fistula**	**Stricture**	**Flare**
Weibull	**137.7**	115.1	**185.9**	**221.0**	244.5	277.3	277.3	522.9
Lognormal	138.4	**112.9**	190.6	223.0	**243.6**	**277.1**	277.3	530.9
Gompertz	138.6	117.9	185.1	222.9	243.5	277.5	277.9	522.6
Exponential	137.1	119.9	186.0	223.3	244.6	281.4	**276.3**	**522.1**
Loglogistic	138.1	113.5	187.8	227.0	244.1	277.1	277.6	531.5

Subgroup analysis: Predicted annual probabilities

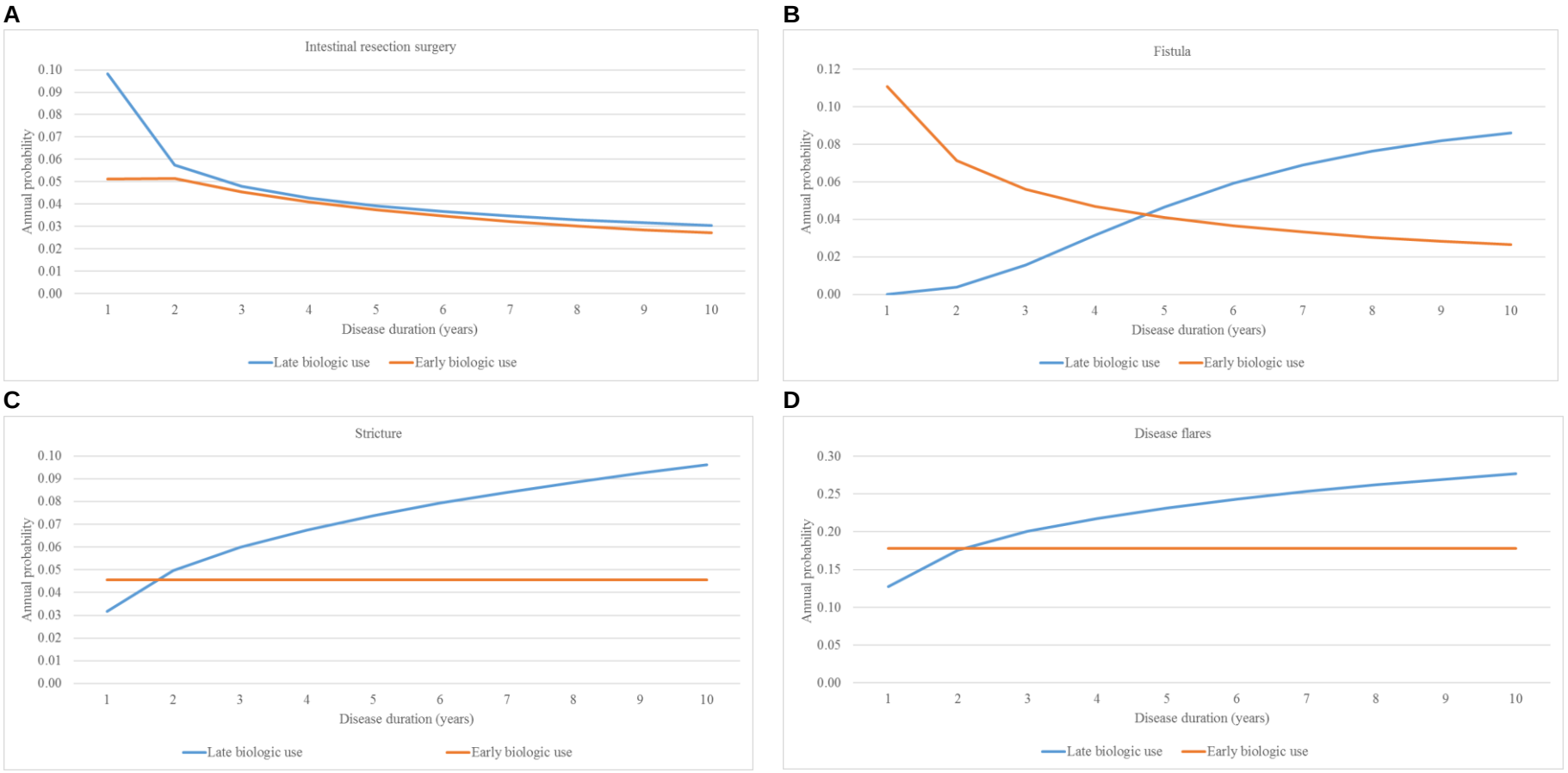


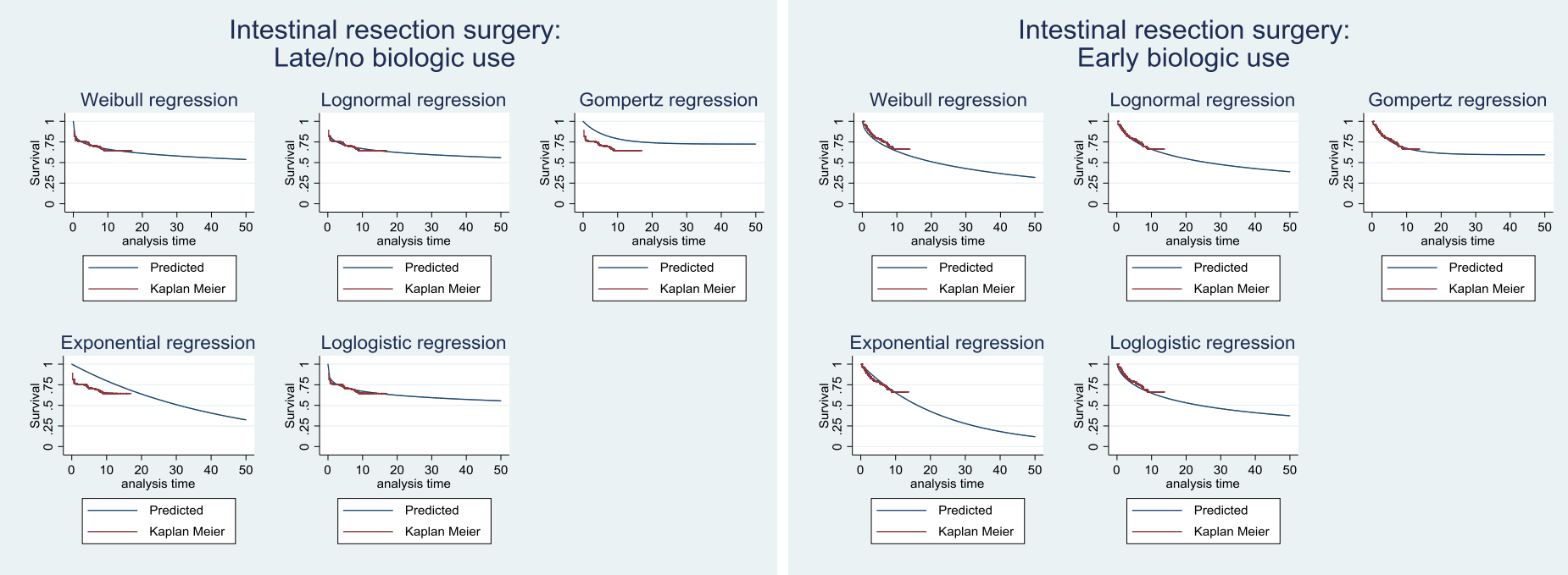
Figure C5* Subgroup analysis: *Annual probabilities of (A) intestinal resection surgery, (B) fistula, (C) stricture, and (D) disease flares over 10 years derived from parametric time-to-event analyses

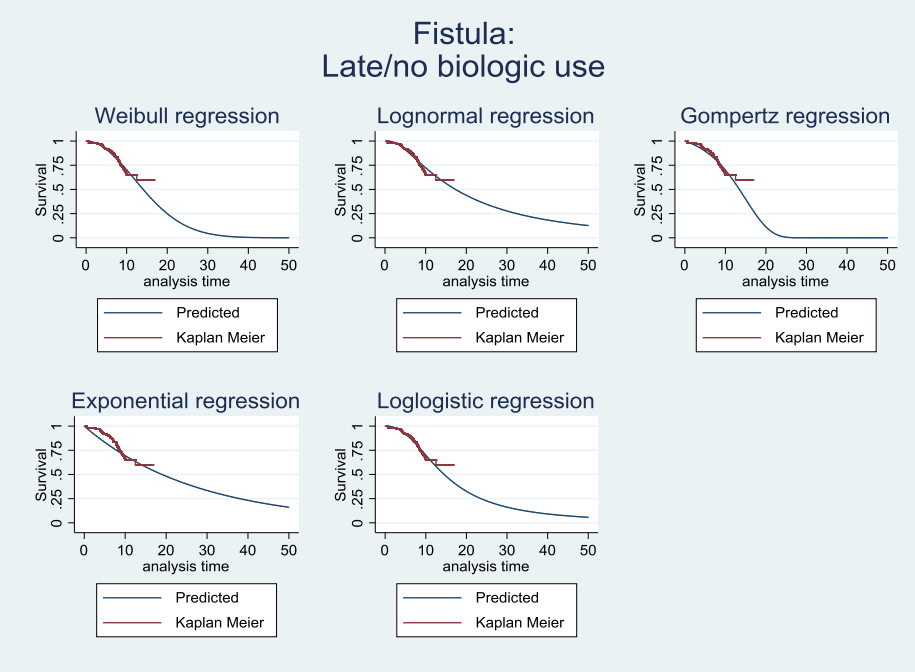
SUPPLEMENTARY FILES D: CHAPTER 5

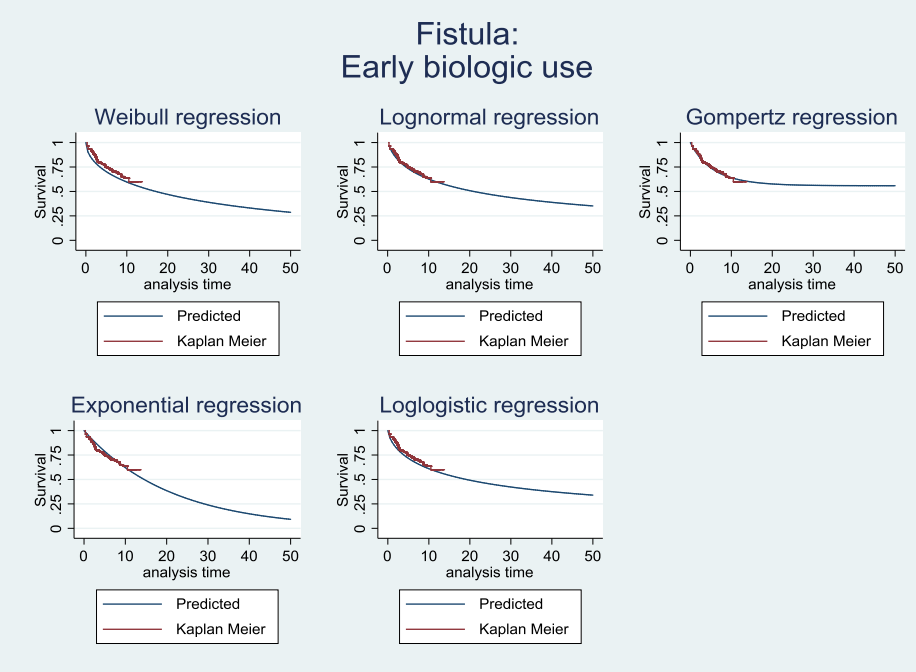
Time to event analysis: Extended methods and results

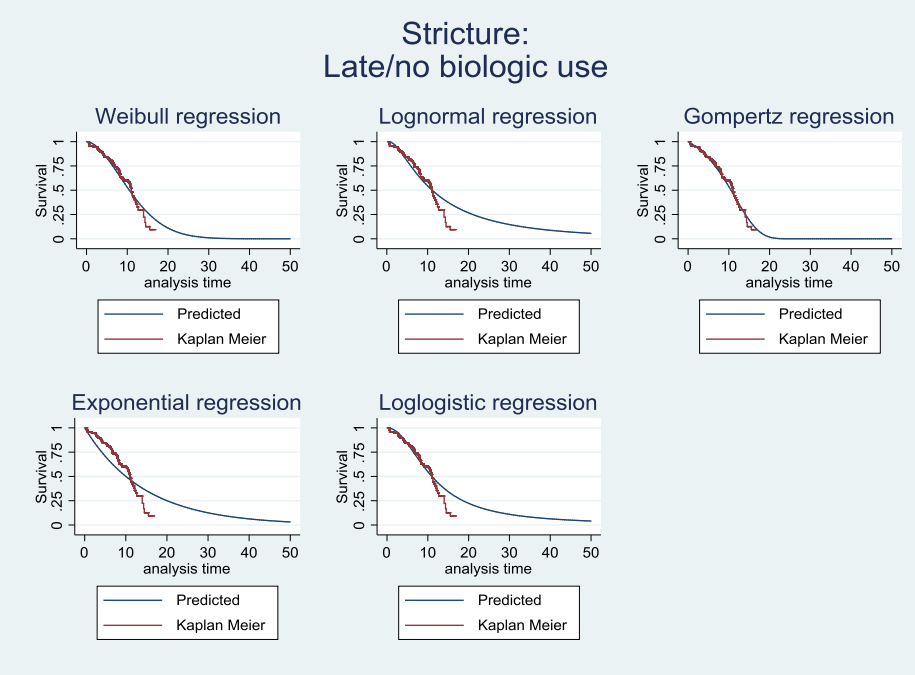
Treatment effects for disease flares, fistula, stricture, and remission were analysed using parametric time-to-event shared frailty models. These model was deemed appropriate for this analysis given the panel data structure with repeated event failures over time. In shared frailty models, the hazard function is adjusted multiplicatively assuming a gamma distribution for the frailty. Conditional predictions of the survivor function, which predict the survivor function averaged over a mean frailty of 1 were generated. A gamma distribution was assumed for the distribution of the frailty effect. Distributions were chosen based on the fit of predicted parametric time-to-event curves to Kaplan-Meier survival curves (*Figure D1*) and using the Akaike information criteria (*Table D1*).

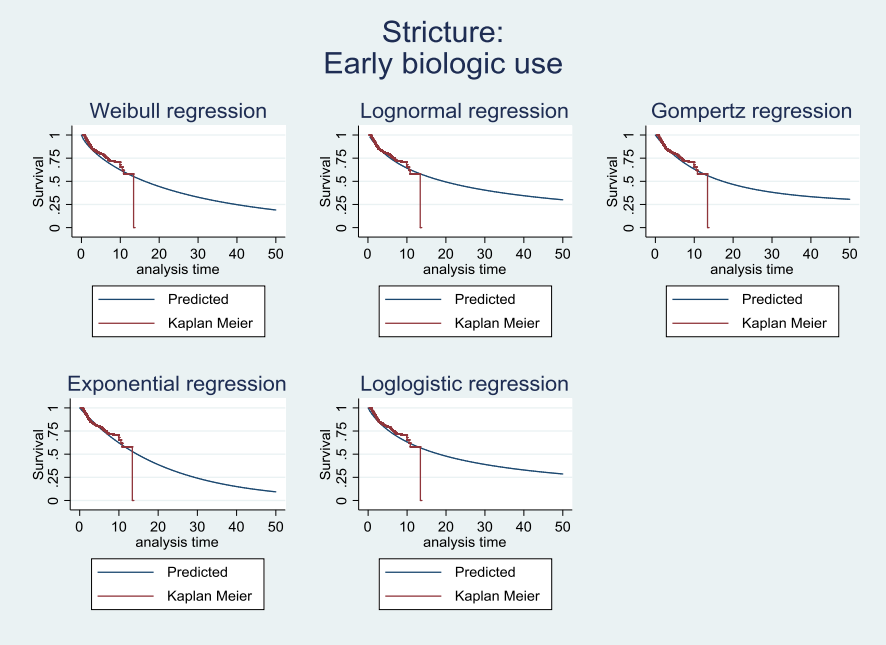
Figure D1 Predicted parametric time-to-event curves (blue) fitted against Kaplan-Meier curves (red) for each treatment group and health state. Used to visually assess goodness-of-fit of predicted time-to-event functions

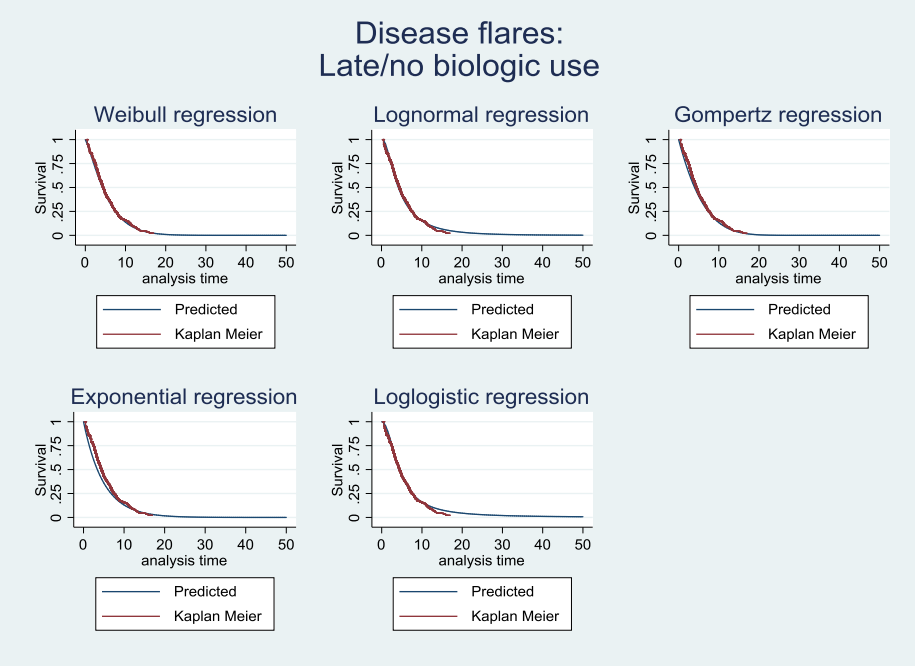


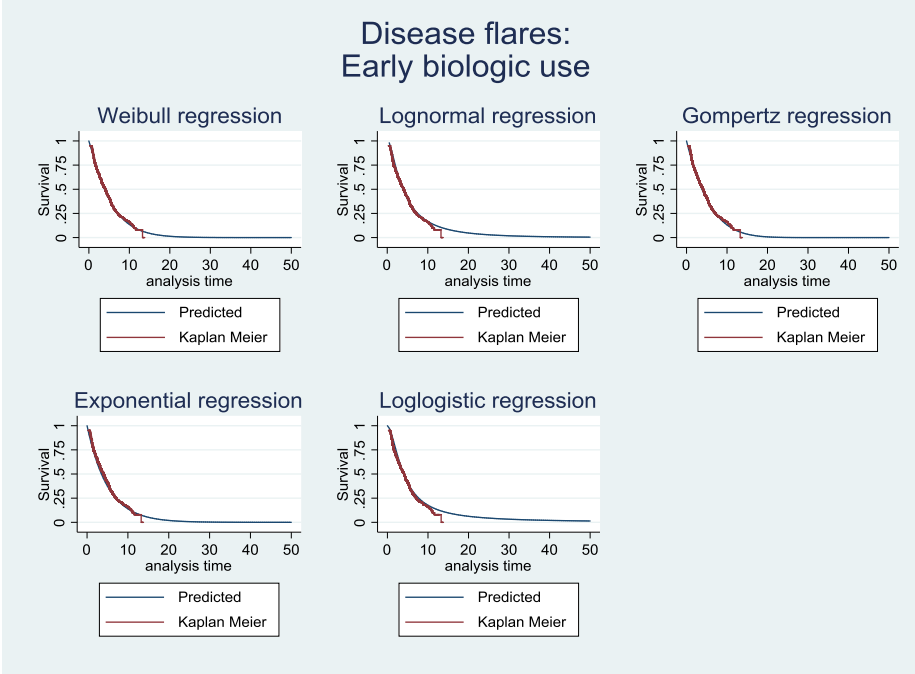

Fistula:
Late/no biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier

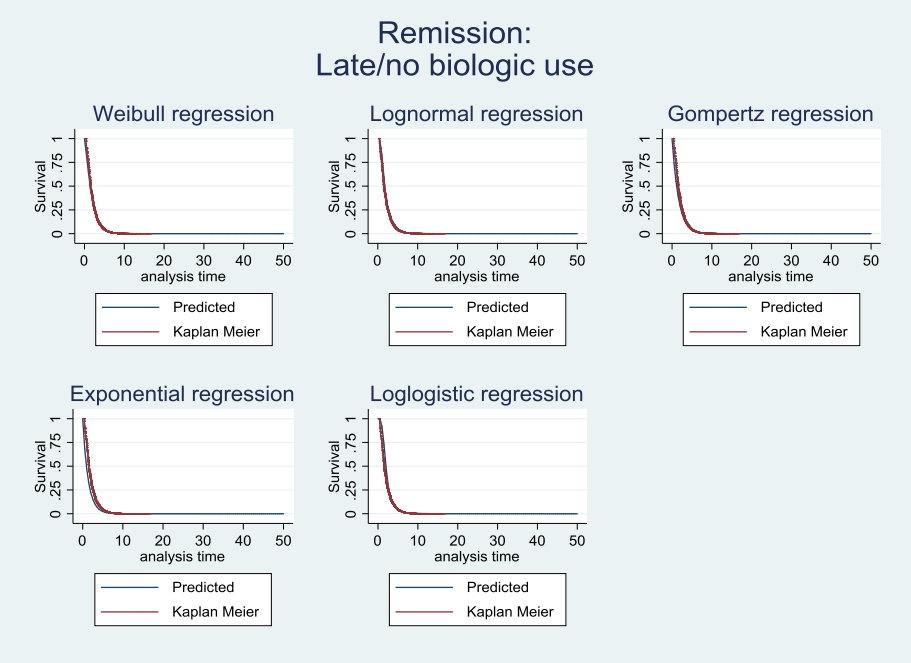

Fistula:
Early biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier


Stricture:
Late/no biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier


Stricture:
Early biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier


Disease flares:
Late/no biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier


Disease flares:
Early biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier


Remission:
Late/no biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier

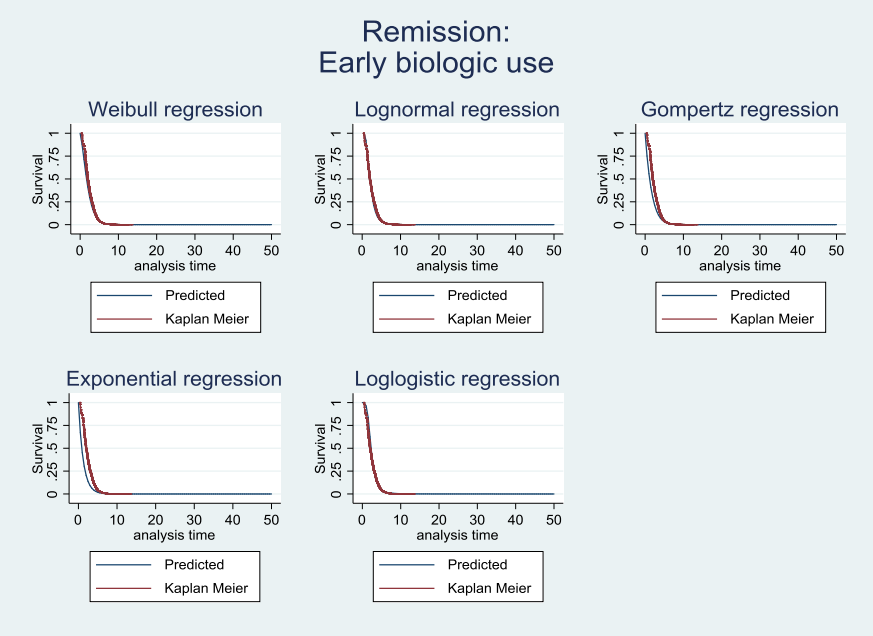

Remission:
Early biologic use
Weibull regression
Lognormal regression
Gompertz regression
Exponential regression
Loglogistic regression
Survival
0 .25 .5 .75 1
0 10 20 30 40 50
analysis time
Predicted
Kaplan Meier

Table D1 Akaike Information Criteria (AIC) for parametric time-to-event models

AIC	Late/no biologic use (Comparator)					Early biologic use (Intervention)				
	Remission	**Disease flares**	**Surgery**	**Fistula**	**Stricture**	**Remission**	**Disease flares**	**Surgery**	**Fistula**	**Stricture**
Weibull	-422.7	**395.9**	**154.4**	142.1	**212.1**	-464.2	532.0	257.4	271.8	283.5
Lognormal	**-381.8**	403.2	154.7	145.3	223.3	**-439.5**	540.3	**257.0**	**271.4**	283.4
Gompertz	-421.0	396.8	159.7	143.3	208.0	-444.7	531.6	257.1	271.5	284.2
Exponential	-412.7	397.9	160.5	147.5	220.8	-415.9	**531.0**	259.7	274.6	**282.7**
Loglogistic	-269.9	403.3	154.6	**141.7**	216.8	-338.2	541.3	257.2	271.5	283.8

**Distribution used in the base case analysis are in bold*

Table D2 Parametric time-to-event model results for distributions used in the base case analysis

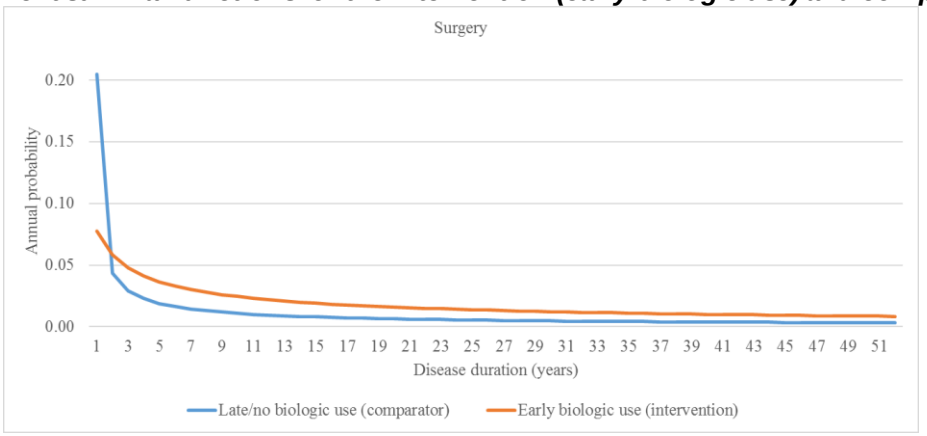
	Late/no biologic use (comparator) N=181				Early biologic use (intervention) N=230			
	Scale (beta, SE)	**Shape (p, SE)**	**Frailty (theta, SE)**	**Distribution**	**Scale (beta, SE)**	**Shape (p, SE)**	**Frailty (theta, SE)**	**Distribution**
Remission	0.56 (0.06)	-0.56 (0.04)	-1.61 (0.24)	Lognormal	0.70 (0.04)	-0.70 (0.03)	-1.94 (0.27)	Lognormal
Disease flares	-2.15 (0.30)	0.21 (0.10)	-0.76 (0.35)	Weibull	-1.63 (0.09)	N/A	-0.30 (0.27)	Exponential
Surgery	-1.47 (1.55)	-1.37 (1.22)	N/A	Weibull	3.26 (0.33)	0.83 (0.23)	N/A	Lognormal
Fistula	2.68 (0.19)	-0.82 (0.19)	2.01 (0.41)	Loglogistic	3.04 (0.41)	0.83 (0.26)	1.60 (0.36)	Lognormal
Stricture	-4.60 (0.63)	0.59 (0.15)	0.77 (0.39)	Weibull	-3.05 (0.18)	N/A	0.79 (0.45)	Exponential

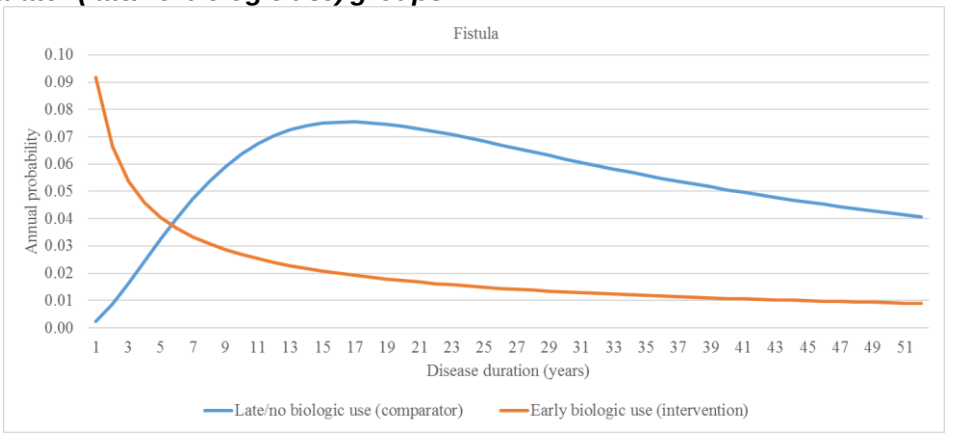
Table D3 Transition matrix for the Markov cohort model outlining possible transitions in the base case analysis

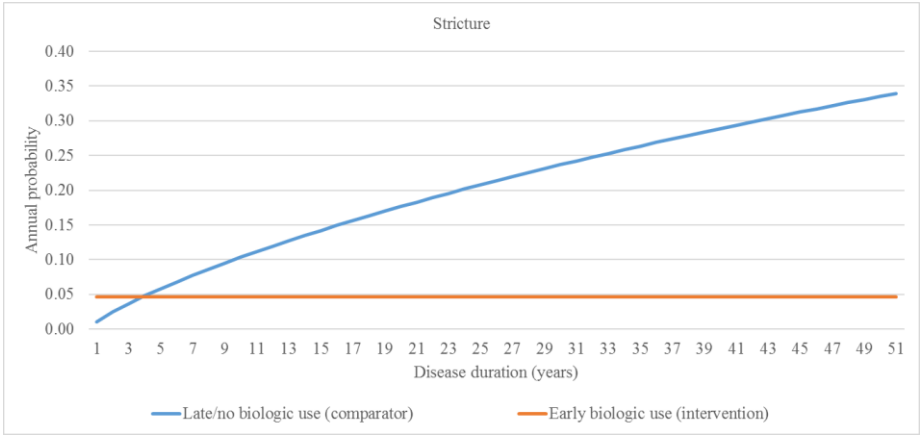
	Disease flares	**Fistula**	**Stricture**	**Surgery**	**Remission**	**Death**
Disease flares	#	p_fistula	p_stricture	p_surgery	p_remission	life tables
Fistula	p_flare	#	p_stricture	p_surgery	p_remission	life tables
Stricture	p_flare	p_fistula	#	p_surgery	p_remission	life tables
Surgery	p_flare	p_fistula	p_stricture	#	p_remission	life tables
Remission	p_flare	p_fistula	p_stricture	p_surgery	#	life tables
Death	0	0	0	0	0	1

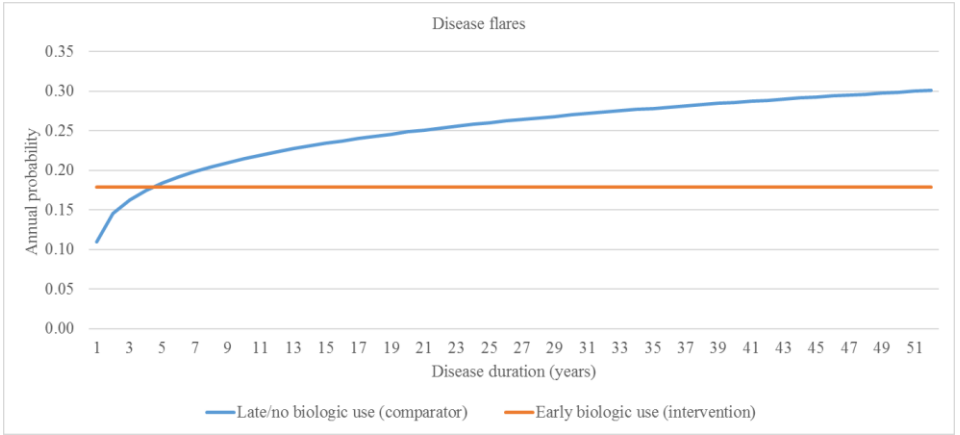
#: 1 minus the sum of all row probabilities
p_: time-varying transition probabilities used for each health state based on time-to-event survival functions; see *Figure D2*

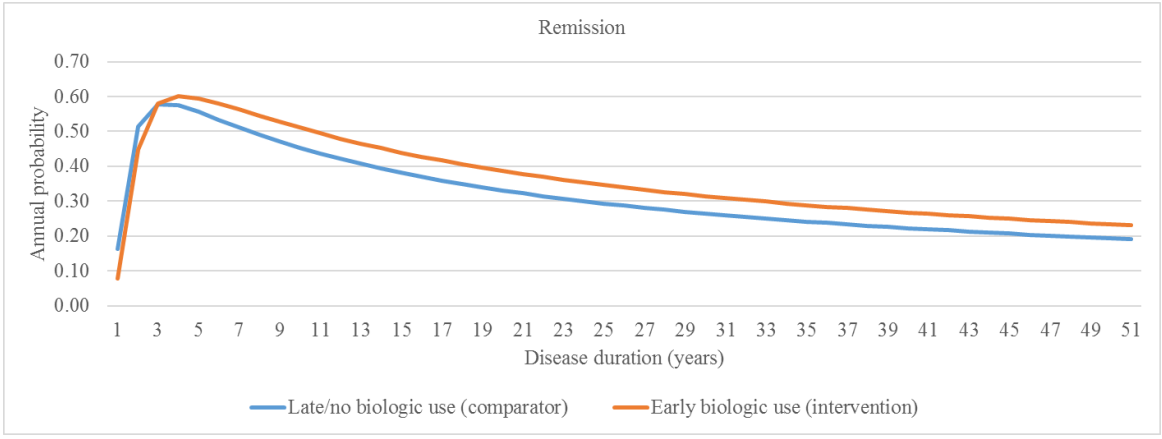
Figure D2 Annual transition probabilities by health state used in the base case analysis and extrapolated for 50 years based on parametric time-to-event survival functions for the intervention (early biologic use) and comparator (late/no biologic use) groups










Remission
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Annual probability
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51
Disease duration (years)
Late/no biologic use (comparator)
Early biologic use (intervention)

Mortality rates

Table D4 Mortality rates for the general Swiss population in 2017 in 10-year age groups

Age group	Mortality rate (%)
20 - 29	0.03%
30 - 39	0.04%
40 - 49	0.10%
50 - 59	0.28%
60 - 69	0.71%
70 - 79	1.86%
80 - 89	6.61%
90+	23.23%
Source:https://www.pxweb.bfs.admin.ch/pxweb/en/px-x-0102020206_102/px-x-0102020206_102/px-x-0102020206_102.px/?rxid=f40d14c2-5353-4268-a894-b6f6464a5d3e	

Labour force participation rates

Table D5 Labour force participation rates for Switzerland in 2017 in age groups

Age group	% participating
20 - 24	80%
25 - 29	91%
30 - 34	91%
35 - 39	91%
40 - 44	90%
45 - 49	90%
50 - 54	90%
55 - 59	85%
60 - 64	63%
65 - 69	23%
70 - 74	13%
75 - 79	7%
80+	3%
Source: https://stats.oecd.org/ Labour participation rates reported as a % of the economically active permanent resident population (≥15 years old) collected through the Swiss Labour Force Survey by the Federal Statistical Office	

Health care and treatment utilisation data

Table D6 List of pharmaceuticals, and inpatient and outpatient events evaluated in this study

Drugs	Outpatient events	Inpatient events
Sulfasalazine	CT scan	Colostomy
Oral 5-ASA	Colonoscopy	General hospitalisation (per day)
Topical 5ASA	MRI scan	Hemicolectomy
6-Mercaptopurine	Ultrasonography	Ileal resection
Azathioprine	Sigmoidoscopy	Ileocecal resection
Cyclosporine	Endoscopy	Ileostomy
Methotrexate	GP outpatient consultation	Proctectomy
Tacrolimus	Gastroenterologist outpatient consultation	Sigmoid resection
Metronidazole	Hospital outpatient department consultation	Subtotal colectomy
Ciprofloxacin	Biologic agent infusions	Total proctocolectomy
Clarithromycin		Seton, abscess drain
Prednisolone		Fistulectomy/Fistulotomy
Methylprednisone		Fistula plug
Deflazacort		Perianal abscess drainage
Budesonide		Seton drainage
Certolizumab pegol		Intra-abdominal abscess drainage
Infliximab		Fibrin glue instillation
Ustekinumab		Adhesiolysis
Vedolizumab		Appendectomy
Adalimumab		Cholecystectomy
Golimumab		
Ursodeoxycholic acid		
Bisphosphonates		
Mutaflor		
Cholestyramine		

Scenario analysis

In scenario analyses, we evaluated the impact of assumptions made to derive transition probabilities on overall results. These are outlined in transition matrices to illustrate how these scenarios differ from the base case analysis: (1) probabilities were evaluated conditional on previously experiencing an active or remission state at least once (*Table D7* and *Table D8*); (2) the probability of remission was parameterised using the complement of all probabilities (*Table D9*); and (3) probabilities were derived directly from Kaplan-Meier curves (instead of predicted parametric models) over 10 years (*Table D10*).

Table D7 Transition matrix used with conditional probability from remission to active health states

	Disease flares	**Fistula**	**Stricture**	**Surgery**	**Remission**	**Death**
Disease flares	#	p_fistula	p_stricture	p_surgery	p_remission	life tables
Fistula	p_flare	#	p_stricture	p_surgery	p_remission	life tables
Stricture	p_flare	p_fistula	#	p_surgery	p_remission	life tables
Surgery	p_flare	p_fistula	p_stricture	#	p_remission	life tables
Remission	p_remission_to_flare[§]	p_remission_to_fistula[§]	p_remission_to_stricture[§]	p_remission_to_surgery[§]	#	life tables
Death	0	0	0	0	0	1

represents 1 minus the sum of all row probabilities
p_: time-varying transition probabilities used for each health state based on survival functions
[§]Conditional probabilities from remission to active health states were estimated from the subgroup of patients who experienced at least 1 remission during follow-up

Table D8 Transition matrix used with conditional probability from active health state to remission

	Disease flares	**Fistula**	**Stricture**	**Surgery**	**Remission**	**Death**
Disease flares	#	p_fistula	p_stricture	p_surgery	p_flare_to_remission[§]	life tables
Fistula	p_flare	#	p_stricture	p_surgery	p_fistula_to_remission[§]	life tables
Stricture	p_flare	p_fistula	#	p_surgery	p_stricture_to_remission[§]	life tables
Surgery	p_flare	p_fistula	p_stricture	#	p_surgery_to_remission[§]	life tables
Remission	p_flare	p_fistula	p_stricture	p_surgery	#	life tables
Death	0	0	0	0	0	1

represents 1 minus the sum of all row probabilities
p_: time-varying transition probabilities used for each health state based on survival functions
[§]Conditional probability from active health states to remission was estimated from the subgroup of patients who experienced the active health state at least once previously

Table D9 Transition matrix when the complement was used to parameterise transitions to remission

	Disease flares	Fistula	Stricture	Surgery	Remission	Death
Disease flares	p_flare	p_fistula	p_stricture	p_surgery	#	life tables
Fistula	p_flare	p_fistula	p_stricture	p_surgery	#	life tables
Stricture	p_flare	p_fistula	p_stricture	p_surgery	#	life tables
Surgery	p_flare	p_fistula	p_stricture	p_surgery	#	life tables
Remission	p_flare	p_fistula	p_stricture	p_surgery	#	life tables
Death	0	0	0	0	0	1

represents 1 minus the sum of all row probabilities
p_: time-varying transition probabilities used for each health state based on survival functions

Table D10 Transition matrix when transition probabilities were estimated directly from Kaplan-Meier curves over 10 years

	Disease flares	Fistula	Stricture	Surgery	Remission	Death
Disease flares	#	p_fistula_KM_10_years	p_stricture_KM_10_years	p_surgery_KM_10_years	P_remission_KM_10_years	life tables
Fistula	p_flare_KM_10_years	#	p_stricture_KM_10_years	p_surgery_KM_10_years	P_remission_KM_10_years	life tables
Stricture	p_flare_KM_10_years	p_fistula_KM_10_years	#	p_surgery_KM_10_years	P_remission_KM_10_years	life tables
Surgery	p_flare_KM_10_years	p_fistula_KM_10_years	p_stricture_KM_10_years	#	P_remission_KM_10_years	life tables
Remission	p_flare_KM_10_years	p_fistula_KM_10_years	p_stricture_KM_10_years	p_surgery_KM_10_years	#	life tables
Death	0	0	0	0	0	1

represents 1 minus the sum of all row probabilities
p_: time-varying transition probabilities used for each health state based on Kaplan-Meier (KM) curves estimated over 10 years

One-way sensitivity analysis: Societal perspective

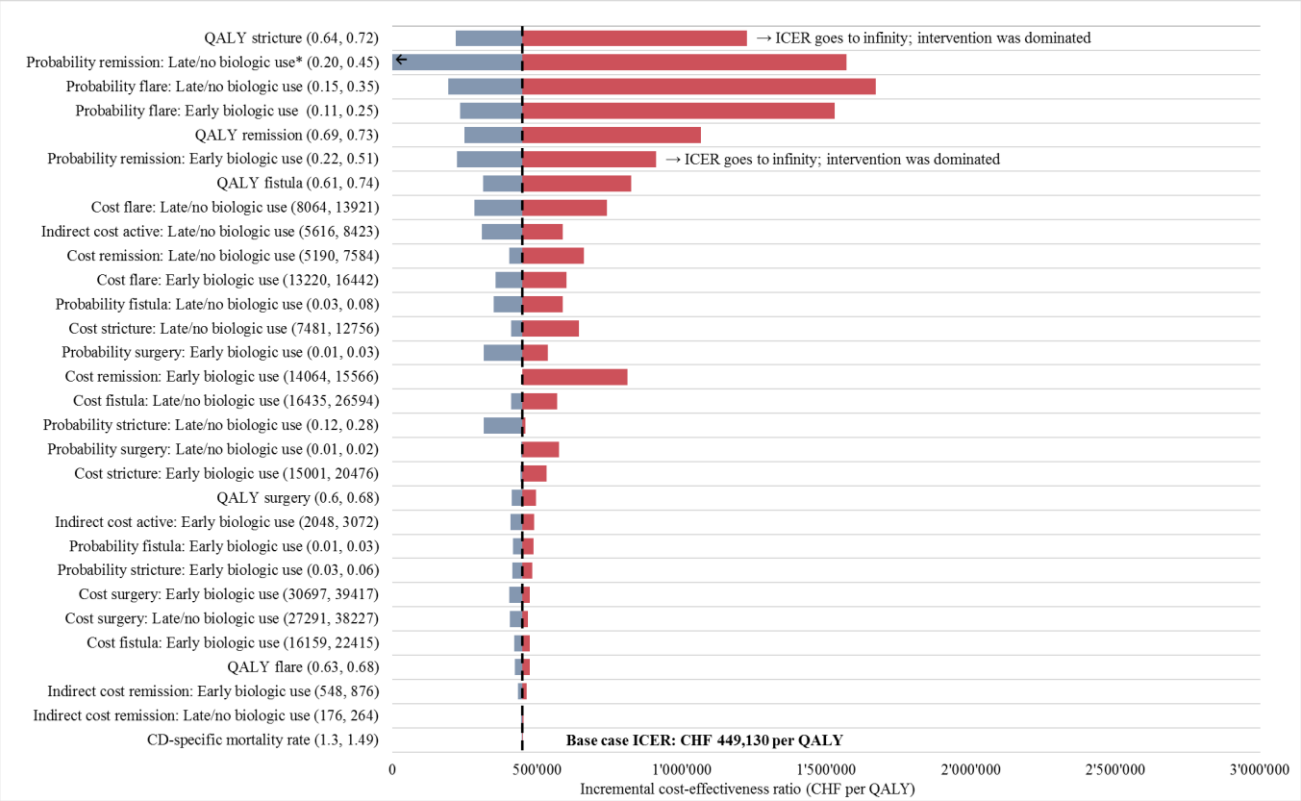


Figure D3 Tornado diagram showing influence of model parameters using in the base case analysis from the societal perspective (includes all direct health care costs and indirect costs associated with work absenteeism); *Indicates ICER turned cost-effective – intervention strategy dominant

Probabilistic sensitivity analysis: Incremental cost-effectiveness scatterplot

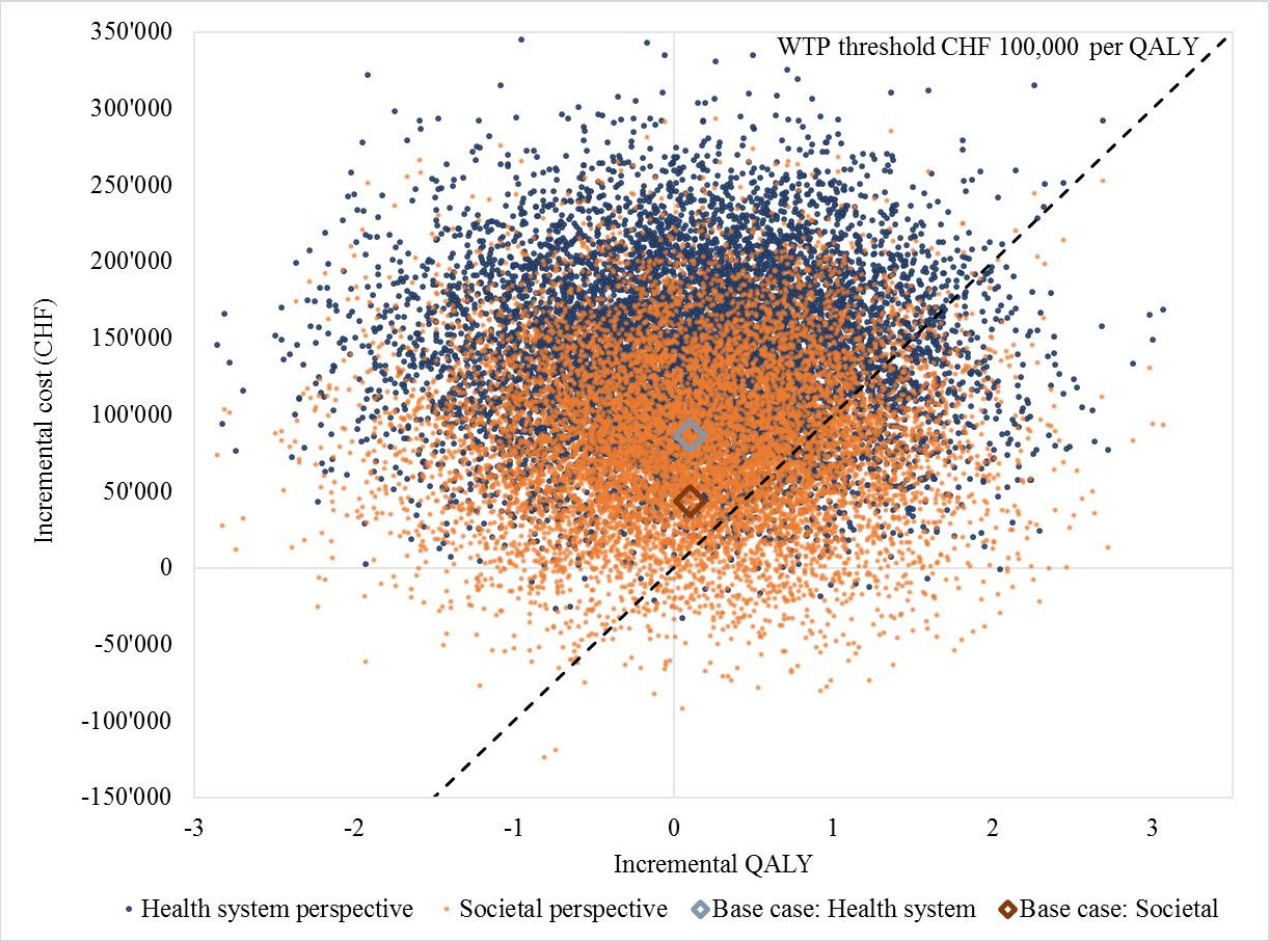


Figure D4 Scatterplot of incremental cost and QALY differences between the intervention and comparator strategies for each of the 10,000 Monte Carlo simulations in the PSA; navy circles: health system perspective; orange circles: societal perspective; base case results indicated by diamond

SUPPLEMENTARY FILES E: ADDITIONAL INFORMATION

Nadia Pillai: Bio

Nadia Pillai is a PhD student at the Center for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland. After completing a Bachelors in Psychology at the University of St Andrews, UK, Nadia pursued a Masters in Public Health from Imperial College London, UK, where she received practical training on quantitative and qualitative research methodologies in public health and health economics, including decision modelling. Prior to starting the PhD, Nadia worked at the Swiss Tropical and Public Health Institute, Basel, Switzerland, on projects related to health care costing in low- and middle-income countries. During this time she gained expertise in primary data collection while implementing studies in Ghana and Tanzania working with local academic institutions, health care professionals, Ministries of Health, and multi-national and development organisations. In addition, she gained consulting experience at IMS Health leading studies to build real world data platforms using electronic medical records, support generation for health technology assessments, and evaluate treatment patterns and patient health outcomes across a range of disease areas and geographies. Nadia's main research interests lie in the application of economic modelling to inform reimbursement decisions, improve efficiency in health care delivery and increase access to care.

List of publications and conference presentations

Pillai N, Dusheiko M, Maillard MH, Rogler G, Brüngger B, Bähler C, Pittet VEH, on behalf of Swiss IBD Cohort Study Group (2019). The evolution of health care utilisation and costs for inflammatory bowel disease over ten years. *Journal of Crohn's and Colitis*. doi: 10.1093/ecco-jcc/jjz003

Pillai N, Dusheiko M, Burnand B, Pittet V (2017). A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *PLoS ONE* 12(10): e0185500. doi.org/10.1371/journal.pone.0185500

Pillai N et al., Evaluating the cost-effectiveness of early biologic agent treatment in Crohn's disease using real world observational data in Switzerland. **Oral presentation** at: 2019 International Health Economics Association World Congress; 13-17 July 2019; Basel, Switzerland

Pillai N. Trends in costs of inflammatory bowel disease in Switzerland and implications for evaluating the cost-effectiveness of novel pharmaceuticals. **Oral presentation** at: 1st conference of the Swiss Society of Health Economics; 14 September 2018; Luzern, Switzerland

Pillai N et al., Evaluating the economic burden of inflammatory bowel disease with the introduction of novel pharmaceutical therapies in Switzerland using real world data. **Oral presentation**: 12th European Conference on Health Economics; 11-14 July 2018; Maastricht, The Netherlands

Summary (French)

Les maladies inflammatoires chroniques de l'intestin (MICI) comprennent la maladie de Crohn (MC) et la rectocolite ulcéro-hémorragique (RCUH). Ces affections chroniques du tractus gastro-intestinal pèsent lourdement sur la santé des individus et sur les coûts du système de santé. L'accessibilité accrue aux médicaments biologiques s'est révélée prometteuse pour améliorer les résultats de santé et réduire le recours aux stéroïdes et à la chirurgie; toutefois, les implications cliniques et financières de leur utilisation à long terme doivent être clairement établies. Le but de cette thèse a été d'évaluer les coûts et le rapport coût-efficacité associés aux biologiques utilisés pour traiter les MICI en Suisse. Les études conduites s'appuient sur des méthodes statistiques et économétriques appliquées aux données du monde réel de la Swiss IBD Cohort Study et aux données liées aux demandes de remboursement.
L'analyse du fardeau économique des MICI a permis d'estimer les coûts de santé moyens par patient et par an à CHF 10'553 pour la MC et CHF 6'334 pour la RCUH. Entre 2006 et 2016, les dépenses ont augmenté en moyenne de 7% par an pour la MC et 10% pour la RCUH. Les dépenses liées aux hospitalisations et soins en ambulatoire, ainsi que les coûts indirects associés à l'absence au travail, sont restés stables dans cette période. L'analyse a mis en évidence un changement important dans la prise en charge des MICI en faveur d'une utilisation accrue des médicaments biologiques.

Dans la MC, de nouvelles stratégies thérapeutiques suggèrent l'utilisation précoce de biologiques pour obtenir une guérison muqueuse et modifier la progression de la maladie à long terme. Cette thèse a montré que les patients avec MC traités par biologiques dans les 2 années suivant le diagnostic n'avaient pas de modification significative de la progression de leur maladie à long terme, ni du taux de recours à la chirurgie, comparativement à des patients à caractéristiques similaires n'ayant pas reçu de biologiques ou en ayant reçu plus de 2 ans après le diagnostic. En outre, avoir eu un biologique précocement, en comparaison avec un biologique tardivement/pas de biologique a été associé à des coûts cumulatifs plus élevés (CHF 384'607 versus CHF 340'800) et à des améliorations mineures de la qualité de vie (QALY: 16.84 versus 16.75). Cette stratégie n'était donc pas été rentable d'un point de vue coût-efficacité, le ratio coût-efficacité incrémental (ICER) dépassant les seuils acceptables du point de vue du système de santé Suisse (CHF 887'450 par QALY) et sociétale (CHF 449'130 par QALY). Toutefois, dans un sous-groupe de patients ayant reçu un traitement biologique, l'initiation précoce a amélioré les résultats cliniques et s'est révélée plus rentable que l'initiation tardive. En outre, l'utilisation future de biosimilaires, dont le prix est plus bas, pourraient contribuer à contenir l'augmentation des coûts et à améliorer le rapport coût-efficacité des stratégies précoces.

Cette thèse souligne la nécessité d'identifier les caractéristiques pouvant influencent le pronostic de la maladie afin de stratifier les patients et cibler les stratégies de traitement agressives sur ceux qui en bénéficieraient le plus. De plus, une surveillance plus étroite de l'efficacité des traitements pourrait permettre de prendre des décisions en temps opportun et assurer une meilleure gestion de la maladie. Plus généralement, ce travail contribue au développement de méthodes utilisant des données du monde réel pour évaluer les résultats de santé à long terme et les aspects coût-efficacité. Il souligne l'importance d'une évaluation continue du rapport coût-efficacité des nouveaux produits pharmaceutiques pour assurer l'optimisation de l'utilisation des ressources du système de santé.