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

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List of abbreviations:

CD: Crohn's disease; CDAI: Crohn's disease activity index; CHF: Swiss francs; CI: confidence interval; EIM: Extra-intestinal manifestations; IBD: inflammatory bowel disease; ICER: Incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life years; RCT: Randomised controlled trials; SD: Standard deviation; SE: Standard error; SIBDCS: Swiss IBD cohort study; WTP: Willingness-to-pay threshold

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ABSTRACT

Background and Aims

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 (CHF384,607; 16.84 QALYs) compared to comparator (CHF340,800; 16.75 QALYs) strategy, resulting in high ICERs (health system: CHF887,450 per QALY; societal: CHF449,130 per QALY). Assuming a threshold of CHF100,000 per QALY, in probabilistic sensitivity analysis the intervention strategy had a 0.1 and 0.25 probability of being cost-effective from the health system and societal perspectives, respectively. In addition, ICERs improved when we assumed a 30% reduction in biologic prices (health system: CHF134,502 per QALY; societal: intervention dominant).

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Conclusions

Early biologic use was not cost-effective considering a threshold of CHF100,000 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.

Keywords: Crohn's Disease; Cost-Effectiveness; Early Biologic Initiation

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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 was associated with a marked increase in health care expenditures placing significant financial pressure on the health system[3]. The changing treatment landscape and a rising prevalence[4] mark an important opportunity 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 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]. Therefore, currently available evidence need to be validated in order to inform health care planning and decision-making in Switzerland.

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.

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MATERIALS AND 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 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 measures the additional costs required to achieve one unit of additional effect, 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 is compared to a willingness-to-pay (WTP) threshold, which captures the assumed value of an additional QALY, to make conclusions about cost-effectiveness[18]. There is no commonly

accepted WTP threshold in Switzerland; therefore, based on previous literature[19-21], we tentatively used a threshold of CHF100,000 (€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[22]. 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[23]. 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. Methods and results of the propensity score model are described in Supplementary Files Table S1.

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 S2). 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 S1). 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 (see Supplementary Files Table S2 for further descriptive characteristics and a comparison of the early compared to no biologic treatment groups). 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 1.

[TABLE 1 HERE]

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 1). 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 1 HERE]

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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 S3). 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. 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[24 25]. 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 S4). 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 S2) and the Akaike Information Criteria (Supplementary Files Table S3).

Transition probabilities did not consider disease history thereby assuming that the probability of recurrent events was independent of previous health states (Supplementary Files Table S5). 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[26] (Supplementary Files Table S6). 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[27].

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 and outpatient events recorded in the SIBDCS were estimated from reimbursement claims data obtained from the Helsana Group (see Supplementary Files Table S8 for a full list of procedures considered). This is a leading health insurance company in Switzerland providing statutory health insurance to 15% of the population[4]. Costs estimated from this dataset are based on national reimbursement tariffs, which are standardised across Switzerland (TARMED[28] in the outpatient sector and Swiss diagnosis-related groups[29] in the inpatient sector) and adjust for regional variations in costs. Unit cost estimates were used to cost-weight the health care utilisation reported in the SIBDCS. Pharmaceutical costs were derived from public price lists[30] using recommended dosing schedules[31]. All costs were inflated to 2017 values using the consumer price index in Switzerland[32]. Indirect costs were calculated using 2017 national median salaries in Switzerland[33] and annual patient-reported days absent from work recorded in the SIBDCS. Swiss national labour participation rates in 2017 were used to adjust indirect costs by age[34]

(Supplementary Files Table S7). Costs are reported in CHF and converted to euros (€) using the average exchange rate in 2017 of CHF1 = €0.89[35].

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 2). 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 3).

[TABLE 2 HERE]

Quality-adjusted life years

Patient-reported quality of life was measured annually using the Short Form 36 (SF-36) questionnaire in the SIBDCS[36]. To generate utilities, patients' responses to each item in the SF-36 were mapped to the SF-6D using published algorithms[36]. Utility valuations from the SF-6D were obtained from a sample of the general population in the UK[37].

Mean utilities (Table 3) 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 3). 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 3). 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 3 HERE]

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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[38].

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 S9 and Table S10). Second, we used the complement of all probabilities in each cycle to parameterise the probability of remission (Supplementary Files Table S11). Finally, we derived transition probabilities from Kaplan-Meier curves (instead of parametric models) over a 10 year time horizon (Supplementary Files Table S12).

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 the base case analysis, we evaluated the balance between treatment groups extensively, including comparing descriptive characteristics of the non-biologic users to early biologic users (Supplementary Files "Descriptive statistics"). Although we did not find any indication of selection bias between the treatment groups after the propensity score matching, we conducted this subgroup analysis in order to address the possibility that non-biologic users might have a different, and potentially milder, disease course compared to patients who required biologic treatment. This subgroup analysis assumed prior knowledge of which patients would be likely to require biologic

therapies during the course of their disease. In this analysis, we excluded patients who did not receive at least one dose of any biologic therapy during follow-up in the SIBDCS. The remaining patients were stratified into early (≤2 years after diagnosis) and late (>2 years after diagnosis) biologic initiation groups. Propensity score matching was used to ensure that patients in each group were comparable based on observed baseline characteristics. The propensity score model was derived as described previously and results are outlined in Supplementary Files Table S13 and Figure S4). Transition probabilities, costs, and QALYs were estimated after propensity score matching as described previously. Descriptive characteristics and annual transition probabilities for this subgroup are summarised in Supplementary Files Table S14 and Figure S5.

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, which were found to be consistent. In addition, we performed quality control of inputted formulae and parameters. Finally, the plausibility of the model structure, inputs and results were compared to previous literature and are discussed.

Ethical approval

Ethical approval for the Swiss IBD Cohort Study was obtained from regional Swiss ethics committees where participants were enrolled [Commission d'éthique du Canton de Vaud/Protocol no. 33/06]. Written informed consent was obtained from all patients enrolled.

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RESULTS

Base case cost-effectiveness analysis

The intervention strategy cost CHF86,562 (€77,464) and CHF43,808 (€39,204) more compared to the comparator over patients' lifetime from the health system and societal perspectives, respectively (Table 4). Despite incurring 0.1 more QALYs and CHF42,754 (€38,261) lower indirect costs, ICERs were above the WTP threshold from both perspectives (health system: CHF887,450/€794,180 per QALY; societal: CHF449,130/€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 2). In addition, patients in the intervention group received biologic therapies for 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 lower lifetime risks of disease flares and strictures, and higher probabilities of being in remission for patients in the intervention strategy (Supplementary Files Figure S3).

[TABLE 4 HERE]

Sensitivity analysis

In one-way sensitivity analysis, the ICER from the health system perspective was most sensitive to changes in the utility value for strictures, the probability of disease flares in the intervention and comparator groups, and the probability of remission in the comparator group (Figure 2). 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 CHF100,000 per QALY when varied over its 95% CI. Similar results were found from the societal perspective (Supplementary Files Figure S6). 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 2 HERE]

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 3). The majority of simulations were clustered above the WTP threshold (Supplementary Files Figure S7).

[FIGURE 3 HERE]

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 5). ICERs remained above the WTP threshold when using alternative transition probabilities and when utility estimates were varied for remission (CHF169,160 per QALY), fistula (CHF311,015 per QALY), and surgery (CHF1,160,000 per QALY) (Table 5).

Assuming a 30% reduction in the price of biologics reduced the ICER from the health system perspective (CHF134,502 per QALY). Moreover, from the societal perspective, costs were lower and QALYs were higher (dominance) for the intervention group (Table 5).

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 S5).

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[TABLE 5 HERE]

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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 CHF100,000 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. These were not fully offset by the QALY improvements associated with a reduced lifetime risk 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 those who received biologic treatments early (Supplementary Files Table S2). Amongst, non-biologic users we observed higher rates of surgery early on in the disease course, which could suggest a preference for surgical treatment instead of biologic treatment for some patients. Thus, widespread adoption of an early biologic treatment strategy could lead to overtreatment of these patients who may respond to alternative treatment approaches, 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[39 40]. 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[41]. 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 course of the disease and therefore would be appropriate to target for early biologic treatment. Thus, a better understanding of the phenotypic, genetic and serological characteristics of patients likely to benefit from and respond to aggressive biologic treatment approaches could help target early treatment strategies to the appropriate patients. Moreover, recent literature has shown that faster escalation of biologic treatments based on closer monitoring of known biomarkers of inflammation (such as C-reactive protein and faecal calprotectin) improved remission rates and was cost-effective compared to the conventional step-up approach where treatments were escalated based on clinical symptoms using disease activity scores[42 43]. Tight monitoring and rapid step-up treatment strategies will also be associated with increased costs due to frequent follow-up tests and consultations. Therefore, developing predictive models might help identify patients with a high likelihood of progressing to biologic treatment.

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[44].

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 45]. 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[45]. 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 analyses 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 CHF100,000 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.

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Conflicts of interest

All co-authors report no conflicts of interest related to the submitted work. Outside the submitted work, MS reports grants from Merck Sharp & Dohme (MSD), Novartis, and Sandoz, and personal fees from Pfizer, BMS, and Sandoz; MM reports grants from Takeda, Vifor, and UCB, and personal fees from Takeda, Abbvie, and MSD.

Authors' contributions

NP, JL, MD, CSS, and VP conceived of and designed the study. NP wrote the original draft of the article and NP, JL, MD, MS, MM, CSS, and VP revised it critically for important intellectual content. NP, JL, MD, MS, MM, CSS, and VP approved the final version of the article to be submitted.

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. *J Crohns Colitis* 2013;7(4):322-37. doi: 10.1016/j.crohns.2013.01.010
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. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 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 t 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. Swiss Supreme Court. Bundesgerichtsentscheid 9C_334/2010—Regeste und Auszüge: Regeste des Entscheids vom 23. November 2010 [Swiss Supreme Court decision 9C_334/2010 - Regest and extracts from 23 November 2010]. *Bioethica Forum* 2011;4(3)
21. Pfeil AM, Reich O, Guerra IM, et al. Cost-effectiveness analysis of sofosbuvir compared to current standard treatment in Swiss patients with chronic hepatitis C. *PLoS One* 2015;10(5):e0126984. doi: 10.1371/journal.pone.0126984 [published Online First: 2015/05/15]
22. Valerie Pittet, Pierre Michetti, Christoph Mueller, 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
23. 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.
24. Cleves M, Gutierrez R, Gould W, et al. An introduction to survival analysis using Stata. 3 ed. College Station, Texas: Stata Press 2010.
25. Gutierrez R. Parametric frailty and shared frailty survival models. *The Stata Journal* 2002;2(1):22-44.
26. 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.
27. 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]
28. FMH. TARMED – umfassender Einzelleistungstarif [Available from: https://www.fmh.ch/ambulante_tarife/tarmed-tarif.html accessed 29 May 2018.
29. Federal Office of Public Health. SwissDRG tariff system 2019 [Available from: https://www.bag.admin.ch/bag/en/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Spitalbehandlung/Tarifsystem-SwissDRG.html accessed 10 October 2019.
30. Bundesamt für Gesundheit. Spezialitätenliste (SL) [Available from: http://www.xn--spezialittenliste-yqb.ch/ accessed 11 Feb 2019.
31. 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]
32. OECD. Inflation (CPI) 2018 [Available from: https://data.oecd.org/price/inflation-cpi.htm#indicator-chart accessed 29 May 2018.
33. 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.
34. Organisation for economic cooperation and development (OECD). Labour force statistics by sex and age - indicators, 2017.
35. 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.
36. 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.
37. 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]
38. IMS Institute for healthcare informatics. Delivering on the potential of biosimilar medicines: The role of functioning competitive markets. Parsippany, NJ, 2016.
39. 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]

40. NHS England. NHS set to save £150 million by switching to new versions of most costly drug, 2018.
41. 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]
42. 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
43. 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]
44. 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]
45. 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]
46. 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.

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FIGURE LEGENDS

Figure 1 Graphical representation of Crohn's disease Markov model structure and movements between health states

Figure 2 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

Figure 3 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

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TABLES AND FIGURES

Table 1 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

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Table 2 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; Source:

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https://www.ecb.europa.eu/stats/policy_and_exchange_rates/euro_reference_exchange_rates/html/eurofxref-graph-chf.en.html

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Table 3 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	Table 2	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)

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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	Table 2	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)

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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)
Annual transition probabilities	**Annual transition probability**	**95% CI**	**Beta distribution (Mean[b], SE[‡])**
Late/no biologic use (comparator): Disease flares	Supplementary Files Figure S3	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)

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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	Supplementary Files Table S6		
Other parameters			
Crohn's disease standardised mortality rate[27]	1.39	1.3, 1.49	N/A

[‡]Standard deviation (SD) defined as 20% of mean

[§]Mean indirect costs were adjusted for the labour participation rates in Switzerland (see Supplementary Files Table S7)

[a]The mean cost value used in PSA reflect the mean cost averaged over disease duration

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[b]The mean transition probability per health state was calculated by averaging annual probabilities over 50 years

*Mean ± 20% used because 95% CI was negative

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

	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)

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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

CHF: Swiss francs

Euros (€)

Table 4 Cost-effectiveness results for the base case analysis

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Table 5 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 S14)	-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

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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					

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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)[45] [ǂ]Gregor et al. (1997)[46] [§]IMS Institute for healthcare informatics (2016)[38] [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					

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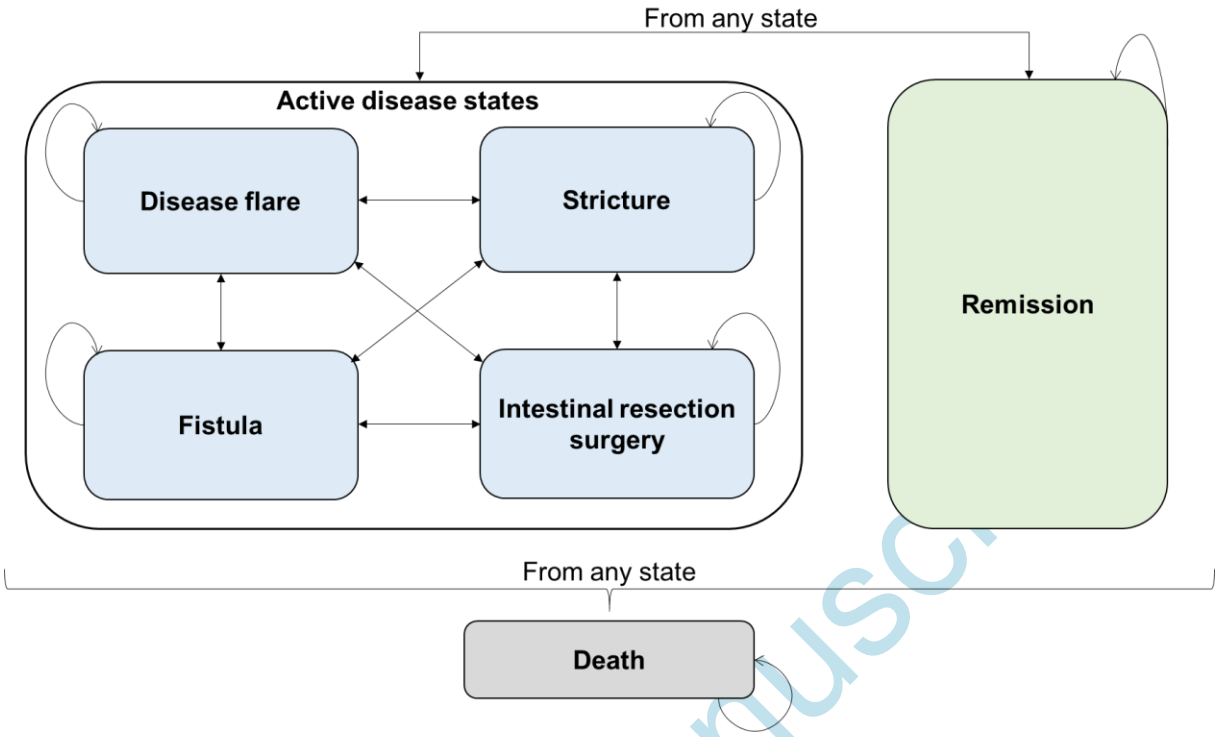

Figure 1 Graphical representation of Crohn's disease Markov model structure and movements between health states

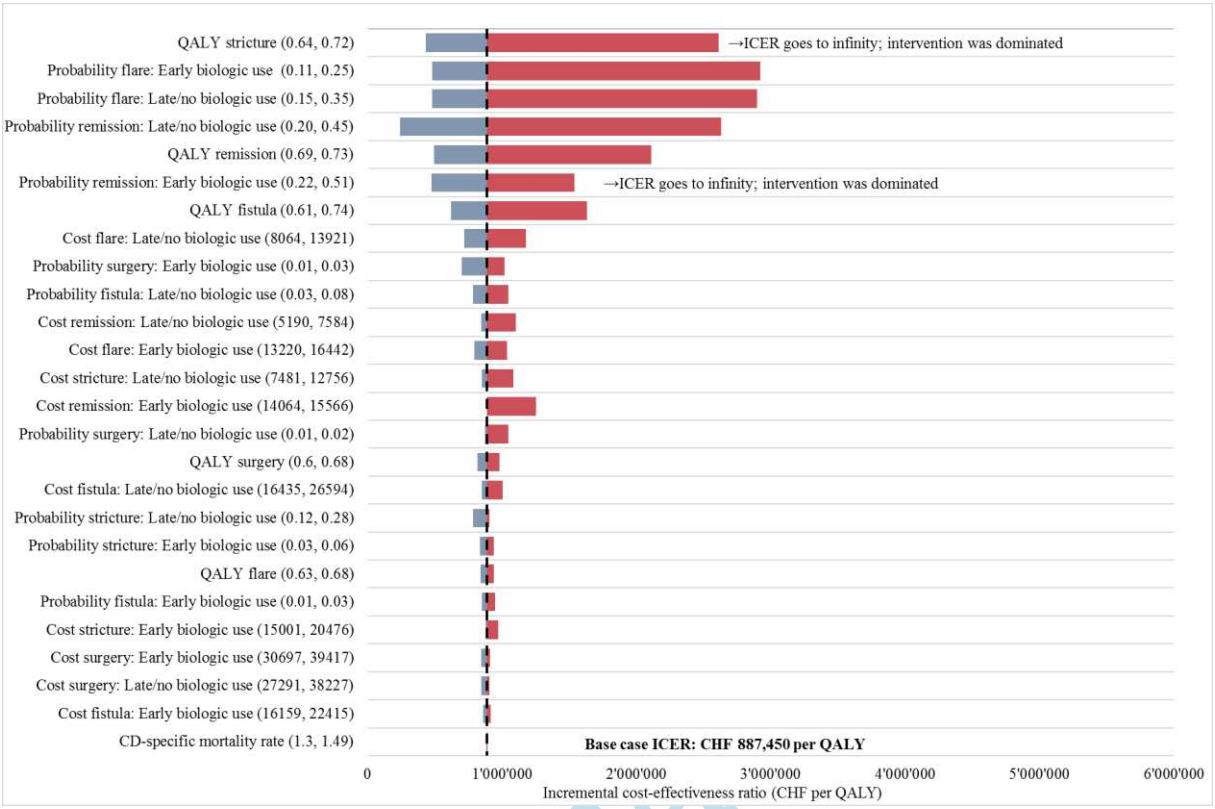

Figure 2 Tornado diagram showing the influence of varying each parameter individually on the ICER from the health system perspective; blue bars indicate ICER was reduced and red bars indicate ICER increased

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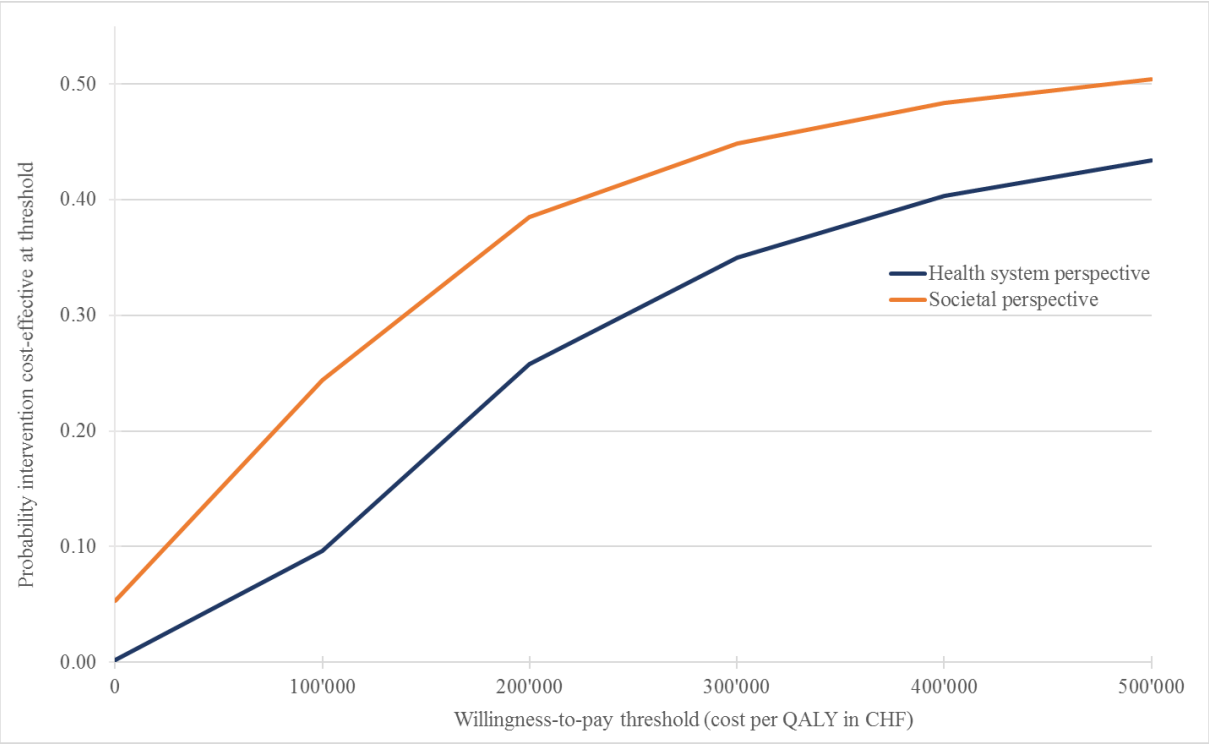

Figure 3 Cost-effectiveness acceptability curve from probabilistic sensitivity analysis after 10'000 Monte Carlo simulations showing the probability that the intervention strategy is cost-effective at different willingness to pay thresholds