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The cost-effectiveness of biological therapy cycles in the management of Crohn's disease

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Abstract

Objectives: to examine the cost-effectiveness of continued treatment for patients with moderate-severe Crohn's disease in clinical remission, with a combination of anti-TNFα (infliximab) and immunosuppressant therapy compared to two different withdrawal strategies (1) withdrawal of the anti-TNFα therapy, and (2) withdrawal of the immunosuppressant therapy, respectively.

Material and methods: A decision-tree model (Markov type) was constructed mimicking three treatment arms: (1) continued combination therapy with infliximab and antimetabolites, (2) withdrawal of infliximab, or (3) withdrawal of the immunosuppressant. Relapses in each arm are managed with treatment intensification. State dependent relapse risks, remission probabilities and quality of life weights were collected from previous published studies.

Results: Combination therapy was less costly and more efficient than the withdrawal of the immunosuppressant, and more costly and more efficient than withdrawal of infliximab. The incremental cost-effectiveness ratio for the combination therapy compared with withdrawal of infliximab was estimated at SEK 755 449 per additional QALY. This is well above the informal willingness-to-pay threshold in Sweden (500 000 SEK/QALY). The estimated cost-effectiveness of the combination therapy was found highly sensitive to the unit cost of infliximab; at a 36% lower unit cost of infliximab, the combination treatment would become cost-effective. The qualitative content of these results were quite robust to changes in the clinical effectiveness and the quality-of-life figures adopted in the calculations. The qualitative content of these results were quite robust to changes in the clinical effectiveness and quality-of-life values.

Conclusions: Combination therapy using a combination of anti-TNFα (infliximab) and immunosuppressant is cost effective in the treatment of Crohn's disease compared to treatment cycles in which the immunosuppressant is withdrawn. Combination treatment is not cost effective compared to treatment cycles in which infliximab is withdrawn, at current pharmaceutical prices.

Key words: infliximab, immunosuppressant, de-escalation, cost-effectiveness

INTRODUCTION

The incidence and prevalence of Crohn's disease (CD) in Western countries range between 5 and 50 per 100 000 inhabitants (Derek et al., 2013). The healthcare costs associated with CD are considerable (Kappelman et al., 2008), and patient's with CD suffer from significant quality-of-life reductions, in particular when the disease is active (Cohen, 2002). Biological treatments, particularly anti-TNF-alpha agents, have been demonstrated to improve treatment outcomes. The most effective therapy for moderate-severe CD is currently a combination of anti-TNF and purine analogues (SONIC trial), which can be considered as the reference standard against which new drugs or drug combinations should be compared. However, the cost of anti-TNF therapy is relatively high (Bodger et al., 2009), although the introduction of bio-similars has brought the cost down considerably (Schmitz et al., 2017). The British National Institute for Health and Clinical Excellence has concluded that maintenance therapy using anti-TNF-alpha agents is not a cost-effective approach compared to available treatment alternatives (NICE, 2010). Furthermore, combination therapy increases the risk of infectious side-effects with a potential of being life-threatening (Toruner, 2008). Thus, to improve safety and contain costs, treatment regimens that cycle the use of these agents in order to achieve and maintain disease remission are of great interest.

The cost-effectiveness of various treatments for Crohn's disease, using anti-TNF-alpha as mono-therapy or in combinations with an antimetabolite, have been estimated an reviewed in a number of studies, for instance Rafia et al. (2016), Erim et al. (2015), Saito et al. (2013), Marchetti et al. (2013), Tang et al. (2013) and Dretzke et al. (2011). A recent systematic review of cost-effectiveness studies comparing conventional and biological treatments for inflammatory bowel disease (Pillai et al., 2017) concluded that treatment with infliximab (and adalimumab) in order to maintain remission is not in general cost effective compared to standard treatment in patient with moderate or severe Crohn's

disease. However, the cost-effectiveness of a particular treatment strategy depends critically both on the exact content of the strategy and on the comparison alternatives (Tang et al. 2013). For instance, maintenance treatment with infliximab as monotherapy was found to be cost effective in treatments of patients with moderate to severe Crohn' disease and when limited to one or two years, see, for instance, Bodger et al. (2009). Only a limited number of studies have compared combination therapy using infliximab and an antimetabolite with either drug as a monotherapy. No published results concerning the cost-effectiveness of maintained combination therapy as compared to treatment strategies in which infliximab and the antimetabolite are withdrawn and reintroduced in case of relapse. The results reported by Marchetti et al. (2013) and Saito et al. (2013) indicate that combination therapy is cost-effective both compared with treatment alternatives that escalate the drug treatment provided, and compared with infliximab as monotherapy. Although there is, to the best of our knowledge, no published results concerning the cost effectiveness of treatment regimens that cycle infliximab and an antimetabolite, the results reported by Saito et al. indicate that sustained combination therapy may be cost effective compared to treatments that withdraw the antimetabolite. Further, although no cost-effectiveness results concerning infliximab biosimilars could be explicitly identified in the literature, the results in recent studies suggest that costs can be reduced and treatment effectiveness maintained using infliximab biosimilars in the treatment of Chron's disease (Kim et al., 2017; Schmitz et al., 2017).

No cost-effectiveness results regarding the cost-effectiveness of different withdrawal strategies in which treatment is de-escalated in periods of remission were found in the literature. The objective of this study was to compare the cost-effectiveness of two de-escalation therapies with continued combination therapy using infliximab and an immunosuppressant in patients with Crohn's disease in clinical remission.

DATA AND METHODS

We constructed a Markov-type decision-tree model mimicking three maintenance therapies, including the two de-escalation strategies mentioned above. Thus, in treatment arm 1 the patients continue the combination therapy as previous to randomization. In treatment arm 2, infliximab treatment is withdrawn and anti-metabolites treatment is continued, while in arm 3, infliximab treatment is continued and anti-metabolites withdrawn. Specific calibrations of the provided pharmaceutical treatments in each arm in case of relapse and remission are reported in the detailed illustration in the appendix (Figures A1 – A3).

Simulation model

The simulation model was constructed in order estimate the cost effectiveness of the combination therapy, using an antimetabolite and infliximab, compared to monotherapy using either the antimetabolite or infliximab. The model performs parallel calculations for the three arms using two medical states in each arm, in which the patient is either in remission or in relapse, a one-month clock frequency, and a time horizon of 2 years. In order to infer the effect on cost effectiveness of a longer time horizon the model was extrapolated an additional 5 years. The model is parametrizised with separate relapse risks and remission probabilities for the three arms, state-dependent quality-of-life weights, and state-dependent healthcare costs. The simulation model was populated with parameter values collected from published previous studies (specified below). In cases were the empirical evidence for a specific parametrization is weak, or non-existent, we have complemented our analysis with extensive sensitivity analysis, in order to deduce the significance of the lack of knowledge for the results obtained in this study. The model structure corresponds to the clinical

situation illustrated in Figures A1 – A3, in the appendix. A more detailed description of the input used in the simulation model is provided in the next section.

Health economic evaluation – the cost-effectiveness measure

This study employs firmly established methods for health economic evaluations (Drummond et al., 2015). The cost-utility analysis provides a method for relating the attained additional treatment effects achieved using a specific intervention (the main alternative) to its additional costs, compared with a specific alternative (the comparison alternative). In principle, this is straightforward, however, in practice it involves several empirical judgements as to what numerical values to use in the calculations. The ratio between cost and effect differences for the compared treatment alternatives is the incremental cost-utility ratio (ICUR), defined as:

$$ICUR = \frac{Cost_{main\ alternative} - Cost_{comparision\ alterative}}{treatment\ effect_{main\ alternative} - treatment\ effect_{comparision\ alternative}}.$$

In general, the cost variable in the expression above should include not only costs associated with the two treatment alternatives, but also the cost for all other healthcare utilization. Moreover, the costs may also include the indirect effect of the compared treatments on productivity, that is, the effects on sickness absenteeism from work and losses that occur due to premature mortality. The dominant effect measure in a cost-utility analysis captures the number of life years (or any other unit of time) associated with each treatment and the quality of life of each year in a combined measure: The quality adjusted life year (QALY). Since neither costs, nor quality of life, can be measured unobjectionably, the reporting of results should be complemented with an analysis of how the core measure, the ICUR, is affected by alternative quality-of-life- and cost measures (deterministic

sensitivity analysis). Beyond these measurement issues, there is also the question of to what extent the parameters that enters into the ICUR measure are afflicted with uncertainty. That is, the effects of a treatment and the associated healthcare costs may contain random components. This may be dealt with using probabilistic analysis.

Given a set of values reflecting costs and effects of two competing treatment alternatives, the incremental cost-utility ratio provides a measure of the incremental cost per QALY associated with the main treatment alternative. Whether or not the main treatment alternative should be regarded as being "cost effective" as compared with the comparison alternative depends on the societal willingness-to-pay for an additional QALY. So, if the incremental cost per QALY gained by using the main treatment alternative instead of the comparison alternative is below that threshold value, the main alternative is to be considered as cost effective (see the appendix for an elaboration of these concepts). The informal willingness-to-pay threshold in Sweden is 500 000 SEK/QALY.

Input data

This section describes the data collection processes and sources. A summary of the base-case numerical specification of the simulation model is reported in Table 1. Specifications as to the probabilistic sensitivity analysis are also provided in Table 1.

Clinical effectiveness

The simulation model incorporates two different parameters reflecting clinical effectiveness, the risk of relapse and the likelihood of remission. Information about these clinical effectiveness parameters was collected for each treatment arm separately. The proportion of the patient population that relapse within 24 months (risk of relapse) were used to calculate the monthly relapse rate in each

treatment arm (Adegbola et al., 2018; Boyapati et al., 2018; Fria Gomes et al., 2018; Torres et al., 2015; Louis et al., 2012). Relapse rates and remission likelihoods in arm 1 and 3 were assumed to be constant over time, while the relapse rater in arm 2 (infliximab withdrawal) was calculated separately for three consecutive time intervals, 2 – 8 months, 9 – 14 months, and 15 – 24 month, using the information that about 50 % of the patients relapse within 24 months (for details, see Table 1). The likelihood of remission after a relapse was assumed to be 65 % in arm 1 (Baert et al., 2013; Chaparo et al., 2011; Lin et al., 2013; Steenholdt et al., 2015), and 70 % in arm 3 (after infliximab escalation and reintroduction of the antimetabolite) (Baert et al., 2013; Chaparo et al., 2011; Lin et al., 2013; Ungar et al., 2017). The corresponding likelihoods in arm 2 were assumed to be 80 % and 90 %, respectively, for the reinstatement of infliximab at 5 mg and 10 mg (Kennedy et al., 2016; Torres et al., 2015).

The validity of the core of the simulation model – how well it projects patients in the different health states – based on the clinical effectiveness parameters used is illustrated by the number of patients, in each arm, who are modelled as being in remission or classified as treatment failure at each point in time. These simulations are illustrated in Figures 1 and 2.

--- Figure 1 about here ---

--- Figure 2 about here ---

Notice, the higher number of treatment failures in the treatment arm in which the antimetabolite is withdrawn is explained by the relatively high likelihood of regaining remission in the treatment arm in which infliximab is withdrawn (see Table 1).

Quality of life

Quality-of-life weights were collected from Saito et al. (2013), Table 1, Quality of life utilities; utility weights for the health states Remission (remission in our model), Mild disease (relapse in our model), and Non-responding active disease (failure in our model).

Pharmaceutical treatment costs

Pharmaceutical treatment costs were calculated using Swedish unit costs (The Dental and Pharmaceutical Benefits Agency) for 2017. The monthly pharmaceutical treatment costs were estimated at SEK 4 924 (infliximab 5 mg), SEK 9 849 (infliximab 10 mg), and SEK 210 (antimetabolites). Pharmaceutical treatment costs in case of treatment failure are assumed to correspond to combination treatment with infliximab 10 mg and antimetabolites.

Medical treatment costs

Medical treatment costs comprise costs associated with outpatient visits and hospitalizations, with and without surgery. Every relapse was assumed to result in either one outpatient visit to hospital clinic, in 90 % – 95 % of the cases, or in hospitalization, in 5 % – 10 % of the cases. Between 0 % and 3 % of the hospitalized were assumed to be subject to surgery. The corresponding figures for those characterized as treatment failures, were 70 % – 80 % are hospitalized and between 3 % and 10 % subject to surgery. No distinctions between treatment arms were considered.

Unit costs were collected from the diagnosis-related groups (DRG) statistics issued by the Swedish National Board of Health and Welfare. The DRG statistics report DRG weights for every medical procedure, and a cost per a one-unit weight (SEK 54 254). Thus, the unit cost for surgery used in our calculations was calculated as the weighted sum of DRG weights for bowel surgery without

complications, with complications and with severe complications. The unit cost for surgery was estimated at SEK 158 313. The unit costs for inpatient- and outpatient care visits were estimated as the costs corresponding to the DRG weights for inpatient- and outpatient care due to inflammatory bowel disease, SEK 42 915 and SEK 4 774, respectively.

Discounting

Following the guidelines issued by National Institute for Health and Care Excellence (NICE), costs and effects were discounted monthly at a 3.5 % annual discount rate.

Sensitivity analysis

We performed both one-way deterministic sensitivity analysis and probabilistic sensitivity analysis, pertaining to the core parameters of the simulation model.

Deterministic sensitivity analysis

We performed one-way deterministic sensitivity analysis for $\mp$ 10 % variation of (1) the relapse rate for patients treated with a combination therapy, in either treatment arm, (2) relapse rates for monotherapies with infliximab or an immunosuppressant, (3) the remission rates for the infliximab 10 mg monotherapy and the combination therapy alternatives, and (4) utility weights for the states remission, relapse, and failure, (5) healthcare costs associated with relapse and treatment failure, respectively, and (6) pharmaceutical (infliximab) costs. Additional sensitivity analyses were performed for (1) the impact of infliximab price reductions on the cost effectiveness of combination therapy were performed, and (2) the relapse rate associated with infliximab withdrawal.

Probabilistic sensitivity analysis

Data on treatment effectiveness, and the associated healthcare utilization, comprises uncertainty due to the fact that a given treatment does not guarantee a specific outcome. Deterministic sensitivity analysis is useful for examining the range of a specific parameter for which the incremental cost-utility ratio falls below a specified threshold value, but it produces no information as to the *probability* of achieving a cost-utility ratio which falls below that threshold value. The distribution of the ICUR can be calculated employing Monte Carlo simulations or bootstrapping (Drummond et al., 2015). The Monte Carlo approach involves specifying statistical distributions for the parameters that are examined, while the bootstrapping method relies on random sampling with replacement from primary data. Thus, while Monte Carlo simulation imposes additional assumptions on the data generation process the bootstrapping method does not. Simulations with either method will produce an estimate of the distribution of the ICUR. In this study, we used Monte Carlo simulations, since primary data for the clinical trial is not yet available.

Monte Carlo simulations involving all relapse rates, remission likelihoods, and healthcare costs were performed. Adopting the method for performing probabilistic sensitivity analysis outlined by Briggs et al. (2006) the following assumptions were made: (1) all probabilities were assumed to be Beta-distributed, and (2) healthcare costs were assumed to be lognormally distributed (for details, see Table 1).

Table 1. Numerical base-case specification of the simulation model. Risks and probabilities are reported as per-month values. Deterministic model and specification of parameters used in the probabilistic sensitivity analysis.

Quality of life weights[+]		**Pharmaceutical and medical treatment unit costs[++]**		**Share of patients being hospitalized and being subject to surgery**	
Remission	0.89	IFX: dose 5mg / 10 mg / 2 months / kg (patient weighing 70 kg)	SEK 4 924 / SEK 9 849[+++]	Hospitalization when relapsing	8 %
Relapse	0.77 (mild disease in Saito)	AZA: dose 5mg/day/kg	SEK 210[+++]	Hospitalization when treatment failure	25 %
Treatment failure	0.40 (non-responding active disease)	Surgery	SEK 158 313	Surgery when relapsing	2 %
		Inpatient care (without surgery)	SEK 42 915	Surgery when treatment failure	4 %
		Outpatient care	SEK 4 774		
Rate of relapse / remission					
First arm (IM + IFX)		**Second arm (discontinuing infliximab)**		**Third arm (discontinuing anti-metabolites)**	
Risk of relapse for combination therapy*	0.0044	Risk of relapse 2-8 months**	0.0353	Risk of relapse (IFX 5 mg)***	0.0093
Probability of remission for combination therapy (IM+IFX 10mg)	0.65	Risk of relapse 9-15 months	0.0299	Probability of remission (IFX 10 mg)****	0.60
		Risk of relapse 15-24 months	0.0221	Probability of remission for combination therapy (IM+IFX 10mg)****	0.25
		Probability of remission (IM+IFX 5mg)	0.8	Risk of relapse for combination therapy (IM+IFX 5mg)*	0.0044
		Probability of remission (IM+IFX 10mg)	0.9	Probability of remission for combination therapy	0.65

				(IM+IFX 5mg)	

Table 1. Continued. Probabilistic sensitivity analysis

		Mean	Standard deviation	Remark
Rate of relapse	Beta distribution	Base-case value above	14 % of base-case value (Saito et al., 2013)	
Rate of regaining remission	Beta distribution	Base-case value above	14 % of base-case value (Saito et al., 2013)	
Quality of life weights	Beta distribution	Base-case value above	10 % of base-case value (Saito et al., 2013)	
Pharmaceutical costs	Log-normal distribution	Base-case value above	40 % of base-case value (Saito et al., 2013)	
Healthcare cost in case of relapse	Log-normal distribution	Base-case value above	40 % of base-case value	No cost range reported in Saito et al., 2013
Healthcare cost in case of failure	Log-normal distribution	Base-case value above	40 % of base-case value (Saito et al., 2013)	

[+] Source: Saito et al. 2013;

[++] Source for Pharmaceutical unit costs: The Dental and Pharmaceutical Benefits Agency. Source for dosage: FASS. Source for surgery cost and cost per hospitalization and outpatient visit: published DRG weights (Diagnose Related Groups) and cost per weight unit, published by the Swedish National Board of Health and welfare.

[+++] Monthly treatment cost in case of treatment failure is 9 849 + 210.

* 10 % of the patient population is relapsing within 24 months. Assuming a constant rate, r, of relapsing we have: $(1-r)^{24} = 0.9$;

** calculated assuming that 50% of the patients relapse over the 24-months trial, and that 50% of the patients relapsing do so between months 2 and 8, 25% of the patients relapse between month 9 and 14, and 25 % of the patients relapse between months 9 and 24.

*** 20 % of the patient population is relapsing within 24 months. Assuming a constant rate, r, of relapsing we have: $(1-r)^{24} = 0.8$;

**** 70 % of patient gain remission after infliximab escalation to 10 mg and reintroduction of AZA. Assuming that 60 % regain remission after the escalation of infliximab. Thus, the additional remission rate, r, is given by $0.6 + (1-0.6)\cdot r = 0.7$

RESULTS

The results are presented in Table 2. For the base-case input data (Table 1), the following outcomes are reported for the 24-month period (per 1000 patients): (1) total incremental intervention cost (the additional pharmaceutical cost imposed by combination treatment compared to discontinuing infliximab and to discontinuing anti-metabolites, respectively), (2) total healthcare costs averted (additional healthcare costs accruing from treatment failure), (3) total QALYs gained (the number of life years gained adjusted for the gain in quality of life obtained by combination treatment), and (4) the incremental cost per QALY gained.

Base-case

Combination treatment is more costly and more efficient than treatment involving discontinuing infliximab. The incremental cost-effectiveness ratio was estimated at 755 449 SEK per additional quality-adjusted life year and, hence, combination treatment is not cost-effective compared with the withdrawal of infliximab, using a 500 000 SEK/QALY threshold. Comparing combination treatment with treatment involving discontinuing antimetabolites shows that combination treatment is both less costly and more efficient, resulting in savings per additional quality-adjusted life year. Thus, for a willingness-to-pay threshold for an additional QALY, maintained combination treatment is cost-effective compare with withdrawing the metabolite and withdrawing infliximab, respectively.

Table 2. Treatment cost, treatment failure cost, quality-adjusted life years, incremental cost-effectiveness. Base case, per 1000 patients				
Treatment arm 1 - combination treatment			Treatment arm 1 vs treatment arm 2	
Treatment cost	121 041 196		Incremental cost	86 952 369
Failure cost	3 870 450		Incremental utility	115
QALYs	1 688		ICUR	755 449
Treatment arm 2 - discontinuing infliximab			Treatment arm 1 vs treatment arm 3	
Treatment cost	33 459 553		Incremental cost	- 3 511 625
Failure cost	4 499 724		Incremental utility	44
QALYs	1 573		ICUR	- 79 933
Treatment arm 3 - discontinuing AZA				
Treatment cost	121 832 925			
Failure cost	6 590 347			
QALYs	1 644			

Sensitivity analyses

The incremental cost-effectiveness ratio was relatively insensitive to ∓ 10 % variations (from base-case values) in the input variables except the unit cost of infliximab, as can be seen from the reporting of the deterministic sensitivity analysis, Table 3. Thus, the qualitative content of the base-case results – that maintained combination treatment is cost effective compared to the withdrawal of the antimetabolite and not cost effective compared to the withdrawal of infliximab – were unaltered by the univariate changes considered. The parameterization of the remission likelihoods in arm 3 (discontinuing the antimetabolite) was particularly inflicted with uncertainty and, hence, we performed additional sensitivity analyses in this case. Varying the remission likelihoods associated with infliximab escalation and reintroduction of the antimetabolite, respectively, by ∓ 50 % from base-case values (60 % and 25 %) resulted in lower costs and additional QALYs for the combination treatment alternative in both cases, and, hence, the qualitative result that maintaining combination

therapy both saves resources and produces more QALYs is robust. Moreover, since the price of infliximab can be expected to decrease in the future, as the utilization of biosimilars increase, we calculated incremental cost-effectiveness ratios for a range of infliximab prices (per 100 mg). The result is illustrated in Figure 7. The infliximab price-threshold for when the combination therapy will be assessed as being cost effective at SEK 1 865/100 mg.

In addition to the sensitivity analyses reported in Table 3, we explored the scenario in which patients who have either a low or a high risk (in relation to the base-case 20 %) of relapse when infliximab is withdrawn can be identified. We estimated the threshold share of patients who relapse within 24 month when infliximab is withdrawn which would make this treatment alternative cost effective compared to continued combination therapy: if 12,8 % (or less) of the patients relapse (within 24 month), infliximab withdrawal produces better quality-of-life outcomes at a lower cost than continued combination therapy. If 60 % (or more) of the patients relapse when infliximab is withdrawn, the combination therapy becomes cost effective. Further, we extrapolated the cost-effectiveness results to a 7-year time perspective, assuming that 80 % of the patients relapse over this period and that all other relapse risks and remission likelihoods remain the same. These calculations show that the incremental cost per QALY increases with the time horizon for the comparison between continued combination therapy and infliximab withdrawal. Combination therapy stays more efficient and less costly than antimetabolite withdrawal.

Table 3. Results of the deterministic sensitivity analysis. Incremental costs, effects, and cost-effectiveness ratios are reported for the arm 1 vs arm 2 and for the arm 1 vs arm 3 comparisons.

	Relapse rates		**Healthcare cost**			
	Changes in treatment arm 1 (relapse for combination therapy, AZA + IFX 5 mg and AZA + IFX 10 mg)		**Changes in medical care cost associated with a relapse**		**Changes in medical care cost associated with treatment failure**	
	+ 10 %	- 10%	+ 10 %	- 10%	+ 10 %	- 10%
Treatment arm 1 vs treatment arm 2						
Incremental cost	87 110 026	86 793 490	86 920 304	86 984 434	86 932 238	86 972 500
Incremental utility	112	118	115	115	115	115
ICUR	776 042	735 798	755 170	755 727	755 274	755 623
Treatment arm 1 vs treatment arm 3						
Incremental cost	- 3 351 189	- 3 673 287	- 3 542 927	- 3 480 324	- 3 553 534	- 3 469 717
Incremental utility	41	47	44	44	44	44
ICUR	- 81 551	- 78 526	- 80 646	- 79 221	- 80 887	- 78 979
	Changes in treatment arm 2 (relapse for AZA-monotherapy)					
Treatment arm 1 vs treatment arm 2						
Incremental cost	84 376 521	89 643 634				
Incremental utility	130	100				
ICUR	647 715	896 595				
	Changes in treatment arm 3 (relapse for IFX monotherapy)					
Treatment arm 1 vs treatment arm 3						
Incremental cost	- 4 401 265	- 2 604 171				
Incremental utility	51	37				
ICUR	- 86 307	- 70 714				

Table 2. Continued.						
	Utility weights, relapse		**Utility weights, remission**		**Utility weights, treatment failure**	
	+ 10 %	- 10 %	+ 10 %	- 10 %	+ 10 %	- 10 %
Treatment arm 1 vs treatment arm 2						
Incremental cost	86 952 369	86 952 369	86 952 369	86 952 369	86 952 369	86 952 369
Incremental utility	112	118	129	101	115	115
ICUR	773 106	738 580	672 037	862 499	756 415	754 485
Treatment arm 1 vs treatment arm 3						
Incremental cost	- 3 511 625	- 3 511 625	- 3 511 625	- 3 511 625	- 3 511 625	- 3 511 625
Incremental utility	43	45	48	40	45	43
ICUR	- 81 897	- 78 062	- 72 735	- 88 713	- 77 983	- 81 983
	Remission rate, IFX 10 mg (arm 3)		**Remission rate, AZA + IFX 5 mg (arm 2)**		**Remission rate, AZA + IFX 10 mg (arm 1)**	
Treatment arm 1 vs treatment arm 2	+ 10 %	- 10 %	+ 10 %	- 10 %	+ 10 %	10%
Incremental cost	-	-	87 333 528	86 571 210	86 913 768	86 990 483
Incremental utility	-	-	114	117	115	115
ICUR	-	-	769 369	741 907	752 534	758 360
Treatment arm 1 vs treatment arm 3						
Incremental cost	- 3 301 276	- 3 720 166	-	-	- 3 929 748	- 3 095 064
Incremental utility	38	50	-	-	46	41
ICUR	- 86 840	- 74 683	-	-	- 84 672	- 74 650
	Pharmaceutical cost (infliximab)					

	+ 10 %	- 10 %				
Treatment arm 1 vs treatment arm 2						
Incremental cost	95 669 857	78 234 881				
Incremental utility	115	115				
ICUR	831 187	679 710				
Treatment arm 1 vs treatment arm 3						
Incremental cost	- 4 271 571	- 2 751 680				
Incremental utility	44	44				
ICUR	- 97 231	- 62 635				

Probabilistic sensitivity analysis were performed for 10 000 random draws of the simulated parameters. The results of probabilistic sensitivity analysis are presented in Figures 3 – 6. Figures 3 and 5 plots all pairs of incremental cost and quality-adjusted life years produced by the Monto-Carlo simulation in the cost-effectiveness plane, while Figures 4 and 6 plots the share of incremental cost-effectiveness ratios falling below certain willingness-to-pay thresholds. It is clear from Figure 3 that most of the random cost-effectiveness pairs are located in the first quadrant in the cost-effectiveness plane indicating that the combination therapy is both more costly and more effective than the alternative of infliximab withdrawal. Whether or not any given point is characterized as being cost effective depend on the willingness to pay (WTP) for an additional quality adjusted life year (QALY). The straight line from the origin marks the SEK 500 000 willingness to pay for an additional QALY and, hence, all points situated below that line encompass cost-effective combinations of incremental costs and effects. Clearly, as the majority of all random pairs are situated above this line, the combination therapy has a low likelihood of being cost effective. Similarly, for the comparison between combination therapy and withdrawal of anti-metabolites roughly half of the random cost-effectiveness pairs are located in the first quadrant, with the majority being below the willingness-to-pay threshold. The random pairs located in the fourth quadrant illustrate situations in which the combination therapy is *less* costly but more effective. Figures 5 and 6 show that the likelihoods of the combination therapy being cost effective when compared to the withdrawal of infliximab and the withdrawal of anti-metabolites, respectively, are about 25 % and 65 %.

FIGURES 3 – 6 ABOUT HERE

CONCLUSION

In this study, we estimated the cost-effectiveness of the biological therapy cycles, which constitute established clinical practice in the management of Crohn's disease. Thus, combination therapy with

infliximab and anti-metabolites were compared with the two treatment alternatives of withdrawing infliximab and anti-metabolites, respectively. For the base-case setting of the parameter values entering into our calculations the costs per additional QALY for the combination therapy, as compared to the withdrawal of infliximab and the withdrawal of the antimetabolite, were estimated at SEK 755 449 and – SEK 79 933 (lower cost and higher effect), respectively. Thus, the combination therapy is not cost-effective as compared to the withdrawal treatment strategy, for the threshold of the willingness-to-pay for an additional QALY that is usually applied in Sweden.

DISCUSSION

We analyzed the cost-effectiveness of a combination treatment for patients with Crohn's disease as compared to two withdrawal/reintroduction strategies, using a two-year time perspective. The medical scientific literature does not provide information on the clinical effectiveness parameters – relapse and remission rates – corresponding exactly to the clinical situations that were compared in this study. Instead, the cost-effectiveness calculations were performed applying parameter values collected from clinical studies corresponding closely to the treatments compared here. This approach was complemented with extensive analyses of the sensitivity of the cost-effectiveness measure to the parameter values.

In the near future primary treatment effectiveness data will be available. The treatment alternatives compared in this study correspond to the three treatment alternatives studied in the on-going SPARE trial, which is an open label, multicenter, trial with three parallel arms, in which patients who are in sustained clinical remission without steroids for at least six months, and have been treated by a combination of antimetabolites and infliximab for at least one year prior to enrollment, are randomized to one of three maintenance therapies. The SPARE trial study design corresponds to the

clinical situation illustrated in Figures A1 – A3 in the appendix. In treatment arm 1 the patients continue the combination therapy as previous to randomization. In treatment arm 2, infliximab treatment is withdrawn and anti-metabolites treatment is continued, while in arm 3, infliximab treatment is continued and anti-metabolites withdrawn. In all treatment arms the pharmaceutical treatment is modified in response to relapse and attained remission. To the best of our knowledge, this is the first study which attempt to estimate the cost-effectiveness of maintained combination treatment, as compared to drug withdrawal and reintroduction/reescalation in case of relapse, in patients with Crohn's disease.

Saito et al. (2013) calculated the cost-effectiveness of induction and maintenance treatment with infliximab in combination with azathioprine as compared to induction and maintenance treatment with infliximab as mono-therapy at about SEK 45 000. Our setting is not identical to the clinical setting analyzed by Saito et al., but the similarities between ours and their setting renders the observation that their estimated cost-effectiveness is in the same range as our figure significance.

The sensitivity analyses performed showed that the estimated cost-effectiveness of the combination therapy, as compared to the two withdrawal treatment strategies, is relatively insensitive to changes in the parameters values used in the calculations. The intuitive explanation for this finding is that, except for risks of relapse, all parameters appear in the cost and effect calculations in all treatment arms. For instance, since infliximab is used by some share of patients in all arms, the effect of an infliximab price change for the treatment cost in arm 1 will be partly offset by a corresponding price change in the comparator arm.

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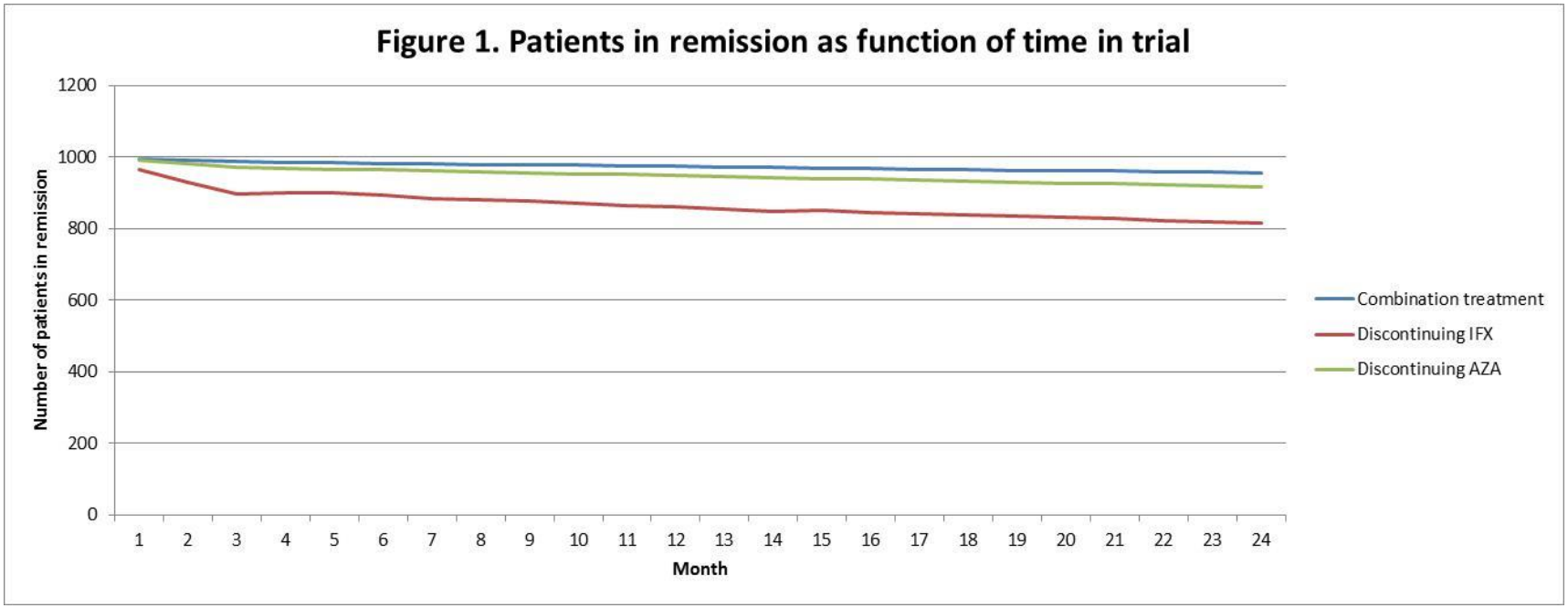


Figure 1. Patients in remission as function of time in trial
Number of patients in remission
1200
1000
800
600
400
200
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Month
Combination treatment
Discontinuing IFX
Discontinuing AZA

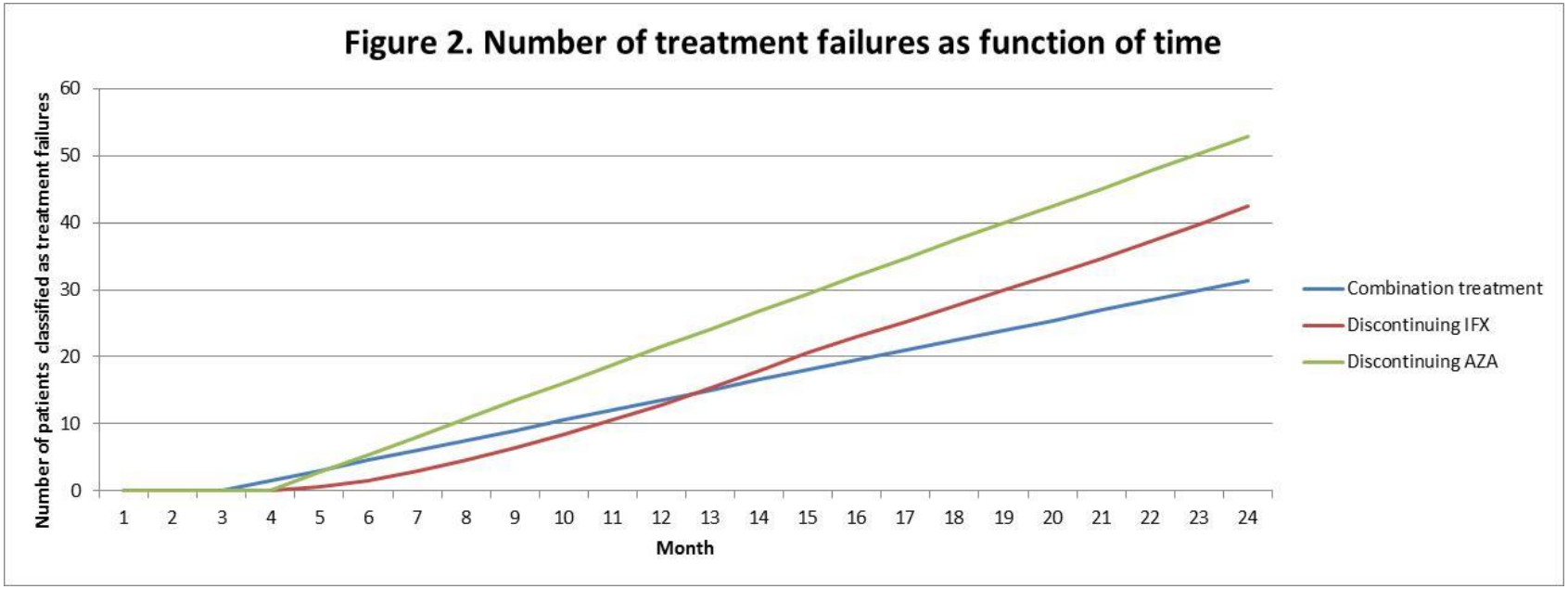


Figure 2. Number of treatment failures as function of time
Number of patients classified as treatment failures
0
10
20
30
40
50
60
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Month
Combination treatment
Discontinuing IFX
Discontinuing AZA

Figure 3. Cost-effectiveness plane - treatment arm 1 vs treatment arm 2

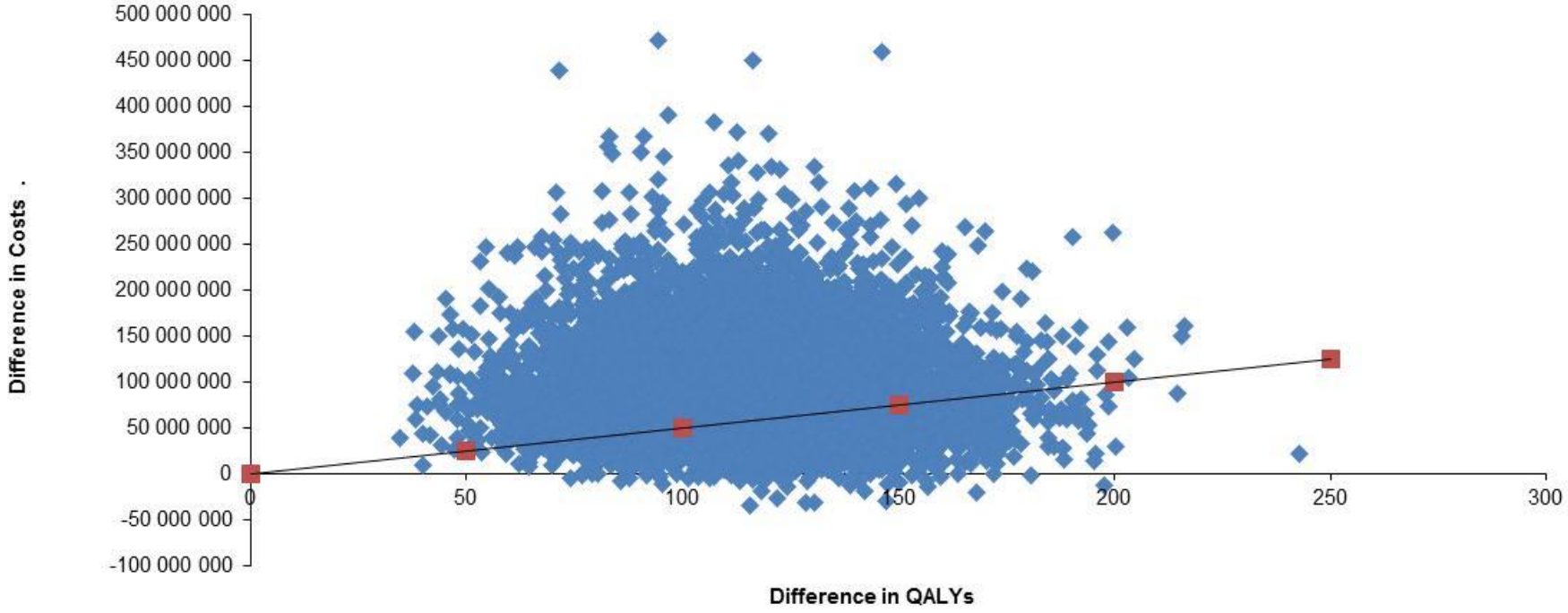


Figure 4. Cost-effectiveness plane - treatment arm 1 vs treatment arm 3

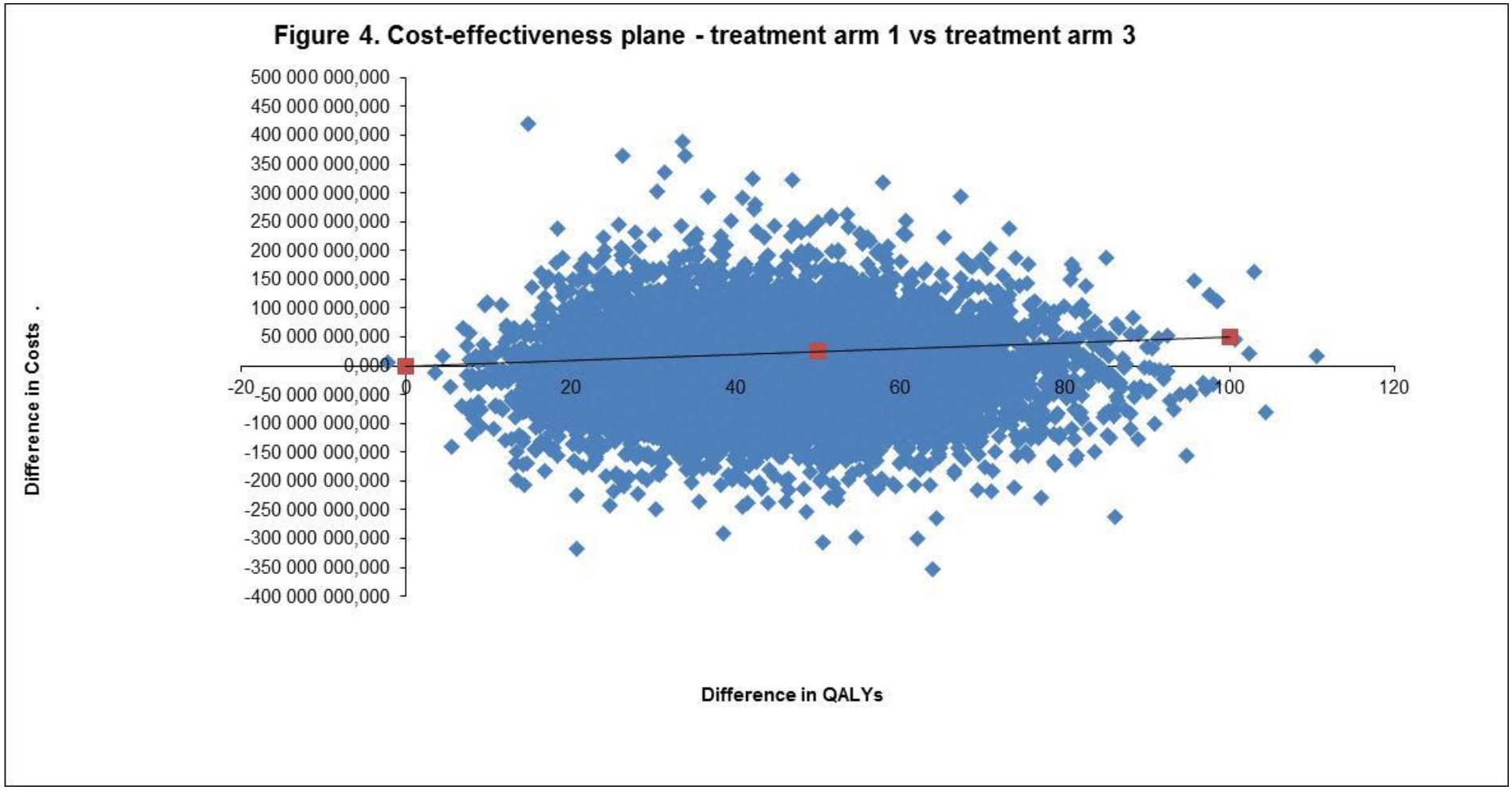
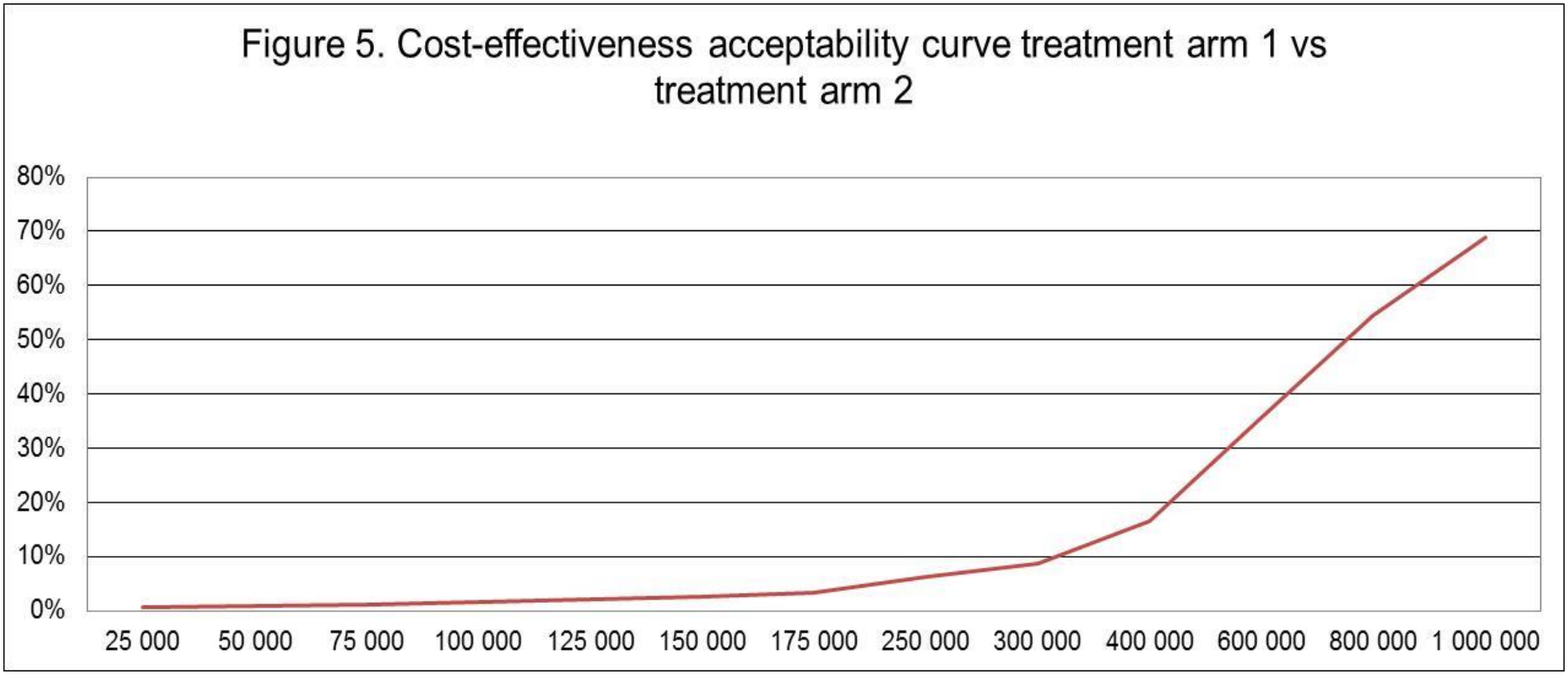


Figure 5. Cost-effectiveness acceptability curve treatment arm 1 vs treatment arm 2



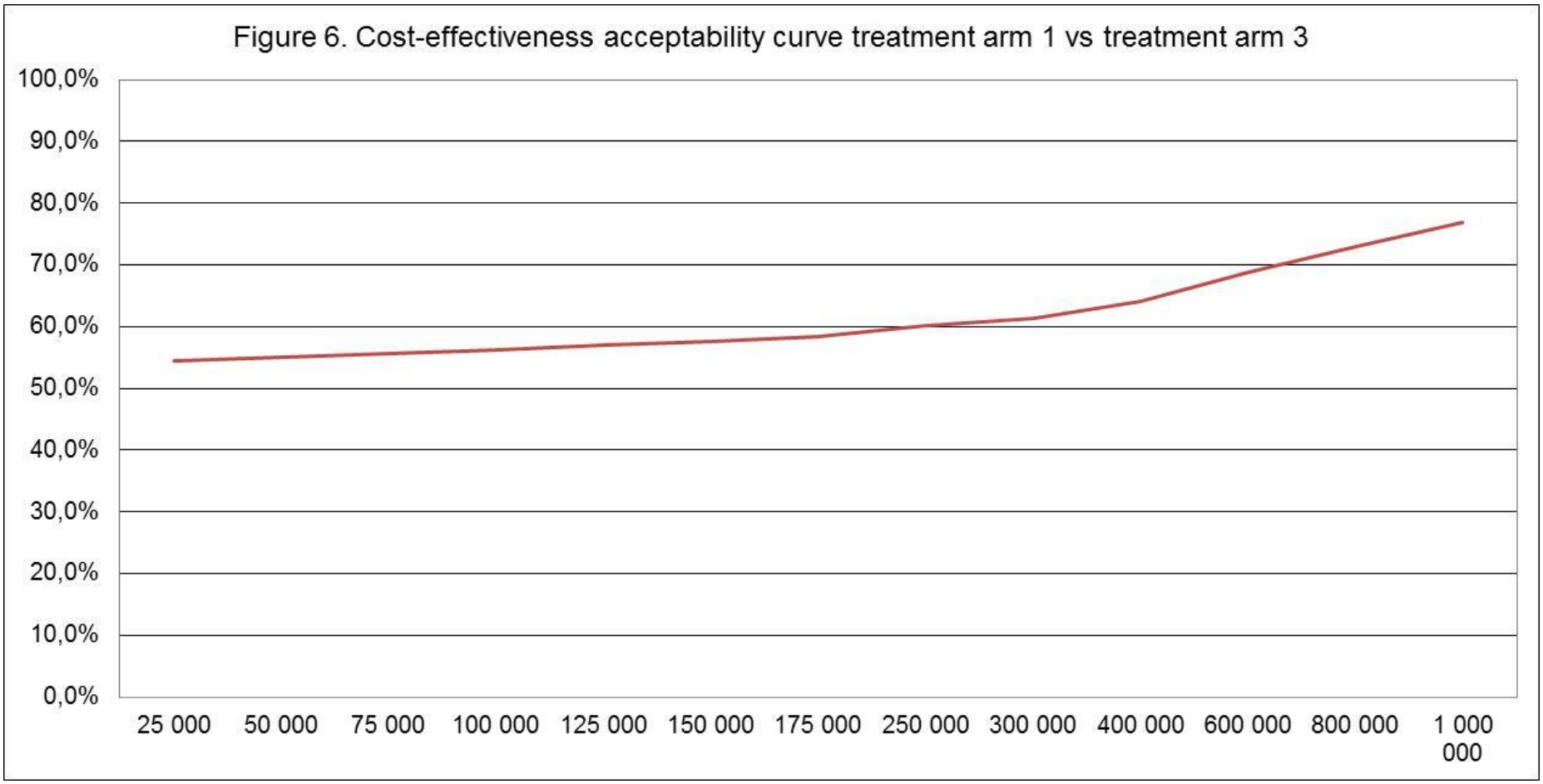


Figure 6. Cost-effectiveness acceptability curve treatment arm 1 vs treatment arm 3
100,0%
90,0%
80,0%
70,0%
60,0%
50,0%
40,0%
30,0%
20,0%
10,0%
0,0%
25 000
50 000
75 000
100 000
125 000
150 000
175 000
250 000
300 000
400 000
600 000
800 000
1 000 000

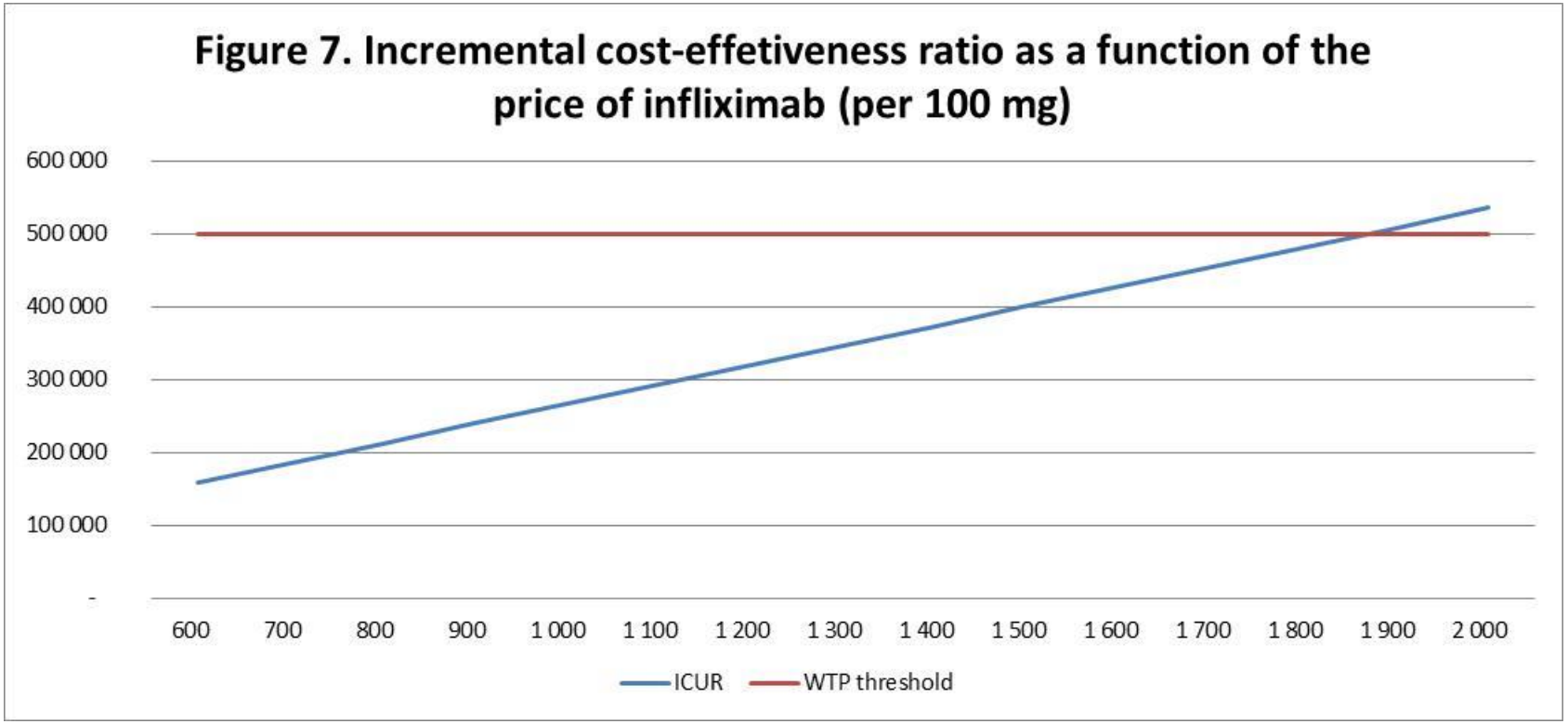


Figure 7. Incremental cost-effetiveness ratio as a function of the price of infliximab (per 100 mg)
600 000
500 000
400 000
300 000
200 000
100 000
-
600
700
800
900
1 000
1 100
1 200
1 300
1 400
1 500
1 600
1 700
1 800
1 900
2 000
ICUR
WTP threshold

APPENDIX

Figure A1. Treatment arm 1 (Continuing the combination therapy)

Assumptions about relapse and remission risks and probabilities: relapse risks equal for every point in time for the 24 months, based on an assumption of a linear decline in the number of patients who has not relapsed. The probability of remission from a relapse depends on the treatment intensification, in this case from AZA+IFX 5mg to AZA+IFX 10 mg. Quality of life weights are assumed independent on treatment paths and depend on the state only. Three different quality-of-life weights are incorporated: for the no relapse/remission state, the relapse state, and the treatment failure state. Treatment after the second relapse repeats the cycle.

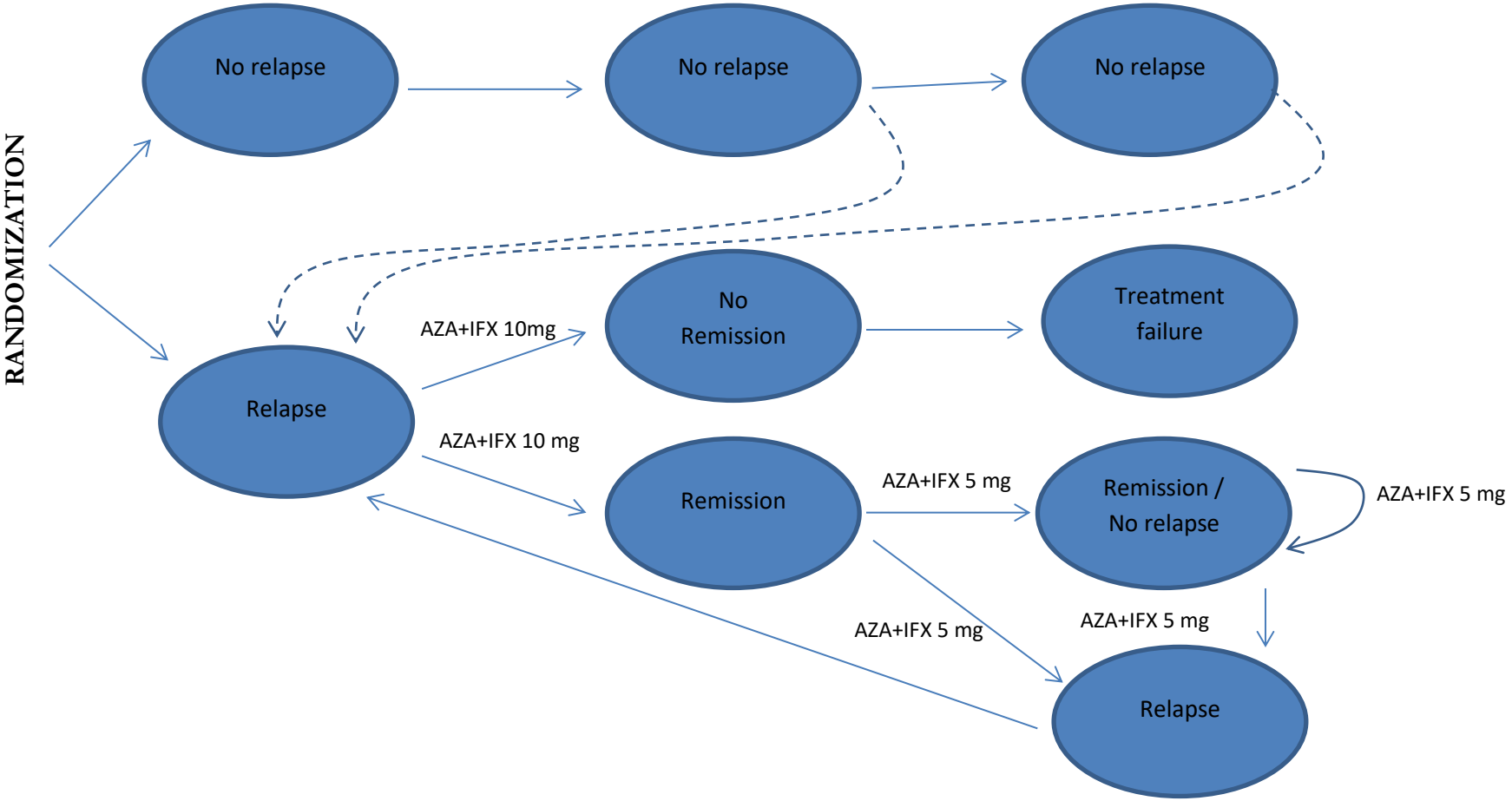
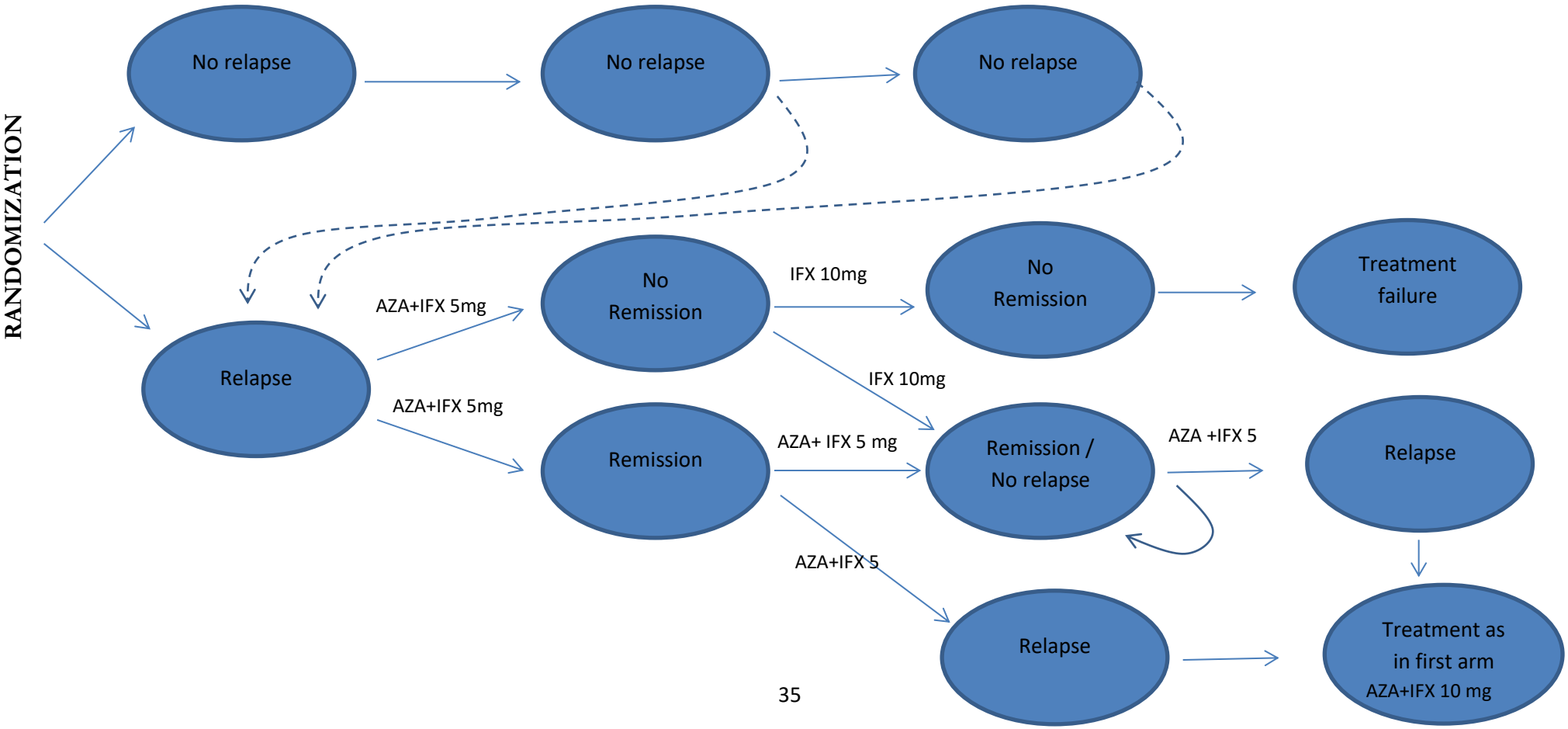


Figure A2. Treatment arms 2 (discontinuing infliximab)

Assumptions about relapse and remission risks and probabilities: relapse risks are different for 2 – 8 months, 9 – 14 months, and 15 – 25 months after randomization. Risks are calculated for these time intervals in accordance with previously discussed diminishing risk over time. After a relapse, once the patient enters the lower part of the three structure, the risk of relapse is the same as before the first relapse, i.e., the risk of relapse depends on time only. The justification for this is that after a relapse and subsequent remission the patient returns to the baseline treatment of the treatment arm. The probability of remission from a relapse depends on the treatment intensification. So, for example, the probability of remission differs from AZA+5 mg IFX and AZA + 10 mg IFX. Quality of life weights are assumed independent on treatment paths and depend on the state only. Three different quality-of-life weights are incorporated: for the no relapse/remission state, the relapse state, and the treatment failure state.



TREATMENT ARM 3 (DISCONTINUING AZA)

Assumptions about relapse and remission risks and probabilities: relapse risks equal for every point in time for the 24 months, based on an assumption of a linear decline in the number of patients who has not relapsed. The probability of remission from a relapse depends on the treatment intensification. Thus, the probability of remission differs between 10 mg IFX and 10 mg IFX + AZA. Quality of life weights are assumed independent on treatment paths and depend on the state only. Three different quality-of-life weights are incorporated: for the no relapse/remission state, the relapse state, and the treatment failure state. Treatment after the second relapse repeats the cycle.