Cost-effectiveness of scheduled maintenance treatment with infliximab for paediatric Crohn's disease

Abstract

Background: Infliximab recently became the only biologic approved for use in paediatric patients with severe active Crohn's disease (CD).

Objectives: To estimate the cost effectiveness of scheduled maintenance treatment with infliximab among children suffering from severe active CD.

Methods: A Markov model was constructed to simulate the progression of a hypothetical cohort of CD children through predefined health states on scheduled maintenance treatment with infliximab (5 mg/kg) based on Targan, ACCENT I and REACH trials. The health states included in the model were remission, responding active disease, non-responding active disease, surgery, post-surgery remission, post-surgery complications and death. Standard care, comprising immunomodulators and/or corticosteroids was used as a comparator. The primary outcome was quality adjusted life years estimated using EQ-5D from a European CD population. A baseline patient weight of 40kg increased by 5 kg/year to account for growth up to 60kg was used to estimate the dose of infliximab. The costs and outcomes were discounted at 3.5% over a period of 5 years. Probabilistic sensitivity analyses were performed by varying the infliximab efficacy estimates, costs and utilities.

Results: The incremental cost effectiveness ratio (ICER) for infliximab treatment was £14,607 compared to standard care. The sensitivity analyses revealed treatment effect of infliximab to be the most influential parameter with ICERs ranging from £10,480-£37,017. Assuming a willingness to pay of £30,000 per QALY, the probability of infliximab being cost effective is 78.6%.

Conclusion: Scheduled maintenance treatment with infliximab (5mg/kg) is a cost effective treatment in children suffering from severe active CD under an 8-week maintenance programme.

Introduction

Crohn's disease (CD) is a common chronic inflammatory bowel disorder of childhood and adolescence. It is estimated that patients younger than 20 years account for around 25–30% of all cases of newly diagnosed CD [1]. Whilst the reported incidence of CD is lower in children than in adults at around 0.2 – 8.5 per 100,000, there are indications that the incidence of CD is increasing [1-4].

Paediatric CD is associated with a number of issues that will not affect adults [4]. Failure to thrive is a significant problem in paediatric CD and may indeed be the initial presenting symptom in children with early-onset disease. In children with severe or poorly controlled disease, growth failure can pose an ongoing problem throughout childhood and adolescence. Psychosocial issues such as social isolation and behavioural problems are common in paediatric CD; in addition, children with CD have a higher prevalence of psychiatric disorders such as depression and anxiety compared with healthy controls or children with other chronic conditions such as Type-I diabetes [4].

Although most therapeutic options available to adult patients are used to treat paediatric CD, there have been few randomised controlled clinical trials performed specifically on paediatric patients. The randomised, controlled REACH study investigated the clinical efficacy and safety of two different dosing regimens of infliximab, for the treatment of CD in children and adolescents aged 6 to 17 years who had not responded to conventional therapy. The results showed that 88% of children treated with induction dose of infliximab achieved a clinical response within 10 weeks, and more than half of these patients subsequently treated with an 8 weeks dosing regimen maintained the clinical remission after one year of treatment [5]. Based on these results, infliximab was granted marketing authorisation for the treatment of moderate to severe paediatric CD at a dose of 5mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter and remains the only biologic to be licensed in paediatric patients. Infliximab is also recommended as an alternative treatment for paediatric patients with severe active CD (Harvey Bradshaw index [HBI] >8, CD activity index [CDAI] >300) who are refractory to or intolerant of steroids and immunosuppression and ineligible for surgery by the European Crohn's and Colitis Organisation (ECCO) [6-8].

The financial impact of adult CD has been reported in a study from the UK which suggested that hospital admissions account for 75% of the overall financial burden, with mean costs over six months nearing £7,000 for adult patients who were hospitalised and £516 for patients who were not [9]. The findings of this study were consistent with research from Sweden and the USA which suggested that hospitalisation accounts for a large proportion of patient treatment costs in CD [10-11]. Although, none of the cost analyses have estimated the burden specifically in children, it is likely to be comparable to adults. Infliximab has been shown to reduce this cost burden [12]. A retrospective study based on 205 patients who received infliximab across seven centres in the UK demonstrated that the mean costs over the six months preceding the initial infusion exceeded the mean costs over the six months following the infusion by an average of £138 per patient. However, the treatment cost of infliximab remains high and raises concerns about its value in the CD treatment pathway.

This economic analysis was performed to assess the cost-effectiveness of infliximab scheduled maintenance treatment compared with standard care in paediatric CD patients. The REACH study evaluated two separate dosing regimens of infliximab and did not include a placebo treatment arm. This presented a significant challenge in estimating the efficacy of standard care treatment in the cost-effectiveness analysis. We extrapolated the placebo treatment results observed in infliximab adult trials to paediatric population in our attempt to derive transitions for the standard care treatment [13-14]. The regulators had taken a similar approach while granting licence to infliximab suggesting this approach to be appropriate and valid [15]. We addressed this uncertainty by substituting the standard care efficacy in our model with infliximab (12 week dosing) results from REACH trial. This presented the best possible efficacy for standard care and worst treatment effect for infliximab.

Methodology

Health-economic model

Patient population and model structure

The economic analysis described in this report was carried out in a hypothetical cohort of children aged 6 to 17 years with active luminal CD, presenting with a paediatric CDAI (PCDAI) score of ≥ 30 at baseline [16]. This patient population was derived from the pivotal REACH trial in paediatric CD patients [5]. The baseline characteristics of these patients are displayed in Table 1.

[Table 1 to appear near here]

A Markov-type decision analysis model was used to simulate the disease progression and track associated costs and outcomes over five years of treatment. The disease activity was characterised using CDAI to facilitate inclusion of adult CD estimates. An overview of the model is presented in Figure 1. The disease severity was characterised by two discrete 'on-treatment' health states, namely *remission* (CDAI ≤ 150) and *responding active* disease (CDAI > 150). For children classified as non-responders or discontinuers, the disease severity was characterised by the 'off-treatment' health state of *non-responding active*. The model also included a total of three additional health states – *surgery*, *post-surgery remission* and *post-surgery complications*, as well as an absorbing health state of *death*.

All children started in the *responding active* health state and remained in this health state for the initial cycle of 2 weeks. At the end of week 2 and each subsequent model cycle, children could either remain in the *responding active* health state, or move to a different health state. Those responding to treatment and achieving remission (CDAI ≤ 150) would move to the *remission* health state and remain on treatment. Responders not achieving remission would remain in the *responding active* health state and continue to receive treatment. A response was defined as 70 or more point reduction in CDAI score from baseline and at least a 25% reduction in the total score [14]. Non-responders at week 2, responders losing response in subsequent cycles or patients choosing to discontinue treatment would end treatment and move to the *non-responding active* state. Patients, who failed treatment and moved to the *non responding active* state would continue treatment with standard care and could not return to infliximab treatment. As a

result, non responders on infliximab would switch to standard care and non responders on standard care would continue with it after entering *non-responding active* state.

Children in the *responding active* and the *non-responding active* health states could transition to *surgery*. In the subsequent model cycle, children undergoing surgery moved to a post-surgery state (*post-surgery remission* or *post-surgery complications*) or had a CD recurrence and moved into the *non-responding active* health state. Children in post-surgery remission could continue in the same health state, enter *surgery* to undergo repeat surgery, enter *post-surgery complications*, or have a recurrence of CD and enter the *non-responding active* state. Similarly, children in *post-surgery complications* could continue in the same health state, enter *surgery* to undergo repeat surgery, enter *post-surgery remission*, or have recurrence of CD and enter the *non-responding active* state. Due to unavailability of any evidence of infliximab re-treatment efficacy on infliximab failures, children with a recurrence of CD were not offered infliximab treatment. Patients in surgery and any of the post-surgery health states could not receive any biologic treatment for their CD but could receive treatment for their post surgery complications.

The cycle length used in the model was selected to facilitate transfer of efficacy estimates from clinical trial into infliximab dosing regimen. Therefore, the first cycle was 2 weeks (wk 0-2) followed by an 8 week and a 20 week cycle (wks 2-10 & 10-30). The cycle length thereafter was 24 weeks.

[Figure 1 to appear near here]

Treatment interventions and transition probabilities

Two separate treatment interventions were modelled and compared, involving an infusion at week 0 of either infliximab 5mg/kg (infliximab scheduled maintenance) or placebo (standard care), followed by repeated infusions for responders at week 2, week 6, and every 8 weeks thereafter.

Transition probabilities for different health states

The primary sources of data for the health state transition probabilities were Targan study [13], ACCENT I trial [14] and REACH trial [5]. Since the REACH trial did not include a placebo treatment arm, data from two studies of infliximab in adult CD patients were used to estimate the transition probabilities. In

ACCENT I trial, all patients received the first dose of infliximab (week 0) and were randomised at week 2. Therefore, we used Targan study to estimate the initial response (0-2 weeks) in both treatment groups [13]. The efficacy estimates from placebo arm of ACCENT I was used for the rest of model time period (week 2-54) in the standard care group [14].

At week 0, all patients were assumed to be in a *responding active* state. The first cycle (week 0–2) transitions in infliximab and standard care were estimated using data from the infliximab and placebo arms of the Targan study [13]. Transitions in the standard care group beyond week 2 were estimated using data from the placebo arm of ACCENT I trial [14]. The corresponding transitions in the infliximab arm were estimated using the infliximab 8 week treatment arm in REACH trial [5]. The transition probabilities for the individual model cycles were estimated using patient level data from the clinical trials mentioned above. The remission and response rates which were used to estimate these transition probabilities are displayed in Figure 2 (A).

Probability of surgery, post-surgical states and CD recurrence

The transition probabilities for the surgery and the post-surgical states were obtained from literature. The probability of surgery was based on an average surgery rate of 64% in ten years obtained from a retrospective database study [17]. The estimated probabilities of post-surgery complications were based on a cohort control study by Marchal and others [18]. The study compared post-surgery complications with and without infliximab and concluded that infliximab treatment did not have any significant impact on the frequency of post-surgery complications. Therefore, a complication rate of 20.5% estimated as a weighted average of complications observed in the comparative treatment arms was used [18]. Reports in the published literature were used to estimate the recurrence rates of 15.6% at one year in adult patients with severe active luminal CD and the repeat surgery rate of 16.7% at one year [19]. In absence of specific estimates in paediatric patients, the rates of surgery, post-surgery outcomes and CD recurrence were assumed to be identical to the adult patients.

Probability of death

It was assumed that the survival rates in paediatric CD were comparable to survival in the general population after adjustment on age and sex and, the standardised mortality ratio from all health states to death was one. Survival rates in the general population were obtained from the UK Office of National Statistics [20].

Time horizon

The efficacy observed in the 54-week trial period was extrapolated up to five years in the base case analysis. A five-year time horizon was assumed to be sufficient to capture all the relevant costs and effects of infliximab in paediatric CD. Other scenarios, including a one year and life-time treatment, were explored in the sensitivity analyses.

Costs

Perspective

The perspective adopted on the costs was that of the National Health Service (NHS) in England and Wales. The reference year for the costs was 2006-07. The productivity costs were excluded due to the choice of the perspective.

Infliximab acquisition and administration

The total cost associated with infliximab treatment was broken down into two components: the acquisition costs and the administration costs. The acquisition cost of infliximab was dependent on the baseline patient weight due to weight based dosing of infliximab. The mean patient weight observed in the REACH trial was 43.8kg as displayed in Table 1. No information was available on weight gain of patients in the REACH trial during or after the trial period. The literature search also did not reveal any estimates for the age related weight gain in CD children. Therefore, we used a baseline patient weight of 40 kg for a 13 year old patient at the beginning of the analysis and gradually increased it up to 60 kg (5 kg/year) during the follow-up period such that the average patient weight was 60 kg at adulthood. The drug administration

cost of £96 per infusion was used which incorporated all tests, assessments and staffing costs associated with the infusion [21]. This resulted in a total cost per infusion of infliximab in the range of £935.24 (40 kg) to £1,354.86 (60 kg).

Concomitant medications and adverse events

The concomitant medication use was estimated using all-patient baseline information in the REACH trial displayed in Table 1 [5]. In our model, we assumed patients in pre-surgery health states maintained their baseline medication use except corticosteroids throughout the analysis period. A linear reduction in corticosteroid use however was assumed such that patients achieving and maintaining remission were assumed to be corticosteroid free by week 54.

Children experiencing serious adverse events discontinued active treatment. Their proportion was estimated using REACH trial [5]. The model did not explicitly account for the costs of adverse events. Potential costs associated with infusion related adverse events such as infusion reactions, headache, dizziness, nausea, injection-site reaction, flushing chest pain, dyspnoea and pruritus, were considered to be incorporated in the administration cost. Serious adverse events, related either to infliximab or other medications for CD such as corticosteroids or immunomodulators, were assumed to be included as part of the hospitalisation costs.

Surgery, hospitalisation and assessments

The estimated average cost per surgical intervention was £4,190 based on the data published in the National Schedule of Reference Costs (NSRC) for 2006-07 (Table 2) [22]. This was an average cost, taking into account elective and non-elective admissions, with or without complications. The treatment related hospitalisation and other assessments were estimated using the study by Jewell and others [12]. The authors estimated the resource use for adult CD patients in UK before and after infliximab use. The study however did not report resource use related to individual health states. Therefore, a post-hoc analysis of ACCENT I by Lichtenstein and others was used to estimate the resource use of patients in different pre-surgery health states [23]. This post-hoc analysis reported a 5.57 fold reduction in

hospitalisation for patients in remission and a 3 fold reductions in hospitalisation for patients in response compared to non-responders.

[Table 2 to appear near here]

No published estimates were available for post-surgery health states. Therefore, the resource use associated with post-surgery remission and post-surgery complications was estimated by a panel of UK gastroenterologists. Each panel member estimated the resource use independently and values used in the economic model were averages of individual estimates. Individual health states were costed using NSRC for 2006-07 [22].

Outcomes

The primary effectiveness measure used in these analyses was Quality Adjusted Life Years (QALYs). Due to lack of available data, the model did not account for any effect of infliximab on survival.

Health state utilities

Once again, due to the lack of robust paediatric data, the health state preference values in this analysis were adapted from findings in the adult CD patients. A dataset provided by Dr Casellas, consisting of 201 adult Spanish CD patients from a published study [24], formed the basis for the estimates used in this analysis. The patients' EQ-5D responses were converted into the corresponding utilities using UK tariffs [25]. To assign a mean utility to individual health states, the HBI was used to classify patients into remission (HBI < 3) and responding active disease (HBI ≥ 3) [6]. No utility for the non-responding active state was available from literature; therefore, a utility decrement of 0.1 was assigned to this state on consultation with a panel of UK gastroenterologists.

The preference values for the surgery and post-surgical health states were estimated from a secondary care database of patients in Cardiff and Vale of Glamorgan covering a population of over 400,000 patients to date [26]. The database identified 41 adult post-surgery CD patients with quality of life information captured using EQ-5D. The utility estimates obtained immediately after surgery (<2 months) were assigned to the health state of surgery, whereas those obtained two or more months following

surgery were assigned to post-surgery remission. There were no estimates available for patients in the post-surgery complications state; therefore, a utility value equivalent to the non-responding active state was assigned to this state. This was based on the assumption that a post-surgery complication would lead to significant hospitalisation along with symptoms of infection, resulting in an impaired quality of life. Table 3 provides a summary of all utility estimates employed in the economic evaluation.

[Table 3 to appear near here]

Cost-effectiveness analyses

The primary cost-effectiveness measure was the incremental cost per QALY gained. Costs and outcomes estimated with half-cycle correction were discounted to present values at 3.5% per annum [27]. Multiple one-way sensitivity analyses were conducted by varying parameters such as patient age and weight, time horizon, discounting rate and the administration cost of infliximab. The uncertainty surrounding other important variables such as transition probabilities associated with the pre-surgery health states, costs of healthcare resources, and health state utilities was explored using probabilistic sensitivity analyses (PSA) with 10,000 simulations. The uncertainty surrounding the transition probabilities and the utility estimates was presented using the beta distributions whereas normal distributions were used for costs. The means and standard deviations derived from data sources were used to estimate the distribution parameters.

Alternate scenarios

The following scenario analyses were conducted to address the uncertainty around the important parameters.

Scenario A: No treatment effect in the extrapolation phase

In the base case, the cost effectiveness was estimated assuming continued efficacy of infliximab and standard care beyond the trial period of 54 weeks. The uncertainty around this continued treatment effect was explored in Scenario A. The worst-case incremental cost effectiveness ratio was calculated assuming no treatment effect in the extrapolation phase. The analysis therefore assumed all patients being taken

off treatment after week 54 with subsequent transitions in the infliximab arm to be identical to those in the standard care treatment arm.

Scenario B: Efficacy of standard care

The efficacy estimates in the base case were derived from three separate trials of infliximab, two of which were adult trials [13-14]. The analysis assumed the treatment effect in children to be identical to that observed in adult patients. The uncertainty introduced by this assumption was explored in Scenario B. The cost effectiveness analysis in Scenario B was entirely based upon the REACH trial in moderate-severe CD children. During the first 10 weeks, the combined arm of REACH trial was assumed to represent both the standard care and infliximab treatments in our analysis. Following the randomisation in REACH at 11th week, the 12-week and 8-week treatment arms of the trial represented the standard care and infliximab treatment arms respectively, in our analysis. Figure 2(B) displays the efficacy thus derived from REACH trial and used in Scenario B.

All patients in REACH trial received the full induction dose of infliximab. Patients randomised to 12-week arm received further doses of infliximab every 12 weeks until week 54. This treatment regimen in which patient continued to receive infliximab throughout the trial period, represented the standard care arm in Scenario B. Hence, the cost effectiveness estimates in this scenario are highly conservative with a minimum treatment effect likely to be observed in clinical practice.

Results

Cost-effectiveness analyses

The cost-effectiveness results for infliximab scheduled maintenance treatment versus standard care in children are shown in Table 3. In the base case, the scheduled maintenance therapy with infliximab derived a mean additional 0.55 QALYs at a mean additional cost of £8,025 compared with standard care. The incremental cost per QALY gained for infliximab versus standard care was £14,607. The corresponding incremental cost effectiveness ratios (ICERs) for infliximab under scenarios A and B were £18,768 and £37,017 respectively as displayed in Table 4.

[Table 4 to appear near here]

Sensitivity analyses

The results of the one-way sensitivity analyses demonstrated that the cost-effectiveness results for infliximab scheduled maintenance treatment compared to standard care without infliximab remained in the range of £10,480 - £37,017 at five years (Table 5). The treatment effect of infliximab had the highest impact on ICER with the least treatment effect estimated in Scenario B resulting in the highest ICER of £37,017. The change in the time horizon had a less significant impact with the ICERs for 1 year and lifetime horizons increasing to £18,624 and £21,223, respectively. The PSA showed that the results were robust with a very small proportion of simulations resulting in quadrant II where infliximab is dominated by standard care. The cost effectiveness acceptability curves for the base case and alternative scenarios are shown in Figure 3.

[Figure 3 to appear near here]

[Table 5 to appear near here]

Discussion

Scheduled maintenance treatment with infliximab is effective in achieving and maintaining remission in paediatric patients with moderate-severe active CD [5]. Infliximab trials in adults have also shown its benefit in reducing the surgeries and hospitalisations [14,28]. The purpose of this analysis was to assess the cost effectiveness of scheduled maintenance treatment with infliximab in paediatric active CD patients over a 5-year time horizon.

Several published studies have estimated the cost effectiveness of infliximab in adult CD patients [29-33]. To our knowledge no study has estimated it in children. Therefore, a direct comparison of our results with the published estimates was not possible. Three of the adult studies used Silverstein patient cohort as a basis to estimate CD progression while the other two used patient cohorts eligible to receive biologic to build their model frameworks. Since our study specifically focussed on moderate-severe patients eligible to receive infliximab, we used the model framework developed by Lindsay and others [33]. This framework allowed inclusion of patient level data from infliximab trials. The results of our base case analysis suggested infliximab to be cost effective and well below the most plausible threshold of £30,000 per QALY used by technology appraisal bodies like National Institute of Health and Clinical Excellence (NICE) in evaluating therapeutic interventions [27]. The ICERs in our study were also lower than most of the published estimates. This can be attributed to the observed higher efficacy in infliximab trials and lower patient weights in paediatric patients. In REACH trial, 63.5% patients maintained their response and 55.8% patients maintained their remission by the end of week 54. These numbers are significantly higher compared to the efficacy observed in adult trials [14,28].

As mentioned above, the base case analysis resulted in an ICER of £14,607 well within the acceptable limit of NICE. The sensitivity analysis however resulted in one scenario (scenario B) where the ICER was above £30,000/QALY. This scenario estimated the minimum incremental treatment effect of infliximab by assigning the active treatment efficacy to standard care treatment. The efficacy thus obtained for standard care treatment is significantly higher than that observed in adult trials [14] and unlikely to be observed in clinical practice. Therefore, this result warrants a careful interpretation of a worst case scenario less likely to occur in a clinical setting.

The choice of time horizon is an important consideration. The efficacy estimates were derived from the trials with a 54-week treatment duration. In the base case we assumed this treatment effect to continue up to 5 years. A comparison of an extrapolated efficacy estimate with the observational data in adult CD patients indicated infliximab to maintain its efficacy beyond the trial period, at least up to 4 years [33] and thus supports our assumption. However no such comparable data were available in children and in absence of any such comparison, we may have overestimated infliximab efficacy in the base case. This assumption was tested in Scenario A. The worst case scenario A assumed no treatment effect beyond 54 weeks. The resultant infliximab ICER of £18,768 further supported the efficacy extrapolation in the base case.

The other important parameter affecting infliximab efficacy was the choice of the data sources. We derived infliximab efficacy based on two adult and a single paediatric trial. In absence of a placebo treatment arm in REACH trial, we used placebo data from an adult trial to estimate the efficacy of standard care treatment arm in our analysis [14]. Such comparisons have previously been drawn by regulatory authorities including FDA while granting licence to infliximab in paediatric CD population [15]. This mix-match approach may have contributed to uncertainty around infliximab's absolute and/or relative treatment effect. In scenario B, we used efficacy estimates derived from the infliximab 12 week dosing arm of REACH trial as proxy for standard care efficacy estimates. In REACH trial, all patients received the full induction dose and the responders were randomised at week 10. This meant that in scenario B, the treatment effect of the induction dose was identical in infliximab and standard care treatment arm. This may have significantly reduced the relative treatment effect of infliximab compared to standard care. In our sensitivity analysis, only in this very conservative scenario, infliximab ICER exceeded the acceptable limit of cost effectiveness.

The other important parameters affecting ICERs were health state preferences and health state costs. Although the utility distributions were adjusted to avoid counterintuitive results, a small proportion of simulations (9.58%) in PSA resulted in a negative incremental QALY gain. This is contrary to the trial evidence found in adult trials where infliximab has been shown to be effective in achieving and maintaining remission and associated QoL benefit. Again, this may be attributable to the multiple data

sources used to derive efficacy estimates as well as health state preferences. The efficacy estimates for a true standard care treatment were not available in REACH trial. Therefore the efficacy estimates from the adult trials were used. This view adopted in our analysis is in concordance with the view taken by regulatory authorities at the time of granting license to infliximab in paediatric CD patients [34]. The REACH trial also did not capture any QoL data. Health state preferences were available from other published studies which did not conform with NICE's analysis framework within which this analysis was conducted [29, 32, 35]. Therefore, we used Casellas patient cohort to derive pre-surgical utilities and HODaR dataset to derive post-surgery utilities. This may have introduced bias resulting in negative QALY gains for active treatment.

We estimated the health state resource use from the Jewell study [12]. The study compared resource use among CD patients before and after introduction of infliximab in UK. Similar estimates were also available from two other studies [36-37]. We however preferred Jewell study as it represented UK clinical practice. The derived estimates were subjected to PSA which showed the predicted results of our model to be comparable to published estimates. The study by Saro and others found surgery rates of 9.8% and 4% one year prior and post infliximab use. The corresponding rates in our model were 5.5% and 2.8% at the end of first year. Once again, infliximab's higher efficacy observed in children may be responsible for the lower surgery rates in our model.

In conclusion, infliximab is a highly effective and safe treatment alternative for moderate-severe children suffering from CD. Our economic analysis demonstrated that the incremental cost of achieving these benefits is reasonable and infliximab represents a cost effective treatment.

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Tables

Table 1: Baseline characteristics of patients in the model

Parameter	Mean	95% CI
Age (years)	13.3	2.5
Weight (kg)	43.8	14.6
Disease duration (years)	2.0	1.4
PCDAI score	41.2	8.3
Concomitant medication use (%)		
6-MP/Azathioprine	89.3	
Methotrexate	9.8	
5-aminosalisylates	52.1	
Concomitant corticosteroids (%)		
≤ 1 mg/kg P. Eq.*	31.3	
> 1 mg/kg P. Eq.*	3.6	

*Prednisone equivalent

Table 2. Hospitalisation and assessments.

Resource	**Published estimate of resource use (n=205)†**		**Cost per patient per cycle (24 weeks)**		**Unit cost**	**Source***
	Pre-infliximab	Post-infliximab	Standard care	Infliximab		
Diagnostic procedures	162	63	£356.04	£138.45	£488.11	TDC
Examination under anaesthetic	50	17	£340.29	£115.71	£1,511.52	TEI, TNEI
In-patient days	1,435	342	£1,761.93	£419.91	£272.68	TEI, TNEI
Out-patient visits	555	534	£231.00	£222.27	£92.44	TCLFUSNFF
Total			**£2,689.29**	**£896.34**		

† Resource use of 205 patients for six months (23); *TDC=Day Cases HRG data; TEI=Elective In Patient HRG data; TNEI=Non Elective In Patient HRG data; TCLFUSFF=Consultant Led Follow up Attendance Outpatient Face to Face

Table 3. Utility estimates

	Markov model health state	Corresponding state from the source	Source	Utility estimate
1	Remission	Remission (HBI <3)	(Casellas, 2007)	
2	Active	Active (HBI >3)	(Casellas, 2007)	
3	Non-responding active	Not available; assigned		
4	Surgery	Post-surgery (<2 months)	(HODaR, 2007)	
5	Post-surgery remission	Post-surgery (>2 months)	(HODaR, 2007)	
6	Post-surgery complications	Not available; assigned		
7	Death (D)	-		-

HBI = Harvey Bradshaw Index (14)

Table 4. Cost effectiveness results for infliximab scheduled maintenance vs standard care in paediatric active CD at 5 years.

Scenario	Std. care Mean costs	IFX Mean costs	Std. care Mean QALYs	IFX Mean QALYs	ICERs
Base case	£25,987	£34,012	2.675	3.224	£14,607
Scenario A (worst case)	£25,987	£31,010	2.675	2.943	£18,768
Scenario B	£23,186	£37,181	3.090	3.468	£37,017

Table 5. One-way sensitivity analysis* – infliximab scheduled maintenance vs standard care in moderate-severe active CD.

Parameter	Base case estimate	Sensitivity estimate	Cost/QALY†
Patient weight	40 kg with progressive weight increase	40 kg (No weight increase)	£10,480
		50 kg (with vial sharing and no weight increase)	£17,036
		60 kg (No weight increase)	£23,592
Time horizon	5 years	1 year	£18,624
		Lifetime	£21,223
Discount rate	Costs – 3.5% QALYs – 3.5%	Cost and QALYs – 1.5%	£14,747
		Cost – 1.5% and QALYs – 6%	£12,935
		Cost – 6% and QALYs – 1.5%	£16,144
		Cost and QALYs – 6%	£14,776
Health state		Increase by 10%	£13,279

utilities		Decrease by 10%	£16,230
Infliximab administration cost	£96.00	£124.00	£15,482

*All results except 'Time horizon' assumes the time horizon of 5 years used in the base case. †Base case: cost per QALY = £14,607.

Figure 1

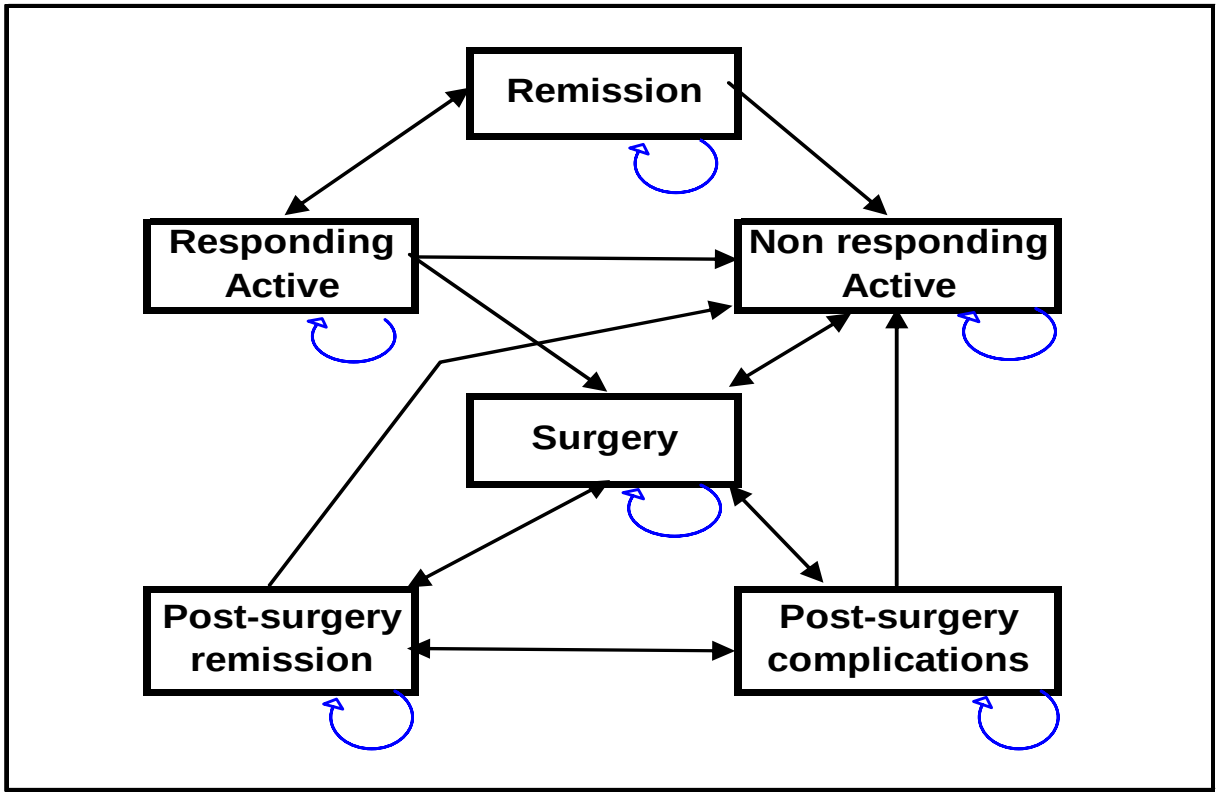

Figure 1: Markov model for moderate-severe paediatric CD

Figure 3: Cost effectiveness acceptability curve in paediatric CD