Appendix I: Cost-effectiveness analysis – Botulinum toxin type A versus Augmentation Cystoplasty

I.1 Introduction

Dysfunction of the urinary bladder during the storage phase of the micturition cycle can take the form of either involuntary contractions of the bladder (neurogenic detrusor overactivity) or a loss of receptive relaxation of the bladder wall leading to a progressive increase in pressure as the bladder fills (reduced bladder compliance). Both neurogenic detrusor overactivity and impaired bladder compliance can lead to symptoms, such as increased urinary frequency, urinary urgency and incontinence. In both conditions deterioration in renal function may occur due to an inability of the upper urinary tract to expel urine in the face of high pressures within the bladder. Incontinence and urinary frequency in patients with neurological disease also occurs in the context of cognitive impairment as a result of difficulties with the interpretation of urinary tract sensations and a loss of the appreciation of the social context of micturition.

There are a number of treatment options available that seek to improve continence through improving the ability of the bladder to store urine. Less invasive treatments such as drug treatments or behavioural management may be preferred by a patient butwill not be effective in somecases. Surgical treatment of incontinence – augmentation cystoplasty – is permanent and requires major open surgery but has been shown to be effective in reducing incontinence (see clinical review). Other, less invasive treatments such as bladder wall injections of botulinum toxin type A are also available as second line treatments. However there remains uncertainty about the cost effectiveness of this treatment due to the unknown length of time to reinjection, the need for repeat reinjection and its long term efficacy. In this analysis botulinum toxin type A will be compared with augmentation cystoplasty as second-line treatments to establish the most cost effective method for preventing incontinence.

There is no, single best treatment for impaired bladder storage function in neurogenic lower urinary tract dysfunction and, due to the heterogeneity of the diseases analysed in the data, it is impossible to state that any one treatment is optimal even for patients with the same condition.. However, it is important to determine if there are wide differences in cost-effectiveness between the different treatments in the neuropathic population as this will provide valuable information for clinicians in circumstances where there is a choice to be made between different treatment options. This analysis looks at the main issues that will impact on the cost effectiveness of second line treatments.

Length of effect will obviously be an important factor as neurogenic lower urinary tract dysfunction is a long term condition and it is important to establish patient compliance and treatment response. Botulinum toxin has a short effectiveness period and requires frequent re-visits to the hospital wheras augmentation is a one-off operation. The data on the continued effectiveness of botulinum toxin type A is limited as this is a relatively new treatment modality. The invasive nature of the treatment and the quality of life lost to adverse events will also be important considerations. While the available data is limited at best, the construction of an economic model allows us to establish and analyse this uncertainty explicitly.

I.2 Methods

I.2.1 Model overview

I.2.1.1 Comparators

The model compares the cost effectiveness of four strategies for the management of incontinence due to neurogenic lower urinary tract dysfunction (NLUTD):

Augmentation Cystoplasty (AC) is a well established, major, open surgical technique where the bladder is made larger or 'augmented' by incorporating a bowel segment into the bladder. Most commonly an ileal segment is used but alternatives include a section of the large intestine. The incorporation of intestine into the bladder prevents effective bladder contractions from occurring and patients usually cannot void completely following the surgery and therefore need to perform clean intermittent self catheterisation.

The second intervention is the injection of *botulinum toxin* type A *(BTX)* into the bladder wall. BTX is currently not licensed for this indication but various trials have shown it to be effective in reducing the frequency of incontinence episodes[1-3] in patients with incontinence due to NLUTD. The protocol for administration of BTX varies but the method used in this model is 30 endoscopic injections of 300u or 200u into the bladder wall. Patients with neurogenic LUT dysfunction will mostly need to use intermittent catheterisation to empty the bladder effectively following the treatment.

The third strategy is whereBTX is administered for two cycles and then AC is conducted in 100% of those that do not respond to BTX (BTX100AC) BTX continues to be administered in those that do respond.

The final comparator is no treatment or "best supportive care" (No-Rx). This comparator is included as an arm where patients opt to manage their incontinence with a mixture of incontinence appliances: pads, indwelling catheters, sheaths and suprapubic catheters.

I.2.1.2 Population

The population in this model is made up of patients with NLUTD (Myelomeningocele, Spinal Cord Injury, Multiple Sclerosis etc.) and bladder over-activity who are unresponsive or intolerant to anticholinergic medication. The patients in the base case are considered to be adults as the paucity of data on children prevents an adequate analysis for the paediatric age group. However the cost effectiveness in children will be tested in a sensitivity analysis.

The trial that the data for BTX[3] utilises measures effectiveness in patients with an average age of 49. The AC study used patients with an average age of 34. The AC study defined its population with a range, 17-66, as the BTX study falls fairly centrally within this range; the base case age was selected as 49. The distribution of men and women across the studies were also defined. In the Cruz study, there were around 40% men and in the AC study, there were 76% men. If a pooled average is taken this comes to a sex distribution of 53% female and 47% male.

Using this base case patient, it is possible to find standard mortality data for the UK [4] and determine life expectancy, thus allowing a lifetime horizon to be considered in the model. The model uses a standardised mortality ratio from a group of patients with spinal cord injury[5]. Standard mortally for the UK will be considered in a sensitivity analysis. Subgroup analysis will be carried out on different patients to determine cost effectiveness in a paediatric population.

However, not all of the comparators are relevant in every situation. For some patients, such as multiple sclerosis patients, the AC comparator is not relevant as they are not suitable for this surgical option. There are therefore two base case comparisons. Base case 1 is all the comparators compared together. The second base case analysis is simply BTX compared with No-Rx.

I.2.1.3 Time horizon, perspective, discount rates used

The time horizon is defined as a lifetime using a 3.5% discount rate per year on both outcomes and costs but this was varied between 0 and 6% for outcomes and costs in a sensitivity analysis as per the NICE reference case[6]. A specific analysis will be done on a discount factor of 1.5% for Quality

Adjusted Life Years (QALYs) and 3.5% for costs. The analysis is conducted from the National Health Service and Personal Social Service perspective.

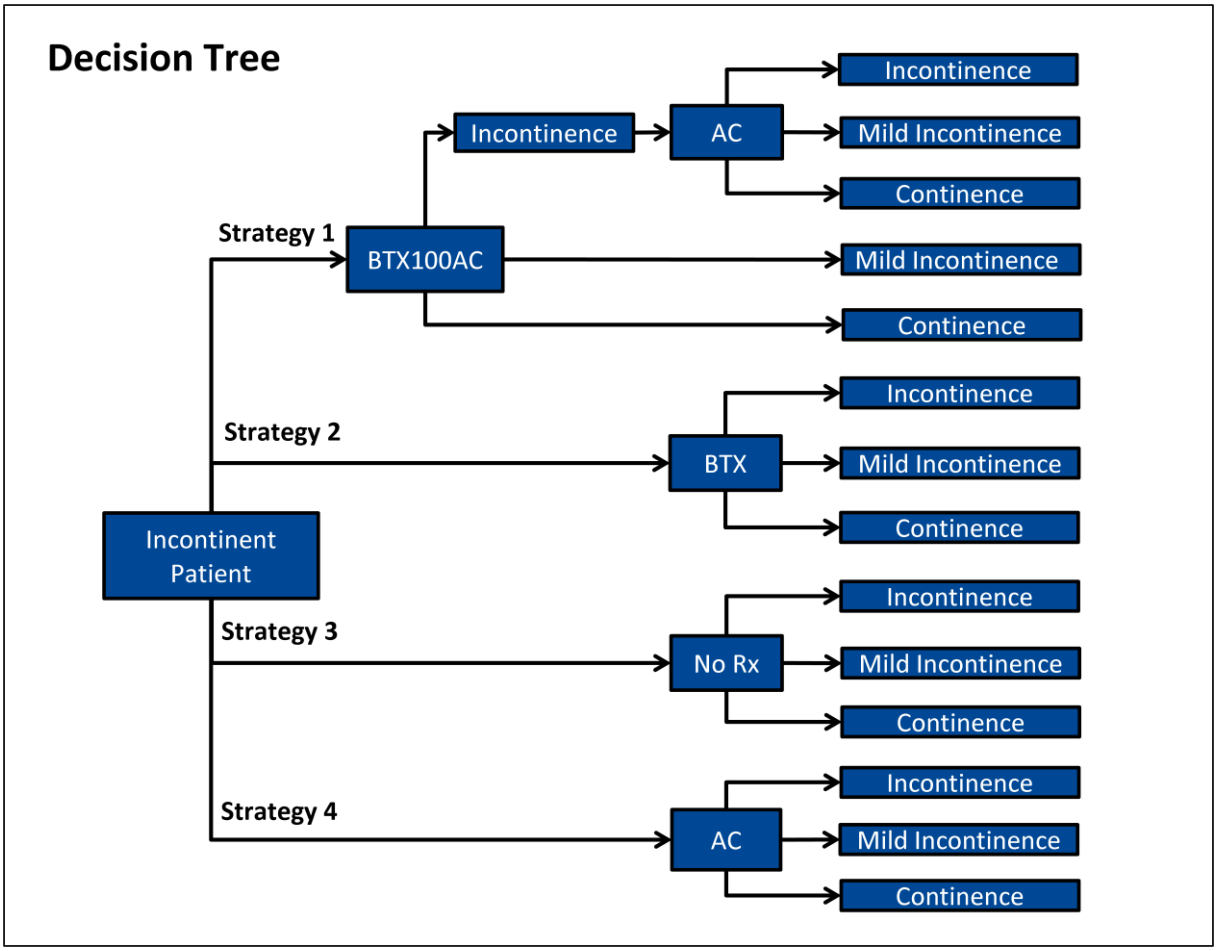
I.2.2 Approach to modelling

A decision tree was constructed in Windows Excel® to model the comparison of cost and effectiveness of the interventions. Life tables were then attached to each of the final health states in the tree and a hypothetical cohort of a thousand patients was run through the model. The trials that were used to inform the model used frequency of incontinence episodes as the main outcome. Quality of Life weights were attached to being either incontinent, continent or having mild incontinence on the basis of the frequency of episodes. As adverse events and the presence or absence of urinary tract infections have important quality of life and cost implications, these were also included. The cost components included costs of the treatment itself, the ongoing costs associated with adverse events and any monitoring or follow up treatments.

I.2.2.1 Model structure

The decision tree compared the three management strategies (AC, BTX and BTX with AC in non-responders) and one no treatment strategy emanating from the initial choice node. Then at each of the chance nodes, a probability is attached that is determined by the effectiveness of the given treatments. At the end of each branch there is a Markov model for each of the outcome states that enable calculation of costs and QALYs over the time horizon. This allows the consideration of mortality data and life expectancy. The structure of the decision tree can be seen in Figure 56.

Figure 56: Decision Tree



BTX100AC : BTX for two attempts then transfer to Augmentation if BTX is unsuccessful. BTX: Botulinum Toxin. NoRx: No Treatment. AC: Augmentation Cystoplasty.

Note: At every health state, a patient may progress to the "absorptive" state, the death state using standard life tables adjusted with condition specific data.

With each of the four options, an incontinent patient upon receiving treatment will either become continent meaning that the treatment was effective, they will have improved continence but will not be fully continent, mild incontinence, or they will remain incontinent. Each of these options is determined by the effectiveness of each treatment. This is true of all the arms but there is a slight difference in the BTX100AC arm. In this arm, the patient will receive two cycles of BTX treatment, however those patients who remain incontinent, rather than remaining in the incontinent state for the rest of the model, they will opt to undergo an AC, incurring all the benefits and harms of that treatment arm. It is assumed that the AC that a patient receives following attempted BTX is as effective as an AC received without attempted BTX. In the BTX only arm, the patients that do not respond will receive BTX for two cycles then will no longer receive BTX and will manage their incontinence using appliances such as pads and catheters.

The frequency of incontinence episodes is used as the main outcome. Due to the inconsistent reporting of the effectiveness of treatments between studies, assumptions had to be made about the frequency of incontinence episodes that constituted each outcome. This was done so that costs and effects could be calculated. It was assumed that in the continent group a patient would suffer from one incontinence episode per week, in the mild incontinent group, they would suffer from two episodes per day and in the incontinent group, they would suffer from five episodes per day. All these options were given an assumed standard error 20% of the mean and normally distributed for the probabilistic analysis.

Table 1: Frequency of incontinence episodes as defined by continence status

	Incontinent	Mild Incontinent	Continent
Number of episodes per day	5	2	0.14

Once a patient is in one of the outcome groups; continent, mild incontinent or incontinent, it is assumed that they will remain within this group for the duration of the lifetime horizon. In order to model this, life tables are attached to each of the outcome groups. Life tables are mortality rates for a given population, in this case England and Wales[4]. In the base case analysis a standardised mortality ratio (SMR) is used that fits the mortality to a more appropriate population. The SMR used was from a retrospective 50 year study in spinal cord injury patients[5]. This SMR increased the mortality rate in patients by a factor of between two and four, depending on age.

The use of a life table allows costs and outcomes to be calculated over a lifetime. It allows the cycle length, the period over which these costs and outcomes are borne, to be varied in a sensitivity analysis. The model uses the mean time that patients requested retreatment with BTX as the cycle length, enabling the costs and outcomes of each intervention to be calculated over the same period. The trial[3] used as the basis of the BTX data reported 8 months mean time to request retreatment and 10 months as the median. Therefore the mean is used as the base case but the median is tested in a sensitivity analysis. This cycle length determined the frequency of reinjection with BTX. Changing the cycle length will not impact on the effectiveness of BTX. BTX is assumed to retain the same effectiveness no matter how long or short the reinjection time is. This is a substantial simplification that reduces the precision of the result, due to the uncertainty about how long the patient will remain continent for. The effectiveness data is only for 12 weeks, however the 8 month reinjection period is based on the same study so there is internal consistency

I.2.2.2 Uncertainty

The model is built probabilistically to take account of the uncertainty around parameter point estimates. In order to do this a probability distribution is defined for each model input. So that when the model is run, a value for each input gets randomly selected from its respective probability distribution simultaneously. This is done repeatedly – 1000 times – and results are summarised. Probability distributions are based on error estimates from data sources, for example: the standard error around a point estimate. The number of simulations used was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using the methods as described by Koehler and colleagues[7]. It is set to ensure that the Monte Carlo error is not more than 5% of the standard error for these parameters.

In addition, various deterministic (one-way) sensitivity analyses were undertaken to test the robustness of model assumptions and data sources. In these, one or more inputs are changed and the analysis is rerun to see the impact on results. This was done using the deterministic (non-probabilistic) data.

I.2.3 Model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data from standard national sources. Model inputs were agreed by clinical members of the GDG.

I.2.3.1 Initial cohort settings

The Model is based on a hypothetical cohort of patients. Baseline patients are defined as patients suffering from incontinence from NLUTD. The patient has undergone treatment with antimuscarinics and is either intolerant or is unresponsive to them. Therefore the baseline patient currently manages their incontinence with catheters in order to void and absorptive pads or incontinence sheaths in order to counteract incontinence episodes. The base case patient is 49 years old, 53% female and 47% male. There was no acceptable data in children for either BTX or AC, therefore the same data is used in the paediatric sensitivity analysis although there are differences in the rate of adverse events.

I.2.3.2 Treatment effects

No studies were identified in the clinical review that compared botulinum toxin (BTX) with augmentation cystoplasty (AC) directly. Therefore studies that compared BTX and AC to "usual care" were used. However considering BTX and AC are both interventions in those where first line treatment had failed, usual care consisted of no treatment (No-RX).

The data for the effectiveness of BTX comes from a randomised controlled trial of 275 patients[3]. This study compared the use of 30 intradetrusor injections of 200U and 300U of "botulinum toxin type A" (BTX) with placebo over a period of 12 weeks. In the base case, this analysis will be looking at 200U of BTX. To measure the effectiveness of the treatment, the frequency of incontinence episodes is used. The study showed a decrease from baseline in the frequency of episodes at 6 and 12 weeks compared to placebo. In the study, the mean frequency of incontinence episodes was reported. However in order to be able to put the data into the model in a comparable form with the AC data, it was necessary to convert it to a categorical variable. The categorical variable was: those patients who did not respond to treatment (incontinent), those who responded but were not completely dry (mild incontinence) and those who were completely dry after treatment (continent). A request was therefore submitted to the authors of the paper for additional data[a]. The data was supplied in the

[a] The Request was submitted to Allergan Limited Marlow International, The Parkway, MARLOW Buckinghamshire, SL7 1YL, UK. Data was not submitted for publication in initial paper.

form of a responder analysis. The data was consistent with that presented in the original paper but was in a more applicable form for this analysis. The study also showed the time to request re-treatment with BTX: mean 8 months median 10 months. A Dirichlet distribution was applied to take into account the uncertainty around the probability point estimates (The Dirichlet distribution is the multivariate generalisation of the beta distribution that confines all the parameters between 0 and 1 and allows order to be maintained between linked probabilities). However there was no long-term, follow-up, data of BTX for the treatment of neurological incontinence. An assumption therefore had to be made on the basis of several studies[8-10] that the bladder wall does not lose responsiveness and that the therapeutic effect of BTX is maintained after long term usage.

There were no randomised controlled trials carried out on Augmentation Cystoplasty (AC) identified in the clinical review. However there were several observational studies conducted that inform the model on the effectiveness of AC. These studies where not meta-analysed due to heterogeneity. All of these studies had relatively low sample sizes and most were from inappropriate settings. One study by Reyblat *et al.* 2009[11] was from a US setting, was of an acceptable size and provided enough data on outcomes to incorporate into the model. This study was therefore selected to form the basis of the analysis of the AC arm of the model. The outcomes of this study were measured using a categorical variable: incontinence, mild incontinence or continence. The probabilistic parameters or the AC outcomes were given using a Dirichlet distribution, in order to maintain the order of probabilities.

It was assumed that in the No-Rx arm, patients remained incontinent throughout. A summary of the treatment effects used in model is provided in Table 2.

Table 2: Overview of treatment effects used in the model

Parameter description	Point estimate	Probability distribution	Source
Treatment Effects			
Continent after BTX (200U)	0.363	Dirichlet	Cruz 2011[3] (Personal communication with authors)
Mild incontinence after BTX (200U)	0.408	Dirichlet	
Incontinent after BTX (200U)	0.229	Dirichlet	
Continent after BTX (300U)	0.377	Dirichlet	
Mild incontinence after BTX (300U)	0.406	Dirichlet	
Incontinent after BTX (300U)	0.217	Dirichlet	
Continent after AC	0.79	Dirichlet	Reyblat 2009[11]
Mild incontinence after AC	0.17	Dirichlet	Reyblat 2009[11]
Incontinent after AC	0.04	Dirichlet	Reyblat 2009[11]

I.2.3.3 Adverse Events

The other impact that these interventions are evaluated for is adverse events (AEs) and urinary tract infections (UTIs). One of the suggested benefits of BTX over AC is the fact that it produces fewer side effects. This is captured in the analysis. The probability of UTIs and AEs can be seen in Table 3. The data used to inform the adverse event and UTI probabilities were from various different study lengths meaning they all had to be standardised to the same cycle length. In order to do this the following equations are used:

Probability to annual rate:

Annual rate to cycle length probability:

The GDG considered that the two most important side effects associated with BTX are haematuria and urinary retention. The probability of a patient experiencing haematuria following BTX treatment is given in a study by Schurch *et al.* 2005[1], this probability was given over one year and was incorporated using the method described above. It was recognised that urinary retention is an adverse event associated with BTX however the costs and effects associated with it are not modelled. This was due to the fact that the entire population is likely to undertake intermittent catheterisation and therefore urinary retention adds no extra burden.

The side effects associated with AC are more extensive. They include: ileus, bowel obstruction, perforation of the augmented bladder, bladder stones and re-augmentation. Some of these AEs represent serious events while the incidence of the various complications varies from the relatively common (bladder stones) to the rare (perforation). Where possible, the probability of experiencing an adverse event was taken from the same study as the clinical effectiveness, i.e. Reyblat *et al.* 2009[11]. This was possible for ileus, bladder stones and bladder obstruction as these were all measured outcomes with an average follow-up of 2.5 years. Ileus was considered in a different way from the other adverse events because it is a one off event. Whereas the probability of stones, obstruction or perforation continued throughout the length of time that a patient was in the model; ileus is a complication arising specifically around the time of the surgery and therefore the associated probability and costs are simply attached to the cost of the AC. The probability of having a perforated augmentation bladder is taken from Metcalfe *et al.* 2006[12], this study, in a young-adult and paediatric population, had an average follow-up of 3.8 years enabling conversion to a one year probability. The probability was therefore considered to be 2.4% per year. However, this figure was thought to be too high for adults and the GDG assumed that this figure was 4 times less in adults: 0.6% per annum. The final adverse event is the probability of redoing the surgery due to an issue with the augmentation bladder. This was assumed by the GDG to be at a probability of 30-40% over 10 years. This was converted to a standardised probability using the midpoint of this estimate, 35% and the range for the sensitivity analyses.

Table 3: Adverse Event Probabilities

Adverse Event	Probability	Distribution	Distributional Parameters	Source
Probability of UTIs when incontinent	0.93	Beta	SE =0.2	Gamé 2008[13]
Probability of UTIs with Mild incontinence	0.28	Beta	α = 0.53b β = 2.13	Gamé 2008[13]
Probability of UTIs with Continence	0.28	Beta	α = 0.53 β = 2.13	Gamé 2008[13]
Probability of Haematuria with BTX	0.04	Beta	α = 2 β = 36	Schurch 2005[1]
Probability of bladder stones with AC	0.019	Beta	α = 5 β = 68	Reyblat 2009[11]

[b] α and β are the parameters used to define the beta distribution. These parameters can be derived in two ways: 1.) α refers to the number of events (or rate) and β refers to the number of people in the study minus the number of events. 2.) Derived using the method of moments, using mean and standard error.

Adverse Event	Probability	Distribution	Distributional Parameters	Source
Probability of bowel obstruction with AC	0.007	Beta	α = 2 β = 71	Reyblat 2009[11]
Probability of perforation of augmented bladder with AC (Children)	0.016	Beta	α = 43 β = 457	Metcalfe 2006[12]
Probability of perforation of augmented bladder with AC (Adults) - Children value *1/4	0.004			Assumption
Probability of Ileus with AC (one off with AC)	0.047	Beta	α = 12 β = 61	Reyblat 2009[11]
Probability of Re do surgery	0.028	Beta	α = 15 β = 30	Assumption

Urinary tract infections (UTIs) are defined as the symptomatic UTIs that require treatment. This definition was used as asymptomatic bacteriuria is universally present in this population of patients. A clear definition of what is classified as a UTI, which UTIs are treated and which UTIs are reported is not available. The baseline rate of UTIs in the population was taken from the study by Gamé *et al.* 2007[13], this study was used because the studies in the clinical review did not report the UTIs associated with continence status which was required so that the UTIs could be standardised for all the interventions. This gave a rate of 1.77 UTIs per patient in the six months running up to BTX injection. As the pre-BTX population is in the same as the pre-AC population, this baseline rate of UTI could apply to both. If this rate is converted to a probability it comes to 93% every 8 months. The Gamé study gives a reduction for patients who are continent to a 28% probability of a UTI after 8 months. The GDG considered that for patients who are continent post AC, a similar reduction is seen. Due to the paucity of data in this area, an assumption was made that the mild incontinent and continent groups experienced the same level of UTIs. This means that the rate of UTIs are associated with the level of incontinence and not with the treatment used. The probability of having UTIs is also tested in a sensitivity analysis.

I.2.3.4 Utilities

The Utility for the main outcome, incontinence, were taken from a study by Hollingworth 2010 [14] this study evaluated the quality of life associated with incontinence, using the SF-6D utility measure. The baseline utility of a patient with neurological incontinence is 0.66 according to the Hollingsworth study, see Table 4. The quality of life weights for "successful" treatment are 0.78 for continence and 0.75 for mild incontinence. The Utility loss from UTI is taken from the Infection Prevention guideline model on catheterisation. This gives a 0.05 reduction in quality of life and is based on UTI in catheterised patients with spinal cord injury. There is a potential limitation in that by counting UTI utility loss, we are double counting. The Utility data associated with incontinence potentially includes UTI quality of life loss. In order to measure the impact that this has on cost effectiveness, a sensitivity analysis was done, setting the utility loss from UTIs to zero.

The utility for haematuria resulting from BTX was not included because it is not considered to be painful nor does it not cause long term negative impacts. Haematuria is normally be followed up due to cancer risk but there is an obvious cause here, so this is considered unlikely. There is some potential for patient anxiety, but with explanation of the situation from the physician this should be relieved.

The AE utility loss comes from a combination of studies. The availability of utility data to populate this part of the model was very poor. Sullivan et al. 2011[15] provide a catalogue of EQ-5D disutilities and was used to input the disutility of a bladder stones which came to -0.02. Another AE was

perforation or rupture of the augmented bladder. For this the Jansen 2007 study was used, although this study was in a different population and the event was not exactly the same, it was considered by the GDG to be a close approximation which came to -0.48. The same study was also used to provide data on bowel obstruction and diarrhoea which when combined came to a utility loss of -0.18. When the utility losses are combined with the probabilities of given events, the utility loss from AC comes to -0.004 per augmentation.

The method used to combine the, per cycle, probabilities with utilities for AEs in AC are given below to demonstrate this type of calculation:

Disutility for bladder stones	= -0.02
Probability of bladder stones per cycle	= 0.019
	= 0.019*-0.02
	= -0.000376
Disutility for bladder perforation	= 0.488
Probability of bladder perforation per cycle	
(assumed 4x less in adult augments)	= 0.00393
	= 0.00393*-0.488
	= -0.00192
Disutility for general bowel disruption	
(Diarrhoea, blockage, Ileus)	= - 0.184
Probability for bowel disruption per cycle	= 0.0074
	= 0.0074*-0.184
	= -0.0014
Combined disutility	= -0.000376 + -0.00192 +-0.0014
	= - 0.0037

This same method is used to generate the other disutilities occurring in the model.

Table 4: Utilities

Utilities	Point estimate	Probability distribution	Distribution parameters	Source
Utility with incontinence	0.66	Gamma	$\kappa = 30.25$ $\theta = 0.02$	Hollingworth 2010[14]
Utility with mild incontinence	0.75	Gamma	$\kappa = 6.35$ $\theta = 0.014$	Hollingworth 2010[14]
Utility with continence	0.78	Gamma	$\kappa = 8.64$ $\theta = 0.014$	Hollingworth 2010[14]
Utility loss from AE per AC	0.004	Gamma	$\kappa = 25$ $\theta = 0.004$	Sullivan 2009 Ref Needed

Utilities	Point estimate	Probability distribution	Distribution parameters	Source
Utility loss from UTI	0.05	Gamma	$\kappa = 2.74$ $\theta = 0.18$	IPC Model

The utilities in Table 4 that need to be are converted into disutilities using the simple conversion of 1-utility. The reason this is done is to limit the utilities by 0 and 1 when the probabilistic analysis is done. The utilities are then combined with the life years to provide a weighting to produce Quality Adjusted Life Years (QALYs). The QALYs are calculated for each cycle and the sum total over a lifetime is divided by the cohort size to provide the number of QALYs per person. Patients who move into the death state accrue zero QALYs.

I.2.3.5 Resource use and cost

It was possible to cost the resource use using official UK sources: NHS reference costs 2009/10, NHS supply Chain Catalogue 2011, the NHS drug tariff and the British National Formulary (BNF) 60. Where an appropriate cost could be found that fully covered the aspect of resource use required, this was attached. However, assumptions had to be made when the cost was not so clear. All the costs that were incorporated into the model can be found in Table 5.

The cost of BTX was constructed using a combination of the NHS reference cost for "injection of substance into bladder wall" and the price of either 200U or 300U of BTX from the BNF-60. However because BTX is not yet licensed for this use, this cost is fairly speculative and was tested in a sensitivity analysis. The adverse events associated with the injection of BTX were haematuria and urinary retention. The cost of haematuria is assumed as the cost of a consultation with a GP.

The cost of AC was simply the cost of a "major open procedure/reconstruction" in the NHS Reference costs 2009/10. This cost could also form the basis of re-augmentation and the cost of repairing a bladder perforation. The cost of bladder stone removal is a combination of endoscopic and open removal. Costing bowel obstruction required the assumption that 70% would simply require an extra week in hospital whereas 30% would require a major surgical procedure to remove the obstruction. The treatment for ileus simply consisted of an extra period in hospital; the Reyblat[11] study put the mean at 4.9 days.

The costs outlined above were the costs of treatment. The long term costs besides continued BTX treatment and the AEs associated with BTX and AC were the costs of each continence state. These included the costs of UTIs and the costs of incontinence appliances. The Cost of a UTI was calculated as the cost of a Healthcare consultation (£32), a dipstick analysis (£0.07), first-line antibiotic treatment (£2) and the dispensing fee (£1.96). In total this came to £36.

The costs of incontinence appliances were costed based on GDG assumptions about the average usage by patients. Pads were costed at £0.25, intermittent catheters costed £0.75, Indwelling catheters costed £5.31 with 30 minutes of district nurse time coming to £32 every 6 weeks and sheaths cost £0.79. All these appliances were used at different rates depending on the health state that the patient was in.

In the Incontinent group it was assumed:

- 25% of men and 50% of women would manage on pads and intermittent catheters.
- 40% of men and 50% of women would manage on indwelling catheters.
- 35% of men would manage with sheaths.

In the Mild Incontinent and Continent groups it was assumed:

- 100% of men and women would use intermittent catheters.

- All of these would wear a pad and manage episodes with pads based on the frequency defined by the treatment effectiveness.

It was also recognised that children use different levels of incontinence appliances. It was assumed, for simplicity, that patients under the age of 10 use pads only if incontinent to manage episodes. The costs of all appliances combined and multiplied by cycle length can be found in Table 5.

Table 5: Unit Costs

Costs	Point estimate	Probability distribution	Distribution parameters	Source
Intervention costs				
Cost of AC operation (also cost of bladder perforation or re-augmentation)	£5929	Gamma	κ = 3.77[c] θ = 1571.25	NHS Reference Costs 2009-2010[16]
Cost of 100U BTX	£138	Assumed fixed		BNF 60[17]
Cost of Injection of substance into bladder wall	£293	Gamma	SE = 145.14	NHS Reference Costs 2009-2010[16]
Cost of Pads	£0.25	Gamma	κ = 2.55 θ = 0.98	NHS Supply Chain Catalogue 2011[18]
Cost of Intermittent Catheter	£0.75	Gamma	κ = 2.5 θ = 0.3	NHS Supply Chain Catalogue 2011
Adverse event costs				
Cost of treating a UTIs	£36	Gamma	κ = 2.5 θ = 0.3	NHS Reference Costs 2009-2010[16]
Bladder stone removal	£522	Gamma	κ = 7.49 θ = 69.69	NHS Reference Costs 2009-2010[16]
Bowel obstruction (70% 1 extra week in hospital 30% major surgical procedure)	£1,251	Gamma	Work out how to present this	NHS Reference Costs 2009-2010[16]
Ileus	£1,381	Gamma	κ = 24.39 θ = 13.61	NHS Reference Costs 2009-2010[16]
Haematuria (GP surgery consultation lasting 11.7 min)	£32	Assumed fixed		PSSRU 2010[19]
Appliance Costs				
Pads	£0.25	Gamma	κ = 2.55 θ = 0.10	NHS supply chain Catalogue 2011[18]
Sheaths	£0.79	Gamma	κ = 3.9 θ = 0.2	NHS Drug tariff
Bags	£6.85	Gamma	κ = 4 θ = 1.71	NHS supply chain Catalogue 2011
Indwelling catheter	£5.31	Gamma	κ = 6.9 θ = 0.77	NHS supply chain Catalogue 2011
District nurse time 30 min	£32	Assumed Fixed		PSSRU 2010[19]
Average costs of intermittent catheters	£0.75	Gamma	κ = 2.47	NHS supply chain

[c] κ and θ are the parameters that describe the Gamma distribution. κ describes the shape of the distribution and θ describes the scale.

Costs	Point estimate	Probability distribution	Distribution parameters	Source
			θ = 0.30	Catalogue 2011
Appliance cost Incontinent (1 cycle)	£759			
Appliance cost Mild incontinent (1 cycle)	£1,078			
Appliance cost Continent (1 cycle)	£966			

These costs are then added to the number of patients in each health state while they remain within the model at each cycle. For AC, the main cost is that of the operation at the beginning, the follow on costs are then the cost multiplied by the probability of any adverse events they may incur at any given time. For BTX, the cost of the injection of BTX is incurred at every cycle as is the cost of any side effects.

I.2.4 Computations

Some methods of eliciting distributional parameters simply require the number of events and the total number in the study. The beta distribution for, example, is defined by α and β, α being the number of events and β being the total study size minus α. However often this data is not available and more complex computations have to be made in order to make the data probabilistic. This usually entails using the mean of a sample as the point estimate and some an error estimate such as a confidence interval or a standard error, is used to determine the shape of a distribution: the slope of the line and the intercept.

To elicit distribution parameters for the beta distribution (α,β) the method of moments was used (μ = mean, s = variance):

In order to elicit the distribution parameters for the gamma distribution, the method of moments was also used:

The distributional parameters for the lognormal distribution were elicited from the mean and standard error using the method of moments:

I.2.5 Sensitivity analyses

Sensitivity analyses are done on certain key parameters to test the impact that they have on the overall result. The parameters to be tested and the ranges that will be altered in are found in Table 6.

Table 6: Sensitivity Analyses

Parameter	Analysis	Reason
Cycle length	10 months	The Cruz study reported the median at 10 months
UTI probability	Varied from 0 to 100% across all outcomes	There is uncertainty about the proportion of UTI depending on treatment and continence status
UTI QoL	Zero change in QoL due to UTI	Possibility of double counting when using incontinence utility data
300U dose of BTX	Change in effectiveness (Cruz 2011) and cost (£414)	Lack of certainty about most appropriate dose
Reduced and increased cost of BTX	Threshold analysis	BTX is not licensed for this indication and the cost is therefore uncertain
Paediatric data	X4 prevalence of stones, Age 13, change in pad and catheter usage	Paediatric data is lacking, assumptions about treatment effectiveness and adverse event rates need testing
Stone prevalence	Changed to 60 % over 10 years	This is the assumption used in the Urinary Incontinence guideline.
Standardised Mortality Ratio (SMR)	No SMR applied	In order to test the impact that the spinal cord injury SMR has on the results
Discount factor	0-6% on both costs and outcomes	NICE Reference case to measure the impact of discounting

(a) The above SAs are all testing assumptions that were made in constructing the model. They are tested to reduce the uncertainty about the results that are seen.

I.2.6 Interpreting results

There is very little comparative data available that compares AC to BTX in any real sense. This model will aid the GDG in making decisions on which treatment or treatments to recommend on the basis of comparative cost effectiveness. The model looks at two scenarios, one, where AC and BTX are both valid options and it will give the GDG some evidence about which intervention to recommend in this case, the second scenario is where AC is not a valid comparator and the model will guide the GDG towards making a well informed and strong recommendation on BTX versus no treatment. There are clear limitations to this model including the fact that comparative data is not available and the limited data on UTI rates, paediatric data and costs of BTX. The model deals with these limitations explicitly and provides evidence is of value in estimating the costs and benefits attached to the different management approaches that are analysed.

I.3 Results

I.3.1 Base case 1 results – All interventions compared

The first base case analysis compared the cost effectiveness of all the interventions outlined in the methods. The analysis revealed that Augmentation Cystoplasty (AC) is the cost effective option when

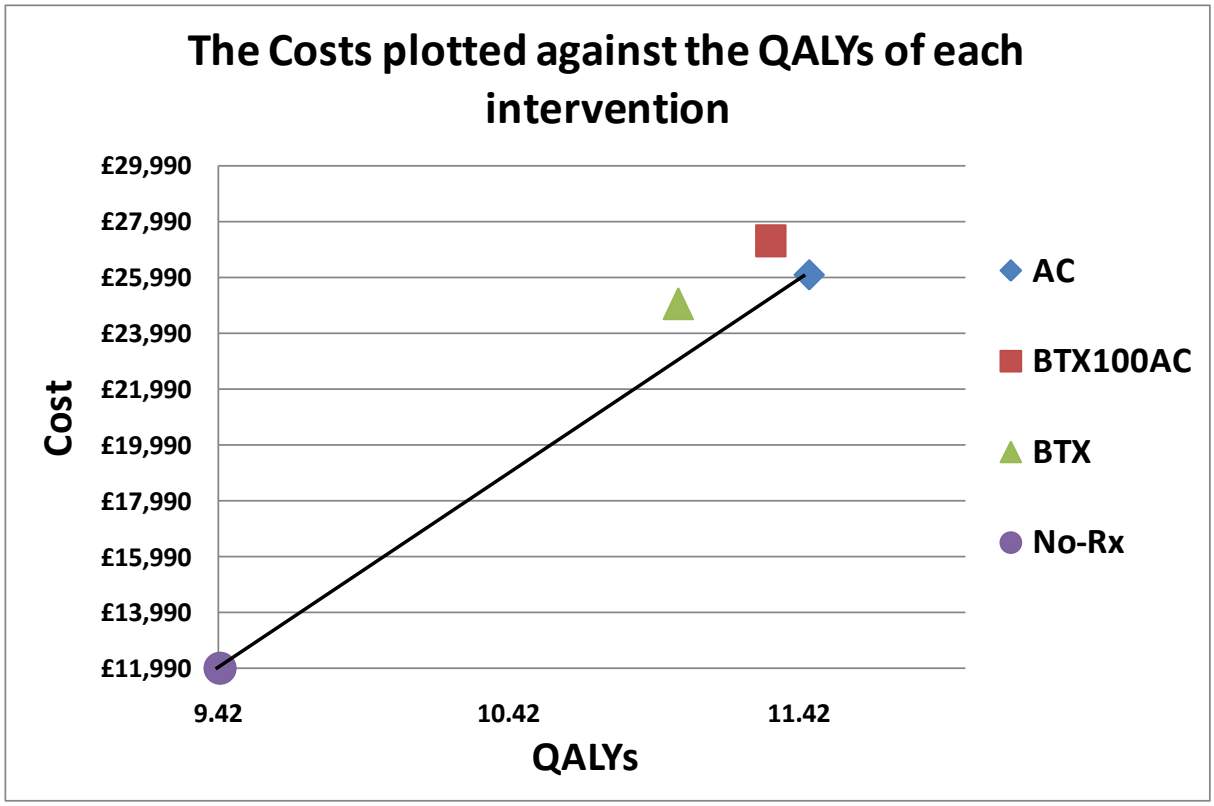
compared to *botulinum toxin* (BTX) and no treatment (No-Rx) for the treatment of incontinence due to NLUTD using a lifetime horizon. The results of the analysis can be seen in Table 7, below. There is a measure of confidence in this result because, at a threshold of £20,000 per QALY, AC is cost effective with a probability of 78%.

Table 7: Base case results

Intervention	Mean Costs	Mean QALYs	NMB[d] at £20,000 per QALY gained	Rank at £20,000 per QALY gained
AC	£26,084	11.46	£1,119,752	1
BTX100AC	£27,315	11.33	£1,105,610	2
BTX	£25,059	11.01	£1,075,757	3
No-Rx	£11,991	9.43	£930,946	4

The cost effectiveness graph below demonstrates these results graphically. We can see that while BTX and AC are similar in cost-effectiveness, AC is more effective but marginally more expensive than BTX alone. The BTX100AC strategy[e] is more effective than the BTX alone strategy but also more expensive; it is more expensive and less effective than AC. No-Rx is the cheapest strategy but it is also the least effective therefore it will only be cost effective at a very low threshold.

Figure 57: Cost effectiveness graph



[d] Net Monetary Benefit (NMB) is a simple rearrangement of the Incremental cost effectiveness ratio calculation. The equation is as follows: Threshold*Effectiveness-cost>0. The resulting figure gives you the QALY gain expressed in monetary form, with each QALY costed at the threshold, net of cost. Meaning that after taking away cost, the intervention with the highest NMB is the most cost effective.

[e] Strategy where if BTX is ineffective after 2 cycles, augmentation is attempted in 100% of patients

When the costs are broken down into the constituent parts, it is possible to pick out the elements that drive the results. This breakdown can be found in Table 8. The increased effectiveness of AC compared with all other interventions is what makes it the most cost effective option. It is cheaper than BTX100AC over a lifetime and is more effective; it is not, however, cheaper than BTX alone over a lifetime.

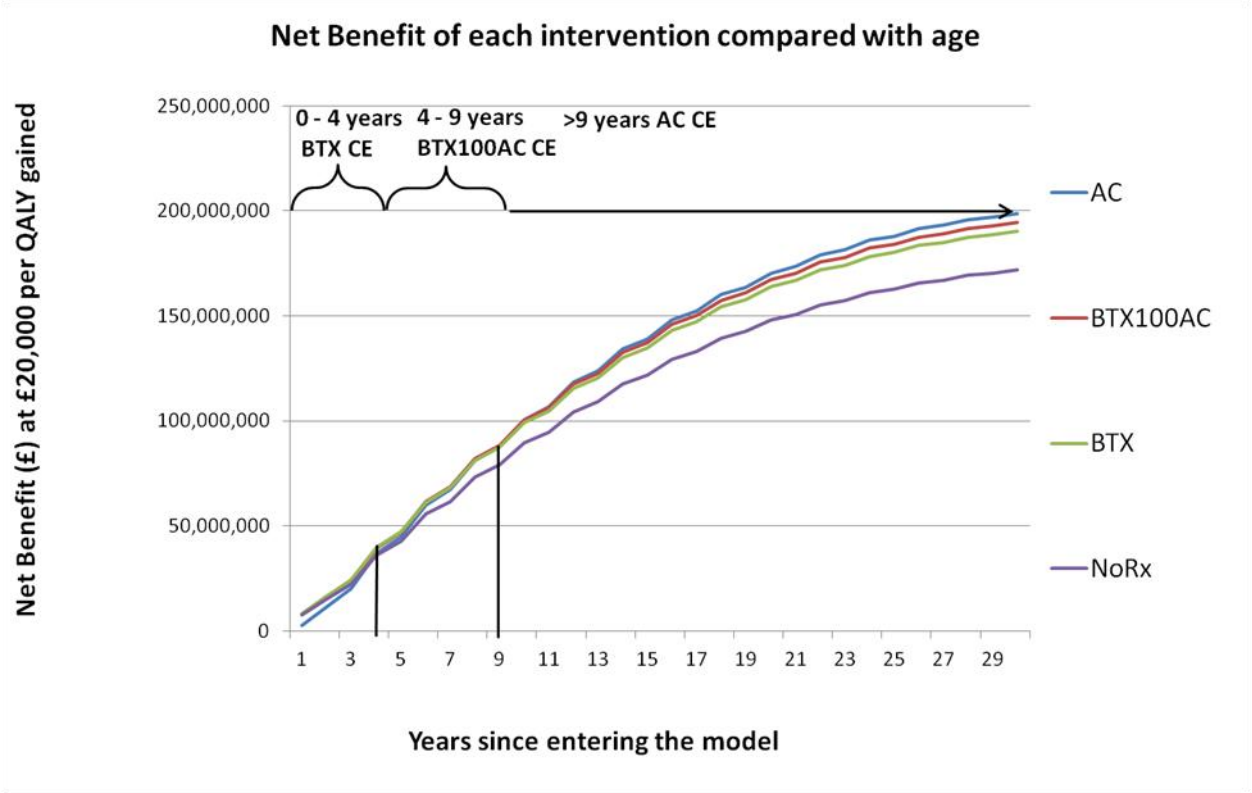
Table 8: Breakdown of costs and outcomes

	Input	BTX100AC	BTX	AC arm	NoRx
Mean Costs (Discounted)	BTX costs	£10,328	£10,328	£0	£0
	AC costs	£1,053	£0	£6,433	£0
	AE costs	£600	£15	£3,705	£0
	UTI costs	£181	£233	£169	£497
	Appliance costs	£15,152	£14,483	£15,776	£11,494
	Total costs	£27,315	£25,059	£26,084	£11,991
Mean Outcomes	Years continent	11	8	18	0
	Years mild incontinent	10	9	4	0
	Years incontinent	2	5	1	23
	Life years	22.71	22.71	22.71	22.71
	QALYs (discounted)	11.33	11.01	11.46	9.43

AC however is higher cost than the BTX alone strategy, this is a function of the discount rate[f]. Using the sensitivity analyses on discount rate [table where these are] we can see that at lower discount rates, BTX is more expensive. This shows that there are higher costs borne later on compared with AC, where the costs are borne earlier. However, AC is more effective and only marginally more expensive than BTX, meaning it is cost effective over a lifetime compared with BTX. A time horizon analysis was also carried out on this comparison in Figure 58; this revealed that for the first 5 cycles, about 3 years, BTX alone is cost effective. Between 5 and 16 cycles, about 10 years, BTX with 100% AC after failed BTX is the cost effective strategy. Beyond 16 cycles, AC is cost effective. This shows that for patients with a poor prognosis and for older patients, BTX is a more cost effective option.

[f] The discount rate is applied to all costs and outcomes. The discount rate is applied to future costs and outcomes to establish their present value. The rate of 3.5% reduction in value per year is based on the interest rate. If we invested now for a future expenditure, how much it would cost in present value.

Figure 58: Net benefit compared with age



Note: CE = Cost Effective

If this is then broken down further into the main comparison, AC-BTX100AC we can see the key drivers behind AC's cost effectiveness in Table 9. The BTX100AC strategy is analysed against AC because it is more cost effective and is the most relevant comparison for sub analysis. A patient with AC only will spend more time in the continent group than those in the BTX100AC arm will, their cost of treatment will be lower in spite of higher adverse event rates. The 18 years compared to 11 spent in the continent arm counts towards an increased QALY gain compared with BTX100AC.

Table 9: Cost Breakdown AC-BTX100AC

	Input	AC arm	BTX100AC	Difference
Mean Costs	BTX costs	£0	£10,328	-£10,328
	AC costs	£6,433	£1,053	£5,380
	AE costs	£3,705	£600	£3,105
	UTI costs	£169	£181	-£12
	Appliance costs	£15,776	£15,152	£624
	Total costs	£26,084	£27,315	-£1,231
Mean Outcomes	Years continent	18	11	7
	Years mild incontinent	4	10	-6
	Years incontinent	1	2	-1
	Life years	22.71	22.71	0.00

	QALYS undiscounted	17.02	16.84	0.18
	QALYs discounted	11.46	11.33	0.13

I.3.2 Base case 2 results – Botulinum Toxin versus No Treatment

As a second analysis we looked at a comparison of BTX with a no treatment comparator. This was to ensure that we captured the full range of potential patients in the analysis. For some patients, such as multiple sclerosis patients, the AC comparator is not relevant as neurological deterioration is likely to occur and render the management of the augmented bladder problematic. In the table below, it is possible to see that BTX is cost effective when compared to no treatment with a cost per QALY of under £9,000. This is well below the usual cost effectiveness threshold of £20,000 per QALY gained.

Table 10: BTX – No Treatment base case results

	Mean Cost	Mean QALY	Incremental Cost Effectiveness Ratio
BTX	£25,059	11.01	
No Rx	£11,990	9.43	
Diff (BTX - No Rx)	£13,068	1.58	£8,277

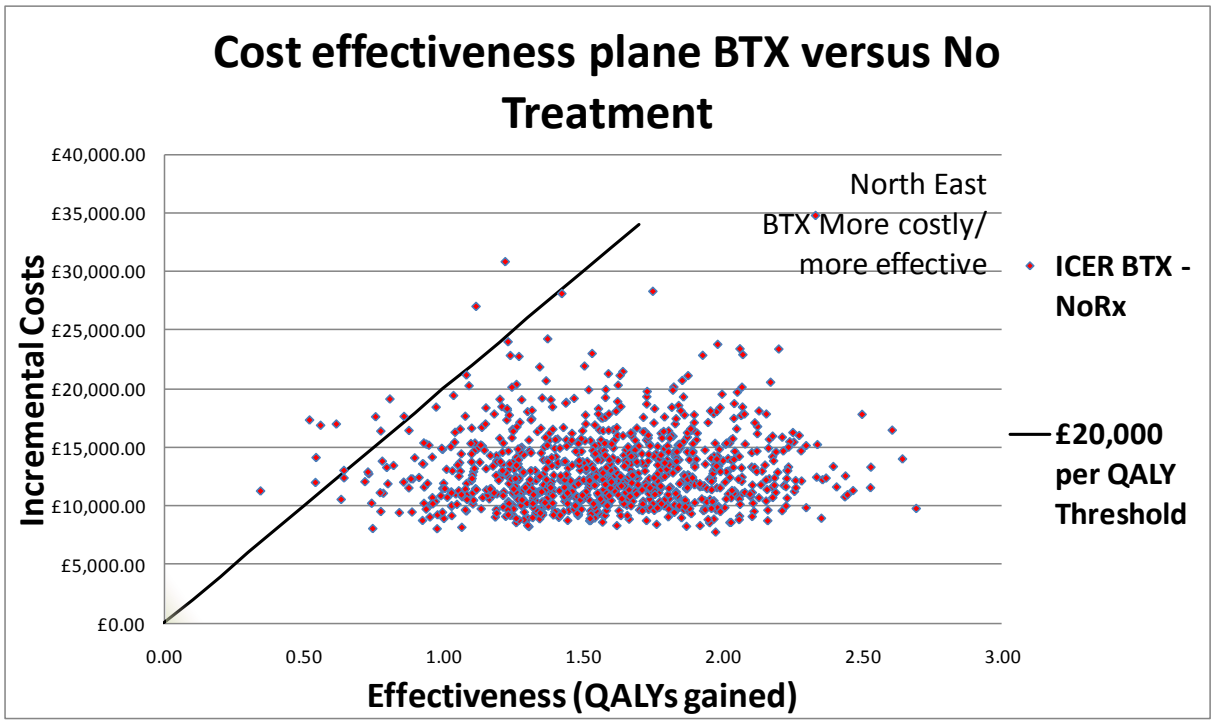
Table 11 shows where the cost and outcome differences lie. The cost of no treatment is lower than BTX but it is not zero. This is due to the cost of incontinence appliances such as pads and catheters. BTX is also more effective with increased time spent in the continence and mild incontinence groups. BTX has higher QALYs but also higher costs so it is cost effective but not dominant.

Table 11: Breakdown of costs and outcomes (BTX – No Rx)

	Input	BTX	NoRx	Difference
Mean Costs	BTX costs	£10,328	£0	£10,328
	AC costs	£0	£0	£0
	AE costs	£15	£0	£15
	UTI costs	£233	£497	-£263
	Appliance costs	£14,483	£11,494	£2,989
	Total costs	£25,059	£11,991	£13,068
Mean Outcomes	Years continent	8	0	8
	Years mild incontinent	9	0	9
	Years incontinent	5	23	-18
	Life years	22.71	22.71	0.00
	QALYS undiscounted	16.35	14.01	2.35
	QALYs discounted	11.01	9.43	1.58

As a result of these costs and of the increased effectiveness of BTX, BTX is more expensive but also more effective with a high degree of certainty. This is displayed on the cost effectiveness plane in Figure 59. This shows that using the probabilistic analysis, all of the cost effectiveness ratios for BTX versus no treatment are to the North East of zero meaning that for all 1000 iterations of the model, BTX is more costly and more effective. And the vast majority, 991, of these ratios fall under the £20,000 per QALY threshold.

Figure 59: Cost effectiveness plane



I.3.3 Sensitivity analysis

Various sensitivity analyses were carried out that explored the uncertainty present in the assumptions that were made in order to construct the model. The Sensitivity analyses are presented in Table 12.

Table 12: Sensitivity analyses results

Intervention	Mean Costs	Mean QALYs	NMB at £20,000 per QALY	Rank at £20,000 per QALY (a)	Change? (b)
Cycle length – 10 months to request retreatment (median – Cruz 2011)					
AC	£31,078	11.57	£200,266	1	No
BTX100AC	£29,551	11.42	£198,792	2	
BTX	£27,053	11.10	£194,875	3	
No-Rx	£15,084	9.49	£174,638	4	
Excluding UTI QoL					
AC	£26,088.58	11.71	£208,105.63	1	No
BTX100AC	£27,498.10	11.57	£203,951.61	2	
BTX	£25,271.63	11.32	£201,075.30	3	
No-Rx	£12,121.38	10.09	£189,670.02	4	
Using 300U BTX instead of 200U					
AC	£26,088.58	11.48	£203,429.74	1	No
BTX100AC	£30,116.97	11.33	£196,538.12	2	
BTX	£28,003.67	11.02	£192,415.95	3	
No-Rx	£12,121.38	9.39	£175,741.72	4	
Paediatric data					
AC	£39,678.25	17.88	£318,013.32	1	No

Intervention	Mean Costs	Mean QALYs	NMB at £20,000 per QALY	Rank at £20,000 per QALY (a)	Change? (b)
BTX100AC	£43,694.78	17.78	£311,870.34	2	
BTX	£42,290.96	17.27	£303,129.24	3	
No-Rx	£31,024.65	14.76	£264,105.93	4	
Stone prevalence					
AC	£26,637.32	11.45	£202,460.43	1	
BTX100AC	£27,584.51	11.32	£198,783.65	2	No
BTX	£25,271.63	10.99	£194,602.92	3	
No-Rx	£12,121.38	9.39	£175,741.72	4	
No standardized mortality ratio applied					
AC	£26,088.58	11.48	£203,429.74	1	
BTX100AC	£27,498.10	11.32	£198,936.30	2	No
BTX	£25,271.63	10.99	£194,602.92	3	
No-Rx	£12,121.38	9.39	£175,741.72	4	
Discount factor analysis					
No Impact on Cost effectiveness but had an impact on the costs and QALYs gained, discussed below.					

(a) Rank denotes the order of cost effectiveness at a £20,000 per QALY threshold.
(b) Change? Refers to whether the result of the sensitivity analysis results in a change in the base case results

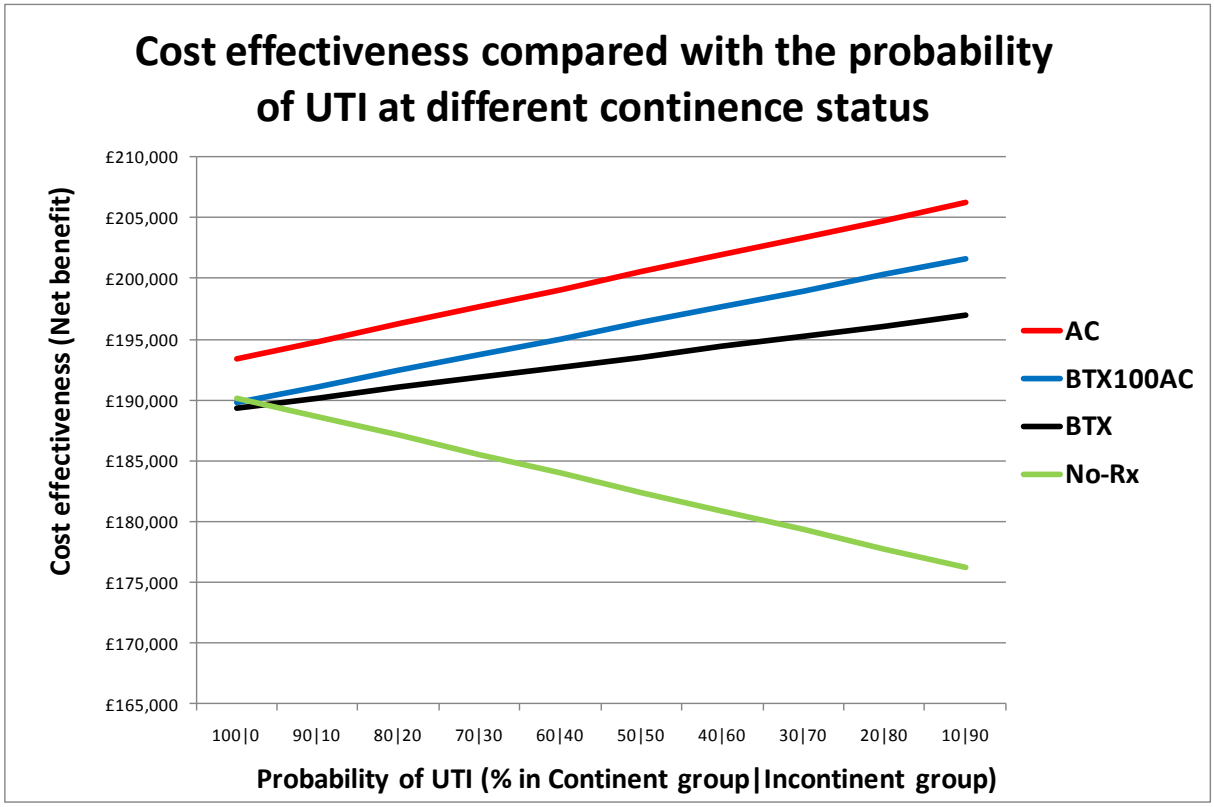
Table 12 shows the impact of various assumptions on the model. The table shows that, varying all of these parameters one by one has no impact on the overall model result at a threshold of £20,000 per QALY. This shows that the model is robust to the error in the assumptions made when constructing the model. There are however two situations where the base case result changes. These are when the cost of 200U of BTX are reduced or increased. One analysis reduced the cost from £276 to £28; at this point BTX100AC becomes more cost effective than AC over a lifetime. This was carried out as a threshold analysis, where the cost is reduced until another strategy becomes cost effective. However, given the cost of BTX currently, this £28 figure is very unlikely to be seen in the future, meaning that this analysis does not represent a realistic situation. The threshold analysis was also taken the other way with the BTX vs No treatment comparison. The cost of BTX was increased to £1,315 per 200U. At this cost, the cost effectiveness ratio of BTX reached the threshold of £20,000 making it no longer cost effective compared to no treatment. Again, this cost is very high and unlikely to be seen, given the current cost of BTX.

The sensitivity analyses set out in table 12 also allow a look at the second base case analysis, BTX vs No-Rx. It is possible to see that BTX alone, is always cost effective when compared to No-Rx, however the variables are altered.

A further factor to consider was the impact of the frequency of UTIs on the cost effectiveness of each intervention at a threshold of £20,000 per QALY. In the base case the probability of UTIs when continent is around 30% per cycle, whereas in incontinent patients the probability is 93% over the same period. However, the GDG felt that this was based on fairly weak evidence and that a sensitivity analysis was required. In order to measure the impact of UTIs, the proportion of UTIs in the incontinent group was reduced from 100% to 0% as the proportion of UTIs in the mild incontinent and continent was increased from 0 to 100%. This gave an idea of how UTIs influence cost effectiveness. In Figure 60 it is possible to see that as the proportion of incontinent UTIs increases so does the cost effectiveness of all the interventions compared to no treatment. The order is also maintained throughout: AC from BTX100AC from BTX from No-Rx. This is true except for one very extreme situation. If incontinent patients have 0% probability of UTIs and continent and mild incontinent patients have 100% probability of UTIs then No-Rx is cost effective compared to both BTX

arms. This situation is extreme, however, and unrealistic. It is much more likely that the true incidence of UTIs in the different groups lies in the range between 80/20 and 20/80, and within this range there is no change to the base case result.

Figure 60: Analysis on the frequency of UTIs by intervention.



I.3.3.1 Impact of discount factor

The discount factor is varied from 0% to 6% per year, in accordance with the NICE reference case. Varying the discount factor makes no difference to the base case result with the same order of Cost effectiveness maintained throughout. However as the discount factor is decreased on costs, BTX alone becomes more costly than AC over a lifetime, with the opposite being true as it is increased. This is in keeping with the fact that with BTX, there are continually high costs throughout, therefore with a high discount rate, costs borne further from the present will decrease in present value. The same, however, is not true of outcomes, as the discount rate is increased or decreased, the QALYs increase or decrease at the same rate as each other, meaning that even though the costs may be changing, the incremental QALYs remain the same so that the order of cost effectiveness is maintained throughout. The specific situation required by the NICE reference case of 3.5% on costs and 1.5% on outcomes results in no change to the results.

I.4 Discussion

I.4.1 Summary of results

The results show that AC is the cost effective intervention at a threshold of £20,000 per QALY over a lifetime horizon. The results also show that BTX is cost effective when compared to no intervention, where AC is not a relevant comparator. BTX100AC is a more cost effective intervention than BTX alone in populations where AC is a relevant comparator. BTX is cost effective for use in patients who have a poorer prognosis or who are likely to deteriorate at such a rate that they will not benefit from

being continent beyond ten years. The results are generally robust to the uncertainty around the assumptions made as shown by the deterministic sensitivity analyses. The probabilistic data shows that at a threshold of £20,000 per QALY gained AC is cost effective with a probability of 78%, again demonstrating the robustness of the model to uncertainty.

I.4.2 limitations & interpretation

The many limitations are almost entirely due to the lack of good quality data to populate the model. Perhaps the most important limitation is the fact that there is no comparative data on AC and BTX. Therefore the comparison between these two interventions is made on the basis of two fairly heterogeneous studies. The BTX vs placebo study was a randomized control trial [3] whereas the study used to provide AC data was based on observational data [11]. This disparity means that the outcomes: continence, mild incontinence and incontinence, are not measured in the same way. It was necessary for the GDG to make assumptions about the definition of what constituted these outcomes, which was not ideal but given the available data was the only solution. The result of this is that it makes the comparison of BTX with no treatment more reliable than the comparison of AC with BTX or no treatment. However, the probabilistic analysis allows us to take this uncertainty into account and deal with it explicitly.

Another issue with the model is the lack of long term data for both AC and BTX. The BTX study followed patients up for less than a year and the AC study was based on follow up of 2.5 years. This meant that we had to assume that the long term efficacy of BTX did not reduce and that people would not change from one outcome group to another later on in the model. This may limit the reliability of the longer term conclusions.

There was a lack of data on children from the clinical review and in the literature more generally. This is probably due to the fact that there is no licence for BTX and therefore clinicians are reluctant to look at BTX in children. However, there was some data for the side effects in AC in children. Using this in a sensitivity analysis allowed some consideration of this limitation even if the effectiveness data had to be extrapolated from the adult data.

The data on UTI was another limitation that restricted the model. Firstly there was an assumption that both mild incontinent and continent had the same frequency of episodes. Secondly, the Game 2008[13] study was used to determine the rates. However, this was a study based on 30 patients and did not provide as much information as would be desirable. The sensitivity analysis looked at this limitation in some detail and found that there is no meaningful difference in cost effectiveness as a result of UTI incidence.

A further limitation was around the cost of BTX. BTX has no licence for this indication and is therefore not costed appropriately in the BNF or NHS drug tariff. The cost used therefore is likely to change if BTX has a licensed approved. However using the sensitivity analyses it is possible to see that only if the cost of BTX becomes extremely cheap or extremely expensive will it change the base case results of this model. This means that the results insensitive to changes in the cost of BTX. The assumptions made about appliance use were kept as simple as possible so as not to over complicate the model. The costs of catheters and appliances that are calculated following the assumptions that have been made about their usage produced a fairly conservative estimation of the differences in appliance use between the comparator groups.

The final limitation to discuss was the problem with the utility data that informed the adverse event rates, these rates were informed by utilities that came from fairly disconnected sources that describe GI and Urinary tract symptoms and perforations more generally rather than the specifics of the AEs that we were looking at. However if the AE utilities are removed or given a value of 0.5, a very high disutility, there is no difference in the overall result although BTX becomes cost effective for more of the time horizon. The model is therefore fairly robust to changes in the utility of AC adverse events.

I.4.3 Generalisability to other populations / settings

The analysis took place in two parts. The first part being the comparison of all interventions in a population where all comparators were relevant, such as a spinal cord injured population. The second part was a comparison of just BTX with no treatment. This was therefore in a population where AC was not a relevant comparator such as patients with multiple sclerosis. This analysis is therefore generalisable to any patient that suffers from incontinence due to NLUTD in the UK. The model is also of potential relevance to populations outside of the UK as the model is fairly robust to changes in costs and impact of adverse events.

Comparisons with published studies

Only one other cost effectiveness study has been done that analyses AC vs BTX. The study by Padmanabhan et al. 2011[20] showed that BTX would cost about $5,000 less than AC per successful intervention. However this analysis only uses adverse events as outcomes and is a five year study from a US payer perspective. This is in keeping with what our model shows as BTX only is shown to be cost effective when compared with AC for the first six years of the model. However as the Padmanabhan study is from a US payer perspective and does not consider outcomes beyond adverse events, its relevance to the UK perspective is limited.

I.4.4 Conclusion = evidence statement

The results of the model allow four main conclusions to be drawn:

1. AC is the cost effective intervention over a lifetime horizon in the populations where it is a relevant comparator.
2. BTX is cost effective compared to AC in patients where the full benefits of surgery are unlikely to be accrued (patients with shorter life expectancy or patients with a rapidly degenerating condition).
3. A BTX strategy where AC is used (and relevant) in 100% of patients after failed BTX is cost effective compared to a 0% progression to AC strategy but is higher cost.
4. BTX is cost effective when compared to no treatment.

I.4.5 Implications for future research

The limitations of this study were fundamentally due to a lack of data in fairly key areas. Lack of comparative data between BTX and AC and AC and no treatment hindered the development of the model. Another area that was lacking in data was longer term outcomes associated with BTX and AC. An area for research that would provide this model with more precise data would be better data on the utilities associated with adverse events stemming from AC.