A Cost-Effectiveness Analysis of Contact X-ray Brachytherapy for treatment of patients with a partial response to Chemoradiotherapy for Rectal Cancer

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# Research Highlights

* Watch-and wait with contact brachytherapy and external beam radiotherapy (WWCXB) was more effective and less costly than both watch-and wait with external beam radiotherapy alone (WWEBRT), and Radical Surgery following chemoradiotherapy (RS) independent of patient cohort age and comorbidity.
* WWCXB was more cost-effective with a high degree of certainty (61.9-76.5%) at a threshold of £20,000/QALY.
* Budget impact analysis suggests that an initial investment of £3.6 million would be required in order to implement a WWCXB strategy in England and Wales.
* WWCXB would be cost-saving by the second year following introduction compared to RS and the fourth year compared to WWEBRT. This could result in a savings of over a five year period of over £8million to the NHS
* A ceiling-value of £8.7million was estimated for further research on the efficacy of WWCXB.

# Abstract

**Background:** A “watch and wait” approach (WW) may provide equivalent survival and oncological outcomes to initial Radical surgery (RS) in patients with a clinical complete response (cCR) following neoadjuvant chemoradiotherapy (CRT). However, over 80% of patients do not achieve a cCR. Contact X-ray Brachytherapy (CXB) enables high doses of radiation to be delivered directly to rectal cancers with minimal damage to adjacent tissue, and can be used in addition to external beam radiotherapy (EBRT) to increase the cCR rate. There is evidence to suggest that CXB may improve the incidence of bowel continuity. The long-term cost-effectiveness of CXB has not been evaluated. Consequently, we aim compare the cost-effectiveness of WW with CXB and EBRT (WWCXB), to WW with EBRT alone (WWEBRT), and RS for patients with rectal cancer treated with CRT.

**Design:** Decision analytical modelling and a Markov simulation were used to model long-term costs, quality-adjusted life years (QALYs), and cost-effectiveness from a third-party payer (NHS) perspective. Sensitivity analysis was used to investigate the effect of uncertainty in model parameters and patient demographics. Budget Impact Analysis and Value of Information Analysis was also performed.

**Results:** WWCXB was more effective than both RS and WWEBRT and less costly independent of patient cohort age and comorbidity. Consequently WWCXB was more cost-effective with a high degree of certainty (61.9-76.5%) at a threshold of £20,000/QALY. Budget impact analysis (BIA) suggests that CXB would be cost saving by the second year following introduction compared to RS and the fourth year compared to WWEBRT. This could result in a savings of over a five year period of over £8million to the NHS. Value of information analysis estimated a ceiling-value of £8.7million for further research on the efficacy of WWCXB.

**Conclusions:** WWCXB is likely to be cost-effective compared to both WWEBRT alone and RS. These findings strongly support the use of CXB boost as an adjunct to a WW strategy. This is further supported by BIA which suggests that implementation of CXB will be cost-saving.

# Keywords: Rectal, radiotherapy, neoadjuvant, watch and wait, complete clinical response, elderly, cost-effectiveness

# Abbreviations

BIA Budget Impact Analysis

cCR Clinical Complete Response

CEAC Cost-effectiveness Acceptability Curve

CET Cost-effectiveness Threshold

cm80 80-year-old male cohort with comorbidities

cPR Clinical Partial Response

CRT Chemoradiotherapy

CXB Contact Brachytherapy

EBRT External Beam Radiotherapy

EVPI Expected Value of Perfect information

fm60 60-year-old male cohort with no comorbidities

fm80 80-year-old male cohort with no comorbidities

HES Hospital Episode Statistics

HRQoL Health-related Quality-of-life

NICE National Institute for Health and Care Excellence

ONS Office of National Statistics

pCR Pathological Complete Responses

QALY Quality-Adjusted Life Years

RS Radical Surgery

WTP Willingness-to-pay

WW Watch and Wait

WWCXB Watch and Wat with EBRT and CXB Boost

WWEBRT Watch and Wait with EBRT alone

# Introduction

The standard of care for locally advanced rectal cancer is currently neoadjuvant chemoradiotherapy (CRT) followed by radical surgery (RS) [1, 2]. Perioperative mortality, particularly in elderly co-morbid patients following RS is significant [3]. There is also significant morbidity associated with RS. Significantly, 83% of patients had a stoma following surgical resection (either because the rectum was removed, or “temporary” defunctioning stomas). Over 50% of patients, however, still had a stoma 18 months following surgery. This unquestionably has a significant effect on patient health-related quality of life (HRQoL) [4].

Significantly, a complete pathological response (pCR), with absence of cancer cells in the resected specimen, however, has been reported in between 10-20% of patients [5, 6]. Subsequently, several studies have demonstrated the safety of adopting a “watch and wait” (WW) strategy after CRT in patients for whom a clinical complete response (cCR) has been achieved where no evidence of residual tumour can be identified [7, 8]. These approaches eliminate perioperative mortality, deliver equivalent oncological outcomes if cCR is maintained, and preserve bowel continuity in patients for whom a stoma is unsuitable or unacceptable [9]. While disease does recur in some patients, limited data suggests that should this occur, subsequent RS can be performed with equivalent oncological outcome to patients initially treated with RS [8, 10]. There is now emerging evidence to suggest that long-term survival and oncological outcomes following WW and RS may be comparable [5]. Modelled data from our group suggests that not only does WW provide equivalent survival, it is also cost-effective [11, 12].

Unfortunately, however the cCR is low with conventional external beam radiotherapy (EBRT). A recent UK series reported that 12% of patients achieved a cCR [5]. Consequently, there is an urgent need to improve and sustain cCR rates following CRT. One practical means to improve and sustain cCR is to escalate the dose of radiation delivered, however this is associated with the side-effects of radiation toxicity. Contact X-ray Brachytherapy (CXB) boost can be used to achieve this with limited collateral damage to surrounding normal tissues [13-15]. Several case series suggest that CXB may improve both the rate and sustainability of a cCR [16, 17]. There is randomised evidence to support an improved cCR following CXB [13]. The effect that this may have on long-term quality-of-life and cost-effectiveness is however uncertain.

Therefore, in this study we aim to compare both the clinical and cost-effectiveness of WW with EBRT and CXB boost (WWCXB), WW with EBRT alone (WWEBRT), and RS following EBRT. We will investigate and quantify the associated uncertainty. We also aim to perform alternative analyses to investigate if these results are sensitive to patient age and comorbidity. Finally, we will perform Budget Impact Analysis (BIA) to investigate the burden of CXB on the consumption of healthcare resources nationally.

# Materials and Methods

Outcomes in patients with a cCR following neoadjuvant CRT treated with WWCXB, WWEBRT, and RS were modelled using a decision analytical model adapted from the published literature consisting of a decision tree and Markov chain simulation (Figure 1) [12]. Details of all interventions that patients undergo in each modelled state have previously been described (Figures 2 and 3) [12]. Table 1 shows clinical parameters used to populate the model. These parameters were used in previous work and represent best available estimates [11, 12]. The economic data used to populate the model is listed in Table 2. Table 3 shows perioperative mortality used to populate the model extracted from the Hospital Episodes Statistics (HES) database, and Table 4 shows baseline mortality data used to populate the model based on UK Office of National Statistics (ONS) Life Tables).

Analysis was performed from a third party-payer perspective (UK National Health Service, NHS) according to the National Institute for Health and Care Excellence guidelines on technology assessment [18]. Costs are reported in UK pound sterling (£) [19]. The effects of interventions were measured in Quality-Adjusted Life Years (QALYs), a composite measure of survival and utility. Incremental costs and effects were calculated for the lifetime of the hypothetical patient cohorts. Costs and effects were discounted at 3.5% per annum according to guidelines on cost-effectiveness analysis [18]. Probabilistic sensitivity analysis was performed to investigate and quantify associated uncertainty [20]. Decision analytical software (TreeAge-Pro, TreeAge; Williamstown, MA) was used to perform the analysis. This study was exempt from Institutional Review Board ethical approval as it is a modelling study and did not require any interface with patients.

## Definition of Treatment Strategies, Modelled Patient Populations and Outcomes of Interest

In our modelled cohorts all patients underwent CRT. In the RS modelled cohort all patients underwent RS after CRT. In the WW cohort patients with a cCR according to strictly defined criteria [11, 21] were managed with WW approach. Patients without a cCR in the WW cohort underwent RS. In the WWCXB patients who initially had a cCR following CRT were treated with a WW approach. Patients without a cPR and a residual tumour greater than 3cm underwent RS, patients with a residual tumour of 3cm or less were given a CXB boost. CXB was delivered as an outpatient treatment every 2 weeks using a Papillon plus machine (Ariane Medical Systems, UK). Patients received a total of 90 Gy delivered in 3 fractions over 4 weeks. We have previously described in more detail the treatment regime for CXB boost [22]. In our modelled cohort patients who had a cCR following CXB boost were managed with a WW approach. Patients without a cPR following CXB boost underwent RS.

We assumed that follow-up for patients undergoing surgery was according to national guidelines [23]. Briefly, these recommend a minimum of 2 CTs of the chest, abdomen, and pelvis in the first 3 years. In addition, a surveillance colonoscopy at 1 year is offered after initial treatment. If this is normal, a further colonoscopy is considered after 5 years. In the WW cohort follow-up was more intensive with 2 CTs per year for the first 3 years, 3 pelvic MRIs a year for the first 2 years and then 2 MRIs in the following year. Clinical examination was performed every 3 months for the first 2 years accompanied by alternating rigid and flexible sigmoidoscopy. In the third year this was performed every 6 months, and subsequently every year until 5 years following initial treatment. Finally, a surveillance colonoscopy at 1 year is offered after initial treatment. If this is normal, a further colonoscopy is considered after 5 years.

We assumed that should tumor recurrence occur in either cohort, patients underwent full oncological restaging and salvage surgery where appropriate. Patients in whom salvage surgery was not possible underwent palliative surgery and chemotherapy. Patients with distant metastasis underwent palliative chemotherapy and a proportion of patients, reflecting actual clinical practice, underwent liver resection [24]. It was assumed that patients received the maximum dose of radiotherapy and so our model did not account for further costs associated with palliative radiotherapy. As less than 1% of patients with colorectal metastasis in the lung undergo resection we did not account for this in our model (Figures 1-3) [25].

To investigate whether the results of our analysis were sensitive to patient age and comorbidities analysis was performed for a 60-year-old male (fm60) and 80-year-old male cohort with mild comorbidities (fm80) (Charlson Score<3), and an 80-year-old male cohort with significant comorbidities (cm80) (Charlson Score≥3). The Charlson Comorbidity Index is an established tool to predict mortality for a patient who may have a range of comorbid conditions [26].

## Model Parameters

Post-operative mortality in the first 90 days for each demographic cohort was obtained from the HES database, a national database which describes the care provided to patients in NHS hospitals (Table 1, Table 3). HES data is widely used for NHS quality assurance, by government agencies and in the academic literature [27]. Baseline mortality estimates were extracted from UK ONS Life Tables (Table 4) [28].

Estimates of other clinical parameters used to populate the model were extracted from published literature [6, 7, 10, 11, 29-41]. The rationale for using these estimates has previously been discussed [11]. Estimates of the costs associated with treatment were based on NHS reference costs [42] or previous NICE reports in the case of palliative chemotherapy [43] (Table 2).

The cCR rate following CXB boost was estimated to be 26% based on data from a randomised study comparing CXB boost with CRT alone [13, 15]. As there was no direct comparative evidence no assumptions were made about an increased durability of cCR following CXB. This represents a conservative estimate of the efficacy of CXB as several case series have reported improved cCR rate (65-98%) and durability (local re-growth rate 8-12%) following CXB [16, 17, 22]. The cCR following CRT was derived from the UK OnCoRe study, as we felt this probably best reflected current UK practice and the populations modelled in this study [5]. It should be noted that the cCR rate is significantly less than that reported in some studies and thus must be considered a conservative estimate of the cCR rate [6, 44]. This is congruent with the findings of other studies [45]. The proportion of patients with a cPR following CRT who were suitable for CXB boost was derived from a recently published study from own centre [22], as this reflects a similar population with similar initial treatment from the same geographical area as those in the OnCoRe study [5]. Finally, the costs associated with CXB boosts were based on a primary costing study undertaken at our own institution using methodology consistent with NHS reference costs [46]. This study is summarised in the supplemental information.

## ***Sensitivity Analysis***

Deterministic sensitivity analysis was performed to investigate the sensitivity of the study to assumptions made about the value of individual model parameters. Each model parameter was varied with plausible ranges (Table 1, Table 2). In order to estimate the combined effect of uncertainty associated with all model parameters, a probabilistic sensitivity analysis was performed using a Monte Carlo simulation. Briefly, all parameters including transition probabilities were randomly sampled from assigned distributions (Table 1, Table 2). It was assumed that parameters were independent, i.e. not correlated with each other. The model was then run to simulate a “virtual” cohort of 1000 “matched” patients using these sampled probabilities for each intervention. All model parameters were then re-sampled and the model was then run again to generate data for a further virtual cohort of 1000 patients. This process was repeated until data had been generated for 1000 matched virtual cohorts of 1000 patients. This allowed QALY payoffs and costs to be estimated for both treatment strategies. Crucially however, it also allowed estimates of the uncertainty associated with these outcomes to be calculated. As cost parameters may by closely correlated, it is possible that the assumption that all model parameters are not correlated may overestimate the uncertainty.

## Budget Impact Analysis

To evaluate the cost of implementation of CXB in England and Wales a Budget Impact Analysis (BIA) was performed. The incidence of rectal cancer and the proportion of patients undergoing neoadjuvant CRT prior to undergoing major resections, was extracted from the National Bowel Cancer Audit report (Table 5) [4]. Unlike in the cost-effectiveness analysis capital investment expenses such as the cost of the Papillion Plus machine were considered separately to the incremental treatment costs for each patient. The initial cost of training the team is covered by the manufacturer (Ariane Medical Systems, UK). It was conservatively assumed that the first 20 patient treatments would be undertaken by the whole team under supervision, and consequently this was also considered in the BIA. It was assumed that each centre could treat a maximum of 150 patients per year, whilst this probably represents a conservative estimate, this would ensure a reasonable geographic coverage to support local MDT, and that the distance patients would be required to travel would not be excessive. Finally the model was populated with a young, fit cohort to ensure that burden of the log-term costs associated with WW follow-up were not underestimated. As surgical costs are significantly less in this cohort (Table 2) this assumption would probably also conservatively account for cost savings associated with CXB. A time horizon of 5 years was adopted for BIA. All assumptions were tested in sensitivity analysis. All parameters used in BIA are described in Table 5.

## Value of Information Analysis

Population Expected Value of Perfect Information (EVPI) was calculated to quantify the cost of the uncertainty associated with the results of the cost-effectiveness analysis and determine a hypothetical ceiling for the value of further research [20]. NICE and the Health Technology Assessment Programme have suggested that EVPI analysis is both a practical and potentially useful method of prioritizing research investment [47], and has been applied to a number of different healthcare interventions [48]. For EVPI analysis the model was populated with an elderly, comorbid cohort in which we anticipated that uncertainty and QALY payoffs would be lowest, thus conservatively estimating the value of further research. The target population was assumed to be the same as for BIA. The lifetime of the technology was conservatively estimated to be ten years. All parameters used in EVPI are described in Table 5.

# Results

In all modelled patient cohorts WWCXB was both less costly and more effective than RS and WWEBRT, and thus could be said to be dominant. Compared to WWEBRT, WWCXB in the fm60 cohort was less costly by £833.96; 95%CI -£1,430.09 to £3,637.33; and more effective by 0.10QALYs; 95%CI -0.42QALYs to 0.61QALYs. In the fm80 cohort it was less costly by £531.21; 95%CI -£1,766.31 to £3,137.96; and more effective by 0.08QALYs; 95%CI -0.15QALYs to 0.33QALYs. In the cm80 cohort it was less costly by £800.29; 95%CI -£1,619.73 to £3,634.94; and more effective by 0.11QALYs; 95%CI -0.11QALYs to 0.36QALYs. Compared to RS, WWCXB in the fm60 cohort WW was less costly by £2,205.5; 95%CI -£1,288.12 to £6,427.99; and more effective by 0.18QALYs; 95%CI -0.64QALYs to 1.02QALYs. In the fm80 cohort it was less costly by £1,555.01; 95%CI -£1,917.85 to £5,535.2; and more effective by 0.15QALYs; 95%CI -0.17QALYs to 0.51QALYs. In the cm80 cohort it was less costly by £2,065.1; 95%CI -£1,857.05 to £6,568.73; and more effective by 0.20QALYs; 95%CI -0.14QALYs to 0.55QALYs (Table 5).

## Deterministic Sensitivity Analysis

The results of deterministic sensitivity analysis at a willingness-to-pay/ cost-effectiveness threshold (CET) of £20,000/QALY is shown in Figure 4. Each panel has the plausible ranges for a variable plotted on each axis. The boundary between the shaded areas represents the tipping point of the model at which there is equipoise. The area shaded green indicates values at which WWCXB is cost-effective, the blue indicates where WWEBRT is cost-effective, and the red indicates RS is cost-effective. Deterministic sensitivity analysis did not suggest that the results of the model were sensitive to individual model parameters, moreover as the bivariate sensitivity analysis in Figure 4 shows, the model remains insensitive to the effect of individual model parameters in all the demographic cohorts modelled.

## Probabilistic Sensitivity Analysis

The results of probabilistic sensitivity analysis are shown Figure 5 demonstrating the effect of the combined uncertainty associated with all model parameters. At a CET of £20,000/QALY, WWCXB is most cost-effective in all modelled cohorts. The cost-effectiveness acceptability curve (CEAC) is a method for summarising information on uncertainty in cost-effectiveness. The CEAC identifies the probability that the intervention is cost-effective compared to the alternative based upon the data provided for a given CET [20]. In the fm60 cohort WWCXB was most cost-effective in 61.9% of model iterations, this increased to 66.7% in the fm80 cohort, and 76.5% in the cm80 cohort at a CET of £20,000/QALY (Figure 5).

## Budget Impact Analysis and Value of Information Analysis

BIA suggests that a capital expenditure of £3.6 million would be required in order to implement a WWCXB strategy in England and Wales. In the first year following implementation WWCXB would save £2.2 million compared to RS, by the second year this will raise to £4.1 million, by the third year £6 million, by the fifth £11.7 million. Compared to WWEBRT the cost savings in the first, second third, and fifth year are £0.78million, £1.6 million, £2.3million, and £4.7million respectively. Consequently after the cost of implementation is subtracted WWCXB would be cost-saving compared to WWEBRT and RS at year 4 and 2 respectively and cost-saving by year 5 with 58.1% certainty compared to WWEBRT and 91% certainty compared to RS (Figure 6). The corresponding population EVPI was £8,698,109.97 (Figure 7) at a CET of £20,000/QALY.

# Discussion

The results of the modelling presented in this study suggest with a high degree of certainty that the addition of CXB boost as an adjunct to WW management in order to optimise the proportion of patients who achieve a cCR and are thus eligible for non-operative management is cost-effective. The degree of certainty associated with these findings is in part because addition of a CXB boost for this indication is both cost-saving and effective, resulting in an increased QALY payoff, and consequently could be said to be dominant. These findings were true in all three modelled demographic cohorts (fm60, fm80, and cm80). Predictably however, as age and patient co-morbidities increase the uncertainty associated with these findings decreases. This is unsurprising as by increasing the cCR rate compared to WWEBRT, WWCXB can result in RS can being avoided in some patients, and the effect of avoiding RS in elderly and co-morbid patients is likely to be more marked. The reason that the incremental QALY payoff is not more marked in elderly in the fm80 and cm80 cohort is that these patients have a significantly lower life-expectancy than the fm60 cohort, and consequently the QALY payoff for each death avoided is consequently less.

Previous work that we have undertaken suggests that WW offers at least comparable clinical to RS [11]. This is supported by emerging clinical evidence [5]. We have also shown that WW is cost-effective compared to RS for patients with a cCR to CRT [12]. In view of these findings, evidence from the literature about the efficacy of CXB boost [13], and the findings of this study on the relative cost-effectiveness of WWEBRT and WWCXB, it is not surprising that WWCXB dominates RS alone in all the modelled demographic cohorts. Whilst this may not be a surprising finding, arguably the cost-savings suggested by this comparison may be most relevant to decision makers as most UK centres which do not have a formal WW programme of any kind yet.

UK National guidelines (NICE) already suggest that CXB in conjunction with external-beam radiotherapy is safe and efficacious in patients who are unable to undergo RS [49]. NICE also suggests that whilst CXB is safe in patients who are able to undergo RS but choose not to, its effectiveness remains uncertain and consequently these patients should be enrolled in clinical audit or research programmes [49]. These guidelines are supported by our study, and as one of a plethora of studies that support the use of CXB boost specifically and WW in general it is possible that these guidelines may need to be further revised.

The cost-savings that this study suggest could be achieved with CXB, without compromising clinical outcomes are particularly relevant in view of the challenges faced in the wider UK healthcare environment. The results of our BIA analysis suggest that within a relatively short period the capital expenditure needed to implement WWCXB would be offset by thehealthcare costs incurred by individual patients. This further supports wider implementation of a WWCXB strategy (Figure 6). In many respects our BIA is quite conservative, not only because of the conservative modelling assumptions described in the methods section, but because this BIA does not consider the role that commissioned CXB centres could have in treating patients with other cancers or rectal cancer for other indications (Palliation, Salvage and T1 polyp cancers for example)

All studies based on decision analytical modelling represent simplification of complex real-world scenarios, and consequently the results of these studies must be interpreted with caution. All models are vulnerable to uncertainty associated with model parameters, and consequently we have endeavoured to populate our model with the most relevant and robust estimates, and to fully quantify the uncertainty associated with these model parameters. We hope that the OPERA trial [50] which is currently recruiting patients will provide empirical support for these modelled findings. Interestingly, the results of the population EVPI analysis which conservatively defines a ceiling of £8,698,109.97 for further research at a CET of £20,000/QALY arguably justifies increased support to help UK centres recruit to the OPERA trial and for continuation and expansion of the UK led prospective CXB outcomes database.

# Conclusions

This study strongly suggests that WWCXB is cost-effective compared to both WWEBRT and RS, and implementation of WWCXB in England and Wales would be cost-saving. This has significant implications both for clinicians working in this field, and policy makers.

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# Figure and Table Legend

***Table 1.*** Estimates of clinical parameters and utilities. cCR = complete clinical response; pCR = complete pathological response; pPR = partial pathological response. Transition probabilities were described by beta distributions based on the listed expected value and range.

***Table 2.*** Economic parameters.

***Table 3.*** Ninety-day mortality data after proctectomy from Hospital Episode Statistics database. Mortality was best described by beta distributions. The mean and SE are used to facilitate comparison with other literature.

***Table 4.*** Age-specific UK baseline mortality.

***Table 5****.* Additional parameters used in budget impact and value of information analysis

***Table 6.*** Summary of the results of cost-effectiveness analysis

***Figure 1.*** Schematic representation of our decision-analytic model, consisting of a decision tree and Markov chain simulation to investigate the long-term outcomes associated with the competing interventions. Decision nodes are represented by boxes in the main figure, and chance nodes are depicted by circles. The decision tree terminates either with the patients dying (in the case of patients who do not survive surgery), shown by a triangle, or a Markov chain simulation, shown by a circle with an “M” inside. The structure of the Markov simulation is depicted by the bubble diagram shown in the insert. The transition probabilities for the Markov simulation which are determined by initial treatment and whether a pCR was achieved after CRT and are described in Table 1.

***Figure 2.*** Detailed description of the costs incurred by hypothetical patients in each Markov state following RS.

***Figure 3.*** Detailed description of the costs incurred by hypothetical patients in each Markov state following WW.

***Figure 4.*** Deterministic (Bivariate) sensitivity analysis at a CET of £20,000/QALY. The boundary between the shaded areas represents the tipping point of the model at which there is clinical equipoise. The area shaded green indicated values at which WWCXB is most cost-effective, the red area corresponds to RS, and the blue area WWEBRT. This figure shows the insensitivity of the analysis to the values of individual model parameters. The top panels show that this is the case as operative mortality varies (Figures A-E), and the bottom panel shows that this is the case as baseline mortality varies (Figures F-J), suggesting that this is the case for all demographic cohorts.

***Figure 5.*** Willingness-to-pay curves showing the proportion of model iterations and hence the certainty with which RS, WW, or WWCXB is most cost-effective for different Willingness-to-pay (Cost-effectiveness thresholds). The results of probabilistic sensitivity analysis from the fm60 cohort is shown in the top panel, the fm80 cohort in the middle panel and the cm80 cohort in the bottom panel.

***Figure 6.*** The cost of implementing WWCXB compared to WWEBRT (Blue line) and RS (Red Line).

***Figure 7.*** Results of the EVPI analysis. Population EVPI is plotted against Willingness-to-pay (Cost-effectiveness thresholds).

Table 1

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model parameter** | **Expected Value** | **Range** | **Distribution** | **α** | **β** |
| % of patients where cCR = pCR after CRT[7, 11, 29, 30] | 70% | 0-100% | Beta | 4.44 | 3.40 |
| Surgical mortality after salvage surgery for primary tumor[11, 27] | See Table 3 | 0-16.4% | Beta | - | - |
| Relapse if true pCR and surgery[6, 11, 30-34] | 17% | 0-30% | Beta | 9.01 | 247.50 |
| % of recurrences that are distant if pCR and surgery[11, 30-34] | 81% | 50-100% | Beta | 18.87 | 5.64 |
| Relapse if true pCR and observation alone[11, 30] | 17% | 0-30% | Beta | 9.01 | 247.50 |
| % of recurrences that are distant if pCR and observation alone[11, 30] | 81% | 50-100% | Beta | 18.87 | 5.64 |
| Relapse if pPR and surgery[11, 30-34] | 36% | 0-80% | Beta | 4.77 | 7.57 |
| % of recurrences that are distant if pPR and surgery[11, 30-34] | 83% | 26-100% | Beta | 8.98 | 3.91 |
| Relapse if pPR and observation alone[11, 30] | 70% | 0-80% | Beta | 6.53 | 6.53 |
| % of recurrences that are distant if pPR and observation alone[11, 30] | 43% | 0-71% | Beta | 6.01 | 9.81 |
| % of patients with cPR who are suitable for CXB[22] | 71% | 50-100% | Beta | 115 | 46 |
| % of patients with cCR following CRT with EBRT alone[5] | 12% | 0-50% | Beta | 31 | 228 |
| % of patients with cCR following CXB Boost[13] | 26% | 0-50% | Beta | 11 | 34 |
| Salvage surgery for local recurrence if prior rectal surgery[11, 30, 35, 36] | 37% | 10-70% | Beta | 8.89 | 13.90 |
| Salvage surgery for local recurrence if observation[10, 11, 30] | 80% | 50-90% | Beta | 31.53 | 11.47 |
| Surgical mortality after salvage surgery for local recurrence[11, 27] | See Table 3 | - | Beta | - | - |
| Survival after local recurrence with surgical salvage[11, 30, 37, 38] | 50% | 20-60% | Beta | 26.27 | 130.81 |
| Survival after local recurrence without surgical salvage[11, 30, 37, 38] | 30% | 0-50% | Beta | 7.55 | 13.18 |
| Survival with distant metastatic disease[11, 30, 35, 38] | 20% | 0-30% | Beta | 12.18 | 17.33 |
| Baseline Mortality (See Table 4)[28] | - | - | - | - | - |
| Utility of observation after radiation[30, 39] | 0.91 | 0.85-1 | Beta | 107.42 | 9.34 |
| Utility of surgery after radiation[30, 40] | 0.86 | 0.7-1 | Beta | 41.87 | 7.20 |
| Utility of Local recurrence with associated morbidity[30, 41] | 0.78 | 0.5-0.85 | Beta | 19.20 | 6.06 |
| Utility of Distant recurrence with associated morbidity[30, 40] | 0.7 | 0.5-0.85 | Beta | 19.92 | 7.24 |

Table 2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model parameter** | **Mean**  **(£)** | **Lower Quartile (£)** | **Upper Quartile (£)** | **Distribution** | **α** | **λ** |
| Cost of Radical Surgery (Abdominoperineal resection) -Comorbidities[42] | 11,885.96 | 7,726.96 | 14,959.0 | Gamma | 4.923 | 0.00042 |
| Cost of Radical Surgery (Abdominoperineal resection) -Without Comorbidities[42] | 9,027.26 | 6,524.94 | 10,527.21 | Gamma | 9.27 | 0.0010 |
| Cost of Liver Resection - Comorbidities[42] | 9,243.24 | 6,396.18 | 10,329.71 | Gamma | 10.06 | 0.0011 |
| Cost of Liver Resection – Without Comorbidities[42] | 6,870.48 | 5,328.16 | 8,133.0 | Gamma | 10.94 | 0.0016 |
| Cost of Palliative Surgery - Comorbidities[42] | 7,014.06 | 4,918.21 | 8,427.36 | Gamma | 7.28 | 0.0010 |
| Cost of Palliative Surgery – Without Comorbidities[42] | 5,422,16 | 4,290.19 | 6,016.5 | Gamma | 17.98 | 0.0033 |
| Cost of Examination under Anesthesia[42] | 1,220.16 | 898.92 | 1,402.57 | Gamma | 10.70 | 0.0088 |
| Cost of Rigid Sigmoidoscopy[42] | 179.58 | 119.88 | 215.0 | Gamma | 6.49 | 0.036 |
| Cost of Flexible Sigmoidoscopy[42] | 197.2 | 105.73 | 244.0 | Gamma | 3.71 | 0.019 |
| Cost of Colonoscopy[42] | 333.84 | 207.46 | 494.0 | Gamma | 2.47 | 0.0074 |
| Cost of Magnetic Resonance Imaging of Pelvis[42] | 138.46 | 103.69 | 160.93 | Gamma | 10.67 | 0.077 |
| Cost of Computerised Tomography of Chest, Abdomen and Pelvis[42] | 128.54 | 94.31 | 161.5 | Gamma | 6.67 | 0.052 |
| Cost of Multi-disciplinary Discussion of Patient Management[42] | 123.17 | 72.64 | 145.36 | Gamma | 5.23 | 0.042 |
| Cost of Outpatient Appointment[42] | 105.04 | 75.23 | 122.71 | Gamma | 8.93 | 0.085 |
| Cost of Palliative Chemotherapy[43] | 53,000 | - | - | Gamma | 7.78 | 0.00015 |
| **Model parameter** | **Mode**  **(£)** | **Lower Limit (£)** | **Upper Limit (£)** | **Distribution** |  |  |
| Cost of Contact Brachytherapy | 1,274.7 | 956.03 | 1,593.38 | Triangular | - | - |

Table 3

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **90 Day Mortality(%) Charlson<3** | | | | | | **90 Day Mortality(%) Charlson>3** | | | | | |
| **Age** | **90 Day Mortality** | **Total Number of Patients** | **Representative Mean Mortality\*** | **Representative SE\*** | **Parameter for Beta Distribution** | | **90 Day Mortality** | **Total Number of patients** | **Representative Mean Mortality\*** | **Representative SE\*** | **Parameter for Beta Distribution** | |
| **** | **** | **** | **** |
| <61 | 49 | 4086 | 1.2 | 0.003 | 49 | 4037 | 47 | 1739 | 2.7 | 0.009 | 47 | 1692 |
| 61-70 | 130 | 5186 | 2.5 | 0.003 | 130 | 5056 | 133 | 2764 | 4.8 | 0.008 | 133 | 2631 |
| 71-80 | 271 | 4883 | 5.5 | 0.005 | 271 | 4612 | 242 | 2613 | 9.3 | 0.011 | 242 | 2371 |
| >80 | 179 | 1512 | 11.8 | 0.021 | 179 | 1333 | 129 | 785 | 16.4 | 0.047 | 129 | 656 |

Table 4

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Baseline Mortality (%)** | **Age** | **Baseline Mortality (%)** | **Age** | **Baseline Mortality (%)** | **Age** | **Baseline Mortality (%)** |
| 60 | 0.9 | 70 | 2.2 | 80 | 6.3 | 90 | 15.6 |
| 61 | 0.9 | 71 | 2.4 | 81 | 7.0 | 91 | 16.7 |
| 62 | 1.0 | 72 | 2.7 | 82 | 7.7 | 92 | 18.8 |
| 63 | 1.1 | 73 | 3.0 | 83 | 8.5 | 93 | 20.9 |
| 64 | 1.3 | 74 | 3.3 | 84 | 9.6 | 94 | 22.8 |
| 65 | 1.4 | 75 | 3.7 | 85 | 10.7 | 95 | 24.9 |
| 66 | 1.5 | 76 | 4.1 | 86 | 11.8 | 96 | 26.6 |
| 67 | 1.7 | 77 | 4.5 | 87 | 12.9 | 97 | 28.7 |
| 68 | 1.9 | 78 | 5.0 | 88 | 14.1 | 98 | 30.3 |
| 69 | 2.1 | 79 | 5.6 | 89 | 14.6 | 99 | 31.4 |

Table 5

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model parameter** | | | | |
| Additional Parameters for BIA and population EVPI Analysis | | | | |
|  | **Mean** | **Standard Deviation** | | **Distribution** |
| Number major resections for rectal cancer annually in England and Wales (Mean over last 5 years) | 4,823 | 78.03 | | Normal |
|  | **Mode** | **Lower Limit** | **Upper Limit** | **Distribution** |
| Proportion of patients undergoing major resections having neoadjuvant CRT | 28% | 18% | 46% | Triangular |
|  | **Mode** | **Lower Limit** | **Upper Limit** | **Distribution** |
| Number of patients that can be treated with WWCXB at each centre annually in the UK | 150 | 100 | 200 | Triangular |
| Cost of purchase of Papillion Plus system | £355,000 | £266,250 | £443,750 |  |
| Cost of learning curve (team training) for each centre – Staffing for 20 sessions | £6, 409.4 | £4,807.05 | £8,011.75 | Triangular |
| Alternative Parameters for BIA | | | | |
|  | **Mode** | **Lower Limit** | **Upper Limit** | **Distribution** |
| Alternative cost of CXB used in BIA excluding cost of capital investment | £961.41 | £721.06 | £1,201.76 | Triangular |

Table 6

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cohort** | **Cost Saving (£)** | | **Incremental Effectiveness (QALY)** | | **Uncertainty; Percentage of model simulations intervention most cost-effective (%)** |
| **Mean** | **95% CI** | **Mean** | **95% CI** | **CET 20,000£/QALY** |
| **WWCXB vs WWEBRT** | | | | | |
| fm60 | 833.96 | -1,430.09 to 3,637.33 | 0.10 | -0.42 to 0.61 | WWCXB - 61.9%, WWEBRT – 16.1%, RS – 22% |
| fm80 | 531.21 | -1,766.31 to 3,137.96 | 0.08 | -0.15 to 0.33 | WWCXB - 66.7%, WWEBRT – 19.8%, RS – 13.5% |
| cm80 | 800.29 | -1,619.73 to 3,634.94 | 0.11 | -0.11 to 0.36 | WWCXB - 76.5%, WWEBRT – 14.3%, RS – 9.2% |
| **WWCXB vs RS** | | | | | |
| fm60 | 2,205.5 | -1,288.12 to 6,427.99 | 0.18 | -0.64 to 1.02 | WWCXB - 61.9%, WWEBRT – 16.1%, RS – 22% |
| fm80 | 1,555.01 | -1,917.85 to 5,535.2 | 0.15 | -0.17 to 0.51 | WWCXB - 66.7%, WWEBRT – 19.8%, RS – 13.5% |
| cm80 | 2,065.1 | -1,857.05 to 6,568.73 | 0.20 | -0.14 to 0.55 | WWCXB – 76.5%, WWEBRT – 14.3%, RS – 9.2% |

Figure 1

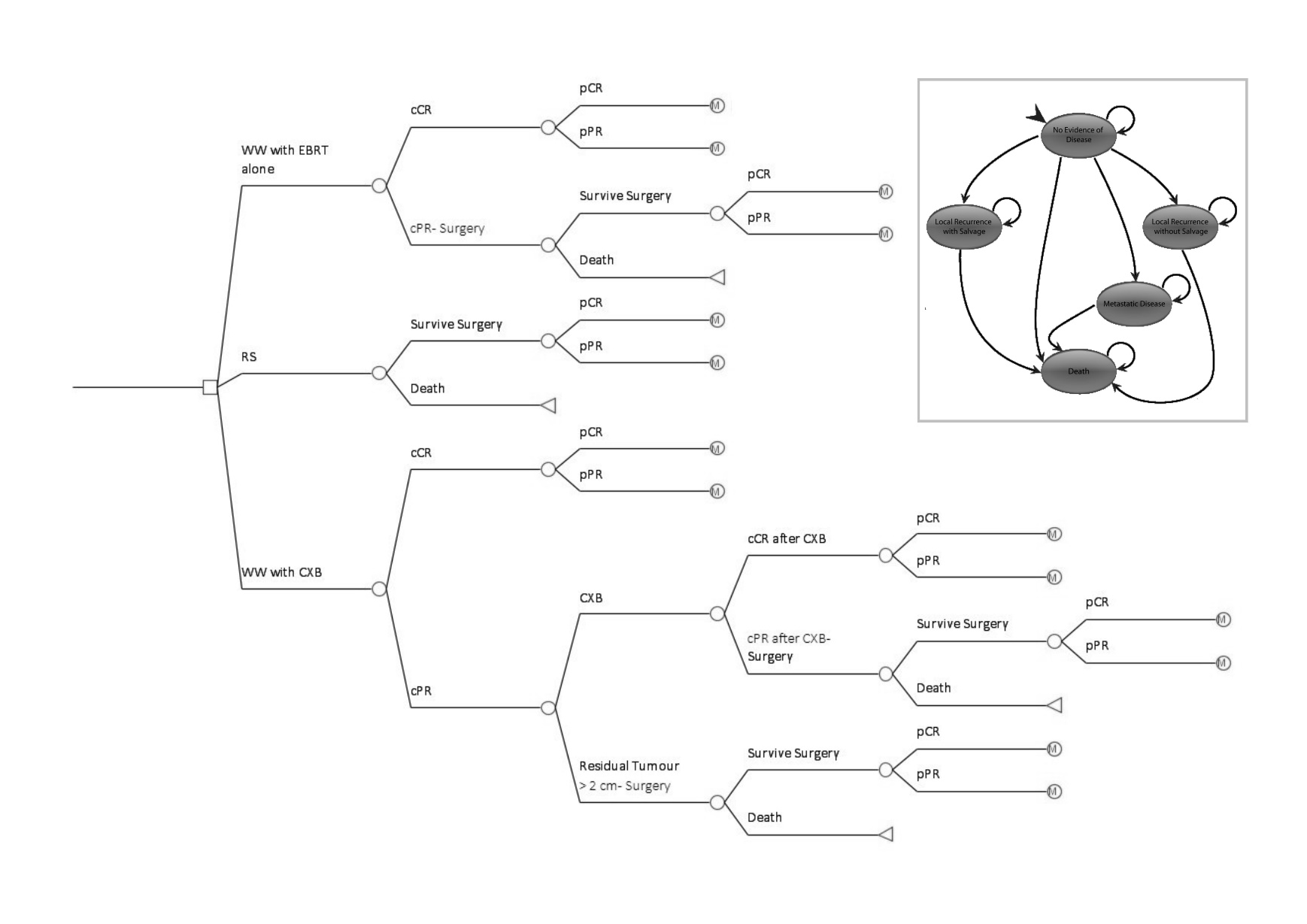


Figure 2



Figure 3



Figure 4

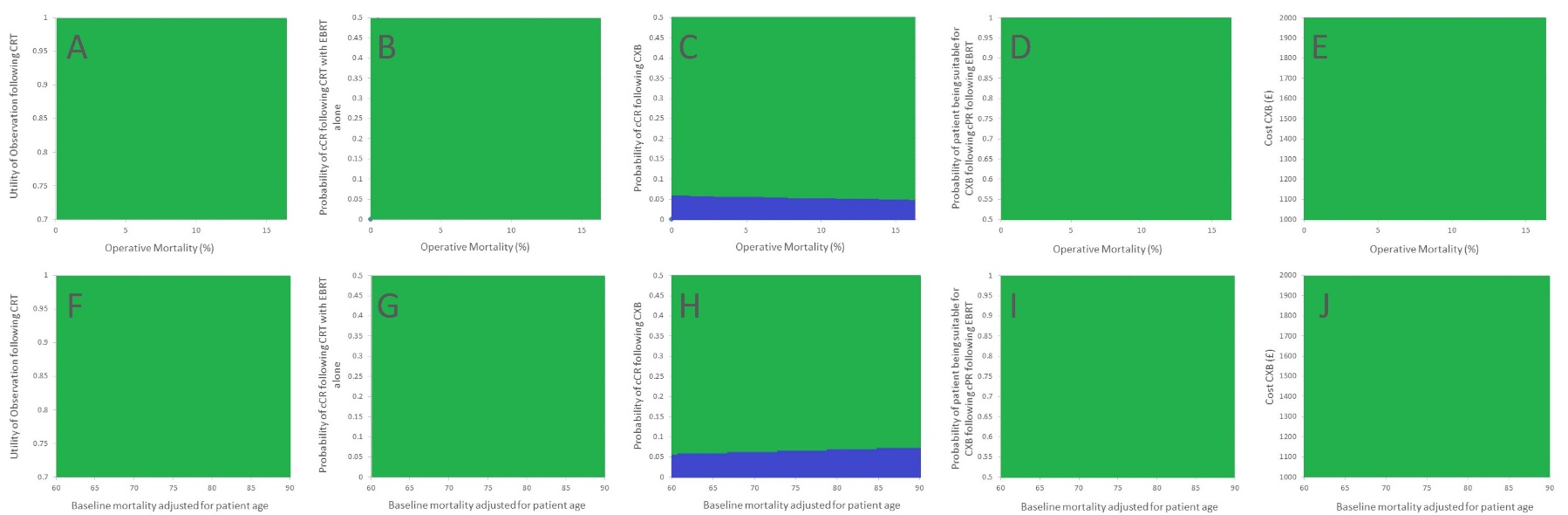
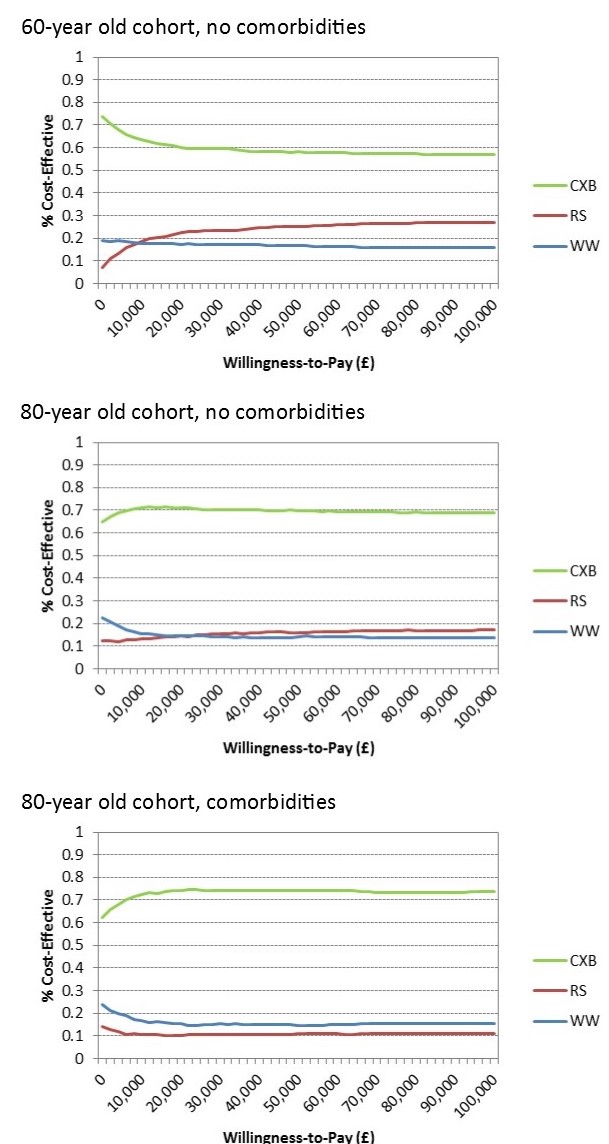
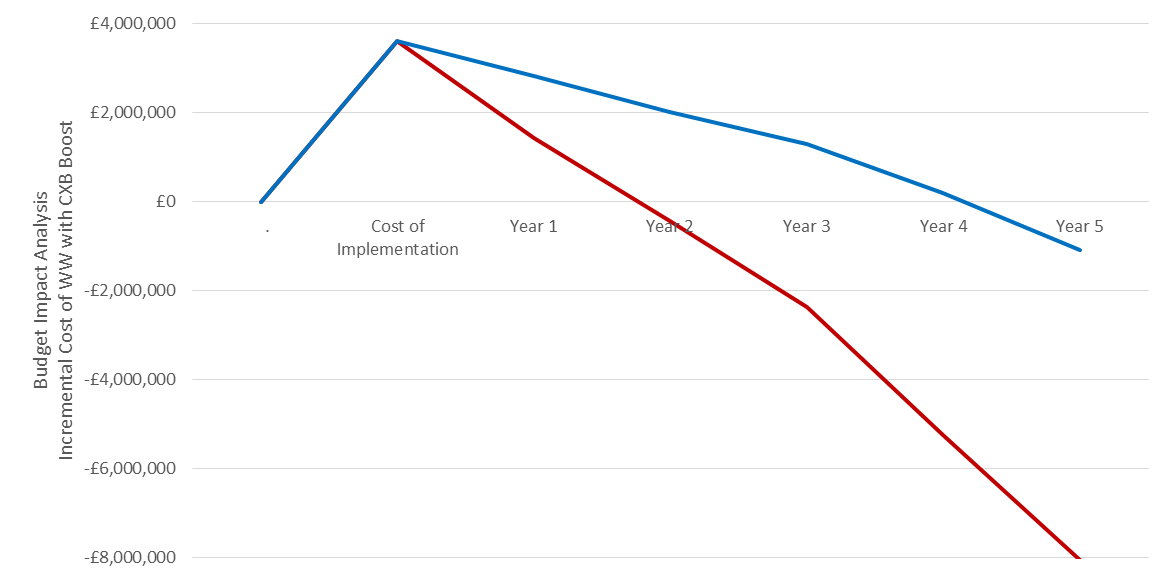


Figure 5



*Figure 6*

**

*Figure 7*

**