Appendix 1 [posted as supplied by author]
The Southampton model: replicating, updating and extending the analysis of Forrest report on breast cancer screening

Aims and background

This paper details the Southampton model which aimed to**:**
a) replicate exactly the Forrest report estimates of the life years saved from breast cancer through the introduction of mammographic screening,
b) reproduce the Forrest Report estimate using as baseline the higher breast cancer mortality rate for England in 1985 in place of the baseline from the two trials used in Forrest,
c) update the Forrest report estimates for mortality reductions due to screening based on the meta analysis of the eight trials,
d) include harms from both false positives and overtreatment and
c) enable sensitivity analyses to be carried out.

A1. The Forrest Report

The 1986 Forrest report[1] which led to the introduction of mammographic breast screening in the UK included an analysis which estimated the cost per Quality Adjusted Life Year gained from screening. The benefits were limited to patients who tested as true positives, measured in both life years and quality adjusted life years (QALYs). Costs were itemised under six headings. Estimates were made for costs and benefits over 15 years. The report put the cost per life year of life year gained at £3,044 and a cost per QALY of £3,309. The latter was based on an 8% decline in the quality of life following treatment of breast cancer, put at 0.92 compared to 1.0 for perfect health. Life years saved were multiplied by 0.92 to express them in QALYs.

The omissions in the Forrest report analysis included:
* "psychological factors" resulting from false positives on mammography, and
* overdiagnosis, which was stated to be 'not a problem'.

The Forrest report relied on the results of the Swedish Two Counties trial[2] and the HIP New York trial[3]. The claim that overdiagnosis was not a problem was based on the New York trial but the Forrest report noted that the Two Counties trial found possible overdiagnosis of 20%. It stated that "Further follow up is required to find out whether this excess persisted" (page 14).

The Forrest report used a life table to estimate the number of life years saved by a hypothetical breast screening programme, specifically single view mammography repeated every 3 years over 15 years on a cohort of 100,000 women invited for screening. The surviving population was re-estimated each year taking account of deaths from breast cancer in both cohorts, using baseline mortality for the unscreened cohort and reduced mortality due to screening in the screened cohort. Death rates from breast cancer were based on the Two Counties trial[2] up to year 9 and extrapolated from year 10 onwards using the New York trial[3]. Both cohorts were exposed to the mortality rate for causes of death other than breast cancer, again taken from the two trials. The surviving population was estimated each year for those screened and not screened, and expressed in life years. The baseline mortality rate for breast

cancer and for all other causes and the relative risk reduction in breast cancer mortality due to screening were also taken from the two trials. [a]

A2. The Southampton model

The Southampton model estimated mortality using the same life table[1] approach as Forrest, but built in Microsoft Excel. It followed two cohorts of 100,000 women aged 50, updated in 1-year cycles, with one cohort screened , the other not. The screening interval was three years, with a 73% attendance rate, as in Forrest, the relevant trials and UK national breast screening practice.

Replicating Forrest

To ensure that the Southampton model could replicate Forrest's results exactly, Forrest's baseline breast cancer mortality rate and year-on-year relative risk reductions were fed into the Southampton model to check that they led to the same number of deaths as Forrest. They produced the same totals for lives saved and for life years.

Reproducing the Forrest Report

Forrest acknowledged that the baseline breast cancer mortality risk in the two trials was well below England's actual breast cancer mortality rate in 1985. Using the rate for England would increase the number of lives and life years saved by screening. Forrest considered that since screening was cost effective using the trial data which underestimated its benefits, he did not need to go further. However, to provide a fair reproduction of Forrest we corrected this underestimate by using as baseline the breast cancer mortality rate for England[4] in 1985, before screening. For breast cancer surgery we took as baselines the English rates for 1985, from the Hospital Inpatient Enquiry[5,6]. We applied relative risks from the meta-analysis of the 8 trials [7] to these baseline rates.

The baseline mortality rates for breast cancer and all other causes were age adjusted. The Hospital Inpatient Enquiry provided data on all surgical procedures on the breast, sub-classified into mastectomies (the largest element) and other[5]. We applied an age distribution to the total for surgery based on an age breakdown of HIPE inpatients with the diagnosis of breast neoplasms [6]. This gave us a rate for breast cancer surgery for women aged 45-64.

The relative risk reduction in mortality and its increase for breast cancer surgery was based on the meta analysis of the 8 trials [7]. All the baseline mortality rates were expressed in annual probabilities[8]. For both the screened and the unscreened cohorts the number of women dying from breast cancer and from all other causes were estimated, along with the number having breast surgery.

The number of false positive diagnoses was based on a published comparison of UK and US rates for 1993-1996[9]. These totals were linked to each round of screening and, as with surgery, were annualised over the 3 years between screens.

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[a] The age of the cohort was not specified in the Forrest report. It plausibly refers to a cohort of women aged 50 since that was Forrest's recommended age for starting screening. Since his breast cancer mortality reduction was based on the two trials, it could refer to a cohort of women with the same age distribution as the two trials. The age ranges were from 40 to 74 and from 40 to 64 in the 2 Counties and New York trials respectively. Taking the means of these (57 and 52) implies a slightly older cohort. Application of the mortality reductions from the trials to a younger 50 year old cohort would lead a slight overestimation of the effect of screening as the impact of screening increases with age. We assume that the Forrest estimates were based on cohorts of women starting screening at 50.

To convert Life Years Gained to QALYs, the Forrest Report multiplied them by 0.92, based on a reduction in quality of life due to surgery from 1.00 to 0.92. This in effect assumed no unnecessary surgery. Inclusion of the harms of unnecessary surgery required reducing the quality of life of all those who had surgery, a number considerably greater than that for those whose lives were saved due to screening. However the Forrest approach was followed in Scenario 1 "Forrest reproduced" by reducing the quality of life only of the additional life years gained by screening), which thus overestimates the gains due to screening. The same approach is applied in Scenario 2 "Forrest Updated Mortality". However, in scenarios 3 to 5 which includes all the harms due to surgery, those harms were linked to the number of women undergoing surgery, whether or not it was necessary. Scenarios 3 to 5 also include the harms due to false positive diagnoses.

In the Southampton model, the number of women who had surgery and the number who had a false positive diagnosis were estimated by screening round and then annually, with stated reductions in their quality of life. The difference in life years and QALYs between the two cohorts were estimated each year based on the quality of life losses outlined below and expressed as cumulative totals for up to 20 years.

Five scenarios were designed as outlined in Table A3 to show the effects of updating the Forrest report estimate of the breast cancer mortality reduction and to include the harmful effects of false positives and unnecessary surgery on the quality of life of women screened.

Table A1 Replicating, updating and extending Forrest Report: Scenarios

Scenario	Key features	Key assumptions/changes
1. Forrest Reproduced	Reproduced Forrest Report estimate of the number of life years gained due to breast cancer screening	Substitutes breast cancer mortality rate for England 1985 for Forrest's baseline from two trials
2. Forrest Updated Mortality	As 1 but updated for mortality reduction from meta-analysis of all 8 trials	Substitutes breast cancer mortality risk reduction from 8 trials for Forrest's risk reduction based on two trials
3. Forrest Updated including Harms	As 2 but with harms added.	Harms include those due to surgery and to false positives. Based on baseline breast cancer surgery rate for England 1985, false positive rates from Smith Bindman et al [10].
4. Gøtzsche & Neilsen	As 3 but with mortality reduction as suggested by Gotzsche & Neilsen	The relative risk reduction for breast cancer mortality in the Cochrane Review meta-analysis of the eight trials was 19% but Gotzsche & Neilsen suggested that it was more likely to be 15%.
5. Nelson et al.	Mortality reduction as in Nelson et al, with harms as in 3 above	The relative risk reduction for breast cancer mortality was split into two groups, 14% for the 50-59 age group and 32% for the 60-69 age group.

Scenario 1, Forrest Reproduced, shows what the original Forrest Report would have obtained if it had used as baseline the breast cancer mortality rate in England in 1985 combined with the relative risk reductions in the two trials then available. This provides a level against which to assess the effects of updating the mortality reduction and including harms. Scenario 2 updated the breast cancer mortality reduction based on meta analytic estimate from all 8 trials in the Cochrane systematic review[5]. Scenario 3 extended Scenario 2 to include harms due to false positives and surgery. Scenario 4 differed from Scenario 3 by substituting Gøtzsche and Nielsen's best estimates for breast cancer mortality reduction and for surgery [7]. Scenario 5 was based on the breast cancer mortality reductions suggested by Nelson et al [10,11] (14% in the 50-59 age group, 32% in the 60-69 age group), with harms as in Scenario 4. The values and key assumptions underlying the 5 scenarios are shown in Table A4.

Data sources for updating the Forrest report

Data for model inputs were drawn from searching the published literature, giving priority to systematic reviews, followed by randomised clinical trials, other published models, followed by observational data supplemented by clearly stated assumptions where necessary. The two systematic reviews [7,10,11] of the screening trials provided estimates of the effects of mammographic breast cancer screening, and a systematic review of health utility values in breast cancer[12] provided estimates of the quality of life losses which we supplemented as required by data from other published models and clinical trials. While the Forrest report was based on two trials, the two systematic reviews included the same set of clinical trials[b].
The Cochrane Review provided a meta-analysis of all trials for all age groups, with an emphasis on those trials considered to have been adequately randomised. In contrast, the US Review by Nelson et al focused on breast cancer mortality reduction by age group[10,11] For the the 60-69 age group, the US study relied on a follow up of five Swedish trials[13].which is used in Scenario 5.

Table 1 in the main article summarised the data inputs used. The following paragraphs discuss the rationale for the choice made.

False positive diagnoses lead to losses in quality of life. The Forrest report acknowledged this but did not quantify it. The 2010 systematic review of the utility losses due to breast cancer included an estimate of a loss of between 11% and 34%[12] but warned that the studies did not give a clear indication of values that could be used in modelling. Three modelling studies included quality of life losses from false positives, Stout et al [14] assumed a 25% quality of life loss for 25 days, equivalent to a loss of 0.017 QALYs (-0.25*25/365= -0.017). The MISCAN model [15] used 10.5% reduction for 5 weeks, equal to a loss of 0.010 QALYs. In a recent model for the UK breast cancer screening programme, Madan et al [16] used a range from 0.000 to 0.030 QALYs. In the base case in the present study, the quality of life loss from false positives was assumed to be 5% for a duration of 0.2 years or 0.010 QALYS. The sensitivity analyses varied the quality of life loss by =/- one third, that is from 3.3% to 6.7%.

Surgery for breast cancer also reduces quality of life. The Forrest report used a quality of life reduction of 8% based on value of 0.92 post treatment compared to 1.00 pre-screening[1].
A US breast cancer screening model [14] assumed a quality of life values for three post treatment states (localised, regional and distant breast cancer) with quality of life values of 0.90, 0.75 and 0.60. The Dutch MISCAN modelling study[15], based on a small sample, provided data on the quality of life loss for two states. For the state 'After mastectomy' the quality of life loss was put at 13.3% for one year and 5.3% beyond 1 year after treatment. For the state 'After breast conservation', the quality of life loss was 8.6% for the first year and 4.0% beyond one year. An Australian study[17] showed greater quality of life losses post treatment.

A 2010 UK trial of the role of MRI in addition to triple assessment in women scheduled for surgery for breast cancer put the quality of life loss due to surgery at 5%, based on 1600 patients[18]. However since the women in this study had relatively small tumours, the quality of life loss may be an underestimate. Given the estimates in the literature, the fact we were excluding other harmful treatments such as chemotherapy and radiotherapy, and the value we

[b] Although reported as nine trials in Gøtzsche and Nielsen's Cochrane review and eight by Nelson et al, they made up the same set of trials as Gøtzsche and Nielsen counted the two Canadian trials separately. Hereafter this set of trials is referred to as the 8 trials.

had assumed for false positives, we considered it reasonable to put the quality of life loss due to surgery at 6% with sensitivity analysis of +/-2%.

The duration of the quality of life loss due to surgery, as noted above, has been less researched. The 2010 systematic review of utility states in breast cancer[12] found that few studies provided estimates by time. Some assumed a return to full health by a particular time whereas other found some evidence that losses were permanent. The Miscan model [16] assumed that the quality of life losses post surgery were higher in the first year and permanent thereafter. A follow up study of a randomised controlled trial of post operative radiotherapy in UK women aged over 65 with low risk breast cancer showed reduced EQ5D scores persisting 5 years after surgery[19]. The work reported here assumes that the quality of life losses due to treatment of breast cancer were permanent, following the example of the Forrest report, but durations of 5 and 10 years were explored in sensitivity analyses.

Other assumptions are listed in the article

Southampton model: Results

The five scenarios are described and graphed in the main report. Table A5 shows the data on which Figure 1 was based.

Table A2
Breast Cancer Screening: QALYs generated by scenario by year

	Forrest: original reproduced	Forrest updated for breast cancer mortality	Forrest updated for Breast Cancer mortality and harms	As 3 but substituting G&N estimates for breast cancer mortality and surgery (Base Case)	As 3 but with breast cancer mortality baseline and reduction as in Nelson (2 age groups)
Scenario	**1. Forrest Original**	**2. Forrest Updated mortality**	**3. Updated Mortality and Harms**	**4. Gøtzsche & Neilsen**	**5. Nelson et al**
Year					
1	20	13	-11	-14	-14
2	61	39	-17	-25	-28
3	122	79	-17	-35	-39
4	203	131	-5	-34	-42
5	**304**	**195**	**12**	**-31**	**-42**
6	430	277	39	-23	-38
7	582	375	75	-8	-29
8	760	489	121	12	-15
9	962	619	176	38	3
10	**1,189**	**764**	**240**	**70**	**27**
11	1,413	928	317	110	78
12	1,635	1,110	407	158	156
13	1,854	1,310	508	215	260
14	2,071	1,526	621	280	390
15	2,285	1,758	746	353	545
16	2,495	2,007	882	434	726
17	2,703	2,271	1,030	523	931
18	2,906	2,550	1,189	620	1,161
19	3,106	2,841	1,358	724	1,412
20	**3,301**	**3,145**	**1,536**	**834**	**1,685**

A6. Sensitivity analyses

Three sensitivity analyses explored:

- Independently varying each of four parameters (relative risk of breast cancer mortality, risk of surgery, quality of life losses due to surgery and to false positives),
- combining the range of estimates of these parameters in a probabilistic sensitivity analysis, and
- varying the duration of harms from surgery. (Since this involved a structural change in the model, it could not be included in the probabilistic sensitivity analysis.)

Scenarios 6 to 15 explored the effects of varying each assumption independently (table A3) compared with the base. For mortality and surgery the 95% confidence intervals set the range. For quality of life the range was +/-33%, covering the range in the literature.

The effects of varying the relative risk of surgery are also shown in Table A6 and Figure A1, with the base case relative risk 1.35 from the Cochrane review's meta-analysis compared with 1.26 (Scenario 6) to 1.44 (Scenario 7), the confidence intervals around 1.35. The results varied as expected with more QALYs in those scenarios with reduced relative risks and vice versa compared to the base case. Even with a relative risk of 1.1 the cumulative QALYs at 20 years were considerably less than either the original Forrest (Scenario 1) or its mortality update (Scenario 2).

Table A3
QALYs by year for sensitivity analyses by Scenario

Cycle/ Scenario	3. Base Case	6. Surgery risk: Low	7. Surgery risk: High	8. False Positive QoL Loss: Low	9. False Positive QoL Loss: High	10. Surgery QoL Loss: Low	11. Surgery QoL Loss: High	12. Relative Risk of BC mortality: Low	13. Relative Risk of BC mortality: High	14. Duration of Surgery QoL Loss: Low (5 y)	15. Duration of Surgery QoL Loss: Medium (10 y)
1	-11	-8	-13	-5	-16	-8	-14	-6	-15	-11	-11
2	-17	-10	-24	-6	-27	-7	-26	-1	-30	-17	-17
3	-17	-3	-31	-2	-33	1	-35	13	-44	-17	-17
4	-5	18	-28	13	-23	25	-35	46	-49	-5	-5
5	**12**	**47**	**-22**	**33**	**-8**	**57**	**-33**	**89**	**-53**	**12**	**12**
6	39	87	-9	62	16	102	-23	147	-54	48	39
7	75	139	12	101	50	158	-7	222	-50	103	75
8	121	202	40	149	93	227	16	312	-43	176	121
9	176	277	76	206	146	307	45	418	-31	266	176
10	**240**	**362**	**119**	**273**	**208**	**400**	**81**	**540**	**-16**	**375**	**240**
11	317	462	173	352	283	507	128	681	6	505	327
12	407	576	237	444	370	629	185	841	34	655	434
13	508	704	312	547	469	765	251	1,020	69	825	562
14	621	845	398	662	580	915	327	1,218	110	1,014	711
15	746	999	493	789	702	1,078	413	1,433	156	1,223	880
16	882	1,166	599	928	837	1,255	509	1,667	210	1,450	1,069
17	1,030	1,346	715	1,078	982	1,445	615	1,918	269	1,696	1,278
18	1,189	1,538	841	1,238	1,139	1,648	729	2,185	335	1,959	1,506
19	1,358	1,741	976	1,409	1,306	1,862	853	2,468	407	2,239	1,751
20	**1,536**	**1,955**	**1,120**	**1,590**	**1,483**	**2,087**	**985**	**2,765**	**483**	**2,534**	**2,013**

The effects of varying the quality of life losses due to false positives are also shown in table A3 and Figure A2, with the QoL loss increased from -3.3% up to -6.7%. As expected, increasing the quality of life loss led to fewer cumulative QALYs after 20 years. Compared to the base case, Scenario 4, the cumulative QALYs at year 20 fall to 1,483 in scenario 9 and increased to 1,590 in Scenario 8. Negative QALYs applied for the first 3 years after screening in Scenario 8 and for 5 years in Scenario 9.

When the Quality of life loss due to surgery was reduced from 6% to 4% (Scenario 10), the number of QALYs increased from 1,536 to 2,087 after 20 years. When the quality of life loss was increased to 8% (Scenario 11) the QALYs fell to 985 after 20 years. Negative net QALYs applied to the end of first two years in Scenario 10 and to year 7 in Scenario 11 (Figure A3)

When the relative risk reduction of breast cancer mortality was reduced to13% (Scenario 12), compared to the base case of 19% reduction, the number of QALYs reduced to 483. When the relative risk reduction was increased to 26%, the number of QALYs increased to 2,765 (Figure A4)

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis the above four parameters (breast cancer mortality risk, surgery risk, quality of life loss from surgery and from false positives) were varied simultaneously. The uncertainty around the relative risk of surgery and the relative risk reduction of breast cancer mortality were taken from the Cochrane reviews meta-analysis of 1.35 (95% CI 1.26 to 1.44) and 0.81 (95% CI 0.74 to 0.87) respectively. The variations at the quality of life loss due to surgery and to false positives were as in one way sensitivity analyses reported above. The distributions shown in Table A4 were sampled for the four variables in 10,000 iterations. The results (table A5 and figure 3 in main paper) put the mean cumulative QALY gain after 20 years at 1,532 with a range from 771 to 2,136.~~,~~ Negative QALYs applied for between 2 and 9 years around a mean of 4.

Table A4
Probabilistic sensitivity analysis: distributions and values used

Parameters	Distribution	Mean Value	se	low value	high value
Relative risk of breast cancer death	Lognormal	0.81	0.0413	0.74	0.87
Relative Risk of Surgery	Lognormal	1.35	0.0341	1.26	1.44
Quality of Life loss due to surgery	Beta	0.06	0.0102	0.04	0.08
Quality of Life loss due to false positives	Beta	0.05	0.0087	0.033	0.067

Table A5
Probabilistic sensitivity analysis: results, varying the changes in breast cancer mortality and in surgery, the effect on quality of life due to surgery and due to false positives.

Average of 10,000 iterations				
Cycle	QALYs	Cumulative QALYs	Lower bound	Upper bound
1	-11	-11	-18	-5
2	-6	-17	-33	-2
3	-1	-17	-47	8
4	12	-5	-51	33
5	17	12	-54	66
6	27	39	-51	112
7	36	75	-43	170
8	46	120	-29	240
9	55	175	-10	322
10	**64**	**239**	**15**	**417**
11	77	316	51	527
12	89	405	95	652
13	101	506	149	791
14	113	619	212	945
15	124	743	282	1,111
16	136	879	363	1,291
17	148	1,027	452	1,484
18	158	1,185	550	1,690
19	169	1,354	657	1,909
20	**178**	**1,532**	**771**	**2,136**

Varying the duration of Quality of Life losses due to surgery

A separate sensitivity analysis explored the effects of reducing the duration of the harms from surgery. This could not be included in the probabilistic sensitivity analysis due to the structure of the model. The base case (Scenario 3) assumed the quality of life losses due to surgery were permanent. Scenarios 14 and 15 reduced the duration of this quality of life loss to 5 and 10 years respectively, with the results as shown in Table A3 and Figure A5. The cumulative QALYs at 20 years were 2,533 and 2,009 respectively, well above the base case total of 1,536. However at 10 years the differences were less, 374 and 239 respectively compared to 239 in the base case. When both the duration of harm and the timeframe was 10 years (Scenario 15) the net QALYs at 10 years were the same as in the base case, as expected. Reducing the duration of harms due to surgery to 5 years led to 2,533 QALYs at 20 years, compared to 1,532 QALYs in the base case.

Figure A1

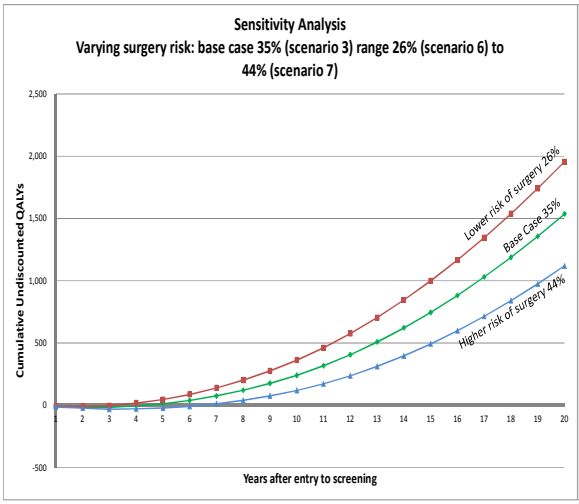


Figure A2

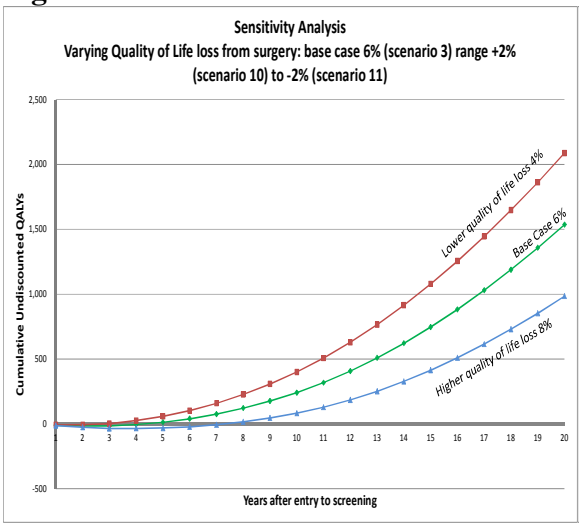


Figure A3

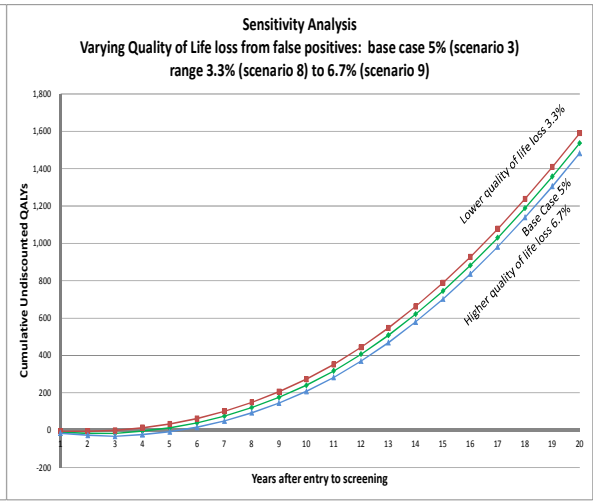


Figure A4

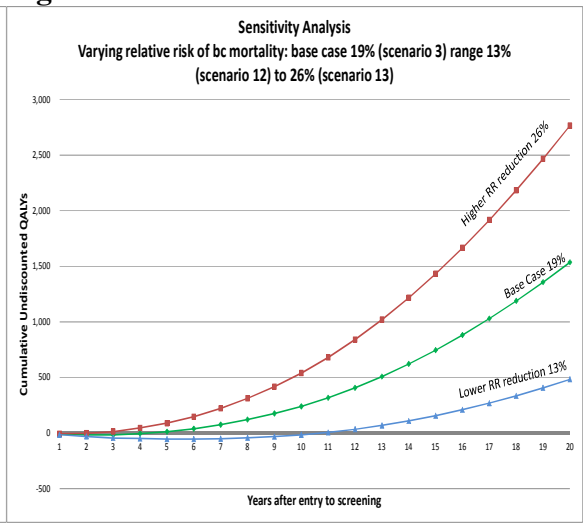
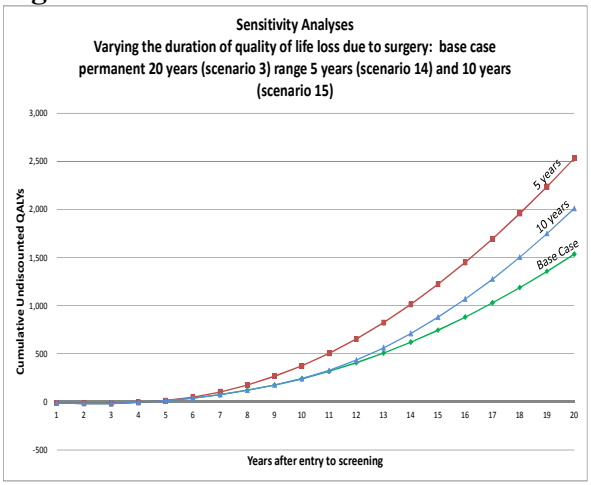


Figure A5



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