Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA 120) [ID481]

SHTAC review of the manufacturer's response to the specification of further work following the Appraisal Committee meeting on 23rd April 2013

Southampton Health Technology Assessments Centre (SHTAC)

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Summary

ABHI has undertaken the additional analyses as requested by the Appraisal Committee. The AG has checked the model structure and parameter inputs and has reproduced the updated results presented by the ABHI using their model. The AG considers that the new results are consistent with those in the original ABHI analyses. The ABHI have conducted all the required analyses specified by NICE and have presented these in the same format as the original submission with 24 rather than 48 subgroups. The ABHI have commented upon the impact of the changes to the model results with respect to any changes in the preferred treatment at the £20,000, £25,000 and £30,000 per QALY thresholds.

In the analysis the ABHI have not concluded which are the specific key drivers of the cost effectiveness results. The AG has undertaken additional sensitivity analyses to explore the impact of some of the parameters that may determine the ICERs. Given the complexity of interpreting the large number of subgroups in the model, the AG focused on three of the subgroups that contained the largest number of patients to illustrate the effects of changes to the different parameters.

Duration of mortality treatment effects

In the ABHI analyses, the model results were robust to changes to the model parameters for the duration of mortality treatment effects at the £30,000 per QALY threshold: for treatment duration the preferred treatment of choice alters in only two of the 24 subgroups (NYHA III, QRS <120 ms and no LBBB and NYHA III, QRS ≥ 150ms and LBBB. At lower thresholds (£20,000 and £25,000 per QALY) the model is more sensitive to changes in the duration of treatment effect, changing the most cost effective treatment in nine of the 24 subgroups.

The AG investigated other assumptions for the duration of the treatment effect (7.5 years treatment effect with no tapering effect, and 7.5 years treatment effect with tapering effect of 10 years) and the effect of changes to the mortality treatment effect (+/– 10%). Changes to these parameters were shown to result in changes to the model results, such that for two of the three subgroups analysed, the preferred treatment of choice alters at the £30,000 per QALY threshold. For the other subgroup the treatment of choice alters at the £20,000 per QALY threshold.

Effect of CRT-D on hospitalisation in NYHA III/IV patients

The AG confirmed that the treatment effect used in the original ABHI's submission was [redacted] and the reporting of this was inaccurate in the original submission. The AG completed sensitivity analyses for three selected subgroups and found changing the treatment effect for hospitalisation has only a small effect on cost effectiveness results.

Inclusion of counselling costs

ABHI reported that inclusion of counselling costs did not change the base case conclusions at any of the three thresholds considered. Sensitivity analyses undertaken by the AG for three selected subgroups confirmed that increasing these costs to a worst case scenario had little impact on the model results.

Device crossover or upgrade in clinical practice
Clinical experts contacted by the AG confirmed that device crossover/upgrade as described in the Specification document is rare in clinical practice.

Resource use and cost parameters
For the changes in device costs relating to the HRG tariff, the preferred treatment of choice alters in two of the 24 subgroups (NYHA III, QRS ≥ 150ms, LBBB, and NYHA IV, QRS ≥ 150 ms, without LBBB) in the ABHI analysis. For these subgroups, the base case ICERs were close to the £30,000 per QALY threshold.

The AG investigated the effect of changes to the manufacturers' device cost (not relating to the HRG tariff) in the three selected subgroups. These showed a similar impact to the model results as for changes to the HRG tariff.

Conclusions
The AG has checked the results for the base case using the ABHI model and considers that the new results are consistent with those in the original analyses. The AG has also checked the additional analyses submitted and replicated these by running the ABHI model. The ABHI analyses and those undertaken by the AG have shown that the ABHI model appears most sensitive to changes in parameter values for the assumptions surrounding the treatment effect of mortality and duration of treatment effect. The impact of the scenarios on the model differed for the different subgroups, but most remained under the £30,000 per QALY gained threshold. For the lower thresholds, some scenarios had the effect of changing the preferred treatment with only a small change in the ICER where the base case ICER was close to the threshold.

Introduction and methods

Following the Appraisal Committee Meeting on 23rd April 2013, the Committee requested that the manufacturers (ABHI) undertake additional analyses as detailed in the specification of further work (Appendix). This document summarises the review of these analyses by the SHTAC Assessment Group (AG).

The AG has checked the results of the ABHI additional analyses by re-running the ABHI model for each of the scenarios presented, and checking the submitted model (structure and parameters) against the original ABHI model. The AG has also used the ABHI model to run additional analyses to aid interpretation of the ABHI results. Given the large number of subgroups in the model, the AG focused on three of the 24 subgroups (Group 1: NYHA II, QRS ≥ 150 ms, LBBB, Group 2: NYHA III, QRS ≥ 150 ms, LBBB; and Group 3: NYHA II, QRS < 120 ms, without LBBB). These subgroups were selected to reflect different patient characteristics and potential treatment options and for their larger sample size in the IPD analysis. However they are not necessarily representative of all the other subgroups. It should be noted that for first subgroup (NYHA II, QRS ≥ 150 ms), CRT-P was excluded as a treatment option in the ABHI model as minimal IPD data were available from the clinical trials.

Clinical experts were asked by the AG to comment on the questions raised by the Appraisal Committee regarding device crossover or upgrade in clinical practice, and on assumptions made by ABHI for counselling costs.

Concerns previously raised by the AG in the assessment report regarding appropriateness of the 48 original subgroups and how these relate to the populations scoped by NICE have not been repeated here.

Suggested presentation of analyses

Please combine the ischaemic and non-ischaemic patient groups together, therefore presenting results for 24 subgroups rather than 48 in the original submission. For these subgroups, for each of the different scenarios presented, please present tables with fully incremental cost-effectiveness results as previously presented in tables 70-71 of the submission.

Please also present a summary of the most optimal strategies at different cost-effectiveness thresholds, for example, at £20,000, £25,000 and £30,000 per QALY gained.

The ABHI has provided the analyses as requested in terms of 24 subgroups rather than 48 in the original submission. The AG has checked the results for the base case using the ABHI model and considers that the new results are consistent with those in the original analyses. Although the results have changed by combining the ischaemic and non-ischaemic groups, there are no differences in the conclusions of the optimal treatment with regard to £30,000 per QALY cost effectiveness threshold for the aggregated results compared to the original results, except for subgroups with very small numbers in the IPD (such as NYHA I, non-ischaemic, QRS ≥ 150 ms without LBBB). For the £25,000 and £20,000 thresholds, there are some differences in the preferred treatment by aggregating the analyses in terms of 24 subgroups rather than 48. For some subgroups, the ischaemic and non-ischaemic ICERs are either side of a threshold. However, for the majority of the subgroups, the ischaemic and non-ischaemic ICERs are similar and aggregating the results does not change the preferred treatment.

With respect to changing the cost-effectiveness threshold, ABHI has presented a summary of optimal strategies at cost-effectiveness threshold vales of £30,000, £25,000 and £20,000 per QALY gained (ABHI Tables 4 to 6). Changing the threshold from £30,000 to £25,000 per QALY changes the optimal strategy in three of the 24 subgroups (NYHA III, QRS <120 ms; and NYHA III, QRS ≥ 150 ms, both LBBB groups). Changing the threshold to £20,000 per QALY changes the optimal strategy in most subgroups. The ABHI requests that the committee note that the ICERs are very close to the threshold values, with the potential impact that very small differences in ICERs could change threshold-decisions. Furthermore, they would expect that the ICERs would fall as acquisition costs of the medical devices reduce over time.

Specification of further work

1. Duration of mortality treatment effects

The manufacturers' base case assumes a constant duration of effect of 7.5 years for all-cause mortality, followed by linear tapering over 20 years. Sensitivity analyses were also provided assuming life-long constant treatment effects without any tapering (MS page 194) as a more optimistic scenario, and assuming a constant duration of effect for 5 years as a more conservative scenario (Appendix 15 page 72-73). Please provide these analyses for the 24 subgroups outlined above, combining the ischaemic and non-ischaemic patient groups.

In addition, please also provide a sensitivity analysis assuming a constant duration of effect up to the average duration of follow up in the trials, followed by linear tapering thereafter?

The ABHI has provided the analyses requested, and the AG has replicated these results using the ABHI model. The results from the changes to the duration of the treatment effect are shown in the ABHI document (Tables 7-12). The ABHI has shown the impact of different treatment effect durations on treatment choice at £30,000, £25,000 and £20,000 per QALY thresholds (ABHI Tables 13- 15). At the £30,000 per QALY threshold the model results are insensitive to the treatment effect duration, and the preferred treatment of choice alters in only two of the 24 subgroups (NYHA III, QRS < 120 ms, without LBBB from ICD to OPT for the worst case scenario with 2.54 years treatment effect; and NYHA III, QRS ≥ 150 ms and LBBB from CRT-D to CRT-P with 5 year treatment effect). At lower thresholds (£20,000 and £25,000 per QALY) the model is more sensitive to changes in the duration of treatment effect, with regard to the most cost effective treatment, as the base case ICERs are close to the thresholds. For example, at the £25,000 threshold, the model is sensitive to the treatment duration being increased (best case scenario) in three of the 24 subgroups, and sensitive to it being decreased (worst case scenarios) in six subgroups (ABHI Table 14). At the £20,000 threshold, the model is sensitive to the treatment duration being increased (best case scenario) in seven of the 24 subgroups, and being decreased (worst case scenario) in two subgroups (Table 15).

The ABHI original submission justified the use of a treatment duration of 7.5 years as this was the maximum follow-up included in the network meta-analysis. Beyond this period, they assumed that the hazard ratio converges to 1 linearly over a 20 year period (linear tapering of the treatment effect). The original submission does not discuss or justify the use of this linear tapering.

The AG notes that alternative plausible assumptions would be that there is no linear tapering of the treatment effect after 7.5 years, or the linear tapering would be for a shorter time period than 20 years, such as 10 years. Another variable that might have had a significant impact on the model results is the treatment effect of the devices. The AG has completed these sensitivity analyses in the *AG further analyses* (see Tables 1 to 3) for three particular subgroups (Group 1: NYHA II, QRS ≥ 150 ms, LBBB, Group 2: NYHA III, QRS ≥ 150 ms, LBBB; and Group 3: NYHA II, QRS < 120 ms, without LBBB).

Subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

For the first subgroup, the cost effectiveness of CRT-D vs. OPT varied between £13,497 and £23,938 per QALY gained (Table 1), for life-long constant treatment effects and 7.5 years treatment effect with no tapering of the treatment effect, respectively (compared to a base case of £17,664 per QALY for this subgroup). The scenarios for a 2.54 year treatment effect (£20,534 per QALY gained) and 10 years with tapering effect (£21,796 per QALY gained) also produced ICERs between the £20,000 per QALY gained and £25,000 per QALY gained thresholds.

The cost effectiveness of CRT-D vs. OPT varied between £15,785 and £19,997 for changes to the mortality treatment effectiveness of CRT-D of +/-10% (Table 1).

Subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

For the second subgroup, the cost effectiveness of CRT-D vs. CRT-P varied between £23,891 and £36,142 per QALY gained (Table 2), for life-long constant treatment effects and 7.5 years treatment effect with no tapering of the treatment effect, respectively (compared to a base case of £28,646 per QALY for this subgroup). All treatment duration effect scenarios, other than the base case and best case scenarios, produced ICERs above the £30,000 per QALY threshold.

The cost effectiveness of CRT-D vs. CRT-P varied between £21,335 and £47,374 for changes to the mortality treatment effectiveness of CRT-D and CRT-P of +/- 10%, respectively (Table 2).

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup, the cost effectiveness of ICD vs. OPT varied between £17,807 and £34,268 per QALY gained (Table 3), for life-long constant treatment effects and 7.5 years treatment effect with no tapering of the treatment effect respectively, (compared to a base case of £24,465 per QALY for this subgroup). All other treatment effect scenarios were between the £20,000 per QALY gained and £30,000 per QALY gained thresholds, except for the scenario of 10 years tapering effect (£30,997 per QALY gained).

The cost effectiveness of ICD vs. OPT varied between £19,514 and £32,761 for changes to the mortality treatment effectiveness of ICD of +/- 10% (Table 3).

The sensitivity analyses undertaken by ABHI and the AG show that the assumptions on the duration of the treatment effect and the mortality treatment effect are the key drivers of the cost effectiveness results. However, the effect of these changes on the recommended treatment for each subgroup depends upon the base case results and the cost effectiveness threshold used. For two of the three subgroups shown above (subgroups 2 and 3), the model results were sensitive to the treatment duration and mortality treatment effect, switching the preferred treatment option at the £30,000 per QALY threshold, whilst for subgroup 1 the model results were insensitive to changes to these parameters. For subgroup 1, where the base case results were less than the £20,000 per QALY threshold, changes to the treatment duration switch the preferred treatment option at the £20,000 per QALY threshold.

2. Effect of CRT-D devices on all-cause hospitalisation for NHYA III/IV

The effect of CRT-D devices on all-cause hospitalisation for NYHA III and IV class patients estimated in the IPD network meta analysis (HR; [redacted]) was not incorporated in the model and the value estimated for CRT-P ([redacted] for NYH III and [redacted] for NYHA IV) was used instead. The manufacturers' stated that it is unlikely that the use of CRT-D will result in a smaller treatment effect than the use of CRT-P in a given patient group, as both include CRT therapy.

However, the Committee would like to see the effect on the *ICERs of a more conservative estimate of effect of CRT D for all cause hospitalisation estimated in the IPD network meta-analysis (that is, HR [redacted])?*

The ABHI reported that the estimated HR [redacted] treatment effect for CRT-D in patients with NYHA III/IV was implemented in the base case and the reporting of this was inaccurate. The AG has checked the model and agrees that this value is implemented in the base case of the original ABHI's submission.

The AG notes that the ABHI has not explored the sensitivity of the model results to changes in the all-cause hospitalisation rates for the devices. The AG explores these in sensitivity analyses in the *AG further analyses* (see Tables 1 to 3) by varying the treatment effect of the hospitalisation rate by +/- 25% for the three selected subgroups (NYHA II, QRS ≥ 150 ms, LBBB; NYHA III, QRS ≥ 150 ms, LBBB; NYHA II, QRS < 120 ms, no LBBB).

Subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

For the first subgroup, the cost effectiveness of CRT-D vs. OPT varied between £17,300 and £18,028 per QALY gained, for an increase and reduction in the treatment effect on hospitalisation of 25%, respectively (compared to a base case of £17,664 per QALY for this subgroup).

Subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

For the second subgroup, the cost effectiveness of CRT-D vs. CRT-P varied between £26,985 and £30,308 per QALY gained, for an increase and reduction in the treatment effect on hospitalisation of 25%, respectively (compared to a base case of £28,646 per QALY for this subgroup).

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup, the cost effectiveness of ICD vs. OPT varied between £23,691 and £25,239, for an increase and reduction in the treatment effect on hospitalisation of 25%, respectively (compared to a base case of £24,465 per QALY for this subgroup).

The results show that changing the treatment effect on hospitalisation has only a small effect on the cost effectiveness results. The effect of these changes on the recommended treatment for each subgroup depends upon the base case results and the cost effectiveness threshold. The base case results for subgroup 2 and 3 were close to the £30,000 and £25,000 thresholds, respectively, and small changes to the results cause the ICERs to exceed these thresholds. Subgroup 1 is close to the

£20,000 per QALY threshold but changes to all-cause hospitalisation do not cause the ICER for CRT-D vs. OPT to exceed this threshold.

3. Inclusion of counselling costs

The Committee heard that defibrillating devices can increase anxiety in some patients. The manufacturers' model does not account for any additional cost of counselling apart from the bi-annual device related outpatient visits for ICD patients and quarterly visits for CRT (CRT-D or CRT-P) patients.

Given the feedback from experts on the importance of counselling, particularly for patients receiving defibrillator devices, what is the impact of this additional resource use on the ICERs?

The submission presented a 'typical lifetime counselling protocol' as follows:

1 x arrhythmic nurse consultation (incurred by 100% of patients)
1 x full psychiatry visit (incurred by 0.5% of patients)
4 x CBT sessions (incurred by 0.5% of patients)

These estimates were thought to be conservative by our experts, as 'many patients need counselling pre and post implant'. It was thought that 2-3% of patients would require a psychology or psychiatry consultation and CBT, with a psychology consultation more common than psychiatry.

The AG is unable to replicate the cost of £27.95 per patient cost of counselling used in the model from the data provided by the ABHI. It is unclear whether the ABHI has made an error in the reporting or in the calculation of the counselling cost. Changing the estimates provided by the ABHI of 0.5% of patients attending full psychiatry visit and CBT sessions to 5% for both gives the reported cost of £27.95. These estimates are more in line with those suggested by our experts.

It may be that the cost of CBT is underestimated. The ABHI has based its costs upon group therapy with 10 people per session, but it may also be that some patients are referred to smaller group or individual CBT. In addition, CBT is often given for more than 4 sessions, sometimes as 6 or 12 sessions. In the case where CBT is given for 6 sessions on an individual basis, the per patient cost of counselling would be as much as £70 (i.e. per patient cost: CBT cost = £15 per session x 6 sessions x 10 individuals x 5% of patients receiving the intervention = £45; Nurse consultation = £22, Psychiatric visit cost £2.95. Total cost £69.95).

The AG has completed sensitivity analyses using this higher counselling cost in the *AG further analyses* (Tables 1 to 3) for the three selected subgroups (NYHA II, QRS ≥ 150 ms, LBBB; NYHA III, QRS ≥ 150 ms, LBBB; NYHA II, QRS < 120 ms, without LBBB). Including counselling costs and increasing these in sensitivity analyses has little impact on the model for the three subgroups shown below.

Subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

For the higher cost of counselling, the cost effectiveness of CRT-D vs. OPT increases only marginally to £17,706 per QALY, for the first subgroup (compared to a base case of £17,664 per QALY).

Subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

For the second subgroup the cost effectiveness of CRT-D vs. CRT-P increases only marginally to £28,782 (compared to a base case of £28,646).

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup the cost effectiveness of ICD vs. OPT increases only marginally to £24,544 (compared to a base case of £24,465).

4. Device upgrade in clinical practice

The manufacturer's model excludes the possibility of crossover or device upgrades, which are possible in clinical practice. Please comment on the likelihood of device upgrades in clinical practice.

In particular, the Committee heard that there may be a subgroup of people indicated for CRT-P who are also likely to need a defibrillator in the near future, so that cardiologists would choose to implant a CRT-D in which the ICD function could be switched on when needed, rather than to implant a CRT-P device which would have to be upgraded to CRT-D at full cost at a later date. Please provide comment on experience with this situation in clinical practice, and on identification of a subgroup of patients for which this situation applies.

a) Likelihood of device upgrades in clinical practice

One AG clinical expert stated that in clinical practice upgrade from CRT-P to ICD is unlikely. CRT-D to ICD would be irrational and an upgrade would generally be CRT-P to CRT-D rather than ICD for technical and clinical reasons. The ICD to CRT-D upgrade rate sounds reasonable and would occur if someone with a pre-existing ICD develops a CRT indication (generally progressive heart failure and QRS prolongation). In view of this risk some authorities have argued in favour of implanting CRT-D rather than ICD in all cases but this view is not widely supported.

b) Upgrade from CRT-P to CRT-D

Two AG clinical experts agreed with the ABHI experts that it would be clinically implausible to implant CRT-D and not switch the defibrillator on. One expert stated that it is recognised that the indication for CRT implies a de-facto risk of arrhythmic death and most countries regard the need for CRT as indicative of a need for CRT-D. If a patient with a pre-existing CRT-P device had an episode of life threatening arrhythmia, they would be upgraded to CRT-D, but if that were anticipated prior to implantation of the initial device a CRT-D would have been implanted in the first place.

5. Deterministic sensitivity analyses for resource use and cost parameters

The Committee considered that further deterministic sensitivity analyses were required for resource use and cost parameters. Please provide such sensitivity analyses, as implementable within the current model structure.

The ABHI has run the following additional analyses:

- +/-25% change to HRG EA12Z (related to ICD/CRT-D based therapy) - used to model non-purchase costs in patients who get an ICD or CRT-D device.
- +/-25% change to HRG EA07Z (CRT-P based therapy) – unlike for CRT-D and ICD, a relevant tariff existed for CRT-P and this was used to cover all up front implant costs.
- +/-25% change to HRG EA39Z - this tariff value was applied to battery replacements for ICD and CRT-D therapy.
- Upper/lower quartile HF and non-HF Hospitalisation costs
- +/-25% change to cost of an outpatient visit

The AG has replicated these results using the ABHI model. The total cost relating to the device used in the model consists of the HRG tariff cost and the manufacturers' device cost. However, the AG notes that the ABHI varies only part of the cost of the devices, relating to the HRG tariff, and the manufacturers' device cost has not been varied. The AG has therefore also included sensitivity analyses varying the device cost by an arbitrary range of +/-10% to illustrate potential uncertainty for the three selected subgroups (see *AG further analyses*, Tables 1 to 3).

Subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

For the first subgroup, the changes to the resource use and cost parameters in the ABHI analyses only have a small effect on the results. The cost effectiveness varies between £16,817 and £18,511 per QALY for CRT-D for changes to the HRG cost for EA12Z (compared to a base case of £17,664 per QALY for this subgroup). Varying the device cost for CRT-D by +/- 10% changed the cost effectiveness results between £16,504 and £18,824 per QALY gained.

Subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

For the second subgroup, the changes to the resource use and cost parameters in the ABHI analyses have a more substantial effect on the model results. The cost effectiveness varies between £23,709 and £33,583 per QALY for CRT-D vs. CRT-P for changes to the HRG cost for EA072 (compared to a base case of £28,646 per QALY for this subgroup). Varying the device cost of CRT-D by +/- 10% changed the cost effectiveness results between £25,311 and £31,982 per QALY gained.

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup, the changes to the resource use and cost parameters in the ABHI analyses only have a small effect on the results. The cost effectiveness varies between £22,904 and £26,027 per QALY for ICD vs. OPT for changes to the HRG cost for EA12Z (compared to a base case of £24,465 per QALY for this subgroup). Varying the device cost of ICD by +/- 10% changed the cost effectiveness results between £22,831 and £26,099 per QALY gained.

The effect of changes to the resource use and cost parameters differs between the subgroups shown above. For subgroups 1 and 3, changes to these costs had only a small impact on model results with ICERs for all scenarios for group 1 remaining below £20,000 per QALY gained and those for group 3 equal to or below £26,000 per QALY gained. For subgroup 2, these changes had a larger effect and switch the preferred treatment option at the £30,000 per QALY threshold from CRT-D to CRT-P for changes to the device cost and HRG cost EA072 and EA12Z. In all other instances the ICERs were between £25,000 and £30,000 per QALY gained.

6. AG further analyses

The ABHI results are presented for 24 categories, which makes interpretation difficult. Whilst the ABHI has largely answered the questions asked for by the NICE committee, i.e. to examine various scenarios and sensitivity analyses, the analysis has not concluded which are the specific key drivers of the cost effectiveness results, and interpretation of this is not intuitive from the results presented.

To examine the relative impact of the input parameters on the cost effectiveness results, the AG has examined the impact of these changes on the model results for three particular subgroups (NYHA II, QRS ≥ 150 ms, LBBB; NYHA III, QRS ≥ 150 ms, LBBB, NYHA II, QRS < 120 ms, no LBBB). These groups were chosen to reflect a range of patients and potential treatment options, and as they included the largest numbers of people in the IPD analyses. Sensitivity analyses are shown in Tables 1 to 3 for those parameters varied in the ABHI's addendum. We have also included other variables which had not been included but might have an impact on the model results, such as treatment effect on mortality rates, treatment effect on hospitalisation rates, device costs and utility values (new analyses completed by AG are shown in bold in Tables 1 to 3). The mortality treatment effect was varied in the AG sensitivity analyses by +/- 10%, as this was similar to the confidence intervals around the ICD treatment effect. The device costs were varied by +/- 10%, an arbitrary range chosen to be illustrative of the potential uncertainty associated with these costs.

The results of these analyses have been summarised in the earlier sections. Tables 1 to 3 show that the model is most sensitive, in terms of magnitude of change to the ICERs, to changes in parameter values for the assumptions surrounding the treatment effect on mortality and the duration of the treatment effect. These changes only impact on the preferred treatment where the base case results are close to the threshold value.

Table 1 Sensitivity analyses for subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

	ICER (£ / QALY)		% change
Scenario	**ICD**	**CRT-D vs. OPT**	**CRT-D**
Base case	Ext Dominated	£17,664	
Treatment effect			
Life-long constant treatment effects	Ext Dominated	£13,497	-23.6%
5 years treatment effect	Ext Dominated	£18,879	6.9%
2.54 years treatment effect	Ext Dominated	£20,534	16.2%
No tapering effect, 7.5 years treatment effect	**Ext Dominated**	**£23,938**	**35.5%**
Tapering effect 10 years	**Ext Dominated**	**£21,796**	**23.4%**
Mortality treatment effect ICD +10%	**Ext Dominated**	**£17,664**	**0.0%**
Mortality treatment effect ICD -10%	**Ext Dominated**	**£17,664**	**0.0%**
Mortality treatment effect CRT-D +10%	**Ext Dominated**	**£15,785**	**-10.6%**
Mortality treatment effect CRT-D -10%	**Ext Dominated**	**£19,997**	**13.2%**
Hospitalisation treatment effect			
All cause hospitalisation treatment effect CRT-D +25%	**Ext Dominated**	**£17,300**	**-2.1%**
All cause hospitalisation treatment effect CRT-D -25%	**Ext Dominated**	**£18,028**	**2.1%**
Counselling costs			
Including counselling costs	Ext Dominated	£17,681	0.1%
Increased counselling costs of £70 per patient	**Ext Dominated**	**£17,706**	**0.2%**
Resource use and cost parameters			
HRG EA12Z -25% (related to ICD/CRT-D)	Ext Dominated	£16,817	-4.8%
HRG EA12Z + 25% (related to ICD/CRT-D)	Ext Dominated	£18,511	4.8%
HRG EA072 - 25% (related to CRT-P)	Ext Dominated	£17,664	0.0%
HRG EA072 +25% (related to CRT-P)	Ext Dominated	£17,664	0.0%
HRG EA39Z -25% (related to ICD/CRT-D)	Ext Dominated	£17,424	-1.4%
HRG EA39Z +25% (related to ICD/CRT-D)	Ext Dominated	£17,904	1.4%
All hospitalisation costs lower estimate	Ext Dominated	£17,704	0.2%
All hospitalisation costs higher estimate	Ext Dominated	£17,627	-0.2%
Outpatient visit -25%	Ext Dominated	£17,279	-2.2%
Outpatient visit +25%	Ext Dominated	£18,049	2.2%
Device cost CRT-D +10%	**Ext Dominated**	**£18,824**	**6.6%**
Device cost CRT-D -10%	**Ext Dominated**	**£16,504**	**-6.6%**
Utility			
Utility gain CRT-D / CRT-P +25%	**Ext Dominated**	**£17,572**	**-0.5%**
Utility gain CRT-D / CRT-P -25%	**Ext Dominated**	**£17,790**	**0.7%**

Analyses in bold are those completed by the AG, not included within the ABHI additional analyses.

Table 2 Sensitivity analyses for subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

	ICER (£ / QALY)		% change from base case	
Scenario	**CRT-P vs. ICD**	**CRT-D vs CRT-P**	**CRT-P**	**CRT-D**
Base case	£10,496	£28,646		
Treatment effect				
Life-long constant treatment effects	£9,928	£23,891	5.41%	16.60%
5 years treatment effect	£10,769	£30,548	-2.60%	-6.64%
2.54 years treatment effect	£11,207	£33,410	-6.77%	-16.63%
No tapering effect, 7.5 years treatment effect	**£11,530**	**£36,142**	**-9.85%**	**-26.17%**
Tapering effect 10 years	**£11,151**	**£33,435**	**-6.24%**	**-16.72%**
Mortality treatment effect ICD +10%	**£10,496**	**£28,646**	**0.00%**	**0.00%**
Mortality treatment effect ICD -10%	**£10,496**	**£28,646**	**0.00%**	**0.00%**
Mortality treatment effect CRT-P +10%	**£9,183**	**£47,374**	**12.51%**	**-65.38%**
Mortality treatment effect CRT-P -10%	**£12,220**	**£21,489**	**-16.43%**	**24.98%**
Mortality treatment effect CRT-D +10%	**£10,496**	**£21,335**	**0.00%**	**25.52%**
Mortality treatment effect CRT-D -10%	**£10,496**	**£43,706**	**0.00%**	**-52.57%**
Hospitalisation treatment effect				
All cause hospitalisation treatment effect CRT-D +25%	**£10,496**	**£26,985**	**0.00%**	**5.80%**
All cause hospitalisation treatment effect CRT-D -25%	**£10,496**	**£30,308**	**0.00%**	**-5.80%**
Counselling costs				
Including counselling costs	£10,496	£28,701	0.00%	-0.19%
Increased counselling costs of £70 per patient	**£10,496**	**£28,782**	**0.00%**	**-0.47%**
Resource use and cost parameters				
HRG EA12Z -25% (related to ICD/CRT-D)	£10,496	£25,937	0.00%	9.46%
HRG EA12Z + 25% (related to ICD/CRT-D)	£10,496	£31,356	0.00%	-9.46%
HRG EA072 - 25% (related to CRT-P)	£8177	£33,583	22.09%	-17.23%
HRG EA072 +25% (related to CRT-P)	£12,816	£23,709	-22.10%	17.23%
HRG EA39Z -25% (related to ICD/CRT-D)	£10,496	£28,098	0.00%	1.91%
HRG EA39Z +25% (related to ICD/CRT-D)	£10,496	£29,194	0.00%	-1.91%
All hospitalisation costs lower estimate	£10,600	£28,429	-0.99%	0.76%
All hospitalisation costs higher estimate	£10,400	£28,849	0.91%	-0.71%
Outpatient visit -25%	£10,153	£28,483	3.27%	0.57%
Outpatient visit +25%	£10,840	£28,809	-3.28%	-0.57%
Device cost of CRT-D +10%	**£10,496**	**£31,982**	**0.00%**	**-11.65%**
Device cost of CRT-D – 10%	**£10,496**	**£25,311**	**0.00%**	**11.64%**
Utility				
Utility gain CRT-D / CRT-P +25%	**£9,855**	**£28,301**	**6.11%**	**1.20%**
Utility gain CRT-D / CRT-P -25%	**£11,367**	**£29,068**	**-8.30%**	**-1.47%**

Analyses in bold are those completed by the AG, not included within the ABHI additional analyses.

Table 3 Sensitivity analyses for subgroup 3: NYHA II, QRS < 120 ms, no LBBB

	ICER (£ / QALY)	% change
Scenario	**ICD**	**ICD**
Base case	£24,465	
Treatment effect		
Life-long constant treatment effects	£17,807	27.2%
5 years treatment effect	£26,181	-7.0%
2.54 years treatment effect	£28,463	-16.3%
No tapering effect, 7.5 years treatment effect	**£34,268**	**-40.1%**
Tapering effect 10 years	**£30,997**	**-26.7%**
Mortality treatment effect ICD +10%	**£19,514**	**20.2%**
Mortality treatment effect ICD -10%	**£32,761**	**-33.9%**
Hospitalisation treatment effect		
All cause hospitalisation treatment effect ICD +25%	**£23,691**	**3.2%**
All cause hospitalisation treatment effect ICD -25%	**£25,239**	**-3.2%**
Counselling costs		
Including counselling costs	£24,497	-0.1%
Increased counselling costs of £70 per patient	**£24,544**	**-0.3%**
Resource use and cost parameters		
HRG EA12Z -25% (related to ICD/CRT-D)	£22,904	6.4%
HRG EA12Z + 25% (related to ICD/CRT-D)	£26,027	-6.4%
HRG EA072 - 25% (related to CRT-P)	£24,465	0.0%
HRG EA072 +25% (related to CRT-P)	£24,465	0.0%
HRG EA39Z -25% (related to ICD/CRT-D)	£24,056	1.7%
HRG EA39Z +25% (related to ICD/CRT-D)	£24,874	-1.7%
All hospitalisation costs lower estimate	£24,552	-0.4%
All hospitalisation costs higher estimate	£24,386	0.3%
Outpatient visit -25%	£24,397	0.3%
Outpatient visit +25%	£24,354	0.5%
Device cost of ICD +10%	**£26,099**	**-6.7%**
Device cost of ICD -10%	**£22,831**	**6.7%**
Utility		
Utility gain CRT-D / ICD +25%	**£24,292**	**0.7%**
Utility gain CRT-D / ICD -25%	**£24,679**	**-0.9%**

Analyses in bold are those completed by the AG, not included within the ABHI additional analyses.

Appendix

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120) [ID481]

Specification of further work following the Appraisal Committee meeting on 23 April 2013

Suggested presentation of analyses

- Please combine the ischaemic and non-ischaemic patient groups together, therefore presenting results for 24 subgroups rather than 48 in the original submission. For these subgroups, for each of the different scenarios presented, please present tables with fully incremental cost-effectiveness results as previously presented in tables 70-71 of the submission.

- Please also present a summary of the most optimal strategies at different cost-effectiveness thresholds, for example, at £20,000, £25,000 and £30,000 per QALY gained.

Specification of further work

1. The manufacturers' base case assumes a constant duration of effect of 7.5 years for all-cause mortality, followed by linear tapering over 20 years. Sensitivity analyses were also provided assuming life-long constant treatment effects without any tapering (MS page 194) as a more optimistic scenario, and assuming a constant duration of effect for 5 years as a more conservative scenario (Appendix 15 page 72-73). Please provide these analyses for the 24 subgroups outlined above, combining the ischaemic and non-ischaemic patient groups.

   In addition, please also provide a sensitivity analysis assuming a constant duration of effect up to the *average* duration of follow up in the trials, followed by linear tapering thereafter?

2. The effect of CRT-D devices on all-cause hospitalisation for NYHA III and IV class patients estimated in the IPD network meta analysis (HR; [redacted]) was not incorporated in the model and the value estimated for CRT-P ([redacted] for NYH III and [redacted] for NYHA IV) was used instead. The manufacturers' stated that it is unlikely that the use of CRT-D will result in a smaller treatment effect than the use of CRT-P in a given patient group, as both include CRT therapy.

   However, the Committee would like to see the effect on the ICERs of a more conservative estimate of effect of CRT D for all cause hospitalisation estimated in the IPD network meta-analysis (that is, HR [redacted])?

3. The Committee heard that defibrillating devices can increase anxiety in some patients. The manufacturers' model does not account for any additional cost of counselling apart from the bi-annual device related outpatient visits for ICD patients and quarterly visits for CRT (CRT-D or CRT-P) patients.

   Given the feedback from experts on the importance of counselling, particularly for patients receiving defibrillator devices, what is the impact of this additional resource use on the ICERs?

4. The manufacturer's model excludes the possibility of crossover or device upgrades, which are possible in clinical practice. Please comment on the likelihood of device upgrades in clinical practice.

   In particular, the Committee heard that there may be a subgroup of people indicated for CRT-P who are also likely to need a defibrillator in the near future, so that cardiologists would choose to implant a CRT-D in which the ICD function could be switched on when needed, rather than to implant a CRT-P device which would have to be upgraded to CRT-D at full cost at a later date. Please provide comment on experience with this situation in clinical practice, and on identification of a subgroup of patients for which this situation applies.

5. The Committee considered that further deterministic sensitivity analyses were required for resource use and cost parameters. Please provide such sensitivity analyses, as implementable within the current model structure.