NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120)
Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Association of British Healthcare Industries (on behalf of the manufacturers: Biotronik, Boston Scientific, Medtronic, Sorin and St Jude Medical)	Executive Summary While the recommendations contained within the ACD would improve patient access in certain patient groups to ICD and CRT devices, we are concerned that in some instances the recommendations do not represent a sound basis for guidance to the NHS. 1. QRS < 120ms, NYHA I-III, LVEF < 35% To exclude the option of ICD therapy in patients with QRS <120ms would place NICE guidance at odds with European and North American guidance. Patients within this group are at high risk of sudden cardiac death and thus gain a mortality benefit from an ICD. To exclude these patients would be counter to the aims of NHS Outcomes Framework Domain 1 'preventing people from dying prematurely'. The Committee did not recommend within this group on the basis of cost-effectiveness. However, the ICERs presented in this group of patients are similar to those in other groups that have received a recommendation for device therapy. The ICERs reduced significantly when the model is re-run using recently collated 2013-14 prices/tariffs (see below). 2. QRS 120-149, LBBB, NHYA II, LVEF < 35% ICD has been recommended in this group despite being extendedly dominated by CRT-D with an ICER of £22,049. Three individual studies have been cited as the reason for this	Comment noted. See also individual responses in each section below. 1. Following consultation, the Committee was persuaded to recommend ICDs in patients with a left ventricular ejection fraction less than 35% with a normal QRS duration with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD section 4.3.17). 2. The Committee considered the RethinQ, EchoCRT and Clelland et al. studies in detail, together with input from clinical specialists, but remained concerned that the subgroups with a QRS duration between 120 and 149 ms were heterogeneous, containing some patients in whom CRT may be inappropriate. The Committee concluded that, without more

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	recommendation. It seems contrary to the principles of evidence evaluation in a Technology Appraisal to select out individual studies that have already been taken into account in the ABHI review of the relevant available data that informs device treatment in this group of patients. Each of the individual studies referred to in the ACD have significant limitations that apparently were not considered. For instance, the Echo-CRT study only is informative about the lack of value of echocardiography in selecting patients with QRS <130ms for CRT. It does not indicate a lack of benefit of CRT in QRS 120-149ms, NYHA II, LVEF <35% patients.	robust analysis, it would be appropriate to take a cautious approach to the use of CRT in this intermediate QRS group. CRT-D was recommended as a treatment option in patients in NYHA class II with a QRS duration between 120 and 149 milliseconds with LBBB. (see FAD sections 4.3.20 and 4.3.21).
	3. QRS >150, LBBB, NYHA III, LVEF < 35% It is clinically counter-intuitive not to recommend CRT-D as an option for these patients when patients without LBBB can be offered CRT-D. Sudden Cardiac Death (SCD) is the most common cause of death in these patients and to exclude patients from the protection offered by CRT-D would be counter to the aims of NHS Outcomes Framework Domain 1 'preventing people from dying prematurely'. The ICER is marginally above £30,000 per QALY when a 5-year constant mortality effect is assumed, however, it is below £30,000 when the 7.5 year constant mortality effect is considered. This effect duration is more conservative than that deemed acceptable in the previous appraisal.	3. The Committee noted that patients in this group were severely symptomatic and at high risk of sudden cardiac death and have the most potential to benefit from a CRT-D device. The Committee therefore concluded that for people in NYHA class III, with QRS duration more than 150 ms with or without LBBB, both CRT-D and CRT-P could be considered cost effective (see FAD section 4.3.24).
	Concluding remarks The ABHI and clinical representation have articulated already, and would	

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	like to emphasize, that the indications proposed herein for ICD and CRT devices do not imply there is a device for every heart failure patient. The heart failure population eligible for any of the devices in this appraisal is a highly selected sub population. The uncertainty that the Committee noted to be present in some of the clinical and economic evidence in this appraisal is remarkably decreased compared to the previous appraisals in TA 095 & 120. The ABHI believes that given the evidence presented for this appraisal, the level of uncertainty is generally at acceptable levels.	
Association of British Healthcare Industries	Provisional Guidance The recommendations for ICD are unchanged in secondary prevention and familial conditions and patients who have undergone surgical repair of congenital heart disease. These indications were not re-evaluated in the current review. The recommendations in this review are: (Note: see Table 1 in ABHI comments document)	Comment noted.
Association of British Healthcare Industries	General comments on Provisional Guidance The Provisional Guidance includes positive developments on TA095 and TA120: • Selected non-ischaemic cardiomyopathy patients are added to the recommended indications for an ICD; • Patients with QRS > 150 ms in NYHA class I-II with LVEF < 35% are added to the recommended indications for a CRT-D; and	Comments noted.

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	• Non-sustained VT, positive VT stimulation study and dys-synchrony proven by echocardiography have been removed as selection criteria. However, the Provisional Guidance has excluded patient groups or device choices, despite the clinical and cost-effectiveness evidence provided by the ABHI that supports the interventions as an efficient use of NHS resources: 1. ICD excluded for patients with QRS < 120ms, NYHA I-III, LVEF < 35% 2. CRT-D excluded for patients with QRS 120-149ms, LBBB, NHYA II, LVEF < 35% 3. CRT-D excluded for patients with QRS >150ms, LBBB, NYHA III, LVEF < 35% The ABHI requests the Committee to consider comments which concern four topics: • Duration of constant mortality benefit included in cost effectiveness model • The consideration of evidence for the use of interventions in three subgroups: • ICD for patients with QRS < 120ms, NYHA I-III, LVEF < 35%; • CRT-D for patients with QRS 120-149ms, LBBB,	1. Following consultation, the Committee was persuaded to recommend ICDs in patients with a left ventricular ejection fraction less than 35% with a normal QRS duration with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD section 4.3.17). 2. The Committee maintained that the subgroups with a QRS duration between 120 and 149 ms were heterogeneous, containing some patients in whom CRT may be inappropriate. The Committee concluded that, without more robust analysis, it would be appropriate to take a cautious approach to the use of CRT in this intermediate QRS group. CRT-D was recommended as a treatment option in patients in NYHA class II with a QRS duration between 120 and 149 milliseconds with LBBB. (see FAD sections 4.3.20 and 4.3.21). 3. The Committee concluded that for people in NYHA class III, with QRS duration more than 150 ms with or without LBBB, both CRT-D and CRT-P

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	NHYA II, LVEF < 35% • CRT-D for patients with QRS >150ms, LBBB, NYHA III, LVEF < 35%	could be considered cost effective (see FAD section 4.3.24).
Association of British Healthcare Industries	Estimated duration of constant mortality benefit The base case analysis submitted by the ABHI assumes that the mortality benefit is constant for 7.5 years followed by a linear tapering until year 20. However, the ACD communicates that the Committee concluded in favour of a constant mortality benefit for 5 years followed by tapering up to 20 years as the most reasonable assumption. The ABHI provided the following evidence in support of a 7.5 year constant mortality benefit: • Longer term analyses of the post-protocol period for two large trials, CARE-HF and MADIT-II. These analyses support that strong treatment effects for devices are maintained at 4.2-7.6 years average follow-up despite high degrees of cross-over from the control to the active trial arms. • Analyses testing the validity of the proportional hazards assumption within the individual patient database found no evidence to suggest that treatment effects waned over time, supporting the use of a 7.5-year mortality benefit.	Following consultation, the Committee noted that long-term follow up data from the CARE-HF trial showed that treatment effects of CRT-P were maintained at around 4 years which was consistent with the Committee's preferred assumption of 5 years. The Committee was also aware that long-term data from MADIT-II indicated that effects of ICDs were maintained at around 7.5 years despite crossover. However, the Committee considered that this would not necessarily apply to CRT devices. The Committee maintained that a constant mortality benefit for 5 years followed by tapering up to 20 years would be the most reasonable assumption (see FAD sections 4.3.13 and 4.3.14).
Association of	The ABHI is concerned that the Committee has taken an overly conservative	The Committee noted that in the current

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British Healthcare Industries	assumption about the duration of a constant mortality benefit. The assumption taken in the ABHI submission already was more conservative than any previous analysis by NICE for ICD and CRT, which have assumed that the benefit of treatment is constant over time. Thus the Committee actually has taken a conservative assumption by the ABHI and made it even more conservative. Unlike medicines, patient non-compliance with a dosing regimen is not a concern, there is no evidence waning of the performance of ICD and CRT devices themselves. We request that the Committee reconsider this decision. Using the model as originally submitted, the Committee's decision to reduce the duration of the constant mortality effect in the cost effectiveness model is important because it increases the cost effectiveness ratios for several patient groups, as follows, to levels that the Committee considered to be not cost effective: • ICER for CRT-D vs. CRT-P became £30,548/QALY in NYHA III patients with QRS ≥150ms, LBBB; • ICERs for ICD vs. OPT became £25,714/QALY, £26,181/QALY and £29,309/QALY in NYHA I, II and III respectively with QRS duration < 120ms, On the other hand, if a constant mortality effect was assumed as in previous	appraisal the manufacturers modelled treatment effect of the devices on all-cause mortality, making tapering essential because the risk of mortality would increase with age due to other factors whereas in the previous models tapering was implicit because constant treatment effect was applied to disease-specific mortality from arrhythmia or worsening of heart failure. The Committee therefore did not consider the current approach including tapering to be necessarily more conservative (see FAD section 4.3.14)

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	evaluations, the results could be acceptable for these two patient groups: • ICERs for ICD vs. OPT become £18,321/QALY, £17,807/QALY and £24,153/QALY in NYHA I, II and III respectively in patients with QRS duration <120ms, • ICER for CRT-D vs. CRT-P becomes £23,891/QALY in NYHA III patients with QRS ≥150ms, LBBB; For patients QRS 120-149, LBBB, NHYA II, LVEF < 35%, ICD has been recommended in the ACD despite being extendedly dominated by CRT-D with an ICER of £22,049. With a constant mortality effect, ICD still is extendedly dominated by CRT-D and the ICER for CRT D becomes £16,302	
Association of British Healthcare Industries	**ICD for patients with QRS < 120ms, NYHA I-III, LVEF < 35%** ICD is not recommended in the ACD for patients with QRS < 120ms, NYHA I-III, LVEF < 35%. The ABHI is concerned about three aspects of this: 1. ABHI analyses indicated cost effectiveness of ICD therapy is in an acceptable range irrespective of QRS duration (within NYHA I III, LVEF < 35%); and 2. a decision to restrict ICD therapy to patients with QRS >=120ms is based on insufficient clinical evidence of an increased treatment effect of ICD in QRS >=120ms compared to QRS < 120ms 3. a NICE recommendation against ICD use in patients with QRS < 120	Comment noted. Following consultation, the Committee explored the approaches used by clinical specialists in defining high risk in people with normal QRS duration. The Committee heard that while age and sex were regarded as important considerations in assessing risk of sudden cardiac death these are not the only factors used in clinical practice. Others may include the degree of left ventricular dysfunction and prior history of myocardial infarction and presence of cardiomyopathy. In addition, a range of other potential prognostic like B-type natriuretic peptide factors may be used. Taking into account the high burden of premature deaths in these subgroups the Committee was persuaded to recommend ICDs in patients with

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	ms would be mis-aligned with European and USA clinical practice guidelines, which threatens to undermine this NICE Guideline in clinical practice because it cannot be soundly explained, for the reasons given above. We are concerned about the basis for excluding this group on cost effectiveness grounds. In ICD patients with QRS < 120ms with NYHA I-III and LVEF < 35%, the ICERS in the original model are £25,714/QALY, £26,181/QALY and £29,309/QALY in NYHA I, II and III respectively in the base-case scenario preferred by NICE. The ACD communicates that the Committee decided ICD is not cost-effective in this group taking into consideration the uncertainties of evidence synthesis and the lack of a full exploration of parameter uncertainty in the model.	a left ventricular ejection fraction less than 35% with a normal QRS duration (less than 120ms) with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD sections 4.3.17).
	As presented in ABHI original submission, real term prices (adjusted to 2011 equivalents) had fallen by 17% for CRT-P, 10.4% for CRT-D and 8% for ICD between 2006 and 2011 (see Appendix 1 in the ABHI comments document). The cost effectiveness ratios presented in the ABHI submission used device and procedure costs from 2011. The ABHI recently was able to obtain cost information for 2013, which show an 11% decrease since 2011 in the total implant costs (device cost and implant procedure cost) for ICD (see Appendix 1 in the ABHI comments document). Using 2013 costs, recalculated ICERs are shown in the Table 2. (see table 2 in the ABHI comments document) It appears the Committee accepted ICERs of £26,192 and £26,586 for other patient groups in this appraisal. The ACD communicates that although the Committee was conscious of the uncertainties surrounding the ICERs in the	The updated costs were not based on average selling prices to the NHS, and therefore the ICERs presented were not considered relevant for the Committee's decision-making

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	patient groups with these ICERs, it considered those ICERs acceptable given the severity of the symptoms and the clinical plausibility of benefit. However, the ICERs for ICD in patients with QRS < 120ms, LVEF < 35% in NYHA class I - III are lower or at least on a par with the above ICERs which were accepted. Given the function of an ICD device is to prevent SCD, and it has a cost effectiveness ratio in NYHA class I-II that is apparently at an acceptable level for other patient groups in this appraisal, we request NICE to reconsider this recommendation. The level of uncertainty about the ICER for ICD in this patient group is not more uncertain than other groups. As shown in Table 3 (please see table 2 in the ABHI comments document), the network meta-analysis included sizeable patient numbers in each of the ICD patient groups with QRS < 120 ms. It is clearly of interest to identify ways to improve the patient risk stratification for ICD devices. As documented in the ACD, QRS duration is understood to impact upon the efficacy of CRT, however, the importance of QRS duration is less well understood as a predictor of ICD efficacy. The relationship between prolonged QRS duration and SCD in patients with heart failure became a controversial issue in 2004 when the US Centers for Medicare and Medicaid (CMS) decided to limit reimbursement coverage of ICDs to patients who meet specific QRS width criteria (> 120 ms) on the basis of a subgroup analysis of the MADIT II trial. The same sub-group analysis led to the previous NICE Guidance for ICDs (TA95) to restrict ICD therapy to those with QRS duration >120ms and LVEF ≤30% in the post-MI population. However, this QRS restriction was removed by CMS when data became available from the SCD-HeFT trial. QRS duration was retained in the final IPD NMA model due to the importance of this variable in predicting CRT efficacy (Table 38, manufacturer submission). The estimated variation in ICD efficacy across QRS duration bands may not represent a sound basis for making different recommendations for ICD use according to QRS duration.	

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	Neither of the principal European nor USA clinical practice guidelines advocate that ICD therapy be restricted according to QRS duration, based on the clinical evidence. The European Society of Cardiology (ESC) recommend ICD regardless of QRS duration in NYHA II-III patients with EF≤35%. Clinical guidance from the US recommends ICD in the same group as well as in NYHA I patients with LV dysfunction due to prior MI who are at least 40 days post-MI, and have LVEF less than 30% (see Appendix 2 for full details in the ABHI comments document). In alignment with the international clinical practice guidelines, a recent meta-analysis (Katritsis et al, 2013) of primary prevention randomized controlled trials comparing ICD and standard medical therapy concluded that QRS duration does not appear to confer any additional value for selection of ICD therapy.	
Association of British Healthcare Industries	**CRT in patients with QRS 120-149ms, LBBB, NYHA II, LVEF < 35%** The ACD communicates that the NICE Committee was concerned that in terms of CRT benefit, the subgroups with a QRS duration between 120 -149 ms were heterogeneous, containing some patients in whom CRT may be inappropriate. Thus, ICD has been recommended in this group despite being extendedly dominated by CRT-D with an ICER of £22,049. The cost effectiveness ratios presented in the ABHI submission used device and procedure costs from 2011, so the ABHI obtained updated cost information for 2013 (see Appendix 1 in the ABHI comments document). The updated ICER indicates that ICD is no longer extendedly dominated, and has an ICER of £20,590. CRT-D now has an ICER versus ICD of £25,233. Two studies and an individual patient meta-analysis are mentioned – the	The Committee considered the RethinQ, EchoCRT and Cleland et al. studies in detail, together with input from clinical specialists, and remained concerned that the subgroups with a QRS duration between 120 and 149 ms were heterogeneous, containing some patients in whom CRT may be inappropriate. The

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	EchoCRT trial, the RethinQ trial, and the Cleland 2013 meta-analysis. From EchoCRT, it is mentioned that that in patients with QRS durations of less than 130 ms, the prognosis could be adversely affected with CRT-D. From RethinQ, it was noted that in this small trial in people with narrow or slightly prolonged QRS durations of less than 130 ms, it was inconclusive overall on mortality, with wide confidence intervals, but the point estimate of effect favoured ICDs. From the analysis by Cleland et al, 2013, it was reported that the clinical benefit of CRT in patients with QRS durations between 120-140 ms was uncertain. ABHI is concerned about the informal way in which these three studies appear to have influenced the Committee's recommendation regarding CRT in patients with intermediate QRS durations (120-149 ms). We wish to draw the attention of the Committee to additional information which must be considered about these studies prior to letting them perhaps unduly influence a decision: • The Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study included patients with NYHA III or IV heart failure, a LVEF < 35%, QRS < 130 ms. In addition, patients were required to have echocardiographic evidence of mechanical dyssynchrony (differences in the timing of contraction of different myocardial segments). Mean baseline QRS in this study was 105 ms, which is far below the minimum QRS of 120 ms conventionally accepted in CRT trials. CRT use in patients with	Committee concluded that, without more robust analysis, it would be appropriate to take a cautious approach to the use of CRT in this intermediate QRS group. CRT-D was recommended as a treatment option in patients in NYHA class II with a QRS duration between 120 and 149 milliseconds with LBBB. (see FAD sections 4.3.20 to 4.3.21).

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	QRS duration of less than 120 ms is unwarranted and should not be considered. The novel result of this study simply is to negate the use of echocardiographic measures of mechanical dyssynchrony in patients with a QRS < 130 ms as a means of identifying those who are most likely to have a good response to CRT. • The RethinQ trial was a small study (172 patients) with a short duration of follow-up (6 months) in patients who had an indication for an ICD and QRS < 130ms. The primary end-point was the proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months. Thus we consider the study does not provide substantive evidence regarding the benefit of CRT in this evaluation. Conversely, if the Committee believes the study has some relevance, it is noted that the sub-group of patients with QRS > 120 ms experienced a significant improvement in the primary end-point of peak oxygen consumption (P = 0.02). • The Cleland et al, 2013, individual patient data level meta-analysis has an important limitation compared to the ABHI analysis submitted to NICE: the lack of access to individual patient data from two large CRT trials. The COMPANION trial (1520 patients) and the MADIT-CRT trial (1820 patients). This analysis found that	

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	the “estimated HR crossed 1.0 at 126 ms for all-cause mortality” and the “95% confidence bounds excluded 1.0 beginning at ~140 ms”. This analysis excluded 18% of the patients randomised to the CRT trials considered in the ABHI analysis. It is not therefore credible to base decisions on these point estimate or statistical significance results. Unlike the findings of the manufacturer network meta-analysis, Cleland et al, 2013 found that after adjusting for QRS duration, LBBB morphology was not a significant predictor of the benefits of CRT. However, their dataset was considerably smaller than the dataset presented to NICE, and furthermore the trials they included were overwhelmingly made up of patients with LBBB (73-87%), thus their analysis may have lacked power to estimate the effects of CRT in patients with or without LBBB.	
Association of British Healthcare Industries	**CRT-D in patients with QRS >150, LBBB, NYHA III, LVEF < 35%** In NYHA III patients with QRS ≥150ms with LBBB, ICERs for CRT-D vs. CRT-P were estimated at £30,548, £28,646 or £23,891 per QALY gained depending on whether a 5 year, 7.5 year or life-long constant treatment effect is assumed. The Committee preferred a 5 year constant treatment effect (discussed above) and it appears that the Committee decided not to recommend CRT-D in this patient group based on the ICER being marginally above £30,000/QALY in that scenario.	Comment noted. The Committee noted the consultation comments that it would be clinically counter-intuitive not to recommend CRT-D in this patient group when CRT-D was recommended in patients in lower risk categories (that is, patients without LBBB) as well as in patients with milder symptoms of heart failure (NYHA classes I and II). The Committee noted that patients in this group were severely symptomatic and at high risk of sudden cardiac death and have the most potential to benefit from a CRT-D device. The

Consultee	Comment	Response
	SCD is the most common cause of death for HF patients in NYHA class III, accounting for 59% of deaths observed in the ABHI network meta-analysis. We are concerned that the Provisional Guidance would exclude defibrillator use in this population. Secondly, it will be illogical and difficult to justify to either a clinician or a patient that someone with QRS >150, NYHA III with LVEF < 35% who does not have LBBB may receive a CRT-D device; whereas a similar patient who has LBBB will not be given the option of a CRT-D device, despite having the same risk of SCD. The ACD view that CRT-D is not cost effective seems to be based largely on the ICER being £30,548/QALY, i.e. marginally above a £30,000 threshold. The ICERs for all devices in this appraisal are not static and are expected to decrease over time: as presented in ABHI original submission, real term prices (adjusted to 2011 equivalents) fell by 17% for CRT-P, 10.4% for CRT-D and 8% for ICD between 2006 and 2011. The cost effectiveness ratios presented in the ABHI submission used device and procedure costs from 2011, so the ABHI obtained updated cost information for 2013. Total implant costs (device cost and implant procedure cost) for CRT-P and CRT-D have fallen by a further 3% and 1% in the meantime, with the effect that the ICER for CRT-D is practically unchanged. The cost effectiveness results are presented in Tables 3 and 4 (see the ABHI comments document).	Committee therefore concluded that for people in NYHA class III, with QRS duration more than 150 milliseconds with or without LBBB, both CRT D and CRT-P could be considered cost effective (see FAD section 4.3.24).

Consultee	Comment	Response
	We request the Committee to recommend CRT-D in patients with QRS >150, LBBB, NYHA III, LVEF < 35% given the ICER between £30,548, £28,646 or £23,891 per QALY gained depending on whether a 5 year, 7.5 year or life-long constant treatment effect (as per original submission). Internationally, CRT-D is widely used in this patient group. Details of the international clinical practice guidelines are included in Appendix 2 (see the ABHI comments document).	
Association of British Healthcare Industries	Additional comments • A minority of heart failure patients receiving an ICD might need frequent ventricular pacing, which means right ventricular (RV) pacing in the case of an ICD. It's been shown that RV pacing is deleterious because it can worsen heart failure and increase the risk of atrial fibrillation. In the ACD, NYHA I-III patients with QRS 120-149 for the most part are eligible for an ICD only. In patients where a high percentage of ventricular pacing is to be expected, we request the Committee to consider if CRT could be made an available choice. • It was remarked in the ACD that in general, patients in the trials were about 10 years younger than the average age of people with heart failure in the UK. However, the UK devices registry data	Comment noted. In patients with a QRS duration between 120 and 149 milliseconds with LBBB, CRT-D was recommended as an option in patients in NYHA class II and III and CRT-P was also recommended in patients in NYHA class III (see FAD sections 4.3.21 and 4.3.22) . Comment noted. The FAD has been updated to include that the age of patients in the trials

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	indicate that the average age of patients who receive a device in the UK is similar patients in the trials.	was comparable with that of people in the UK who receive devices (see FAD section 4.3.11).
British Heart Rhythm Society (formerly Heart Rhythm UK)	The British Heart Rhythm Society (BHRS, formerly Heart Rhythm UK) is pleased to have the opportunity to comment on the Appraisal Consultation Document for implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120), published in January 2014. We recognise the complexity of combining two sets of technology appraisal guidance into a single unified document. We applaud the careful analysis of clinical and cost effectiveness data and the work of the Southampton and ABHI groups in analysing the clinical trial results. This has produced innovative data which shed new light on efficacy in sub-groups which have been difficult to study in individual trials. In particular, we are pleased that the committee has agreed with BHRS's assessments regarding left ventricular function assessment, non-ischaemic cardiomyopathy, non-sustained ventricular tachycardia, induction of ventricular arrhythmias, atrial fibrillation, echocardiographic dyssynchrony, and the utility of left bundle branch block in patients with QRS durations between 120 and 149ms. No change has been proposed to secondary prevention guidance and this is appropriate. The proposed guidance can be summarised in the following table. (see table	Comment noted.

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	in the BHRS comments document). We would welcome the use of a similar table in the final appraisal documents for clarity. Whilst we recognise that these proposals significantly improve on previous guidance, much more closely reflecting the current published trial data, meta-analyses and international guidance, we have major concerns in four patient categories: people with severe left ventricular impairment (LVEF ≤35%) and QRS <120ms; people with severe left ventricular impairment (LVEF ≤35%), QRS 120-149ms with LBBB and NYHA I or II heart failure symptoms; and people with severe left ventricular impairment (LVEF ≤35%), QRS ≥150ms with LBBB and NYHA III heart failure symptoms. We also question the selection of ICD therapy over CRT-D in patients with NYHA III symptoms and QRS 120-149ms without LBBB	
British Heart Rhythm Society	We recognise that QRS duration is critical in the selection of patients who benefit from CRT and that in the meta-analyses used in the appraisal, QRS duration is associated with baseline risk and treatment effect. However, QRS duration has never been used as an inclusion criterion for an ICD trial, and we are concerned that there is significant heterogeneity between patients with QRS <120ms, and that many are at high-risk of sudden cardiac death. Data from the ABHI network meta-analysis published previously has shown	Comment noted. The Committee explored the approaches used in defining high risk in people with normal QRS duration. Taking into account the high burden of premature deaths in these subgroups, the Committee was persuaded to recommend ICDs in patients with a LVEF less than 35% with a normal QRS duration (less than 120 milliseconds) with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD

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	highly favourable hazard ratios in all sub-groups other than women over 60-years-old: Gender / Age / QRS / ICD vs. OMT Female / <60 / <120 / 0.82 (0.60, 1.13) Female / >=60 / <120 / 1.01 (0.76 , 1.36) Male / <60 / <120 / 0.62 (0.48 , 0.79) Male / >=60 / <120 / 0.76 (0.62 , 0.94) In the light of these data, BHRS requested the ABHI network meta-analysis group to provide further details on ICER calculations within these subgroups. These show ICERs for men under 60-years of £16,572 in NYHA I, £17,317 in NYHA II and £19,378 in NYHA III. The committee has recognised (section 4.3.9) "that some patient characteristics, such as age, sex, QRS duration and LBBB, were predictors of benefit from the different devices (effect modifiers)" and we are very concerned at the prospect of denying ICD therapy to groups of patients who derive significant clinical benefit. As stated in the original BHRS submission, sub-set analysis of the MADIT II data was used in previous NICE guidance to restrict ICD therapy to those with QRS duration >120ms and LVEF ≤30%. However, there were no statistically significant differences in the effect of ICD therapy on survival when patients were stratified by QRS duration. This Forest plot (please see BSHR comments in the evaluation report) also demonstrates a greater benefit from ICD therapy in those <60 years. Sub-set analyses of SCD-HeFT, do show a lower hazard ratio for patients with QRS ≥120ms than those <120ms but the relative risk reduction in those with normal QRS duration is 16% at 5 years: (please see BSHR comments in the evaluation report) This also demonstrates the greater benefit from ICD therapy in males and	section 4.3.17).

Consultee	Comment	Response
	those <65 years. International guidance supports the implantation of ICDs in patients with QRS <120ms: a) North America Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (Epstein et al. Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American ACC/AHA/HRS 2008. J Am Coll Cardiol 2008;51:e1-e62 http://content.onlinejacc.org/cgi/content/full/51/21/e1): plot (please see BSHR comments in the evaluation report for details) b) European Society of Cardiology Current ESC guidance (Guidance on the diagnosis and treatment of acute and chronic heart failure 2012, McMurray et al. European Heart Journal 2012;33:1787-1847) states: plot (please see BSHR comments in the evaluation report for details) c) UK Current NICE guidance (Technology Appraisal 95 Implantable cardioverter defibrillators for arrhythmias, January 2006) states that ICD implantation is recommended for patients: A history of previous (more than four weeks) myocardial infarction (MI) and: either	

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	• Left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure), and Non-sustained VT on Holter (24 hour electrocardiogram [ECG]) monitoring, and Inducible VT on electrophysiological (EP) testing or • Left ventricular dysfunction with an LVEF of less than 30% (no worse than class III of the New York Heart Association functional classification of heart failure), and • QRS duration of equal to or more than 120ms Supported by trial data and meta-analyses, we BHRS that the absence of non-sustained ventricular tachycardia or inducible VT on electrophysiology testing does not identify a low-risk group. The current appraisal consultation document does not recommend ICD therapy for any of these patients who are currently receiving this therapy. It should be noted that the majority of patients with QRS <120ms require only single chamber ICDs. These have a lower cost and greater battery longevity than the mean figures quoted in the ACD and would therefore be expected to be reflected in lower ICERs. BHRS would like to reassure the committee that although ICD shocks can cause distress, ICDs are not designed to be a primarily symptomatic	

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	treatment. When patients understand that the alternative to a shock would usually be sudden death, they are very accepting of this treatment and actively choose to continue it. We urge the committee to reconsider the recommendation in this category of patients in whom the ICERs for ICD therapy are £25,714 to £29,309 as there is no other appropriate treatment to reduce their risk of sudden death.	
British Heart Rhythm Society	2) LVEF ≤35%, QRS 120-149ms The table below shoes ICERs using the committee's preferred model of a constant mortality treatment effect for 5 years followed by tapering over 20 years, taken from the original submission. Treatments with ICERs <£30,000 are shown in bold, the treatment recommended in the ACD is shown in red: (please see the table in the BSHR comments in the evaluation report) BHRS has concerns in 3 categories: 1) It is unclear why the guidance recommends ICD rather than CRT-D in patients with QRS 120-149ms without LBBB and NYHA III symptoms when it is extended dominated and CRT-D has an ICER of £24,311. 2) It is unclear why the guidance recommends ICD rather than CRT-D in patients with QRS 120-149ms with LBBB and NYHA I symptoms when the ICER for CRT-D is £23,080, below that accepted in for patients similar ECG characteristics and NYHA III symptoms. 3) It is unclear why ICD implantation is recommended for patients with QRS 120-149ms with LBBB and NYHA II symptoms when this is extended dominated by CRT-D with an ICER of £22,049. In section 4.3.17, the committee considered evidence from two trials	Comment noted. The Committee considered the RethinQ, EchoCRT and Clelland et al. studies in detail, together with input from clinical specialists, and remained concerned that the subgroups with a QRS duration between 120 and 149 ms were heterogeneous, containing some patients in whom CRT may be inappropriate. The Committee concluded that, without more robust analysis, it would be appropriate to take a cautious approach to the use of CRT in this intermediate QRS group. CRT-D was recommended as a treatment option in patients in NYHA class II with a QRS duration between 120 and 149 milliseconds with LBBB. (see FAD sections 4.3.20 to 4.3.22).

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	(RethinQ, N Engl J Med 2007;357:2461-71, and EchoCRT, N Engl J Med 2013;369:1395-1405) and a meta-analysis (Cleland et al. Eur Heart J 2013;34:3547-3556) in which an absence of benefit from CRT was found in patients with narrow QRS and "was concerned that the subgroups with a QRS duration between 120 and 149ms were heterogeneous, containing some patients in whom CRT may be inappropriate". RethinQ was a trial of CRT in 172 patients with an LVEF less than 35%, NYHA class III heart failure symptoms, caused by either ischemic or non-ischemic cardiomyopathy and a QRS duration of less than 130ms. A trend to benefit from CRT was seen, with statistically significant improvements in peak oxygen consumption in the pre-specified subgroup with QRS ≥120ms (p=0.02), and NYHA class in patients with both QRS ≥120ms (p=0.01) and QRS <120ms (p=0.04): (please see the figure in the BSHR comments document for details) However, there was no statistically significant change in the primary end point of the proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months. EchoCRT was a software randomised trial of CRT in 809 patients with NYHA class III or IV heart failure, LVEF ≤ 35%, QRS duration of < 130 ms, and echocardiographic evidence of left ventricular dyssynchrony. It concluded that CRT did not reduce the rate of death or hospitalization for heart failure in this group: (please see the figure in the BSHR comments document for details) It must be noted that the mean QRS duration of the patients in this trial was only 105ms, well below the selection criterion proposed in this guidance. Only 55 patients with QRS 120 to 129ms received CRT. Furthermore, on subset analysis of QRS duration, the only group for which the confidence	

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	intervals do not cross unity, was mortality in patients with QRS <120ms: (please see the forest plot in the BSHR comments document for details) Unfortunately, LBBB was not reported in this trial so the effect of CRT in patientswith QRS 120-129ms with LBBB cannot be determined. The network meta-analysis published by Cleland et al. (Eur Heart J 2013;34:3547-3556) used data from 5 of the trials included in the individual patient data network meta-analysis adopted in this appraisal. The authors concluded that QRS duration was a powerful predictor of the effects of CRT on morbidity and mortality in patients with symptomatic HF and left ventricular systolic dysfunction. Patients who did not have LBBB appeared to have less benefit from CRT, especially in the composite outcome, but differences were not statistically significant. Their model predicts mortality benefit from CRT in patients with QRS of approximately ≥ 126ms: (please see the figure in the BSHR comments for details) With the confidence intervals shown, and the trend to increased benefit in those with LBBB, these findings are consistent with the BHRS recommendation for CRT in patients with QRS 120-129ms and LBBB and the ICERs of £22,049 and £23,080. BHRS would like to reassure the committee that there is no clinical concern about an adverse effect of CRT in patients with QRS 120-149ms and LBBB and would urge reconsideration of this recommendation.	
British Heart	3) LVEF ≤35%, QRS ≥150ms with LBBB, NYHA III BHRS has serious	The Committee noted the consultation

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Rhythm Society	concerns about the risk of sudden cardiac death in patients with LVEF ≤35%, NYHA III, QRS duration ≥150ms and LBBB. It is counter-intuitive to implant a CRT-P device rather than CRT-D in patients with these characteristics when patients in lower risk categories – the absence of LBBB and/or milder symptoms – are recommended to undergo CRT-D implantation. Whilst a CRT-P device will improve patient symptoms, it cannot prevent sudden cardiac death due to ventricular arrhythmias, and SCD this remains the commonest cause of death in this group of NYHA III patients. BHRS would like to ask the committee to reconsider CRT-D treatment in this patient group with an ICER of just over £30,000.	comments that it would be clinically counter-intuitive not to recommend CRT-D in this patient group when CRT-D was recommended in patients in lower risk categories (that is, patients without LBBB) as well as in patients with milder symptoms of heart failure (NYHA classes I and II). The Committee noted that patients in this group were severely symptomatic and at high risk of sudden cardiac death and have the most potential to benefit from a CRT-D device. The Committee therefore concluded that for people in NYHA class III, with QRS duration more than 150 milliseconds with or without LBBB, both CRT-D and CRT-P could be considered cost effective (see FAD section 4.3.24).
British Heart Rhythm Society	4) Other points BHRS would like to ask the committee to consider including the following points in its final guidance: a) Congenital heart disease For secondary prevention, the guidance should state that ICD implantation is indicted for “high risk” patients who have undergone surgical repair of congenital heart disease. b) Patient choice While a patient may have a recognised cost-effective indication for an ICD and/or a CRT device, they may have carefully considered reasons why they do not want to undergo such a procedure. The advantages and disadvantages of the treatment options must be clearly and honestly discussed and, as far as possible, individualised for that patient in order for them to come to a fully informed decision. Patient literature and	Comment noted. a) Because there was no new randomised evidence, the Committee was satisfied that the recommendations for implantable cardioverter defibrillators in NICE technology appraisal guidance 95 about secondary prevention of ventricular arrhythmias did not need to be changed (see FAD section 4.3.3). b) The importance of patient choice and counselling has been emphasised in the FAD (see FAD section 4.3.8)

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	decision aids should be developed to help in this discussion and decision making. The patient's wishes must be respected. c) End of life care Defibrillators can be deactivated by simple non-invasive re-programming, and this is appropriate in a patient receiving terminal care for heart failure cancer or any other reason. Deactivation of defibrillator therapy will prevent the patient receiving painful and futile shocks at the end of their life. It is both legal and ethical to deactivate implanted devices after full discussion and agreement with a competent patient. Advice is provided in a British Heart Foundation booklet written by Dr James Beattie in 2009, Implantable cardioverter defibrillators in patients who are reaching the end of life" which is available from the BHF website (http://publications.bhf.org.uk/publications.aspx M105 ICDs end of life booklet). Deactivation of CRT and/or bradycardia pacing is not required in this situation as pacing stimulation is asymptomatic. ICD therapy can be deactivated with affecting pacing. The depletion of a device battery should always allow reassessment of the continuing need for device therapy. d) National data collection National audit data collected by the national pacemaker and ICD database (www.devicesurvey.com) has demonstrated significant disparity in ICD and CRT implantation rates across the UK which cannot be explained by disease prevalence. The cause of this apparent inequality of access is unknown and requires further research. We suggest that NICE guidance should require each implanting centre to submit complete and timely audit data to the national database with a minimum	c) The information on end of life care in patients with a defibrillator device has been included (see FAD section 4.3.8) d) NICE usually produces a clinical audit tool containing clinical audit standards based on NICE guidance to help with monitoring of local practice.

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	data set including aetiology, NYHA functional class, left ventricular ejection fraction, QRS duration, history of ventricular arrhythmias (primary or secondary prevention) and complication rates. Expected implant rates for ICD and CRT have been very helpful in planning services and we would welcome revised rates in the new guidance. e) Reassessment When a patient is assessed and found not to fulfil NICE guidance criteria for device implantation, we recommend reassessment at annual review or when there is a clinical event or other change in symptoms or treatment. f) Implantation and follow-up The implantation of ICD and CRT devices is complex and can be time consuming. The complication rates are significantly higher than for bradycardia pacemakers. Device follow-up is also complex and time consuming with a requirement for individualisation of programming to optimise response and minimise the risk of inappropriate therapy. This includes the requirement for optimisation of programming in CRT devices with echocardiographic assessments, particularly in those who do not initially improve following implantation. In addition, patients with indications for ICD and CRT are complex and most have heart failure and other co-morbidity. They require frequent and expert clinical review to optimise symptoms and prevent decompensation and sudden death. Because of the effects of their underlying disease and treatment, many patients require psychological assessment and support. Implant and follow-up centres also need robust databases and protocols to deal with device	e) Comment noted. Guidance on reassessment is beyond the scope of this appraisal. f) Comments noted. This is an implementation issue and is beyond the remit of the NICE Appraisal Committee. g) Comments noted.

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	complications and advisories with 24-hour cover for emergencies. It is BHRS's view that to maintain clinical the cost-effectiveness seen in the clinical trials, these devices should be implanted by high-volume operators in high-volume centres. g) Other key points 1) All patients should receive optimal pharmacological and other therapies. 2) All patients with cardiovascular disease should be fully assessed in order to identify patients who would benefit from device therapy. 3) Patients who are found not to have a device indication should be reassessed annually or sooner if there is a change in their clinical status. 4) The advantages and disadvantages of device therapy should be discussed with all patients to allow them to come to a fully informed decision. 5) Patients with a high risk cardiac condition and a history of syncope are at similar risk of sudden cardiac death as those resuscitated from cardiac arrest and benefit from ICD implantation. 6) There are no large randomised controlled trials of primary prevention ICD therapy in patients with rare high risk cardiac conditions. The best available contemporary evidence of risk factors should be used to guide therapy. 7) Patients with QRS prolongation caused by necessary right ventricular pacing benefit from up-grade to a CRT device. 8) Patients with a bradycardia pacing indication and impaired ventricular function benefit from CRT. 9) The benefit of CRT shown in patients in atrial fibrillation is similar to sinus	

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	rhythm providing a high proportion of beats are biventricularly paced. This may require pharmacological treatment or ablation.	
British Heart Rhythm Society	5) BHRS recommendations 1) All patients should undergo appropriate diagnostic tests to establish the aetiology and optimal management of their heart condition. It is essential to identify patients with conditions which can be cured with ablation therapy such as fascicular tachycardia or right ventricular outflow tract tachycardia. 2) All patients should receive optimal pharmacological therapy for their condition. 3) Patients should undergo revascularisation when indicated (NICE clinical guideline 126 – Management of Stable Angina. July 2011. http://guidance.nice.org.uk/CG126). 4) All patients should be assessed for relative and absolute contraindications to device therapy and co-morbidity which increases the risk of treatment or reduces its efficacy. These include myocardial infarction or revascularisation within 4 weeks unless the patient has had a secondary prevention ICD indication. This should be explained to the patient and weighed in decision making. 5) All patients should have their condition and its management options discussed with them to make a fully informed decision. 6) If a decision is made not to implant a device, this should be reviewed at least annually or when there is a significant change in the patient's condition.	Comments noted. Detailed guidance on the treatment and care pathway for patients with left ventricular dysfunction is beyond the remit of this appraisal.

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	Based on the currently available data, BHRS recommends that in the absence of a fully reversible cause (including an arrhythmia which can be prevented by ablation therapy), patients on optimal pharmacological therapy, with expectation of life expectancy of ≥1 year and with a quality of life acceptable to the patient: Patients with LVEF ≤35% (regardless of aetiology) should routinely be considered for a device based on their symptoms (NYHA functional class) and QRS duration: NYHA	

NYHA I		**NYHA II**	**NYHA III**	**ambulant NYHA IV**
QRS <120ms	ICD	ICD	ICD	OPT
120-149 no LBBB	ICD	ICD	CRT-D	CRT-D
120-149 + LBBB	CRT-D	CRT-D	CRT-D	CRT-D
≥150ms	CRT-D	CRT-D	CRT-D	CRT-D

CRT-P (pacemaker) implantation should be offered in place of CRT-D (defibrillator) when ICD therapy is contraindicated or declined by the patient.

1) Patients with LVEF >35% (without NYHA IV symptoms):

- with spontaneous sustained ventricular arrhythmias or

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	• with inherited conditions with high risk features for sudden cardiac death according to the best available evidence should routinely be considered for: ICD 2) ICD implantation should not be performed within 4 weeks of a myocardial infarction or revascularisation unless the patient has a secondary prevention indication.	
British Society for Heart Failure	We would like to thank NICE for a much improved document. This has shrunk considerably from two large volumes to 71 pages, and the standard of writing is dramatically better. Although there have been a number of positive developments as a result of this provisional guidance, there are a number of omissions/anomalies that give us cause for concern. Positive findings: 1) The inclusion of selected patients with non-ischaemic cardiomyopathy for ICD therapy (a population that was previously not considered in the previous TA95) 2) Patients with a broad QRS (>150ms), severe LVSD (LVEF ≤35%), and NYHA I-II are added to the recommendations for CRT-D 3) Removal of the need for non-sustained VT or positive EP studies as selection criteria for ICD therapy 4) The removal of echo dyssynchrony as a selection criterion for CRT	Comment noted.

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	Concerns: 1) ICDs are not recommended in the provisional guidance for patients with a QRS <120ms. This group represents a large proportion of heart failure patients that might be denied important life-saving therapy, and is the group largely represented by the MADIT-II study where half of patients had a narrow QRS (N Engl J Med 2002;346:877-83). In this study, there was a 31% RRR in overall mortality, with no difference in outcome in those with a narrow QRS on subgroup analysis. Meta-analysis including the results from SCD-HeFT suggests that QRS duration has little effect on the benefit to be gained from ICD (Heart Rhythm 2013;10:200-6). 2) Particularly with regards to defibrillators, it would seem appropriate to emphasise that guidance does not mandate therapy. This is particularly relevant is certain demographic subgroups. a. AGE - As has been mentioned in the document, the mean age in clinical studies is younger than those in the general heart failure population. Generally, elderly patients are more interested in symptomatic improvement rather than reduction in sudden death, and in such a cohort, ICD therapy may be inappropriate or undesired. Furthermore, there is evidence from a meta-analysis of ICD studies (Santangeli et al. Ann Intern Med. 2010;153:592-599) that ICDs primarily benefit younger patients (<60 years). b. GENDER - There is evidence from a large American registry	1-2) The Committee explored the approaches used in defining high risk in people with normal QRS duration. The Committee heard that while age and sex were regarded as important considerations, these are not the only factors used in clinical practice. Others may include the degree of left ventricular dysfunction, history of myocardial infarction including extent and location of myocardial damage and presence of cardiomyopathy. In addition, a range of other potential prognostic factors may be used, like B-type natriuretic peptide. Taking into account the high burden of premature deaths in these subgroups, the Committee was persuaded to recommend ICDs in patients with a LVEF less than 35% with a normal QRS duration (less than 120 milliseconds) with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD section 4.3.17).

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	(National Cardiovascular Data Registry 2012) and sub-group analyses from SCD-HeFT and MADIT-II, that it is male patients that seem to confer benefit from primary prevention ICDs. Women on the other hand appear to have a higher complication rate following ICD implantation. 3) The discrepancy in patients with NYHA class III and QRS>150ms. Those with LBBB have been allocated CRT-P, and those with non-LBBB allocated CRT-D. CRT has a much stronger evidence base in LBBB, and those with a wide QRS are at particular risk. We would suggest the same recommendation of "CRT-D or CRT-P" in either category. This is in keeping with the 2012 ESC heart failure guidelines – see below (from European Heart Journal doi:10.1093/eurheartj/ehs104): (please see BSHF comments in the evaluation report for details) 4) The exclusion of CRT-D in patients with NYHA II heart failure, LVEF≤35%, LBBB and QRS 120-149ms. Again, this is at odds with the ESC Guidelines who recommend "CRT, preferably CRT-D" in patients with a QRS duration ≥130ms (please see BSHF comments in the evaluation report for details).	3) The Committee noted the consultation comments and has recommended CRT-P or CRT-P for people in NYHA class III, with QRS duration more than 150 milliseconds with LBBB (see FAD section 3.4.24). 4) The Committee noted the consultation comments and has recommended CRT-D for people with NYHA class II symptoms with a QRS duration between 120 and 149 milliseconds with LBBB (see FAD section 4.3.21)
British Society for Heart Failure	We would be grateful if NICE would consider these points. In summary, the BSH are happy with the guidance for the categories highlighted in green in the figure below, but we feel strongly that the alterations to the	Comments noted.

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	recommendation (highlighted in yellow) should be given serious consideration (please see BSHF comments in the evaluation report for details).	
British Cardiovascular Society	The British Cardiac Society (BCS) welcomes the review of TA95 and TA120. The combination of both into a single document is a positive step. The review is thorough and utilises all of the relevant evidence in the literature. Many notable improvements have been made to the guidelines. However, there are a couple of recommendations that fall outside of standard practice and will come as a surprise to the majority of clinicians who work in this field. BCS would like to highlight some concerns regarding the recommendations for devices in patients with LVSD (EF<35%). We also have minor comments to make regarding the format of the document itself.	Comment noted.
British Cardiovascular Society	Significant concerns: A) Recommendation for no device therapy in patients with LVSD <35%, QRS<120msec, NYHA I-III. 1) The recommendation to not implant ICDs in patients with EF<35%, QRS<120msec is out of line with clinical opinion in the UK. 2) ICDs are recommended for this group in both American guidelines	The Committee explored the approaches used in defining high risk in people with normal QRS duration. The Committee heard that while age and sex were regarded as important considerations, these are not the only factors used in clinical practice. Others may include the degree of left ventricular dysfunction, history of myocardial infarction including extent and location of myocardial damage and presence of cardiomyopathy. In addition, a range of other potential prognostic factors may be used, like B-type natriuretic peptide. Taking into account the high burden of premature

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	(Epstein et al, J Am Coll Cardiol 2008;51:el-e62) and European guidelines (McMurray et al. European Heart Journal 2012;33;1787-1847). 3) There is no evidence to support the assertion that patients in this category do not benefit (in terms of prognosis) from implantation of an ICD. Indeed the randomised controlled trials clearly demonstrate a survival benefit in this cohort. Consensus amongst clinicians is that use of QRS<120msec to differentiate those patients with EF<35% eligible for ICD implantation is fundamentally flawed and not evidence based. 4) The cost-effectiveness analysis submitted by the manufacturers relating to EF<35%, QRS<120msec is very confused. Patients with QRS<120msec cannot by definition have LBBB or non-LBBB. Therefore QRS <120msec 'LBBB' and 'Non-LBBB' can't have different ICERs. The committee acknowledge this issue regarding the cost effectiveness analysis yet appear to use these data to exclude ICD implantation (despite ICERs < £30000 and comparable to devices recommended in other patient groups). 5) The committee are aware that subgroups of patients within this cohort are at highest risk and therefore benefit most from ICD implantation e.g. men <60yrs. Specific guidance could be made recommending implantation in this sub group. The risk factors of age and gender are used to guide intervention in other circumstances e.g. anticoagulation in Atrial Fibrillation using the CHA2DS2VASc scoring system (see NICE Atrial	deaths in these subgroups, the Committee was persuaded to recommend ICDs in patients with a LVEF less than 35% with a normal QRS duration (less than 120 milliseconds) with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD section 3.4.16 and 3.4.17).

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	Fibrillation guidance published for consultation 14.1.14). We do however recognise difficulties in using gender and age when writing guidance. A compromise might be along the lines of: 'ICD implantation is not routinely recommended in patients with NYHA I-III, EF<35%, QRS<120msec however may be considered in those patients where it is deemed clinically appropriate.' BCS strongly suggests that the committee reconsider the recommendation not to implant ICDs in patients with EF<35%, QRS<120msec.	
	B) Recommendation for CRT-P rather than CRT-D in patients with NYHA III heart failure, LVSD<35% and LBBB>150msec 1) It seems perverse to implant a CRT-P device into the cohort of patients that have repeatedly shown the most benefit from CRT-D in clinical trials, whilst offering CRT-D to patients at less risk of sudden arrhythmic death. This is the exact group of patients that benefit most from CRT-D and were targeted for this therapy in the previous NICE guidance. 2) The committee acknowledge that differentiation of NYHA II and NYHA III can be difficult for the clinician. Patients also move between these two NYHA classes during disease progression. The decision to implant a	The Committee noted the consultation comments and has recommended CRT-D or CRT-P for people in NYHA class III, with QRS duration more than 150 milliseconds with LBBB (see FAD section 3.4.24).

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	CRT-P or a CRT-D will therefore prove problematic and open to interpretation. BCS strongly suggests that the committee reconsider the recommendation not to implant CRT-D in patients with EF<35%, QRS>150msec, LBBB and NYHAIII symptoms.	
	C) Recommendation for ICD rather than CRT-D in patients with NYHA I-II heart failure, LVSD<35% and LBBB 120--149msec Similarly to above, it is unclear why CRT is not recommended for patients in this cohort. Firstly, NYHA II symptoms are often difficult to distinguish clinically from NYHA III (where CRT-D is an option). Secondly, MADIT-CRT provides clear evidence of clinical benefit in this group. Thirdly, the calculated ICER for CRT-D appears less than that in NYHA III where CRT-D is recommended.	4) The Committee noted the consultation comments and has recommended CRT-D in people with NYHA class II symptoms with a QRS duration between 120 and 149 milliseconds with LBBB (see FAD section 4.3.20)
	Minor Comments 1) We welcome the combination of ICD and CRT recommendations into a single guideline. The proposed format could however be improved as the guideline is quite cumbersome and difficult to read in its current state. A summary table of recommendations for the primary prevention cohort with	Comment noted. 1) A table had been included. Please see FAD section 1.2

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	LVSD (EF<35%) would be helpful. E.g. (please see BCS comments in the evaluation report for details) 2) The description of three populations of patients is unhelpful to the clinician. There is significant overlap between 'Population 2' (LVSD and heart failure) and 'Population 3' (LVSD and heart failure and risk of sudden cardiac death). We would recommend removal of this classification.	2) Comment noted. This comment relates to the approach taken by the Assessment Group which was consequently considered by the Committee. In line with the NICE process, all evidence that was part of the Committee's deliberations is presented in the FAD.
Royal College of Physicians	The RCP is grateful for the opportunity to respond to the above ACD. We have had sight of the submissions from the British Cardiovascular Society (BCS) and the British Society for Heart Failure (BSH) and wish to endorse both sets of comments, which are consistent in their concerns.	Comment noted. Please see responses to the comments by BHRS and BSHF above.
Arrhythmia Alliance	Arrhythmia Alliance is delighted to have the opportunity to comment on the Appraisal Consultation Document on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120), published in January 2014. It is clear that the proposals are indeed an improvement on current guidelines; however we are extremely concerned that should the proposed guidance be approved, then those patients with LVEF ≤ 35% and QRS< 120ms will be at high risk of sudden cardiac death. These patients as detailed above are included for devices in the American College of Cardiology Guidelines, AHA Guidelines and HRS Guidelines, more	Comment noted. The Committee noted the consultation comment and has revised its preliminary recommendation in patients with LVEF less than 35% and with a normal QRS duration (see FAD section 3.4.17)

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	importantly; the ESC Guidelines also include these patients. We would question why UK patients should be denied access to the same therapy and in turn quality of life as their European counterparts.	

Comments received from commentators

Commentator	Comment	Response
Healthcare Improvement Scotland	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results? 1) Data included is up to date and fairly comprehensive. No guidance is offered for patients with heart failure and atrial fibrillation and I think that it should be emphasised that patients with atrial fibrillation may be less likely to benefit from CRT, particularly if their heart rate is not well controlled. 2. Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice? If not, please explain. 2) Yes 3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?	Comments noted.

Commentator	Comment	Response
	3) Yes although the cost of an admission to hospital with heart failure, in my opinion, seems to be an underestimate thereby increasing the ICER of device therapy 4. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? 4) Yes 5. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? I think that they are directly applicable in Scotland 6. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. Patient numbers treated with CRTP and CRTD will increase due to the expanded implantation criteria. Further financial and human resource in implanting and follow-up centres will be required to deal with this increased activity. In particular, all follow-up centres should have dedicated arrhythmia nurses to help counsel patients before and after device implantation where needed	

Commentator	Comment	Response
	7. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. No 8. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment I welcome the updated NICE guidance on device therapy. CRT in particular has made an enormous difference to my patients and it can completely transform their lives and without doubt prevents recurrent admissions to hospital. The costs are decreasing rapidly year on year and the net cost of these devices has fallen dramatically as demonstrated by this document.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1 (Appraisal Committee's preliminary recommendations)	In general I think the guidelines are excellent, however, I have one are of major concern. One group of patients at high risk of SCD who will be disadvantaged are younger patients with extensive infarction who do not have QRS duration > 120ms. As a practicing devices cardiologist I not infrequently see patients with premature coronary disease (age < 60 years) and EF < 35%. Often these patients have younger families and they have a high risk of sudden arrhythmic death. Whilst I appreciate that NICE cannot discriminate on basis of age, it cannot be right that this group are denied potentially lifesaving treatment because of a narrow QRS whereas an 85 year old with a QRS of 125ms would qualify especially since the QRS duration criteria are based on subgroup analysis of studies and thus lacks statistical validity. I strongly feel that the current CRG guidelines which are consistent with ESC and ACC/AHA guidelines for this group should be considered as a reasonable way to proceed.	The Committee explored the approaches used in defining high risk in people with normal QRS duration. The Committee heard that while age and sex were regarded as important considerations, these are not the only factors used in clinical practice. Others may include the degree of left ventricular dysfunction, history of myocardial infarction including extent and location of myocardial damage and presence of cardiomyopathy. In addition, a range of other potential prognostic factors may be used, like B-type natriuretic peptide. Taking into account the high burden of premature deaths in these subgroups, the Committee was persuaded to recommend ICDs in patients with a LVEF less than 35% with a normal QRS duration (less than 120 milliseconds) with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD section 3.4.16 and 3.4.17).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional	1 (Appraisal Committee's preliminary recommendations)	These preliminary recommendations are at odds with current clinical practice which follows the European guidelines. These advocate ICD therapy for patients with a narrow QRS (duration less than 120 ms). If these guidelines are implemented then defibrillator therapy will be withheld from a high risk group of patients namely those who are male and under 60 years of age who have had a large anterior myocardial infarction resulting in severe LVSD with a QRS duration of less than 120ms.	The Committee explored the approaches used in defining high risk in people with normal QRS duration. The Committee heard that while age and sex were regarded as important considerations, these are not the only factors used in clinical practice. Others may include the degree of left ventricular dysfunction, history of myocardial infarction including extent and location of myocardial damage and presence of cardiomyopathy. In addition, a range of other potential prognostic factors may be used, like B-type natriuretic peptide. Taking into account the high burden of premature deaths in these subgroups, the Committee was persuaded to recommend ICDs in patients with a LVEF less than 35% with a normal QRS duration (less than 120 milliseconds) with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death (see FAD section 3.4.16 and 3.4.17)
	3 (The technologies)	The technology has become considerably cheaper since this analysis. The cost of a complete ICD system is now far less than that quoted and this has considerable bearing on the ICER and QALY calculations used to determine if therapy is cost effective or not.	Comment noted.
	4 (Evidence and interpretation)	The recommendation that ICD therapy be withheld from patients with a QRS less than 120 ms seems to have been influenced by the belief that inappropriate shocks are common and distressing in this subgroup of people. Although inappropriate shocks can happen they are not commonplace in everyday practice. The committee appear to have neglected to recognise that young male patients (under 60) with severe LVSD due to IHD are in fact a high risk group and that denying this subgroup ICD therapy will result in an increase in sudden cardiac deaths. Other technologies have been assessed against an acceptable ICER of £30000 per QALY which would indicate that ICD therapy for the normal QRS group is cost effective.	Comment noted. See FAD sections 4.3. 8 and 4.3.17