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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Advisory Committee – Tuesday 16 April 2024

Algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices

The following documents are made available to the Committee:

1. **Overview**

2. **Professional organisation submission from NHSE**

3. **Updated External Assessment Report (dated 20 March 2024)** produced by Newcastle Technology Assessment Review Group, Newcastle University. ***Note, this report is an updated version to the one issued to stakeholders on 14 February 2024. The updates are listed on page 3-6 of the report.***

4. **EAR addendum**

5. **External Assessment Report (EAR) consultation comments and responses**

Evidence overview: Heart failure algorithms for remote monitoring in people with cardiac implantable electronic devices

This overview summarises the main issues the diagnostics advisory committee needs to consider. It should be read together with the final scope and the diagnostics assessment report.

1 Aims and scope

Heart failure (HF) is a clinical syndrome caused by any structural or functional cardiac disorder that impairs the heart's ability to function efficiently and pump blood around the body. Cardiac implantable electronic devices (CIED) are recommended as treatment options for specific people who have or are at high risk of heart failure. Monitoring is recommended for people who have CIEDs. CIEDs may have remote monitoring enabled, whereby data can be transmitted wirelessly and automatically (both in real-time and at scheduled intervals) to a remote monitoring system. Healthcare professionals can then access these data online, negating the need for the patient to be physically present. The frequency of reviews varies according to the person’s condition. Clinical experts highlighted that there is a lot of variation in current standard of care, and sometimes reviews are only triggered if worsening symptoms are reported by the person with the CIED.

CIEDs may have algorithm-based remote monitoring incorporated in the device. HF algorithms are intended to analyse and collate different clinical data recorded by the device to detect gradual worsening of HF. The system can send alerts to healthcare professionals to prompt a review of the stored data, enabling proactive investigation into the cause of the suspected decompensation before the patient has symptoms. The aim of this assessment is to determine whether algorithm-based remote monitoring for

detecting HF in people with CIEDs represents a clinically and cost-effective use of NHS resources.

Around 920,000 people in the UK were living with HF in 2018 with an estimated 200,000 new diagnoses each year. HF mainly affects people over the age of 65, with an average age of diagnosis of 77, and risk increases significantly with age. Around 1 in 35 people aged 65–74 years have HF, which increases to 1 in 15 of people aged 75–84 years, and to just over 1 in 7 people those aged above 85 years.

The NICE guidelines for diagnosis and management of chronic HF in adults recommend that monitoring of people with chronic HF should include a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status, a review of medication, and an assessment of renal function.

Decision question

Does algorithm-based remote monitoring of heart failure in people with CIEDs represent a clinical and cost-effective use of NHS resources?

Populations

1. People who have a CIED and do not have a diagnosis of chronic HF but are at high risk of new onset acute heart failure. Potential subgroups are people who:

    - have a CRT-P device
    - have a CRT-D device
    - have an ICD device
    - have a pacemaker device.

2. People who have a CIED and a diagnosis of chronic HF. Potential subgroups are people who:

    - have a CRT-P device

- have a CRT-D device
- have an ICD device
- have a pacemaker device
- have a diagnosis of heart failure New York Heart Association (NYHA) class I and II, or III and IV (at study recruitment)
- have a prior heart failure hospitalisation or urgent care visit within the last 12-months.

Interventions

HF algorithms for monitoring data in people with CIEDs:

- CorVue and Merlin.net patient care network (Abbott Medical)
- HeartInsight and BIOTRONIK home monitoring (Biotronik)
- HeartLogic and Latitude NXT patient management system (Boston Scientific)
- TriageHF and CareLink remote monitoring (TriageHF Plus; Medtronic).

Comparator

Standard care for remote monitoring of HF in people with CIEDs.

Healthcare setting

Secondary care

Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the final scope.

2 Clinical effectiveness evidence

The external assessment group (EAG) did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of algorithm-based remote monitoring. Find the full systematic review methods and results from page 35 of the external assessment report (EAR).

2.1 Overview of included studies

In total, 42 studies (reported in 81 publications) met eligibility criteria and were included in the review. Section 9.6 (page 237) of the EAR gives the characteristics of the included studies for clinical effectiveness. Overall, 8 studies were done in the UK: 6 for Triage-HF and 2 for HeartLogic. Five of the studies were (at the time of the review) awaiting publication but have results which were synthesised in the systematic review (see table 49 [page 236] in the EAR for full details).

Most studies (n=37) are single-arm cohort studies which provide information on the prognostic ability of the algorithms, indicating whether the algorithms can correctly classify patients by risk status or alert status. Evidence comparing the effectiveness of the algorithms to no algorithm use was limited to 5 studies, covering 3 of the interventions (Table 1).

Table 1 Summary of the comparative studies identified

Authors (year)	Population	Intervention	Comparator
Shapiro (2017)	n=120	CorVue	No CorVue-activated device
Treskes (2021)	n=68	HeartLogic	Remote monitoring pre-activation of the algorithm
Feijen (2023)	n=161	HeartLogic	No HeartLogic algorithm
Chang (2020)	n=140	HeartLogic	Pre device implantation
Ahmed (unpublished)	n=758	TriageHF	TriageHF-compatible devices without automated transmission activated

2.2 Study quality

All studies reporting prognostic accuracy outcomes underwent risk of bias assessments at the study level using the PROBAST tool. All non-randomised studies reporting clinical outcomes underwent risk of bias assessment at the study level using ROBINS-I. If a study reported both prognostic and clinical outcomes, the study was appraised using both PROBAST and ROBINS-I. See section 3.4 (page 43) of the EAR for more details.

All CorVue studies assessed using PROBAST have a high risk of bias, with particular concern regarding the conduct or poor reporting of the analysis

methods. Studies assessed using the ROBINS-I tool have either a serious or critical risk of bias because of the inherent limitations associated with confounding in cohort study designs, particularly retrospective designs.

The 1 published HeartInsight study was found to have a high risk of bias using the PROBAST tool because of concerns around the conduct or reporting in the analysis (such as missing data and the statistical analysis). Using ROBINS-I, the study was found to have an overall serious risk of bias because of concerns about missing data and concerns of confounding.

All HeartLogic studies which evaluated prognostic accuracy outcomes were found to be at high risk of bias using PROBAST because of a lack of robust analysis and small number of included participants with the outcome. Six of the studies which included clinical outcomes were at critical risk of bias according to ROBINS-I, because of a lack of robust analysis to attempt to control for confounding and small participant numbers. Studies including comparative data for HeartLogic (Feijen et al., Treskes et al.) were at serious risk of bias because of classification of interventions and problems with uncontrolled confounding. Gardner et al. (2018, n=900), a post hoc analysis from a prospective cohort was the only study to be considered as low risk of bias in all 7 domains of ROBINS-I.

For TriageHF, 1 study (Gula, 2014) was assessed as having low risk of bias according to PROBAST. All other studies were assessed as high, serious, critical or unclear risk of bias (because of abstracts containing limited information). The only study to provide comparative data for Triage-HF was judged to be at critical risk of bias, because of missing information including whether propensity score matching was successful, and most hospitalisations being unrelated to HF or cardiovascular disease.

Most clinical studies identified in the systematic review were at serious or critical risk of bias because of a lack of controlling for confounding factors in the statistical analysis. Specifically, age, sex, New York Heart Association (NYHA) classification, smoking status and other co-morbidities were largely

uncontrolled for in most studies. In addition, the inherent risk of bias because of the retrospective and single-arm design of many studies is likely to lead to an overestimation of the findings.

2.3 Prognostic accuracy

Evidence for the prognostic accuracy of the algorithms was available in 24 studies: 5 on CorVue, 1 on HeartInsight, 8 on HeartLogic, and 10 on TriageHF. Table 15 (page 51) in the EAR summarises the studies reporting predictive accuracy measures for all interventions. Study endpoints used for measuring prognostic accuracy varied across studies for all interventions, which meant that it was not possible for the EAG to do meta-analysis. Some studies report prognostic accuracy measures for different numerical thresholds. Alerts are triggered when the index exceeds the specified numerical threshold for the algorithm.

CorVue

The lowest reported sensitivity was 20% (Benezet Mazuecos, 2016), with a corresponding specificity of 77% (the highest reported specificity). The highest reported sensitivity was 68%, (Wakabayashi, 2021), but specificity was not reported for this study. In Palfy (2020), specificity was reported as 70% with a corresponding sensitivity of 24% (Table 2).

HeartInsight

D'Onofrio (2022) used the primary study endpoint of the first post-implant worsening of heart failure (HF) leading to hospitalisation. At a threshold of 3.5, the sensitivity was 72.4% and specificity was 75.8%. When the threshold was increased to 4, sensitivity decreased to 65.5% and specificity increased to 82.4%. At the threshold of 4.5, sensitivity remained at 65.5% and specificity increased to 86.7% (

Table 3).

HeartLogic

Accuracy was reported for a range of numerical thresholds and endpoints. The lowest reported sensitivity was 66% for which specificity was not reported. The highest reported sensitivity was 100% (reported in 2 studies). In 1 of these studies, the corresponding specificity was reported as 93% (also the highest reported specificity), and in the other study specificity was not reported. The lowest reported specificity was 61% for the numerical threshold of 16, and specificity in this study was reported as 92% (Table 4).

TriageHF

The area under the curve (AUC) was reported in 3 studies assessing worsening HF (AUC = 0.75), mortality (AUC = 0.61), and hospital admissions (AUC = 0.81). Sensitivity for patients with a high-risk score showed great variability, with a range of 31.5% to 98.6%. Specificity for high-risk status also varied, with a range of 59.4% to 90.2% (Table 5).

Table 2: Studies reporting prognostic accuracy for CorVue

Author (year)	Study design (n)	Study endpoint	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Binkley (2012)	Retrospective (n = 61)	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	61.9	NR	40.6	NR
Forleo (2013)	Prospective (n = 80)	HF events of HF hospitalisations requiring treatment changes	61.5 (46 to 75)	NR	42.9 (31 to 56)	NR
		HF hospitalisations alone	53.8 (29 to 77)	NR	17.9 (9 to 33)	NR
Benezet Mazuecos (2016)	Cohort, unclear (n = 70)	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening and unplanned office visits	20	77	5	94
Palfy (2018)	Prospective (n = 53)	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	24	70	6	93
Wakabayashi (2021)	Retrospective (n = 49)	HF event defined by the Framingham Heart Study	68 (48 to 84)	NR	21 (13 to 30)	NR

Table 3: Studies reporting prognostic accuracy for HeartInsight

Author (year), Study design (n)	Study endpoint	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
D'Onofrio (2022)	Primary: First post implant worsening HF hospitalisation	3.5 = 72.4 (52.8 to 87.3) 4.0 = 65.5 (45.7 to 82.1) 4.5 = 65.5 (45.7 to 82.1)	3.5 = 75.8 (75.6 to 75.9) 4.0 = 82.4 (82.3 to 82.5) 4.5 = 86.7 (86.6 to 86.8)	NR	NR

Prospective (validation cohort, n=461)	Secondary: any HF hospitalisation, outpatient IVI or death	3.5 = 64.5 (51.3 to 76.2) 4.0 = 59.7 (46.4 to 71.9) 4.5 = 54.8 (41.7 to 67.5)	3.5 = 75.3 (75.2 to 75.4) 4.0 = 82.0 (81.9 to 82.2) 4.5 = 86.5 (86.4 to 86.6)	3.5 to 4.5 = 5.3 to 7.7	3.5 to 4.5 = 96.6 to 96.7

Table 4: Studies reporting prognostic accuracy for HeartLogic

Author (year), Study design (n)	Study endpoint	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Boehmer (2017) Prospective (n = 400)	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	Validation = 70.0 (55.4 to 82.1)	Validation = 85.7	11.3	99.98
De Juan Baguda (2022). Phase 1 (n = 101) and 2 (n = 94) are retrospective Phase 3 (n = 267) is prospective	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	Phase 1 = 100 Phase 2 and 3 = 98	Phase 1 = 93 Phase 2 and 3 = 90	Phase 1= 18 Phase 2 and 3=29	Phase 1 = 100 Phase 2 and 3 = 99.9
Vigdor (2020) Prospective (n = 80)	HF events of unscheduled visits or HF hospitalisations within 6-weeks of initial alert	Threshold ≥16 = 92 ≥20 = 69	Threshold ≥16 = 61 ≥20 = 90	Threshold ≥16 = 32 ≥20 = 56	Threshold ≥16 = 98 ≥20 = 94
De Ruvo (2019) Prospective (n = 101)	Hospitalisations and unplanned office visits	100	NR	58	NR
Santobuono (2023) Prospective (n = 568)	Hospitalisation or death	Hospitalisation alone: 66 (52-78) Hospitalisation or death: 67 (57-75)	NR	NR	NR
Treskes (2021) Retrospective (n = 68)	Hospital admission	90 (77-97)	89 (79-95)	NR	NR

Henry (2022) Retrospective (n = NR)	HF events (undefined)	70	NR	NR	NR
Wariar (2023) Retrospective (n = 1567)	HF events (undefined)	82 (78.1-85.5)	NR	NR	NR

Table 5 Studies reporting prognostic accuracy for TriageHF

Author (year)	Study design (n)	Study endpoint	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Burri (2018)	Retrospective (n = 722) All values are for high-risk status.	Cardiovascular hospitalisations	25.5 (18.8 to 33.6)	90.2 (88.6 to 91.5)	5.8 (3.9 to 8.5)	98.0 (97.5 to 98.4)
		HF hospitalisations	37.4 (26.5 to 49.8)	90.1 (88.6 to 91.5)	4.1 (2.5 to 6.7)	99.1 (98.7 to 99.4)
		Non-HF cardiovascular related hospitalisations	15.4 (9.2 to 24.7)	89.9 (88.3 to 91.3)	1.7 (0.9 to 3.0)	98.9 (98.5 to 99.2)
Okumura (2020)	Prospective (n = 315)	HF hospitalisations requiring treatment changes	High vs. medium + low = 31.5 High + medium vs. low = 78.7	High vs. medium + low: 89.0 High + medium vs. low: 44.4	High vs. medium + low: 4.1	High + medium vs. low: 99.3
Sammut-Powell (2022)	Prospective (n = 435)	All cause hospitalisations	High risk = 37.3	High risk = 86.2	NR	Non-high risk = 97.5
		Cardiovascular hospitalisations	High risk = 39.3	High risk = 85.7	NR	Non-high risk = 99.1
		HF related hospitalisations	High risk = 62.5	High risk = 85.6	NR	Non-high risk = 99.7
Koehler (2019)	Retrospective analysis of	HF hospitalisation,	High risk = 41	High risk = 86	NR	NR

	registry data (n = 13,122)	outpatient IVI, or death				
Cowie (2013)	Retrospective analysis of seven studies (n = 1310)	Hospital admission	Low/medium risk (5%) = 82.8 Medium/high risk (20%) = 46 Risk score 10% = 68.7	Low/medium risk (5%) = 45.8 Medium/high risk (20%) = 90.2 Risk score 10% = 71.6	NR	NR
Bachtiger (2021)	Prospective (n = 72)	Worsening HF	High risk = 87.9 (77.0 to 99.0)	High risk = 59.4 (50.0 to 69.0)	High risk = 40.3	High risk = 94.0
Ahmed (2020)	Prospective (n = 231)	Worsening HF (undefined)	High risk = 98.6 (92.5 to 100)	High risk = 63.4 (55.2 to 71.9)	NR,	NR
Zile (2020)	Retrospective (monthly downloads n = 22 901; alert triggered n = 21,356; daily downloads n = unclear)	HF events (undefined)	Monthly downloads high risk score = 39 Monthly downloads medium risk score = 85 Alert triggered high risk score = 47 Daily downloads high risk score = 51 Daily downloads medium risk score = 93	Monthly downloads high risk score = 89 Monthly downloads medium risk score = 44	NR	NR

False positives and unexplained alerts

Evidence of false positives and/or unexplained alerts was reported in 21 studies: 7 on CorVue, 1 on HeartInsight, 11 on HeartLogic and 2 on TriageHF. Studies reporting data on the number of false positives and false positive rates are shown in Table 6. Table 7 summarises the studies reporting on the number of unexplained alerts and unexplained alert rate. See table 16 (page 59) and table 17 (page 64) in the EAR for the full summary of evidence for false positives and unexplained alerts.

Table 6 Evidence for the number of false positives for the algorithms

Author (year)	Intervention	False positive rate	Number of false positives
Santini (2012)	CorVue	NR	10 of 23 alerts in 16 patients
Benezet Mazuecos (2016)	CorVue	NR	99 of 104 alerts in 40 patients
Forleo (2013)	CorVue	0.6 alerts per patient year	23 patients with 32 episodes
Binkley (2012)	CorVue	0.63 (SD: 0.1) alerts per patient year	19 of 32 alerts
Palfy (2015)	CorVue	NR	99 of 105 alerts
Wakabayashi (2021)	CorVue	NR	76 of 96 alerts
Boehmer (2017)	HeartLogic	1.56 (95% CI: 1.41 to 1.77)	NR
Vigdor (2020)	HeartLogic	NR	26 of 38 alerts
Wariar (2023)	HeartLogic	1.401 (95% CI: 1.332 to 1.475)	NR
Santobuono (2023)	HeartLogic	Cardiovascular hospitalisation = 0.99 (95% CI: 0.93 to 1.05) Cardiovascular hospitalisation or death = 0.94 (95% CI: 0.89 to 0.99)	NR
De Juan Baguda (2022)	HeartLogic	Phase 1 = 0.39 alerts per patient year Phase 2 and 3 = 0.64 alerts per patient year	NR
Feijen (2023)	HeartLogic	NR	33 of 130 alerts

Treskes (2021)	HeartLogic	NR	8 of 51 alerts
Garner (2022)	TriageHF	NR	68 of 376 alerts
Zile (2020)	TriageHF	0.48 per patient year	NR

Table 7: Unexplained alert rates

Author	Intervention	Unexplained alert rate (per patient year)	Number of unexplained alerts
Forleo (2013)	CorVue	NR	32 of 56 alerts
Santini (2012)	CorVue	NR	10 of 23 alerts
D'Onofrio (2022)	HeartInsight	0.63 to 0.99	NR
Treskes (2021)	HeartLogic	0.16	9 of 51 alerts
Henry (2022)	HeartLogic	0.7	NR
Boehmer (2017)	HeartLogic	1.47	NR
Perez Serrano (2019)	HeartLogic	NR	2 of 11 alerts
De Juan Bagunda (2022)	HeartLogic	Phase 1 = 0.52 Phase 2/3 = 0.39	Phase 1 = 53 of 73 alerts Phase 2/3 = 120 of 277 alerts
De Ruvo (2019)	HeartLogic	0.41	NR
Treskes (2021)	HeartLogic	0.16	9 of 51 alerts
Santini (2020)	HeartLogic	NR	29 of 100 alerts
Feijen (2023)	HeartLogic	0.2	NR

Changes to clinical management

Changes to clinical management were used to define prognostic ability in some studies. If a change in clinical management closely follows an alert, then earlier appropriate treatment could be attributed to the alert. The percentage of alerts that result in immediate treatment change has predictive value. No studies reported a relative rate of change in clinical management IN versus OUT of alert, consequently the EAG concluded that the evidence only provides direction of effect (whether alerts tend towards an increase in change in clinical management). See table 18 (page 69) in the EAR for the results of all studies reporting the changes to clinical management for the algorithms.

Evidence for HeartLogic consistently showed a trend towards HeartLogic alerts resulting in more clinical actions compared with OUT of alert.

Hernandez et al. (2022, n=191) reported increased changes in treatment for the first 12 months of the study when IN alert compared with OUT of alert for the HeartLogic algorithm. Additionally, when IN alert 74% of cases led to medication changes. Pecora et al. (2020, n=104) found a significant increase in changes to treatment when IN alert compared with OUT of alert ($p < 0.001$). A similar result was observed when comparing actionable alerts from HeartLogic (43%) to monthly remote monitoring of data (1%), suggesting HeartLogic alerts lead to more actionable events (alerts resulting in active clinical actions to manage the HF condition; $p < 0.001$).

Hospitalisations

Evidence associating hospitalisations with prognostic ability of the HF algorithms was available in 7 studies: 0 for CorVue, 0 for HeartInsight, 2 for HeartLogic and 5 for TriageHF. See table 19 (page 76) in the EAR for full detail of these studies.

The 2 studies for HeartLogic, Calo (2021, n=366) and Santobuono (2023, n=568), report an increased risk of hospitalisation when IN alert with the algorithm compared with OUT of alert. Santobuono et al. reported higher hospitalisation rates when IN alert compared with OUT of alert (IN alert=0.23, OUT of alert=0.02, incidence rate ratio [IRR]=12.98). The evidence for HeartLogic suggests that there is an increased risk of hospitalisation when IN alert vs OUT of alert, indicating good prognostic ability of the algorithm.

For TriageHF, a number of composite endpoints involving hospitalisation were used across the 5 studies to show prognostic ability. Across the endpoints, the results consistently show that there is an increased risk for HF, cardiovascular, and non-HF cardiovascular related hospitalisation when in a high-risk or medium-risk status, compared with low-risk status. Garner et al. (2022) showed that an increased number of high-risk alerts (3 or more high-risk alerts) was associated with a statistically significant increased likelihood of HF-related hospitalisation (hazard ratio for hospitalisation for patients with 3 or

more high risk alerts=2.5, p=0.03). A number of these studies report statistical significance of these findings.

Rate of heart failure events

Association data for rate of heart failure events were reported in 3 studies: 2 for HeartLogic and 1 for TriageHF. All studies considered varying heart failure events, with heart failure being a generic term to encompass numerous outcomes. See table 20 (page 80) in the EAR.

Evidence from the 2 studies for HeartLogic suggest an increased risk of a HF event when IN alert compared with OUT of alert. Calo (2021) reports an IN vs OUT of alert hazard ratio of 30.63 for the rate of heart failure events. Gardner et al. (2018) reported a statistically significant increased HF event rate ratio when IN alert for a HF event (IN alert event rate ratio = 7.05, p<0.001). This remained significant when adjusted for chronic kidney disease and history of atrial fibrillation (IN alert event rate ratio adjusted = 4.78, p<0.001).

The 1 study reporting on this outcome for TriageHF, Zile (2020), reported statistically significant increased odds of HF when in medium (odds ratio=2.8, p<0.001) and high-risk status (odds ratio=9.2, p<0.001) compared with low-risk status.

Heart failure related mortality

Heart failure events leading to death were reported in 4 studies: 3 for HeartLogic and 1 for TriageHF. See table 21 (page 82) in the EAR.

The 3 studies for HeartLogic report an increased hazard for HF-related mortality when IN alert compared with OUT of alert. These results were statistically significant.

The EAG concluded from the evidence in the 1 study for TriageHF that a TriageHF high-risk alert was not a statistically significant predictor of mortality.

All-cause related mortality

All-cause events leading to death were reported in 4 studies, 2 for HeartLogic and 2 for TriageHF. See table 22 (page 86) in the EAR.

One study for HeartLogic, D'Onofrio (2023, n=568), found a statistically significant increased risk of death for those IN alert compared with OUT of alert ($p<0.001$). Additionally, increased risk of death was present for having at least one HeartLogic alert and the time spent IN alert.

For TriageHF, Ahmed (2022, n=439), showed a greater likelihood of death when at high risk compared with not being at high risk (odds ratio=3.07, $p=0.002$). The other study reporting on this outcome, Zile (2020), found a statistically significant increased hazard ratio for patients in high and medium risk vs low risk.

2.4 Comparative outcomes

Evidence was sought to compare use of the interventions to standard care (no algorithm use).

Rate of heart failure events

HeartLogic:

- Feijen (2023, n=161) reported a statistically significant reduced number of HF events in HeartLogic patients compared with propensity-matched controls receiving conventional remote monitoring. The HeartLogic group had a median of 1 HF event while the control group had a median of 2 HF events ($p=0.004$).

Hospitalisation

HeartLogic:

- Feijen (2023, n=161) reported a non-statistically significant difference between the number of patients being admitted to hospital, when comparing those with and without the HeartLogic algorithm ($p=0.096$).

- Treskes (2021) compared pre- to post-activation of the HeartLogic algorithm, reporting a statistically significant reduction in HF related hospitalisation once the algorithm was turned on (p=0.005).
- Chang (2020, n=140) compared pre- to post-activation of HeartLogic, reporting less hospitalisation post activation in the HeartLogic group (not statistically significant).

TriageHF:

- Ahmed (unpublished, n=758) reported an incidence rate ratio (IRR) for hospitalisation of 0.42 (95% CI: 0.23 to 0.76) when comparing people with the TriageHF algorithm with people without the TriageHF algorithm. This indicates that there were fewer hospitalisations in the algorithm group than the comparator group.

CorVue:

- Shapiro (2017, n=758) compared CorVue to a control group in which patients had no implanted device, but were receiving home health care (n=120). Those with a CorVue enabled device were less likely to be hospitalised compared with those without the algorithm (p<0.001).

Length of hospital stay

HeartLogic:

- Treskes (2021, n=68) reported a non-statistically significant difference in the number of days in hospital pre-activation (mean = 16, SD = 14) compared with post activation (mean = 7, SD = 5; p = 0.079).
- Feijen (2023, n=161) reported the length of hospital stay as being statistically significantly longer for those without the HeartLogic algorithm (median number of days = 8, IQR: 5-12) compared with those with the HeartLogic algorithm (median number of days = 5, IQR: 2-7; p = 0.025).

Number of emergency or urgent care visits

- Treskes, (2021, n=68) compared pre and post activation of the HeartLogic algorithm, observing no statistically significant differences in the number of clinic or ambulatory visits.

- Feijen (2023, n=161) compared patients with a HeartLogic algorithm to patients receiving conventional remote monitoring. A statistically significant reduction in clinic visits (p=0.0001) for patients with the HeartLogic algorithm was reported.

2.5 Implementation outcomes

Time between an alert and a heart failure event

HeartLogic:

- Ebrille (2021) reported that the median time between crossing the alert threshold and a HF clinical event was 11 (IQR: 2 to 19) days.
- De Ruvo (2019) reported the median number of days for an early warning of hospitalisation (median = 38 days) and clinical visits (median = 12 days).
- Calo (2021) reported that the median time between an alert onset to a HF event was 29 (IQR: 4 to 83) days.
- Lerman (2023) reported the median number of days from the first sensor alert to first hospitalisation was 145 (IQR: 1 to 380) for all causes, 63 (IQR: 26 to 229) for HF related, and 240 (147 to 497) for non-HF related.

TriageHF:

- Ahmed (2022) reported time between the last transmitted risk status alert and death. The median time from the high-risk status to death was 111 (IQR: 57-226) days. The time between last maximum recorded risk and death was 233 (IQR: 91-390) days.

Software failure rate

HeartInsight:

- D'Onofrio (2022) reported 39 of 918 patients (4.2%) had connection issues for home monitoring remote transmissions because they could not establish sufficient GSM (Global System for Mobile communication) coverage.

HeartLogic:

- Hernandez (2022) reported that alerts not generated were caused by the home communicator not being powered or not being able to send data, the patient being out of range, or the alert threshold was adjusted from nominal. Of the total 3290 weekly alerts, 2934 (89%) were communicated to the sites (median delivery time <1 day, max 129 days), 2894 (88%) were documented as received by sites.

TriageHF:

- Ahmed (2022, n=439) reported that if a patient fails to record a transmission within a 425-day window, data is lost. It was reported that 36 patients had 45 episodes over 65 days that were not transmitted. Debski (2020) reported that 130 (33%) episodes were not transmitted within 30 days of the final day of a high-risk status.

Number of monitoring reviews

TriageHF:

- Ahmed (2022) reported the average minutes per week call time (hospital 1: 13.5 mins; hospital 2: 12.9 mins; hospital 3: 18.2 mins) and workload (hospital 1: 25.3 mins; hospital 2: 24.2 mins; 46.9 mins) associated with using the TriageHF plus care pathway.

HeartLogic:

- Calo et al. reported that of 273 alerts 204 did not require extra in-office visits and were managed remotely. Of the 69 in-office visits, 42 were scheduled examinations that were previously planned (within 7 days of the alert). The median number of phone contacts per alert period was 1 (IQR: 1-2).
- De Juan Baguda et al. reported most alerts were managed remotely. Patient phone contacts during phase 2 was 35 (0.65 contacts per patient year) and during phase 3 was 287 (1.12 contacts per patient year).

2.6 Ongoing studies

The EAG identified 5 potentially relevant ongoing studies from searches of international clinical trial registries. All studies are in a heart failure population.

Table 8 Ongoing studies

Study details	Intervention	Study design	Estimated completion date	Primary Outcome
NCT0357964 (2018) USA, Australia, Canada, China, Europe, UK	HeartLogic	Prospective	Results submitted Dec 2023 (not yet published)	Association of HeartLogic sensors with 30-day HF re-admission
NCT04619888 (2020) France	HeartLogic	Prospective	July 2023	Annual rate of unplanned hospitalisations for heart failure
Garcia, (2022) France	HeartLogic	Cohort	Jan 2027	Unscheduled hospitalisation for heart failure
NCT04489225 (2020) USA, Europe, Switzerland and the UK.	TriageHF	Prospective	Sept 2027	Positive predictive value of HFRS High Risk Status associated with worsening heart failure
NCT05761249 (2023)	HeartInsight	Prospective	Unknown	Rate of worsening heart failure hospitalization after HeartInsight activation

3 Cost effectiveness evidence

The external assessment group (EAG) did a systematic review to identify any published economic evaluations of algorithm-based remote monitoring of heart failure data in people with cardiac implantable electronic devices (CIEDs). The EAG also reviewed a model submitted by Medtronic for the TriageHF algorithm and constructed a de novo economic model to assess the cost effectiveness of algorithm-based remote monitoring of heart failure data in people with CIEDs.

3.1 Systematic review of cost-effectiveness evidence

In the review, 5 Markov model studies were identified as relevant by the EAG. Additionally, 1 study comparing the clinical and economic impacts of HeartLogic in a group of patients before and after HF algorithm activation (Treskes et al., 2021) was included.

Only 1 of the 5 Markov model studies named the intervention (Burri et al., 2013). Burri et al. assessed the non-algorithm-based version of the HeartInsight technology. This study is a cost–consequence analysis of daily continuous remote monitoring of implantable cardiac defibrillator and resynchronization devices in the UK. Based on the univariate sensitivity analysis, remote monitoring was found to be cost saving in the base case and 6 other scenarios. None of the 5 included Markov model studies included an algorithm-based intervention. The EAG commented that the results were therefore only useful for the development of the de-novo economic model, including structure, outcomes, model cycles and parameters.

Treskes et al. (2021, n=68) evaluated the clinical and economic impact of HeartLogic compared with standard care in HF patients. The number of patients hospitalized because of HF event declined from 21 (pre-activation) to 7 (post activation) (p= 0.005), and the hospitalization length of stay reduced from average 16 to 7 days (p= 0.079). There was a substantial drop in

average total costs per patient including and excluding deceased patients respectively.

Additional searches

Utility of remote monitoring systems in heart failure

The EAG did a search focussed on utilities. They identified 3 studies which reported on utility values and quality-adjusted life year (QALY) estimates of using remote monitoring, with 12-16 months follow-up. QALYs in the standard care arm ranged from 0.85 to 5.65 across the studies, and QALYs in the remote monitoring arm ranged from 0.87 to 6.29. See table 30 (page 120) in the EAR for full detail of these studies.

Resource use of remote monitoring systems in heart failure

A search for studies evaluating resource use was done, with 4 papers being identified which compared the costs of using remote monitoring with standard care practice in different countries. No UK-specific studies were identified. These studies show that remote monitoring generally resulted in fewer follow-up visits and hospitalisations, and also reduced overall costs.

3.2 Company submission

The EAG considered a model submitted by Medtronic on the TriageHF algorithm. The EAG concluded that they adopted the same model structure as Medtronic in their de novo model. The EAG noted that the Ahmed et al. study underpinning the Medtronic model was found to have a critical risk of confounding and the study did not report enough detail to allow an assessment of all potential biases. A number of inputs used in the EAG's de novo model (in both the base case scenario and scenario analysis) were taken from the Medtronic company submission. See section 5 (page 123) of the EAR for full detail of the Medtronic company submission.

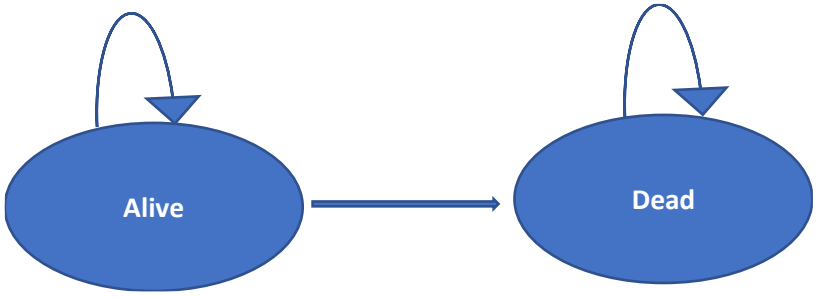
3.3 De novo economic analysis

The EAG developed a de novo economic model to estimate the cost-effectiveness of algorithm-based remote monitoring of heart failure data in people with CIEDs. The interventions evaluated in the model were CorVue, HeartInsight, HeartLogic and TriageHF. For full details, see section 6 (page 126) of the EAR.

Model structure

The model uses a cohort Markov structure with alive and dead states, modelling costs and outcomes for each intervention over a lifetime horizon (Figure 1). The base case assumption for age in the model is 60 years old, and 72.2% of the patients in the model were assumed to be male. After each monthly cycle, the hypothetical cohort of patients remained in the state "Alive" or transitioned to the state "Dead" (absorbing state) according to the probability of death assigned for each monthly cycle. In each cycle, the patients who were alive experienced an average number of monthly hospitalisations, follow-up visits, and days in hospital. Each patient then accrued lifetime QALYs and healthcare costs according to the model state they were in. Costs and benefits in the model were discounted at a rate of 3.5% per year.

Figure 1 Model structure



Mortality rates, risk of hospitalisation, clinic visits (scheduled and unscheduled) and length of stay (LoS) per hospitalisation differ by technology and are independently modelled. Where there is evidence on the difference in outcomes with and without remote monitoring, the cost-effectiveness of

remote monitoring is estimated. Where there was no evidence on an outcome difference, either no difference for that outcome is assumed or different scenarios were modelled. If remote monitoring is not cost-effective in a conservative scenario, then threshold analysis was done on those outcomes to identify the effectiveness required for the technology to be cost-effective at thresholds recommended by NICE.

Population

The patient population considered in the model is people implanted with one of the named CIEDs in the scope of the assessment, who have previous experience of heart failure or are at risk of new onset heart failure.

Comparator

The comparator was standard care (one of the CIEDs in the scope of the assessment without remote monitoring).

Clinical model inputs

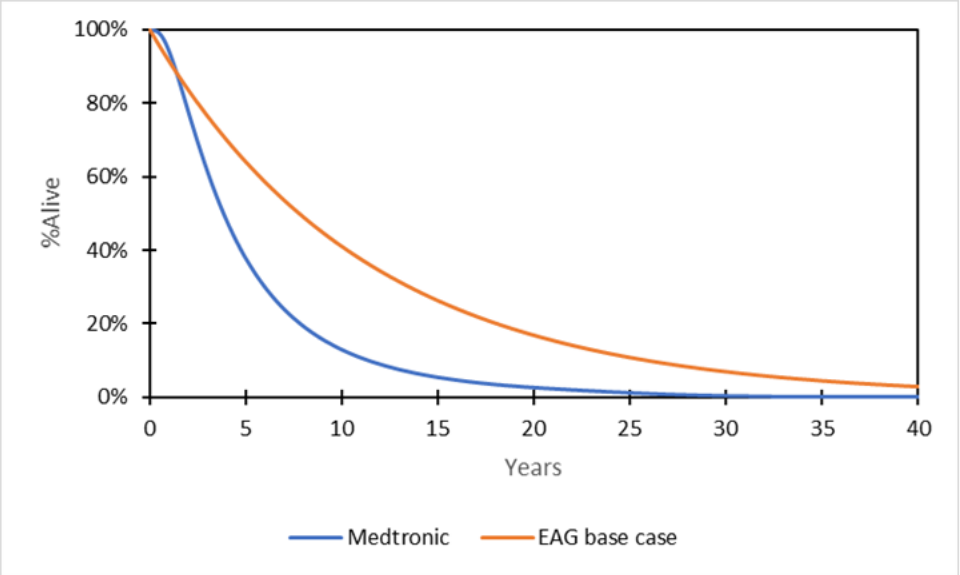
Find the full list of base case model parameters in table 42 (page 141) of the EAR.

Mortality

No comparative evidence was identified for mortality for any of the interventions. Mortality rates for patients with CIEDs were therefore assumed to be the same with and without algorithm-based remote monitoring.

The base case mortality rate in the model was assumed to be 36% at 5 years (Bottle et al. 2021). The survival curve used by Medtronic was used in scenario analysis of the EAG's model. Medtronic selected the log-normal parametric model because it showed the most appropriate external validity based on a study by Taylor et al. This survival curve assumes that survival rates were 81% at 1 year, 48% at 5 years and 26% at 10 years. See Figure 2.

Figure 2 Survival curves used in the EAG model and Medtronic model



Hospitalisation

See Table 9 for full detail of the hospitalisation rates used in the EAG model.

For TriageHF, the average number of hospitalisations per person-year ([redacted]) for the comparator (no HF algorithm) was obtained from the unpublished TriageHF Plus study. This average number of hospitalisations for the comparator was multiplied by the incidence rate ratio (IRR) of 0.42 to give the average number of hospitalisations in the intervention arm, giving a value of [redacted] per person-year. This study was assessed at critical risk of bias because of confounding.

For HeartLogic, the average number of hospitalisations per person-year for both the comparator and HeartLogic groups was obtained from Treskes et al. For the comparator group, this was reported to be 0.39 (SD = 0.08). The average number of hospitalisations per person-year for the HeartLogic group was reported to be 0.11 (SD = 0.04). This study was assessed at serious risk of bias because of confounding.

No evidence that could be used in the model for the average number of hospitalisations per person-year was reported for CorVue or HeartInsight. For the comparator, the average number of hospitalisations per person-year was

assumed to be the average of the rates for TriageHF and HeartLogic ([redacted]). In the base case scenario for CorVue and HeartInsight, a conservative assumption was made of no difference in hospitalisation between the intervention and comparator groups. Threshold analysis was used to determine the IRR for hospitalisation that would result in these interventions being cost effective.

Table 9 Rates of hospitalisation in the base case

Remote monitoring system	Average number of hospitalisations per person-year (base case)		Incidence rate ratio
	Comparator	Intervention	
CorVue	[redacted]	[redacted]	1
HeartInsight	[redacted]	[redacted]	1
HeartLogic	0.39	0.11	0.282
TriageHF	[redacted]	[redacted]	0.42

Follow-up visits

No evidence was identified in the systematic review on follow-up visits for the comparator (without remote monitoring) or any of the interventions (with algorithm based remote monitoring). Pan-European data in Heidbuchel et al. identified in the focused review reported 2 scheduled follow-up visits per year in the group without remote monitoring, giving a monthly scheduled follow-up rate of 0.17 visits. This rate was used in the base case for the comparator arms and all intervention arms.

Unscheduled visits were modelled as the number of alerts of people who are high risk. All alerts are reviewed, and it is assumed that high-risk cases have a follow-up visit. Heidbuchel et al. reported 0.31 unscheduled visits over 1 year for the comparator group, giving a monthly rate of 0.026 unscheduled visits. This rate was used in the model for the comparator arms and any interventions without data on this outcome, namely CorVue and HeartInsight.

For TriageHF and HeartLogic, unscheduled visits were modelled as the number of alerts of people who are high risk. For TriageHF, 1 study (Ahmed et al.) reports an annual high-risk alert rate of [redacted] (monthly rate of [redacted]

assumed in the base case). In the TriageHF company model, [redacted]% of high-risk alerts had an initial consultation, and [redacted]% had a second consultation. In the EAG's model, this is modelled as 100% of high-risk alerts having 1 in-office consultation, which is roughly the same cost.

For HeartLogic, an annual alert rate of 0.71 (monthly rate of 0.0592) was used in the base case (Santobuono et al., 2023). In the base case it was assumed, the same as for TriageHF, that [redacted]% of alerts and had an initial consultation, and [redacted]% of alerts had a second consultation (100% of alerts have 1 in-office consultation).

To account for the possibility of a proportion of unscheduled follow-up visits taking place remotely, the following scenarios were tested:

- Assuming that 50% of alerts have 1 in-office consultation, and 25% have a phone call review.
- 50% of alerts have an in-office consultation and 50% have non-face-to-face contact
- Using evidence from De Juan Baguda et al. (2021): 19% of the alerts in the intervention group require in-office follow-up visits and 81% of the alerts only require non-face to-face contact.

Further scenarios were tested in which other combinations of scheduled and unscheduled visits were used in the model, to allow for different scenarios regarding the degree to which the technology displaces current monitoring practice. Scheduled visits in the HF algorithm arm were tested assuming 1 and 0 visits per year (instead of the 2 visits assumed in the base case). Unscheduled visits were tested assuming 2 times and 4 times the number of unscheduled visits assumed in the base case. See Table 10.

Table 10 Follow-up visits in the model

Intervention	Average follow-up visits per year	
	Comparator	Intervention

CorVue	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled: 0.31 (base case), 0.62, 1.24
HeartInsight	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled: 0.31 (base case), 0.62, 1.24
HeartLogic	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled: 0.71 (base case), 1.42, 2.84
TriageHF	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled: [redacted] (base case), [redacted], [redacted]

Length of stay

Evidence for a difference in length of hospital stay between remote monitoring and standard care was only identified for HeartLogic. Base case values for HeartLogic were obtained from Treskes (2021), in which length of stay per hospitalisation event was reported as 16 days for the comparator and 7 days for HeartLogic. Alternative lengths of stay in hospital were obtained from Feijen (2023), which reported 8 days in the comparator group and 5 days in the HeartLogic group (used in scenario analysis).

For all interventions other than HeartLogic, the length of stay for both the intervention and comparator was assumed to be the same as the length of stay in the comparator group in the HeartLogic study (16 days). See Table 11.

Table 11 Length of hospital stay in the model

Intervention	**Length of stay per hospitalisation event (days)**	
	Comparator	**Intervention**
CorVue	16	16
HeartInsight	16	16
HeartLogic	16 (base case)	7 (base case)
	8 (scenario analysis)	5 (scenario analysis)
TriageHF	16	16

Adverse events

No adverse events were considered in the model because none of the studies in the systematic review reported any adverse events directly linked to the use of the algorithm based remote monitoring systems for each of the CIEDs.

Health-related quality of life

HF population utilities in sub-groups of New York Heart Association (NYHA) class were obtained from Griffiths et al. To ensure that the utility estimates for the heart failure population did not exceed that of the general population, the utility value for a UK general population (0.84) was subtracted from HF population utilities in sub-groups of NYHA class to derive utility decrements for each NYHA class. The weighted average utility decrement for the HF population was calculated using the percentage of patients in each NHYA class, obtained from the Medtronic submission (Table 12).

Utility decrements were also applied for hospitalisation events. Utility decrements for hospitalisation by NYHA class were obtained from Griffiths et al. Weighted averages were calculated using the NYHA class distribution from the Medtronic submission (Table 13). HF utility decrements were applied to HF population alive at each model cycle, however hospitalisation decrement was only applied to the proportion hospitalised in each cycle.

Table 12 Heart failure utility decrements

Heart failure subgroup	Population (%)	Mean utility	Population utility	Derived utility decrement
Undiagnosed	8.7%	0.82	0.84	-0.02
NYHA class I	20.8%	0.82		-0.02
NYHA class II	43.3%	0.74		-0.11
NYHA class III	26.6%	0.64		-0.20
NYHA class IV	0.5%	0.46		-0.39
Weighted average heart failure utility decrement				-0.107

Table 13 Hospitalisation utility decrements

Heart failure subgroup	Derived utility decrement
Undiagnosed	-0.040
NYHA class I	-0.040

NYHA class II	-0.070
NYHA class III	-0.100
NYHA class IV	-0.290
Weighted average hospitalisation utility decrement	-0.070

Estimating absolute utility decrements for both HF and hospitalisations could result in lower QALY gains from the intervention. Scenario analysis was done where the relative utility decrements were used (instead of absolute values) to assess the impact on QALYs of the approach taken in estimating the utility decrement from HF and hospitalisations. In this case, the utility decrement is described as a percentage of the general population age-related utility.

Costs

Find the full list of costs used in the model in section 6.6 (page 134) of the EAR.

Remote monitoring system costs

The remote monitoring system costs were based on information submitted to NICE by companies (Table 14). These were variable because of the heterogeneity in devices and associated maintenance costs. The following components were included:

- Costs of the remote monitoring device for each patient
- Maintenance/consumable costs.

Table 14 Remote monitoring system costs

Intervention	Cost (excluding VAT)	Unit	Modelled cost
CorVue	Free of charge with the device; no additional maintenance or consumables costs	One-off	£0
HeartInsight	£450/patient; no additional maintenance or consumables costs	One-off	£450 per patient
HeartLogic	£3,650/patient no additional maintenance or consumable costs	One-off	£3,650 per patient
TriageHF	£100/patient/year; no additional maintenance or consumable costs	Yearly	£8.33 per month per patient

Implementation costs

The implementation costs considered in the economic model were staff training time and staff time needed to review and respond to remote monitoring system alerts. Staff time was based on information submitted to NICE by companies (Table 15) and the cost of hospital-based band 6 physiologist taken from PSSRU (£53 per hour; Table 16).

Table 15 Staff time for training and responding to alerts

Intervention	Staff time for training	Staff time to respond to 1 alert
CorVue	30 minutes	5 minutes to read an alert and evaluate the diagnostic trend data
HeartInsight	1 hour	20 minutes per case; 40 minutes for complex cases; average 30 minutes
HeartLogic	1 hour (assumed)	5 minutes to review an alert plus 10-20 minutes to action an alert; average 20 minutes
TriageHF	1 hour (assumed)	30 minutes per week

Table 16 Costs for staff training and responding to alerts

Intervention	Number of alerts / patient / year	Cost of staff training time (one-off)	Cost of staff time to respond to an alert (monthly)
CorVue	0.31	£26.50	£0.11
HeartInsight	0.31	£53	£0.69
HeartLogic	0.71	£53	£1.31
TriageHF	[redacted]	£53	[redacted]

Hospitalisation

The same unit cost estimate of hospitalisation was used for the comparator in each of the pair wise comparisons (£3,758.18). This was based on the weighted average of the costs for the Healthcare Resource Group (HRG) 'Heart Failure or Shock' (EB03A-EB03E) based on the Non-Elective Inpatient-Long Stay data obtained from NHS reference costs. Weighted average of the costs (£666.43) for the HRG 'Heart Failure or Shock' based on the Non-Elective Inpatient Short Stay data was used in a scenario analysis.

Length of stay

For HeartLogic, for which there was evidence for a difference in length of stay, the cost of an extra day in hospital (£290) was multiplied by the difference in days and this was subtracted from the comparator cost of hospitalisation to determine the cost of hospitalisation for the intervention.

Follow-up visits

It was assumed that both scheduled and unscheduled follow-up visits have the same unit cost (£169). This was based on an outpatient attendance for cardiology services (both consultant led, and non-consultant led; service code: 320) from the NHS reference costs.

For the scenario analyses, where non-face-to-face follow-up contacts are modelled, the cost was £97.44 and was based on non-admitted, non-face-to-face attendance follow-up (non consultant led), for cardiology services (service code:WF01C) from the NHS reference costs.

3.4 Model results

The cost-effectiveness of each of the 4 included CIEDs with an algorithm based remote monitoring system compared with the same device without the algorithm-based remote monitoring system was evaluated. The analyses undertaken varied by technology according to the availability of comparative evidence on outcomes. The full list of base case analyses is available in table 41 (page 139) in the EAR.

Comparative evidence was sought for hospitalisation rates, follow-up visits, mortality, and length of stay. Hospitalisation was selected as the most important outcome, followed by follow-up visits, then mortality, and finally length of stay. This hierarchy was set to define the model scenarios and analyses undertaken. For example, if comparative evidence on hospitalisation and follow-up visits were available for a technology, but no evidence on mortality or length of stay, then no difference in mortality or length of stay could be assumed.

Base case results

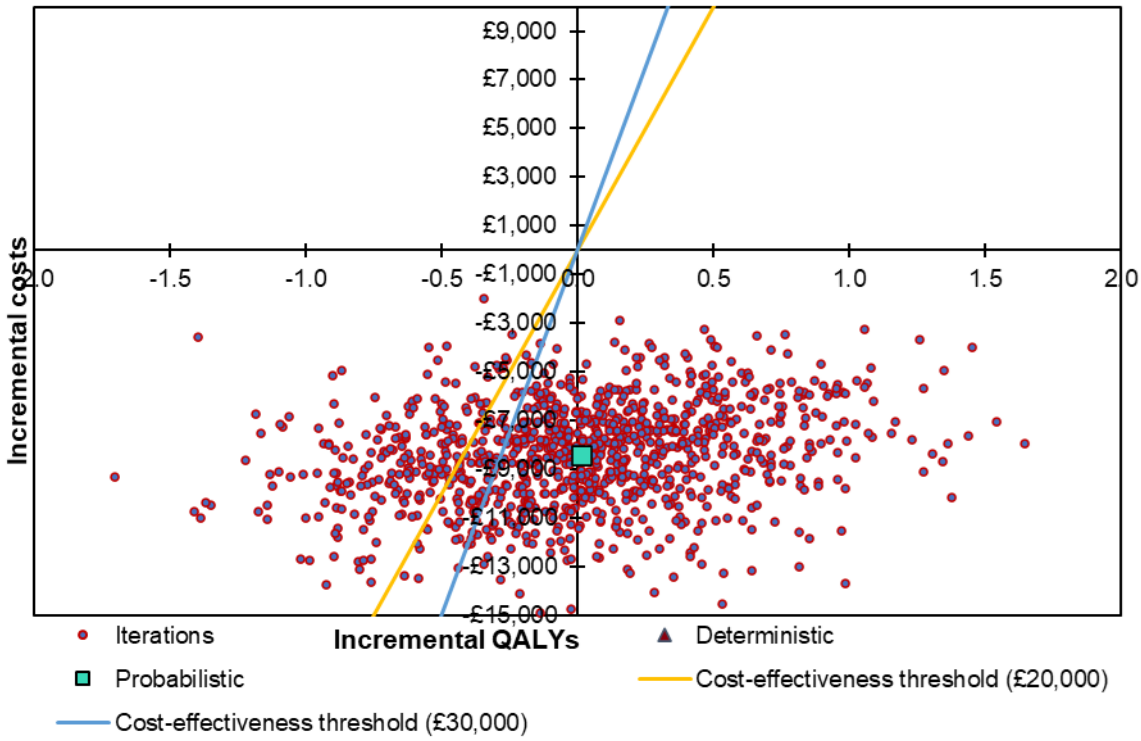
Table 17 shows the deterministic base-case results for each intervention and comparator in the pairwise analysis. Both HeartLogic and TriageHF were dominant (that is, less costly and more effective than the comparator). It can also be seen that there are lower hospitalisations per person and shorter length of hospital stay for the HeartLogic and TriageHF groups. There are also more unscheduled visits associated with these algorithm groups. When a confidential discounted price for HeartLogic was assumed in the model, the results show that HeartLogic still appears dominant.

For the base-case scenario assuming no difference in hospitalisations, CorVue and HeartInsight were cost increasing because of the cost of the remote monitoring technology and reviewing alerts. A summary of the cost breakdown in the base case cost-effectiveness analysis is available in table 45 (page 151) of the EAR.

Probabilistic results

Probabilistic sensitivity analysis (PSA) was done for the HeartLogic and TriageHF interventions, for which there was evidence of effectiveness (Table 18). The PSA results are similar to the deterministic results, with HeartLogic and TriageHF appearing dominant.

The cost-effectiveness plot for HeartLogic is shown in Error! Reference source not found.**Figure 3: Cost-effectiveness plane for HeartLogic**



. All iterations sit in either the south-east or south-west quadrants of the plane, indicating that the intervention is either less costly and more effective, or less costly and less effective than the comparator. The cost-effectiveness acceptability curve (CEAC, **Error! Reference source not found.**) shows that the probability of HeartLogic being cost-effective at a threshold of £20,000 was 81% whereas at £30,000 the probability of cost-effectiveness was 73%. When a confidential discounted price for HeartLogic was assumed in the model, the results of the PSA were similar.

The cost-effectiveness plot for TriageHF is shown in Figure 5, with all iterations sitting in either the south-east or south-west quadrants of the plane. The CEAC (

Figure 6) shows that the probability of TriageHF being cost-effective was 85% at a threshold of £20,000 and 76% at a threshold of £30,000.

Table 17 Deterministic base-case results

Intervention	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER	Incremental hospitalisations	Incremental length of stay	Incremental unscheduled visits
CorVue	17855	5.83	37	0	Cost Increasing	0	0	0
Comparator	17848	5.83	-	-	-	-	-	-
HeartInsight	18415	5.83	568	0	Cost Increasing	0	0	0
Comparator	17848	5.83	-	-	-	-	-	-
HeartLogic	9349	5.84	-8400	0.01	Dominant	-3.05	-59.58	4.34
Comparator	17748	5.83	-	-	-	-	-	-
TriageHF	11665	5.84	-9048	0.01	Dominant	-3.66	-59	1.31
Comparator	20712	5.82	-	-	-	-	-	-

Table 18 Probabilistic sensitivity analysis results

Intervention	Costs (£)	QALYs	Incremental Costs (£)	Incremental QALYs	ICER	Incremental hospitalisations	Incremental length of stay	Incremental unscheduled visits
HeartLogic	9354	5.84	-8437	0.013	Dominant	-3.06	-60	4.33
Comparator	17790	5.83	-	-	-	-	-	-
TriageHF	11674	5.84	-9183	0.02	Dominant	-3.71	-59	1.31
Comparator	20857	5.82	-	-	-	-	-	-

Figure 3: Cost-effectiveness plane for HeartLogic

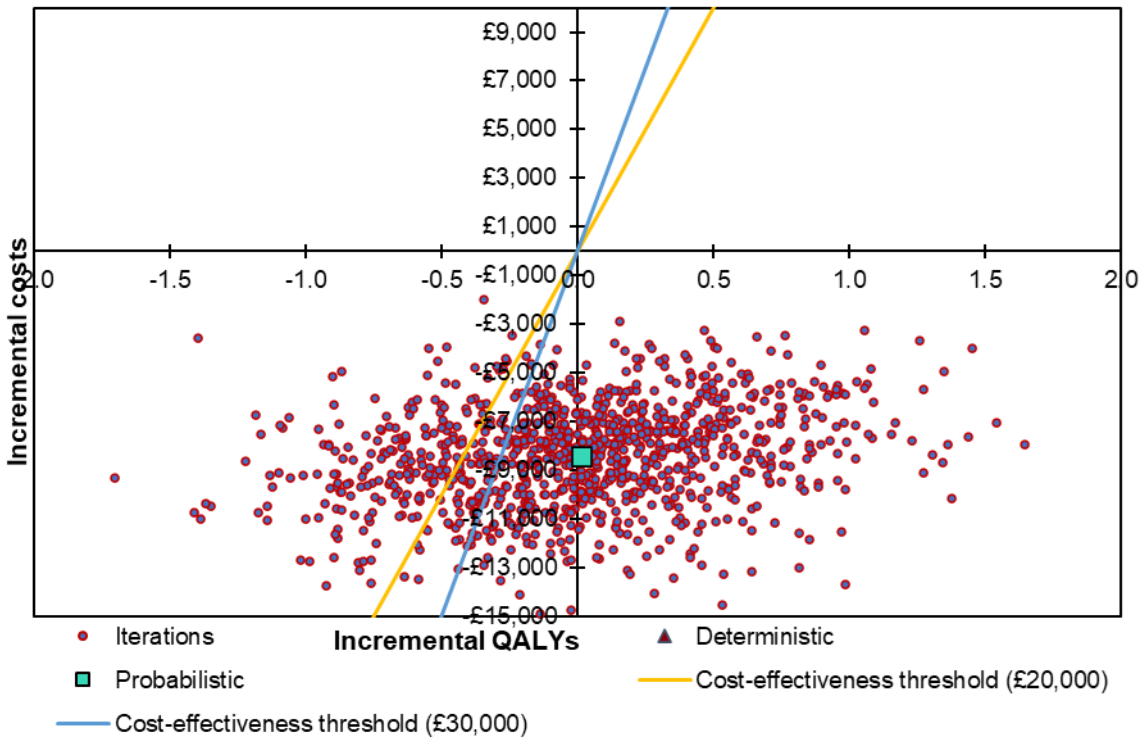


Figure 4 Cost effectiveness acceptability curve for HeartLogic

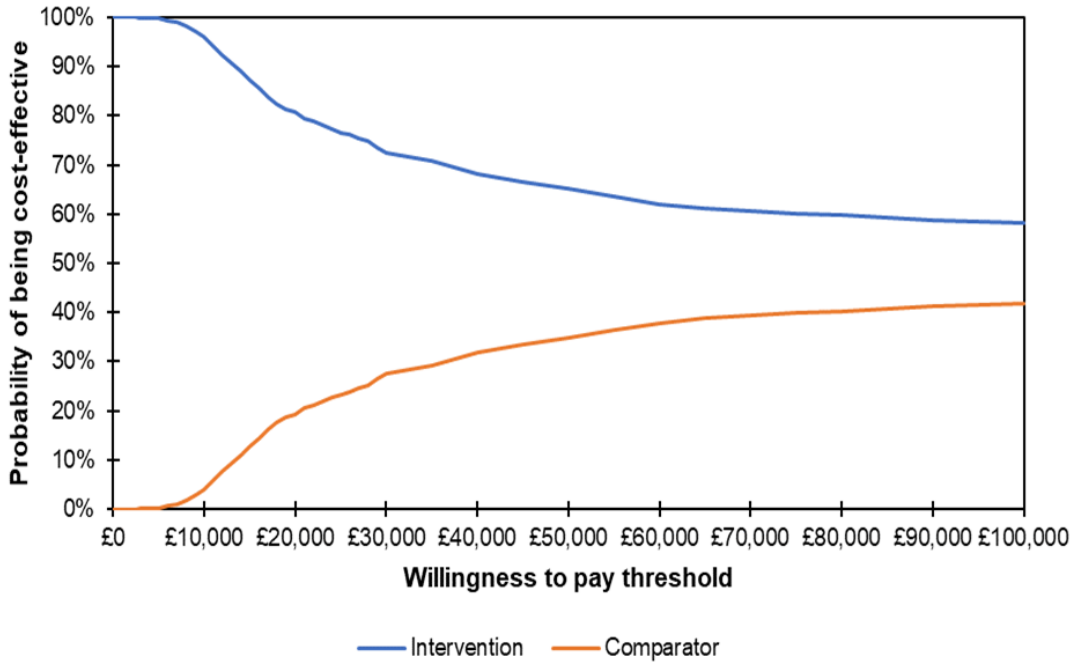


Figure 5 Cost effectiveness plane for TriageHF

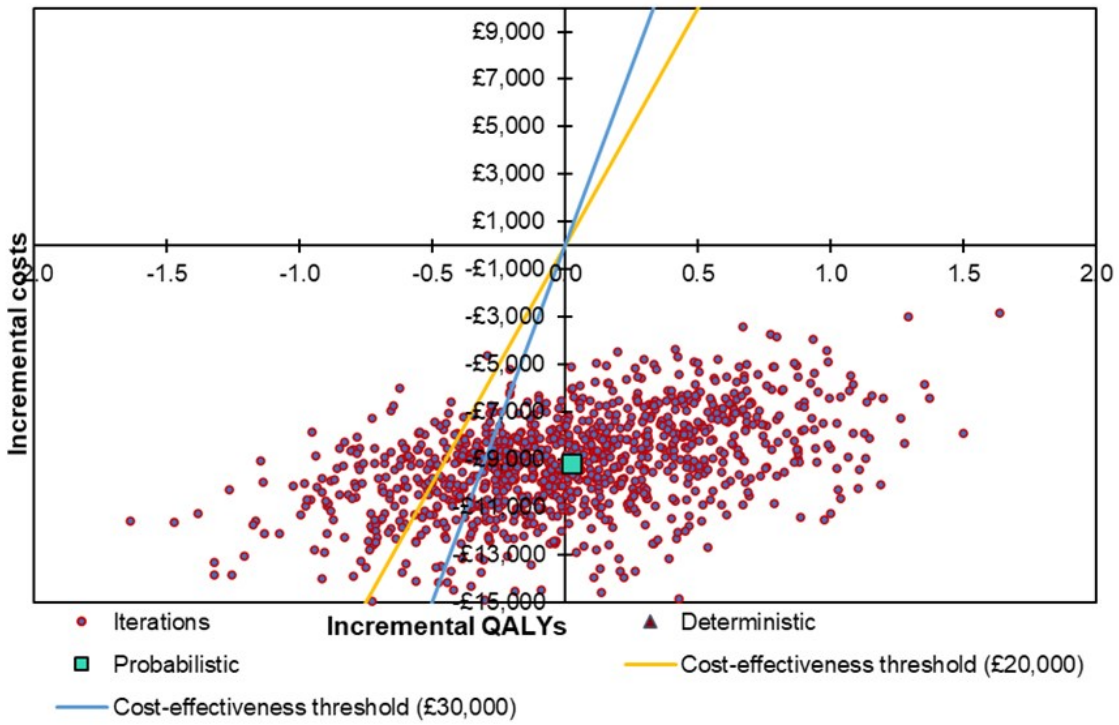
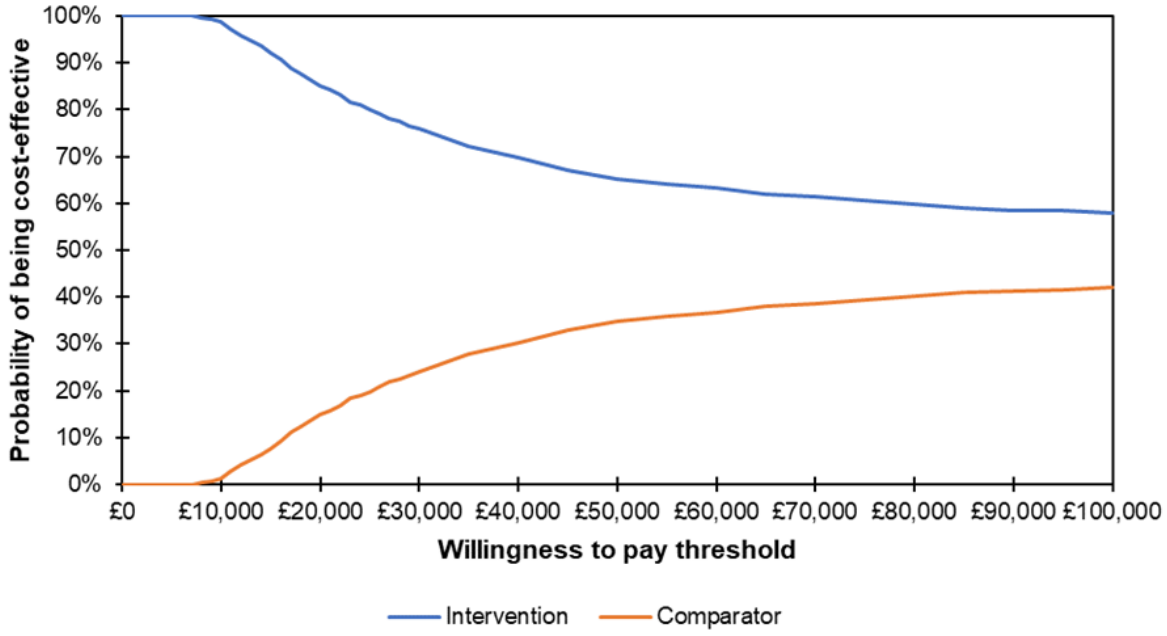


Figure 6 Cost-effectiveness acceptability curve for TriageHF



Threshold analysis

Threshold analysis was done on the incidence rate ratio (IRR) of hospitalisation for CorVue and HeartInsight, in the absence of hospitalisation

outcome evidence. The IRR was reduced (the rate of hospitalisation of the intervention reduced) until the incremental cost-effectiveness ratio (ICER) of the technology became lower than £20,000/QALY. The value of the IRR at which the ICER threshold of £20,000/QALY is crossed gives the minimum effectiveness required of the intervention for it to be cost-effective at that threshold. For the base case scenarios for CorVue and HeartInsight, threshold analysis showed that IRRs for hospitalisation below 0.99 and 0.96 respectively would make these interventions dominant (that is, less costly and more effective than the comparator).

Secondary scenario analysis

HeartLogic and TriageHF remained dominant for all combinations of the number of scheduled and unscheduled visits in the HF algorithm arm that were tested in scenario analysis. These interventions will be cost saving as long as the reduction in the number of scheduled visits is greater than additional unscheduled visits.

In the scenarios where unscheduled follow-up visits in the intervention group were doubled or quadrupled, CorVue and HeartInsight remained cost increasing. Threshold analysis for these scenarios show that an IRR of hospitalisation below 0.91 and 0.87 respectively would make these interventions dominant. When scheduled follow-up visits in the intervention arm were assumed as 1 or 0 per year (that is, lower than the 2 visits assumed for the comparator), CorVue and HeartInsight were cost saving.

Sub-group analysis

There was evidence available on hospitalisation IRR for ICT, CRT-P and CRT-D for TriageHF, which was obtained from the company submission. The IRR of hospitalisation varied from [redacted] to [redacted]. The EAG noted that these differences will have no effect on the cost-effectiveness results for TriageHF.

There was no evidence on hospitalisation IRR for patients with a CIED without a diagnosis of chronic heart failure. It was reported in the TriageHF Plus study that [redacted]% of the population had a prior diagnosis of heart failure.

Tertiary scenario analyses

The EAG did a variety of tertiary scenario analyses which can be found in table 47 (page 155) of the EAR. The scenarios tested were:

- length of stay in the intervention equal to that of comparator in the base case
- lower hospitalisation costs (£666.43)
- higher costs of staff time (£58 per hour)
- Medtronic survival rates
- increased IRR hospitalisation halfway between the base case value and 1 (for HeartLogic and TriageHF)
- doubled alert monitoring time.
- excluding uncertainty in mortality in the PSA
- calculating utility decrement as relative values instead of absolute differences
- assuming only 50% of alerts in the intervention group require in-office follow-up visits and 25% of alerts only require non-face-to-face contact
- assuming 50% of alerts are followed by in-person visits and 50% by non-face-to-face contact.

The results of most scenarios were similar to those observed in the base case analyses for all interventions. In the scenarios assuming 25% and 50% of follow-up visits required non-face-to-face contact, CorVue appeared cost saving.

4 Summary

4.1 Clinical effectiveness

Overall, the external assessment group (EAG) considers the evidence to be limited for all HF algorithms. Most evidence was derived from single cohort studies (prospective and retrospective) that lacked a comparator group. Such studies give an indication of the prognostic ability of the algorithms.

Evidence for the accuracy of CorVue showed low sensitivity, while specificity was not generally reported. False positive rates were high in most studies. There was limited association data regarding the risk of a heart failure (HF) event. Some evidence suggested low hospitalisation rates when in high-risk alert. There was 1 comparative study, a retrospective medical chart review of hospitalisations. This study showed that those with a CorVue enabled device were less likely to be hospitalised compared with those without the algorithm.

For HeartInsight only 1 published study was identified, which showed adequate sensitivity and specificity for HF events and a significant association between increased risk score and HF related hospitalisation. False positive rates were moderate in this study. No evidence was identified that compared use of HeartInsight with no algorithm use. The EAG noted that HeartInsight is the only algorithm-based remote monitoring system that provides daily transmissions, whereas the other technologies occur less frequently.

HeartLogic was associated with adequate to high sensitivity and specificity for the prediction of HF events, and false positive rates were considered to be low. There is evidence for an association of greater risk between being IN alert compared with OUT of alert of HF events. There was a numerical trend towards reductions in HF events when using HeartLogic compared with no algorithm use, but these were not always statistically significant. Of the 3 studies which included comparative data for HeartLogic compared with no algorithm, 2 are considered at serious risk of bias, and 1 at critical risk of bias.

There was substantial heterogeneity in TriageHF prognostic accuracy measures, estimates of sensitivity and specificity varied widely between studies. There is evidence for an increased risk of HF events when in high-risk status compared with low-risk status with TriageHF. There was 1 study comparing TriageHF with no algorithm, providing data on hospitalisations in a UK setting. However, this study was assessed as having critical risk of bias.

The EAG noted that HeartLogic and HeartInsight are only available on ICD and CRT-D cardiac implantable electronic devices (CIEDs). TriageHF and CorVue are available on ICD, CRT-D and CRT-P CIEDs. Currently, only CRT-P CIEDs are recommended for those with NYHA class IV HF.

4.2 Cost effectiveness

The model structure captured the key costs and outcomes associated with HF algorithms given the available evidence. There may be other benefits associated with the use of algorithms that are not included in the model, but there was limited evidence on these other potential benefits. There was some evidence on hospitalisation, follow-up visits and length of stay outcomes for HeartLogic and TriageHF that could be used in the EAG's economic model. However, this evidence was at risk of bias because of confounding. Making assumptions of no difference in mortality and scheduled follow-up visits, HeartLogic and TriageHF were dominant over standard practice (that is, they were cost saving and increased QALYs). These interventions remained dominant in all scenario analyses.

For HeartLogic and TriageHF, the outcome evidence was based on patients with a CIED who had had a diagnosis of HF. Consequently, the cost-effectiveness estimates are applicable to that subgroup. There was clinical evidence for different CIEDs in the evidence submission by Medtronic for the TriageHF algorithm. The variation in effectiveness estimates was very small across the CIEDs.

There was no evidence on hospitalisation, mortality, and follow-up visits or length of hospital stay for CorVue or HeartInsight. Consequently, no estimate of the cost-effectiveness of CorVue or HeartInsight could be produced. Making assumptions of no difference in hospitalisations, mortality, scheduled and unscheduled follow-up visits and length of stay, CorVue and HeartInsight were cost increasing compared with standard practice. Given the much larger cost of a hospitalisation compared with other costs in the model, the technologies only need to reduce the rate of hospitalisation by a very small amount (1 to 4%) for them to become cost-effective in the EAG model. In the scenario assuming 50% alerts require in-office follow-up visits and 25% require non-face-to-face contact, CorVue was cost-saving.

4.3 Issues for consideration

Population

It was only possible to estimate the cost-effectiveness of the interventions in people who have a CIED and have a diagnosis of chronic heart failure. No cost-effectiveness estimate could be produced for people who have a CIED and do not have a diagnosis of chronic heart failure but are at high risk of new onset acute heart failure.

Prognostic accuracy

A number of study endpoints were used for reporting prognostic accuracy, and accuracy has been reported for different numerical thresholds and risk statuses for each of the interventions. There is heterogeneity in some of the accuracy results for the interventions, which may make it difficult to draw conclusions on whether the algorithms can accurately predict HF events.

Comparative evidence

There is limited evidence for how the algorithms perform compared with no algorithm. Furthermore, many studies did not include adjusted analyses, which could inflate the reported effectiveness of the algorithm. The EAG concluded that the primary research priority should be to do further studies

looking into the clinical impact and usefulness of the remote monitoring algorithms.

Evidence quality

Some evidence was considered to be at a serious or critical risk of bias. The cost-effectiveness estimates of HeartLogic and TriageHF are therefore based on evidence that is at risk of bias. The overall quality of the studies used to inform the economic model may impact the reliability and uncertainty within decision making.

Modelling of scheduled visits

The number of scheduled visits in the base case is 2 per year, in both the intervention and comparator arm. This assumption was informed by Pan-European data in Heidbuchel et al. In practice, not all people will receive 2 follow-up visits per year, because of resource constraints or other reasons. There were 3 different scenarios modelled for the intervention arms: 0 scheduled follow-up visits per year, 1 scheduled follow-up visit per year, and 2 scheduled follow-up visits per year (base case scenario). In each of these scenarios, the number of scheduled visits in the comparator arm remained as 2 per year. The EAG explained that a lower number of scheduled visits in standard practice was not modelled because the number of scheduled visits with an algorithm was assumed to be the same or lower than that for the comparator. Consequently, assuming there is 1 scheduled annual visit for the comparator and 0 for with an algorithm produces the same difference in cost as assuming 2 scheduled per year for the comparator and 1 with an algorithm.

Modelling of unscheduled follow-up visits

It was assumed in the base case that all alerts are reviewed, and everyone with a high-risk alert has an unscheduled follow-up visit. The EAG explained that an unscheduled visit is defined in the model as an in-office visit. In practice, alerts may be followed by a remote interaction (for example, phone call) to determine whether an in-office visit is necessary. Scenarios were tested in which a proportion of unscheduled follow-up visits were assumed to

be non-face-to-face contact. In addition, scenarios have been tested in which the base case number of interactions in the intervention arm is doubled and quadrupled.

Uncaptured benefits in the model

The model may underestimate the benefit of the algorithms because of the lack of evidence for a number of outcomes. There was a lack of comparative evidence (HF algorithm versus no algorithm use) on clinical and patient outcomes such as changes in NYHA classification of symptoms, HF mortality, quality of life and patient experience. Stakeholders commented that the main benefit of the algorithms in the model is the reduction in HF hospitalisations, yet HF hospitalisations are associated with important mortality and quality of life implications.

Digital exclusion

In order for the remote monitoring interventions to transmit data, a mobile phone app with Wi-Fi or Bluetooth technology. CorVue and TriageHF may be used with a landline connection. This may make some of the interventions unsuitable or inaccessible to some patient groups.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. The following potential equality issues are related to the condition:

- Heart failure can have a substantial and long-term adverse effect on a person’s ability to carry out normal day to day activities. Therefore, people with the condition may be covered under the disability provision of the Equality Act (2010).
- Heart failure is more common in men, people who are over 65 years old and those in lower socio-economic groups.

The following potential equality issues are related to use of remote monitoring systems:

- People with heart failure who are no longer able to drive to hospital appointments may additionally benefit from remote monitoring.
- Access to technologies for remote monitoring may be restricted in some populations because of internet or smart phone requirements. This may mean that people in rural or lower socio-economic areas could be less able to adopt remote monitoring because they may not have access to a home Wi-Fi connection or a smartphone.
- NICE guidance on chronic heart failure (NG106) highlights that serum natriuretic peptide levels can be reduced in people who are obese, have an African or African–Caribbean family background, or people having treatment with diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, angiotensin II receptor blockers (ARBs) or mineralocorticoid receptor antagonists (MRAs). The guidance recommends that measuring serum natriuretic peptide should be considered as part of a treatment optimisation protocol only in a specialist care setting for specific people. Technologies may offer an added benefit to people for whom testing for the natriuretic peptide surrogate biomarker may not be well suited. Clinical experts highlighted that in practice these tests are rarely used.
- People with cognitive or physical impairment may need a carer to assist with using the transmitter hardware for these technologies.
- Wider availability of remote monitoring may allow greater access to care for people who are less able to attend in-person appointments (because of costs associated with travel, poor public transport, time taken from work, physical impairments, or anxiety).

6 Implementation

Restricted access

Clinical experts highlighted that eligibility for the new technology will vary between people, because of compatibility issues with older devices. They also

noted that some technologies need access to the internet or mobile networks (such as 4G), which may restrict access for some people who live in rural areas. Appropriate IT infrastructure and phone services also need to be in place for both clinicians and people with cardiac implantable electronic devices (CIEDs).

Capacity constraints

Experts have highlighted that chronic understaffing of heart failure services and recent increases in the number of heart failure patients may make implementation difficult. Experts have highlighted that this may create issues in terms of capacity such as responding to alerts and managing streams of data.

Informed consent

Patient and clinical experts highlighted that it is important to have informed consent from people using the technology because they need to understand what they are getting. This could improve uptake of the technology.

Authors

Sophie Harrison (Topic lead)

Frances Nixon (Health technology assessment adviser)

7 Glossary

Incidence rate ratio (IRR)

Calculated as the incidence rate of one group (intervention group) divided by the incidence rate of another group (comparator group).

Incremental cost-effectiveness ratio (ICER)

An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect).

NICE National Institute for Health and Care Excellence

Diagnostics Assessment

Algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices
NHS organisation submission (NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	Professor Nicholas John Linker
2. Name of organisation	NHS England
3. Job title or position	National Clinical Director for Heart Disease

4. Are you (please select Yes or No):	Commissioning services for NHS England in general? ~~Yes~~ or No Commissioning services for NHS England for the condition for which NICE is considering this technology? ~~Yes~~ or No An expert in treating the condition for which NICE is considering this technology? Yes or ~~No~~ An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes or ~~No~~ Other (please specify):
5. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE NG 106 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, it is well defined.
8. What impact would the technology have on the current pathway of care?	This type of technology will help to better manage patients with heart failure, however, there is concern that this may increase health inequalities.

The use of the technology

9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is already in use in the NHS and is similar to technology developed by other CIED (cardiac implantable electronic device) manufacturers.
10. How does healthcare resource use differ between the technology and current care?	This will help, to a degree, to ease some workforce pressures in managing patients with heart failure. However, there is also an increase in work in terms of monitoring the reports from the system, but on balance, likely to be beneficial.

11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology will need to be monitored by cardiac physiologists or specialist nurses in secondary or tertiary care, although the intention is to enable patients to remain at home or in community care.
12. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The is a cost associated with the technology as it requires the use of more high specification CIEDs (hence more expensive) and there will be a training requirement for cardiac physiologists and/or heart failure specialist nurses.
13. What is the outcome of any evaluations or audits of the use of the technology?	There are a number of studies that demonstrate that the use of such technology can improve the management of heart failure patients and decrease hospital admissions.

Equality

14. Are there any potential equality issues that should be taken into account when considering this treatment?	There is a concern that this technology is more likely to be adopted by higher socio-economic class patients and less likely to be used by minorities. There is also a concern over digital inequality. There is also an argument that patients who do not have Medtronic CIEDs are disadvantaged as they will not be able to access the technology.
15. Consider whether these issues are different from issues with current care and why.	The greater use of technology may be an issue, bearing in mind the majority of heart failure patients are elderly and may have difficulty in using the technology.

Other issues

16. Please include here any other issues you would like the committee to consider when evaluating this technology	I would point out that TRIAGE HF is proprietary technology from Medtronic. There are other manufacturers who have developed similar products and I would strongly urge NICE to consider a generic position on the use of remote monitoring technology for heart failure, rather than supporting a single manufacturer, which is likely to result in pressure from Medtronic to clinicians to use their products.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - ~~YES~~ or NO

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Assessment Group's Report

Algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices

Produced by	Newcastle Technology Assessment Review Group, Newcastle University
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Date completed	20/3/2024

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ryan Kenny contributed to the protocol, the systematic review and the writing of the clinical effectiveness sections of the report.

Nawaraj Bhattarai contributed to the protocol, developed the economic model, contributed to the writing of the cost-effectiveness sections of the report and performance of the economic analysis.

Nicole O'Connor, contributed to the protocol, the systematic review and the writing of the clinical effectiveness sections of the report.

Sonia Garcia Gonzalez, contributed to the protocol, produced search strategies and performed the search and writing of the methods in the clinical and cost-effectiveness sections.

Hannah O'Keefe, contributed to the protocol, produced search strategies and performed the search, formatting of the report and references.

Sedighe Hosseini-Jebeli, contributed to the protocol, conducting of systematic review and focussed review of the health economics section, validation of the economic model, and writing of the economics section.

Nick Meader, contributed to the protocol and oversight of the clinical effectiveness review.

Stephen Rice, contributed to the protocol, writing of the cost-effectiveness sections of the report, validation of the economic model, performance of the economic analysis, and had the overall responsibility of the cost-effectiveness sections and the whole project.

Copyright statement

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

DAR Amendments

Changes to the original report

The original EAG report was submitted to NICE on 8 February 2023. Since that submission changes have been made to respond to correct errors.

The changes are summarised in the table below.

Location in report	**Edit made**
Throughout	Minor grammatical and format changes
Tables 15, 16, 17 and 25	D'Onforio name corrected to D'Onofrio.
Tables 15, 16, 17, 25 and appendix 9.7	D'Onofrio (2022), reference number 45, number of participants corrected from 744 to 918.
Table 15	Omitted a study by Wakabayashi et al (2021), this has been added.
Table 16 and section 3.5.2	Corrected reference for Feijen 2023, originally reference 19, corrected to reference 36.
In section 7.2.2 Limitations	Added the following text to highlight the lack of confounding consideration in the analyses: "Most clinical studies identified in the systematic review were at serious or critical risk of bias. Many of the studies were at serious or critical risk of bias due to a lack of controlling for confounding factors in the statistical analysis. Specifically, age, sex, NYHA classification, smoking status and other co-morbidities were largely uncontrolled for in the majority of studies. In addition, the inherent risk of bias due to the retrospective and single-arm design of many studies are likely to lead to an overestimation of the findings." Added text to state crossover of values with HeartInsight and other algorithms: "However, the one published study did provide similar prognostic accuracy measures to the other

	algorithms, as evidence by the crossover of confidence intervals." Added text to identify that TriageHF and CorVue are the only algorithms that can be used in CRT-P CIEDs: "The EAG also note that two of the algorithms (HeartLogic and HeartInsight) are currently not available on all CIEDs. They are available on ICD and CRT-D devices, while TriageHF and CorVue are also available on CRT-P devices. Currently, only CRT-P devices are recommended for those with NYHA class IV HF."
In section 6.5	The text has been updated to describe the utility calculations; and the References in the Tables, and the footnotes have been updated.
Table 9	Date of reference (D'Onofrio) changed from 2020 to 2022.
Table 11	ROBINS-I assessment for D'Onofrio (2023) has been added to table 11.
Table 10	Capitalised the c in cohort in table 10
Table 15	Corrected a typo changed visits to visits
Section 7.1.1.	Included a sentence to highlight that TriageHF had a number of UK based studies: "It is worth noting that a number of studies evaluating TriageHF were undertaken in a UK setting (n = 5)." Adjusted phrasing around one comparative study based on company feedback: "Only a single study for TriageHF was comparative, providing **real-world** data on hospitalisations **in a UK setting**. However, this study was rated at critical risk of bias using ROBINS-I."
Section 3.5.2 and table 16	Data added for false positive rates from one study (Zile 2020) for TriageHF algorithm.
Section 3.5.3	Added text to state one study for TriageHF used the terms false positive and unexplained

	detections interchangeably and that the evidence is in section 3.5.2.
Section 3.5.4 and table 18	Included information from unpublished study (Ahmed AiC). Added data from Calo 2021 (HeartLogic).
Section 3.7.5	Included median remote monitoring rates percentages information for HeartInsight algorithm.
Section 7.1.1.	Highlighted in the discussion that HeartInsight is the only system to provide daily reports: "The EAG do note that HeartInsight is the only monitoring system that provides daily transmissions, whereas the other technologies occur less frequently. This could have implications for missing data."
Section 3.5.6	Added text relevant to rate of heart failure events. Evidence for decreased rate of further events if clinical action was undertaken: "The same study also identified a decreased rate of events when an alert was followed by a clinical action (HR = 0.37, 95% CI: 0.14 to 0.99), with similar results if analyses was conducted from day 7 post clinical action (HR = 0.34, 95% CI: 0.12 to 0.96)."
Section 3.7.2	Moved information from section 3.7.3 to here as it fits the definition better: "Another study reported an average time of 20 days from alert to hospitalisation."
Table 14	Updated wording for HeartLogic algorithm components.
Section 4.1.4 and 4.2, Figure 3, Table 29	To add information from Treskes et al 2021 and summarise the findings including reporting quality assessment
Section 4.5	Text edited to make the text clear.

Section 6.2.2 and later sections	Updated the Algorithm name for HeartLogic
Section 6.4.1	Edited text to remove McGee et al 2022, incorrect reference reported in stakeholder comments
Section 6.4.3. Alerts and follow-up visits with algorithm based remote monitoring	Edited text to clarify the follow-up visits.
Section 6.5, and Tables 35,36 and 37	Edited text and Table footnotes to clarify the utility calculations and references
Section 6.6	Added text to state additional scenario analysis on the utility decrement calculations to reflect stakeholder comments
Section 6.6.5	Added further information on the costs used in the additional scenario modelled
Table 43	Added details for additional scenarios modelled.
Section 6.8.4 and Table 47	Added text to summarise the results from additional scenario analyses modelled
Section 6.9	Added further text
Section 3.1	Records identified changed from 2700 to 2699
Section 3.4.1	Number of CorVue studies changed from five to six
Section 3.4.1, Table 6	PROBAST results for Benezet-Mazuecos (2016) added
Section 3.4.3, Table 11	ROBINS-I results for D'Onofrio (2023) added
Section 3.4.4, Table 12	PROBAST results for Ahmed (2020) added
Section 3.4.4, Table 12	PROBAST results for Ahmed (2022) added
Section 3.6.4	The text was added to the report following comments from the developers of HeartLogic. "Hernandez reports a rate of HF hospitalisation during the study as 67% lower (rate ratio [95% CI]: 0.33 [0.23, 0.47]) compared to the pre-study 12-month HF hospitalisation rate.82"

ABSTRACT

Background

Heart Failure (HF) is a clinical syndrome caused by any structural or functional cardiac disorder that impairs the heart's ability to function efficiently and pump blood around the body. Symptoms can also be monitored using cardiac implantable electronic devices, some of which may also deliver a therapeutic benefit (e.g. pacemakers), whilst others only monitor metrics over time.

Implantable devices can include algorithms that aim to predict the occurrence of a HF event. They are intended to be used alongside clinical judgement and make treatment decisions.

Objectives

To determine the clinical and cost effectiveness of the four remote monitoring algorithms (CorVue, HeartInsight, HeartLogic and TriageHF) for detecting heart failure in people with cardiac implantable electronic devices.

Methods

We performed systematic reviews of clinical, cost-effectiveness, quality of life and cost outcomes. We searched MEDLINE and other sources of published and unpublished literature, including manufacturers' websites and clinical trial registries between June and August 2023. For the clinical effectiveness review, study selection was completed by two independent reviewers at both title and abstract, and full text screening stages. Data extraction and study quality appraisal was completed by a single reviewer and checked for accuracy by a second. Due to heterogeneity, no statistical analyses were performed and a narrative synthesis was reported.

A *de novo* two state Markov model (with Alive and Dead states) was used to estimate the cost-effectiveness of algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices over a lifetime.

Results

There was reasonable evidence to suggest HeartLogic and TriageHF can accurately predict heart failure events. Results for CorVue for heterogeneous. There was only a single published HeartInsight study, which suggested similar accuracy to the other algorithms.

Cost-effectiveness estimates could only be produced for HeartLogic and TriageHF, which were less costly and more effective. For all technologies, only a small reduction in hospitalisation rates were required for them to be cost effective.

Limitations

The evidence for each algorithm was limited in terms of comparative evidence. Additionally, available evidence was often of low quality. The comparative outcome evidence for economic model was very limited.

Conclusions

There was a lack of comparative evidence across all technologies included in the scope. Evidence for HeartLogic and TriageHF suggest they may have acceptable prognostic accuracy for predicting heart failure events. However, further evidence is required to confirm these results. Specifically, further comparative evidence (e.g. randomised controlled trials) is required to show the benefit of the algorithms compared to standard practice in intermediate and clinical outcomes. CorVue's prognostic accuracy is less clear due to high heterogeneity in findings between studies. For example, some studies suggested high false positive rates and low sensitivity. Only a single published study was identified for HeartInsight, therefore there is insufficient data to draw conclusions on prognostic accuracy and the benefits on clinical and intermediate outcomes. It is likely remote monitoring systems for CorVue, HeartInsight, HeartLogic and TriageHF would be cost-effective were they to result in fewer hospitalisations in heart failure patients.

PLAIN ENGLISH SUMMARY

Four technologies (called algorithms) which can be monitored remotely by doctors and nurses to detect worsening heart failure in people who have cardiac implantable electronic devices (CIEDs) inserted may detect heart failure earlier than routine in-person health-checks and result in faster treatment times. The technologies are called CorVue (made by Abbott Medical), HeartInsight (Biotronik), HeartLogic (Boston Scientific) and TriageHF (Medtronic). This project assessed if the algorithms work as intended (prognostic accuracy) and provide a health benefit to the patient (clinical effectiveness). Lastly, the researchers assessed if the algorithm provides enough benefit for it to be good value for money to the public citizens (economic analysis).

To answer whether each of the algorithms are clinically and cost effective, the researchers searched medical publication databases and the manufacturers' websites to identify relevant studies. The researchers assessed the quality of the studies and reviewed their results.

The accuracy of each technology was assessed. HeartLogic and TriageHF reported acceptable accuracy measures for prediction heart failure events, for example, hospitalisation. There is more evidence needed to confirm this. Ideally, more evidence comparing outcomes with and without the technologies needs to be developed as there is a current lack of this type of information available. The accuracy of CorVue is less clear. This is because there is a lot of variation in outcomes between studies and the measures of accuracy vary to a large amount. Only one study was found for HeartInsight, which means we cannot conclude anything, due to a lack of information.

For the clinical effectiveness there was limited evidence of high enough quality to draw any conclusions for CorVue and HeartInsight. In comparison, there was more evidence to suggest HeartLogic and TriageHF might provide a clinical value in terms of detecting heart failure events and reduced risk of death. Health-related quality of life data was limited to one Triage HF study.

An economic analysis was conducted to investigate whether algorithm based remote monitoring for these four cardiac implantable electronic devices would add value in terms of money spent and benefits offered. There was very limited evidence on the benefits, but there is a potential for these devices to be good value for money if they reduce the hospitalisation rates compared to standard care.

SCIENTIFIC SUMMARY

Background

Heart Failure (HF) is a clinical syndrome caused by any structural or functional cardiac disorder that impairs the heart's ability to function efficiently and pump blood around the body. The most common symptoms of HF are breathlessness, fatigue, and oedema. Conditions that can cause HF include coronary heart disease, high blood pressure, heart rhythm or valve abnormalities and conditions affecting the heart muscle (cardiomyopathies and myocarditis).

Around 920,000 people in the UK were living with HF in 2018 with an estimated 200,000 new diagnoses each year. HF mainly affects people over the age of 65, with an average age of diagnosis of 77, and risk increases significantly with age. Around 1 in 35 people aged 65–74 years have HF, which increases to 1 in 15 of people aged 75–84 years, and to just over 1 in 7 people of those aged above 85 years.

The NICE guidelines for diagnosis and management of chronic HF in adults recommend that monitoring of people with chronic HF should include a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status, a review of medication, and an assessment of renal function. The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF add that HF management may involve in-person service models or home-based telemonitoring, and that the COVID-19 pandemic has highlighted some of the potential advantages of the latter. While care is usually followed up by HF clinics, suitable patients may be followed up by community HF nurses or a GP with a special interest in HF - a clinical expert commented that there is no standard HF service model.

Patients who have cardiac implantable electronic devices (CIEDs) due to heart failure or who are at risk of HF may have a remote monitoring system incorporated in the device. The remote monitoring system includes a predictive algorithm for heart failure. The system can send alerts and/or the stored data can be reviewed. There is additional cost to access and use the remote monitoring system. The decision question is whether the algorithm-based remote monitoring of heart failure risk data in people with CIEDs represent a clinical and cost-effective use of NHS resources and should be recommended for use.

Four relevant remote monitoring algorithms were identified for consideration.

- CorVue algorithm with integrated CIED (Abbott Medical)
- HeartInsight algorithm with integrated CIED (Biotronik)
- HeartLogic algorithm with integrated CIED (Boston Scientific)
- TriageHF algorithm with integrated CIED (Medtronic)

Objectives

To determine the clinical and cost effectiveness of the four remote monitoring algorithms for detecting heart failure in people with CIEDs

Methods

Systematic review

The Systematic review was conducted following the general principles recommended by the Centre or Reviews and Dissemination (CRD) guidance.

A comprehensive range of databases and sources of grey literature were searched for the identification of studies relating to the use of algorithm-based remote monitoring of heart failure risk data in people with CorVue, HeartInsight, HeartLogic or TriageHF cardiac implantable electronic devices. The bibliographic databases searched were MEDLINE and Embase (via Ovid), CINALH (EBSCO), The Cochrane Database of Systematic Reviews and The Cochrane Register of Controlled Trials (CENTRAL) (via The Cochrane Library) and the Database of Abstracts of Reviews of Effects (via The Centre for Reviews and Dissemination). International clinical trial registries such as the US clinicaltrials.gov, European EudraCT, the World Health Organisation ICTRP registry and ScanMedicine, a multinational open access clinical trial database, were searched for the identification of ongoing clinical trials. Additionally, we searched for health technology assessment reports in the International HTA database and for protocols of systematic reviews in PROSPERO and INPLASY, both international registers of systematic reviews. Finally, we searched for pre-print manuscripts in MedRxiv, a pre-print server for health sciences. We performed backwards and forwards citation chaining to identify potentially relevant studies cited or citing the included studies. Company submission documents and company websites were also searched for additional relevant studies.

Data extraction of the study characteristics and outcome data was done by one reviewer and checked by another reviewer. The risk of bias was assessed using ROBINS-I where clinical outcomes were reported in non-randomised intervention studies and PROBAST where prognostic outcomes, including sensitivity and specificity, were reported. The Cochrane RoB tool was not used because none of the included studies were randomised controlled trials.

Due to diversity across the studies, meta-analysis was not performed and the evidence was synthesized narratively and in tabular format.

Economic Review

A broad search for cost-effectiveness studies was undertaken in the following sources: MEDLINE and Embase (Ovid), The Cochrane Database of Systematic Reviews and The Cochrane Central Register of Controlled Trials (Cochrane Library), The Center for Reviews and Dissemination Database of Abstracts of Reviews of Effects and HTA database and NHS Economic Evaluations Database, the International HTA database and NIHR Journal library. Whenever appropriate to the database we used a validated SIGN search filter for the identification of cost-effectiveness studies.

Additionally, in August 2023 we performed focussed searches for resource utilization, QALY and utility values to populate the economic model. We searched MEDLINE and Embase via Ovid and used two validated economic filters for cost-of-illness studies and quality-of-life studies. We also searched specialist sources such as CEA Registry, RePEC and ScHARRHUD (the health utilities database from the School of Health and Related Research at The University of Sheffield).

Economic Modelling

A *de novo* two state Markov model (with Alive and Dead states) was used to estimate the cost-effectiveness of algorithm-based remote monitoring of heart failure risk data in people with cardiac

implantable electronic devices. The model structure captured the key costs and outcomes associated with CRM. Patients in the Alive state experienced a number of hospitalisations per year, made a number of clinic visits (scheduled and unscheduled) and were at risk of dying. CorVue, HeartInsight, HeartLogic and TriageHF were modelled separately and outcome differences for one device were not assumed to apply to another device. QALYs gained was the measure of benefit for the economic evaluation.

Results

Clinical effectiveness

Eighty-one reports comprising 42 studies of clinical effectiveness were included in the systematic review. Eight studies evaluated CorVue, 1 published study evaluated HeartInsight, 19 studies evaluated HeartLogic and 14 studies evaluated TriageHF. Of the included studies the great majority were single arm cohort designs (retrospective and prospective). No randomized controlled trials were identified and five studies provided some comparative data (CorVue; n=1, HeartLogic; n=3, Triage HF; n=1).

The greatest amount of evidence for prognostic accuracy was identified in studies assessing the TriageHF algorithm (n=10). Of these, the area under the curve (AUC) was reported in three studies assessing worsening HF (AUC = 0.75), mortality (AUC = 0.61), and hospital admissions (AUC = 0.81). Sensitivity for high risk status for HF related events (e.g. hospitalisations) showed great variability (range = 37.4 to 87.9%). Specificity also varied (range = 44.4 to 90.2%). A similar amount of evidence was identified for prognostic accuracy outcomes evaluating HeartLogic (n=8). Validation studies for HeartLogic to predict HF events (hospitalizations and clinical visits) reported sensitivity as adequate to high (range = 66 to 100%); similarly, specificity was adequate to high (range = 61 to 93%). False positive rates were generally low in the seven studies reporting this outcome; conversely, one study reported a high false positive rate (26 of 38 alerts). In comparison to HeartLogic and TriageHF, there was limited evidence for CorVue (n=5) and HeartInsight (n=1) overall and for prognostic outcomes. The CorVue algorithm demonstrated inadequate sensitivity for HF events, defined as hospitalisations (range = 20 to 68%). Specificity was only reported in two studies at 70% and 77%. The low predictive accuracy was also accompanied by a high false positive rate. The one published study for HeartInsight algorithm had 65.5% sensitivity and 86.7% specificity for first post-implant HF hospitalisations. Additionally, 54.8% sensitivity and 86.5% specificity for HF hospitalisation, outpatient intravenous intervention or death. False positive rates were low.

Reported clinical outcomes included HF events, mortality and adverse events (morbidity). Twelve studies reported HF events for three algorithms (HeartLogic, n=7; CorVue n=3, Triage HF n=2). Only one of these studies was comparative, with data showing less HF events when the HeartLogic algorithm was utilised. For non-comparative evidence using HeartLogic there was evidence that when IN alert compared to OUT of alert related to increased risk of HF events occurring. Similarly, TriageHF showed an increased risk of HF events when in high or medium risk status. No comparative evidence was generated for CorVue and only numerical data was presented. No evidence was identified for HeartInsight. There was limited evidence for HF related deaths. Three HeartLogic studies demonstrated an increased risk of death when IN alert compared to OUT of alert. One study assessing differences between unplanned HF hospitalisations and medical admissions for TriageHF reported more deaths occurring during HF hospitalisations. Only two studies reported adverse events (HeartInsight n=1, HeartLogic n=1).

For the patient-reported outcome measures, one single prospective cohort evaluating the TriageHF algorithm provided outcomes for health-related quality of life by using the 6-minute walk test (6MWT) and Minnesota living with heart failure (MLWHF). There was a decrease in walking distance at 8 months follow-up and no statistically significant change in the MLWHF from baseline to follow up at 8 months.

Cost-effectiveness

There was no comparative evidence on hospitalisation, mortality and follow-up visits or LoS for CorVue or HeartInsight. CorVue and HeartInsight were cost increasing when a conservative assumption of no difference in hospitalisation, mortality, follow-up visits (scheduled/unscheduled) was made. Threshold analysis for these two devices showed that even a very small reduction in the incidence rate of hospitalisation would make them cost-effective.

HeartLogic had some evidence on LoS, and hospitalisation rates and the cost-effectiveness estimates showed it to be dominant (i.e. less costly and more effective than the comparator). TriageHF also had some evidence on hospitalisation rates, and was also dominant. The studies supplying the hospitalisation and LoS evidence were either at serious or critical risk of bias due to confounding.

Due to the high cost of hospitalisation, the RMS devices for these technologies only need to reduce the hospitalisation rates by small percentage for them to become cost-effective. The lack of hospitalisation outcome evidence for CorVue or HeartInsight means it is not possible to produce cost-effectiveness estimates for these technologies. The cost-effectiveness estimates of HeartLogic and TriageHF are based on evidence that is at risk of bias. There was also limited evidence on healthcare contact outcomes.

Discussion

The majority of the evidence base for all algorithms is derived from single cohort (prospective and retrospective) studies and provide mixed results. Only five included studies reported comparative evidence.

The available evidence for the HeartLogic algorithm showed adequate to high sensitivity and specificity for the prediction of HF events (i.e. hospitalisations). False positive rates were low.

TriageHF accuracy measures varied substantially between low and high sensitivity and specificity. False positive rates were only reported in one study and were relatively low.

Evidence for the accuracy of CorVue showed low sensitivity, and specificity was generally not reported. False positive rates were high in most studies.

One study evaluating the clinical effectiveness of HeartInsight was identified. It was a development and validation study and reported adequate sensitivity and specificity for HF events. False positive rates were moderate in this single study. No comparative evidence was identified for the use of HeartInsight.

There was a paucity of data for some of the outcomes listed in the protocol, including patient-reported outcome measures for health-related quality of life and satisfaction and adherence to treatment. In addition, mortality and adverse events were not widely reported. Lastly, there was limited reporting for the software failure rate.

The assumptions around parameters may not be applicable to all populations or sub-group and may not reflect real-world experience. Limited device specific comparative evidence on outcomes mean that the cost-effectiveness findings in this report need to be interpreted with caution. Further research and comparative evidence on effectiveness might be needed to confirm cost-effectiveness.

Conclusions

The evidence for HeartLogic and TriageHF showed a potential to be of use in clinical practice; however, there are important uncertainties due to a lack of comparative evidence. HeartLogic had the highest and most consistent accuracy measures (i.e. sensitivity of ≥70%); the data suggest being IN alert is linked to greater risk of HF events, however these estimates were generally derived from composite outcomes (e.g. hospitalisations and outpatient visits). TriageHF showed similar accuracy, but with further degree of variation, for detecting such HF events when in a high risk status, however these estimates were more commonly reported from single endpoint studies. HeartInsight reported comparable accuracy to HeartLogic and TriageHF (sensitivity of 65%); however, this was only based on one published study, therefore it is uncertain whether further studies will replicate these findings. CorVue prognostic accuracy data varied substantially (i.e. sensitivity reported to be as low as 20%). For all technologies, most studies were judged to be at high risk of bias, which reduces certainty about the evidence.

All remote monitoring algorithms only needed to reduce hospitalisations by a small amount for them to be cost-effective given the evidence on incremental healthcare visits use compared to no remote monitoring algorithm. Better quality and adequately powered evidence on both hospitalisations and healthcare contacts (visits, calls), which also records time spent reviewing remote monitoring data, would help inform the cost-effectiveness of the remote monitoring algorithms.

Suggested priorities for further research

Further studies on the effectiveness of remote monitoring should be prospectively designed and compare outcomes for people with a CIED and remote monitoring algorithm to people with a CIED with no remoted monitoring algorithm. In addition, inclusion of relevant patient-reported outcome measures, and patient involvement to capture the patient voice and preferences, would facilitate a more complete evaluation of the technologies' benefits.

Abbreviations

6MWT, 6-minute walking test
AAD, antiarrhythmic drugs
Abstr, Abstract
ACE, Angiotensin-converting enzyme
ACEI, Angiotensin-converting enzyme
AF, Atrial fibrillation
AF, Atrial fibrillation;
APPG, All Party Parliamentary Group
ARA, Aldosterone receptor antagonists
ARB, Angiotensin II receptor blockers
ARNI, Angiotensin receptor/neprilysin inhibitor
AUC, Area under the curve
BHRS, The British Heart Rhythm Society
BMI, Body mass index.
Ca, Calcium
CABG, Coronary artery bypass grafting
CABG, Coronary artery bypass grafting
CAD, Coronary artery disease
CEAC, Cost-effectiveness acceptability curve
CFU, Conventional follow up
CI, Confidence interval
CIED, Cardiac Implantable Electronic Devices
COPD, Chronic obstructive pulmonary disease
CRD, Centre for Reviews and Dissemination
CRM, Cardiac Remote Monitoring
CRT-D, Cardiac resynchronisation therapy device

CRT-P, cardiac resynchronisation therapy pacemaker
CSHS, Cost of a Standard Hospital Stay
EAG, Evidence Assessment Group
ECG, Electrocardiogram
ESC, The European Society of Cardiology
FAST, The Fluid Accumulation Status Trial
FT, Full text
FU, Follow up
GEE, Generalised estimating equations
HF, Heart Failure
HFmrEF - HF with mildly reduced ejection fraction
HFmrEF – HF with reduced ejection fraction
HFpEF, HF with preserved ejection fraction
HR, Hazard ratio
HRG, Healthcare Resource Group
ICD, Implantable cardioverter defibrillator
ICD-DR, Implantable cardioverter defibrillator dual chamber
ICD-VR, Implantable cardioverter defibrillator single chamber
ICER, Incremental cost-effectiveness ratio
IQR, Interquartile range
IRR, Internal rate of return
IRR, Incidence Relative Ratio
LoS, Length of Stay
LVEF, Left ventricular ejection fraction
MI, Myocardial infarction
MLWHF, Minnesota living with heart failure
MORE-CARE, The MOnitoring Resynchronization dEvices and CARdiac patiEnts

MRA, Mineralcorticoid Receptor Antagonists
MultiSENSE, Evaluation of Multisensor Data in Heart Failure Patients With Implanted Devices
NICE, The National Institute for Health and Care Excellence
NPV, Negative predictive value
NT-proBNP, N-terminal pro-B-type natriuretic peptide
NYHA, New York Heart Association
PMI, Post-pacemaker implantation
PPM, Permanent pacemaker
PPV, Positive predictive value
PRECEDE-HF,
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROBAST, Prediction model Risk Of Bias Assessment Tool
PSA, Probabilistic Sensitivity Analysis
PSS, Personal Social Services
QALY, Quality adjusted life years
RIW, Resource Intensity Weight
RMS, Remote monitoring services
ROBINS-I, Risk Of Bias In Non-randomized Studies-of Interventions
SD, Standard deviation
TIA, Transient ischaemic attack
VF, Ventricular fibrillation
VT, Ventricular tachycardia
WTP, Willingness to pay

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Glossary

Cost-effectiveness analysis: An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Economic modelling: A theoretical construct that allows the comparison of the costs and outcomes of alternative healthcare interventions.

Incremental cost-effectiveness ratio: The difference in the mean costs of two interventions divided by the difference in the mean outcomes in the population of interest.

Markov model: An analytical framework that is commonly used to conduct economic evaluation of interventions and particularly suitable to model mutually exclusive health states and disease progression over time.

Sensitivity: Proportion of people with the condition of interest who have a positive test result.

Specificity: Proportion of people without the condition of interest who have a negative test result.

True negative: Correct negative test result – number of non-diseased persons with a negative test result.

True positive: Correct positive test result – number of diseased persons with a positive test result.

False negative: Incorrect negative test result – number of diseased persons with a negative test result.

False positive: Incorrect positive test result – number of non-diseased persons with a positive test result.

Area under the curve: Area under a receiver operator characteristic curve (for assessing diagnostic accuracy).

1 Background and definition of decision problem

1.1 Heart failure

Heart Failure (HF) is a clinical syndrome caused by any structural or functional cardiac disorder that impairs the heart's ability to function efficiently and pump blood around the body. The most common symptoms of HF are breathlessness, fatigue, and oedema. Conditions that can cause HF include coronary heart disease, high blood pressure, heart rhythm or valve abnormalities and conditions affecting the heart muscle (cardiomyopathies and myocarditis). The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure highlight that atrial fibrillation and heart failure frequently coexist, and they can cause or exacerbate each other.[1]

HF may present as acute or chronic, depending on whether a person has an established diagnosis of HF and speed of symptom onset. People with chronic HF may experience sudden deterioration in heart function and worsening of symptoms, which is known as acute decompensated HF.

The British Heart Foundation website[2] explains that HF can be grouped into different categories depending on the strength of the heart, that is, the left ventricular ejection fraction (LVEF), which is the amount of blood squeezed out of the main chamber of the heart with every beat. Depending on the percentage ejection fraction (where 50% or greater is considered normal), HF may be classed as the following:[2]

- HFpEF - HF with preserved ejection fraction (>50%)
- HFmrEF - HF with mildly reduced ejection fraction (40% - 49%)
- HFmrEF – HF with reduced ejection fraction (<40%)

HF may also be grouped by symptom severity and limitation of physical activity according to the New York Heart Association (NYHA) functional classification of HF, ranging from class I (no limitations) to class IV (inability to carry out any physical activity without discomfort and symptoms which may be present at rest).

HF mainly affects people over the age of 65, with an average age of diagnosis of 77, and risk increases significantly with age. Around 1 in 35 people aged 65–74 years have HF, which increases to 1 in 15 of people aged 75–84 years, and to just over 1 in 7 people those aged above 85 years.[3]

Around 920,000 people in the UK were living with HF in 2018 with an estimated 200,000 new diagnoses each year.[4] The incidence of HF in the UK is 140 per 100,000 men and 120 per 100,000 women.[5] The prevalence of HF is increasing over time because of population ageing and a rise in the prevalence of associated comorbidities.

HF has a poor prognosis - estimates of 1-year mortality vary, but a long-term registry of people with HF found a mortality rate of 23.6% for people with acute HF and 6.4% for those with chronic HF across Europe.[6] A UK-based population study conducted between 2000 and 2017 found that patients diagnosed with HF had a 1 year survival rate of 75.9%, 5-year survival of 45.5% and 10-year survival of 24.5%.

HF accounts for a total of 1 million inpatient bed days – 2% of all NHS inpatient bed-days – and 5% of all emergency medical admissions to hospital. The figures from NHS Hospital Episode Statistics indicate that there were 98,884 hospital admissions for HF in 2021/22 compared with 86,474 in 2018/19.[7, 8]

This is at significant cost to the NHS – a 2016 All Party Parliamentary Group (APPG) report on HF found that the condition costs the NHS around £2 billion per year, or approximately 2% of the total NHS budget.[9]

Patients who have cardiac implantable electronic devices (CIEDs) due to heart failure or who are at risk of HF may have a remote monitoring system incorporated in the device. The remote monitoring system includes a predictive algorithm for heart failure. The system can send alerts and/or the stored data can be reviewed. There is an additional cost to access and utilise the remote monitoring system. The decision question is whether the algorithm-based remote monitoring of heart failure risk data in people with CIEDs represent a clinical and cost-effective use of NHS resources and should be recommended for use.

1.2 Description of current practice

1.2.1 Monitoring Heart Failure patients

The NICE guidelines for diagnosis and management of chronic HF in adults recommend that monitoring of people with chronic HF should include a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status, a review of medication, and an assessment of renal function.[3] The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF add that HF management may involve in-person service models or home-based telemonitoring, and that the COVID-19 pandemic has highlighted some of the potential advantages of the latter.[1] While care is usually followed up by HF clinics, suitable patients may be followed up by community HF nurses or a GP with a special interest in HF - a clinical expert commented that there is no standard HF service model.

People should have additional monitoring if they have comorbidities, are taking co-prescribed medications or if their condition has deteriorated since their last review. The frequency of monitoring is dependent on the clinical status and stability of the person's condition. For people whose condition is unstable, monitoring may be offered as frequently as every few days, up to every 2 weeks. Reviews are offered every 6 months for people whose condition is stable. Early follow-up visits are recommended at 1-2 weeks following hospital discharge to assess signs of congestion and drug tolerance. Levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide) may be monitored as a surrogate biomarker for HF in people under 75 who have HF with reduced ejection fraction and an estimated glomerular filtration rate above 60 ml per minute per 1.73 m^2.

Clinical experts highlighted that in practice a combination of the ESC guidelines and the NICE guidelines are followed in the NHS. The ESC guidelines for the diagnosis and treatment of acute and chronic HF recommend that an ECG should be done annually to detect prolonged QRS duration, so that conduction disturbances and atrial fibrillation may be recognised and to identify people with prolonged QRS duration who may become candidates for cardiac resynchronisation therapy.[1] Repeat ECGs are also advised if there has been a deterioration in clinical status, and 36 months after optimisation of standard therapies for HFrEF.

Symptoms can also be monitored using cardiac implantable electronic devices (CIEDs), some of which may also deliver a therapeutic benefit (such as pacemakers, implantable cardioverter defibrillators (ICDs), and cardiac resynchronisation therapy (CRT) devices), whilst others only monitor metrics over time.

Pressure sensors placed in the pulmonary artery that work in combination with an external monitor may also be used to wirelessly monitor symptoms of HF. NICE's interventional procedures guidance states that the evidence on efficacy and safety of percutaneous implantation of pulmonary artery pressure sensors for monitoring treatment of chronic HF is sufficient to support standard arrangements for use.[10]

Implantable loop recorders which are placed under the skin are capable of continuous monitoring of heart rate and rhythm and last around three years, with data checked at regular intervals by a clinician. A clinical expert commented that most newer devices allow for remote monitoring, but older devices may require the patient to attend an in-person appointment so that data collected from the device may be downloaded. The British Heart Rhythm Society's clinical standards and guidelines for the follow up of cardiac implantable electronic devices (CIEDs) for cardiac rhythm management states that most modern implantable pulse generators are also equipped with algorithms that provide reliable pacing threshold management.[11]

1.2.2 Follow up of people with CIEDs

Clinical experts explained that people at risk of HF or worsening HF who have a CIED are usually managed in multiple clinics. For example, a HF clinic manages the medication review, and a cardiac physiologist led clinic manages the follow up of the CIED. The extent to which these services overlap varies between centres.

The British Heart Rhythm Society's (BHRS) clinical standards and guidelines for the follow up of cardiac implantable electronic devices (CIEDs) for cardiac rhythm management state that managing HF is a multidisciplinary process and recommends that monitoring includes a regular technical review of device function, monitoring of symptoms, and management of new and changing conditions. The guidelines also state that clear local protocols should be in place for suspected worsening HF.[11]

The BHRS standards also state that alert-based remote follow up should be considered as standard care for CIED patients, including those with pacemakers, and annual in-person follow up is not mandated for all CIED patients. However, device follow up may also include in person evaluation and can differ according to clinic policies, the capabilities and maintenance needs of the CIED, and patient needs or preferences.

1.2.3 Treatment of chronic heart failure

The NICE guidelines for diagnosis and management of chronic HF in adults is summarised in Figure 1. The NICE guidelines recommend the use of pharmacological treatments including routine use of diuretic therapy, which should be started using a bolus or infusion strategy.

In cases where people have potentially reversible cardiogenic shock, inotropes or vasopressors may also be recommended if given in a cardiac care unit or high dependency unit or an alternative setting where at least level 2 care can be provided.

People with acute onset heart failure may also require ventilation. If a person has cardiogenic pulmonary oedema with severe dyspnoea and acidaemia consider starting non-invasive ventilation without delay, while invasive ventilation may be appropriate where heart failure is leading to or is complicated by either respiratory failure or reduced consciousness or physical exhaustion.

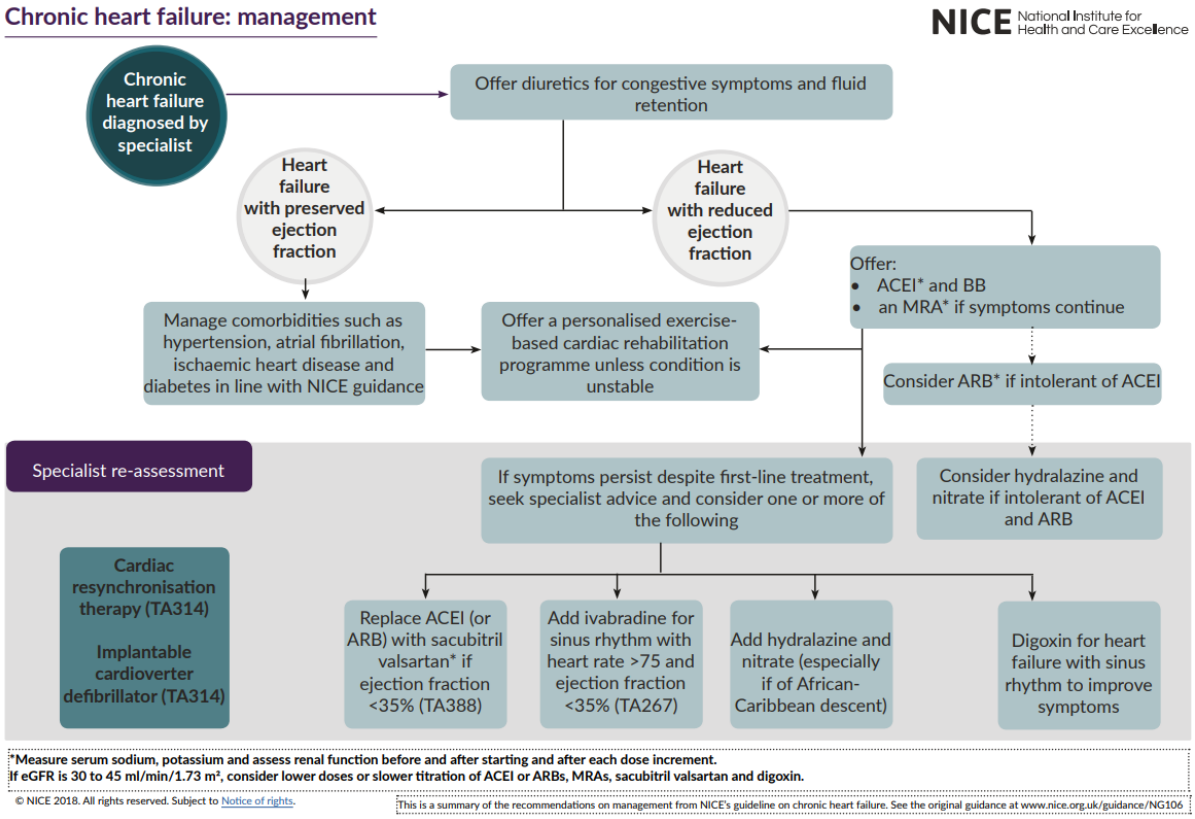


Figure 1: NICE guidelines on chronic heart failure management.[3]

In the case of HF with reduced ejection fraction, the NICE guidelines for diagnosis and management of chronic HF in adults recommend that an angiotensin-converting enzyme (ACE) inhibitor, or angiotensin II receptor blockers (ARBs) licensed for HF if the person is intolerant to ACE inhibitors, should be offered as a first line treatment in combination with a beta-blocker licensed for HF.[3] If people are continuing to experience symptoms, mineralocorticoid receptor antagonists (MRAs) may be used in addition to first line therapies. The ESC guidelines also recommend the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors as a first line therapy in people with reduced ejection fraction.[3] The NICE technology appraisal guidance on Dapagliflozin for treating chronic heart failure with reduced ejection fraction also supports the use of an SGLT2 inhibitor in these people,[12] as an add-on to optimised standard care with:

- angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers, and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or
- sacubitril valsartan, with beta blockers, and, if tolerated, MRAs.

The ESC guidelines states that intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic people with heart failure who have recently been hospitalised for heart failure, who have left ventricular ejection fraction below 50% and an iron deficiency to reduce the risk of heart failure hospitalisation.[1]

A person should be referred to a specialist multidisciplinary HF team (where available) or cardiology service for specialist treatment if a person has:

- Severe HF (NYHA class IV)
- HF that does not respond to treatment in primary care or can no longer be managed in the home setting
- HF resulting from valvular heart disease
- Left ventricular ejection fraction of 35% or less
- A NT pro-BNP level above 2000 ng/L (236 pmol/L). These people should be referred urgently for specialist assessment and transthoracic echocardiography within 2 weeks
- A NT pro-BNP level between 400 and 2000 ng/L (47–236 pmol/L). These people should be referred to have specialist assessment and transthoracic echocardiography within 6 weeks

Specialist pharmacological treatments for HF with reduced ejection fraction may include ivabradine, sacubitril valsartan, hydralazine in combination with nitrate and digoxin.

In people with both reduced ejection fraction and chronic kidney disease, lower doses of pharmacological treatments being offered should be considered. Specialist referral for transplantation should be considered for HF patients with severe refractory symptoms or refractory cardiogenic shock. People suitable for transplantation may also be offered a left ventricular assist device (LVAD) to support pumping of blood around the body either while waiting for a suitable transplant to become available or as a permanent intervention.

1.2.4 Treatment for acute heart failure

Acute HF can present as acute decompensation of chronic HF in addition to new-onset HF in people without known cardiac dysfunction. The NICE guidelines for diagnosis and management of acute HF in adults recommend that people requiring immediate treatment for acute HF should be offered intravenous diuretic therapy, which should be started using a bolus or infusion strategy.[13]

In cases where people have potentially reversible cardiogenic shock, inotropes or vasopressors may also be recommended if given in a cardiac care unit or high dependency unit or an alternative setting where at least level 2 care can be provided.

People with acute onset HF may also require ventilation. If a person has cardiogenic pulmonary oedema with severe dyspnoea and acidaemia consider starting non-invasive ventilation without delay, while invasive ventilation may be appropriate where HF is leading to or is complicated by either respiratory failure or reduced consciousness or physical exhaustion.

1.2.5 Devices and surgical procedures for heart failure

As the condition becomes more severe, cardiac function and symptoms may no longer be controlled by pharmacological treatment alone. The NICE Technology appraisal TA314 recommends the use of implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) as treatment options for people with HF who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less depending

on NYHA functional classification, QRS duration and presence of left bundle branch block (LBBB) (see Table 1).[5]

Table 1: Recommended cardiac implantable electronic devices for people with different symptoms and QRS intervals where LVEF is 35% or less

	NYHA classification of symptoms			
QRS interval	**I**	**II**	**III**	**IV**
<120 milliseconds	**ICD if there is a high risk of sudden cardiac death**			**ICD and CRT not clinically indicated**
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P

NYHA: New York heart association, ICD: Implantable cardiac device, CRT-P: Cardiac resynchronisation therapy with pacing, CRT-D: Cardiac resynchronisation therapy with defibrillation, LBBB: Left bundle branch block

1.3 Description of the technologies under assessment

This assessment evaluated remote monitoring systems, consisting of data collection, heart failure predictive algorithms and the software and data management platforms to send, receive, store and present data and alerts for implanted cardiac devices. These remote monitoring systems are only compatible with specific devices manufactured by the same company. The CIED remotely monitors physiological parameters measured by an implanted cardiac device. The predictive algorithm determines whether an alert should be sent to healthcare professionals via the remote monitoring system software and data management platform when HF metrics worsen. All the technologies are intended for use within a single person with an implanted device, none are reprogrammable for use with another person. All require an internet connection to access their relevant data management platforms.

Every CIED has its own remote monitoring system with its own unique heart failure predictive algorithm for sending alerts. Where possible, outcomes for patients utilising the remote monitoring system were compared to patients without the remote monitoring system for each CIED. Remote monitoring systems were not compared with each other as that would require additional assumptions about equivalent effectiveness of the CIEDs or evaluation of the relative effectiveness of the CIEDs, which is beyond the scope of this report. The CIEDs would also need to be considered for use in the same population.

Four CIEDs (see Table 2) and their remote monitoring systems were assessed. These CIEDs were considered in the NICE scope because they are:

- intended for use in people with an implanted cardiac device
- available in the UK
- hold a CE-mark
- therapeutic, not just monitoring

.

Table 2: Product properties

Algorithm-based remote monitoring system	Manufacturer	Components	Compatible CIEDs
CorVue and Merlin.net Patient Care Network	Abbott Medical	• CorVue algorithm (integrated within CIED) • Transmitter mobile app (myMerlinPulse) or remote monitoring unit (Merlin@Home) if app-based smartphone transmitter not used • Management system (Merlin.net PCN platform)	Abbott devices: Gallant Single Chamber ICD, Gallant Dual Chamber ICD, Gallant HF, Quadra Allure MP CRT-P Pacemaker, Quadra Assura MP CRT-D, Ellipse Single, Chamber ICD, Ellipse Dual Chamber ICD, Fortify Assura Single Chamber ICD, Fortify Assura Dual Chamber ICD, Unify Assura CRT-D, Assurity Dual Chamber PPM, Assurity Single Chamber PPM
HeartInsight and BIOTRONIK Home Monitoring	Biotronik	• Management system (BIOTRONIK Home Monitoring Service Centre) • HeartInsight algorithm (integrated within management system) • Transmitter (CardioMessenger) • Optional BIOTRONIK mobile app	BIOTRONIK heart devices: Acticor/Rivacor, Ilivia Neo/Intica Neo, Ilivia/Intica /Inlexa -5 and -7 series ICD DX/DC and CRT-D

HeartLogic and Latitude **NXT** Patient Management System	Boston Scientific	• Latitude Communicator HeartLogic algorithm (integrated within the CIED) • LATITUDE NXT Patient Management system • Optional MyLATITUDE mobile app	Boston Scientific devices: Perciva, Momentum EL, Resonate EL, Vigilant EL, and CRT-Ds: Resonate X4, Vigilant X4, Momentum X4 and Momentum
TriageHF and CareLink remote monitoring (TriageHF Plus)	Medtronic	• TriageHF risk algorithm (integrated within CIED) • CareLink monitoring platform • Optional MyCareLink heart mobile app	Medtronic CIEDs with OptiVol measurement capability

1.3.1 HeartInsight and BIOTRONIK Home Monitoring

The BIOTRONIK Home Monitoring system (HMSC) and HeartInsight algorithm are intended for monitoring cardiac function in people who have implanted BIOTRONIK pacemakers, implantable cardiac defibrillators (ICDs) or cardiac resynchronization therapy (CRT) devices. It is indicated for heart failure patients with NYHA Class II or III. The HeartInsight algorithm is integrated within the HMSC and has a Class III CE-mark.

The system includes the handheld CardioMessenger device which transmits data from the implanted cardiac device to the BIOTRONIK HMSC via a mobile phone network. The system has an integrated HeartInsight algorithm to identify people with a higher risk of decompensation and predict HF hospitalisations.

The HeartInsight algorithm combines seven parameters into one composite score (calculated daily): atrial burden, heart rate variability, general activity, thoracic impedance, heart rate, heart rate at rest and premature ventricular contractions, with an optional additional baseline rate parameter. HeartInsight triggers an alert to healthcare professionals (via text message and/or email) once the threshold is exceeded for three consecutive values (days), indicating higher risk of worsening heart failure. The system is set to raise an alert to health professionals according to customised parameters and the reports use a traffic light system for prioritising alerts. Information collected by HeartInsight can be accessed and reviewed by healthcare professionals on the BIOTRONIK HMSC website platform.

Following an alert, the person is automatically sent a Heart Failure Screening Questionnaire (HFQ) via the BIOTRONIK Patient App to report any relevant behaviours and symptoms. The BIOTRONIK Patient App is an optional tool to use as an electronic symptom diary or self-monitoring device information. The app is free of charge and can be downloaded to the person's smartphone.

There are no known contraindications with its use; however, HeartInsight is not recommended in patients without a lead capable of atrial sensing, with a deactivated atrial lead or with permanent atrial fibrillation. It is also not recommended in patients with insufficient mobile network coverage or the inability to use BIOTRONIK Home Monitoring.

1.3.2 HeartLogic and Latitude NXT Patient Management System

The HeartLogic algorithm and LATITUDE NXT HF Patient Management system (Boston Scientific) is intended for remote monitoring of HF in people who have compatible implanted devices. The HeartLogic algorithm is integrated within the implanted device and has a Class III implantable CE-mark.

It is intended to be used alongside in-person or remote clinical evaluations. The HeartLogic device has an integrated HeartLogic algorithm which automatically analyses measurements. In addition to the implanted device, the Latitude NXT Patient Management system includes a wireless LATITUDE Communicator and optional weighing scales and a blood pressure monitor. The LATITUDE NXT system is further described in the NICE Medtech innovation briefing MIB67.[14] HeartLogic is currently in use in 13 NHS Trusts.

Measurements including heart sounds, thoracic impedance, respiration, heart rate and activity are collected by the implanted device, which the HeartLogic algorithm combines into 1 composite index that indicates decompensation. The data are transferred to the Latitude NXT patient management system via the Latitude Communicator. The system has daily data transfers to the clinical team. The Communicator can use a mobile phone connection or an internet connection to relay the data. The system is configured to send an alert to a health professional when the index is over a set threshold (customisable by the clinician). Health professionals need to log on to the Latitude NXT website to receive alerts. Secondary notification of alerts may be through email or text message.

1.3.3 TriageHF and CareLink remote monitoring (Triage HF Plus)

TriageHF Plus is a monitoring system for identifying and managing an increased risk of HF or worsening HF in people with CIEDs. The TriageHF algorithm is integrated within the implanted device and has Active Implantable Medical Devices (AIMD) classification.

TriageHF is an alert-based algorithm that is hosted on the Medtronic CareLink network platform for collaborative patient management between clinical teams. CareLink uses a plug-in monitor or a smartphone app for transmitting data. Using a mobile or landline connection, data are transmitted from the CIED to the CareLink network where it can be accessed by healthcare professionals. Data can be transmitted manually by patients if they perceive symptoms, automatically based on TriageHF algorithm alert triggers, or through a scheduled transmission based on a predefined date to replace a routine check. For each day the data is transmitted, the TriageHF algorithm generates a daily risk status of a heart failure event occurring in the next 30 days (low, medium or high risk) based on the maximum daily risk status for the previous 30 days. A heart failure management report is generated on the daily risk status.

TriageHF algorithm uses physiological parameters measured by the CIED (compatible Medtronic devices that monitor the OptiVol Fluid Status [thoracic impedance over time]) to create a hospitalisation risk score. The following parameters factor into the algorithm: atrial tachycardia (AT) or atrial fibrillation (AF) burden, ventricular rate during AT or AF, OptiVol fluid index (which tracks changes in thoracic impedance over time), general activity, night ventricular rate, heart rate variability, percent of ventricular pacing, treated ventricular tachycardia or ventricular fibrillation, and defibrillator shocks.

The CareLink network sends an alert for people who have high risk score so that they are contacted for a telephone consultation with a heart failure nurse. A set of standardised questions are used to distinguish between worsening heart failure and other issues. Healthcare professionals can also be

notified of alerts via text messaging or email. The manual states that there are no known contraindications for the use of TriageHF Plus. The TriageHF Plus care pathway is currently in use in 12 NHS Trusts, of which over 80% already have the CareLink platform installed.

1.3.4 CorVue and Merlin.net patient care network

The CorVue algorithm and Merlin.net patient care network (PCN) platform are intended for the remote monitoring of early signs of heart failure in people who have compatible implanted devices. The CorVue algorithm is integrated with the implanted device and has Active Implantable Medical Devices (AIMD) classification.

The CorVue algorithm collects intrathoracic impedance (ITI) data from the implanted device and transmits to the Merlin.net PCN platform via the mobile app (myMerlinPulse) using Bluetooth technology and an internet or mobile network connection to generate an alert. Alternatively, a remote monitoring unit (Merlin@Home) connected via wifi, mobile or landline connection, can be provided by the company instead of using the app-based smartphone transmitter. Healthcare professionals can view the data transmitted by the algorithm and device on the Merlin.net PCN platform. Access to Merlin.net and the mobile transmitter is provided as part of the CIED, and the CorVue algorithm comes free of charge with the CIED devices.

The CorVue algorithm automatically calculates the mean daily impedance (from 12 measurements taken daily) and collects reference impedance data based on the previous 12-14 days which changes continuously based on new impedance readings. If a consistent drop of daily impedance values is detected (13 or 14 consecutive days in congestion) then a congestive event is reported and detected during device check-up. Patient alerts can be activated via remote monitoring if the person wishes. Any medical condition that causes ITI to decrease (for example, a chest infection) may create a false positive. CorVue is suitable for people who have a CIED and congestive heart failure with ventricular dyssynchrony.

1.4 Population and relevant subgroups

The two populations, and their subgroups included in the NICE scope are listed below:

1. People who have a CIED and do not have a diagnosis of chronic heart failure but are at high risk of new onset acute heart failure

If data allowed analyses on the following subgroups were included. People who:

   a) have a CRT-P device

   b) have a CRT-D device

   c) have an ICD device

   d) have a pacemaker device

2. People who have a CIED and have a diagnosis of chronic heart failure

If data allowed, analyses on the following subgroups were included. People who:

   a) have a CRT-P device

b) have a CRT-D device

c) have an ICD device

d) have a pacemaker device

e) have a diagnosis of heart failure New York Heart Association (NYHA) class I and II, or III and IV (at study recruitment)

f) have a prior heart failure hospitalisation or urgent care visit within the last 12-months

1.5 Comparators

The current standard of care for monitoring HF risk for people who have CIEDs is periodic reviews of device function with a cardiac physiologist or cardiologist, and ad-hoc reviews of symptoms with a GP, specialist nurse, cardiologist or a heart failure team. Clinicians explained that reviews can be over the telephone or in-person, and that they are most commonly triggered by self-reporting of symptoms from the person with the CIED. The number and timing of the reviews varies in practice depending on patient symptoms. Clinical experts explained that reviews can be over the telephone or in-person, and that they are most commonly triggered by self-reporting of worsening symptoms from the person with the CIED. The organisation of heart failure monitoring pathways varies in practice between different trusts, and even between different hospitals.

For each of the technologies under assessment reported in Section 1.3, the comparator is the current standard of care for monitoring HF risk described above with the same CIED associated with the technology.

1.6 Care pathways

CIEDs are recommended as treatment options for specific people who have or are at high risk of HF. These devices include pacemakers, implantable cardiac defibrillators (ICDs) or cardiac resynchronization therapy (CRT) devices. Monitoring is recommended for people who have CIEDs. As a minimum, monitoring currently includes a clinical assessment, a review of medication, and renal function assessments. The frequency of the reviews varies according to the person's condition. Clinical experts highlighted that currently reviews are commonly triggered by worsening symptoms reported by the person with the CIED.

Remote monitoring systems capable of identifying new onset acute HF or worsening signs of HF (decompensation) using measurements captured by CIEDs could help clinicians identify people who need a review. When used within a monitoring pathway alongside standard care, earlier identification of people at risk of new onset acute HF or worsening signs of HF (decompensation) could ensure earlier access to interventions. This could help to prevent symptoms occurring or worsening, reducing cardiac events, improving health outcomes and resulting in fewer hospitalisations. Remote monitoring could also reduce the number of unnecessary follow-up appointments or face-to-face reviews, freeing up NHS resources, and travel, stress and anxiety for people with CIEDs.

1.7 Outcomes

Four key types of outcomes were considered: firstly, intermediate measures of prognostic accuracy and usage of the equipment; secondly, clinical outcomes concerned with mortality and morbidity (including adverse events from treatments); thirdly, patient-reported outcomes, such as health-related quality of life; fourthly, the cost-effectiveness of the intervention.

Intermediate outcomes

Technology performance, time, clinical management and resource outcomes were included as intermediate outcomes:

- Prognostic accuracy (including the number of false positive alerts)
- Changes to clinical management (including non-pharmacological treatment and medications)
- Time between an alert and a heart failure event
- Alert response rates (including time between an alert, clinical review and change in clinical management)
- Number of heart failure and all cause hospitalisations
- Number of emergency or urgent care visits
- Length of hospital stay
- Software failure rate (including failed data transmissions)
- Number of monitoring reviews (remote and face-to-face)

Clinical outcomes

Clinically defined health-related events and states were included as clinical outcomes:

- Rate of heart failure events
- Rate and category of atrial fibrillation (subclinical, paroxysmal or persistent/permanent)
- Morbidity (including adverse events from treatments)
- Changes in NYHA classification of symptoms
- Mortality (cardiac and all-cause mortality)

Patient-reported outcomes

Eligible outcomes that may be reported by patients include:

- Health-related quality of life
- Patient reported outcome measures such as satisfaction, anxiety and stress

- Patient adherence to treatment (as agreed between the prescriber and the person taking the medication)

Cost-effectiveness outcomes

Cost-effectiveness outcomes include cost-consequences, cost-effectiveness, cost-utility and cost-benefit outcomes.

1.8 Aims and Objectives

The aim of the project is to determine the clinical and cost-effectiveness of remote monitoring devices for identifying new onset acute HF or worsening signs of HF in people with CIEDs of the four technologies described in Section 1.3.

The objectives are:

Clinical effectiveness

- To perform a systematic review, narrative synthesis and, if feasible, a meta-analysis of the prognostic accuracy of the four remote monitoring systems
- To perform a systematic review, narrative synthesis and, if feasible, a meta-analysis of the clinical impact, such as morbidity and mortality, of the remote monitoring systems
- To perform a systematic review and narrative synthesis of patient and physician opinions on the value and ease-of-use of the remote monitoring systems

Cost effectiveness

- To conduct a systematic review of existing economic evaluation studies of the remote monitoring systems for identifying new onset acute HF or worsening signs of HF in people with CIEDs.
- To develop an in-house decision model to estimate the cost-effectiveness of remote monitoring systems for identifying new onset acute HF or worsening signs of HF in people with CIEDs.

2. Assessment of clinical effectiveness

2.1 Methods for reviewing clinical effectiveness

A systematic review of the clinical effectiveness of the included interventions was conducted following the general principles recommended by the Centre for Reviews and Dissemination (CRD) guidance.[15] We utilised Chapter 6 of the Cochrane Handbook for searching and selecting studies of diagnostic accuracy studies.[16]

2.1.1 Search Strategies

Comprehensive searches of published and unpublished literature were undertaken to identify all completed and ongoing studies relating to the use of algorithm-based remote monitoring of heart failure risk data in people with CorVue, HeartInsight, HeartLogic or TriageHF cardiac implantable electronic devices. Searches were designed following published guidance on how to search for medical devices[17] and included a combination of key and text words and controlled vocabulary search terms whenever supported by the database. An Information Specialist (HO'K) designed the search strategy in Ovid MEDLINE in collaboration with the lead Information Specialist (SG) and the rest of the team. The strategy consisted of title, abstract and key word search terms describing the interventions in scope (e.g. name of implantable device) and intended purpose or health condition. To maximise sensitivity, all known development names and device codes (FDA approved device codes) were used and combined with the Boolean operator 'OR'. The algorithm-based components of the interventions were searched separately in title, abstract and key word fields. Manufacturers' names indexed in specialist database fields designed to capture these data were also included. Algorithm and manufacturers' search strings were subsequently combined with the Boolean operator 'OR' and then combined with 'AND' with strings that described the intended purpose of the algorithm (e.g. Monitor or triage), and strings that focus on the health condition or subject of this appraisal (e.g. Heart failure). The final search strategy approach consisted of the following concepts:

[(**implantable device names) OR (algorithm names AND Purpose AND Condition)**]

Date, language, and study design limits were not applied. The final MEDLINE strategy was adapted for use in all resources searched. The searches were carried out between 14th and 20th of June 2023. The bibliographic databases and grey literature sources searched are reported in Table 3. Database results were downloaded into reference manager software EndNote 20 (Clarivate Analytics, US) for de-duplication. Supplementary search methods (e.g. backward and forward citation chasing) were used to identify potentially relevant studies cited or citing the included studies and in six reviews.[18-22] Company submission documents and company websites were also searched for additional relevant studies.

Search strategies are reported in Appendix 9.1.

Table 3: Databases searched

Source name	Platform/URL
MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions	Ovid
Embase	Ovid
CINAHL	EBSCO

Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library available at https://www.cochranelibrary.com/cdsr/reviews
Cochrane Central Register of Controlled Trial (CENTRAL)	Cochrane Library available at https://www.cochranelibrary.com/central
Database of Abstracts of Reviews of Effects (DARE)*	Centre for Reviews and Dissemination available at https://www.crd.york.ac.uk/CRDWeb/
PROSPERO (International prospective register of systematic reviews)	National Institute for Health and Care Research (NIHR) available at https://www.crd.york.ac.uk/PROSPERO/
INAHTA (International HTA database)	The International Network of Agencies for Health Technology Assessment available at https://database.inahta.org/
NIHR Journal Library	National Institute for Health and Care Research (NIHR) journals library available at https://www.journalslibrary.nihr.ac.uk/#/
INPLASY	International Platform of Registered Systematic Review and Meta-analysis Protocols available at https://inplasy.com/
Clinicaltrials.gov	National Library of Medicines (US National Institute for Health) clinical research studies online database available at https://clinicaltrials.gov/
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database available at https://www.clinicaltrialsregister.eu/ctr-search/search/
ICTRP	International Clinical Trials Registry Platform (World Health Organisation) available at https://trialsearch.who.int/Default.aspx
ScanMedicine	NIHR Innovation Observatory open access clinical trial database available at https://scanmedicine.com/
MedRxiv	Pre-print server for health sciences available at https://www.medrxiv.org/

* Content updated until 2015

2.1.2 Eligibility criteria

Population

People who have one of the CIEDs listed in Table 2 and do not have a diagnosis of chronic HF but are at high risk of new onset acute HF; and people who have a CIED and have a diagnosis of chronic HF.

Interventions

Algorithm-based remote monitoring systems for heart failure risk data in people with CIEDs (including Implantable cardioverter defibrillators [ICD] and Cardiac Resynchronization Therapy [CRT] devices):

CorVue and Merlin.net patient care network (Abbott Medical)

HeartInsight and BIOTRONIK home monitoring system (Biotronik)

HeartLogic and Latitude NXT Patient management system (Boston Scientific)

TriageHF and CareLink remote monitoring (Triage HF Plus; Medtronic)

Comparators

The comparator is standard care. The current standard of care for monitoring heart failure for people who have CIEDs is without use of remote monitoring. It includes periodic reviews of device function with a cardiac physiologist or cardiologist, and ad-hoc reviews of symptoms with a GP, specialist nurse, cardiologist or a heart failure team. The number and timing of the reviews varies depending on patient symptoms. The organisation of heart failure monitoring pathways varies in practice between different trusts, and even between different hospitals. For prognostic accuracy studies a reference standard will be implemented. This may vary between the studies and the definition of the reference standard will be extracted from the individual included studies.

Outcomes

See Table 4.

Study designs

We will consider all study designs that provide relevant outcome data as listed in Table 4.

Table 4: Outcomes eligible for inclusion

Outcome Type	Outcome(s) Assessed
Intermediate	• Prognostic accuracy (including the number of false positive alerts) • Changes to clinical management (including non-pharmacological treatment and medications) • Time between an alert and a heart failure event • Alert response rates (including time between an alert, clinical review and change in clinical management)

	• Number of heart failure and all cause hospitalisations • Number of emergency or urgent care visits • Length of hospital stay • Software failure rate (including failed data transmissions) • Number of monitoring reviews (remote and face-to-face)
Clinical	• Rate of heart failure events • Rate and category of atrial fibrillation (subclinical, paroxysmal or persistent/permanent) • Morbidity (including adverse events from treatments) • Changes in NYHA classification of symptoms • Mortality (cardiac and all-cause mortality)
Patient-reported	• Health-related quality of life • Patient reported outcome measures such as satisfaction, anxiety and stress • Patient adherence to treatment (as agreed between the prescriber and the person taking the medication)

2.1.3 Study Selection

The deduplicated citations in Endnote were exported to Rayyan, an online tool used to speed up the review process for title and abstract screening.[23] Ten percent of the records were piloted independently by two reviewers to assess initial agreement. Once complete, the same two independent reviewers assessed the remaining titles and abstracts (RK and NO'C). Full texts of any records that were deemed to be relevant at title and abstract were obtained. The two reviewers then independently screened these records (RK and NO'C). At all stages of the study selection process, disagreements were resolved through discussion.

2.1.4 Data extraction

We created and piloted a data extraction form, using four randomly chosen included studies. This allowed for the data extraction form to be refined and ensure its suitability. The data of the included studies were extracted by one reviewer using the standardised form and checked for accuracy by a second reviewer. Any discrepancies were resolved by discussion. Information extracted included the study design, methodology, intervention characteristics, patient baseline characteristics, and outcome measures. Studies with multiple publications were grouped and the most recent full-text publication chosen as the primary record, relevant outcome data was extracted from all grouped records, where the

same outcome data was reported in multiple publications the most up to date or complete report was used.

2.1.5 Quality assessment

The quality of prognostic/diagnostic test accuracy studies was assessed using the PROBAST (Prediction model Risk Of Bias Assessment Tool) tool.[24, 25]

Non-randomised studies were assessed using the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool.[26] Many of the included studies were single cohort designs (prospective and retrospective); that is, there was no comparative group. As such, any signalling questions attaining to the comparisons between two groups were not considered for these study designs. As no RCT evidence was identified for inclusion, we did not use the Cochrane risk of bias (RoB) tool.[27]

2.1.6 Method of data synthesis

The results of data extraction are presented in structured tables and as a narrative summary. A statistical synthesis using meta-analysis was proposed in the protocol. However, due to the diversity in conduct and outcomes reported it was judged inappropriate to combine any studies in meta-analysis.

3. Clinical effectiveness review results

3.1 General summary of evidence

The literature searches of bibliographic databases and registers identified 2699 references. Of those, 662 were duplicates and were removed. After screening of titles and abstracts, 512 were considered potentially relevant and the full-text articles were obtained. Eighty-one reports comprising 42 studies were ultimately included and 431 references excluded. Six of the included studies were identified from additional searching (company submission and websites).[28-33] Eighty-six supporting references were submitted by the four companies. The full study selection process is illustrated in the PRISMA diagram in Figure 2. The 431 studies excluded at full text stage are listed in Appendix 9.3 Table 48 along with their reasons for exclusion.

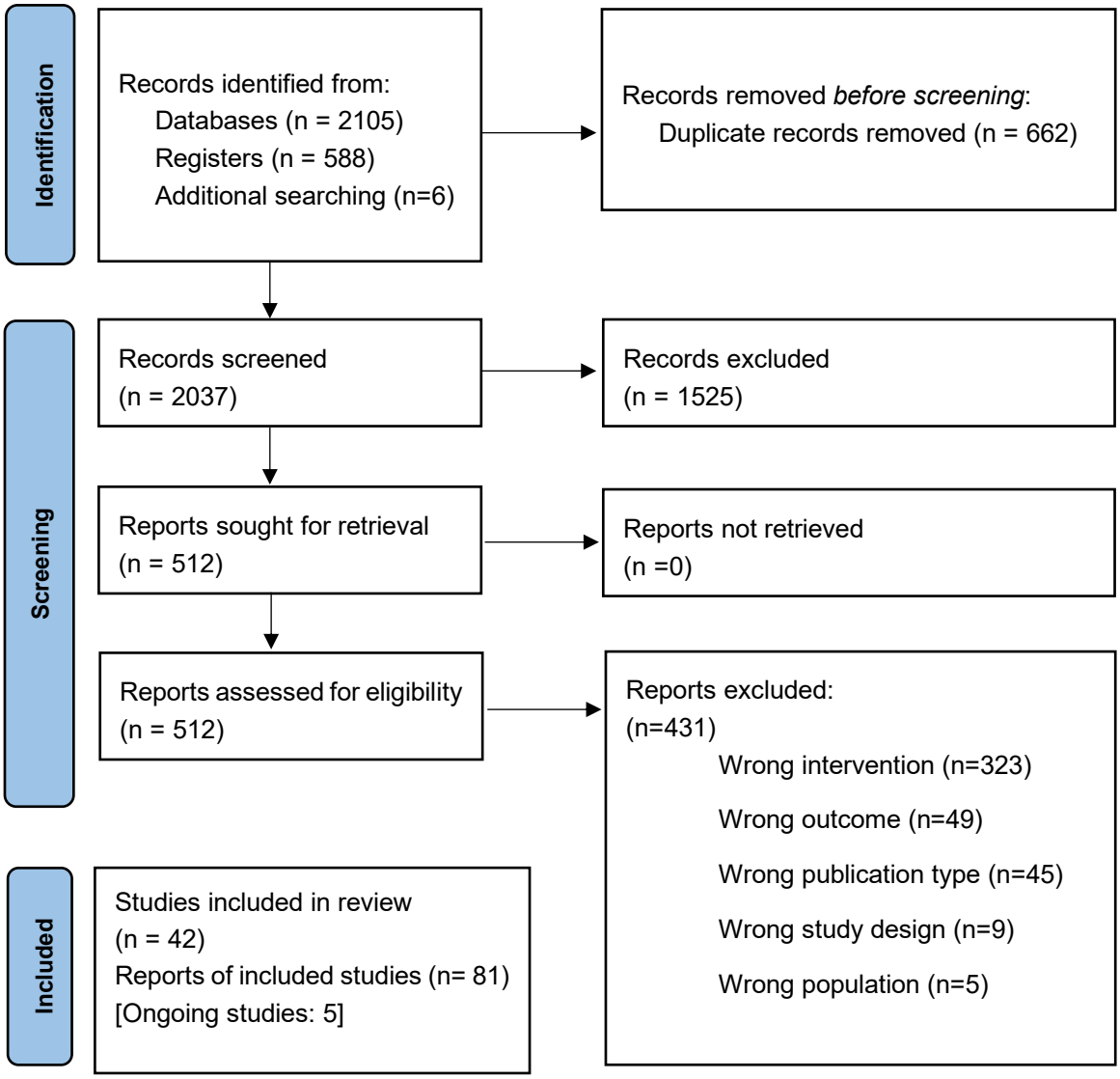


Figure 2: PRISMA flow diagram of the study selection process for clinical effectiveness review

3.2 Overview of the included studies

Five studies have been placed in awaiting classification Appendix 9.4 (Table 49). Forty-two studies met the eligibility criteria and have results which are synthesised in this systematic review. The study characteristics of the 42 included studies are given in Appendix 9.5 (Table 50, Table 51, Table 52, Table 53). In summary, one study was identified for the HeartInsight algorithm (Biotronik), eight for the CorVue algorithm (Abbott medical), 14 for TriageHF (Medtronic) and lastly, 19 for HeartLogic (Boston Scientific). One study for CorVue was comparative,[34] three studies for HeartLogic were comparative,[35-37] and one study for TriageHF was comparative.[28] The one identified HeartInsight study was conducted in Italy and Spain. Where stated, most studies for CorVue were carried out in the USA, most studies evaluating TriageHF were conducted in the UK, studies of HeartLogic were mostly conducted in Italy followed by the USA. Overall, eight studies were conducted in the UK, six for Triage-HF and two for HeartLogic.

Of the 42 included studies, 26 were reported as being prospective cohorts, 10 were retrospective cohorts, four were described as cohorts and two as development and validation studies using datasets from observational and randomised controlled trials. There were no randomised controlled trials included and comparative evidence was limited to five studies.[28, 34-37]

3.3 Summary of study designs and outcomes

Outcomes provide evidence on the prognostic performance of an algorithm and association with clinical outcomes, comparative effectiveness of an algorithm, and implementation characteristics of an algorithm. Observational, single cohort study designs may provide evidence on prognostic performance, association with clinical outcomes and implementation characteristics. A single cohort study that reports the relative risk of hospitalisation IN or OUT of alert may be considered to have some predictive value. Comparative study designs (before-and-after or concurrent controlled studies) may provide evidence on comparative effectiveness and implementation characteristics. Especially poor quality studies providing evidence on comparative outcomes include single cohort studies that are treated as before-and-after studies where the baseline measure is considered an outcome measure in the absence of the intervention and retrospective medical chart reviews of CorVue compared to standard care.

Broad definitions of heart failure events used to determine the prognostic accuracy of the algorithms included combinations of changes to clinical management, hospitalisations and, to a lesser extent, mortality. Comparative outcomes could have included mortality, hospitalisations, changes to clinical management and length of hospital stay and patient-reported outcomes; but no comparative evidence was reported for mortality and patient-reported outcomes. Implementation characteristics may include alert response rates, software failure rate and number of monitoring reviews.

Outcomes are reported under the following sections:

- prognostic and association outcomes,
- comparative outcomes, and
- implementation outcomes

All the outcomes listed in the NICE scope and DA protocol are included in each of these sections as appropriate. All of the protocol outcomes (see section 1.7) were categorised into one of three groups: intermediate outcomes (diagnostic accuracy and predictive values), intermediate outcomes (other),

and clinical outcomes. Table 4 provides a more detailed description of the outcome domains assessed within the three categories.

Table **5** categorises outcomes at the broadest level (prognostic, comparative, implementation). Outcome domain and quality of reporting varied within and across technologies**.**

Table 5: Categorisation of outcomes at the broadest level (prognostic, comparative effectiveness, implementation)

Research outcome type and study design	**Intervention, clinical, patient outcome type**	**Scope/protocol outcomes**
Prognostic accuracy and associations (Single cohort study)	Intermediate- accuracy	False-positives, unexplained alert rates
	Intermediate- other	Not applicable
	Clinical	Changes to clinical management, hospitalisations, rate of heart failure events and mortality (cardiac and all-casue), heart failure events
	Patient reported	Not applicable
Comparative (Before-and-after study, controlled concurrent study, poor quality single cohort study)	Intermediate- accuracy	Not applicable
	Intermediate- other	Not applicable
	Clinical	Heart failure events, hospitalisations, mortality
	Patient reported	Quality of life
Implementation (Single cohort, before-and-after or controlled concurrent study	Intermediate- accuracy	Not applicable
	Intermediate- other	Changes to clinical management, time between alert and heart failure event, alert response rates, number of emergency or urgent care visits, software failure rates, adverse events, number of monitoring reviews
	Clinical	Adverse events
	Patient reported	Quality of life

3.4 Study quality

All studies that reported prognostic outcomes including sensitivity and specificity underwent risk of bias assessments at the study level using PROBAST. All non-randomised studies reporting clinical outcomes relevant to the PICO underwent risk of bias assessment at the study level using ROBINS-I. If a study reported both prognostic and clinical outcomes, they were appraised using both PROBAST and ROBINS-I. No studies were appraised using RoB because none of the included studies were randomized controlled trials. For prognostic outcomes, most eligible studies were external validations of previously developed predictive algorithms. Therefore, quality assessments were mainly conducted on validation studies, as data on the development of these algorithms were not available.

3.4.1 Risk of bias assessments for CorVue

Six external validation studies reported prognostic outcomes (Table 6).[24, 25, 29, 38-42] These were all assessed as being of high risk of bias. Of particular concern was the conduct or poor reporting of the analysis methods (for example, small sample sizes and limited numbers of participants who experienced the outcome).

Table 6: PROBAST risk of bias and applicability assessment summary for CorVue studies

Study	Study design	Risk of Bias				Applicability			Overall	
Author, Year		1.Participants	2. Predictors	3. Outcome	4. Analysis	1.Participants	2. Predictors	3. Outcome	**Risk of Bias**	**Applicability**
Benezet Mazuecos, 2016	Cohort	?	+	?	-	+	+	+	-	+
Binkley, 2012	Cohort	-	-	-	-	-	+	+	-	+
Forleo, 2013	Cohort	+	?	+	-	-	?	+	-	+
Palfy, 2015	Cohort	?	?	?	?	+	+	+	-	+
Palfy, 2018	Cohort	+	+	?	-	+	+	+	-	+
Wakabayashi, 2021	Cohort	-	?	-	-	-	?	+	-	+

Key	
+	Low risk of bias/concern
-	High risk of bias/concern
?	Unclear risk of bias/concern

Five studies evaluating the CorVue algorithm reported relevant clinical outcomes and underwent risk of bias assessment using ROBINS-I[26] (see Table 7). All studies were considered to be at serious or critical risk of bias due to the inherent limitations associated with confounding in cohort study designs, particularly retrospective designs.[34, 42-44]

Shapiro *et al.*[34] was the only CorVue study that included comparative data from patients who did not have the CorVue algorithm. The comparator was based on a retrospective medical chart review at substantial risk of confounding.

Table 7: ROBINS-I risk of bias assessment summary for CorVue studies

Study Author, year	Study design	D1	D2	D3	D4	D5	D6	D7	Overall
Benezet Mazuecos, 2016	Cohort								Serious

Forleo, 2013	Prospective Cohort								Serious
Santini, 2012	Cohort								Serious
Shapiro, 2017	Cohort with external comparator								Critical
Wakabayashi, 2021	Retrospective Cohort								Critical

D1: Bias due to confounding
D2: Bias due to selection of participants
D3: Bias in classification of interventions
D4: Bias due to deviation from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result

Key	
	Low risk of bias
	Moderate risk of bias
	Serious risk of bias
	Critical risk of bias
	No information

3.4.2 Risk of bias assessments for HeartInsight

One prospective cohort evaluated the prognostic accuracy in the development (sensitivity, specificity) and validation (sensitivity, specificity, NPV and PPV) of HeartInsight. This study was judged to be at high risk of bias due to concerns around the conduct or reporting in the analysis (such as missing data and the statistical analysis) (Table 8). There were no concerns about the applicability of the participants, predictors and outcomes to our research question (Table 8).

Table 8: PROBAST risk of bias and applicability assessment summary for HeartInsight

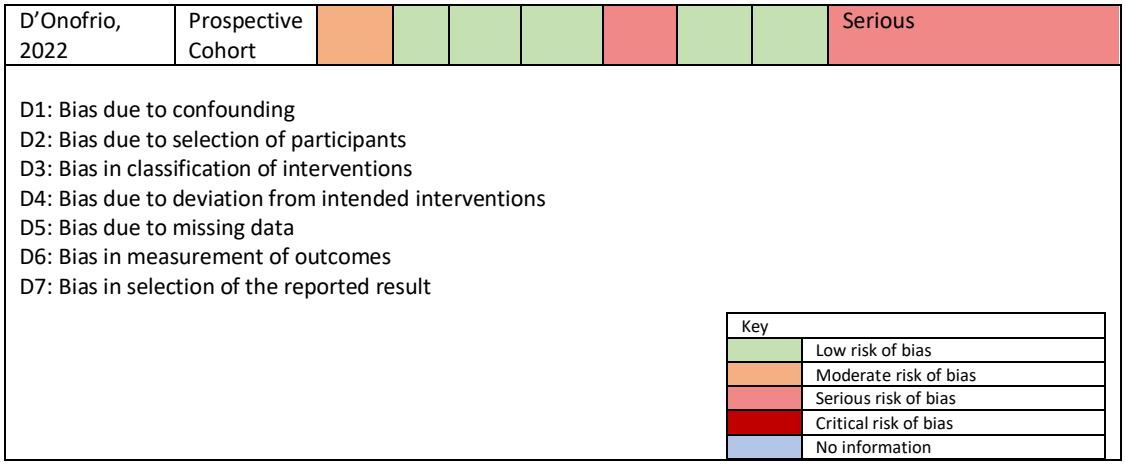
Study	Study design	Risk of Bias				Applicability			Overall	
Author, Year		1.Participants	2. Predictors	3. Outcome	4. Analysis	1.Participants	2. Predictors	3. Outcome	**Risk of Bias**	**Applicability**
D'Onofrio, 2022	Prospective cohort	+	+	+	-	+	+	+	-	+

Key	
+	Low risk of bias/concern
-	High risk of bias/concern
?	Unclear risk of bias/concern

Important concerns about missing data in the D'Onofrio *et al.* study were identified, which led to an overall risk of bias rating of serious concerns.[45] In addition, moderate concerns about confounding were also identified (Table 9).

Table 9: ROBINS-I risk of bias assessment for HeartInsight

Study Author, year	Study design	D1	D2	D3	D4	D5	D6	D7	Overall



3.4.3 Risk of bias assessments for HeartLogic

There was judged to be high risk of bias associated with the analysis methods used in all eligible studies evaluating prognostic accuracy outcomes for HeartLogic. These issues can be attributed to a lack of robust analysis, and small number of included participants with the outcome. There were no concerns regarding the applicability of the primary studies to our review question (Table 10).

Table 10: PROBAST risk of bias and applicability assessment summary for HeartLogic

Study	Study design	Risk of Bias				Applicability			**Overall**	
Author, Year		1. Participants	2. Predictors	3. Outcome	4. Analysis	1. Participants	2. Predictors	3. Outcome	**Risk of Bias**	**Applicability**
Boehmer, 2017	Prospective Cohort	+	+	+	-	+	+	+	-	+
De Juan Baguda, 2022 (phase 1)	Retrospective Cohort	+	?	?	-	+	?	+	-	+
De Juan Baguda, 2022 (phase 2 and 3)	Prospective Cohort	+	?	?	-	+	?	+	-	+
De Ruvo, 2019	Prospective Cohort	-	?	?	-	+	?	+	-	+
Henry, 2022	Retrospective Cohort	+	?	+	-	+	?	+	-	+
Santobuono, 2023	Prospective Cohort	?	?	+	-	+	?	+	-	+
Treskes, 2021	Retrospective pre-post study design	+	+	+	-	+	+	+	-	+
Vigdor, 2020	Prospective Cohort	?	?	+	-	+	?	+	-	+
Wariar, 2023	Retrospective Cohort	?	?	?	-	+	?	+	-	+

Key	
+	Low risk of bias/concern
-	High risk of bias/concern
?	Unclear risk of bias/concern

Five of the studies which included clinical outcomes were at critical risk of bias, and caution should be given when interpreting the findings because the studies are too problematic to draw inferences with any degree of reliability (Table 11).[35, 46-50] The critical risk of bias for all studies, including Chang *et al*., a retrospective cohort with comparative data, can be explained by a lack of robust analysis to attempt to control for confounding and small participant numbers. The only other studies to include comparative data for HeartLogic, a propensity matched cohort by Feijen *et al.* and a pre-post study by Treskes *et al*., was at serious risk of bias due to classification of interventions and problems with uncontrolled confounding, respectively. Gardner *et al*., a post hoc analysis from a prospective cohort, was the only study to be considered as low risk of bias in all seven domains.

Table 11: ROBINS-I risk of bias assessments for HeartLogic

Study Author, year	Study design	D1	D2	D3	D4	D5	D6	D7	Overall
Calo, 2021	Prospective Cohort	+	+	+	+	+	-	+	Moderate
Chang, 2020	Retrospective Cohort with external comparator	-	+	+	+	+	+	+	Critical
De Juan Baguda, 2022 (phase 1)	Retrospective Cohort	-	+	+	+	+	+	+	Serious
De Juan Baguda, 2022 (phase 2/3)	Prospective Cohort	-	-	-	+	+	-	+	Serious
D'Onofrio 2023	Prospective Cohort	-	+	+	+	+	+	+	serious
Ebrille, 2021	Prospective Cohort	-	-	+	+	-	+	+	Critical
Feijen, 2023	Retrospective Cohort (propensity matched)	+	+	-	+	-	-	+	Serious
Gardner, 2018	Prospective Cohort (secondary analysis)	+	+	+	+	+	+	+	low
Guerra, 2022	Prospective Cohort	-	+	-	+	+	-	+	Moderate
Henry, 2022	Retrospective Cohort	-	+	+	+	-	+	?	Critical
Hernandez, 2022	Prospective Cohort	-	+	-	-	+	-	+	Serious
Lerman, 2023	Retrospective Cohort	-	-	-	+	+	-	+	Critical
Pecora, 2020	Prospective Cohort	-	-	-	+	+	-	?	Serious
Perez Serrano, 2019	Prospective Cohort	-	-	-	-	-	-	?	Critical
Santini, 2020	Prospective Cohort	-	+	-	+	+	-	+	Serious

Santobuono, 2023	Prospective Cohort								Moderate
Treskes, 2021	Retrospective pre-post study design								Serious
Vigdor, 2020	Prospective Cohort								Serious

D1: Bias due to confounding
D2: Bias due to selection of participants
D3: Bias in classification of interventions
D4: Bias due to deviation from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result

Key	
	Low risk of bias
	Moderate risk of bias
	Serious risk of bias
	Critical risk of bias
	No information

3.4.4 Risk of bias assessments for TriageHF

The overall risk of bias and applicability is unclear for three of the studies assessed because they were abstracts and contained limited information (Table 12).[51-53]

Table 12: PROBAST risk of bias and applicability assessment summary for TriageHF

Study	Study design	Risk of Bias				Applicability			Overall	
Author, Year		1.Participants	2. Predictors	3. Outcome	4. Analysis	1.Participants	2. Predictors	3. Outcome	**Risk of Bias**	**Applicability**
Ahmed, 2020	Cohort	+	+	-	-	-	+	-	High	High
Ahmed 2022	Cohort	+	+	-	-	-	+	+	High	High
Bachtiger, 2021	Prospective Cohort	?	?	?	?	+	?	?	Unclear	Unclear
Burri, 2018	Cohort (secondary analysis)	+	+	+	?	+	+	+	Unclear	Low
Cardoso, 2021	Prospective Cohort	?	?	+	?	?	?	+	Unclear	Unclear
Cowie, 2013	Validation and development study - observational and randomised	+	+	+	?	+	+	+	Unclear	Low
Gula, 2014	Validation study -using data from RCT	+	+	+	+	-	+	-	Low	High
Koehler, 2019	Cohort	+	?	+	?	?	?	+	Unclear	Unclear
Okumura, 2020	Prospective Cohort	+	+	-	-	+	+	+	High	Low
Sammut-Powell, 2022	Prospective Cohort	+	+	+	-	+	+	+	High	Low
Zile, 2020	Retrospective Cohort	+	+	-	-	+	+	+	High	Low

Key	
+	Low risk of bias/concern
-	High risk of bias/concern
?	Unclear risk of bias/concern

Ahmed *et al.*, the only study to provide comparative data for Triage-HF, is at critical risk of bias due to missing information, including whether propensity score matching was successful and the majority of hospitalisations being unrelated to heart failure or cardiovascular disease (Table 13). In addition, three other studies are at critical risk of bias due to issues with confounding and four are at serious risk of bias because of confounding or the poor reporting of data. No studies that were assessed using ROBINS-I were at low risk of bias.

Table 13: ROBINS-I risk of bias assessment summary for TriageHF

Study Author, year	Study design	D1	D2	D3	D4	D5	D6	D7	**Overall**
Ahmed (AiC)	Prospective Cohort with comparator								Critical
Burri, 2018	Cohort (secondary analysis)								Critical
Debski, 2021	Prospective Cohort								No information
Garner, 2022	Prospective Cohort								Critical
Virani, 2018	Prospective Cohort								Critical
Zile, 2020	Retrospective Cohort								Serious
Zile, 2021	Prospective Cohort								Serious

D1: Bias due to confounding
D2: Bias due to selection of participants
D3: Bias in classification of interventions
D4: Bias due to deviation from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result

Key	
	Low risk of bias
	Moderate risk of bias
	Serious risk of bias
	Critical risk of bias
	No information

3.5 Prognostic accuracy and association outcomes

3.5.1 Prognostic accuracy

This section reports the development of algorithm analytics to determine alerts, and prognostic accuracy defined as sensitivity and specificity. All measures of predictive accuracy associated with algorithm alerts (sensitivity, specificity, rate ratios, hazard ratios, relative risks, odds ratios and percentages of clinical outcomes) for specific outcomes are reported in subsequent sections for each outcome definition.

Results for the accuracy of the algorithms were available in 24 studies: HeartLogic n = 8, CorVue n = 5, TriageHF n = 10, and HeartInsight n = 1.

HeartInsight was developed and externally validated using data from the selection of potential predictors of worsening heart failure (SELENE-HF) study.[45] The algorithm was developed using both CRT-D and ICD devices. An index was developed using remote monitoring variables (see Table 14) to develop a linear combination of the variables after numerical processing. In this study, index levels of 3.5, 4.0, and 4.5 were assessed.[45] In the development cohort, a unitary increase of the index value was associated with an OR of 2.73 (95% CI: 1.98 to 3.78, p <0.001) for the first post-implant worsening HF hospitalisation.[45] The results suggested that the nominal threshold of 4.5 had the potential to identify worsening HF related to hospitalisations (see Table 14).[45]

Table 14: Algorithm components and alert threshold for CorVue, HeartInsight, HeartLogic and TriageHF

Algorithm components and threshold for alerts			
CorVue	HeartInsight	HeartLogic	Triage HF[54] (CRT-D, DR-ICD, VR-ICD, CRT-P and DR-IPG)
1. Intrathoracic impedance (ITI) *,†	1. Atrial burden 2. Heart rate variability 3. General activity 4. Thoracic impedance 5. Heart rate 6. Heart rate at rest 7. Premature ventricular contractions 8. Baseline rate parameter Seattle Heart Failure Model (SHFM) (optional)	1. Heart sounds (S1 & S3) 2. Thoracic impedance 3. Respiratory rate & tidal volume 4. Nocturnal heart rate 5. Activity level	1. OptiVol 2. Patient activity 3. AT/AF burden‡ 4. Ventricular rate during AT/AF‡ 5. % Ventricular pacing§ 6. Shocks¶ 7. Treated VT/VF¶ 8. Night ventricular rate 9. Heart rate variability
12 measurements are taken daily (every two hours) and compared to a reference impedance (mean impedance of previous 12-14 days). If the mean daily impedance is less than the reference impedance for 13-14 consecutive days (ICD and CRT-D respectively) an alert is triggered.	Transmissions were calculated daily; HF scores equal to or greater than the nominal threshold of 4.5 triggered an alert. Following an alert, the threshold was reduced to a recovery threshold of 3.5. When a HF score dropped below 3.5 the alert was cancelled	Alerts are triggered when the index exceeds the nominal threshold of 16 and moves into an 'alert-state'. Alerts continue until the index falls below the threshold of 6 and moves to an 'out-of-alert state'.	HF risk is calculated based on the parameters measured from previous 30 days the risk status is calculated into low (<0.054), medium (0.054-0.20) and high risk (≥0.20) of HF.[55]

* ITI measured as a multi-vector between right ventricular ring to can and right ventricular coil to can for ICD devices[40]

† ITI measured as a multi-vector left ventricular ring to can and right ventricular coil to can for CRT-D devices

‡ Not applicable for VR- implantable cardioverter defibrillators (ICDs)

§ Not applicable for DR-ICD, VR-ICD and DR-implantable pulse generator (IPG)

¶ Not applicable for CRT-P (Cardiac Resynchronization Therapy-Pacemaker) and DR-IPG devices

HeartLogic was developed and externally validated using data from the evaluation of multisensory data in heart failure patients with implanted devices (MultiSENSE) study.[56] The algorithm was developed using only CRT-D devices. An index was developed using remote monitoring variables (see Table 14), from which a nominal threshold was developed (i.e. ≥16). If this threshold was crossed the algorithm was deemed to be IN alert, if not the patient was classified as OUT of alert.[56] The nominal threshold was suggested to be effective at predicting HF events (see Table 14).[56] One study assessed the accuracy of the HeartLogic algorithm in a management strategy, where they applied the nominal threshold of ≥16 and also a threshold of ≥20.[57]

The feasibility of using the CorVue algorithm, which uses impedance measures derived from a number of vector combinations (see Table 14), was assessed using a retrospective cohort, showing low sensitivity with patients implanted with CRT-Ds (see Table 15).[29] Similar results were reported when assessing HF events in other retrospective cohorts (see Table 15) (Forleo 2013; Wakabayashi 2021).[38, 42] Further cohort studies reported a much lower sensitivity (<30%) and suggested the use of the CorVue algorithm could provide misleading information (see Table 15).[40, 43]

TriageHF was developed and externally validated using data collected in a number of trials (development: OFISSER,[58] Italian Clinical Service Project,[59] and CONNECT;[60] validation: PARTNERS-HF,[61] FAST,[62] PRECEDE-HF,[63] and SENSE-HF[64]).[30] The algorithm includes multiple parameters (see Table 14) with the aim of developing a risk score for the identification of patients at higher risk of HF. Patients with a high risk score were identified as being 10 times more likely to have a HF hospitalisation in the next 30 days (Hazard Ratio (HR) = 10, 95% CI: 6.4 to 15.7, p <0.001) compared to the low risk group. Results were similar when adjusted for the presence of HF hospitalisation in the last 30 days (HR = 8.2, 95% CI: 5.1 to 13.1, p <0.001).[30] The Triage HF risk score was also reported to have acceptable discriminatory ability when assessing worsening HF, compared to clinical diagnosis alone or alongside an acute medical problem (see Table 15).[65] In contrast, data from the MORE-CARE study was utilised to assess the impact of a high risk score from the Triage HF algorithm with sensitivity reported <40% for 30-day HF hospitalisations, cardiovascular hospitalisations and non-HF related cardiovascular hospitalisations (see Table 15).[33, 66] Sensitivity was also low for all cause, cardiovascular and HF hospitalisations in a prospective cohort (see Table 15).[67] Similar results were observed in a prospective analysis of patients in high risk compared to medium and low risk categories. However, when combining high and medium risk, compared to low risk, sensitivity was improved (see Table 15).[68]

One study assessed the accuracy of Triage HF and reported calibration, comparing Triage HF with an updated version (this model was not considered in this review as we were only concerned with the current Triage HF model).[69] However, the original version of Triage HF showed reasonable calibration (calibration in the large = 0.15, 95% CI: -0.74 to 2.09; slope = 1.08, 95% CI: 0.57 to 2.07), but its discriminatory ability of predicting HF related mortality was low (see Table 15).[69]

Table 15: Studies reporting predictive accuracy measures (studies are grouped by outcomes: hospitalisation, clinic visits and changes to treatment; hospitalisation or death; hospital admission alone; worsening HF; mortality alone; and HF events (undefined); with solid black lines showing the end of each outcome group; if threshold is not reported the nominal threshold was used: see Table 14).

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
Boehmer (2017)[56]	Prospective cohort (overall n = 900*; validation n = 400)[$]	HeartLogic	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	NR	70.0 (55.4 to 82.1)	85.7	11.3	99.98
De Juan Baguda (2022)[70]	Phase 1 (n = 101) and 2 (n = 94) are retrospective cohorts Phase 3 (n = 267) is a prospective cohort	HeartLogic	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	NA	Phase 1 = 100 Phase 2 and 3 = 98	Phase 1 = 93 Phase 2 and 3 = 90	Phase 1 = 18 Phase 2 and 3 = 29	Phase 1 = 100 Phase 2 and 3 = 99.9
Vigdor (2020)[57]	Prospective cohort (n = 80)	HeartLogic	HF events of unscheduled visits or HF hospitalisations within 6-weeks of initial alert This study assessed the standard	NA	Threshold ≥16 = 92 ≥20 = 69	Threshold ≥16 = 61 ≥20 = 90	Threshold ≥16 = 32 ≥20 = 56	Threshold ≥16 = 98 ≥20 = 94

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
			threshold of ≥16 and an alternative threshold of ≥20					
De Ruvo (2019)[71]	Prospective cohort (n = 101)	HeartLogic	hospitalisations and unplanned office visits	NA	100	NR	58	NR
Binkley (2012)[29]	Retrospective cohort (n = 61*)	CorVue	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	NA	61.9	NR	40.6	NR
Forleo (2013)[38]	Prospective cohort (n = 80)	CorVue	HF events of HF hospitalisations requiring treatment changes and HF hospitalisations alone	NA	HF events = 61.5 (46 to 75) HF hospitalisations = 53.8 (29 to 77)	NR	HF events = 42.9 (31 to 56) HF hospitalisations = 17.9 (9 to 33)	

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
Benezet Mazuecos (2016)[43]	Cohort, unclear (n = 70)	CorVue	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening and unplanned office visits	NR	20	77	5	94
Palfy (2018)[40]	Prospective cohort (n = 53)	CorVue	HF events of hospitalisations and clinic visits with change to treatment with primary cause of HF worsening	NR	24	70	6	93
Burri (2018)[33]	Retrospective analysis of a single study (n = 722)	Triage HF	Cardiovascular or HF or non-HF related hospitalisations	NR	All values are for high risk status Cardiovascular hospitalisations = 25.5 (18.8 to 33.6) HF hospitalisations = 37.4 (26.5 to 49.8)	All values are for high risk status Cardiovascular hospitalisations = 90.2 (88.6 to 91.5) HF hospitalisations = 90.1 (88.6 to 91.5)	All values are for high risk status Cardiovascular hospitalisations = 5.8 (3.9 to 8.5) HF hospitalisations = 4.1 (2.5 to 6.7)	All values are for high risk status Cardiovascular hospitalisations = 98.0 (97.5 to 98.4) HF hospitalisations

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
					Non-HF cardiovascular hospitalisations = 15.4 (9.2 to 24.7)	Non-HF cardiovascular hospitalisations = 89.9 (88.3 to 91.3)	Non-HF cardiovascular hospitalisations = 1.7 (0.9 to 3.0)	= 99.1 (98.7 to 99.4) Non-HF cardiovascular hospitalisations = 98.9 (98.5 to 99.2)
Okumura (2020)[68]	Prospective cohort (n = 315)	Triage HF	HF hospitalisations requiring treatment changes	NR	High vs. Medium + low = 31.5 High + Medium vs. low = 78.7	High vs. Medium + low: 89.0 High + Medium vs. low: 44.4	High vs. Medium + low: 4.1 High + Medium vs. low: 2.1	High vs. Medium + low: 98.8 High + Medium vs. low: 99.3
Sammut-Powell (2022)[67]	Prospective cohort (n = 435)	Triage HF	All cause or cardiovascular or HF related hospitalisations	NR	For high risk All cause hospitalisation = 37.3 Cardiovascular hospitalisation = 39.3 HF hospitalisations = 62.5	For high risk All cause hospitalisation = 86.2 Cardiovascular hospitalisation = 85.7 HF hospitalisations = 85.6	NR	For non-high risk All cause hospitalisation = 97.5 Cardiovascular hospitalisation = 99.1 HF hospitalisations = 99.7

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
D'Onofrio (2022)[45]	Prospective cohort (overall n = 918*; validation n = 461)[$]	HeartInsight	Secondary: any HF hospitalisation, outpatient IVI or death	Secondary endpoint NR	3.5 = 64.5 (51.3 to 76.2) 4.0 = 59.7 (46.4 to 71.9) 4.5 = 54.8 (41.7 to 67.5)	3.5 = 75.3 (75.2 to 75.4) 4.0 = 82.0 (81.9 to 82.2) 4.5 = 86.5 (86.4 to 86.6)	3.5 to 4.5 = 5.3 to 7.7	3.5 to 4.5 = 96.6 to 96.7
Koehler (2019)[53]	Retrospective analysis of registry data (n = 13 122)	Triage HF	HF hospitalisation, outpatient IVI, or death	NR	High risk = 41	High risk = 86	NR	NR
Santobuono (2023)[72]	Prospective cohort (n = 568)	HeartLogic	Hospitalisation or death	NA	Hospitalisation alone 66 (52-78) Hospitalisation or death 67 (57-75)	NR	NR	NR
Treskes (2021)[37]	Retrospective pre-post analysis (n = 68)	HeartLogic	Hospital admission	NA	90 (77-97)	89 (79-95)	NR	NR
Cowie (2013)[30]	Retrospective analysis of seven studies (overall n = 2231, development n = 921, validation n = 1310)	Triage HF	Hospital admission	NR	Low/medium risk score (5%) = 82.8 Medium/high risk score (20%) = 46 Risk score 10% = 68.7	Low/medium risk score (5%) = 45.8 Medium/high risk score (20%) = 90.2 Risk score 10% = 71.6	NR	NR

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
Cardoso (2020)[52]	Prospective cohort (n = 94)	Triage HF	Hospital admission	0.812	NR	NR	NR	NR
D'Onofrio (2022)[45]	Prospective cohort (overall n = 918; validation n = 378)[$]	HeartInsight	Primary: First post implant worsening HF hospitalisation	Primary endpoint NR	3.5 = 72.4 (52.8 to 87.3) 4.0 = 65.5 (45.7 to 82.1) 4.5 = 65.5 (45.7 to 82.1)	3.5 = 75.8 (75.6 to 75.9) 4.0 = 82.4 (82.3 to 82.5) 4.5 = 86.7 (86.6 to 86.8)	NR	NR
Bachtiger (2021)[51]	Prospective cohort (n = 72)	Triage HF	Worsening HF	NR	High risk = 87.9 (77.0 to 99.0)	High risk = 59.4 (50.0 to 69.0)	High risk = 40.3	High risk = 94.0
Ahmed (2020)[65]	Prospective cohort (n = 231)	Triage HF	Worsening HF (undefined)	0.75 (0.69 to 0.80)	High risk = 98.6 (92.5 to 100)	High risk = 63.4 (55.2 to 71.9)	NR	NR
Wakabayashi (2021)[42]	Retrospective cohort (n = 49)	CorVue	HF event defined by the Framingham Heart Study	NR	68 (48 to 84)	NR	21 (13 to 30)	NR
Ahmed (2022)[69]	Prospective cohort (n = 439)	Triage HF	Mortality	0.61 (0.56 to 0.66)	NR	NR	NR	NR
Zile (2020)[73]	Retrospective cohort (monthly downloads n = 22 901; alert	Triage HF	HF events (undefined)	NR	Monthly downloads high risk score = 39	Monthly downloads high risk score = 89	NR	NR

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
	triggered n = 21,356; daily downloads n = unclear)				Monthly downloads medium risk score = 85 Alert triggered high risk score = 47 Daily downloads high risk score = 51 Daily downloads medium risk score = 93	Monthly downloads medium risk score = 44 Alert triggered high risk score = NR Daily downloads high risk score = NR Daily downloads medium risk score = NR		
Henry (2022)[47]	Retrospective cohort (n = NR)	HeartLogic	HF events (undefined)	NA	70	NR	NR	NR
Wariar (2023)[74]	Retrospective cohort (n = 1567)	HeartLogic	HF events (undefined)	NA	82 (78.1-85.5)	NR	NR	NR

NR = Not Reported; NA = Not Applicable; HF = Heart Failure; *denotes number analysed; $denotes that the study reported development and validation cohorts but only the validation is reported in the table

3.5.2 False positive rates

Results of false positives tests were reported in 15 studies, HeartLogic n = 7, CorVue n = 7, TriageHF n = 2, and HeartInsight n = 1 (see Table 16). The false positive rate is the most important statistic. The percentage of alerts that are false is less useful because it provides less information on the burden on the health system. The EAG has not calculated the percentage of alerts that were false to focus attention on false positive rates.

HeartInsight

The study reporting the accuracy of HeartInsight defined the false positive alert as an alert that was not followed by the primary or secondary study endpoint (see Table 16).[45]

CorVue

One CorVue study defined a false positive as an alert after which no HF event occurred within 14 days.[38] Another defined a false positive as an alert that began more than 30 days before a clinical event was classified.[29] One study did not define a time period for false positives and merely stated that a false positive occurred if an alert was detected without subsequent clinical event.[40] Three studies did not explicitly define a false positive.[42,43,75]

HeartLogic

Two HeartLogic studies defined the false positive rate as the ratio of the total number of alerts that were not true positive alerts over the total usable follow up duration.[56,72] One study defined a false positive as three consecutive remote evaluations (at 2, 6 and 10 weeks after the initial alert) with consistently fewer than two symptoms or signs of HF at each evaluation, an ongoing alert was disregarded.[19, 36] Similarly, Treskes *et al.* defined a false positive as occurring after three remote evaluations with no or less than two symptoms or signs of HF per evaluation, where the alert was then disregarded.[37] One study defined false positive alerts as unexplained alerts plus explained alerts.[70]

TriageHF

One TriageHF study included here did not explicitly report false positives but the false positives were calculated based on the number of high risk alerts that did not require any further intervention.[31] The other reported false positives (also termed unexplained detections) per patient year.[73]

Table 16: Evidence for the outcome of number of false positives and false positive rates for the algorithms

Author (year)	Study design (n)	Intervention	Number of false positives	False positive rate
Santini (2012)[75]	Cohort, unclear (n = 38)	CorVue	10 of 23 alerts in 16 patients	NR
Benezet Mazuecos (2016)[43]	Cohort, unclear (n = 70)	CorVue	99 of 104 alerts in 40 patients	NR
Forleo (2013)[38]	Prospective cohort (n = 80)	CorVue	23 patients with 32 episodes	0.6 alerts per patient year (32 episodes/53.477 patient years)
Binkley (2012)[29]	Retrospective cohort (n = 61*)	CorVue	19 of 32 alerts	0.63 (SD: 0.1) alerts per patient year
Palfy (2015)[41]	Cohort, unclear (n = 65)	CorVue	78 of 83 alerts in 32 patients	NR
Palfy (2018)[40]	Prospective cohort (n = 53)	CorVue	99 of 105 alerts	NR
Wakabayashi (2021)[42]	Retrospective cohort (n = 49)	CorVue	76 of 96 alerts	NR
Boehmer (2017)[56]	Prospective cohort (overall n = 900*, development n = 500, validation n = 400)	HeartLogic	Development = NR Validation = NR	False positive rate^ Development = NR Validation = 1.56 (95% CI: 1.41 to 1.77)
Vigdor (2020)[57]	Prospective cohort (n = 80)	HeartLogic	26 of 38 alerts	NR
Wariar (2023)[74]	Retrospective cohort (n = 1567)	HeartLogic	NR	False positive rate^ = 1.401 (95% CI: 1.332 to 1.475)
Santobuono (2023)[72]	Prospective cohort (n = 568)	HeartLogic	NR	False positive rate^ reported by study endpoint

Author (year)	Study design (n)	Intervention	Number of false positives	False positive rate
				Cardiovascular hospitalisation = 0.99 (95% CI: 0.93 to 1.05) Cardiovascular hospitalisation or death = 0.94 (95% CI: 0.89 to 0.99)
De Juan Baguda (2022)[70]	Phase 1 (n = 101) and 2 (n = 94) are retrospective cohorts Phase 3 (n = 267) is a prospective cohort	HeartLogic	Phase 1 = NR Phase 2 and 3 = NR	Phase 1 = 0.39 alerts per patient year Phase 2 and 3 = 0.64 alerts per patient year
Feijen (2023)[19, 36]	Propensity matched retrospective cohort (n = 161)	HeartLogic	33 of 130 alerts	NR
Treskes (2021)[37]	Retrospective pre-post analysis (n = 68)	HeartLogic Remote monitoring pre-activation	8 of 51 alerts	NR
Garner (2022)[31]	Prospective cohort (n = 749)	TriageHF	68 of 376 alerts	NR
Zile (2020)[73]	Retrospective cohort (monthly downloads n = 22 901; alert triggered n = 21,356; daily downloads n = unclear)	Triage HF		High risk status = 0.48 per patient year

Author (year)	Study design (n)	Intervention	Number of false positives	False positive rate
D'Onofrio (2022)[45]	Prospective cohort (overall n = 918, development n = 457, validation n = 461)	HeartInsight	Development = NR Validation = NR	False positive rate per patient year reported by study endpoint and varying thresholds Development = NR Validation (per patient year (95% CI)) First post implant HF hospitalisation Threshold 3.5 = 1.07 (1.00 to 1.13) Threshold 4.0 = 0.86 (0.80 to 0.92) Threshold 4.5 = 0.69 (0.64 to 0.74) Any HF hospitalisation, outpatient IV, or death related to HF Threshold 3.5 = 1.05 (0.99 to 1.12) Threshold 4.0 = 0.85 (0.79 to 0.91)

Author (year)	Study design (n)	Intervention	Number of false positives	False positive rate
				Threshold 4.5 = 0.67 (0.62 to 0.73)

NR = Not Reported; CI = Confidence Interval; *denotes number analysed; ^denotes false positive rate was defined as the ratio of the total number of alerts that were not true-positive alerts over the total usable follow-up duration.

3.5.3 Unexplained alert rates

Unexplained alerts were reported in 10 studies: HeartLogic n = 7, CorVue n = 2, TriageHF n = 0, HeartInsight n = 1 (see Table 17).

HeartInsight

HeartInsight unexplained alerts were defined as a false positive alert that was not followed by an adverse event.[45]

HeartLogic

For HeartLogic there were numerous interpretations of an unexplained alert. Henry *et al*. (2022)[47] defined the unexplained alert rate as the number of alerts per patient-year not followed by a HF event within 2 months. Boehmer *et al.* (2017)[56] reported that an unexplained alert was recorded when there was no HF event, including HF admissions with a secondary cause of HF or oral HF therapy in an outpatient setting, as well as events that did not meet data availability criteria or occurred within 45 days of device conversion. Treskes *et al.* (2021) used a similar definition to Boehmer *et al*. (2017). An unexplained alert was recorded when there was no HF event, including HF admissions with a secondary cause of HF or oral HF therapy in an outpatient setting, as well as events that did not meet data availability criteria or occurred within 45 days of device conversion.[37] Feijen *et al*. (2023)[36] defined the unexplained alert rate as the number of alerts that could not be explained by worsening HF per patient year. De Juan Baguda *et al*. (2022)[70] reported that an unexplained alert was recorded when there was no HF decompensation or no relevant clinical conditions were identified (e.g. dietary or medication indiscretion) that could produce HF decompensation. One HeartLogic study reported 105 alerts of 242 were not followed by HF therapy changes as they were deemed nonactionable, unexplained, or associated with non-HF related conditions.[76]

CorVue

For CorVue unexplained alerts were defined in varying ways. Forleo *et al*. (2013)[38] unexplained detections occurred when congestion alert was not followed by a HF event within 2 weeks. Another study did not specifically state unexplained events, however, reported alerts were patients were asymptomatic without any sign of HF.[75]

TriageHF

No studies reported unexplained alert rates for the TriageHF algorithm. One study used the terms false positives and as unexplained detections interchangeably, the evidence for this can be seen in the previous section.[73]

Table 17: Evidence for studies reporting unexplained alert rates for the algorithms

Author (year)	Study design (n)	Intervention	Number of unexplained alerts	Unexplained alert rate
D'Onofrio (2022)[45]	Prospective cohort (overall n = 918, development n = 457, validation n = 461)	HeartInsight	NR	Unexplained alert rate per patient year reported by study endpoint and varying thresholds Development = NR Validation (per patient year (95% CI)) First post implant HF hospitalisation Threshold 3.5 = 0.99 (0.93 to 1.05) Threshold 4.0 = 0.79 (0.74 to 0.85) Threshold 4.5 = 0.63 (0.58 to 0.68) Any HF hospitalisation, outpatient IV, or death related to HF Threshold 3.5 = 0.98 (0.92 to 1.05) Threshold 4.0 = 0.79 (0.73 to 0.85) Threshold 4.5 = 0.63 (0.58 to 0.68)
Treskes (2021)[37]	Retrospective pre-post analysis (n = 68)	HeartLogic	9 of 51 alerts	0.16 per patient year

Author (year)	Study design (n)	Intervention	Number of unexplained alerts	Unexplained alert rate
Henry (2022)[47]	Retrospective cohort (n = NR)	HeartLogic	NR	0.7 per patient year
Boehmer (2017)[56]	Prospective cohort (overall n = 900*, development n = 500, validation n = 400)	HeartLogic	NR	Development = 1.33 per patient year Validation = 1.47 per patient year
Perez Serrano (2019)[50]	Prospective cohort (n = 18)	HeartLogic	2 of 11 alerts	NR
De Juan Baguda (2022)[70]	Phase 1 (n = 101) and 2 (n = 94) are retrospective cohorts Phase 3 (n = 267) is a prospective cohort	HeartLogic	Phase 1 = 53 of 73 alerts Phase 2/3 = 120 of 277 alerts	Phase 1 = 0.52 per patient year Phase 2/3 = 0.39 per patient year
Santini (2020)[44]	Prospective cohort (n = 104)	HeartLogic	29 of 100 alerts	NR
De Ruvo (2019)[71]	Prospective cohort (n = 101)	HeartLogic	NR	0.41 per patient year
Treskes (2021)[37]	Retrospective pre-post analysis (n = 68)	HeartLogic Remote monitoring pre-activation	9 of 51 alerts	0.16 per patient year
Feijen (2023)[36]	Propensity matched retrospective cohort (n = 161)	HeartLogic Conventional remote monitoring	NR	0.2 per patient year
Forleo (2013)[38]	Prospective cohort (n = 80)	CorVue	32 of 56 alerts	NR

Author (year)	Study design (n)	Intervention	Number of unexplained alerts	Unexplained alert rate
Santini (2012)[75]	Cohort, unclear (n = 38)	CorVue	10 of 23 alerts	NR

NR = Not Reported; *denotes number analysed

3.5.4 Changes to clinical management

Changes to treatment were reported in 16 studies, HeartLogic n = 12, CorVue n = 2, TriageHF n = 5, and HeartInsight n = 0 (see Table 18).

Changes to clinical management associated with worsening HF was used to define prognostic accuracy (sensitivity and specificity) in a few studies.

If a change in clinical management closely follows an alert and the subsequent clinic visit, then earlier appropriate treatment could be attributed to the alert. The percentage of alerts that result in immediate treatment change has predictive value. This requires the study to report that clinical changes met this criterion. The proximity of clinical management changes to the start of the IN alert period was not clearly reported in any study that reported percentage statistics.

If patients stay in alert for significant periods of time and change in clinical management could occur at any time during the IN alert period then earlier appropriate treatment can no longer be attributed to the alert. In this case, the relative rate of change in clinical management IN versus OUT of alert has the most predictive value (the frequency of occurrence IN alert versus frequency of occurrence OUT of alert). No studies reported a relative rate of change in clinical management IN versus OUT of alert, consequently the information reported below only provides direction of effect (whether alerts tend towards an increase in change in clinical management).

HeartLogic

The majority of the evidence was derived from single cohort studies evaluating outcomes IN alert versus OUT of alert. Hernandez *et al*. (2022) reported increased changes in treatment for the first 12 months of the study when IN alert compared to OUT of alert for the HeartLogic algorithm. Additionally, when IN alert, 74% of cases led to medication changes (see Table 18).[48] Pecora *et al*. (2020) compared the changes of treatment occurring in a single prospective cohort (i.e. repeated measures) following monthly remote follow-ups (OUT of alert) to those occurring when IN alert with the HeartLogic algorithm.[77] They found a significant increase in changes to treatment related to actionable HF events when IN alert compared to OUT of alert (at scheduled follow-ups) ($p < 0.001$). A similar result was observed when comparing actionable alerts from HeartLogic (43%) to treatment actions from scheduled, monthly remote monitoring of data (1%), suggesting HeartLogic alerts lead to more actionable events (alerts resulting in active clinical actions to manage the HF condition; $p < 0.001$).[44]

CorVue

Changes to treatment were identified as part of a composite outcome in four studies assessing prognostic accuracy (see Table 18).[29,38,42,43] However, no association data was reported in these studies, with two studies reporting the number of treatments changed only when in alert (see Table 18).[43,75]

TriageHF

HF hospitalisations requiring treatment changes was a study endpoint in one prognostic accuracy study,[68] no further composite study endpoints were identified with this outcome (see Table 18). One study assessing TriageHF compared the impact of the algorithm on Mineralocorticoid Receptor Antagonists (MRA) treatment. Specifically, the authors aimed to assess the correlation between TriageHF burden with patients' medical management. Since prescription of MRA is a marker of advanced disease, the TriageHF score was assessed in those with and without MRA use.[78] The majority of patients (69%) remained in the same medication group at study entry and exit. After an 8-month

follow-up period there was a statistically significant reduction in the risk score for non-MRA users (p = 0.03), but not in MRA users (p = 0.6). The difference between the groups at baseline (p = 0.68) and study exit (p = 0.51) were not statistically different. Additionally, there was no statistically significant difference in the mean difference between the two groups (p = 0.33). The authors suggest the lack of a statistically significant reduction in the risk score of patients is linked to advanced HF in MRA treated patients, which are more difficult to impact even with optimal care (see Table 18).[78]

One study reported the number of medication changes in medium and high risk alerts, without providing statistical analysis.[55] One study reported the number of medication changes in alerts.[79] Another study reported number of referrals to other services when in high risk status.[31] Another reported changes to medication, guideline directed medical therapy, investigations, advice, and referrals.[28]

HeartInsight

No evidence was identified for this outcome for this technology.

Table 18: Evidence from studies reporting changes to treatment

Author (year)	Study design (n)	Intervention	Alerts leading to change in treatment	Treatments changed
Hernandez (2022)[48]	Prospective cohort (n = 191)	HeartLogic	434 of 585 alerts 1777 of the 3290 weekly re-alerts until the HeartLogic index recovered below the nominal alert threshold	Diuretics = 1590 beta-blockers = 185 MRA - 132 ARNI = 124 ACE/ARBs = 108 Vasodilators = 69
Vigdor (2020)[57]	Prospective cohort (n = 80)	HeartLogic	12 of 38 alerts	Diuretic adjustments
Perez Serrano (2019)[50]	Prospective cohort (n = 18)	HeartLogic	5 of 11 alerts	NR
Pecora (2020)[77]	Prospective cohort (n = 104)	HeartLogic	43 of 100 alerts 11 of 1284 monthly remote follow-ups	NR
Ebrille (2021)[46]	Prospective cohort (n = 54)	HeartLogic	5 of 9 alerts Note: 3 of the events occurred due to inappropriate discontinuation of HF therapy	Diuretic dosage increase = 4 Electrical cardioversion (new onset AF) = 1
De Juan Baguda (2022)[70]	Phase 1 (n = 101) and 2 (n = 94) are retrospective cohorts	HeartLogic	Phase 1 = NR Phase 2 = 12 of 44 alerts Phase 3 = 91 of 233 alerts	Phase 2 Diuretics or other drugs = 11 Change to device programming = 1

Author (year)	Study design (n)	Intervention	Alerts leading to change in treatment	Treatments changed
	Phase 3 (n = 267) is a prospective cohort			Patient education = 1 Phase 3 Diuretics or other drugs = 75 Chance to device programming = 13 Patient education = 6 Cardioversion = 4 CPAP = 2 AVN ablation = 1
Santini (2020)[44]	Prospective cohort (n = 104)	HeartLogic	43 of 100 alerts	Diuretic dosage increase or other drug adjustment Device reprogramming/revision Cardioversion Patient education
Guerra (2022)[76]	Prospective cohort (n = 229)	HeartLogic	137 of 242 alerts	Diuretic dosage/switch to bioavailable diuretic = 56 Mixed interventions (n = 81) Diuretic changes = 26 Non-diuretic medicinal changes = 50

Author (year)	Study design (n)	Intervention	Alerts leading to change in treatment	Treatments changed
				Patient education = 25 Device reprogramming and/or cardioversion = 7
De Ruvo (2019)[71]	Prospective cohort (n = 101)	HeartLogic	26 of 44 alert, associated with worsening HF and/or influenced clinical decisions for changes to management	NR
Calo (2021)[80]	Prospective cohort (n = 366)	HeartLogic	117 of 273 alerts	Most frequents actions taken were: Diuretic dosage increase = 77 Other drug adjustment = 40 Patient education = 7 Device reprogramming = 3
Santini (2012)[75]	Cohort, unclear (n = 38)	CorVue	13 of 23 alerts	Diuretics = 13
Benezet-Mazuecos (2016)[43]	Cohort, unclear (n = 70)	CorVue	5 of 104 alerts	Diuretics = 2 (3 hospitalisations)
Garner (2022)[31]	Prospective cohort (n = 749)	TriageHF	72 of 376 high risk alerts	Referral to service Cardiology for review = 47 GP for further action = 21

Author (year)	Study design (n)	Intervention	Alerts leading to change in treatment	Treatments changed
				Palliative care = 4
Virani (2018)[55]	Prospective cohort (n = 100)	TriageHF	High risk alerts = 13 of 24 Medium risk alerts = 24 of 31	High risk alert Medication changes = 4 Medium risk alert Medication changes = 12
Virani (2016)[78]	Prospective cohort (n = 100)	TriageHF	NR	Change in risk score (Mean (SD)) Non-MRA Baseline = 1.59 (1.29) Exit = 1.19 (0.87) Difference = -0.39 (1.51), p = 0.03 MRA Baseline = 1.99 (2.39) Exit = 1.49 (1.31) Difference = -0.49 (2.21), p = 0.60
Zile (2021)[79]	Prospective cohort (n = 66)	TriageHF	26 of 49 alerts	PRN, 22 were completed and 19 led to impedance recovery

Author (year)	Study design (n)	Intervention	Alerts leading to change in treatment	Treatments changed
Ahmed (unpublished)[28]	Retrospective single-arm with time-matched standard care controls (n overall = 758, intervention = 443, control = 315)	TriageHF Control: TriageHF Compatible devices but were not capable of performing automated transmissions	77 of 196 alerts	High risk alert led to the following number of clinical actions Diuretics = 31 GDMT = 19 Investigations = 18 Advice (daily lifestyle/long-term management) = 35 Referral to specialist = 11 Referral to primary care team <5

NR = Not reported; HF = Heart Failure; AF = Atrial Fibrillation; CPAP = Continuous Positive Airway Pressure; AVN = Atrioventricular Node; MRA = Mineralocorticoid Receptor Antagonists; PRN = diuretic up-titration

3.5.5 Hospitalisations

The prognostic accuracy was reported in four studies for hospitalisations as a singular endpoint and 12 reported it as a composite outcome, usually with clinic visits or similar. Results for prognostic accuracy of hospitalisations were reported in 16 studies: HeartLogic = 5, CorVue = 4, TriageHF = 6, HeartInsight = 1. Association results were reported for hospitalisations of HF and all-cause in 7 studies: HeartLogic n = 2, CorVue n = 0, TriageHF n = 5, and HeartInsight n = 0 (see Table 19).

HeartLogic

One study assessed hospital admissions as a singular endpoint, reporting good sensitivity (90%).[37] The four other studies included similar study endpoints, with variations of hospitalisations and clinic visits. In the development study, the sensitivity reduced from 89% to 70% when validated at the nominal threshold (≥16) (see Table 15).[56] This sensitivity level was generally maintained in the three other studies (range = 66% to 100%). One study assessed the accuracy of the HeartLogic algorithm in a management strategy, where they applied the nominal threshold of ≥16 and also a threshold of ≥20.[57] The results suggested increasing the threshold to ≥20 improved specificity while maintaining acceptable sensitivity (see Table 15).[57]

Two studies reported increased risk of hospitalisation when IN alert compared to OUT of alert (see Table 19). However, one of these studies is a composite outcome of hospitalisation or death and does not provide data individually.[80] One of these studies reported higher hospitalisation rates when IN alert compared to OUT of alert (see Table 19).[72] Experiencing at least 1 HeartLogic alert, after correction for chronic kidney disease and AF at implantation, was linked to an increased risk of cardiovascular hospitalisation (HR = 3.44, 95% CI: 1.22 to 9.76, p = 0.021), as was time IN alert ≥20% (HR = 4.14, 95% CI: 2.20 to 7.79, p <0.001).[72]

De Juan Baguda *et al*. (2022) included three phases, phase one and two were retrospective, and phase three was prospective.[70] Phase one reported a HeartLogic IN alert event rate for hospitalisation of 1.23 per patient years. No hospitalisations occurred outside of an alert in phase 1, and only 1 alert occurred outside of an alert in phase 2 and 3 (combined).

Another study assessed hospitalisations in patients with left ventricular assist devices, observing lower index value than the recommended threshold (i.e. ≥16) 48 hours prior to HF related hospitalisation (mean = 12). However, the index value was higher 48 hours prior to non-HF related hospitalisations (mean = 18.6).[49]

TriageHF

Two studies reported hospital admission as the study endpoint and assessed prognostic accuracy.[30,52] One of these studies reported an AUC of 0.8, suggesting good prognostic ability.[52] Two studies reported prognostic accuracy for the study endpoint of cardiovascular or HF related hospitalisations,[33,67] and one reported a study endpoint hospitalisation requiring treatment changes.[68] The final study reported a composite study endpoint of hospitalisation, outpatient IVI or death.[53] Across the outcomes there was a variation in sensitivity when in high risk status (range = 25% to 82%; see Table 15).

In single group studies for TriageHF, which compared high and medium risk to low risk status, there was a statistically significant increased risk for HF, cardiovascular, and non-HF cardiovascular related hospitalisation when in a high risk status, compared to low risk status (see Table 19).[30, 32, 33, 68] Using a generalised estimating model (GEE), within each risk status group (i.e. repeated measures), to estimate

the risk of HF related hospitalisation, the study reported statistically significant risk in the high risk group (GEE = 4.07, 95% CI: 2.82 to 5.84) and in the medium risk group (GEE = 1.57, 95% CI: 1.09 to 2.26), but not in the low risk group (GEE = 0.73, 95% CI: 0.45 to 1.17).[68] There was also evidence that an increased number of high risk alerts was associated with an increased likelihood of HF related hospitalisation for the TriageHF algorithm.[31] Gula *et al.* (2014) also reported similar risks for CRT-D (medium risk group = 3.3, 95% CI: 2.0 to 5.4; high risk group = 11.3, 95% CI: 6.5 to 19.7) and ICD (medium risk = 2.3, 95% CI: 1.2 to 4.6; high risk = 9.6, 95% CI: 4.6 to 19.7) devices for HF related hospitalisations.[32]

CorVue

Four study endpoints were reported assessing the prognostic accuracy of CorVue, with a variation of hospitalisations and clinic visits with changes to treatment (see Table 15).[29,38,40,43] Sensitivity varied to a high degree (20-61.9%), indicating inadequate prognostic accuracy.

No studies reported measures of association for this algorithm; however, three studies did report a low number of alerts led to hospitalisations (9 of 20 alerts;[41] 6 of 105 alerts;[40] and 5 of 104[43]).

HeartInsight

One published study assessed prognostic accuracy for HeartInsight. The primary endpoint was for the first post implant hospitalisation due to worsening HF. The secondary endpoint was a composite outcome of hospitalisation, outpatient IVI or death. In the development cohort, a unitary increase of the index value was associated with an OR of 2.73 (95% CI: 1.98 to 3.78, p <0.001) for the first post-implant worsening HF hospitalisation.[45] The results suggested that the nominal threshold of 4.5 had the potential to identify worsening HF related to hospitalisations (see Table 15).[45] The number of hospitalisations was reported but no further association data is available.

Table 19: Evidence for studies reporting the number of hospitalisations and the association between algorithm alert status from all-causes

Author (year)	Study design (n)	Intervention	Hospitalisations (n)	Other
Santobuono (2023)[72]	Prospective cohort (n = 568)	HeartLogic	IN alert = 35 OUT of alert = 18	Event rates IN alert = 0.23 (95% CI: 0.16 to 0.32) Out of alert = 0.02 (95% CI: 0.01 to 0.03) IRR = 12.98 (95% CI: 7.16 to 24.35)
Calo (2021)[80]	Prospective cohort (n = 366)	HeartLogic	13 patients died of other causes	Event rate of hospitalisation or death = 0.12 per patient year (44 events in 27 patients) 35 alerts were associated with HeartLogic in alert state (0.92 per patient year), 9 events occurred while out of alert (0.03 per patient year)
Burri (2018)[33]	Retrospective analysis of a single study (n = 722)	TriageHF	Cardiovascular related 191 patients with 288 cardiovascular related hospitalisations in 268 different months (2.2% per month) HF related 89 patients with 142 HF related hospitalisation in 135 different months (1.1% per month) Non-HF related	Relative Risk (95% CI); low risk reference group Cardiovascular related Medium risk = 1.8 (1.3 to 1.5), p<0.001 High risk = 4.5 (3.1 to 6.6), p<0.001 HF related Medium risk = 1.5 (1.0 to 2.5), p = 0.065 High risk = 6.3 (3.9 to 10.2), p<0.001 Non-HF related

Author (year)	Study design (n)	Intervention	Hospitalisations (n)	Other
			146 non-HF related hospitalisation in 137 different months (1.1% per month); number of patients NR	Medium risk = 2.3 (1.5 to 3.5), p<0.001 High risk = 3.5 (2.0 to 6.0), p<0.001
Cowie (2013)[30]	Retrospective analysis of seven studies (overall n = 2231, development n = 921, validation n = 1310)[5]	Triage HF	HF related; hospitalisations/evaluations (%) Development Low risk = 15/4525 (0.3) Medium risk = 47/4018 (41) High risk = 29/1247 (13) Validation Low risk = 28/4838 (0.6) Medium risk = 60/4717 (1.3) High risk = 75/1100 (6.8)	Hazard ratio (95% CI); low risk reference group Development Medium risk = 3.7 (2.0 to 6.7), p<0.001 High risk = 6.2 (3.1 to 12.3), p<0.001 Validation Medium risk = 2.1 (1.3 to 3.4), p = 0.001 High risk = 10.0 (6.4 to 15.7), p<0.001
Garner (2022)[31]	Prospective cohort (n = 749)	TriageHF	Overall = 76 Unplanned = 53 HF = 24 Medical admission = 29	Patients with >3 high risk alerts likelihood of HF hospitalisation Hazard ratio = 2.5 (95% CI: 1.1 to 5.6), p = 0.03
Gula (2014)[32]	Retrospective analysis of a single study (n = 1 224)	TriageHF	Overall = 258 (0.68% per month) Low risk = 33 (0.21% per month) Medium risk = 123 (0.66% per month)	Relative risk (95% CI); low risk reference group Medium risk = 2.9 (2.0 to 4.4)

Author (year)	Study design (n)	Intervention	Hospitalisations (n)	Other
			High risk = 102 (2.61% per month)	High risk = 10.7 (6.9 to 16.6)
Okumura (2020)[68]	Prospective cohort (n = 315)	Triage HF	HF Related Low risk = 19 of 239 patients Medium risk = 42 of 268 patients High risk = 28 of 161 patients	Relative risk (95% CI); low risk reference group Medium risk = 2.18 (1.23 to 3.85) High risk = 5.78 (3.34 to 10.01)

HF = Heart Failure; NA = Not Applicable; IV = Intravenous; CI = Confidence Intervals; IRR = Incidence Rate Ratio; NR = Not Reported; *denotes number analysed; IRR = Incidence Rate Ratio

3.5.6 Rate of heart failure events

Association data for rate of heart failure events were reported in 12 studies: HeartLogic n = 2, CorVue n = 0, TriageHF n = 1, and HeartInsight n = 0 (see Table 20). All studies considered varying heart failure events (e.g. hospitalisations), with heart failure being a generic term to encompass numerous outcomes. In three studies a HF event was not explicitly defined (see Table 15).[37,74,73] Here we report studies which provide association data of the occurrence of heart failure events.

HeartLogic

Evidence from the studies suggests an increased risk of a HF event when IN alert vs OUT of alert (see Table 20).[80, 81] For example, one of the studies reported an increased HR when IN alert for a HF event, which remained statistically significant when adjusted for chronic kidney disease and history of atrial fibrillation (see Table 20).[80] The same study also identified a decreased rate of events when an alert was followed by a clinical action (HR = 0.37, 95% CI: 0.14 to 0.99), with similar results if analyses was conducted from day 7 post clinical action (HR = 0.34, 95% CI: 0.12 to 0.96).

Two studies reported the number of people who had a HF event, but did not perform statistical analyses. One study reported a single HF event, which occurred OUT of alert.[57] Another reported that three of ten HF events occurred OUT of alert.[47]

CorVue

No studies for CorVue reported association data for this outcome. However, one study states 20 HF developments occurred while in alert (of 96); however, the study also reported that there were a total of 28 HF development episodes with 19 of these related to an alert.[42] The reason for the two values is unclear.

TriageHF

The singular study identified for this outcome reported increased odds of HF when in medium and high risk status compared to low risk (see Table 20).[73]

HeartInsight

No studies for HeartInsight reported on this outcome.

Table 20: Evidence for studies reporting rate of heart failure events

Author (year)	Study design (n)	Intervention	Heart failure events	Other statistics
Gardner (2018)[81]	Secondary analysis of a prospective cohort (n = 900)	HeartLogic	145 HF events from 88 patients^	IN alert = 0.8 events per patient year OUT of alert = 0.08 events per patient year Event ratio = 10.6 Average event rate = 0.2 per patient year IN alert event rate ratio = 7.05 (95% CI: 4.69 to 10.61), p<0.001 IN alert event rate ratio adjusted = 4.78 (95% CI: 2.94 to 7.75), p<0.001
Calo (2021)[80]	Prospective cohort (n = 366)	HeartLogic	273 alerts in 150 patients (up to 6 times per patient)	Alerts = 0.76 per patient year IN vs OUT of alert event rates HR = 30.63 (95% CI: 13.04 to 71.95) Adjusted HR[a] = 24.53 (95% CI: 8.55 to 70.38)
Zile (2020)[73]	Retrospective cohort (monthly downloads n = 22 901; alert triggered n = 21,356; daily downloads n = unclear)	Triage HF	30-day risk of HF events Monthly downloads 2 102 had an event	Odds ratio (95% CI) Medium vs low risk = 2.8 (2.5 to 3.2), p<0.001

Author (year)	Study design (n)	Intervention	Heart failure events	Other statistics
			Low risk = 0.25% Medium risk = 0.70% High risk = 2.23% Alert-triggered downloads 1 812 patients 2853 events	High vs medium risk = 9.2 (8.1 to 10.3), p<0.001

HF = Heart Failure; NA = Not Applicable; CI = Confidence Interval; HR = Hazard Ratio; *denotes a lack of definition for event rate; ^number analysed; [a]adjusted for chronic kidney disease and history of atrial fibrillation

3.5.7 Mortality

3.5.7a Heart failure related mortality

Heart failure events leading to death were reported in 4 studies: HeartLogic n = 3, CorVue n = 0, TriageHF n = 1, and HeartInsight n = 0 (see Table 21).

HeartLogic

Three prospective cohorts reported increased hazard for HF related mortality when IN compared to OUT of alert.[45,72,80]

TriageHF

One study reported the prognostic accuracy of TriageHF for the study endpoint of mortality. This prospective cohort showed an inadequate AUC (i.e. <0.7) for the prediction of mortality (see Table 15).

One study assessed TriageHF as a prognostic factor, specifically the number of alerts (>3). Whilst there was a statistically significant relationship between high risk alerts (>3) and hospitalisation (HR = 2.5, see Table 21), the algorithm was not a statistically significant predictor of mortality (see Table 21).[31]

CorVue

No studies for CorVue reported on this outcome.

HeartInsight

No studies for HeartInsight reported on this outcome.

Table 21: **Evidence for studies reporting the number of deaths related to heart failure**

Author (year)	Study design (n)	Intervention	Number of deaths	Other statistics
D'Onofrio (2023)[45]	Prospective cohort (n = 568)	HeartLogic	33	HR[a] At least one alert = 6.07 (95% CI: 6.19 to 12.97), p = 0.004 ≥20% time in alert = 5.59 (95% CI: 2.51 to 12.44), p <0.001
Calo (2021)[80]	Prospective cohort (n = 366)	HeartLogic	8	IN alert vs Out alert HR[b] = 11.45 (95% CI: 5.55 to 23.60), p<0.001
Santobuono (2023)[72]	Prospective cohort (n = 568)	HeartLogic	IN alert = 37 OUT of alert = 18	Cardiovascular hospitalisations or death IN alert ER = 0.48 (95% CI: 0.37 to 0.60) OUT of alert ER = 0.04 (95% CI: 0.03 to 0.05) IRR = 13.35 (95% CI: 8.83 to 20.51) HR = 1.92 (95% CI: 1.05 to 3.51), p = 0.036
Garner (2022)[31]	Prospective cohort (n = 749)	TriageHF	Unplanned hospital admission Overall = 10	Unadjusted HR (95% CI) for mortality in patients with high risk alerts

Author (year)	Study design (n)	Intervention	Number of deaths	Other statistics
			HF admission = 7 Medical admission = 3	Number of high-risk alerts >3 alerts = 0.94 (0.4 to 2.2) HF admission = 2.12 (0.6-7.2) Unplanned admissions = 0.76 (0.3 to 2.5) Rockwood clinical frailty score (>6) = 3.26 (1.5 to 7.3) Charlson Comorbidity Score (>6) = 2.64 (1.2 to 5.7)

NA = Not Applicable; HR = Hazard Ratio; ER = Event Ratio; IRR = Incidence Rate Ratio; CI = Confidence Interval; adjusted for age, ischemic cardiomyopathy, chronic kidney disease, atrial fibrillation on implantation and HeartLogic IN alert; adjusted for HeartLogic alert, chronic kidney disease, and atrial fibrillation history.

3.5.7b All-cause related mortality

All-cause events leading to death were reported in 4 studies: HeartLogic n = 2, CorVue n = 0, TriageHF n = 2, and HeartInsight n = 0 (see Table 22).

HeartLogic

One study evaluated the predictive ability of the HeartLogic algorithm to predict deaths.[45] They reported 55 deaths, with 46 of these experiencing one or more alerts during follow-up. There was an increased risk of death for those IN alert compared to OUT of alert (see Table 22). Additionally, an increased risk of death was present for having at least one HeartLogic alert and time IN alert (≥20%, see Table 22).[45]

TriageHF

A study assessing TriageHF showed greater likelihood of death when at high risk compared to not being in high risk (see Table 22).[69] Similar results were observed another TriageHF study reporting high and medium risk status was associated with significantly higher hazard of all-cause mortality.[73]

CorVue

No studies for CorVue reported on this outcome.

HeartInsight

No studies for HeartInsight reported on this outcome.

Table 22: Evidence for studies reporting the number of deaths from all-causes

Author (year)	Study design (n)	Intervention	Number of deaths	Other statistics
D'Onofrio (2023)[45]	Prospective cohort (n = 568)	HeartLogic	55	IN vs OUT of alert 0.25 (95% CI: 0.17 to 0.34) vs 0.02 (95% CI: 0.01 to 0.03) per patient years, p <0.001 At least one HeartLogic alert HR = 2.08 (95% CI: 1.16 to 3.73), p = 0.039 Time IN alert ≥20% HR = 4.07 (95% CI: 2.19 to 7.54), p <0.001 Time to death after start of IN and OUT of alert HR = 11.00 (95% CI: 6.19 to 19.48), p<0.001
Calo (2021)[80]	Prospective cohort (n = 366)	HeartLogic	13 patients died of other causes	Event rate of hospitalisation or death = 0.12 per patient year (44 events in 27 patients) 35 alerts were associated with HeartLogic in alert state (0.92 per

				patient year), 9 events occurred while out of alert (0.03 per patient year)
Ahmed (2022)[69]	Prospective cohort (n = 439)	Triage HF	Overall = 60 Cardiovascular = 35 Respiratory disease = 7 Cancer = 6 Renal failure <5 Falls <5 Diabetes <5 Dementia <5 Missing = 6	High risk versus not high risk OR 3.07, 95% CI: 1.57 to 6.58, p = 0.002
Zile (2020)[73]	Retrospective cohort (n = 22 542)	Triage HF	Overall = 2 489 Low risk = 14% Medium risk = 20% High risk = 38% Note: unclear what percentage represents	Adjusted HR (95% CI)[a] High vs low risk = 3.5 (2.8 to 4.3), p<0.001 Medium vs low risk = 1.8 (1.4 to 2.2), p<0.001

NR = Not Reported; HR = Hazard Ratio; CI = Confidence Interval; CV = Cardiovascular; *number included in analysis; adjusted for age, gender, clinical history, hypertension, myocardial infarction, coronary artery disease, HF, atrial fibrillation, vascular disease, chronic kidney disease, and stroke, transient ischaemic attack

3.5.8 Summary of prognostic performance

Meta-analysis of the available accuracy data was not completed due to a number of reasons. Many studies did not sufficiently report the data (e.g. only sensitivity was reported and a 2x2 contingency table could not be calculated from available data). Furthermore, there was variation in the definitions of study endpoints which would make validity of comparisons challenging, even within technologies. Finally, the risk of bias in many studies was high, meaning the quality of the evidence is low and may not produce accurate results.

TriageHF

The greatest amount of prognostic accuracy evidence was identified in studies assessing the TriageHF algorithm (n = 10). Of these, the area under the curve (AUC) was reported in three studies assessing worsening HF (AUC = 0.75),[65] mortality (AUC = 0.61),[69] and hospital admissions (AUC = 0.81).[52] Sensitivity for high risk status for HF related events (e.g. hospitalisations) showed great variability (range = 37.4% to 87.9%). Specificity also varied (range = 44.4% to 90.2%). False positive rates were reported with the consideration of duration of follow up (i.e. patient years).[38,29,56,74,72,45,73]

Evidence of associations between being in an algorithm-defined high risk status, compared to a low risk status, suggested a higher risk of hospitalisation (n = 5), heart failure events (n = 1), and mortality from all-causes (n = 2). The HR of hospitalisation ranged from 6 to 11 and was consistently statistically significant, when compared to low risk status of the algorithm.[30,31,32,33,68] The single study for heart failure events suggested a high HR when in high risk status compared to low risk status (HR = 9.2).[73] Mortality from all-causes was at a statistically significantly greater risk when in high risk status compared to low (HR = 3.5)[73] and compared to not high risk (i.e. medium and low risk: HR = 3.07).[69] Mortality from HF was only available in a single study, which only assessed the number of high-risk alerts (>3 alerts).[31] While this study was linked to an increased risk of hospitalisation with increasing number of alerts, death was not statistically significantly associated with number of alerts (HR = 0.94, 95% CI: 0.4 to 2.2).[31]

HeartLogic

A similar amount of prognostic accuracy evidence was identified assessing the HeartLogic algorithm (n = 8). In the original development and validation study for HeartLogic, the development sensitivity was 82% and this dropped to 70% in the validation cohort for the prediction of HF events of hospitalisation and clinic visits.[56] In further validation studies, which generally assessed HF hospitalisation events, sensitivity was adequate to high (range = 66% to 100%) as was specificity (range = 61% to 93%). False positives were reported in seven studies and generally showed low false positive rates. One study did report quite a high false positive alert rate (26 of 38 alerts; 68%).[57]

There was evidence that being IN alert, compared to OUT of alert, suggested a higher risk of hospitalisations (n = 2), heart failure events (n = 2) and mortality from HF (n = 3) or all-causes (n = 2). The hospitalisation IRR suggested a statistically significant increased rate of hospitalisations when IN alert compared to OUT of alert (IRR = 12.98).[72] An adjusted (for chronic kidney disease and history of atrial fibrillation) HR for heart failure events was reported, suggesting a high risk of such an event occurring when IN alert vs OUT of alert (HR = 24.53). [80] Mortality from HF was statistically significantly associated with being IN alert compared to OUT of alert in two studies (HR range = 2 to 11).[72,80] One other study reported a statistically significant association for mortality from HF and from all-causes was statistically significantly associated with having at least one HeartLogic alert (HF HR =

6.07; all-causes HR = 2.08), more time in alert (HF HR = 5.59; all-causes HR = 4.07), and was more likely to occur when IN alert vs OUT of alert (0.25 vs 0.02 per patient years).[45]

CorVue

Less evidence for prognostic accuracy was identified for the CorVue algorithm (n = 5). The CorVue algorithm showed inadequate sensitivity for HF events, generally HF hospitalisations (range = 20 to 68%). While specificity was only reported in two studies at 70%[40] and 77%.[43] Additionally, false positive rates were high in the seven studies reporting the number of false alerts (percentage range of false alerts = 43 to 95%).[29,38,40,41,42,43,75]

No association data was available for hospitalisation; however, three studies did report low rates of hospitalisations following an alert.[40,41,43] No further association data was reported for the other outcomes.

HeartInsight

A single published study was identified for HeartInsight. At the nominal threshold of 4.5, the algorithm had 65.5% sensitivity and 86.7% specificity for first post-implant HF hospitalisations. Additionally, it had 54.8% sensitivity and 86.5% specificity for HF hospitalisation, outpatient IVI or death. An AUC was only reported for HF hospitalisations in the development cohort (AUC = 0.89). For HeartInsight false positive rates were calculated as the number of false positive alerts (not followed by either the primary or secondary study endpoint) per patient year: nominal threshold of 4.5 were <0.7 for both study endpoints.[45]

In the development cohort, a unitary increase of the index value was associated with an OR of 2.73 (95% CI: 1.98 to 3.78, p <0.001) for the first post-implant worsening HF hospitalisation. No further data of associations is available for any outcome.[45]

3.6 Comparative outcome results

3.6.1 Rate of heart failure events

One comparative study was identified for this outcome, which assessed the HeartLogic algorithm.

HeartLogic

The propensity-matched controlled study did show a statistically significant difference in HF events, with less events occurring in the HeartLogic intervention group compared to those without the algorithm (see Table 23).[36]

CorVue

No comparative evidence reporting on this outcome.

TriageHF

No comparative evidence reporting on this outcome.

HeartInsight

No comparative evidence reporting on this outcome.

Table 23: Comparative evidence for studies reporting rate of heart failure events

Author (year)	Study design (n)	Intervention/Control	Heart failure events
Feijen (2023)[36]	Propensity matched retrospective cohort (n = 161)	HeartLogic Conventional remote monitoring	Worsening HF median (IQR) Control group = 2 (0-4) HeartLogic = 1 (0-3) Less worsening HF for HeartLogic group (p = 0.004)

3.6.2 Rate and category of atrial fibrillation

No evidence was identified for this outcome.

3.6.3 Changes in NYHA classification of symptoms

No evidence was identified for this outcome.

3.6.4 Hospitalisation

HeartLogic

One comparative study for HeartLogic utilised a propensity-matched retrospective cohort design.[36] This study reported a non-statistically significant difference between the number of patients being admitted to hospital, when comparing those with and without the HeartLogic algorithm (see Table 24).[36] One single cohort study did compare pre to post activation of the HeartLogic algorithm, reporting statistically significant reductions in HF related hospitalisation once the algorithm was turned on (see Table 24).[37] One retrospective study compared pre-post activation of HeartLogic within a cohort and to an external cohort, reporting less hospitalisation post activation in the HeartLogic group. However, statistical analysis showed no statistically significant difference (see Table 24). Hernandez reports a rate of HF hospitalisation during the study as 67% lower (rate ratio [95% CI]: 0.33 [0.23, 0.47]) compared to the pre-study 12-month HF hospitalisation rate.[82]

CorVue

A retrospective medical chart review, which included a control group, showed that those with a CorVue enabled device were less likely to be hospitalised compared to those without a device (see Table 24).[34]

TriageHF

Comparative evidence using the TriageHF algorithm was available from a single study, which suggested a reduced incidence rate ratio (IRR) when comparing those with a TriageHF capable device to those with devices that were TriageHF capable but did not send automatic transmissions (see Table 24).[28]

HeartInsight

No comparative evidence was identified for this outcome assessing HeartInsight.

Table 24: Comparative evidence for studies reporting the number of hospitalisations from all-causes

Author (year)	Study design (n)	Intervention/Control	Hospitalisations (n)	Between-group differences for hospitalisation
Treskes (2021)[37]	Retrospective pre-post analysis (n = 68)	HeartLogic Remote monitoring pre-activation	HF related Pre-activation of HeartLogic = 27 Post-activation of HeartLogic = 7	Reduction in HF-related hospitalisations for HeartLogic group vs those without the algorithm (p = 0.005) Hospitalisation per patient years (SD) Pre-activation = 0.39 (0.08) Post-activation = 0.11 (0.04) reduction in hospitalisation per patient years for HeartLogic group (p = 0.003)
Feijen (2023)[36]	Propensity matched retrospective cohort (n = 161)	HeartLogic Conventional remote monitoring	HF related Control = 17 Intervention = 8	Intervention vs control, p = 0.096
Chang (2020)[35]	Retrospective cohort with external control (Intervention = 40; control = 100) and pre-post activation	HeartLogic Remote monitoring	Pre device implantation Intervention = 17 of 40 patients Control = 33 of 100 patients Post device implantation Intervention = 4 of 40 patients Control = 17 of 100 patients	Between groups statistical comparisons Pre device implantation, p = 0.33 Post device implantation, p = 0.35

Shapiro (2017)[34]	Retrospective medical chart review of CorVue device compared to standard protocol (n = 120)	CorVue No implanted device but receiving home health care	Intervention = 0 of 60 patients Control = 14 of 60 patients	Intervention vs control: $X^2 = 15.849$, $p < 0.001$
Ahmed (unpublished)[28]	Retrospective single-arm with time-matched standard care controls (n overall = 758, intervention = 443, control = 315)	TriageHF TriageHF Compatible devices but were not capable of performing automated transmissions	[redacted]	Reduced risk of at least one hospitalisation for the TriageHF group compared with controls (IRR = 0.42, 95% CI: 0.23 to 0.76)

IRR = Incidence Rate Ratio; HF = Heart Failure

3.6.5 Length of hospital stay

Only two studies reported length of hospital stay, both of which assessed the impact of the HeartLogic algorithm.[37,36] One study included a control group[36] and the other was a single cohort compared pre and post activation.[37]

HeartLogic

The length of hospital stay was reported as being significantly longer for those without a HeartLogic algorithm (median number of days = 8, IQR: 5-12) compared to those with a device (median number of days = 5, IQR: 2-7; p = 0.025).[36] Similar results for the HeartLogic algorithm were reported for number of days in hospital pre-activation (mean = 16, SD = 14) compared to post activation (mean = 7, SD = 5), although this was not statistically significant (p = 0.079).[37]

CorVue

No studies for CorVue reported on this outcome.

HeartInsight

No studies for HeartInsight reported on this outcome.

TriageHF

No studies for TriageHF reported on this outcome.

3.6.6 Mortality

No comparative evidence was identified for this outcome for any of the technologies.

3.6.7 Health related quality of life

No comparative evidence was identified for any technology on this outcome. One prospective cohort did assess quality of life outcomes at baseline and study exit, which is reported here.[55]

TriageHF

A single prospective cohort study (n = 100) which assessed the TriageHF algorithm provided evidence for health related quality of life via the 6-minute walk test (6MWT; n = 60) and the Minnesota living with heart failure (MLWHF; n = 88).[55] Walking distance for the 6MWT was reported to decrease from baseline (mean = 323, SD = 115 minutes) to end of follow up at 8 months (mean = 295, SD = 116), which was statistically significant (p = 0.01). No statistically significant differences between baseline (mean = 32.8, SD = 21) and end of follow up at 8 months (mean = 30.0, SD = 21.6) for the MLWHF was found (p = 0.19). However, a decrease in the overall score for the MLWHF is deemed as an improvement.[55]

CorVue

No studies for CorVue reported on this outcome.

HeartLogic

No studies for HeartLogic reported on this outcome.

HeartInsight

No studies for HeartInsight reported on this outcome.

3.6.8 Patient experience

No evidence was identified for any technology on this outcome.

3.6.9 Summary of comparative outcomes

For each algorithm there was a lack of comparative evidence. HeartLogic was identified as providing the most comparative evidence (n = 3). TriageHF and CorVue each had a single comparative study. However, one study for TriageHF assessing quality of life was included as a comparative study in this section as it compared baseline to study exit. No comparative evidence was identified for the HeartInsight algorithm. Due to the lack of comparative data for each algorithm it is difficult to make any conclusions about how effective they are compared to standard care. All studies were rated as serious or critical with the risk of bias tool (ROBINS-I).

TriageHF

Hospitalisations were reported to be at a reduced risk for those with a TriageHF device compared to those with Triage HF capable devices but were not performing automated transmissions (IRR = 0.42).[28]

TriageHF was the only algorithm to have evidence for quality of life. One study assessed the 6MWT and MLWHF. The results showed statistically significant decrease in the 6MWT at baseline and study exit. This implies a negative impact between baseline and study exit as the length walked was significantly less. However, a non-statistical reduction in the MLWHF was reported, which is considered important as a decrease in the score is deemed as an improvement.[55]

No comparative data for any other outcomes was identified for this algorithm.

HeartLogic

Rate of heart failure events was reported in a single propensity-matched controlled study, which reported less worsening HF in those with a HeartLogic device than those without (p = 0.004).[36]

Hospitalisations were shown to be statistically reduced in one retrospective pre-post study when a patient had a HeartLogic enabled device compared to having conventional remote monitoring. [37] Two other comparative studies showed numerical trends towards a reduction in hospitalisations when having a HeartLogic device compared to conventional remote monitoring, but the differences were not statistically significant.[35,36] Similar results were observed for the length of hospital stay outcome; one study reported a statistically significant (p = 0.025) reduction in time in hospital for those with a HeartLogic device compared to those without a HeartLogic device (5 vs 8 days, respectively).[36] While another study reported pre-activation length of hospital stay was longer than post-activation hospital stay (16 vs 7 days, respectively), but this was not statistically significant (p = 0.079).[37]

CorVue

Hospitalisations were statistically significantly reduced in those with a CorVue enabled device compared to those with no implanted device receiving standard home care.[34]

No comparative data for any other outcomes was identified for this algorithm.

HeartInsight

No comparative evidence was identified for any outcome for this algorithm. We therefore cannot draw any conclusions regarding its efficacy in comparison to other modes of clinical follow up.

3.7 Implementation outcome results

3.7.1 Interventions following an alert

HeartLogic

Guerrera *et al*. (2022) reported a quicker decrease of the IN alert state when decongestive treatments were administered in the first two weeks, compared to no decongestive treatments in the first four weeks of alert. Similarly, multivariate analysis showed that a higher algorithm index value when IN alert with the HeartLogic algorithm (OR = 1.11, 95% CI: 102 to 1.20) and late intervention (OR = 5.11, 1.09 to 24.48) were significantly associated with the need for further treatment to resolve the alert.[76] One study also reported the time to treatment, with 56 decongestive treatment adjustments being made within 2 weeks of the first alert (early action average time from alert to intervention mean = 5 days, SD = 4 days). There were also 26 late actions for treatment (mean = 40 days, SD = 27 days).[76]

TriageHF

No studies assessing TriageHF were identified for this outcome.

CorVue

No studies assessing CorVue were identified for this outcome.

HeartInsight

No studies assessing HeartInsight were identified for this outcome.

3.7.2 Time between an alert and a heart failure event

HeartLogic

Four single cohort studies assessing the HeartLogic algorithm reported time between an alert and an event occurring.[49,71,46,80] The median time between crossing the alert threshold and a HF clinical event in one study was 11 (IQR: 2-19) days.[46] Another reported the median number of days for an early warning of hospitalisation (median = 38 days) and clinical visits (median = 12 days).[71] One study reported the median time between an alert onset to an HF event was 29 (IQR: 4 to 83) days.[80] Another study reported the median number of days from the first sensor alert to first hospitalisation was 145 (IQR: -1 to 380) for all causes, 63 (IQR: -26 to 229) for HF related, and 240 (147 to 497) for non-HF related.[6] Another study reported an average time of 20 days from alert to hospitalisation.[70]

TriageHF

One single cohort study assessing the TriageHF algorithm reported time between the last transmitted risk status alert and death.[69] The median time from the high risk status to death was 111 (IQR: 57-226) days.[69] The time between last maximum recorded risk and death was 233 (IQR: 91-390) days.[69]

CorVue

No studies for CorVue reported on this outcome.

HeartInsight

No studies for HeartInsight reported on this outcome.

3.7.3 Alert response rates

The alert response or time in alert was reported in 11 studies: HeartLogic n = 8, CorVue n = 0, TriageHF n = 2, and HeartInsight n = 1 (see Table 25).

HeartLogic

Mean and median duration spent IN alert varied slightly between study (36 to 42 days).[48,76,80,81] One study reported an average of 14 days from alert to review.[77 70] Finally, one study reported the mean time spent IN alert was 36 days (see Table 25).[36]

TriageHF

One study reported the number of responses required during a high risk status.[31] Another reported the number of high risk episodes during the event and after (see Table 25).[83]

HeartInsight

Time in alert was reported for the validation cohort only (median = 42 days; see Table 25).[45]

CorVue

No studies for CorVue reported on this outcome.

Table 25: Non-comparative evidence for studies reporting alert response rates and time in alert

Author (year)	Study design (n)	Intervention	Alert response rates	Time in alert (days)
Gardner (2018)[81]	Secondary analysis of a prospective cohort (n = 900)	HeartLogic	NR	IN alert mean = 37.8 (median = 30) OUT of alert mean = 145.2 (median = 88)
Feijen (2023)[36]	Propensity matched retrospective cohort (n = 161)	HeartLogic	NR	Mean (SD) = 36 (9)
Calo (2021)[80]	Prospective cohort (n = 366)	HeartLogic	NR	Median (IQR) = 42 (24-61) Overall time IN alert = 38 patient years
Guerra (2022)[76]	Prospective cohort (n = 229)	HeartLogic	NR	Median (IQR) = 42 (25-60)

Author (year)	Study design (n)	Intervention	Alert response rates	Time in alert (days)
				Overall time IN alert = 33 patient years
Santini (2020)[44]	Prospective cohort (n = 53)	HeartLogic	NR	15% of total observation period was spent IN alert
De Juan Baguda (2022)[70]	Phase 1 (n = 101) and 2 (n = 94) are retrospective cohorts Phase 3 (n = 267) is a prospective cohort	HeartLogic	NR	11% of follow up period spent IN alert
Pecora (2020)[77]	Prospective cohort (n = 104)	HeartLogic	NR	Alert to review Mean (SD) = 14 (8) days 14% of observed period IN alert
Hernandez (2022)[48]	Prospective cohort (n = 191)	HeartLogic	NR	Mean = 36 Median = 27 17% of follow up time related to IN alert state
Feijen (2023)[36]	Propensity matched retrospective cohort (n = 161)	HeartLogic Conventional remote monitoring	NR	Mean (SD) = 36 (9)
Garner (2022)[31]	Prospective cohort (n = 749)	TriageHF	Response to 367 high risk alerts Telephone contact = 303 No intervention required = 128	NR
Debski (2020)[83]	Prospective registry (n = 132)	TriageHF	Number of high risk alerts = 398 During high risk episode= 38%	Median delay for transmission when receiving after the

Author (year)	Study design (n)	Intervention	Alert response rates	Time in alert (days)
			After high risk episode = 62%	delay = 10 (IQR: 15) days
D'Onofrio (2022)[45]	Prospective cohort (overall n = 918*, development n = 457, validation n = 461)	HeartInsight	NR	Development Median = NR Validation Median = 42 days

NR = Not Reported; SD = Standard Deviation; IQR = Inter Quartile Range

3.7.4 Number of emergency or urgent care visits

The number of emergency or urgent care visits was reported in 11 studies: HeartLogic n = 6, CorVue n = 3, TriageHF n = 2, and HeartInsight n = 0 (see Table 26 and Table 27).

Non-comparative evidence

HeartLogic

Four of the six studies for HeartLogic were single cohort study designs. These studies reported the number of emergency or urgent care visits.

CorVue

The three studies for CorVue were all single cohort studies (see Table 26).

TriageHF

Non-comparative evidence

Two studies for TriageHF were single cohort studies (see Table 26).

HeartInsight

No studies for HeartInsight reported on this outcome.

Comparative evidence

HeartLogic

One study was comparative and compared pre and post activation of the HeartLogic algorithm, observing no statistically significant differences between clinic or ambulatory visits (see Table 27).[37] The one controlled comparative study showed a statistically significant increase in clinic visits for diuretics post-activation.[36]

CorVue

No comparative evidence for this outcome.

TriageHF

No comparative evidence for this outcome.

HeartInsight

No comparative evidence for this outcome.

Table 26: Non-comparative evidence from studies reporting number of emergency and urgent care visits

Author (year)	Study design (n)	Intervention	Emergency and urgent care visits (n)	Other
Pecora (2020)[77]	Prospective cohort (n = 104)	HeartLogic	17 of 100 alerts required in-office visits	Overall 282 scheduled and 56 unscheduled in-office visits were performed during follow-up
De Juan Baguda (2022)[70]	Phase 1 (n = 101) and 2 (n = 94) are retrospective cohorts Phase 3 (n = 267) is a prospective cohort	HeartLogic	Unscheduled consultations (in-person or telephone) Phase 1 = 3 of 73 alerts Phase 2/3 = 46 of 277 alerts	NA
Boehmer (2017)[56]	Prospective cohort (overall n = 900*, development n = 500, validation n = 400)	HeartLogic	Outpatient visits Development = 132 Validation = 60	NA
Santini (2020)[44]	Prospective cohort (n = 104)	HeartLogic	In-office examinations Unscheduled = 56 Scheduled = 282	NA
Palfy (2015)[41]	Cohort, unclear (n = 65)	CorVue	11 of 20 episodes in 14 patients led to emergency room/ambulatory treatment modification	NA
Palfy (2018)[40]	Prospective cohort (n = 53)	CorVue	13 of 25 episodes in 18 patients led to emergency room/ambulatory treatment modification	NA
Benezet Mazuecos (2016)[43]	Cohort, unclear (n = 70)	CorVue	13 of 25 episodes in 16 patients led to emergency room/ambulatory treatment modification	NA

Author (year)	Study design (n)	Intervention	Emergency and urgent care visits (n)	Other
Virani (2018)[55]	Prospective cohort (n = 100)	TriageHF	Medium risk = 2 High risk = 0	NA
Debski (2020)[83]	Prospective registry (n = 132)	TriageHF	Unscheduled alerts^ = 44% Care alerts^ = 32%	NA

NA = Not Applicable; *denotes number analysed; ^denotes information is undefined

Table 27: Comparative evidence from studies reporting number of emergency and urgent care visits

Author (year)	Study design (n)	Intervention/Control	Emergency and urgent care visits (n)	Other
Treskes (2021)[37]	Retrospective pre-post analysis (n = 68)	HeartLogic Remote monitoring pre-activation	Pre- vs post-activation of HeartLogic One day clinic visits Pre-activation = 32 Post-activation = 42 Proportion of patients with 1 day clinic visit Pre-activation = 24 Post-activation = 19 Ambulatory visits Pre-activation = 132	One day clinic visits p = 0.732 Ambulatory visits p = 0.757 Proportion of patients with 1 day clinic visit p = 0.461

Author (year)	Study design (n)	Intervention/Control	Emergency and urgent care visits (n)	Other
			Post-activation = 117	
Feijen (2023)[36]	Propensity matched retrospective cohort (n = 161)	HeartLogic Conventional remote monitoring	Clinic visits for increasing diuretics, median (IQR) Control = 2 (0-3) HeartLogic = 1 (0-2)	Difference between groups, p = 0.0001

3.7.5 Software failure rate

HeartInsight

HeartInsight observed 39 of 918 patients, in a single cohort, had connection issues for home monitoring remote transmissions as they could not establish sufficient GSM (Global System for Mobile communication) coverage. The median remote monitoring rate was 91.3% of days (IQR = 83.5% to 95.8%) in the development cohort and 90.8% (IQR = 83.1% to 95.5%) in the validation cohort.[45]

HeartLogic

A single study reported reasons for ungenerated alerts using the HeartLogic algorithm.[48] Delays or ungenerated alerts were reportedly caused by the home communicator not being powered or could not send data, or the patient was out of range, or alert threshold was adjusted from nominal. Of the total 3 290 weekly alerts, 2 934 (89%) were communicated to the sites (median delivery time <1 day, Q3 <1 day, max 129 days), 2 894 (88%) were documented as received by sites.[48]

CorVue

No studies for CorVue reported on this outcome.

TriageHF

All evidence for TriageHF was derived from a single group for this outcome. It was reported that, if a patient fails to record a transmission within a 425 day window, data is lost.[69] In one study they reported 36 patients had 45 episodes over 65 days that were not transmitted.[69] Another reported 130 (33%) episodes were not transmitted within 30 days from the final day of a high risk status.[83]

3.7.6 Number of monitoring reviews

TriageHF

One study utilising the TriageHF algorithm reported remote monitoring with co-management (i.e. HF specialist alerted). One third of transmission (368 alerts) were sent to co-management.[83] One comparative study for TriageHF did report the average minutes per week call time (hospital 1: 13.5 mins; hospital 2: 12.9 mins; hospital 3: 18.2 mins) and workload (hospital 1: 25.3 mins; hospital 2: 24.2 mins; 46.9 mins) associated with using the TriageHF plus care pathway.[28]

HeartLogic

One study reported that of 273 alerts 204 did not require extra in-office visits and were managed remotely. OF the 69 in-office visits, 42 were scheduled examinations that were previously planned (within 7 days of the alert). The median number of phone contacts per alert period was 1 (IQR: 1-2).[80] De Juan Baguda *et al.* reported most alerts were managed remotely. Patient phone contacts during phase 2 was 35 (0.65 contacts per patient year) and during phase 3 was 287 (1.12 contacts per patient year).[84]

HeartInsight

No studies for HeartInsight reported on this outcome.

CorVue

No studies for CorVue reported on this outcome.

3.7.7 Adverse events

No other morbidity outcomes were identified, therefore we only focus on the available data for adverse events.

Non-comparative evidence

HeartInsight

The single published study assessing HeartInsight did report the number of HF related adverse events in the development group; however, these were not directly linked to the use of the algorithm and are therefore not presented.[45]

HeartLogic

A single cohort study for HeartLogic study reported 691 overall adverse events, with 50 related to HeartLogic. Five of 301 severe adverse events occurred in 4 of 157 patients with alerts (0.015 per patient year) and were classified as abnormal lab values, renal insufficiency/failure HF (n = 2), dizziness-HF, and syncope-HF.[48]

CorVue

No studies for CorVue reported on this outcome.

TriageHF

No studies for TriageHF reported on this outcome.

Comparative evidence

There was no comparative evidence reported on this outcome for any technology.

3.7.8 Summary of implementation outcomes

There is a lack of evidence for a number outcomes, with many of these outcomes being supported by a single study for some algorithms and no evidence for other algorithms. Due to this, it is difficult for the EAG to make conclusive remarks regarding the implementation of the algorithms in clinical practice. The majority of evidence was available for the HeartLogic algorithm. The majority of studies were rated as high risk of bias.

TriageHF

Software failure may occur where the patient is unable to send an alert. After 425 days data is lost and cannot be assessed.[69] One study found that 33% of episodes were not transmitted.[83] Implementation regarding the number of monitoring reviews was reported in two studies. One of these studies reported the average workload in minutes for using the TriageHF plus care pathway.[28] No conclusions can be drawn based on the available data.

HeartLogic

There was evidence to suggest that being at a higher IN alert value and the amount of time IN alert was associated with further treatment needs to resolve the alert.[76] The median time between an alert and HF

event varied between 11 and 63 days.[6,71,46,80] This may provide evidence that if an IN alert status is triggered, quick actions could reduce HF events but if left unattended they may progress and require further treatment adaptations.

Comparative evidence reported a reduction in clinic visits when utilising the HeartLogic algorithm compared to a conventional remote monitoring group.[36] However, a pre-post analysis showed no statistically significant changes in one day clinic or ambulatory visits.[37] Therefore, we cannot draw any conclusions on the impact of the HeartLogic algorithms effect on clinic visits.

There is a potential for an issue with software failure, where the alerts are not generated or are delayed due to varying factors (e.g. home communicator not being powered or could not send data, or the patient was out of range, or alert threshold was adjusted from nominal).[48] One study found that 11% of weekly alerts were not received by sites.[48]

Adverse events associated with using the HeartLogic algorithm were reported in one study. Rates were relatively low with 50 of 691 adverse events being associated with HeartLogic.[48]

The evidence retrieved for HeartLogic for implementation is varied and sparse.

CorVue

Three studies reported the number of alerts leading to clinic visits. [40,41,43] No further data is reported for any outcome. No conclusions can be drawn based on the available data.

HeartInsight

The single published study identified for HeartInsight reported a potential for software failure if there were connection issues for home monitoring transmissions (e.g. there was not sufficient GSM coverage).[45] No numerical data is reported for this outcome. No conclusions can be drawn based on the available data.

4. Assessment of existing cost effectiveness evidence

This section provides a summary of the systematic review of studies evaluating the cost-effectiveness of remote monitoring algorithms (Heartlogic, HeartInsight, CorVue and TriageHF) compared to usual in-person clinic visits. This section includes search methods, study selection, data extraction process, quality assessment and summary of results. See Section 5 for a brief description of company economic evaluation evidence submitted before 27th October 2023.

4.1 Methodology of the cost-effectiveness review

The purpose of this systematic review of published economic evaluations studies was:

- To inform the conceptualisation and development of our *de novo* economic model.
- To review existing economic evaluation studies of remote monitoring systems identifying new onset acute HF or worsening signs of HF in people with CIEDs.

By reviewing the documents provided by companies manufacturing these devices, it was anticipated that there would be a lack of relevant economic evidence for the above-mentioned monitoring devices. Therefore, to inform the development our decision-analytic model, a broader review of cost-effectiveness studies including all remote monitoring devices was undertaken.

4.1.1 Searches

Following the same approach taken for the clinical effectiveness searches, between 14th and 20th of June 2023 we undertook a comprehensive search of the economic and cost-effectiveness literature. Table 28 presents a summary of the sources searched. We used a validated search filter to identify cost-effectiveness studies.[85] Search strategies are reported in Appendix 9.2.

Table 28: Databases searched for cost-effectiveness studies

Source name	Platform/URL
MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions	Ovid
Embase	Ovid
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library available at https://www.cochranelibrary.com/cdsr/reviews
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library available at: https://www.cochranelibrary.com/central
Database of Abstracts of Reviews of Effects (DARE)*	Centre for Reviews and Dissemination available at https://www.crd.york.ac.uk/CRDWeb/
HTA Database**	Centre for Reviews and Dissemination available at https://www.crd.york.ac.uk/CRDWeb/
The NHS Economic Evaluation Database (NHS-EED)*	Centre for Reviews and Dissemination available at https://www.crd.york.ac.uk/CRDWeb/

INAHTA (International HTA database)	The International Network of Agencies for Health Technology Assessment available at https://database.inahta.org/
NIHR Journal Library	National Institute for Health and Care Research (NIHR) journals library available at https://www.journalslibrary.nihr.ac.uk/#/

*Content updated until 2015; ** Content updated until 2018

4.1.2 Selection process

All the citations retrieved were screened based on the title and abstract by two reviewers (SH, NB) using EndNote. Two EndNote files were then merged to see discrepancies. The result was discussed between two reviewers and a final list of 33 papers were selected for full text review. Full texts of any records that were agreed to be relevant were obtained and those citations without full text were excluded. The two reviewers then independently reviewed the full texts and disagreements were resolved through discussions.

4.1.3 Data extraction

A data extraction form was developed by reviewers based on the economic evaluation requirements recommended by the CHEERS checklist. [86] The included studies were extracted by one reviewer (SH) using the standardised form and it was then checked by a second reviewer (NB) for accuracy. Information extracted included the PICO (Population, Intervention, Comparator and Outcome) as well as type of economic evaluation, modelling, costing approach, outcome valuation, discount rate, price year and currency.

4.1.4 Quality assessment

A total of 19 economic evaluation studies were summarised of which 5 studies employed Markov model which suits our modelling practice. Therefore, we undertook a quality appraisal of these 5 studies employing CHEERS checklist.[86] A summary of this quality assessment can be found below in Table 29. Furthermore, 12 of 19 studies were trial-based economic evaluations of remote monitoring systems of which only 1 study [Treskes 2021] was found eligible comparing the clinical and economic impacts of an algorithm-based RMS in a group of patients before and after RMS activation.[37]

4.2. Results of the cost-effectiveness review for remote monitoring systems

A PRISMA diagram of studies identified in the systematic review is presented in Figure 3. The initial search identified a total of 224 citations of which 190 were screened after removing duplicated one. A total of 33 studies were identified as potentially relevant from their titles and/or abstracts. Following the full text review, 10 studies were found eligible in terms of PICO criteria. 9 eligible studies were also added from the hand searching. Of 19 studies included, 13 were trial-based economic evaluations, metanalysis or survival studies which neither have implications for our modelling purposes nor for the review of economic evaluation of algorthim-based RMS technologies. Therefore, we just included 5 Markov model studies and 1 economic evaluation study of one of the technologies in the scope of this study which are summarized below. It should be noted that none of the studies with a Markov model mentioned the name of the device used for remote monitoring except the Burri *et al.* (2013)[87] study which assessed the BIOTRONK technology. BIOTRONIK is one of the technologies included in our

protocol although the non-algorithm-based version of it was used in this study. Treskes 2021 study was also the economic evaluation of HeartLogic™ algorithm which is included in our protocol.

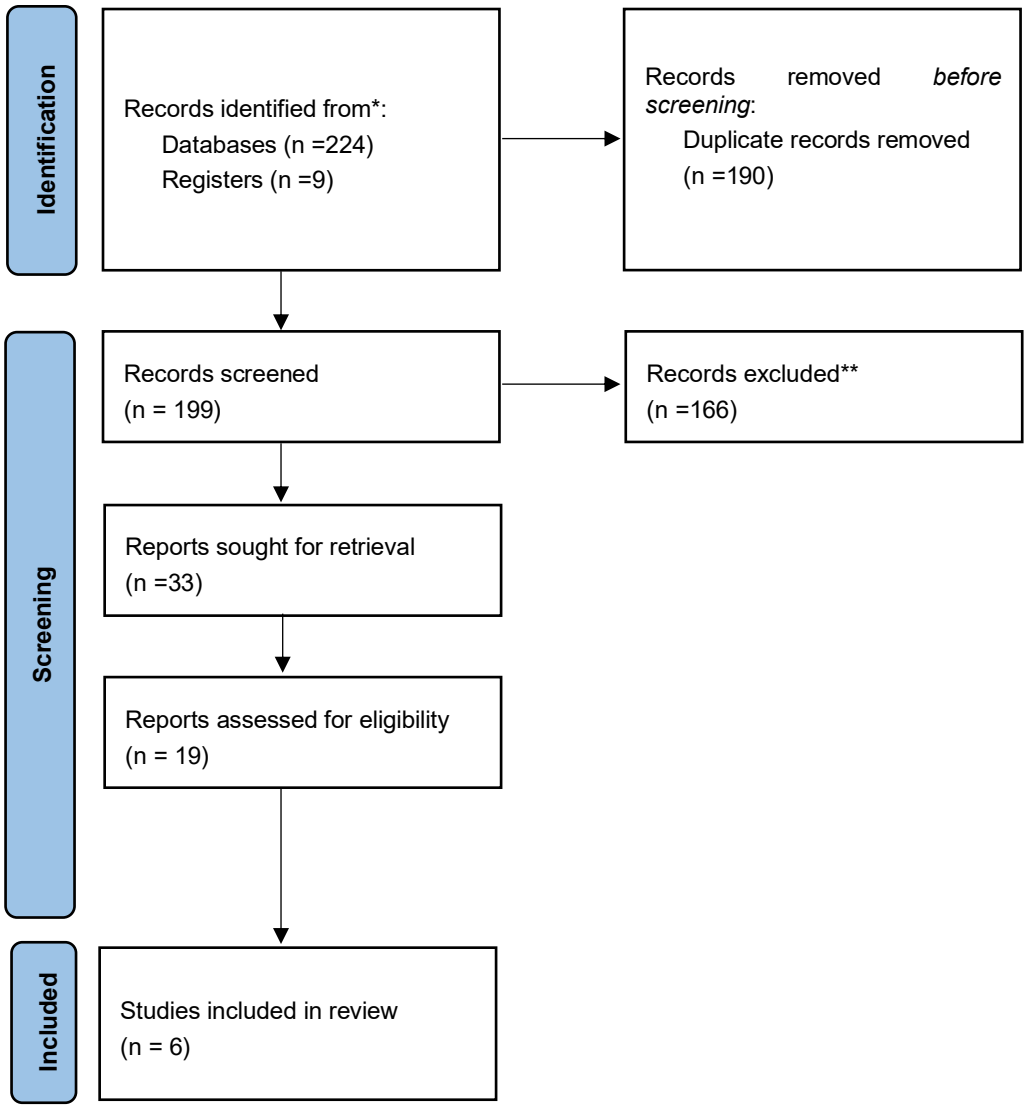


Figure 3: Flow diagram of the study selection process for the cost-effectiveness review

Burri *et al.* (2013) was a "Cost–consequence analysis of daily continuous remote monitoring of implantable cardiac defibrillator and resynchronization devices in the UK" study employing a deterministic four states (Well, Post-stroke, Post ADHF and Death) Markov cohort model.[87] Clinical and cost data were identified through a systematic review of literature. Most of the event data were taken from (RCTs) for HM transmitter (Cardio Messenger II, BIOTRONIK) synthesised using meta-analysis, where required. All costs were UK specific. Data specific for ICD and CRT-D patients or for gender were weighted, based on the number of procedures performed in the UK or the gender split in the UK population. Key findings of this study include:

- HM transmitter was predicted to be cost neutral at about £11,500 per patient in both treatment arms from the UK NHS perspective, with all initial and ongoing costs of remote monitoring included. Based on the univariate sensitivity analysis, remote monitoring was found cost-saving in the base case and 6 other scenarios.

- Fewer inappropriate shocks (−51%) reduced the need for replacing devices for battery exhaustion (−7%), and the number of FU visits was predicted to be halved by using HM.

Chew *et al.* (2022) study investigated the clinical and economic outcomes associated with remote monitoring for CIEDs using a population-based cohort study in Canada.[88] A two state, alive-dead Markov model was employed. Outcomes included life-years (LY) based on all-cause mortality, and quality-adjusted life-years (QALY), and total costs. Utilities for the CIED cohort were derived from a cross-sectional survey administered to a sample of CIED patients in Alberta using the EuroQOL-5D tool. Costs for inpatient hospitalization, outpatient hospital visits, and emergency room visits were calculated based on top-down methods using the Resource Intensity Weight (RIW) and the Cost of a Standard Hospital Stay (CSHS). Key finding include:

- Over the base case time horizon of 5 years, patients following an RM strategy accrued 3.640 QALY for a total cost of $40,314 while patients following an in-clinic strategy accrued 3.637 QALY for a total cost of $52,508.

- Although QALY gains were found to be similar for each strategy, RM was associated with incremental cost savings over a 5-year period compared with in-clinic visits alone ($12,195 per person), indicating that RM technology was associated with similar patient outcomes and cost savings from healthcare perspective.

- Based on the sensitivity analysis, the differences in hospitalization rates and inpatient costs were the primary driver of cost savings in the model. In a scenario that excluded hospitalization costs from the model, there were no longer cost savings associated with the RM group.

Kawakami *et al.* (2023) was cost-effectiveness analysis of remote monitoring after pacemaker implantation for bradycardia in Japan.[89] They developed a six states Markov model incorporating QALY and cost data. The health states included "Post-pacemaker implantation (PMI)," "AF without OAC," "AF with OAC," "Post-stroke," "Device trouble," and "Dead". The health outcome information was obtained from literature by searching the words "utility" and "quality of life," in conjunction with the health states. Key findings:

- It was found that RM was more effective but more costly than conventional follow-up (CFU) for all CHADS2[1] scores, and higher CHADS2 scores were associated with higher costs and lower QALYs.

[1] CHADS is a scoring system to assess the risk of stroke in patients. It stands for (c) congestive heart failure, (h) hypertension, (a) age, (d) diabetes, and previous history of (s) stroke.

- Based on the results of Probabilistic Sensitivity Analysis (PSA), RM did not show clear cost-effectiveness for patients with a CHADS2 score of 2. However, for CHADS2 scores of 4 and 6 RM was found to be a cost-effective option compared with CFU at WTP thresholds >3,500,000 JPY and >1,500,000 JPY, respectively.

It should be noted that only direct medical cost and long-term care costs were taken into account and social costs and patient incurred ones were not included.

Sequiera *et al*. (2020) investigated cost-effectiveness of remote monitoring of implantable cardioverter-defibrillators in France.[90] It was a meta-analysis and an integrated economic model derived from randomized controlled trials. A Markov multi-state model with 1-month cycle was employed, in which each patient existed in one of three mutually exclusive states: 1- stable outpatient, 2- CV hospitalization, or 3- dead. Key findings:

RM resulted in cost-savings of €4142 per patient over a 5-year time horizon, with a quality-adjusted life year (QALY) gain of 0.29. The incremental cost-effectiveness ratio was €14,136/QALY, in favour of RM from French healthcare system perspective. PSA confirmed that the RM strategy was dominant over SC in 70% of cases.

- RM resulted in cost-savings of €4142 per patient over a 5-year time horizon, with a quality-adjusted life year (QALY) gain of 0.29. The incremental cost-effectiveness ratio was €14,136 /QALY, in favour of RM from French healthcare system perspective.

Health Quality Ontario (2018) conducted a health technology assessment to compare Remote Monitoring of ICD, CRT and permanent pacemakers with clinic visits.[91] A four states (Stable arrhythmia, post hospitalized non stroke, post stroke and death) Markov model was developed that followed patients during the maintenance phase (3 months after successful implantation). The two model populations were: (1) ICD and CRT-D recipients with heart failure and (2) pacemaker recipients with arrhythmia.

Health utility estimates for ICD and CRT-D recipients were derived from literature which all used the EQ-5D5L/3L questionnaires. Utility studies used for the pacemaker recipients (Model 2) employed non–preference-based measures (SF-36 questionnaire, Minnesota Living with Heart Failure Questionnaire). All the costs were specific to Canadian healthcare system mostly obtained from the Ontario Health Insurance Schedule and administrative data.

Treskes *et al.* (2021) evaluated the "clinical and economic impact of HeartLogic compared with standard care in heart failure patients".[37] The data were obtained from a multicentre non-blinded single-arm 1-year trial. They compared the rate of HF events in 68 patients who completed the follow up period before and after activation of monitoring algorithm. They also measured the associated costs pre and post activation of monitoring algorithm in 1 centre including 30 patients.

- Number of patients hospitalized because of HF event declined from 21 (pre-activation) to 7 (post activation) (P= 0.005), and the hospitalization length of stay reduced from average 16 to 7 days (P= 0.079).
- There was a substantial drop in average total costs per patient including and excluding deceased patients respectively (- €9958 and - €8286). The difference mainly comes from the

hospitalization cost (€9972 and €8523) while the ambulatory cost was not found to be significantly different.

Key findings:

- Treskes 2021 was the only study which compared the economic benefits of an algorithm-based RMS (HeartLogic) technology included in the scope of this study before and after the activation of this system. Although they found a significant drop in average total costs, it should be noted that the sample size was rather small, and data were obtained only from one medical centre.
- The other 5 studies which employed a Markov model have not used an algorithm-based RMS technology. The study results therefore do not apply to the technologies investigated in this DA, but the study details are useful to inform the development of a model.
- For ICD and CRT-D recipients, remote monitoring plus in-clinic follow ups strategy was more costly (incremental value of $4,354 per person) and more effective, providing higher quality-adjusted life years (incremental value of 0.19), compared to in-clinic follow-up alone.
- Among pacemaker recipients, remote monitoring plus in-clinic follow ups strategy was less costly (with an incremental saving of $2,370 per person) and more effective (with an incremental value of 0.12 quality-adjusted life years) than with in-clinic follow-up alone.
- It was estimated that publicly funding remote monitoring could result in cost savings of $14 million over the first five years.
- Based on the one-way sensitivity analyses, the most sensitive variables were the transition probabilities for emergency visits and hospitalizations as the main drivers of cost. Furthermore, in the deterministic sensitivity analysis, the payment for remote interrogation were changed from a 0% reduction to a 100% reduction, compared to a clinic visit. Among ICD and CRT-D recipients, the simulated ICERs remained cost-effective under commonly used thresholds.

Quality assessment of the studies

Based on the assessment of the included studies (Table 29) using the CHEERS checklist, all the 6 studies included the population, comparator, and interventions as compatible with our protocol. Economic evaluation perspective taken for all studies were healthcare system and time horizon considered in the model were 5 to 10 years. Treskes 2021 compared 12 months before and 12 months after the activation of the algorithm based RMS.[37] The only study which discussed the generalisability issue is Health Quality Ontario HTA.[91]

4.3 Methodology of the review of studies evaluating resource use and utility of remote monitoring systems in Heart Failure

4.3.1 Searches

Additionally, we performed focussed searches for resource utilization, QALY and utility values to populate the economic model. We searched MEDLINE and Embase via Ovid and used two validated economic filters for cost-of-illness studies and quality-of-life studies.[92, 93] We also searched specialist

sources such as CEA Registry (available at https://cevr.tuftsmedicalcenter.org/databases/cea-registry), RePEC (available at http://repec.org/) and ScHARRHUD (the health utilities database from the School of Health and Related Research at The University of Sheffield, available at https://www.scharrhud.org/).

4.3.2 Selection Process

Title and abstract of all the citations were screened by two reviewers (SH, NB) using EndNote. The result was discussed between two reviewers and a final list of 12 papers was selected for full text review. Papers were reviewed and summarized by one reviewer (SH) and 7 papers were finally included, of which 4 papers included cost parameters and 3 included utility values.

4.3.3 Data extraction

The included studies were summarized by one reviewer (SH) using a form developed by reviewers. Information extracted included the different categories of costing, county, currency, utility values, instruments used and QALY estimates.

Table 29: Summary of quality assessment of the included studies

Item	Burri 2013[87]	Chew 2022[88]	Kawakami 2023[89]	Sequeira 2020[90]	Ontario HTA 2018[91]	Treskes 2021 [37]
Title	**Page 1**	**Page 1**	**Page 1**	**Page 1**	**Page 1**	**Page 1**
Title	Cost–consequence analysis of daily continuous remote monitoring of implantable cardiac defibrillator and resynchronization devices in the UK	Clinical and Economic Outcomes Associated with Remote Monitoring for Cardiac Implantable Electronic Devices: A Population-Based Analysis	A cost-effectiveness analysis of remote monitoring after pacemaker implantation for bradycardia in Japan	Cost-effectiveness of remote monitoring of implantable cardioverter-defibrillators in France: a meta-analysis and an integrated economic model derived from randomized controlled trials	Remote Monitoring of Implantable Cardioverter-Defibrillators, Cardiac Resynchronization Therapy and Permanent Pacemakers: A Health Technology Assessment	Clinical and economic impact of HeartLogic compared with standard care in heart failure patients
Abstract	**Page 1**	**Page 1 -2**	**Page 1**	**Page 1**	**Page 3-4**	**Page 1**
Abstract	Structured with aims, method, results and conclusion	Structured with aims, method, results and conclusion	Structured with aims, method, results and conclusion	Structured with aims, method, results and conclusion	Structured with aims, method, results and conclusion	Structured with aims, methods and results, and conclusion
Introduction	**Page 2**	**Page 2**	**Page 2**	**Page 2**	**Page 13**	**Page 1-2**
Background & objectives	Background, study objectives and policy implications reported.	Background and study objectives reported.	Background and study objectives reported.	Background and study objectives reported.	Background, study objectives and policy implications reported	Background and study objectives reported

Methods	**Pages 2-4**	**Pages 2-4**	**Pages 3-8**	**Page 3 -7**	**Page 64**	**Page 2-5**
Health economic analysis plan	NO	NO	NO	NO	Not a separate HEAP as this is a comprehensive HTA report	No
Study population	ICD and CRT-D patients	Adults with ICD or CRT-D	elderly Japanese patients with pacemakers for bradycardia	ICD patients	ICD patients	>18 years of age patients with HF and an ICD featuring the HeartLogic multisensor algorithm
Setting and location	UK	Alberta, Canada	Japan	France	Canada	Belgium, Netherlands and Switzerland
Comparators	Remote monitoring and Routine follow up visits	Remote monitoring and Routine follow up visits	RM follow up relative to that of conventional in-office follow up (CFU)	RM and standard care	Remote monitoring + clinic visits vs clinic visits only	Pre-activation and post-activation within each patient
Perspective	UK National Health Service perspective	Canadian public health system payer	healthcare provider	healthcare system	Ontario Ministry of Health and Long-term Care	Belgian healthcare perspective
Time horizon	10 years	5 years	10 years	5-year	5-year	12 months before activation and 12 months after activation
Discount rate	3.5%	1.5%	2%	NO	1.5%	Not applicable
Selection of outcomes	Twelve consequences were examined in the model.	The primary end point was all-cause mortality. Secondary end points included time to first hospitalization for a cardiovascular (CV) cause, cumulative incidence of CV hospitalization, hospital length of stay,	quality-adjusted life years (QALYs).	CV hospitalization Death Utilities	Mortality Health care use Health-related quality of life	Primary end point was decompensated HF. Secondary outcomes were the number of patients hospitalised for decompensated HF, the mean number of HF hospital

		cumulative incidence of emergency department visits, cumulative incidence of outpatient physician visits				admission per patient, mean length of stay in days. In addition, the total number of 1 day clinic visits, mean number of 1 day clinic visits per patient, and the number of patients with 1 day clinic visit was evaluated.
Measurement of outcomes	Page 1	Page 2	Page 4	Page 7-8	Mortality Page 73-75 Utility page 80	Page 3
Valuation of outcomes	NA	NA	Page 4	NA	Mortality Page 73-75 Utility page 80	NA
Measurement and valuation of resources and costs	NO	top-down methods using the Resource Intensity Weight (RIW)	direct medical costs for the therapies, as well as costs for long-term disability care were included (page 3)	Page 7-8	Page 83-85	Page 3
Currency, price date, and conversion	GBP Page 3	Costs were valued in 2019 Canadian dollars using the Consumer Price Index for Goods and Services, if required	JPY	Euro – Price year Unknown	CAN $ - Price year ?	Euro- Price year unknown
Rationale and description of model	Page 2	Page 3	Page 2	Page 6-7	Page 68	Not applicable as this a before after study.
Analytics and assumptions	Page 3	Page 3	Page 2	NO	Page 67	Page 5

Characterising heterogeneity	NO	NO	NO	NO	NO	No
Characterising distributional effects	NO	NO	NO	NO	NO	No
Characterising uncertainty	Page 4	Page 4	Page 5	Page 7	Page 87-88	Page 5; Interquartile range and standard deviations used to present results
Approach to engagement with patients and others affected by the study	NO	NO	NO	NO	NO	No
Results	**Page 4**	**Page 4-5**	**Pages 5-8**	**Page 8-9**	**Page 89**	**Page 5-7**
Study parameters	Page 4	Page 4		Page 9- table 3	Table 35-36	Page 6-7
Summary of main results	Page 4	Page 5	NO	Page 8- CEA paragraph	Page 89- reference case analysis	Table 4 and 5 , page 8
Effect of uncertainty	Page 4	Page 5	Page 4	Page 10- Figure 4 – PSA	Page 93	No
Effect of engagement with patients and others affected by the study	NO	NO	NO	NO	NO	No

Discussion	**Page 4-6**	**Page 5-7**	**Page 8**	**Page 9**	**Page 95**	**Page 7-9**
Study findings, limitations, generalisability, and current knowledge	No generalisability	All included expect generalisability	No generalisability reported	No generalisability	All Included: page 89 and 94	All included, except generalisability
Other relevant information	**Page 7**	**Page 8**	**Page 9**	**Page 11**	**NO**	**Page 9**
Source of funding	This work was supported by Biotronik. H.B was supported in part by a grant from la Tour Foundation for Cardiovascular Research.	This study was funded by Alberta Innovates Health Solutions Collaborative Research and Innovations Opportunities and by the Partnership for Research and Innovation in the Health System Grants, Government of Alberta	This research was supported by JSPS KAKENHI [grant number 22K17327]	NO external funding	--	Boston Scientific Corporation (reference number: ISRRM11793)
Conflict of interest	Page 7	Page 8	Page 9	Page 10	--	Page 10

4.4 Results of the targeted review of studies evaluating resource use and utility of remote monitoring systems in Heart Failure

The utility values from 3 papers are reported in Table 30.

Table 30: Summary of utility values identified in the review

Citation	Utility SC (Mean, SD)		Utility RM		QALY SC	QALY RM
	Baseline	16 months	Baseline	16 months		
EVOLVO Study[94]: Cost-Utility Analysis of the EVOLVO Study on Remote Monitoring for Heart Failure Patients with Implantable Defibrillators: Randomized Controlled Trial	0.737 (0.234)	0.711 (0.305)	0.793 (0.179)	0.754 (0.275)	0.966 (0.231)	1.032 (0.177)
PREDICT Study[95]: Outcomes and costs of remote patient monitoring among patients with implanted cardiac defibrillators: An economic model based on the PREDICT RM database	--	--	--	--	5.65	6.29
TARIFF study[96]: Economic analysis of remote monitoring of cardiac implantable electronic devices: Results of the Health Economics Evaluation Registry for Remote Follow-up (TARIFF) study	Baseline	12 months	Baseline	12 months	**QALY SC**	**QALY RM**
	0.86 ± 0.18	0.85 ± 0.18	0.87 ± 0.13	0.87 ± 0.16	0.85 ± 0.17	0.87 ± 0.13

Summaries of four papers which estimated and compared the costs of using remote monitoring versus standard care practice in different countries are provided below.

Hein Heidbuchel *et al.* undertook a study in 5 European countries, including UK, to evaluate net financial impact of using remote monitoring on providers (taking national reimbursement into account) and costs.[97] The price year in this study was 2013 and all costs were reported in Euro. The study was from payer perspective, so the unit costs were based on diagnosis-related groups tariffs, national or regional fee-for-service tariffs or public general hospital tariffs.

Key results:

Resource use for remote monitoring were clearly different from the standard care group (all these results are statistically meaningful):

- Less FU visits (3.79+1.67 vs. 5.53+2.32)
- Small increase of unscheduled visits (0.95+1.50 vs. 0.62+1.25)
- More non-office-based contacts (1.95+3.29 vs. 1.01+2.64)
- More Internet sessions (11.02+15.28 vs. 0.06+0.31) and more in-clinic discussions (1.84+4.20 vs. 1.28+2.92)

There found to be numerically fewer hospitalizations (0.67+1.18 vs. 0.85+1.43) and shorter length-of-stay (6.31+15.5 vs. 8.26+18.6) although not statistically significant.

Josep A. Ladapo *et al*. investigated health care utilization and expenditures associated with remote monitoring in ICD patients in USA assessing current direct costs of 1-year ICD follow-up based on RM compared with conventional quarterly in-hospital follow-ups employing a linear regression model.[98]

Key results:

- They reported on inpatient admission, inpatient admission through ED, outpatient office/ED visits.
- Across almost all three subgroups (ICD, CRT-D and PPM) before and after matching, there were found to be fewer/same admissions and visits for RM group. Only outpatient office visits for ICD and CRT-D patients were slightly higher (12.18 vs 11.99 and 13.68 vs 13.57 respectively) for RM group after matching.
- Remotely monitored patients with ICDs experienced fewer emergency department visits resulting in discharge (p = 0.050).
- Remote monitoring was associated with lower health care expenditures in office visits among patients with PPMs (p =0.025) and CRT-Ds (p = 0.006) and lower total inpatient and outpatient expenditures in patients with ICDs.

Laurence Gue´don-Moreau *et al*. investigated costs of remote monitoring vs. ambulatory follow-ups of ICD patients in the randomized ECOST study in France from French health insurance system perspective. The use of RM was found to be cost saving.[99]

Key results:

- Over a follow-up of 27 months, the mean non-hospital costs per patient-year were €1695+1131 in the RM, vs. €1952+1023 in the control group (P = 0.04), a €257 difference mainly due to device management.
- The hospitalization costs per patient-year were €2829+6382 and €3549+9714 in the RM and control groups, respectively (P = 0.46). Adding the ICD to the non-hospital costs, the savings were €494 (P = 0.005) or, when the monitoring system was included, €315 (P = 0.05) per patient-year.

Piotr Buchta *et al*. undertook a study to assess the impact on costs for the healthcare system of RM in patients with ICD or CRT-D in Poland over three years follow up. The perspective taken were National

Healthcare system; therefore, they used payer costs based on diagnosis-related groups and public general hospital tariffs.[100]

Key results:

- The reduction in the costs of treatment for National Health Care in the RM group was 33.5% (median value, $p < 0.001$) over three years follow up period. In patients with implanted CRT-D, the reduction reached 42.7% ($p = 0.011$) while it was 31.3% in ICD patients ($p = 0.007$).

- There was no significant reduction in the median hospitalisation costs in the three-year follow-up in the RM group despite a 25% drop in the mean value.

- The costs of outpatient visits were slightly higher in the RM group although it was not found to be statistically significant.

4.5 Conclusions of the assessment of existing cost-effectiveness evidence

A systematic review was conducted to obtain cost-effectiveness evidence for the algorithms included in this study and to retrieve studies to inform our model as well as compare the results with our model results at the end. There was only one study that was included that evaluated the cost-effectiveness of a remote monitoring algorithm.[37] Most studies reported int his section were studies employing Markov models regardless of technologies they used for the purpose of informing our *de novo* model, including structure, outcomes, model cycles and parameters.[87-91]

To obtain resource use and utility values of using remote monitoring algorithms compared to standard care, we conducted a focused review of the literature. Among the studies retrieved, three of them reported on utility values and QALY estimates of using remote monitoring in two treatment arms with 12-16 months follow-up.[94-96] As for resource utilization, no UK-specific study was identified. Four studies conducted in different countries were reported, which used modelling techniques with longer follow up periods of ICD patients who were being remotely monitored.[97-100] This allows the estimates to be more generalizable rather than using a single centre trial-based study with short follow-up period.

Outcome event data, resource use and utility data were used to inform the parameters in our economic model. It should be noted that unit cost of each resource were obtained from UK national databases such as NHS reference cost schedule.[101]

5. Company submissions

5.1 Overview

Medtronic submitted a cost-effectiveness model in Excel and a report for this technology assessment on the TriageHF algorithm in late October 2023.[102] An abstract related to the TriageHF Plus clinical study underpinning the evidence submission was included in the systematic review Ahmed *et al*.[28] Further details regarding the clinical study were included in the evidence submission.

A cost-utility analysis comparing TriageHF Plus with standard of care (SoC) HF monitoring was included. Two populations were defined in analyses: (a) all people (aged 18 years or older) with a TriageHF compatible ICD or CRT who had a prior diagnosis of HF, (b) the trial population of TriageHF Plus ([redacted]% had a prior diagnosis of HF). Subgroups were defined by CIED: ICD, CRT-P, CRT-D.

The economic decision model was a two-state (dead and alive) Markov model. The time horizon was lifetime. The Study was conducted from the perspective of the English and Welsh NHS and Personal Social Services (PSS). Costs and benefits were discounted at an annual rate of 3.5%.

5.2 Outcomes

5.2.1 Hospitalisations

The rate of hospitalisations, follow-up consultations and mortality were included in the model.

For the comparator, the annual rate of hospitalisations was estimated as the number of events divided by the number of person-years. The average number of hospitalisations per person-year ([redacted]) for the comparator was obtained from the company submission.[102] There were [redacted] events over [redacted] person-years. This was obtained from the TriageHF Plus study. The results have not yet been published. The incidence rate ratio (IRR) was estimated using a Poisson Generalised Linear Mixed Model (GLMM) with log link. The mean IRR was 0.42 (95% CI: 0.23, 0.76, p=0.004, SE = 0.3).[102] The average number of hospitalisations per person-year was therefore calculated to be [redacted] in the model for TriageHF. The rate was converted to a monthly probability in the model. The EAG thinks that an average rate or Poisson distribution probability calculations are appropriate methods. In each case, the annual value is divided by 12 to derive the monthly value. However, the practical difference is small in this case and not a cause for concern.

Analysis sets from TriageHF Plus specific to the defined populations were used to estimate hospitalisations.

Because the study overlapped with the Covid pandemic, a total analysis set and pre-COVID analysis sets were defined. The total analysis set was used in the base case analysis.

5.2.2 Follow-up visits

For the algorithm-based remote monitoring system, the contacts with the healthcare system other than those related to alerts were assumed to be the same as for the CIED without the algorithm-based remote monitoring system. Healthcare contacts included GP visits, A&E visits, consultant visits and others. The number of tests associated with these visits were also assumed to be the same.

For patients with an alert, [redacted] had an initial consultation, and [redacted] had a second consultation. Tests and treatment were also costed for these.

5.2.3 Mortality

There was insufficient evidence to evaluate the hazard ratio of mortality, so it was assumed that there was no difference in mortality rates. Survival analysis was conducted using a standard selection of parametric survival models.[103] and the log-normal parametric model was selected due to the most appropriate external validity based on a study by Taylor *et al*.[104] Survival rates were 81% at 1 year, 48% at 5 years and 26% at 10 years. The Kaplan-Meier curve and fitted parametric models are reproduced in Figure **4**.

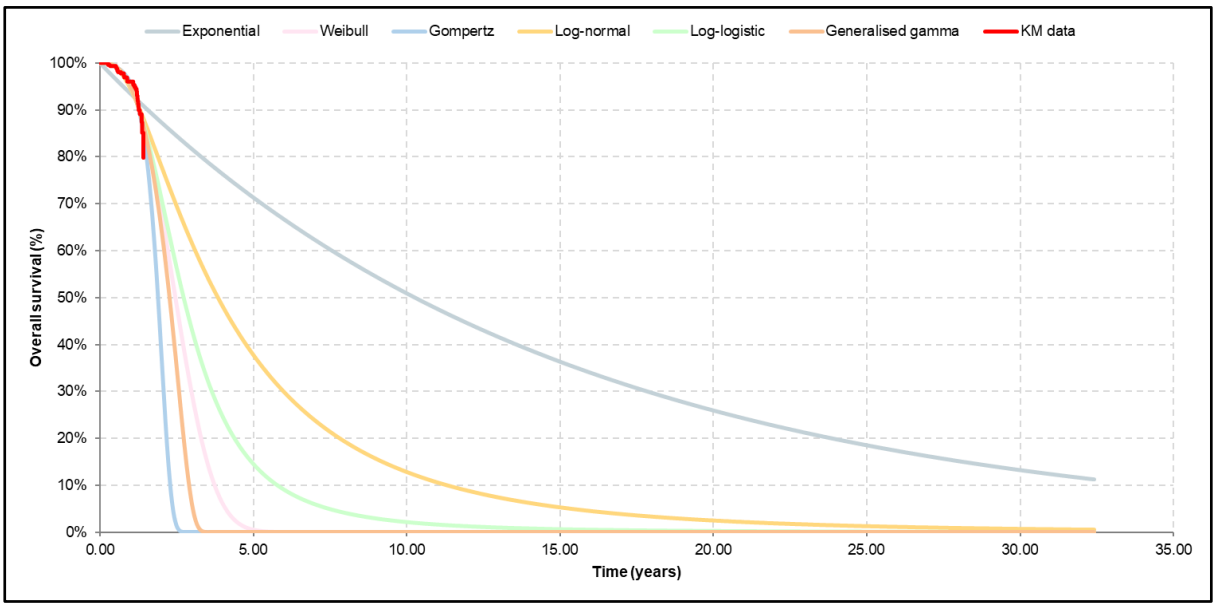


Figure 4: Kaplan-Meier curve and fitted parametric models (reproduced from Figure 3.2 in the Medtronic submission)

5.3 Health utilities

General population utilities were assigned to patients alive, and an annual hospitalisation utility decrement was applied.

5.4 Results

The company conducted deterministic analysis and probabilistic sensitivity analysis (PSA). Based on the PSA results, the average ICER was -£610,120 per QALY gained for all patients across the total study analysis set in TriageHF Plus. TriageHF results in a reduction of costs of approximately [redacted] per person and an increase in QALYs of [redacted]. Therefore, TriageHF was dominant and cost-effective compared to SoC.

The deterministic incremental cost and QALY outcome also sits close to the middle of the PSA iterations, reducing the uncertainty associated with the deterministic model results.

The probability of TriageHF being cost-effective compared to SoC across multiple WTP thresholds was represented using a CEAC. TriageHF is 99.5% more likely to be cost-effective than SoC at every WTP threshold per QALY gained.

It should be noted that hospitalization costs found to be the main driver of the cost-utility outcomes. This happens because of a [redacted] reduction in hospitalisation costs as the lifetime number of hospitalisation events decreases from [redacted] per person in the SoC arm to [redacted] in the TriageHF arm.

The company conducted threshold analysis to find the value of the IRR at which TriageHF was no longer dominant. The breakeven value was [redacted].

5.5 Discussion

The company adopted the same model structure that the EAG adopted. The following assumptions were made regarding outcomes: equal mortality rates for intervention and comparator; alert-related follow-up visits were additional to the SoC healthcare contacts for TriageHF; there was no difference in LoS between the intervention and comparator. Consequently, it was assumed that there would be no benefit for TriageHF associated with these outcomes.

The clinical study that underpinned this evidence submission was found to have a critical risk of confounding and information was missing for several categories (see Section 3.4.4, Table 13). The bias would need to be considerable for the IRR estimate to be greater than 0.91, the point at which TriageHF is no longer dominant, instead of the study estimate of 0.42 (95% CI: 0.23, 0.76, p=0.004, SE = 0.3).

6. Independent economic assessment-Newcastle model

6.1 Overview

A *de novo* decision analytic model was developed to estimate the cost-effectiveness of algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices. The model structure is designed to capture the key costs and outcomes associated with CRM. The conceptualisation, development and parameterisation of the economic model was informed by the economic modelling studies of remote monitoring devices described in Section 4.2. A cohort Markov model was developed with alive and dead states. The model structure captured the key costs and outcomes associated with CRM. Patients in the Alive state experienced a number of hospitalisations per year, made a number of clinic visits (scheduled and unscheduled) and were at risk of dying. Mortality rates, risk of hospitalisation, clinic visits (scheduled and unscheduled) are independently modelled, which may differ by technology. Length of stay (LoS) per hospitalisation may also differ by technology.

Each device is modelled separately. Evidence on the outcome differences for one device are not assumed to apply to another device. Where there is evidence on the difference in outcomes with and without CRM, the cost-effectiveness of CRM is estimated. Where there is no evidence on an outcome difference, either no difference in an outcome is assumed or different scenarios are modelled. These scenarios are more or less conservative with respect to CRM. Where there is evidence on the relative risk of hospitalisation, cost-effectiveness estimates are produced for the relevant scenarios. If CRM is not cost-effective in a conservative scenario, then threshold analysis is conducted on those outcomes to identify the effectiveness required for the technology to be cost-effective at cost-effectiveness thresholds recommended by NICE.[105]

Costs are expressed in UK £ sterling (2021/22) and evaluated from the perspective of the NHS and personal social services (PSS). In line with the NICE reference case[105], both costs and outcomes were discounted at a 3.5% annual discount rate. The costs and outcomes were evaluated over a lifetime horizon. The model was built in Microsoft Excel. Probabilistic analysis was conducted where appropriate, using appropriate probability distributions for the model parameters where these could be fitted, and monte carlo simulation,[106] is used to capture uncertainty in input parameters and overall cost-effectiveness results. Scenario analyses are conducted to explore the robustness of the results to changes in input parameters.

The decision problem, the model structure, and overview of key assumptions along with the data sources of model input parameters are outlined in the sections below.

6.2 Decision problem and population

The decision problem the economic model seeks to address is whether algorithm based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices (CorVue, HeartInsight, HeartLogic and TriageHF) is cost-effective.[107]

6.2.1 Population

The patient population considered in the model are those implanted with the named cardiac implantable electronic devices listed above in Section 5.3, have previous experience of heart failure or at risk of new onset heart failure and are >18 years of age.

6.2.2 Intervention strategies/comparator

The interventions assessed were the algorithm based remote monitoring systems for cardiac implantable electronic devices which are capable of identifying new onset or worsening signs of heart failure. Remote monitoring of data from cardiac implantable remote monitoring devices in people at risk of heart failure, when used alongside standard care, could enable early identification of heart failure risk and ensure early access to treatments. Early treatments could ultimately improve health outcomes and reduce costs of unnecessary health care resource utilisation. Remote monitoring systems for any cardiac implantable electronic device are only compatible with the specific devices, therefore the economic evaluation compared remote monitoring system for each implanted device with no remote monitoring system for that specific device.

The economic evaluation considered the following algorithm based remote monitoring systems as outlined in the final scope by NICE:[108]

i) CorVue and Merlin.net Patient care network

ii) HeartInsight and BIOTRONIK Home Monitoring

iii) HeartLogic and Latitude NXT Patient Management System TriageHF and CareLink remote monitoring (TriageHF Plus)

6.3 Model structure

A decision analytic model, informed by previous economic modelling studies of remote monitoring devices in heart failure, was developed to estimate the costs and health outcomes (QALYs) associated with algorithm based remote monitoring of heart failure risk data in people with cardiac implantable devices compared to those without remote monitoring. The economic evaluation utilised a Markov model with two states: Alive and Dead (Figure 5). The Markov model design with estimates of clinical outcomes was selected over a model with prognostic and clinical outcomes linked to the prognostic outcomes because of the variation in definitions of prognostic outcomes and the anticipated difficulty of finding evidence on clinical outcomes linked to the prognostic outcomes.

QALYs gained was the primary measure of benefit in the economic evaluation. Mortality, hospitalisation, follow-up visits, and length of stay in the hospital were inputs to the model. The Markov model took a lifetime horizon in the base-case. Monthly cycles were used and at each monthly cycle, the hypothetical cohort of patients remained in the state “Alive” or transitioned to the state “Dead” (absorbing state) according to the probability of death assigned for each monthly cycle. In each cycle, the patients who were alive experienced an average number of monthly hospitalisations, follow-up visits, and days in hospital. Each patient then accrued lifetime QALYs and health-care costs according to the model state they were in.

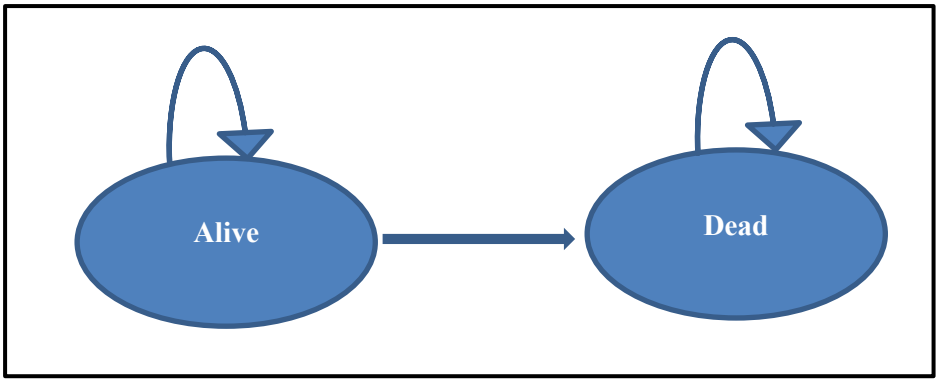


Figure 5: Schematic outline of the Markov model

6.4 Outcome parameters

6.4.1 Mortality

No comparative evidence (intervention vs comparator) for mortality was available for the devices assessed in this study.[109] Therefore, considering the absence of evidence, mortality rates for patients with CIEDs were assumed to be the same with and without RMS.

Findings from an analysis of Implantable cardio-verter defibrillator (ICD) and Cardiac resynchronization therapy (CRT) implantation in England from April 2011 to March 2013 by Bottle *et al* 2021 using the national hospital administrative database showed a five-year survival of 64% and 58% after ICD and CRT implantation, respectively.[110] Another study which assessed the long-term survival after pacemaker implantation in patients with severe and/or symptomatic bradycardia showed a similar (65.5%) five-year survival.[111] We utilised the 64% 5-year survival estimate. This is equivalent to mortality of 36% over 5 years. 5-year mortality used in the base case analysis is summarised in Table 31. This is used to derive a mortality rate and then monthly probabilities of dying in the decision model using an exponential distribution. The survival curve used in the EAG model is compared against that used in the Medtronic model in Figure 6. The survival curve used in the Medtronic model was used in scenario analysis.

Table 31: Mortality rates and assumptions in the economic model

RMS in general	Mortality	Source	Hazard Ratio (HR) compared to the intervention
Base case			
Implantable cardio-verter defibrillator (ICD) implantation	36% at 5 years	Bottle *et al* 2021	1 (Assumed; as there was no evidence on mortality for the intervention)

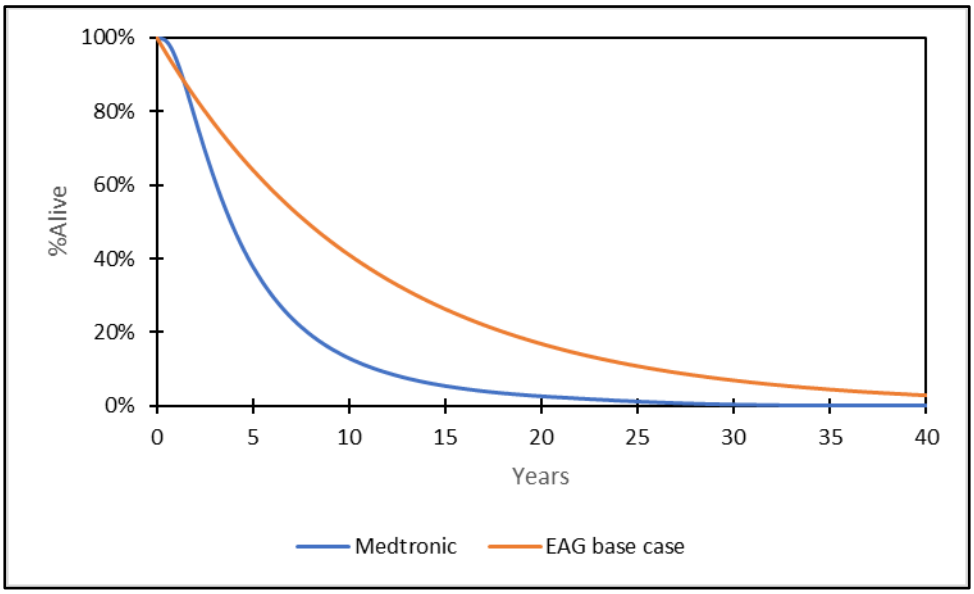


Figure 6: Survival curves used in the EAG model and Medtronic model.

6.4.2 Hospitalisation

For TriageHF, the average number of hospitalisations per person-year ([redacted]) for the comparator was obtained from the company submission.[102] There were [redacted] events over [redacted] person-years. This was obtained from the TriageHF Plus study. The results have not yet been published. This study was assessed at critical risk of bias due to confounding (see Section 3.3.4).

The incidence rate ratio (IRR) was estimated using a Poisson Generalised Linear Mixed Model (GLMM) with log link. The mean IRR was 0.42 (95% CI: 0.23, 0.76, p=0.004, SE = 0.3).[102] The average number of hospitalisations per person-year was therefore calculated to be [redacted] in the model.

For HeartLogic, the average number of hospitalisations per person-year (0.39, SD = 0.08) for the comparator was obtained from Treskes *et al*. included in the systematic review (see Section 3.4.5).[37] This study was assessed at serious risk of bias due to confounding (see Section 3.3.3).

The average number of hospitalisations per person-year for the HeartLogic group was reported to be 0.11, SD = 0.04. The incidence rate ratio derived by the EAG from these numbers is 0.282.

No evidence for the average number of hospitalisations per person-year was reported for CorVue or HeartInsight. For the comparator, the average number of hospitalisations per person-year was assumed to be the average of the rates for TriageHF and HeartLogic ([redacted]). Threshold analysis was required for the IRR for these two CIEDs (see Section 6.7.1 for a description).

The hospitalisation rates and the IRRs used in the models are summarised in Table 32.

Table 32: Rates of hospitalisation

RMS	Average number of hospitalisations per person-year		Source
	Comparator	Intervention	
CorVue and Merlin.net Patient care network	[redacted] (Assumed average of HeartLogic and TriageHF)	No evidence (threshold analysis)	
HeartInsight and BIOTRONIK Home Monitoring	[redacted](Assumed average of HeartLogic and TriageHF)	No evidence (threshold analysis)	
HeartLogic and Latitude NXT Patient Management System	0.39 in a year (used in base case)	0.11 in a year (rate ratio =0.11/0.39 i.e., 0.282) (used in base case)	[37]
	17% in a year	10% in a year	[35]
TriageHF and CareLink remote monitoring (TriageHF Plus)	[redacted]	Incidence rate ratio of 0.42, 95% CI:[redacted] [redacted] is used in the model to indicate [redacted]lower rate of hospitalisations in the intervention group. Average number of hospitalisations calculated was 0.24 per person per year.	TriageHF company submission.[102]

6.4.3 Alerts and follow-up visits

Follow-up visits without algorithm-base remote monitoring

In the NICE scope for this Diagnostic Assessment, "clinical experts emphasised that there is no standard heart failure service model and current practice is highly varied". A combination of the ESC guidelines and the NICE guidelines are likely used.[1, 3] The ESC guidelines recommend follow-up at intervals no longer than 6 months.[1] The NICE guidelines for diagnosis and management of chronic heart failure in adults recommend that reviews are offered every 6 months for people whose condition is stable.[3] In the scope, the clinical experts also highlighted that "in practice most people would be reviewed annually whilst some people with a stable condition may not have a review at all. Early follow up visits are recommended at 1 to 2 weeks following hospital discharge to assess signs of congestion and drug tolerance."[1] Unstable cases have more frequent follow-up frequencies.

No evidence was identified in the systematic review on follow-up visits without CRM. Pan-European data in Heidbuchel *et al*. identified in the focused review (see Section 4.4) reported 2 scheduled follow-up visits per year in the CIED without remote monitoring group.[97] Since this seemed consistent with the guidelines, this was used in the base case for the CIED without remote monitoring in every case.

Heidbuchel *et al*. also reported 0.62 unscheduled visits over 2 years (or 0.31 over 1 year) for the control group.[97]

The Medtronic company model costed other background costs such as GP visits for their economic model. They also assumed that those costs were the same for both the CIED with remote monitoring and the CIED without remote monitoring. It is assumed here that other background costs would be the same for both groups, and have been excluded for simplicity.

Alerts and follow-up visits with algorithm-based remote monitoring

Two NICE clinical experts responded to a question on the follow-up visit schedule associated with the use of a CIED remote monitoring system. One replied that the alerts produced by the remote monitoring system would be supplementary to the existing follow-up schedule, while another replied that it was intended to replace the existing system. To recognise different possible uses of the technology, 3 different scenarios were modelled: 0 scheduled follow-up visits per year, 1 scheduled follow-up visit per year, and 2 scheduled follow-up visits per year. In the 2 scheduled follow-up visits per year scenario, the number of scheduled follow-up visits is the same in both the remote monitoring group and the non-remote monitoring group.

Unscheduled visits were modelled as the number of alerts of people who are high risk. All alerts are reviewed (see Section 6.6.2 for the cost estimate), but it is assumed that only high-risk cases have a follow-up visit. Three scenarios were modelled: the same number of unscheduled visits as for the comparator, 2 times the number of comparator unscheduled visits, and 4 times the number of comparator unscheduled visits.

For TriageHF, 196 high-risk alerts (transmissions) were received over [redacted] patient-years of follow-up.[102] This is an annual alert rate of [redacted]. In the TriageHF company model, [redacted] of patients had an initial consultation, and [redacted] of patients had a second consultation.[102] In the model, this is modelled as 100% of high risk alerts have 1 in-office consultation. There was no evidence for unscheduled visits for the control group. Two scenarios were modelled: 2 times the unscheduled follow-up visits per year in the intervention, and 4 times the unscheduled follow-up visits per year in the intervention.

For HeartLogic, an annual alert rate estimate of 0.71 was obtained from Santobuno et al 2023[72]. No control evidence was provided. In the base case it was assumed, the same as for TriageHF, that [redacted] of alerts and had an initial consultation, and [redacted] of alerts had a second consultation (100% of alerts have 1 in-office consultation). In a scenario analysis, it was assumed that 50% of alerts have 1 in-office consultation, and 25% have a phone call review. Two further scenarios were modelled: 2 times the unscheduled follow-up visits per year for the intervention group, and 4 times the unscheduled follow-up visits per year in the intervention.

The scheduled and unscheduled follow-up visits used in the EAG model are summarised in Table 33.

Table 33: Follow-up visits

RMS	Average follow-up visits per year	
	Comparator	**Intervention**
CorVue and Merlin.net Patient care network	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled (alerts): 0.31, 0.62, 1.24

HeartInsight and BIOTRONIK Home Monitoring	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled (alerts): 0.31, 0.62, 1.24
HeartLogic and Latitude NXT Patient Management System	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled (alerts): 0.71, 1.42, 2.84
TriageHF and CareLink remote monitoring (TriageHF Plus)	Scheduled: 2 Unscheduled: 0.31	Scheduled: 0, 1, 2 Unscheduled (alerts): [redacted]

*Scheduled: 0,1,2: 0 visits, 1 visit, and 2 visits per year were modelled as different scenarios

6.4.4 Length of stay

No evidence was identified for a difference in LoS for any of the devices (with and without CRM), except for HeartLogic. Consequently, in the base case a fixed cost was assumed for every hospitalisation. Clinical studies and economic models of related to, but not, the technologies included in this technology appraisal have included differences in average length of stay for the remote monitoring compared to no remote monitoring. For the purpose of sensitivity analysis, the difference in days of LoS was included in the model.

Evidence for average length of stay (LoS) in the hospital for both the intervention and comparator were taken from the literature (see Section 6.6.2). Where evidence was not available, assumptions were made. The evidence used in the EAG model is summarised in Table 34.

Table 34: Length of stay in hospital

RMS	Length of stay		Source
	Comparator	Intervention	
CorVue and Merlin.net Patient care network	No evidence (fixed cost of a hospitalisation episode used in base case)	No evidence (fixed cost of a hospitalisation episode used in base case)	
HeartInsight and BIOTRONIK Home Monitoring	No evidence (fixed cost of a hospitalisation episode used in base case)	No evidence (fixed cost of a hospitalisation episode used in base case)	
HeartLogic and Latitude NXT Patient Management System	16 days per hospitalisation event (used in base case)	7 days per hospitalisation event (used in base case)	[37]
	8 days (IQR:5-12) per hospitalisation event	5 days (IQR: 2-7) per hospitalisation event	[36]
TriageHF and CareLink remote monitoring (TriageHF Plus)	No evidence (fixed cost of a hospitalisation episode used in base case)	No evidence (fixed cost of a hospitalisation episode used in base case)	

6.4.5 Adverse events

No adverse events were considered in the model because none of the studies in the systematic review reported any adverse events directly linked to the use of the remote monitoring systems for each of the cardiac implantable electronic devices.

6.5 Health-related quality of life

The targeted literature review (Section 4,4) informed the utility estimates for being alive with heart failure or at risk of heart failure and with one of the CIEDs considered in the economic evaluation [(CorVue:[96] comparator (0.85 ± 0.18), intervention (0.87 ± 0.16), and TriageHF:[94] comparator (0.711;0.305), intervention (0.754;0.275)]. In addition to this, the UK population-based utility estimates for heart failure patients reported in a recent systematic literature review ranged from 0.52 (SD 0.26) to 0.696 (SD 0.26).[112] However, these mean utilities reported for heart failure were not time dependent and also would be higher than the mean utilities in the UK general population, something not reflecting the HF population in the UK setting. Therefore, to ensure that the utility estimates for heart failure population do not exceed that of the general population, we utilised the approach taken in a company submission for TriageHF.[102]

HF population utilities in sub-groups of NYHA class (Table 35) were obtained from Griffiths et al.[114] The EAG made the assumption that the mean utility for the undiagnosed sub-group was the same as for the NYHA class 1 sub-group. The UK general population utility 0.84[113,115] was subtracted from the HF population utilities in sub-groups of NYHA class (Table 35) to derive the utility decrement for HF population in each NYHA class (Table 36). The percentage of patients in each NHYA class was obtained from the Medtronic submission[100], and this was used to calculate the weighted average utility decrement for a patient with HF (Table 36). In addition, a separate utility decrement for a hospitalisation event was calculated. Utility decrements for hospitalisation by NHYA class were also obtained from Griffiths et al.[114] These were multiplied by the same patient distribution across NYHA class percentages from the Medtronic submission[100] to derive the weighted average utility decrement for hospitalisation (Table 37). HF utility decrements were applied to HF population alive at each model cycle; however, the hospitalisation decrement was only applied to the proportion hospitalised in each cycle.

Table 35: Heart failure utilities

HF Sub-groups	Mean Utility	Population (%)	Source
Undiagnosed	0.82	8.7%	Mean utility [114] Population (%)[100]
NYHA class I	0.82	20.8%	
NYHA class II	0.74	43.3%	
NYHA class III	0.64	26.6%	
NYHA class IV	0.46	0.5%	

Table 36: Population utility used to derive HF utility decrement

HF Sub-groups	Population utility	Source	Utility decrement derived*
Undiagnosed	0.84	[113,115]	-0.02
NYHA class I			-0.02
NYHA class II			-0.11
NYHA class III			-0.20

NYHA class IV			-0.39
Weighted average HF utility decrement derived using population distribution in Table 35			-0.107

*0.84 subtracted from mean utility in Table 35. Estimates rounded to 2 decimal places.

Table 37: Hospitalisation utility decrement

HF Sub-groups	Mean Utility Decrement (derived)	Source
Undiagnosed	-0.040	[114]
NYHA class I	-0.040	
NYHA class II	-0.070	
NYHA class III	-0.100	
NYHA class IV	-0.290	
Weighted average hospitalisation utility decrement derived using population distribution in Table 35	-0.070*	

*Calculated using the weights reported in Table 35

6.6 Costs

The resource use and costs considered in the model were remote monitoring system costs along with any implementation costs (e.g., Training costs and device maintenance costs), hospitalisation, length of stay in the hospital, and follow-ups for patients with (intervention) and without remote monitoring systems (comparator).

Estimating absolute utility decrements for both HF and hospitalisations could result in lower QALY gains from the intervention. A scenario analysis, where the relative utility decrements (instead of absolute values) was undertaken to assess the impact on QALYs of the approach taken in estimating the utility decrement from HF and hospitalisations. In this case, the utility decrement is described as a percentage of the general population age-related utility.

6.6.1 Remote monitoring system costs

The remote monitoring system costs were variable because of the heterogeneity in devices and any other associated maintenance costs for these devices. The costs of the remote monitoring devices considered the following components:

i. Costs of the remote monitoring device for each patient
ii. Any maintenance/consumable costs of the remote monitoring systems

These costs of remote monitoring systems to the NHS were based on company responses to the NICE request for information. The costs of remote monitoring system for each CIED considered in the model are reported in Table 38.

Table 38: Remote monitoring system costs

Remote monitoring system	Cost (exc. VAT)	Unit	Modelled cost
CorVue and Merlin.net Patient care network	Free of charge with the device; No additional consumables and maintenance costs	One-off	£0
HeartInsight and BIOTRONIK Home Monitoring	£450/patient; no additional charge on maintenance/consumables	One-off	£450/patient
HeartLogic and LATITUDE NXT Heart Failure Management System	[redacted] patient; [redacted] No additional consumable or maintenance costs	One-off	[redacted]
TriageHF and CareLink remote monitoring (TriageHF Plus)	£100/patient/year No additional charges	Yearly	£8.33 per month per patient

6.6.2 Implementation costs

Time for staff training and responding an alert are presented in Table 39. The implementation costs considered in the economic model were the staff training time costs and cost of staff time needed to respond/review remote monitoring system alerts. These implementation costs reported in Table 40 were based on company responses to the NICE request for information on training time and time spent actioning an alert. There was heterogeneity in the implementation cost for each CIED considered in the model. The unit costs for staff time were taken from secondary source.[116]

Table 39: Time for staff training and responding an alert

Remote monitoring system	Staff time	
	Training time	Time to respond to 1 alert
CorVue and Merlin.net Patient care network	30 min	5 mins to read an alert and evaluate the diagnostic trend data
HeartInsight and BIOTRONIK Home Monitoring	1 hour	20 minutes per case, 40 minutes for complex cases. Average 30 minutes used.

HeartLogic and LATITUDE NXT Heart Failure Management System	1 hour (assumed)	5 minutes to review alerts, plus 10-20 min to action an alert. Average 20 min (15 min to action alert plus 5 minutes to review alerts) used.
TriageHF and CareLink remote monitoring (TriageHF Plus)	1 hour (assumed)	30 min per week

Table 40. Costs of staff training and actioning an alert

Remote monitoring system	Number of RMS alerts per patient per year	Cost		Unit cost of staff time (source: PSSRU)[116]
		Staff training time*	Staff time per alert**	
CorVue and Merlin.net Patient care network	0.31 (Assumed equal to unscheduled visits)[97]	£26.50	£0.11	£ 53 per hour [Cost of hospital-based Band 6 Physiologist-used in the base case analyses]
HeartInsight and BIOTRONIK Home Monitoring	0.31 (Assumed equal to unscheduled visits)[97]	£53	£0.69	
HeartLogic and	0.71 [117]	£53	£1.31	£59 per hour [Cost of hospital-based

LATITUDE NXT Heart Failure Management System				specialist nurse- used in the scenario analyses]
TriageHF and CareLink remote monitoring (TriageHF Plus)	[redacted]	£53	[redacted]	

* one-off costs, derived as a product of staff training time for each device in Table 39 and unit cost of £53 per hour of staff time, ** monthly costs, derived as a product of average number of alerts per month, average time spent per alert and unit cost of £53 per hour of staff time

6.6.3 Hospitalisation

To ensure consistency across models of each device, the same unit cost estimate of hospitalisation was used for the comparator in each model. The unit cost estimate of each hospitalisation was £3,758.18. This was based on the weighted average of the costs for the Healthcare Resource Group (HRG) 'Heart Failure or Shock' (EB03A-EB03E) based on the Non-Elective Inpatient- Long Stay data obtained from NHS reference costs.[101] Weighted average of the costs (£666.43) for the HRG 'Heart Failure or Shock' (EB03A-EB03E) based on the Non-Elective Inpatient- Short Stay data obtained from NHS reference costs [101] was used in the scenario analysis.

Where there was no evidence for a difference in LoS of a hospitalisation, the average LoS for a hospitalisation was assumed to be the same for both CRM and no CRM; the unit cost estimate of each hospitalisation was £3,758.18 for both CRM and no CRM. Where there was evidence for a difference in LoS between CRM and no CRM, the cost of a day in hospital was multiplied by the difference in days and this was added or subtracted from £3,758.18 to determine the cost of hospitalisation for the intervention. See Section 6.6.4 for the cost estimate of one day in hospital.

6.6.4 Length of stay

Where there was no evidence for a difference in LoS of a hospitalisation, the average LoS for a hospitalisation was assumed to be the same for both CRM and no CRM. The cost assigned for a hospitalisation was the average cost of hospitalisation (see Section 6.6.3).

Where there was evidence for a difference in LoS, the cost of an extra day in hospital was multiplied by the difference in days and this was subtracted from the comparator cost of hospitalisation. The cost

of an extra day in hospital was £290, listed in the 2022/23 national tariff workbook (Annex A) - updated for national insurance changes.[118]

6.6.5 Follow-up visits

The unit cost estimate of a follow-up visit was £169. This was based on an Outpatient attendance for Cardiology services (both consultant led and non-consultant led) (Service code: 320) from the NHS reference costs.[101] It was assumed that both the scheduled and unscheduled follow-up visits would have same unit costs. For the scenario analyses, where non face-to-face follow-up contacts are modelled, the costs was £97.44 and was based on non-admitted, non-face-to-face attendance follow-up (Non consultant led), for cardiology services (Service code:WF01C) from the NHS reference costs.[101]

6.7 Analysis

6.7.1 Analysis scenarios

The cost-effectiveness of each implantable device with an algorithm based remote monitoring system compared to the same device without the remote monitoring system was evaluated. Four technologies were included in the scope. The analyses undertaken varied by technology according to the availability of comparative evidence on outcomes.

Sub-group analyses were only undertaken if there was relevant comparative outcome estimates, and differences in the estimates were likely to significantly affect the cost-effectiveness results.

The incremental cost-effectiveness ratio (ICER) is calculated as

$$ICER = \frac{C_I - C_C}{Q_I - Q_C},$$

where C_I is the total cost associated with the intervention, C_C is the total cost associated with the comparator, Q_I is the total Quality Adjusted Life Years (QALYs) associated with the intervention, and Q_C is the total QALYs associated with the comparator.

If the ICER < threshold, then the technology is considered cost-effective at that threshold. The cost-effectiveness thresholds recommended in the NICE guidance are used in this report: £20,000/QALY, and £30,000/QALY.

Comparative evidence was sought for hospitalisation rates, follow-up visits, mortality and LoS. Based on the clinical studies included in the systematic review and the studies included in the systematic review of cost-effectiveness studies, hospitalisation was selected as the most important outcome. This was followed by follow-up visits, then mortality, and finally LoS. This hierarchy was set to define the model scenarios and analyses undertaken. For example, if comparative evidence on hospitalisation and follow-up visits were available for a technology, but no evidence on mortality or LoS, then no difference in mortality and LoS could be assumed and a cost-effectiveness analysis conducted.

If there was no evidence on follow-up visits, 9 different scenarios of the numbers of scheduled and scheduled visits for the intervention were defined (see Section 6.6.5). Given that two scheduled follow-up visits were assumed for Standard Care, either 2, 1 or 0 scheduled visits per year were assumed for the intervention. This was done to allow for different scenarios regarding the degree to which the technology displaced current monitoring practice. Given the lack of evidence on unscheduled visits, the unscheduled visits for the intervention were assumed to be either the same as in current practice, twice

as many or four times as many. This meant that threshold analysis could be conducted on the incidence rate ratio of hospitalisation for scenarios defined for the other outcomes of interest. In the base case scenario, the number of yearly scheduled and unscheduled visits were assumed to be the same for RMS and SoC. The other combinations of scheduled and unscheduled visits were secondary scenarios.

Threshold analysis involves increasing or decreasing the value of a parameter until the cost-effectiveness threshold is crossed or a technology changes from being dominant to non-dominant or vice-versa. This is often done when a technology is not cost-effective using the base case value. Suppose, for example, there is no evidence on any of the outcomes, we may assume that there is no difference in mortality or in LoS and we define scenarios for scheduled and unscheduled follow-up visits. We also assume that there is no difference in rate of hospitalisation. The incremental cost-effectiveness ratio (ICER) of the technology is *greater* than £20,000/QALY in a couple of scenarios. In this situation we could conduct threshold analysis on the incidence rate ratio (IRR) of hospitalisation. We reduce the IRR (which means that the rate of hospitalisation of the intervention reduces) until the ICER of the technology becomes *lower* than £20,000/QALY. This value of IRR at which the £20,000/QALY threshold is crossed is the minimum effectiveness required of the intervention for it to be cost-effective at that threshold.

Threshold analysis can also be done where there is an effectiveness estimate and the technology is cost-effective, but due to concerns about the risk of bias or generalisability associated with the effectiveness estimate the size of effectiveness is reduced until the technology is no longer cost-effective.

The device specific analyses conducted at the baseline is summarised in Table 41.

Table 41: Summary of the base case analyses conducted.

RMS	Evidence	Analyses
CorVue and Merlin.net Patient care network	No evidence on any outcome	Base case scenario assumed: no difference in mortality, LoS, SoC Scheduled visits = 2 SoC Unscheduled visits = 0.31 RMS Scheduled visits = 2 RMS Unscheduled visits = 0.31 Secondary scenarios: other combinations of Scheduled visits (0, 1, 2) and Unscheduled (alerts) visits (0.31, 0.62, 1.24) for RMS Threshold analysis conducted on IRR of hospitalisation if technology not cost saving assuming IRR =1. Tertiary scenarios for other parameters (see Section 6.7.3)

HeartInsight and BIOTRONIK Home Monitoring	No evidence on any outcome	Base case scenario assumed: no difference in mortality, LoS, SoC Scheduled visits = 2 SoC Unscheduled visits = 0.31 RMS Scheduled visits = 2 RMS Unscheduled visits = 0.31 Secondary scenarios: other combinations of Scheduled visits (0, 1, 2) and Unscheduled (alerts) visits (0.31, 0.62, 1.24) for RMS Threshold analysis conducted on IRR of hospitalisation if technology not cost saving assuming IRR =1. Tertiary scenarios for other parameters (see Section 6.7.3)
HeartLogic and LATITUDE NXT Heart Failure Management System	Evidence on rate of hospitalisation and unscheduled visits.	Base case scenarios assumed: no difference in mortality, LoS, SoC Scheduled visits = 2 SoC Unscheduled visits = 0.31 RMS Scheduled visits = 2 RMS Unscheduled visits = 0.71. Secondary scenarios: RMS scheduled visits (0,1) and Unscheduled (alerts) visits (1.42, 2.84) for RMS Cost-effectiveness analysis conducted for base case and secondary scenarios using comparative evidence for IRR of hospitalisation and IRR of unscheduled visits. Tertiary scenarios for other parameters (see Section 6.7.3)
TriageHF and CareLink remote monitoring (TriageHF Plus)	Evidence on rate of hospitalisation and unscheduled visits.	Base case scenarios assumed: no difference in mortality, LoS, SoC Scheduled visits = 2 SoC Unscheduled visits = 0.31 RMS Scheduled visits = 2 RMS Unscheduled visits = [redacted] Secondary scenarios: RMS scheduled visits (0,1) and Unscheduled (alerts) visits ([redacted]) for RMS

		Cost-effectiveness analysis conducted for base case and secondary scenarios using comparative evidence for IRR of hospitalisation and IRR of unscheduled visits. Tertiary scenarios for other parameters (see Section 6.7.3)

Deterministic analyses were conducted for the scenarios which included the most conservative assumptions or estimates for the RMS technology. If the RMS technology was cost-effective in this scenario, then it would be even more cost-effective in other scenarios, and deterministic analyses were not conducted for those scenarios in that situation.

Probabilistic sensitivity analysis (PSA) involves simultaneously sampling from parameter distributions that have been specified in the model to reflect uncertainty in the parameter estimate. For the PSAs conducted here, 1000 iterations were run, resulting in 1000 estimates of incremental cost, incremental effectiveness, and cost-effectiveness. PSA was run when there was evidence of effectiveness. PSA was not run when a threshold analysis was conducted.

Incremental costs, incremental QALYs, incremental cost-effectiveness ratio (ICER) along with other intermediate outcomes (e.g., Mortality, LOS, Hospitalisation and Follow-up) were estimated and reported in tables. The 1000 estimates of incremental cost and incremental effectiveness for each PSA were presented as a cost-effectiveness scatter plot. The probability that a technology was cost-effective was calculated from the PSAs across a range of cost-effectiveness thresholds, and the results presented as a cost-effectiveness acceptability curve (CEAC). In addition, scenario analyses were conducted to explore the significance of different parameter values on the cost-effectiveness results.

The base-case parameters and their associated assumptions along with their sources are presented in Table 42.

Table 42: Base case parameters and assumptions

Parameter	Values	Source/Assumptions	Probabilistic model
Age	60	Assumed	NA
Proportion of male	72.2%	[102] assumed same across devices	NA
Discount rate -costs	3.5%	In line with NICE guidance	NA
Discount rate-benefits	3.5%	Same as above	NA
Utility			

HF utility decrement	-0.107	[102] assumed same across devices	NA
Hospitalisation utility decrement	-0.070	Same as above	NA
Costs			
Per Patient cost of the RMS-CorVue	£0	One-off; company provided information	Yes
Per Patient cost of the RMS-HeartInsight	£450	One-off, company provided information	Yes
Per Patient Cost of the RMS-HeartLogic	[redacted]	One-off, company provided information	Yes
Per Patient Cost of the RMS-TriageHF	£8.33	Per month, company provided information	Yes
Per Patient cost of RMS maintenance/consumables – All devices	£0	No additional costs of maintenance/consumables-company provided information	NA
Training cost of cardiac physiologist nurse- CorVue	£26.50	One-off, estimated as a product of time spent in training (company provided information) and per min cost of specialist nurse	Yes
Training cost of cardiac physiologist nurse-HeartInsight	£53	One-off, estimated as a product of time spent in training (company provided information) and per min cost of specialist nurse	Yes
Training cost of cardiac physiologist nurse-HeartLogic	£53	One off, estimated as a product of time spent in training (company provided information) and per min cost of specialist nurse	Yes
Training cost of cardiac physiologist nurse-TriageHF	£53	One off, estimated as a product of time spent in training (company provided information) and per min cost of specialist nurse	Yes

Per patient cost of alert monitoring time spent-CorVue	£0.11	Per month, estimated as a product of cost of time spent actioning an alert (company provided information) and alert per month. The alerts per month were assumed to be equal to the unscheduled visits.	No
Per patient cost of alert monitoring time spent-HeartInsight	£0.69	Per month, estimated as a product of cost of time spent actioning an alert (company provided information) and alert per month. The alerts per month were assumed to be equal to the unscheduled visits.	No
Per patient cost of alert monitoring time spent-HeartLogic	£1.31	Per month, estimated as a product of cost of time spent actioning an alert (company provided information) and alert per month per patient (derived from 0.71 alerts per patient per year provided by company; assumed same across devices)	No
Per patient cost of alert monitoring time spent-TriageHF	[redacted]	Per month, estimated as a product of cost of time spent actioning an alert (company submission document) and alert per month per patient (derived from [redacted] alerts per patient per year provided by company; assumed same across devices)	No
Cost per hospitalisation-All devices	£3758.18	Weighted average of the costs for the Healthcare Resource Group (HRG) 'Heart Failure or Shock' (EB03A-EB03E) based on the Non-Elective Inpatient- Long Stay[101]	Yes
Cost per follow-up visit-All devices	£169	NHS Reference costs-costs of Outpatient attendance for Cardiology	Yes

		services (both consultant led and non-consultant led) (Service code: 320)[101]	
Cost per specialist nurse/cardiac physiologist per hour- All devices	£53	Cost of hospital-based Band 6 Physiologist: £53 per hour.[116]	Yes
Cost per day in hospital- All Devices	£290	Cost per day in the hospital[101, 118]	
Hospitalisation			
Hospitalisation rate per month (Comparator)- CorVue	0.0404	Derived as an average of comparator hospitalisation in HeartLogic and TriageHF	No
Hospitalisation rate per month (Comparator)- HeartInsight	0.0404	Derived as an average of comparator hospitalisation in HeartLogic and TriageHF	No
Hospitalisation rate per month (Comparator)- HeartLogic	0.033	[37]	No
Hospitalisation rate per month (Comparator)- TriageHF	[redacted]	[redacted]	No
Hospitalisation Rate Ratio (RR)- CorVue	1	No difference between intervention and comparator assumed	Yes
Hospitalisation Rate Ratio (RR)- HeartInsight	1	No difference between intervention and comparator assumed	Yes
Hospitalisation Rate Ratio (RR)- HeartLogic	0.282	[37]	Yes
Hospitalisation Rate Ratio (RR)- TriageHF	0.42	[102]	Yes
Follow-up- Scheduled			
Scheduled follow-up visits per month (Comparator and Intervention)- All devices	0.17	Derived from assumed 2 visits per year;[97] equal visits considered in the intervention and comparator	Yes
Follow-up-Unscheduled			

Unscheduled follow-up visits (Comparator)-All devices	0.026	[97] monthly estimates derived from 0.31 follow-up visits per year (0.31/12)	Yes
Unscheduled follow-up visits (Intervention)-CorVue and HeartInsight	0.026	Assumed no difference between the comparator and intervention	Yes
Unscheduled follow-up visits (Intervention)-HeartLogic	0.0592	[72] Assumed equal to 0.71 alerts per year (0.0592 per month)	Yes
Unscheduled follow-up visits (Intervention)-TriageHF	[redacted]	[102] monthly estimates derived from [redacted] follow-up visits per year	Yes
LoS in hospital			
LoS days per hospitalisation (Comparator)-All devices	16	[37] No evidence available for devices other than HeartLogic; assumed same as HeartLogic for all devices	Yes
LoS days per hospitalisation (Intervention)-CorVue, HeartInsight and TriageHF	16	No Evidence available; assumed no difference to the comparator	Yes
LoS days per hospitalisation (Intervention)-HeartLogic	7	[37]	Yes
Mortality			
All Devices- Hazard Ratio (HR)	1	[110] Comparator mortality percentage at 5 years =0.36 was used to derive monthly probability as 0.00741	Yes

6.7.2 Sub-group analysis

The model also considered a number of sub-groups of patients. The evidence for these sub-groups were not available at the time the model was developed, however, the model provides a flexibility to make changes (or add new) to the model parameters as and when they become available for each sub-group in the future. The sub-groups outlined in the protocol and considered in the model are:[107]

i. People who have a CIED and do not have a diagnosis of heart failure but are at risk of new onset acute heart failure

a. Have a CRT-P device
b. Have a CRT-D device
c. Have an ICD device
d. Have a pacemaker device

ii. People who have a CIED and have a diagnosis of chronic heart failure
a. Have a CRT-P device
b. Have a CRT-D device
c. Have an ICD device
d. Have a pacemaker device
e. Have a diagnosis of heart failure New York Heart Association (NYHA) class I and II
f. Have a diagnosis of heart failure NYHA class III and IV
g. Have a prior heart failure hospitalisation or urgent care visit within the last 12-months

6.7.3 Tertiary scenario analyses

In addition to the base case scenario and secondary scenarios defined in Section 6.7.1, a few tertiary scenario analyses were undertaken to test the robustness of the base case results to key uncertainties in the model. The EAG acknowledges the difference in survival estimates used in the EAG model and the Medtronic company submission model (Figure 6: Survival curves used in the EAG model and Medtronic modelTherefore, the EAG conducted a scenario analysis of the results using the survival analysis from the Medtronic model into the EAG model. Considering the potential biases in the evidence for hospitalisation rates for HeartLogic and TriageHF, the EAG also conducted a scenario analysis of increasing the IRR of hospitalisation halfway between 1 and the IRR used in the base case. Details of base case and variations made in the scenario analyses are presented in Table 43.

Table 43: Details of the parameters considered for scenario analyses.

Scenario	Parameter	Base-case	RMS	Scenario Analysis
1.	LOS in hospital-intervention- HeartLogic	7	All	16 (assumed same as comparator)
2.	Cost per hospitalisation - All Devices	£3758.18	All	£666.43
3.	Cost of Nurse/Physiologist time per hour- All Devices	£53	All	£58

4.	Survival rates	Survival based on fixed monthly mortality rate of 0.00741	All	Survival based on Medtronic company submission model
5.	IRR Hospitalisation	0.282	HeartLogic	0.641 (Assumed half-way between the base case value and 1)
6.	IRR Hospitalisation	0.42	TriageHF	0.71 (Assumed half-way between the base case value and 1)
7.	Alert monitoring time - CorVue	5 min	CorVue	10 min
8.	Alert monitoring time - HeartInsight	30 min	HeartInsight	60 min
9.	Alert monitoring time - HeartLogic	20 min	HeartLogic	40 min
10.	Alert monitoring time - TriageHF	30 min	TriageHF	60 min
11.	Excluding uncertainty in Mortality in the PSA	10% uncertainty was modelled in the PSA	HeartLogic and TriageHF	No uncertainty in the the mortality estimates was modelled in the PSA.
12.	Caclulating utility decrement as relative values instead of absolute differences	Absolute utility decrements were used for heart failure and hospitalisation in the model	All	Relative utility decrements were used for heart failure and hospitalisation in the model.

13.	Assuming only 50% of the alerts in the intervention group require in-office follow-up visits and 25% of the alerts only require are non-face-to-face contacts	Assumed that all alerts would lead to face-to-face follow-up visit	CorVue, HeartInsigh, HeartLogic	Assumed only 50% of the alerts would lead to a face-to-face visit, and 25% of the alerts would have non-face-to-face contact with the health worker. The cost of non-face-to-face contact was assumed £97.44 (the cost of Non consultant led cardiology service (WF01C), Non Admitted face-to-face attendance follow-up)[101]

6.7.4 Model validation

The model was developed in Microsoft Excel by NB and validated by two other health economists (SR, and SH). Internal validation involved varying model input parameters and assessing whether the model results were sensitive and logical.

6.8 Model results

The economic evaluation consisted of base-case analysis (both deterministic and probabilistic) and few scenario analyses. The economic evaluation was conducted for each of the four RMS strategies, i.e. CorVue, HeartInsight, HeartLogic and TriageHF.

6.8.1 Base case scenario and secondary scenario results

Deterministic base-case findings are presented in Table 44 and the costs breakdown are presented in Table 45.

There was no hospitalisation outcome evidence for CorVue and HeartInsight. For the base-case scenario assuming no difference in hospitalisations, RMS for CorVue and HeartInsight were cost increasing because of the cost of the RMS technology and reviewing alerts. In the scenarios where unscheduled follow-up visits in the intervention group were doubled or quadrupled, RMS for CorVue and HeartInsight remained cost increasing. However, when scheduled follow-up visits in the intervention were assumed as 1 or 0 per year (i.e. lower than 2 visits assumed for the comparator), the RMS intervention was cost saving for CorVue and HeartInsight.

For the base case scenarios for CorVue and HeartInsight, threshold analysis showed that an IRR of hospitalisation below 0.99 and 0.96 respectively would make RMS of these devices dominant (i.e., less costly, more effective). For the scenario where the unscheduled follow-up visits were quadrupled for CorVue and HeartInsight, threshold analysis showed that an IRR of hospitalisation below 0.91 and 0.87 respectively would make RMS of these device devices dominant.

There was hospitalisation outcome evidence for HeartLogic and TriageHF. In the base case analyses both HeartLogic and TriageHF were dominant (i.e., less costly, more effective). HeartLogic and TriageHF both remain dominant if the scheduled follow-up visits are 1 or 0 per year for RMS and will be more cost-saving as long as the reduction in the number of scheduled visits is greater than additional unscheduled visits. In the scenarios where unscheduled follow-up visits in the intervention group per year were doubled or quadrupled the RMS for HeartLogic and TriageHF remained dominant.

The probabilistic sensitivity analysis estimates for HeartLogic and TriageHF (Table 46) were similar to the deterministic estimates, where RMS for HeartLogic and TriageHF were both dominant (i.e. less costly and more effective compared to standard care). The cost-effectiveness acceptability curve (CEAC) (Figure 8) shows that the probability cost-effectiveness for HeartLogic RMS at willingness to pay (WTP) value of £20,000 was 88% whereas at £30,000 the probability cost-effectiveness was 77%. The probability of cost-effectiveness for TriageHF RMS at WTP values of £20,000 and £30,000 were respectively 85% and 76% (Figure 10). These results observed in CEACs are also reflected in the cost-effectiveness scatterplots (Figure 7 and Figure 9).

Table 44: Deterministic cost-effectiveness results of the base case analysis

Items	CorVue		HeartInsight		HeartLogic		TriageHF	
	I	*C*	*I*	*C*	*I*	*C*	*I*	*C*
Total								
Costs (£)	17855	17848	18415	17848	[redacted]	17748	11665	20712
QALYs	5.83	5.83	5.83	5.83	5.84	5.83	5.84	5.82
Cumulative hospitalisations per person	5.28	5.28	5.28	5.28	1.20	4.25	2.65	6.31
Cumulative days in hospital	84.48	84.48	84.48	84.48	8.38	67.96	42.42	101
Cumulative Follow-up_1*	22.22	22.22	22.22	22.22	22.22	22.22	22.22	22.22
Cumulative Follow-up_2**	3.40	3.40	3.40	3.40	7.74	3.40	4.70	3.40
Proportion died after 40 years	0.97	0.97	0.97	0.97	0.97	0.97	0.97	0.97
Incremental (intervention versus comparator)								
Costs (£)	37		568		[redacted]		-9048	
QALYs	0		0		0.01		0.01	
Cumulative hospitalisations per person	0		0		-3.05		-3.66	
Cumulative days in hospital	0		0		-59.58		-59	
*Cumulative Follow-up_1**	0		0		0		0	
*Cumulative Follow-up_2***	0		0		4.34		1.31	
Proportion died after 40 years	0		0		0		0	
ICER	Cost increasing		Cost Increasing		Dominant		Dominant	

I: Intervention; C: Comparator;

* Follow-up_1: Scheduled visits; **Follow-up_2: Unscheduled visits

Table 45: Cost breakdown in the base case cost-effectiveness analysis

Costs (£)	CorVue		HeartInsight		HeartLogic		TriageHF	
	I	*C*	*I*	*C*	*I*	*C*	*I*	*C*
Total								
RMS	26.40	0	501.14	0	[redacted]	0	857	0
Monitoring alert	11.08	0	66.49	0	126.15	0	92	0
Cumulative days in hospital	14651	14651	14651	14651	1795	14552	7357	17516
Cumulative Follow-up_1*	2772	2772	2772	2772	2772	2772	2772	2772
Cumulative Follow-up_2**	4244	424	424	424	965	424	587	424
Incremental costs (£) (intervention versus comparator)								
RMS	26.40		501.14		[redacted]		857	
Monitoring alert	11.08		66.49		126.15		92	
Cumulative days in hospital	0		0		-12757		-10159	
*Cumulative Follow-up_1**	0		0		0		0	
*Cumulative Follow-up_2***	0		0		541		163	
Incremental total costs (£)	37		568		[redacted]		-9048	

I: Intervention; C: Comparator;
* Follow-up_1: Scheduled visits; **Follow-up_2: Unscheduled visits

Table 46: Probabilistic cost-effectiveness results of the base-case analysis

Items	HeartLogic		TriageHF	
	I	*C*	*I*	*C*
Total				
Costs (£)	[redacted]	17955	11674	20857
QALYs	5.85	5.83	5.84	5.82
Cumulative hospitalisations per person	1.20	4.28	2.66	6.37
Cumulative days in hospital	8.35	68.25	42.18	101.31
Cumulative Follow-up_1*	22.33	22.21	22.29	22.17
Cumulative Follow-up_2**	7.76	3.40	4.72	3.41
Proportion died after 40 years	0.97	0.97	0.97	0.97
Incremental (intervention versus comparator)				
Costs (£)	[redacted]		-9183	
QALYs	0.02		0.02	
Cumulative hospitalisations per person	-3.08		-3.71	
Cumulative days in hospital	-60		-59	
*Cumulative Follow-up_1**	0		0	
*Cumulative Follow-up_2***	4.39		1.31	
Proportion died after 40 years	0		0	
ICER	Dominant		Dominant	

I: Intervention; C: Comparator;
* Follow-up_1: Scheduled visits; **Follow-up_2: Unscheduled visits;

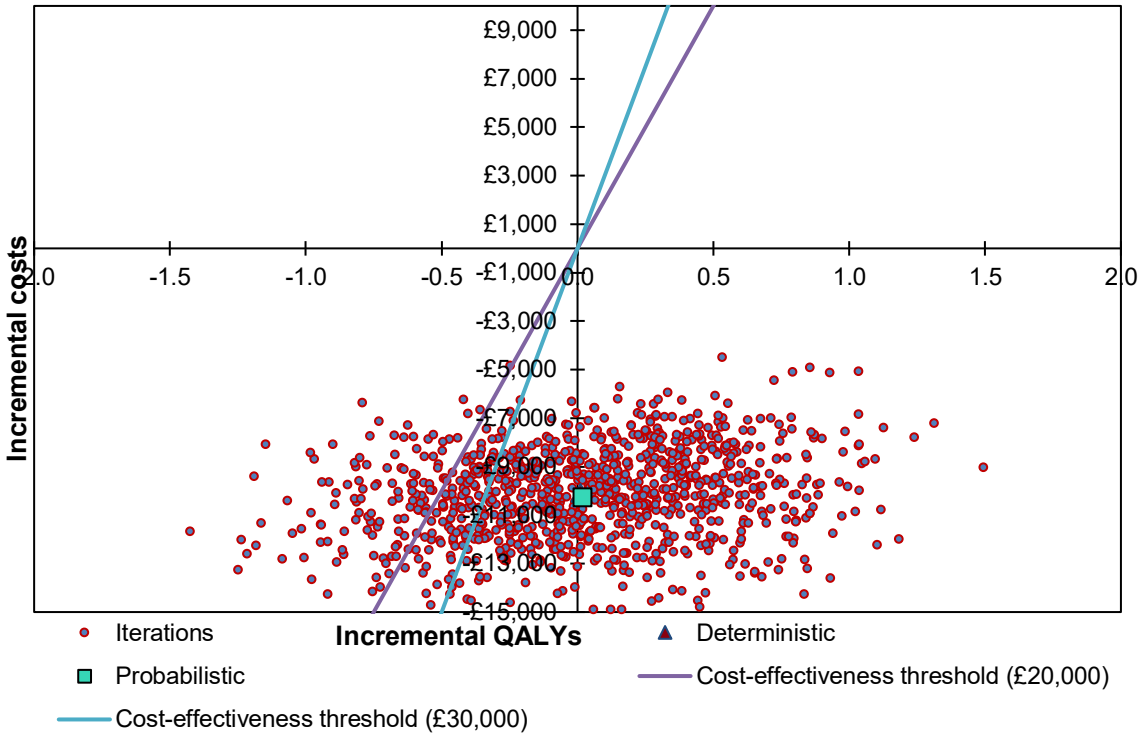


Figure 7: Cost-effectiveness plot-HeartLogic

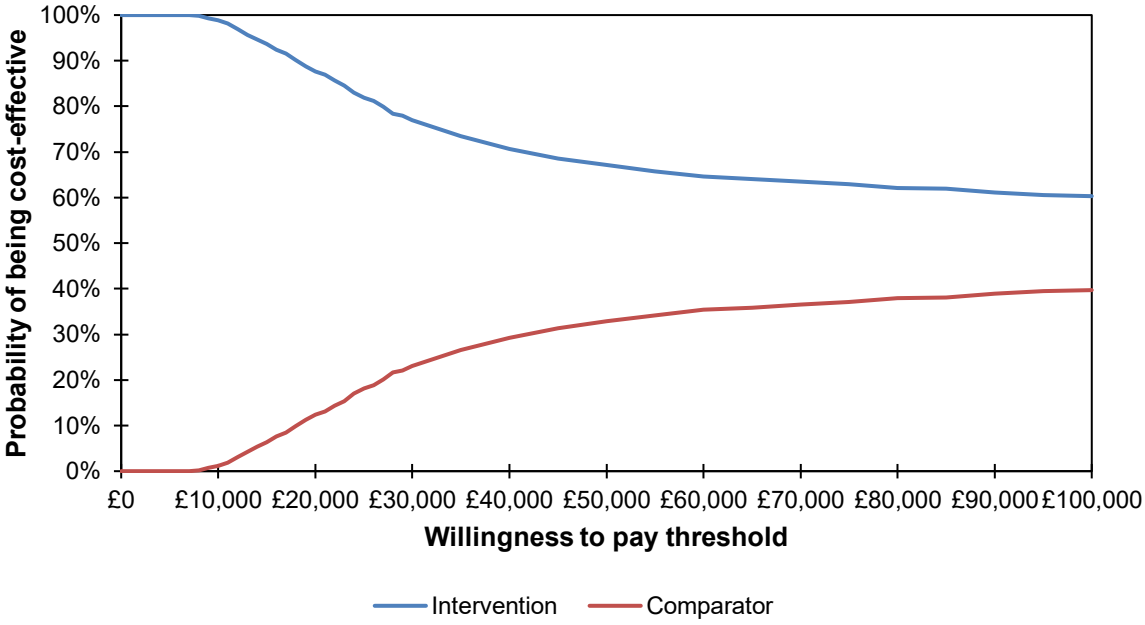


Figure 8: Cost-effectiveness acceptability curve-HeartLogic

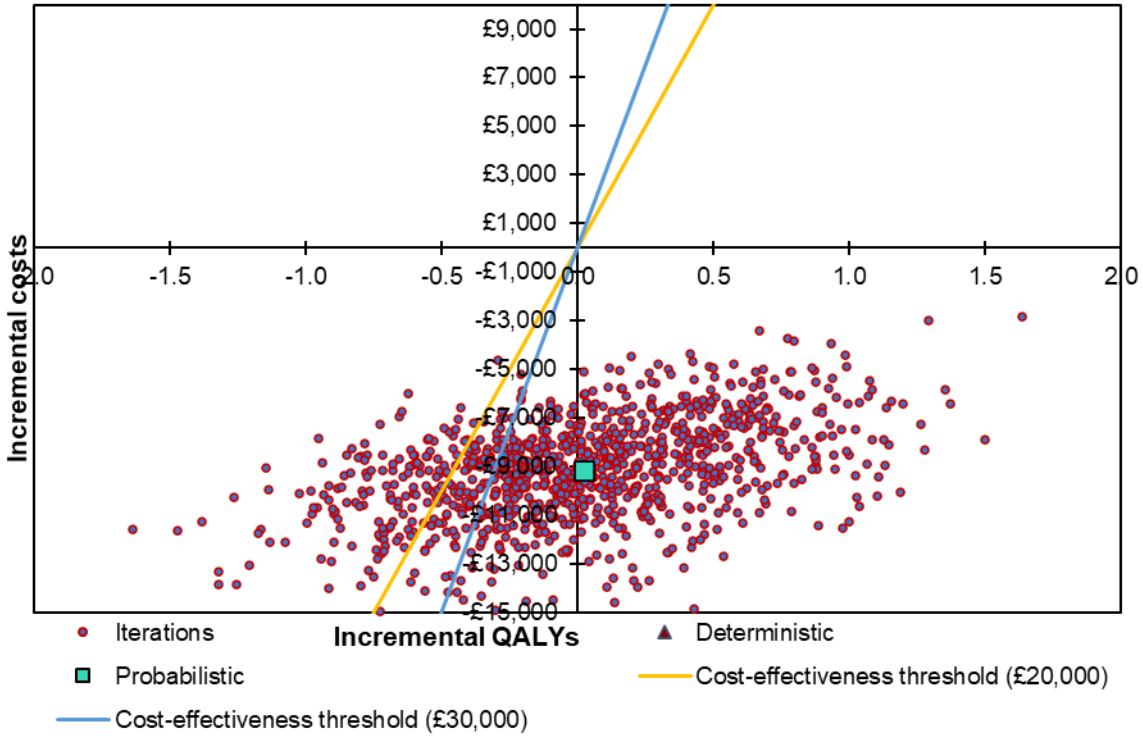


Figure 9: Cost-effectiveness plot-TriageHF

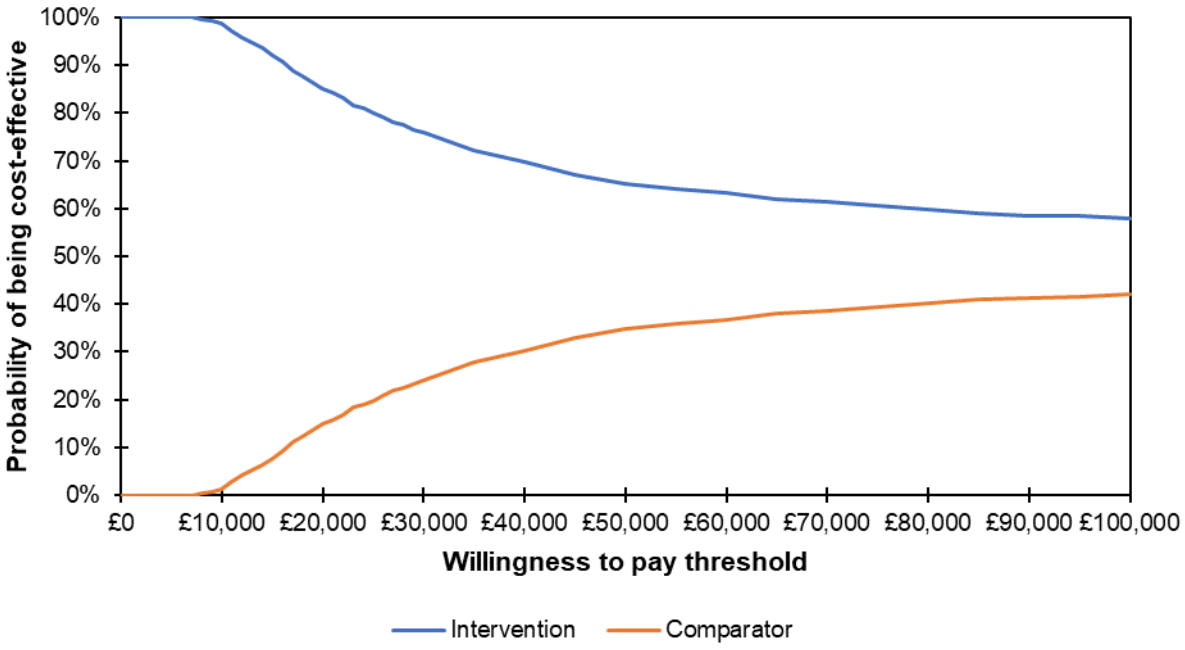


Figure 10: Cost-effectiveness acceptability curve-TriageHF

6.8.2 One-way sensitivity analyses

The EAG could not conduct a one-way sensitivity analysis for base case results because it was not feasible to derive an ICER when the results were either cost saving, cost increasing or dominant.

6.8.3 Sub-group analyses:

There was only evidence on hospitalisation IRR for ICT, CRT-P and CRT-D for TriageHF, which was in the company submission. The IRR of hospitalisation for TriageHF varied from [redacted] to [redacted]. These differences will have no effect on the cost-effectiveness results for TriageHF.

There was no evidence on hospitalisation IRR for patients with a CIED without a diagnosis of chronic heart failure. [redacted] of the population of TriageHF Plus had a prior diagnosis of HF.

6.8.4 Tertiary scenario analyses

The EAG conducted a variety of tertiary scenario analyses.

Scenario A included no difference in LoS between intervention and comparator for HeartLogic (LoS for the intervention was assumed same as comparator in the base case). Additional scenario analyses for HeartLogic and TriageHF involved increasing the IRR of hospitalisation (scenario F), and using survival data from Medtronic company submitted model for all RMS devices (scenario E), doubling the base case alert monitoring time spent by nurse (scenario G), lower costs of hospitalisation (scenario B) and higher costs of staff time (scenario C).

Scenario analyses results are presented in Table 47. The results are similar to the ones observed in the base case analyses for all devices. When no difference in the LoS between the intervention and comparator was assumed for HeartLogic, then the RMS was dominant. The use of Medtronic submitted survival data did not change the cost-effectiveness of the devices- the results were generally similar to the base case. In addition, not modelling uncertainty in the mortality parameter in the PSA did not change the results for HeartLogic and TriageHF; however, the probability of cost-effectiveness was 100% at WTP values of £20k and £30k for both the devices. Increasing the IRR of hospitalisation halfway between the base case value and 1, did not change the dominance of RMS observed in the base case. Changing the approach of estimating the utility decrements did not change the study conclusions; however, the QALYs gains from the interventions were higher for HeartLogic and TriageHF when relative utility decrements were used in the model. Assuming only 50% of the alerts in the intervention group would require in-office follow-up visits and 25% of the alerts would only require non-face-to-face contacts, did change Corvue from being "cost increasing" in the basecase to "cost saving", whilst there was no change in the study conclusions for HeartInsight and HeartLogic.

Table 47: Scenario analyses cost-effectiveness results

Label	Scenario	Device-Cost-effectiveness			
		CorVue	HeartInsight	HeartLogic	TriageHF

A	LoS in the intervention equal to that of comparator in the base case	-	-	Dominant	-
B	Lower hospitalisation costs (£666.43)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.98 will have cost-effective RMS)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.808 will have cost-effective RMS)	Dominant	Dominant
C	Higher costs of staff time (£58 per hour)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.99 will have cost-effective RMS)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.96 will have cost-effective RMS)	Dominant	Dominant
D	LoS in the intervention equal to the comparator	-	-	Dominant	-
E	Medtronic Survival rates	Cost increasing (threshold analysis shows that IRR hospitalisation <0.99 will have cost-effective RMS)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.93 will have cost-effective RMS)	Dominant	Dominant
F	Increased IRR hospitalisation halfway between the base case value and 1	-	-	Dominant	Dominant
G	Doubled Alert monitoring time	Cost increasing (threshold analysis shows that IRR hospitalisation	Cost increasing (threshold analysis shows that IRR hospitalisation	Dominant	Dominant

		<0.99 will have cost-effective RMS)	<0.95 will have cost-effective RMS)		
H	Excluding uncertainty in Mortality in the PSA	-	-	Dominant (the probability of cost-effectiveness was 100% at WTP value of £20k and £30k; however, in the basecase the probability was 88% at £20k, and 77% at £30K WTP value)	Dominant (the probability of cost-effectiveness was 100% at WTP value of £20k and £30k; however in the basecase the probability was 85% at £20k, and 76% at £30k WTP value)
I	Caclulating utility decrement as relative values instead of absolute differences	Cost increasing	Cost increasing	Dominant (QALYs gained 0.02 which is higher than 0.01 observed in the basecase analysis)	Dominant QALYs gained 0.02 which is higher than 0.01 observed in the basecase analysis)
J	Assuming only 50% of the alerts in the intervention group require follow-up visits and 25% of the alerts only require non face-to-face contacts	Cost saving	Cost increasing	Dominant	-

6.9 Summary of the economic analysis

The EAG utilised a *de novo* two state Markov model (with Alive and Dead states) to estimate the cost-effectiveness of algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices. CorVue, HeartInsight, HeartLogic and TriageHF were modelled separately and outcome differences for one device were not assumed to apply to another device. The model structure captured the key costs and outcomes associated with RMS given the available evidence. There may be other benefits associated with the use of algorithms that are not included in the model, but there was limited quality evidence for the benefits included in the model Mortality rates, risk of

hospitalisation, clinic visits (scheduled and unscheduled) and Length of stay (LoS) per hospitalisation were independently modelled. QALYs gained was the primary outcome for economic evaluation.

There was no comparative evidence on hospitalisation, mortality and follow-up visits or LoS for CorVue or HeartInsight. CorVue and HeartInsight were cost increasing when a conservative assumption of no difference in hospitalisation, mortality, follow-up visits (scheduled/unscheduled) was made. Threshold analysis for these two devices showed that even a very small reduction in the IRR of hospitalisation would make them cost-effective.

HeartLogic had some evidence on LoS, and hospitalisation rates and the cost-effectiveness estimates showed it to be dominant (i.e. less costly and more effective than the comparator). TriageHF also had some evidence on hospitalisation rates, and was also dominant. The studies supplying the hospitalisation and LoS evidence were either at serious or critical risk of bias due to confounding.

Due to the high cost of hospitalisation, the RMS devices for these technologies only need to reduce the hospitalisation rates by small percentage for them to become cost-effective. The lack of hospitalisation outcome evidence for CorVue or HeartInsight means it is not possible to produce cost-effectiveness estimates for these technologies. The cost-effectiveness estimates of HeartLogic and TriageHF are based on evidence that is at risk of bias.

7. Discussion

7.1 Statement of principal findings

7.1.1. Clinical effectiveness

Overall, the EAG considers the evidence were limited for all the algorithms. Most evidence for algorithms were derived from single cohorts (prospective and retrospective studies) that lacked a comparator group.

HeartLogic was associated with adequate to high sensitivity and specificity for the prediction of HF events (i.e., hospitalisations). False positive rates for HeartLogic were also low. Only three comparative studies were identified for HeartLogic,[35-37] with the majority of the evidence derived from single cohort studies that compare IN and OUT of alert status (i.e. high vs low risk categories based on the algorithm). Two of the comparative studies also utilised single cohorts, assessing pre and post algorithm activation. There is evidence for an association of greater risk between being IN alert compared to OUT of alert of HF events (e.g. hospitalisations). Compared to no algorithm, there was a mix of statistically significant and non-significant results, however, there was a numerical trend towards reductions in HF events (e.g. hospitalisations) when using HeartLogic.

There was substantial heterogeneity in TriageHF prognostic accuracy measures, estimates of sensitivity and specificity varied widely between studies. False positive rates were only reported in one study and were relatively low. Only a single study for TriageHF was comparative, providing real-world data on hospitalisations in a UK setting. However, this study was rated at critical risk of bias using ROBINS-I.[28] The remaining evidence was single cohort studies comparing risk status (high, medium and low). There is evidence for an increased risk of HF events when in high risk status compared to low risk status (e.g. hospitalisations). The lack of comparative data means we cannot draw conclusions on TriageHF use compared to standard care (i.e. no algorithm). It is worth noting that a number of studies evaluating TriageHF were undertaken in a UK setting (n = 5).

Evidence for the accuracy of CorVue showed low sensitivity, while specificity was not generally reported. False positive rates were high in most studies. There was one comparative study, a retrospective medical chart review of hospitalisations.[34] The remaining evidence was all single cohort studies, which generally compared alert to no alert. There was a lack of association data regarding the risk of an HF event. There was some evidence to suggest low hospitalisation rates when in high risk alert. However, some comparative evidence suggests a potential to reduce hospitalisations in those using CorVue compared to no device with standard home care.[34]

For HeartInsight only one published study was identified, which was the development and validation study and showed adequate sensitivity and specificity for HF events. False positive rates were moderate in this single study. No comparative evidence was identified for the use of HeartInsight. There was a lack of evidence for the HeartInsight algorithm, as we only identified one study. This study did find a significant association with increasing risk score and HF related hospitalisation.[45] No comparative evidence was available. The EAG do note that HeartInsight is the only monitoring system that provides daily transmissions, whereas the other technologies occur less frequently. This could have implications for missing data.

7.1.2. Cost-effectiveness

There was no hospitalisation, mortality, follow-up visits or LoS outcome evidence for the RMS for CorVue or HeartInsight. Consequently, no estimate of the cost-effectiveness of CorVue or HeartInsight could be produced. Making the assumptions of no difference in hospitalisation, mortality, scheduled/unscheduled follow-up visits, and LoS, both CorVue or HeartInsight would be cost-increasing due to the cost of the technology and the cost of reviewing alerts produced by the RMS. Given the much larger cost of a hospitalisation compared to other costs, the technologies only need to reduce the rate of hospitalisation by a very small amount (1-4%) for them to become cost-effective.

There was some evidence on hospitalisation, follow-up visits or LoS outcomes for the RMS for HeartLogic and TriageHF. This evidence was at risk of bias due to confounding. Making the assumption of no difference in mortality and scheduled follow-up visits, HeartLogic and TriageHF were dominant (i.e. they were cost-saving as well as reducing hospitalisations). Threshold analysis showed that HeartLogic and TriageHF only needed to reduce hospitalisations by a few percent in order for them to be dominant.

For HeartLogic and TriageHF, the outcome evidence was mostly based on patients with a CIED who had had a diagnosis of heart failure. Consequently, the cost-effectiveness estimates are applicable to that subgroup. There was clinical evidence for different CIEDs in evidence submission by Medtronic. The variation in effectiveness estimates was very small across the CIEDs and the same cost-effectiveness results for all CIEDs apply to each individual CIED.

7.2. Strengths and limitations

7.2.1 Strengths

This is the first complete systematic review of HeartLogic, TriageHF, CorVue and HeartInsight. The review utilised extensive database and grey literature searches to identify all published evidence on the included technologies. Additionally, all included studies and previous reviews (narrative and systematic) were citation chained to identify any further literature. We also assessed their risk of bias and undertook a thorough narrative synthesis of the results. As such, this is the first review of these technologies.

The economic evaluation was based on outcome evidence identified from a systematic review of the literature and a company evidence submission. The economic decision model structure was the same as analyses in the literature and the Medtronic evidence submission. Hospitalisation, mortality and follow-up visits were directly included in the model.

7.2.2 Limitations

During the review process we completed single data extraction and quality appraisal assessments, rather than in duplicate. However, this is mitigated by the checking for accuracy of both assessments by a second reviewer.

Cost-effectiveness estimates could only be produced for HeartLogic and TriageHF as there was outcome evidence for those technologies only. No cost-effectiveness estimate could be produced for patients who had not had a diagnosis of heart failure. There was only evidence for hospitalisations and follow-up visits, and these were at high risk of bias due to confounding. The outcomes included in the model were limited by the evidence available, and there was limited evidence for the outcomes included.

Limitations of the evidence stem from the type of evidence available. The majority of the evidence was derived from single cohort studies that did not distinguish between having and not having the algorithm. While this does provide data from a real-world standpoint (e.g. correct categorisation of patients and risk associated with an HF event such as hospitalisation), there is a lack of evidence for how the algorithms perform compared to no algorithm (i.e., standard remote monitoring). Furthermore, many studies did not include adjusted analyses, which could inflate the reported effectiveness of the algorithm.

Most clinical studies identified in the systematic review were at serious or critical risk of bias. Many of the studies were at serious or critical risk of bias due to a lack of controlling for confounding factors in the statistical analysis. Specifically, age, sex, NYHA classification, smoking status and other co-morbidities were largely uncontrolled for in the majority of studies. In addition, the inherent risk of bias due to the retrospective and single-arm design of many studies are likely to lead to an overestimation of the findings.

For study endpoints there was a degree of variation between studies as to what constituted a HF event. Additionally, in some cases composite outcomes were utilised (e.g., HF hospitalisation, clinic visit or death). Future studies should look to adequately power their analyses to assess the endpoints individually, rather than using composite outcomes. There is also an issue with a lack of statistical comparisons within studies, with simple numerical changes generally reported. In addition, concerns at quality appraisal were linked to statistical analysis shortcomings. For example, the lack of consideration for confounding factors, which should be considered in future research.

The evidence for HeartLogic appears to have higher accuracy than the other algorithms, but it is still hampered by a lack of comparative data, with only two studies presenting a control condition. Of the three studies which included some comparative data for clinical outcomes, two are considered at serious risk of bias,[36, 37] and one at critical risk of bias.[35] The majority of remaining cohorts were at critical or serious risk of bias mostly due to unaddressed issues with confounding. Four cohorts were at moderate or low risk of bias.[72, 76, 80, 81] All studies reporting prognostic outcomes were at overall high risk of bias but there were no concerns with their applicability to this review.

The evidence for TriageHF suggest it has varying accuracy and is, like HeartLogic, hampered by an overall lack of comparative data between people with and without the algorithm. The one study reporting comparative data is at critical risk of bias; using the clinical outcome results in a meta-analysis is not recommended. Many studies were abstracts, lacking in information and are subsequently of unclear risk of bias.[51-53]

The evidence for CorVue suggests the accuracy of the algorithm is generally low and produces high false positive alerts, which would be a concern from a clinical point of view. Increased false positives could increase the burden for clinical staff. All studies reporting prognostic accuracy outcomes are at high risk of bias, although there are no concerns regarding their applicability to this review. All studies reporting clinical outcomes were at serious or critical risk of bias. Shapiro *et al*.[34] includes limited comparative evidence and is at critical risk of bias, current recommendations are to avoid using data from studies at critical risk of bias in meta-analysis and to interpret studies at serious risk of bias with caution.

The evidence for HeartInsight suggests the accuracy of the algorithm is moderate but is yet to be further validated in external studies. The lack of evidence for this algorithm, both single cohort and comparative data, means that the EAG cannot provide any recommendations on its potential use in clinical practice.

However, the one published study did provide similar prognostic accuracy measures to the other algorithms, as evidence by the crossover of confidence intervals. D'Onofrio, *et al.*,[45] is at high risk of bias as assessed using PROBAST, there are no concerns regarding the applicability of the study to this review question. In addition, the study is at serious risk of bias when applying ROBINS-I because of issues with confounding, the reported clinical outcome results should be interpreted with caution.

The EAG also note that two of the algorithms (HeartLogic and HeartInsight) are currently not available on all CIEDs. They are available on ICD and CRT-D devices, while TriageHF and CorVue are also available on CRT-P devices. Currently, only CRT-P devices are recommended for those with NYHA class IV HF.[5]

7.3 Evidence gaps

The EAG have identified several gaps across the varying outcomes.

For intermediate outcomes there was a lack of evidence for several outcomes. There was no evidence for the number of monitoring reviews. Software failure rate was not commonly reported; this is potentially a key variable for remote monitoring services and future research should report this detail. Length of hospital stay also had minimal evidence; however, there was a greater evidence base for number of hospitalisations.

For clinical outcomes there was no evidence for changes in NYHA classification of symptoms or rate and category of atrial fibrillation. There was also minimal evidence for the rate of HFs, with only HeartLogic and CorVue reporting data for this outcome. The number of adverse events was only reported in two studies (one HeartInsight and one HeartLogic). Finally, the effect of having the algorithms on HF and all-cause mortality was seldom reported. To address these shortcomings future studies should aim to address these outcomes in greater depth. Whilst there is a lack of evidence for mortality, the EAG is aware of an ongoing trial using the HeartLogic algorithm with the primary outcome to assess mortality between those with and without the algorithm.

There was very little evidence in the way of patient reported outcomes. Only one single prospective cohort study included some health-related quality of life outcomes (6MWT and MLWHF). No further evidence was identified. Additionally, there was no evidence of patient experience with the algorithms. Future research should endeavor to include patient involvement in studies. This is especially important where false positive alerts are produced, as such alerts could cause great anxiety to the individual.

For all algorithms it is also imperative that further comparative evidence in provided to show the efficacy of the algorithms compared to no algorithm (e.g. remote monitoring without algorithm). Whilst an RCT would be the gold standard for such comparative data, further retrospective and prospective studies which are non-randomised would also be beneficial to assess each algorithm compared to no algorithm.

7.4 Equality, diversity, and inclusion

The EAG obtained the views of the Diagnostic Assessment Specialist Committee members during the review process. In addition, the research question and subsequent eligibility criteria did not exclude any patient characteristics based on demographic or socio-economic factors, all individuals with heart failure and CIED implanted were eligible for inclusion.

8. Conclusions

Implications for service provision

The EAG considers there was promising evidence for HeartLogic and TriageHF. However, there is substantial uncertainty regarding the impact of these algorithms on intermediate and clinical outcomes. Further evidence generation using comparative study designs will potentially reduce this uncertainty. HeartLogic was consistently associated with the highest and most consistent accuracy measures, with data also suggesting that when IN alert state the patient is at greater risk of a HF event (e.g. hospitalisation or death). However, the majority of the studies assessing predictive accuracy for HeartLogic utilised a composite outcome, which broadened their study endpoint and may have increased the accuracy of the algorithm. Being in a high-risk status when patients used TriageHF also appeared to be linked to such events, although there was less evidence for some outcomes (e.g. mortality). Additionally, the majority of predictive accuracy evidence from TriageHF utilised a single (i.e. not a composite) outcome. Therefore, evidence suggests that using these two algorithms could potentially identify those at greater risk of an impending HF event, which would allow for effective and timely clinical response. However, since no study has directly compared any of the algorithms included in the scope, any conclusions are subject to uncertainty.

The EAG only identified one study of interest for HeartInsight. Therefore, we consider it too early to draw conclusions on the potential usefulness of this algorithm for clinical practice. However, the reported accuracy measures suggest it could provide similar accuracy to HeartLogic and TriageHF; although the sensitivity was <70%. However, we did not perform any meta-analytical techniques and therefore, these quantifications are based on numerical trends only and should be interpreted with caution.

The EAG consider CorVue evidence to be more heterogenous and due to this, we cannot draw firm conclusions on the accuracy and efficacy of the algorithm in clinical practice, based on the literature available. Like the other algorithms assessed, there is a lack of comparative data. However, there is also literature reporting high false positive rates and also a low sensitivity (i.e.~20%). However, sensitivity in some studies was also reported to be similar to the other three algorithms (i.e. >60%).

When assessing the quality of the studies from the evidence base, across all algorithms, there were several studies that were reported as at high risk of bias. This makes the reliability of the evidence uncertain and should be considered when assessing the clinical usefulness of all the technologies.

All remote monitoring algorithms only needed to reduce hospitalisations by a small amount for them to be cost-effective given the evidence on incremental healthcare visits use compared to no remote monitoring algorithm. Better quality and adequately powered evidence on both hospitalisations and healthcare contacts (visits, calls), which also records time spent reviewing remote monitoring data, would help inform the cost-effectiveness of the remote monitoring algorithms.

Suggested research priorities

The primary research priority should be to conduct further studies into the clinical impact and usefulness of the remote monitoring algorithms. There should be a particular focus on comparative evidence, as all devices were lacking in this area. HeartInsight should focus on expanding their evidence base as there is currently too little evidence to make a judgement on its clinical effectiveness. Ideally, RCT evidence comparing the devices to standard clinical management without the use of remote monitoring

or remote monitoring without the algorithm should be conducted. Cluster RCTs (clustered by centre or clinic) and quasi-randomised trials would also be valuable evidence. Further non-randomised evidence would be valuable to further support the implementation of the algorithms into practice, although great care in the design needs to be taken so they are not at high risk of bias.

Currently there is a lack of evidence for the following outcomes and should be key considerations for future research:

- Intermediate outcomes, including the number of monitoring reviews required, length of hospital stay (ideally between those with and without the algorithm), and time between an alert and HF event.
- Clinical outcomes, including adverse events, morbidity, rate and category of atrial fibrillation, changes in NYHA classification of symptoms, and HF mortality.
- Patient reported outcomes, including quality of life and patient experience.

More comparative evidence (e.g. comparing those with and without the algorithm) should be conducted for the majority of the outcomes (with the exception being prognostic accuracy studies).

All of these trials should examine whether clinical benefits vary according to key patient subgroups, such as symptom severity, NYHA classification or without a diagnosis of chronic heart failure. Studies should consider how the inclusion of these algorithms effects current remote monitoring practices. The implementation of algorithms may vary in practice and study designs should reflect the likely (or recommended) monitoring schedule in practice alongside the use of remote monitoring. The monitoring schedule may affect clinical outcomes and it will affect the cost-effectiveness of remote monitoring algorithms due to the associated healthcare cost.

The EAG considers collecting further prognostic accuracy evidence as a lower priority for HeartLogic and TriageHF, but would still be useful in providing further information. CorVue and HeartInsight do require further prognostic accuracy evidence. CorVue due to the observed heterogeneity in the measures. HeartInsight due to only identifying a single study. Future studies should also adequately power their studies as to not include composite outcomes.

9. Appendix

9.1 Clinical effectiveness searches

Medline

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to June 19, 2023

Via: https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi

Date range searched: Inception to 19th June 2023

Date of search: 20th June 2023

Records retrieved: 385

1.	(Triage?HF* or "Triage HF" or CareLink Network* or MyCareLink* or "my care link" or "00763000351656").ti,ab,kw,kf.
2.	(Latitude* NXT or Mylatitute* or "my latitude" or HeartLogic* or "heart logic" or "00802526562105" or "00802526573408" or "00802526584107" or "00802526590306" or "00802526592102" or "00802526613876").ti,ab,kf,kw.
3.	(biotronik home monitor* or CardioMessenger* or "cardio messenger" or HeartInsight* or "heart insight" or "04035479139360" or "04035479159115" or "04035479177768").ti,ab,kw,kf.
4.	(CorVue* or mymerlinimpact or "my merlin impact" or "merlin@home" or "merlin @ home" or "merlin at home" or "merlin.net").ti,ab,kw,kf.
5.	or/1-4
6.	Optivol.ti,ab,kw,kf.
7.	viva.ti,ab,kw,kf.
8.	acticor.ti,ab,kw,kf.
9.	rivacor.ti,ab,kw,kf.
10.	ilivia.ti,ab,kw,kf.
11.	intica.ti,ab,kw,kf.
12.	inlexa.ti,ab,kw,kf.
13.	resonate.ti,ab,kw,kf.
14.	vigilant.ti,ab,kw,kf.
15.	momentum.ti,ab,kw,kf.
16.	perciva.ti,ab,kw,kf.
17.	gallant.ti,ab,kw,kf.
18.	quadra.ti,ab,kw,kf.
19.	ellipse.ti,ab,kw,kf.
20.	assura.ti,ab,kw,kf.

21.	assurity.ti,ab,kw,kf.
22.	(biotronik or medtronic or "boston scientific" or abbott).ab,in,go,ci.
23.	or/6-22
24.	(algorithm* adj2 (monitor* or triag*)).ti,ab,kw,kf.
25.	(remot* adj2 (monitor* or triag*)).ti,ab,kw,kf.
26.	or/24-25
27.	exp arrhythmias, cardiac/ or heart defects, congenital/ or exp heart failure/ or heart valve diseases/ or heart disease risk factors/
28.	(heart adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
29.	(cardiac adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
30.	(atrial adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
31.	(ventricular adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
32.	Defibrillators, Implantable/
33.	or/27-32
34.	23 and 26 and 33
35.	5 or 34

Embase

Embase 1974 to 2023 June 14

Via: https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi

Date range searched: Inception to 19th June 2023

Date of search: 20th June 2023

Records retrieved: 1146

1.	(Triage?HF* or "Triage HF" or CareLink Network* or MyCareLink* or "my care link" or "00763000351656").ti,ab,kw.
2.	(Latitude* NXT or Mylatitute* or "my latitude" or HeartLogic* or "heart logic" or "00802526562105" or "00802526573408" or "00802526584107" or "00802526590306" or "00802526592102" or "00802526613876").ti,ab,kw.
3.	(biotronik home monitor* or CardioMessenger* or "cardio messenger" or HeartInsight* or "heart insight" or "04035479139360" or "04035479159115" or "04035479177768").ti,ab,kw.
4.	(CorVue* or mymerlinimpact or "my merlin impact" or "merlin@home" or "merlin @ home" or "merlin at home" or "merlin.net").ti,ab,kw.
5.	or/1-4
6.	Optivol.ti,ab,kw.
7.	viva.ti,ab,kw.
8.	acticor.ti,ab,kw.

9.	rivacor.ti,ab,kw.
10.	ilivia.ti,ab,kw.
11.	intica.ti,ab,kw.
12.	inlexa.ti,ab,kw.
13.	resonate.ti,ab,kw.
14.	vigilant.ti,ab,kw.
15.	momentum.ti,ab,kw.
16.	perciva.ti,ab,kw.
17.	gallant.ti,ab,kw.
18.	quadra.ti,ab,kw.
19.	ellipse.ti,ab,kw.
20.	assura.ti,ab,kw.
21.	assurity.ti,ab,kw.
22.	(biotronik or medtronic or "boston scientific" or abbott).ab,mf,my,mv,dm,dv,in,tn,go,so,dc,de,ct.
23.	or/6-22
24.	(algorithm* adj2 (monitor* or triag*)).ti,ab,kw.
25.	(remot* adj2 (monitor* or triag*)).ti,ab,kw.
26.	or/24-25
27.	exp heart arrhythmia/ or congenital heart malformation/ or exp heart failure/ or valvular heart diseases/ or heart disease risk factor/
28.	(heart adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
29.	(cardiac adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
30.	(atrial adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
31.	(ventricular adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
32.	implantable cardioverter defibrillator/
33.	or/27-32
34.	23 and 26 and 33
35.	5 or 34

CINAHL

Via: https://search.ebscohost.com/Login.aspx

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 129

S40	S5 OR S39
S39	S24 AND S27 AND S38
S38	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S37	(MH "Defibrillators, Implantable")
S36	TI (ventricular N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR AB (ventricular N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR SU (ventricular N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))
S35	TI (atrial N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR AB (atrial N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR SU (atrial N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))
S34	TI (cardiac N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR AB (cardiac N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR SU (cardiac N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))
S33	TI (heart N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR AB (heart N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*)) OR SU (heart N2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))
S32	(MH "Heart Diseases/RF")
S31	(MH "Heart Valve Diseases")
S30	(MH "Heart Failure+")
S29	(MH "Heart Defects, Congenital")
S28	(MH "Arrhythmia+")
S27	S25 OR S26

S26	TI (remot* N2 (monitor* OR triag*)) OR AB (remot* N2 (monitor* OR triag*)) OR SU (remot* N2 (monitor* OR triag*))
S25	TI (algorithm* N2 (monitor* OR triag*)) OR AB (algorithm* N2 (monitor* OR triag*)) OR SU (algorithm* N2 (monitor* OR triag*))
S24	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S23	TI (biotronik OR medtronic OR "boston scientific" OR abbott) OR AB (biotronik OR medtronic OR "boston scientific" OR abbott) OR SU (biotronik OR medtronic OR "boston scientific" OR abbott)
S22	TI assurity OR AB assurity OR SU assurity
S21	TI assura OR AB assura OR SU assura
S20	TI ellipse OR AB ellipse OR SU ellipse
S19	TI quadra OR AB quadra OR SU quadra
S18	TI gallant OR AB gallant OR SU gallant
S17	TI perciva OR AB perciva OR SU perciva
S16	TI momentum OR AB momentum OR SU momentum
S15	TI vigilant OR AB vigilant OR SU vigilant
S14	TI resonate OR AB resonate OR SU resonate
S13	TI inlexa OR AB inlexa OR SU inlexa
S12	TI intica OR AB intica OR SU intica
S11	TI intica OR AB intica OR SU intica

S10	TI ilivia OR AB ilivia OR SU ilivia
S9	TI rivacor OR AU rivacor OR SU rivacor
S8	TI acticor OR AB acticor OR SU acticor
S7	TI viva OR AB viva OR SU viva
S6	TI Optivol OR AB Optivol OR SU Optivol
S5	S1 OR S2 OR S3 OR S4
S4	TI (CORVue* OR mymerlinimpact OR "my merlin impact" OR "merlin@home" OR "merlin @ home" OR "merlin at home" OR "merlin.net") OR AB (CORVue* OR mymerlinimpact OR "my merlin impact" OR "merlin@home" OR "merlin @ home" OR "merlin at home" OR "merlin.net") OR SU (CORVue* OR mymerlinimpact OR "my merlin impact" OR "merlin@home" OR "merlin @ home" OR "merlin at home" OR "merlin.net")
S3	TI (biotronik home monitOR* OR CardioMessenger* OR "cardio messenger" OR HeartInsight* OR "heart insight" OR "04035479139360" OR "04035479159115" OR "04035479177768") OR AB (biotronik home monitOR* OR CardioMessenger* OR "cardio messenger" OR HeartInsight* OR "heart insight" OR "04035479139360" OR "04035479159115" OR "04035479177768") OR SU (biotronik home monitOR* OR CardioMessenger* OR "cardio messenger" OR HeartInsight* OR "heart insight" OR "04035479139360" OR "04035479159115" OR "04035479177768")
S2	TI (Latitude* NXT OR Mylatitute* OR "my latitude" OR HeartLogic* OR "heart logic" OR "00802526562105" OR "00802526573408" OR "00802526584107" OR "00802526590306" OR "00802526592102" OR "00802526613876") OR AB (Latitude* NXT OR Mylatitute* OR "my latitude" OR HeartLogic* OR "heart logic" OR "00802526562105" OR "00802526573408" OR "00802526584107" OR "00802526590306" OR "00802526592102" OR "00802526613876") OR SU (Latitude* NXT OR Mylatitute* OR "my latitude" OR HeartLogic* OR "heart logic" OR "00802526562105" OR "00802526573408" OR "00802526584107" OR "00802526590306" OR "00802526592102" OR "00802526613876")
S1	TI (Triage#HF* OR "Triage HF" OR CareLink NetwORk* OR MyCareLink* OR "my care link" OR "00763000351656") OR AB (Triage#HF* OR "Triage HF" OR CareLink NetwORk* OR MyCareLink* OR "my care link" OR "00763000351656") OR SU (Triage#HF* OR "Triage HF" OR CareLink NetwORk* OR MyCareLink* OR "my care link" OR "00763000351656")

Cochrane Library

Cochrane (CENTRAL, CDSR)

Via: https://www.cochranelibrary.com/advanced-search

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 100

#1 (Triage?HF* or "Triage HF" or CareLink Network* or MyCareLink* or "my care link" or "00763000351656"):ti,ab,kw

#2 (Latitude* NXT or Mylatitute* or "my latitude" or HeartLogic* or "heart logic" or "00802526562105" or "00802526573408" or "00802526584107" or "00802526590306" or "00802526592102" or "00802526613876"):ti,ab,kw

#3 (biotronik home monitor* or CardioMessenger* or "cardio messenger" or HeartInsight* or "heart insight" or "04035479139360" or "04035479159115" or "04035479177768"):ti,ab,kw

#4 (CorVue* or mymerlinimpact or "my merlin impact" or "merlin@home" or "merlin @ home" or "merlin at home" or "merlin.net"):ti,ab,kw

#5 23-#4

#6 (Optivol):ti,ab,kw

#7 (viva):ti,ab,kw

#8 (acticor):ti,ab,kw

#9 (rivacor):ti,ab,kw

#10 (ilivia):ti,ab,kw

#11 (intica):ti,ab,kw

#12 (inlexa):ti,ab,kw

#13 (resonate):ti,ab,kw

#14 (vigilant):ti,ab,kw

#15 (momentum):ti,ab,kw

#16 (perciva):ti,ab,kw

#17 (gallant):ti,ab,kw

#18 (quadra):ti,ab,kw

#19 (ellipse):ti,ab,kw

#20 (assura):ti,ab,kw

#21 (assurity):ti,ab,kw

#22 (biotronik or medtronic or "boston scientific" or abbott):ti,ab,kw

#23 {OR #6-#22}

#24 (algorithm* NEAR/2 (monitor* or triag*)):ti,ab,kw

#25 (remot* NEAR/2 (monitor* or triag*)):ti,ab,kw

#26 48-#25

#27 MeSH descriptor: [Arrhythmias, Cardiac] explode all trees

#28 MeSH descriptor: [Heart Defects, Congenital] this term only

#29 MeSH descriptor: [Heart Failure] explode all trees

#30 MeSH descriptor: [Heart Valve Diseases] this term only

#31 MeSH descriptor: [Heart Disease Risk Factors] this term only

#32 (heart NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#33 (cardiac NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#34 (atrial NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#35 (ventricular NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#36 MeSH descriptor: [Defibrillators, Implantable] this term only

#37 44-#36

#38 #23 AND #26 AND #37

#39 #5 OR #38

Centre for Reviews and Dissemination (Prospero, DARE)

Via: https://www.crd.york.ac.uk/PROSPERO/ & https://www.crd.york.ac.uk/CRDWeb/

Date range searched: Inception to June 2023 (Prospero)/ 2015(DARE – date of discontinuation)

Date of search: 20th June 2023

Records retrieved: 2

1 (TriageHF* OR "Triage HF" OR CareLink NetwORk* OR MyCareLink* OR "my care link" OR "00763000351656")

2 (Latitude* NXT OR Mylatitute* OR "my latitude" OR HeartLogic* OR "heart logic" OR "00802526562105" OR "00802526573408" OR "00802526584107" OR "00802526590306" OR "00802526592102" OR "00802526613876")

3 (biotronik home monitOR* OR CardioMessenger* OR "cardio messenger" OR HeartInsight* OR "heart insight" OR "04035479139360" OR "04035479159115" OR "04035479177768")

4 (CORVue* OR mymerlinimpact OR "my merlin impact" OR "merlin@home" OR "merlin @ home" OR "merlin at home" OR "merlin.net")

5 #1 OR #2 OR #3 OR #4

6 (Optivol)

7 (viva)

8 (acticor)

9 (ravicor)

10 (ilivia)

11 (intica)

12 (inlexa)

13 (resonate)

14 (vigilant)

15 (momentum)

16 (perciva)

17 (gallant)

18 (quadra)

19 (ellipse)

20 (assura)

21 (assurity)

22 (biotronik OR medtronic OR "boston scientific" OR abbott)

23 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

24 (algorithm* NEAR2 (monitor* OR triag*))

25 (remot* NEAR2 (monitor* OR triag*))

26 #24 OR #25

27 MeSH DESCRIPTOR Arrhythmias, Cardiac EXPLODE ALL TREES

28 MeSH DESCRIPTOR Heart Defects, Congenital

29 MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES

30 MeSH DESCRIPTOR Heart Valve Diseases

31 MeSH DESCRIPTOR Heart Disease Risk Factors

32 (heart NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

33 (cardiac NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

34 (atrial NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

35 (ventricular NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

36 MeSH DESCRIPTOR Defibrillators, Implantable

37 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36

38 #23 AND #26 AND #37

39 #5 OR #3

INAHTA

Via: https://database.inahta.org/

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 5

((((ventricular) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ((atrial) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ((cardiac) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ((heart) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ("Heart Disease Risk Factors"[mh]) OR ("Heart Valve Diseases"[mh]) OR ("Heart Failure"[mhe]) OR ("Heart Defects, Congenital"[mh]) OR ("Arrhythmias, Cardiac"[mhe])) AND (((remot*) AND ((monitor*) OR (triag*))) OR ((algorithm*) AND ((monitor*) OR (triag*)))) AND (((biotronik) OR (medtronic) OR ("boston scientific") OR (abbott)) OR ((optivol) OR (viva) OR (acticor) OR (rivacor) OR (ilivia) OR (intica) OR (inlexa) OR (resonate) OR (vigilant) OR (momentum) OR (perciva) OR (gallant) OR (quadra) OR (ellipse) OR (assura) OR (assurity)))) OR (((CORVue*) OR (mymerlinimpact) OR ("my merlin impact") OR ("merlin@home") OR ("merlin @ home") OR ("merlin at home") OR ("merlin.net")) OR (((biotronik home monitor*) OR (CardioMessenger*) OR ("cardio messenger") OR (HeartInsight*) OR ("heart insight") OR ("04035479139360") OR ("04035479159115") OR ("04035479177768"))) OR (((Latitude* NXT) OR (Mylatitute*) OR ("my latitude") OR (HeartLogic*) OR ("heart logic") OR ("00802526562105") OR ("00802526573408") OR ("00802526584107") OR ("00802526590306") OR ("00802526592102") OR

("00802526613876"))) OR ((TriageHF*) OR ("Triage HF") OR (Triage-HF*) OR ((CareLink Network*)) OR (MyCareLink*) OR ("my care link") OR ("00763000351656")))

NIHR Journals Library

Via: https://www.journalslibrary.nihr.ac.uk/#/

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 4

"remote monitoring"

"heart monitoring"

"cardiac monitoring"

Cardiac AND remote AND monitoring

Cardiac AND monitoring

Heart AND monitoring

INPLASY

Via: https://inplasy.com/

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 1

"remote monitoring"

"heart monitoring"

"cardiac monitoring"

Clinicaltrials.gov

Via: https://clinicaltrials.gov/

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 224

Condition: cardiac events + *other terms:* remote monitoring

Condition: cardiac disease + *other terms:* remote monitoring

Condition: heart failure + *other terms:* remote monitoring

TriageHF

Latitude NXT

HeartLogic

HeartInsight

CardioMessenger

CorVue

EUDRACT

Via: https://www.clinicaltrialsregister.eu/ctr-search/search/

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 1

Cardiac AND "remote monitoring"

Heart AND "remote monitoring"

TriageHF

Latitude NXT

HeartLogic

HeartInsight

CardioMessenger

CorVue

ICTRP

Via: https://trialsearch.who.int/Default.aspx

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 103

Cardiac AND “remote monitoring”

Heart AND “remote monitoring”

TriageHF

Latitude NXT

HeartLogic

HeartInsight

CardioMessenger

CorVue

ScanMedicine

Via: https://scanmedicine.com/

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 260

Cardiac AND “remote monitoring”

Heart AND “remote monitoring”

TriageHF

Latitude NXT

HeartLogic

HeartInsight

CardioMessenger

CorVue

MedRxiv

Via: https://www.medrxiv.org/

Date range searched: Inception to June 2023

Date of search: 20th June 2023

Records retrieved: 333

Cardiac AND remote AND monitoring

TriageHF

Latitude AND NXT

HeartLogic

HeartInsight

CardioMessenger

CorVue

9.2 Economic evaluation searches

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to June 14, 2023

Via: https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi

Date range searched: Inception to 14th June 2023

Date of search: 15th June 2023

Records retrieved: 25

1.	(Triage?HF* or "Triage HF" or CareLink Network* or MyCareLink* or "my care link" or "00763000351656").ti,ab,kw,kf.
2.	(Latitude* NXT or Mylatitute* or "my latitude" or HeartLogic* or "heart logic" or "00802526562105" or "00802526573408" or "00802526584107" or "00802526590306" or "00802526592102" or "00802526613876").ti,ab,kf,kw.
3.	(biotronik home monitor* or CardioMessenger* or "cardio messenger" or HeartInsight* or "heart insight" or "04035479139360" or "04035479159115" or "04035479177768").ti,ab,kw,kf.
4.	(CorVue* or mymerlinimpact or "my merlin impact" or "merlin@home" or "merlin @ home" or "merlin at home" or "merlin.net").ti,ab,kw,kf.
5.	or/1-4
6.	Optivol.ti,ab,kw,kf.
7.	viva.ti,ab,kw,kf.
8.	acticor.ti,ab,kw,kf.
9.	rivacor.ti,ab,kw,kf.
10.	ilivia.ti,ab,kw,kf.
11.	intica.ti,ab,kw,kf.
12.	inlexa.ti,ab,kw,kf.
13.	resonate.ti,ab,kw,kf.
14.	vigilant.ti,ab,kw,kf.
15.	momentum.ti,ab,kw,kf.
16.	perciva.ti,ab,kw,kf.
17.	gallant.ti,ab,kw,kf.
18.	quadra.ti,ab,kw,kf.
19.	ellipse.ti,ab,kw,kf.
20.	assura.ti,ab,kw,kf.
21.	assurity.ti,ab,kw,kf.
22.	(biotronik or medtronic or "boston scientific" or abbott).ab,in,go,ci.
23.	or/6-22

24. (algorithm* adj2 (monitor* or triag*)).ti,ab,kw,kf.
25. (remot* adj2 (monitor* or triag*)).ti,ab,kw,kf.
26. or/24-25
27. exp arrhythmias, cardiac/ or heart defects, congenital/ or exp heart failure/ or heart valve diseases/ or heart disease risk factors/
28. (heart adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
29. (cardiac adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
30. (atrial adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
31. (ventricular adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kf,kw.
32. Defibrillators, Implantable/
33. or/27-32
34. 23 and 26 and 33
35. 5 or 34

Combined with the following filter using 'AND'

1. Economics/
2. "Costs and Cost Analysis"/
3. "Cost Allocation"/
4. Cost-Benefit Analysis/
5. "Cost Control"/
6. "Cost Savings"/
7. "Cost of Illness"/
8. "Cost Sharing"/
9. "Deductibles and Coinsurance"/
10. Medical Savings Accounts/
11. Health Care Costs/
12. Direct Service Costs/
13. Drug Costs/
14. Employer Health Costs/
15. Hospital Costs/
16. Health Expenditures/
17. Capital Expenditures/
18. "Value of Life"/

19.	exp Economics, Hospital/
20.	exp Economics, Medical/
21.	Economics, Nursing/
22.	Economics, Pharmaceutical/
23.	exp "Fees and Charges"/
24.	exp Budgets/
25.	(low adj cost).mp.
26.	(high adj cost).mp.
27.	(health?care adj cost$).mp.
28.	(fiscal or funding or financial or finance).tw.
29.	(cost adj estimate$).mp.
30.	(cost adj variable).mp.
31.	(unit adj cost$).mp.
32.	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
33.	or/1-32

Embase 1974 to 2023 June 14

Via: https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi

Date range searched: Inception to 14th June 2023

Date of search: 15th June 2023

Records retrieved: 90

1.	(Triage?HF* or "Triage HF" or CareLink Network* or MyCareLink* or "my care link" or "00763000351656").ti,ab,kw.
2.	(Latitude* NXT or Mylatitute* or "my latitude" or HeartLogic* or "heart logic" or "00802526562105" or "00802526573408" or "00802526584107" or "00802526590306" or "00802526592102" or "00802526613876").ti,ab,kw.
3.	(biotronik home monitor* or CardioMessenger* or "cardio messenger" or HeartInsight* or "heart insight" or "04035479139360" or "04035479159115" or "04035479177768").ti,ab,kw.
4.	(CorVue* or mymerlinimpact or "my merlin impact" or "merlin@home" or "merlin @ home" or "merlin at home" or "merlin.net").ti,ab,kw.
5.	or/1-4
6.	Optivol.ti,ab,kw.
7.	viva.ti,ab,kw.
8.	acticor.ti,ab,kw.
9.	rivacor.ti,ab,kw.

10. ilivia.ti,ab,kw.
11. intica.ti,ab,kw.
12. inlexa.ti,ab,kw.
13. resonate.ti,ab,kw.
14. vigilant.ti,ab,kw.
15. momentum.ti,ab,kw.
16. perciva.ti,ab,kw.
17. gallant.ti,ab,kw.
18. quadra.ti,ab,kw.
19. ellipse.ti,ab,kw.
20. assura.ti,ab,kw.
21. assurity.ti,ab,kw.
22. (biotronik or medtronic or "boston scientific" or abbott).ab,mf,my,mv,dm,dv,in,tn,go,so,dc,de,ct.
23. or/6-22
24. (algorithm* adj2 (monitor* or triag*)).ti,ab,kw.
25. (remot* adj2 (monitor* or triag*)).ti,ab,kw.
26. or/24-25
27. exp heart arrhythmia/ or congenital heart malformation/ or exp heart failure/ or valvular heart diseases/ or heart disease risk factor/
28. (heart adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
29. (cardiac adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
30. (atrial adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
31. (ventricular adj2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)).ti,ab,kw.
32. implantable cardioverter defibrillator/
33. or/27-32
34. 23 and 26 and 33
35. 5 or 34

Combined with the following filter using ‘AND’

1. socioeconomics/
2. "cost benefit analysis"/
3. "cost effectiveness analysis"/
4. "cost of illness"/

5. "cost control"/
6. economic aspect/
7. financial management/
8. "health care cost"/
9. health care financing/
10. health economics/
11. "hospital cost"/
12. (fiscal or financial or finance or funding).tw.
13. "cost minimization analysis"/
14. (cost adj estimate$).mp.
15. (cost adj variable$).mp.
16. (unit adj cost$).mp.
17. or/1-16

Cochrane (CENTRAL, CDSR)

Via: https://www.cochranelibrary.com/advanced-search

Date range searched: Inception to June 2023

Date of search: 15th June 2023

Records retrieved: 100

#1 (Triage?HF* or "Triage HF" or CareLink Network* or MyCareLink* or "my care link" or "00763000351656"):ti,ab,kw

#2 (Latitude* NXT or Mylatitute* or "my latitude" or HeartLogic* or "heart logic" or "00802526562105" or "00802526573408" or "00802526584107" or "00802526590306" or "00802526592102" or "00802526613876"):ti,ab,kw

#3 (biotronik home monitor* or CardioMessenger* or "cardio messenger" or HeartInsight* or "heart insight" or "04035479139360" or "04035479159115" or "04035479177768"):ti,ab,kw

#4 (CorVue* or mymerlinimpact or "my merlin impact" or "merlin@home" or "merlin @ home" or "merlin at home" or "merlin.net"):ti,ab,kw

#5 23-#4

#6 (Optivol):ti,ab,kw

#7 (viva):ti,ab,kw

#8 (acticor):ti,ab,kw

#9 (rivacor):ti,ab,kw

#10 (ilivia):ti,ab,kw

#11 (intica):ti,ab,kw

#12 (inlexa):ti,ab,kw

#13 (resonate):ti,ab,kw

#14 (vigilant):ti,ab,kw

#15 (momentum):ti,ab,kw

#16 (perciva):ti,ab,kw

#17 (gallant):ti,ab,kw

#18 (quadra):ti,ab,kw

#19 (ellipse):ti,ab,kw

#20 (assura):ti,ab,kw

#21 (assurity):ti,ab,kw

#22 (biotronik or medtronic or "boston scientific" or abbott):ti,ab,kw

#23 {OR #6-#22}

#24 (algorithm* NEAR/2 (monitor* or triag*)):ti,ab,kw

#25 (remot* NEAR/2 (monitor* or triag*)):ti,ab,kw

#26 48-#25

#27 MeSH descriptor: [Arrhythmias, Cardiac] explode all trees

#28 MeSH descriptor: [Heart Defects, Congenital] this term only

#29 MeSH descriptor: [Heart Failure] explode all trees

#30 MeSH descriptor: [Heart Valve Diseases] this term only

#31 MeSH descriptor: [Heart Disease Risk Factors] this term only

#32 (heart NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#33 (cardiac NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#34 (atrial NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#35 (ventricular NEAR/2 (failure* or defect* or disease* or arrhythm* or fibrillat* or monitor*)):ti,ab,kw

#36 MeSH descriptor: [Defibrillators, Implantable] this term only

#37 44-#36

#38 #23 AND #26 AND #37

#39 #5 OR #38

Centre for reviews and dissemination (NHS-EED, DARE, HTA)

Via: https://www.crd.york.ac.uk/CRDWeb/

Date range searched: Inception to 2015 (date of discontinuation)

Date of search: 15th June 2023

Records retrieved: 0

1 (TriageHF* OR "Triage HF" OR CareLink NetwORk* OR MyCareLink* OR "my care link" OR "00763000351656")

2 (Latitude* NXT OR Mylatitute* OR "my latitude" OR HeartLogic* OR "heart logic" OR "00802526562105" OR "00802526573408" OR "00802526584107" OR "00802526590306" OR "00802526592102" OR "00802526613876")

3 (biotronik home monitOR* OR CardioMessenger* OR "cardio messenger" OR HeartInsight* OR "heart insight" OR "04035479139360" OR "04035479159115" OR "04035479177768")

4 (CORVue* OR mymerlinimpact OR "my merlin impact" OR "merlin@home" OR "merlin @ home" OR "merlin at home" OR "merlin.net")

5 #1 OR #2 OR #3 OR #4

6 (Optivol)

7 (viva)

8 (acticor)

9 (ravicor)

10 (ilivia)

11 (intica)

12 (inlexa)

13 (resonate)

14 (vigilant)

15 (momentum)

16 (perciva)

17 (gallant)

18 (quadra)

19 (ellipse)

20 (assura)

21 (assurity)

22 (biotronik OR medtronic OR "boston scientific" OR abbott)

23 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

24 (algorithm* NEAR2 (monitor* OR triag*))

25 (remot* NEAR2 (monitor* OR triag*))

26 #24 OR #25

27 MeSH DESCRIPTOR Arrhythmias, Cardiac EXPLODE ALL TREES

28 MeSH DESCRIPTOR Heart Defects, Congenital

29 MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES

30 MeSH DESCRIPTOR Heart Valve Diseases

31 MeSH DESCRIPTOR Heart Disease Risk Factors

32 (heart NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

33 (cardiac NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

34 (atrial NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

35 (ventricular NEAR2 (failure* OR defect* OR disease* OR arrhythm* OR fibrillat* OR monitor*))

36 MeSH DESCRIPTOR Defibrillators, Implantable

37 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36

38 #23 AND #26 AND #37

39 #5 OR #3

INAHTA

Via: https://database.inahta.org/

Date range searched: Inception to June 2023

Date of search: 15th June 2023

Records retrieved: 5

((((ventricular) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ((atrial) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ((cardiac) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ((heart) AND (failure*) OR (defect*) OR (disease*) OR (arrhythm*) OR (fibrillat*) OR (monitor*)) OR ("Heart Disease Risk Factors"[mh]) OR ("Heart Valve Diseases"[mh]) OR ("Heart Failure"[mhe]) OR ("Heart Defects, Congenital"[mh]) OR ("Arrhythmias, Cardiac"[mhe])) AND (((remot*) AND ((monitor*) OR (triag*))) OR ((algorithm*) AND ((monitor*) OR (triag*)))) AND (((biotronik) OR (medtronic) OR ("boston scientific") OR (abbott)) OR ((optivol) OR (viva) OR (acticor) OR (rivacor) OR (ilivia) OR (intica) OR (inlexa) OR (resonate) OR (vigilant) OR (momentum) OR (perciva) OR (gallant) OR (quadra) OR (ellipse) OR (assura) OR (assurity)))) OR (((CORVue*) OR (mymerlinimpact) OR ("my merlin impact") OR ("merlin@home") OR ("merlin @ home") OR ("merlin at home") OR ("merlin.net")) OR (((biotronik home monitor*) OR (CardioMessenger*) OR ("cardio messenger") OR (HeartInsight*) OR ("heart insight") OR ("04035479139360") OR ("04035479159115") OR ("04035479177768"))) OR (((Latitude* NXT) OR (Mylatitute*) OR ("my latitude") OR (HeartLogic*) OR ("heart logic") OR ("00802526562105") OR ("00802526573408") OR ("00802526584107") OR ("00802526590306") OR ("00802526592102") OR ("00802526613876"))) OR ((TriageHF*) OR ("Triage HF") OR (Triage-HF*) OR ((CareLink Network*)) OR (MyCareLink*) OR ("my care link") OR ("00763000351656")))

NIHR Journals Library

Via: https://www.journalslibrary.nihr.ac.uk/#/

Date range searched: Inception to June 2023

Date of search: 15th June 2023

Records retrieved: 4

“remote monitoring”

“heart monitoring”

“cardiac monitoring”

Cardiac AND remote AND monitoring

Cardiac AND monitoring

Heart AND monitoring

9.3 Focussed searches

Focussed economic searches were run as above (clinical effectiveness searches) with the addition of the economic filters detailed below.

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

Via: https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi

Date range searched: Inception to 6th August 2023

Date of search: 7th August 2023

Records retrieved: 16

1. (cost? adj2 (illness or disease or sickness)).tw.
2. (burden? adj2 (illness or disease? or condition? or economic*)).tw.
3. ("quality-adjusted life years" or "quality adjusted life years" or QALY?).tw.
4. Quality-adjusted life years/
5. "cost of illness"/
6. Health expenditures/
7. (out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.
8. (expenditure? adj3 (health or direct or indirect)).tw.
9. ((adjusted or quality-adjusted) adj2 year?).tw.
10. or/1-9

1. quality-adjusted life years/

2. sickness impact profile/

3. (quality adj2 (wellbeing or well-being)).ti,ab.

4. sickness impact profile.ti,ab.

5. disability adjusted life.ti,ab.

6. (qal* or qtime* or qwb* or daly*).ti,ab.

7. (euroqol* or eq5d* or eq 5d*).ti,ab.

8. (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.

9. (health utility* or utility score* or disutilit*).ti,ab.

10. (hui or hui1 or hui2 or hui3).ti,ab.

11. health* year* equivalent*.ti,ab.

12. (hye or hyes).ti,ab.

13. rosser.ti,ab.

14. (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.

15. (sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.

16. (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

17. (sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.

18. (sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.

19. (sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.

20. or/1-19

Embase

Via: https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi

Date range searched: Inception to 6th August 2023

Date of search: 7th August 2023

Records retrieved: 88

1. (cost? adj2 (illness or disease or sickness)).tw.
2. (burden? adj2 (illness or disease? or condition? or economic*)).tw.
3. ("quality-adjusted life years" or "quality adjusted life years" or QALY?).tw.
4. Quality-adjusted life years/
5. "cost of illness"/
6. Exp “health care cost”/
7. (out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.
8. (expenditure? adj3 (health or direct or indirect)).tw.
9. ((adjusted or quality-adjusted) adj2 year?).tw.
10. or/1-9

1. quality adjusted life year/

2. "quality of life index"/

3. short form 12/ or short form 20/ or short form 36/ or short form 8/

4. sickness impact profile/

5. (quality adj2 (wellbeing or well-being)).ti,ab.

6. sickness impact profile.ti,ab.

7. disability adjusted life.ti,ab.

8. (qal* or qtime* or qwb* or daly*).ti,ab.

9. (euroqol* or eq5d* or eq 5d*).ti,ab.

10. (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.

11. (health utility* or utility score* or disutilit*).ti,ab.

12. (hui or hui1 or hui2 or hui3).ti,ab.

13. health* year* equivalent*.ti,ab.

14. (hye or hyes).ti,ab.

15. rosser.ti,ab.

16. (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.

17. (sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.

18. (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

19. (sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.

20. (sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.

21. (sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.

22. or/1-21

Databases searched in addition to the clinical effectiveness and economic review sources were searched as detailed below.

CEA Registry

Via: https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Date range searched: Inception to August 2023

Date of search: 7th August 2023

Records retrieved: 6

"remote monitoring"

"heart monitoring"

"cardiac monitoring"

RePEc

Via: https://ideas.repec.org/

Date range searched: Inception to August 2023

Date of search: 7th August 2023

Records retrieved: 2

“remote monitoring”

“heart monitoring”

“cardiac monitoring”

ScHARRHUD

Via: https://www.scharrhud.org/

Date range searched: Inception to August 2023

Date of search: 7th August 2023

Records retrieved: 4

Title OR abstract:

Heart failure AND remote monitoring

Cardiac AND remote monitoring

9.4 List of excluded records

Wrong intervention (n=323)

Wrong outcome (n=50)

Wrong publication type (n=45)

Wrong study design (n=9)

Wrong population (n=5)

Table 48: Excluded records and reasons for exclusion

Reason for exclusion	Reference
Wrong intervention (n=323)	1. Zile MR, Costanzo MRR, Butler J, Ippolito EM, Zhang Y, Stapleton RB*, et al.* Safety and Effectiveness of an Individualized Risk Stratification Based Medication Intervention Strategy: The Intervene HF Study. *Journal of Cardiac Failure* 2019;**25**:S101. https://doi.org/doi:https://dx.doi.org/10.1016/j.cardfail.2019.07.289 2. Zanotto G, Visentin E, rini D, Bassi M, Cassinadri E, Rocchetto E*, et al.* Implementation of a fully remote monitoring model for pacemakers: 3 years assessment of the in-hospital visits. *European Heart Journal* 2016;**37**:1044. https://doi.org/doi:https://dx.doi.org/10.1093/eurheartj/ehw434 3. Zambon E, Miani D, Narciso M, Comisso J, Indrigo S, Facchin D*, et al.* Remote monitoring of ICD patients by carelink system. *Giornale Italiano di Cardiologia* 2011;**12**:157S-8S. https://doi.org/doi:https://dx.doi.org/10.1714/641.7477 4. Zakeri R, Morgan JM, Phillips P, Kitt S, Ng GA, McComb JM*, et al.* Impact of remote monitoring on clinical outcomes for patients with heart failure and atrial fibrillation: results from the REM-HF trial. *European journal of heart failure* 2020;**22**:543-53. https://doi.org/doi:https://dx.doi.org/10.1002/ejhf.1709 5. Zabel M, Willich SN, Geller JC, Brachmann J, Kuhlkamp V, Dissmann R*, et al.* A randomized comparison of economic and clinical effects of automatic remote monitoring versus control in patients with ICDS: The monitor-ICD study. *Heart Rhythm* 2017;**14**:S58. https://doi.org/doi: 6. Zabel M, Willich SN, Geller JC, Brachmann J, Kuehlkamp V, Dissmann R*, et al.* The MONITOR-ICD study: A randomized comparison of economic and clinical effects of automatic remote monitoring versus control in patients with ICDs. *European Heart Journal* 2017;**38**:868. https://doi.org/doi:https://dx.doi.org/10.1093/eurheartj/ehx502.P4254 7. Xhaet O, Deceuninck O, Sprimont P, Dormal F, Ballant E, Go-vaerts G*, et al.* Prospective evaluation of the impact of remote monitoring to follow patient with implantable device in the routine practice of an

electrophysiological centre. *Acta Cardiologica* 2014;**68**:98-9. https://doi.org/doi:https://dx.doi.org/10.2143/AC.69.1.3011350

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11. Watanabe E, Yamazaki F, Goto T, Asai T, Yamamoto T, Hirooka K*, et al.* Remote Management of Pacemaker Patients With Biennial In-Clinic Evaluation: Continuous Home Monitoring in the Japanese At-Home Study: A Randomized Clinical Trial. *Circulation Arrhythmia and electrophysiology* 2020;**13**:e007734.
https://doi.org/doi:https://dx.doi.org/10.1161/CIRCEP.119.007734

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Wrong study design (n=9)	1. Capucci A, Ammirati F, Favale S, Pecora D, Petracci B, Calo L*, et al.* Preliminary experience with the multisensor HeartLogic algorithm for heart

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Wrong population (n=5)	1. Yoruk A, Aktas MK, Huang DT, Gosev I, Black C, Kutyifa V*, et al.* Assessment of Arrhythmia Burden through the Use of an Implantable Cardiac Monitor in Patients with a Continuous Flow Left Ventricular Assist Device. *Journal of Heart and Lung Transplantation* 2020;**39**:S190. https://doi.org/doi:https://dx.doi.org/10.1016/j.healun.2020.01.782 2. El Oualid Amara M, Montagnier C, Cheggour S, Boursier M, Gully C, Barnay C*, et al.* Early detection and treatment of supraventricular arrhythmia

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9.5 Ongoing studies

Table 49: Ongoing studies

Study details	Study design	Population	Intervention	Primary Outcome	Estimated completion date
NCT03579641, (2018)[119] USA, Australia, Canada, Hong Kong, Europe and the UK	Prospective Cohort	Heart Failure	HeartLogic	Association of HeartLogic sensors with 30-day HF re-admission	Results submitted Dec 2023 (not yet published)
NCT04619888, (2020)[120] France	Prospective Cohort	Heart Failure	HeartLogic	Annual rate of unplanned hospitalisations for heart failure	July 2023
NCT04489225, (2020)[121] USA, Europe, Switzerland and the UK.	Prospective Cohort	Heart Failure	Triage-HF	Positive predictive value of HFRS High Risk Status associated with worsening heart failure	Jan 2027
NCT05761249, (2023)[122]	Prospective Cohort	Heart Failure	HeartInsight	Rate of worsening heart failure hospitalization after HeartInsight activation	Sept 2027
Garcia, (2022)[123] France	Cohort	Heart Failure	HeartLogic	Unscheduled hospitalisation for heart failure	Unknown

9.6 Characteristics of included studies for the clinical effectiveness

Table 50: Characteristics of included studies and baseline demographics for CorVue

Study details: Author (year) Country Study population	Publication type	Study design	Age (yrs) Mean (SD) unless otherwise specified	NYHA Class n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Benezet - Mazuecos (2016) Unclear HF	Abstr.	Cohort	71 (11)	NR	56 (80)	ICD: 35 CRT-D: 35	NR	NR
Binkley (2012) USA Risk of acute HF	FT	Retrospective Cohort (Development and validation)	66 (12) range: 42-85	III: 72 (96) IV: 3 (4)	52 (69)	CRT-D: 75	ACEI/ARB: 65 (87) Beta blocker: 69 (92) Diuretics: 68 (91) Antiarrhythmics, class I or class III: 11 (15) Cardiac glycosides: 27 (36) Nitrates: 22 (29)	Prior myocardial infarction: 33 (44) Prior unstable angina: 10 (13) Prior CABG: 23 (31) Prior coronary revascularization, PTCA/stents: 25 (33) Ischemic cardiomyopathies: 42 (56) Nonischemic cardiomyopathies: 33 (44)

Study details: Author (year) Country Study population	Publication type	Study design	Age (yrs) Mean (SD) unless otherwise specified	NYHA Class n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Forleo (2013) (Forleo, 2011) Italy HF	FT Abstr.	Prospective Cohort	69 (9.9)	mean (SD) 2.5 (0.7)	64 (80%)	NR	B-blocker at discharge: 78 ACE and/or ARB at discharge: 73	Hypertension: 65 History of AF: 22 Diabetes: 30 Coronary artery disease: 45
Palfy (2015) Unclear Unclear	Abstr.	Cohort	70 (1)	I: 38 (59%) II: 20 (31%) III: 7 (11%)	78%	ICD: 36 CRT-D: 29	NR	NR
Palfy 2018 (Martinez Milla 2017) Unclear Unclear	FT Abstr.	Prospective Cohort	67 (1)	I: 27 (51.9%) II: 18 (34.0%) III: 8 (15.1%)	42 (79.2%)	CRT-D: 26 ICD: 27	Beta-blockers: 53 (100) ACEI/ARB: 47 (88.7) MRA: 33 (62.3) Digoxin: 6 (11.3) Diuretics: 39 (79.6)	NR
Santini (2012) Unclear HF	Abstr.	Cohort	66 (10.3)	NR	35 (92%)	NR	NR	NR

Study details: Author (year) Country Study population	Publication type	Study design	Age (yrs) Mean (SD) unless otherwise specified	NYHA Class n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Shapiro (2017) USA HF	FT	Retrospective Cohort (Medical Chart Review) of CorVue device compared to standard protocol	Range 65 - 88	III: 120 (100)	89 (74.2%)	ICD: 60 No implantable device: 60	β-blockers: NR Angiotensin-converting enzyme inhibitors: NR Angiotensin receptor blockers: NR Diuretics: NR Digoxin: NR Nitrates and hydralazine in combination: NR Aldosterone antagonists: NR Anticoagulants or alternate anti-clotting medications: NR	NR
Wakabayashi (2021) Japan HF	FT	Retrospective Cohort	Mean (range) 79 (71–84)	NR	33 (67.3)	PPM: 23 (46.9) ICD: 20 (40.8) CRT-D: 6 (12.2)	Antiplatelet agents: 18 (36.7) Anticoagulant agents: 17 (34.7) β-Blockers: 20 (40.8) ACEIs or ARBs: 21 (42.9) Calcium blockers: 13 (26.5) Diuretics: 22 (44.9) Statins: 9 (18.4)	BMI (kg/m2) mean (range): 23.1 (20.8–25.0) Hypertension: 21 (42.9%) Diabetes mellitus: 17 (34.7%) Dyslipidemia: 28 (57.1%) Previous HF: 10 (20.4%) Valvular heart disease: 8 (16.3%) Coronary artery disease: 8 (16.3%)

Abbreviations: NYHA, New York Heart Association; FT, full text; Abstr, Abstract; ICD, Implantable cardioverter defibrillator; CRT-D, Cardiac resynchronisation therapy device; PPM, permanent pacemaker; ACEI, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers; MRA, Aldosterone receptor antagonists; NR, not reported; HF, Heart Failure; BMI, Body mass index.

Table 51: Characteristics of included studies and baseline demographics for HeartInsight

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs) Mean (SD) unless otherwise specified	NYHA Class n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
D'Onofrio (2022) (D'Onofrio 2019) (Padeletti, 2015) (NCT01836510) Italy and Spain HF	FT Abstr. Protocol ClinicalTrial	Prospective Cohort	Median (IQR) All = 69.1 (60.7-75.9) Development = 69 (60.7-757) Validation = 69 (60.8-76.1)	All II: 446 (48.8) III: 467 (51.2) Derivation II: 225 (49.4) III: 230 (50.6) Validation II: 221 (48.2) III: 237 (51.8)	All 744 (81.0) Derivation 366 (80.1) Validation 378 (82.0)	All CRT-D: 403 (43.9) Derivation CRT-D: 202 (44.2) Validation CRT-D: 201 (43.6)	All Diuretics: 797 (86.8) Beta blockers: 793 (86.4) ACE: 523 (57.0) Aldosterone antagonists: 240 (26.1) ARB: 196 (21.3) calcium channel blockers: 75 (8.2) Statins: 553 (60.2) Antiplatelets: 596 (64.9) Anticoagulants: 228 (24.8) Amiodarone: 169 (18.4) Derivation Diuretics: 400 (87.5) Beta blockers: 395 (86.4) ACE: 259 (56.7) Aldosterone antagonists: 133 (29.1) ARB: 100 (21.9) Calcium channel blockers: 36 (7.9) Statins: 286 (62.6) Antiplatelets: 298 (65.2) Anticoagulants: 109 (23.9) Amiodarone: 81 (17.7) Validation Diuretics: 397 (86.1) Beta blockers: 398 (86.3) ACE: 264 (57.3) Aldosterone antagonists: 107 (23.2) ARB: 96 (20.8) Calcium channel blockers: 39 (8.5) Statins: 267 (57.9) Antiplatelets = 298 (64.6)	All History of hypertension: 604 Diabetes: 323 Chronic kidney disease: 194 Atrial fibrillation history: 129 Stroke/TIA: 69 Valvular surgery: 68 Derivation History of hypertension: 295 (64.6) Diabetes: 153 (33.6) Chronic kidney disease: 107 (23.4) Atrial fibrillation history: 68 (15) Stroke/TIA: 33 (7.2) Valvular surgery: 37 (8.1) Validation History of hypertension: 309 (67) Diabetes: 170 (37.2) Chronic kidney disease: 87 (18.9) Atrial fibrillation history: 61 (13.3) Stroke/TIA: 36 (7.8) Valvular surgery: 31 (6.7)

							Anticoagulants = 119 (25.8) Amiodarone = 88 (19.1)	

Abbreviations: NYHA, New York Heart Association; FT, full text; Abstr, Abstract; ICD, Implantable cardioverter defibrillator; CRT-D, Cardiac resynchronisation therapy device; ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers; HF, Heart Failure; TIA, Transient ischaemic attack.

Table 52: Characteristics of included studies and baseline demographics for HeartLogic

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs.) Mean (SD) unless otherwise specified	NYHA n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Boehmer (2017) (Boehmer, 2017) USA, Czech Republic, Germany, Hong Kong, Hungary, Israel, Italy, Malaysia, Netherlands, Slovakia, Thailand, United Kingdom HF	FT Abstr. Trial entry	Prospective Cohort	Development 66 (10.9) Validation 67 (10.3)	Development I: 5% II: 64% III: 27% IV: 0% Validation I: 4% II: 64% III: 25% IV: 1%	Development 387 (73) Validation 314 (71)	NR	Development Anticoagulants: 462 (88) Beta blockers: 490 (94) Diuretics: 399 (76) ACE, ARBs: 436 (83) Aldosterone: 196 (37) Vasoactive drugs: 123 (23) Cardiac glycosides: 139 (27) Antiarrhythmic meds: 113 (22) Calcium channel blockers: 42 (8) Validation Anticoagulants: 356 (82) Beta blockers: 405 (93) Diuretics: 340 (78) ACE, ARBs: 354 (81) Aldosterone: 193 (44) Vasoactive drugs: 102 (23) Cardiac glycosides: 107 (25) Antiarrhythmic meds: 97 (22) Calcium channel blockers: 31 (7)	Development History of cardiac ischemia: 277 (52) History of dilated cardiomyopathy: 301 (57) History of valvular disease: 162 (31) History of valve surgery: 50 (9) Previous MI: 211 (40) Previous CABG: 156 (29) AF: 136 (26) Renal disease: 143 (27) Validation History of cardiac ischemia: 217 (49) History of dilated cardiomyopathy: 271 (61) History of valvular disease: 130 (29) History of valve surgery: 40 (9) Previous MI: 171 (39) Previous CABG: 128 (29) AF: 118 (27) Renal disease: 101 (23)
Calo (2021) (Calo, 2020) (Calo, 2021) Italy HF	FT Abstr. Abstr.	Prospective Cohort	69 (11)	I: 25 II: 197 III: 135 IV: 9	286 (78)	CRT: 281 (77)	Beta blocker: 333 ACEi, ARB, ARNI: 288 Aldosterone antagonist: 110 Diuretic: 326 Antiarrhythmic: 106 Ivabradine: 37	AF history: 144 AF on implantation: 77 Valvular disease: 77 Coronary artery disease: 165 Diabetes: 112 COPD: 73 Chronic kidney disease: 121 Hypertension: 240

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs.) Mean (SD) unless otherwise specified	NYHA n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Chang (2020) USA HF	Abstr.	Retrospective Cohort with external control	NR	NR	NR	CRT-D: 40	NR	NR
De Juan Baguda (2022) (De Juan Baguda 2021) (De Juan Baguda 2021) Spain HF	FT Abstr. Abstr.	Prospective Cohort (phase 3) and Retrospective Cohort (phase 1 and 2)	68 (10)	I: 47 (16) II: 166 (58) III: 75 (26)	222 (77)	CRT-D: 234 (81) ICD: 241 (84)	beta blockers: 274 (95) ACEI, ARB, or valsartan/sacubitril: 265 (92) valsartan/sacubitril: 145 (50) MRAs: 215 (75) Diuretics: 207 (72) Amiodarone: 64 (22) Ivabradine: 35 (12)	History of AF = 112 (39) AF at implantation = 66 (23) Hypertension = 214 (74) Diabetes = 116 (40) Dyslipidemia = 169 (59) Smoking = 175 (64) (incl. 144 ex smokers) COPD = 48 (17) Chronic kidney disease = 77 (27) On haemodialysis = 5 (2) Previous stroke = 31 (11) sleep apnea-hypopnea syndrome = 33 (11)
De Ruvo (2019) (De Ruvo, 2019) (D'Onofrio, 2019) Italy HF	Abstr. Abstr. Abstr.	Prospective Cohort	71 (10)	NR	74 (73)	NR	NR	NR
Ebrille (2021) Italy HF	Abstr.	Prospective Cohort	73 (7)	NR	39 (72)	CRT: 54	NR	NR

Study details: **Author (year)** **Country** **Study population**	**Publication type**	**Study design**	**Age (Yrs.) Mean (SD) unless otherwise specified**	**NYHA n (%) unless otherwise specified**	**Sex (male) n (%) unless otherwise specified**	**Device type n (%) unless otherwise stated**	**Treatments at baseline n (%) unless otherwise stated**	**Comorbidities n (%) unless otherwise stated**
Feijen (2023) (Feijen, 2022) Europe HF	FT Abstr.	Retrospective Cohort (propensity matched)	Median (IQR) before matching non-HL = 67 (59.3-74) HL = 68 (58.3-75) after matching non-HL = 68 (60.5-75) HL = 68 (58.5-75.5)	Before matching Non-HeartLogic III and IV: 67 (30.2) HeartLogic III and IV: 47 (30.5) After matching Non-HeartLogic III and IV: 39 (30.7) HeartLogic III and IV: 38 (29.9)	Before matching Non-HeartLogic 173 (77.9) HeartLogic 123 (79.9) After matching Non-HeartLogic 101 (79.5) HeartLogic 102 (80.3)	No CRT function before matching (only ICD) non-HL = 124 (55.9) HL = 52 (33.8) after matching non-HL = 52 (40.9) HL = 52 (40.9)	NR	before matching non-HL Ischemic etiology = 117 (52.7) Diabetes = 63 (28.4) HL Ischemic etiology = 71 (46.1) Diabetes = 25 (16.2) after matching non-HL Ischemic etiology = 62 (48.8) Diabetes = 28 (22) HL Ischemic etiology = 58 (45.7) Diabetes = 25 (19.7)
Gardner (2018) Czech Republic, Germany, Hong Kong, Hungary, Israel, Italy, Malaysia, Netherlands, Slovakia, Thailand, United Kingdom, United States	FT	Prospective Cohort (secondary analysis)	67 (10.5)	I: 43 (5) II: 605 (67) III: 241 (27) IV: 4 (<1) Not available: 7 (1)	654 (73)	CRT-D: 900	ACE/ARB: 748 (83) Beta blocker: 839 (93) Mineralocorticoid receptor antagonists: 360 (40) Diuretics: 694 (77) Vasodilators: 210 (23) Cardiac glycosides: 231 (26) Antiarrhythmic medications: 193 (21)	History of cardiac ischemia = 457 (51) Diabetes = 380 (42) History of renal disease = 226 (25) History of AF or atrial flutter = 306 (34)

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs.) Mean (SD) unless otherwise specified	NYHA n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
HF								
Guerra (2022) (Guerra, 2022) (Guerra, 2022) Italy HF	FT Abstr. Abstr.	Prospective Cohort	69 (11)	I: 13 (6) II: 101 (44) III: 108 (47) IV: 7 (3)	171 (75)	CRT: 197 (86%)	beta blocker: 204 (89) ACE, ARB, ARNI: 198 (86) Diuretics: 207 (90) Antiarrhythmic: 191 (28) Ivabradine: 26 (11)	Coronary artery disease: 108 (47) AF history: 91 (40) Diabetes: 75 (33) COPD: 47 (20) Chronic kidney disease: 85 (37) Hypertension: 153 (67)
Henry (2022) Belgium HF	Abstr.	Retrospective Cohort	NR	NR	NR	ICD: NR CRT-D: NR	NR	NR

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs.) Mean (SD) unless otherwise specified	NYHA n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Lerman (2023) USA HF (LVAD pts.)	FT	Retrospective Cohort	Median (IQR) 69 (66-72)	NR	10 (71)	NR	MRA: 7 (50) Loop diuretics: 13 (92.9) beta blockers: 13 (92.9) ACEi/ARB: 11 (78.6) Cal channel blockers: 3 (21.4) Hydralazine: 7 (50) Nitrates: 1 (7.1)	Chronic pulmonary disease: 7 (50) Atrial fibrillation/flutter: 10 (71.4) Hypertension: 12 (85.7) Coronary disease: 14 (100) Diabetes = 7 (50) BMI >30 = 8 (57.1) Myocardial infarction = 4 (28.6) CKD grade 3 or higher = 10 (71.4)
Pecora (2020) Italy HF	Abstr.	Prospective Cohort	71 (10)	NR	76 (73)	NR	NR	NR
Perez Serrano (2019) Spain Unclear	Abstr.	Prospective Cohort	66	NR	15 (83)	ICD: NR CRT-D: NR	NR	NR
Santini (2020) (Santini, 2020) Italy HF	FT Abstr.	Prospective Cohort	71 (10)	I: 2 (2) II: 46 (44) III: 53 (51) IV: 3 (3)	76 (73)	CRT: 96 (92)	Beta blocker: 97 (93) ACE: 54 (52) Diuretics: 97 (93) Antiarrhythmic: 27 (26) Ivabradine: 12 (11)	AF history: 44 (42) AF on implantation: 23 (22) Valvular disease: 24 (23) Diabetes: 32 (31) COPD: 21 (19) Chronic kidney disease: 38 (36) Hypertension: 79 (76)

Study details: **Author (year)** **Country** **Study population**	**Publication type**	**Study design**	**Age (Yrs.) Mean (SD) unless otherwise specified**	**NYHA n (%) unless otherwise specified**	**Sex (male) n (%) unless otherwise specified**	**Device type n (%) unless otherwise stated**	**Treatments at baseline n (%) unless otherwise stated**	**Comorbidities n (%) unless otherwise stated**
Santobuono (2023) (D'Onofrio 2023) (Santobuono, 2022) Italy HF	FT FT Abstr.	Prospective Cohort	69 (10)	I: 36 (6) II: 351 (62) III: 171 (30) IV: 10 (2)	453 (80)	ICD: 158 CRT-D: 410	Beta blocker: 520 (92) ACE-I, ARB or ARNI: 536 (94) Diuretics: 506 (89) Antiarrhythmic: 116 (20)	Diabetes: 167 (29) COPD: 89 (16) Chronic kidney disease: 153 (27) Hypertension: 334 (59)
Treskes (2021) Belgium, the Netherlands and Switzerland HF	FT	Retrospective pre-post study design	67 (10.3)	I: 15 (20) II: 35 (47) III: 24 (32)	62 (84)	CRT-D: 64 ICD: 10	Pre activation Beta blocker: 56 (82) ACE-I/ARB/ARNI: 56 (82) MRA: 36 (53) Diuretics: 47 (69) Ivabradine: 3 (4) Post activation Beta blocker: 61 (89) ACE-I/ARB/ARNI: 56 (82) MRA: 45 (66) Diuretics: 48 (70) Ivabradine: 3 (4)	Diabetes: 15 (20)
Vigdor (2020) USA HF	Abstr.	Prospective Cohort	NR	NR	NR	NR	NR	NR

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs.) Mean (SD) unless otherwise specified	NYHA n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Wariar (2023) (Wariar, 2022) USA HF	Abstr. Abstr.	Retrospective Cohort	Predominantly 65 years and older	NR	Predominately male	CRT-D: 1078 (69) ICD: 31%	NR	Hypertension: 87.4% Hyperlipidemia: 80.3% Diabetes: 51.3% Ischemic heart disease: 87.7% Congestive heart failure: 84.7% Atrial fibrilation: 40.1% Coronory obstructive pulmonary disease: 30.6% Chronic kidney disease: 54.2%
Hernandez (2022) (Hernandes, 2021) (NCT03237858) USA HF	FT Abstr. Trial entry	Prospective Cohort	67 (12)	NR	129 (68)	CRT-D: 132 (69) ICD: 59 (31)	Loop diuretic: 158 (83) Thiazide diuretic: 17 (9) ACEI or ARB: 103 (54) ARNI: 51 (27) MRA: 82 (43) Beta-blocker: 184 (96) Vasodilators: 35 (18)	Ischemic heart disease: 90 (47) Dilated cardiomyopathy: 75 (39) Idiopathic cardiomyopathy: 20 (11) Valvular disease: 48 (25) Myocardial infarction: 73 (38) coronary artery bypass grafting: 49 (26) chronic obstructive lung disease: 28 (15) pulmonary hypertension: 14 (7) Peripheral vascular disease: 25 (14) Cerebrovascular disease: 32 (17) Renal dysfunction: 50 (26) Hypertension: 144 (76) Diabetes: 69 (36) Hyperlipidemia: 134 (70) Sleep apnea: 45 (25) Depression: 34 (18) Hepatic disease: 11 (6) Anaemia: 27 (14)

Abbreviations: NYHA, New York Heart Association; FT, full text; Abstr, Abstract; ICD, Implantable cardioverter defibrillator; CRT-D, Cardiac resynchronisation therapy device; ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers; MRA, Aldosterone receptor antagonists; ARNI, Angiotensin receptor/neprilysin inhibitor; HF, Heart Failure; TIA, Transient ischaemic attack; COPD, Chronic obstructive pulmonary disease; AF, atrial fibrillation; CABG, coronary artery bypass grafting; BMI, Body mass index.

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs.) Mean (SD) unless otherwise specified	NYHA n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated

Table 53: Characteristics of included studies and baseline demographics for Triage-HF

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs) Mean (SD) unless otherwise specified	NYHA Class n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Ahmed (2022) (Ahmed, 2023 unpublished) (Ahmed, 2021) (Ahmed, 2021) UK HF and no HF	Abstr. FT Abstr. Abstr.	Prospective Cohort (dataset Sept 2019 – June 2021	66 (15.5)	No HF: 62 (14.1) I: 56 (12.8) II: 151 (34.4) III: 147 (33.5) Not available: 23 (5.2)	278 (63.3)	CRT-D: 167 CRT-P: 172 ICD: 36 PPM: 64	Beta blockers: 320 (79.6) Ace-I/ARB/ARNI: 274 (68.5) MRA: 149 (37.3) Diuretic: 206 (51.5)	Ischaemic heart disease: 238 (55.5) Adult congenital heart disease: 39 (9.0) Prior ablation: 71 (16.4) Prior myocardial infarction (MI): 141 (34.1) Chronic obstructive pulmonary disease (COPD): 55 (13.0) Diabetes: 28 (19.2) Chronic kidney disease stage (CKD) >_3: 135 (31.0)
Bachtiger (2021) UK Unclear	Abstr.	Prospective Cohort	NR	NR	NR	NR	NR	NR
Burri (2018) Unclear Unclear	FT	Cohort (Secondary analysis using data from the MORE-CARE randomised trial)	66 (10)	I: 52 (7.3%) II: 226 (31.8%) III: 413 (58.2%) IV: 19 (2.7%) Not reported: 12 (1.7%)	549 (76.3%)	CRT-D: 722	Diuretic: 648 (91.3) Beta-blocker: 640 (90.1) ACE-inhibitor or ARBII: 579 (81.5) Anti-arrhythmic: 183 (25.8) Anti-platelet: 439 (61.8) Oral anticoagulants: 160 (22.5)	Ischemic heart disease: 316 (44.1) History of AF: 125 (17.5) History of sustained VT/VF: 81 (11.3) Previous valve surgery: 62 (8.7) Diabetes: 246 (35.0) Hypertension: 327 (46.0) Previous TIA or stroke: 52 (7.3) COPD: 104 (4.6)

Study details: **Author (year)** **Country** **Study population**	**Publication type**	**Study design**	**Age (Yrs) Mean (SD) unless otherwise specified**	**NYHA Class n (%) unless otherwise specified**	**Sex (male) n (%) unless otherwise specified**	**Device type n (%) unless otherwise stated**	**Treatments at baseline n (%) unless otherwise stated**	**Comorbidities n (%) unless otherwise stated**
Cardoso (2020) Portugal Unclear	Abstr.	Prospective Cohort	68 (9.8)	II, III and IV: 46%	NR	CRT: NR	NR	NR
Cowie (2013) Unclear Unclear	FT	Development study - observational and randomised Validation study - observational and randomised	Development 68 (11) Validation 67 (11)	Development set I: 2 II: 19 III: 76 IV: 3 Validation set I: 4 II: 22 III: 70 IV: 4	Development set 69 Validation set 74	Development set ICD: 0 CRT-D: 100 Validation set ICD:4 CRT-D: 96	Development set ACE/ARB: 70% Beta-blockers: 87% Diuretics: 77% Digoxin: 29% Aldosterone antagonist: 26% AAD: 18% Anti-platelet or anticoagulant: 86% Warfarin: 33% Validation set ACE/ARB: 84% Beta-blockers: 88% Diuretics: 87% Digoxin: 33% Aldosterone antagonist: 22% AAD: 22% Anti-platelet or anticoagulant: 61% Warfarin: 25%	Development set Ischaemic: 63% Myocardial infarction: 43% Hypertension: 70% Diabetes: 37% History of AF: 21% LVEF 35%: 96% Validation set Ischaemic: 61% Myocardial infarction: 48% Hypertension: 62% Diabetes: 38% History of AF: 32% LVEF 35%: 92%

Study details: **Author (year)** **Country** **Study population**	**Publication type**	**Study design**	**Age (Yrs) Mean (SD) unless otherwise specified**	**NYHA Class n (%) unless otherwise specified**	**Sex (male) n (%) unless otherwise specified**	**Device type n (%) unless otherwise stated**	**Treatments at baseline n (%) unless otherwise stated**	**Comorbidities n (%) unless otherwise stated**
Debski (2021) UK HF	Abstr.	Prospective Cohort	74 (10)	NR	82%	CRT-D:132	NR	NR
Garner (2022) UK Unclear	FT	Prospective Cohort	70 (11.5)	NR	147 (78)	CRTD: 176 (94) CRTP: 9 (5) ICD: 3 (1)	ACE/ARB: 126 (67) ARNI: 34 (18) Beta blocker: 175 (93) MRA: 116 (62) Diuretic: 135 (72)	Diabetes: 71 (38) BMI Mean (SD): 29.6 (6.2) Clinical frailty score Mean (S.D): 4.1 (1.5) Charleson comorbidity score Mean (S.D): 5.5 (2.3)
Gula (2014) 34 International centres (RAFT trial) HF	FT	Validation study using data from RCT	66 (9)	II: 1062 (87) III: 162 (13)	1013 (83)	CRT-D: 741 ICD: 483	Angiotensin converting enzyme inhibitor: 967 (79) Angiotensin receptor blocker: 269 (22) Beta-Blockers: 1,100 (90) Diuretics: 1,005 (82) Statins: 847 (69) Nitrates: 329 (27) Digoxin: 393 (32) Ca Channel Blocker: 137 (11) Antiarrhythmic drug: 175 (14) Anti-coag/platelet: 1093 (89)	Ischemic: 798 (65%) Renal Dysfunction: 213 (17%) Pulmonary: 308 (25%) Hypertension: 530 (43%) Diabetes: 408 (33%) Chronic AF: 133 (11%) VT/VF: 226 (18%) Mean left ventricular ejection fraction (SD): 23% (±5)

Study details: Author (year) Country Study population	Publication type	Study design	Age (Yrs) Mean (SD) unless otherwise specified	NYHA Class n (%) unless otherwise specified	Sex (male) n (%) unless otherwise specified	Device type n (%) unless otherwise stated	Treatments at baseline n (%) unless otherwise stated	Comorbidities n (%) unless otherwise stated
Koehler (2019) Unclear HF	Abstr.	Cohort	NR	NR	NR	CRT-D: NR ICD: NR	NR	NR
Okumura (2020) Japan Unclear	FT	Prospective Cohort	68 (11.9)	I: 20 (6) II: 162 (52) III: 128 (41) IV: 4 (1)	220 (69.8)	CRT-D: 315	β-blocker: 264 (83.8) ACE-I: 136 (43.2) ARB: 88 (27.9) Diuretic: 249 (79.0) Nitrate: 16 (5.1) Statin: 116 (36.8) MRA: 177 (56.2)	Ischemic cardiomyopathy: 74 (23.5) Non-ischemic cardiomyopathy: 184 (58.4) AF: 126 (40) Paroxysmal AF: 63 (20) Persistent AF: 15 (4.8) Long-standing persistent AF: 48 (15.2) Hypertension: 100 (31.7) Chronic kidney disease: 99 (31.4) Diabetes: 93 (29.5) Type I: 3 (1.0) Type II: 90 (28.6) Sleep apnea: 30 (9.5) Bronchial asthma: 14 (4.4) Chronic obstructive pulmonary disease: 6 (1.9)
Sammut-Powell (2022) (Ahmed, 2022) (Ahmed, 2020) (Ahmed, 2020) (Ahmed, 2018)	FT FT FT Abstr. Abstr.	Prospective Cohort	66 (15.5)	No HF: 62 (14.3) I: 55 (12.6) II: 151 (34.7) III and IV: 145 (33.3)	276 (63.4)	CRT-D: 166 (38.2) CRT-P: 170 (39.0) ICD: 36 (8.3) PPM: 63 (14.5)	β Blockers: 319 (79.8) ACE-I/ARB/ARNI: 273 (68.6) MRA: 149 (37.5) Diuretic: 206 (51.8)	Diabetes: 103 (23.7) chronic obstructive pulmonary disease: 54 (12.4) Chronic kidney disease stage ≥3: 134 (30.8) At least one comorbidity: 388 (89.2)

Study details: **Author (year)** **Country** **Study population**	**Publication type**	**Study design**	**Age (Yrs) Mean (SD) unless otherwise specified**	**NYHA Class n (%) unless otherwise specified**	**Sex (male) n (%) unless otherwise specified**	**Device type n (%) unless otherwise stated**	**Treatments at baseline n (%) unless otherwise stated**	**Comorbidities n (%) unless otherwise stated**
(Ahmed, 2018) UK HF	Abstr.							
Virani (2018) (Virani 2016 - outcome changes to clinical mgmt) (Virani, 2016) (Zieroth 2016) Canada Unclear	FT Abstr. Abstr. Abstr.	Prospective Cohort	67 (11.0)	I: 16 (16) II: 50 (50) III: 32 (32) IV: 0 (0) Not available: 2 (2)	78 (78%)	CRT-D: 69 (69) ICD-DR: 20 (20) ICD-VR: 11 (11)	Beta-blockers: 95 (95) ACE inhibitors: 56 (56) Angiotensin II receptor blocker: 28 (28) Mineralocorticoid antagonist: 49 (49) Diuretic: 81 (81) Nitrate: 17 (17)	History of ventricular arrhythmia: 30 (30%) Type II diabetes: 41 (41%) COPD: 17 (17%) Sleep apnoea: 16 (16%) Hypertension: 64 (64%)
Zile (2020) (Zile, 2020) (Zile, 2020) USA HF and risk of acute HF	FT Abstr. Abstr.	Retrospective Cohort	66 (12)	NR	16,371 (71)	ICD: 11,878 (52) CRT-D: 11,023 (48)	ACE-I/ARB: 16,118 (70) Beta-blockers: 11,998 (52) Diuretics: 15,085 (66) Spironolactone: 6558 (29) Sacubitril/ valsartan: 194 (1) Vasodilator/nitrate: 12,767 (56) Anti-arrhythmic drug: 16,919 (74) Anticoagulation: 9524 (42)	Hypertension: 15,450 (67) HF: 14,276 (62) Diabetes: 7623 (33) CAD: 14,574 (64) MI: 7365 (32) Vascular disease: 2643 (12) Atrial fibrillation: 8222 (36) Renal dysfunction: 5211 (23) Stroke/TIA: 4289 (19)

Study details: **Author (year)** **Country** **Study population**	**Publication type**	**Study design**	**Age (Yrs) Mean (SD) unless otherwise specified**	**NYHA Class n (%) unless otherwise specified**	**Sex (male) n (%) unless otherwise specified**	**Device type n (%) unless otherwise stated**	**Treatments at baseline n (%) unless otherwise stated**	**Comorbidities n (%) unless otherwise stated**
Zile 2021 USA With and without HF	FT	Prospective Cohort	73 (9) range 46-92	Class II: 27 (41) Class III: 39 (59)	Male 46 (70)	CRT-D: 66	ACE-I/ARB/ARNI: 48 (73) Beta blockers: 57 (86) Diuretics: 55 (83) MRAs: 19 (29) Vasodilators: 17 (26) Digitalis compounds: 16 (24) Anti-arrhythmic drugs: 15 (23) Calcium channel blockers: 3 (4) HCN channel blockers: 2 (3)	Ischemic cardiomyopathy: 38 (58) Non-ischemic cardiomyopathy: 21 (32) Hypertrophic cardiomyopathy: 1 (1) Hypertension: 42 (64) Myocardial infarction: 27 (41) Peripheral vascular disease: 18 (27) Atrial fibrillation: 40 (61) Atrial flutter: 7 (11) Chronic obstructive pulmonary disease: 13 (20) Diabetes mellitus: 28 (42) Chronic renal dysfunction: 16 (24) Stroke: 8 (12)

Abbreviations: NYHA, New York Heart Association; FT, full text; Abstr, Abstract; ICD, Implantable cardioverter defibrillator; CRT-D, Cardiac resynchronisation therapy device; CRT-P, cardiac resynchronisation therapy pacemaker; ICD-VR, Implantable cardioverter defibrillator single chamber; ICD-DR, Implantable cardioverter defibrillator dual chamber; PPM, Permanent pacemaker; AAD, antiarrhythmic drugs; Ca, Calcium; ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers; MRA, Aldosterone receptor antagonists; ARNI, Angiotensin receptor/neprilysin inhibitor; HF, Heart Failure; TIA, Transient ischaemic attack; COPD, Chronic obstructive pulmonary disease; AF, atrial fibrillation; CABG, coronary artery bypass grafting; BMI, Body mass index; CAD, coronary artery disease; MI, Myocardial infarction; VT/VF, ventricular tachycardia/ventricular fibrillation.

9.7 Studies reporting development and validation cohorts in the same study, full results including development cohort

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
D'Onofrio (2022)[45]	Prospective cohort (overall n = 918, development n = 457, validation n = 378)	HeartInsight	Primary: First post implant worsening HF hospitalisation Secondary: any HF hospitalisation, outpatient IVI or death	Primary endpoint Development = 0.89 (0.83 to 0.95) Validation = NR Secondary endpoint Development = NR Validation = NR	Development 3.5 to 4.5 = 81.5 (61.9 to 93.7) to 63.0 (42.4 to 80.6) Validation; primary endpoint 3.5 = 72.4 (52.8 to 87.3) 4.0 = 65.5 (45.7 to 82.1) 4.5 = 65.5 (45.7 to 82.1) Validation; secondary endpoint 3.5 = 64.5 (51.3 to 76.2) 4.0 = 59.7 (46.4 to 71.9) 4.5 = 54.8 (41.7 to 67.5)	Development 3.5 to 4.5 = 82.6 (78.2 to 86.5) to 90.7 (89.0 to 94.9) Validation; primary endpoint 3.5 = 75.8 (75.6 to 75.9) 4.0 = 82.4 (82.3 to 82.5) 4.5 = 86.7 (86.6 to 86.8) Validation; secondary endpoint 3.5 = 75.3 (75.2 to 75.4) 4.0 = 82.0 (81.9 to 82.2) 4.5 = 86.5 (86.4 to 86.6)	Development NR Validation; primary endpoint NR Validation; secondary endpoint 3.5 to 4.5 = 5.3 to 7.7	Development NR Validation; primary endpoint NR Validation; secondary endpoint 3.5 to 4.5 = 96.6 to 96.7
Boehmer (2017)[56]	Prospective cohort (overall n = 900, development n =	HeartLogic	HF events of hospitalisations and clinic visits with change to treatment with primary cause	Development = NR Validation = NR	Development = 82.0 Validation = 70.0 (55.4 to 82.1)	Development = NR Validation = 85.7	Development = NR Validation = 11.3	Development = NR Validation = 99.98

Author (year)	Study design (n)	Intervention	Study endpoint	AUC (95% CI)	Sensitivity (95% CI; %)	Specificity (95% CI; %)	PPV (95% CI; %)	NPV (95% CI; %)
	500, validation n = 400)		of HF worsening					

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Addendum to Assessment Group's Report

Algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices

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Declared competing interests of the authors

None.

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Contents

1. HeartLogic algorithm list price

The following tables report the cost-effectiveness results using the list price (one-off £3650 per patient and no additional consumable or maintenance costs) for the HeartLogic algorithm. The EAR includes a confidential price for the HeartLogic algorithm.

Table 1. (Table 44 in EAR, Page 150) Deterministic cost-effectiveness results of the base case analysis

Items	**CorVue**		**HeartInsight**		**HeartLogic**		**TriageHF**	
	I	*C*	*I*	*C*	*I*	*C*	*I*	*C*
Total								
Costs (£)	17855	17848	18415	17848	9349	17748	11665	20712
QALYs	5.83	5.83	5.83	5.83	5.84	5.83	5.84	5.82
Cumulative hospitalisations per person	5.28	5.28	5.28	5.28	1.20	4.25	2.65	6.31
Cumulative days in hospital	84.48	84.48	84.48	84.48	8.38	67.96	42.42	101
Cumulative Follow-up_1*	22.22	22.22	22.22	22.22	22.22	22.22	22.22	22.22
Cumulative Follow-up_2**	3.40	3.40	3.40	3.40	7.74	3.40	4.70	3.40
Proportion died after 40 years	0.97	0.97	0.97	0.97	0.97	0.97	0.97	0.97
Incremental (intervention versus comparator)								
Costs (£)	37		568		-8400		-9048	
QALYs	0		0		0.01		0.01	
Cumulative hospitalisations per person	0		0		-3.05		-3.66	
Cumulative days in hospital	0		0		-59.58		-59	
*Cumulative Follow-up_1**	0		0		0		0	
*Cumulative Follow-up_2***	0		0		4.34		1.31	

Proportion died after 40 years	0	0	0	0
ICER	Cost increasing	Cost Increasing	Dominant	Dominant

I: Intervention; C: Comparator;

* Follow-up_1: Scheduled visits; **Follow-up_2: Unscheduled visits

Table 2: (Table 45 in EAR, Page 151) Cost breakdown in the base case cost-effectiveness analysis

Costs (£)	**CorVue**		**HeartInsight**		**HeartLogic**		**TriageHF**	
	I	*C*	*I*	*C*	*I*	*C*	*I*	*C*
Total								
RMS	26.40	0	501.14	0	3689	0	857	0
Monitoring alert	11.08	0	66.49	0	126.15	0	92	0
Cumulative days in hospital	14651	14651	14651	14651	1795	14552	7357	17516
Cumulative Follow-up_1*	2772	2772	2772	2772	2772	2772	2772	2772
Cumulative Follow-up_2**	4244	424	424	424	965	424	587	424
Incremental costs (£) (intervention versus comparator)								
RMS	26.40		501.14		3689		857	
Monitoring alert	11.08		66.49		126.15		92	
Cumulative days in hospital	0		0		-12757		-10159	
*Cumulative Follow-up_1**	0		0		0		0	
*Cumulative Follow-up_2***	0		0		541		163	
Incremental total costs (£)	37		568		-8400		-9048	

I: Intervention; C: Comparator;

* Follow-up_1: Scheduled visits; **Follow-up_2: Unscheduled visits

Table 3: (Table 46 in EAR, Page 152) Probabilistic cost-effectiveness results of the base-case analysis

Items	HeartLogic		TriageHF	
	I	*C*	*I*	*C*
Total				
Costs (£)	9354	17790	11674	20857
QALYs	5.84	5.83	5.84	5.82
Cumulative hospitalisations per person	1.20	4.26	2.66	6.37
Cumulative days in hospital	8.43	68.12	42.18	101.31
Cumulative Follow-up_1*	22.26	22.27	22.29	22.17
Cumulative Follow-up_2**	7.74	3.41	4.72	3.41
Proportion died after 40 years	0.97	0.97	0.97	0.97
Incremental (intervention versus comparator)				
Costs (£)	-8437		-9183	
QALYs	0.013		0.02	
Cumulative hospitalisations per person	-3.06		-3.71	
Cumulative days in hospital	-60		-59	
*Cumulative Follow-up_1**	0		0	
*Cumulative Follow-up_2***	4.33		1.31	
Proportion died after 40 years	0		0	
ICER	Dominant		Dominant	

I: Intervention; C: Comparator;

* Follow-up_1: Scheduled visits; **Follow-up_2: Unscheduled visits;

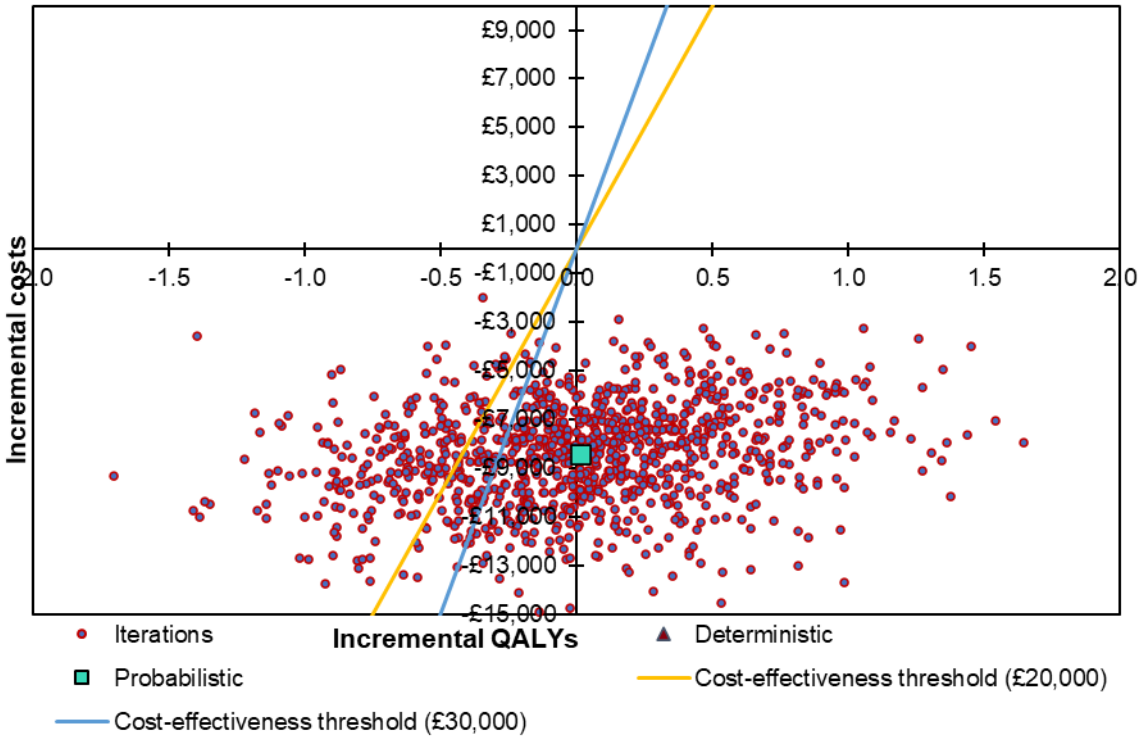


Figure 1: (Figure 7 in EAR, Page 153) Cost-effectiveness plot-HeartLogic

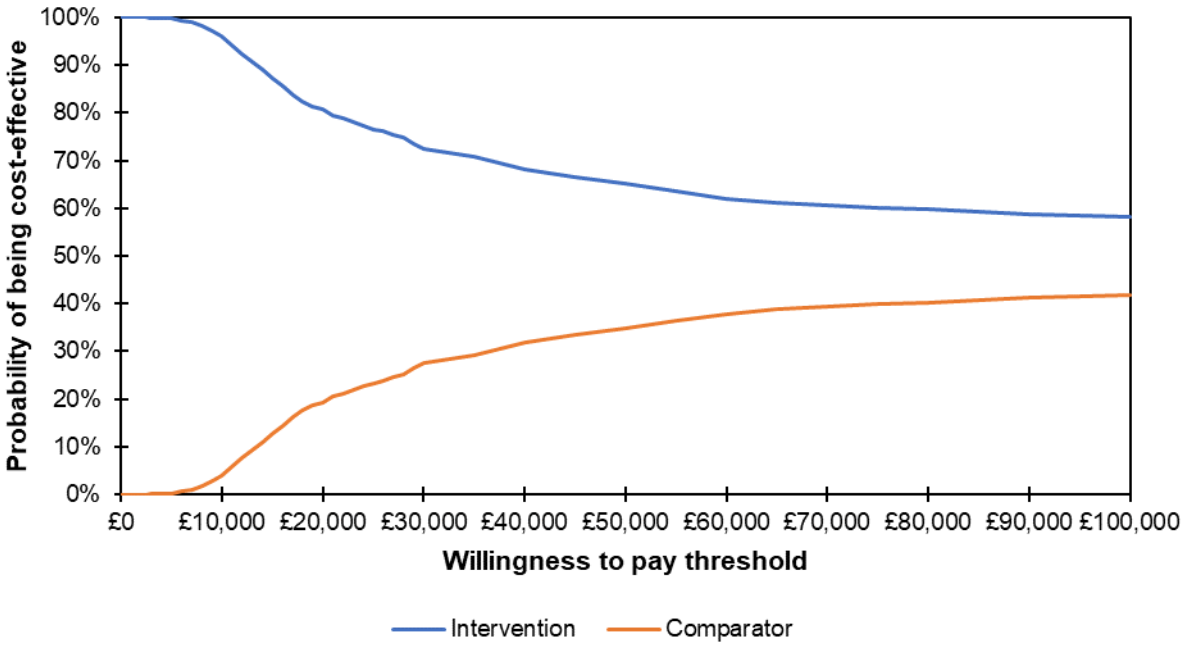


Figure 2: (Figure 8 in EAR, Page 153) Cost-effectiveness acceptability curve-HeartLogic

The cost-effectiveness acceptability curve (CEAC) (Figure 2) shows that the probability cost-effectiveness for HeartLogic RMS at willingness to pay (WTP) value of £20,000 was 81% whereas at £30,000 the probability cost-effectiveness was 73%.

Table 4: (Table 47, Page 155) Scenario analyses cost-effectiveness results

Label	Scenario	Device-Cost-effectiveness			
		CorVue	**HeartInsight**	**HeartLogic**	**TriageHF**
A	LoS in the intervention equal to that of comparator in the base case	-	-	Dominant	-
B	Lower hospitalisation costs (£666.43)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.98 will have cost-effective RMS)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.808 will have cost-effective RMS)	Dominant	Dominant
C	Higher costs of staff time (£58 per hour)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.99 will have cost-effective RMS)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.96 will have cost-effective RMS)	Dominant	Dominant
D	LoS in the intervention equal to the comparator	-	-	Dominant	-
E	Medtronic Survival rates	Cost increasing (threshold analysis shows that IRR hospitalisation <0.99 will have cost-effective RMS)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.93 will have cost-effective RMS)	Dominant	Dominant
F	Increased IRR hospitalisation	-	-	Dominant	Dominant

	halfway between the base case value and 1				
G	Doubled Alert monitoring time	Cost increasing (threshold analysis shows that IRR hospitalisation <0.99 will have cost-effective RMS)	Cost increasing (threshold analysis shows that IRR hospitalisation <0.95 will have cost-effective RMS)	Dominant	Dominant
H	Excluding uncertainty in Mortality in the PSA	-	-	Dominant (the probability of cost-effectiveness was 100% at WTP value of £20k and £30k; however, in the basecase the probability was 88% at £20k, and 77% at £30K WTP value)	Dominant (the probability of cost-effectiveness was 100% at WTP value of £20k and £30k; however in the basecase the probability was 85% at £20k, and 76% at £30k WTP value)
I	Calculating utility decrement as relative values instead of absolute differences	Cost increasing	Cost increasing	Dominant (QALYs gained 0.02 which is higher than 0.01 observed in the basecase analysis; the probability of cost-effectiveness was 82% at WTP value of £20k and 73% at WTP value of £30k; however, in the basecase the probability	Dominant QALYs gained 0.02 which is higher than 0.01 observed in the basecase analysis)

				was 81% at £20k, and it was also 73% at £30K WTP value	
J	Assuming only 50% of the alerts in the intervention group require in-office follow-up visits and 25% of the alerts only require non-face to-face contacts	Cost saving	Cost increasing	Dominant	-

2. Additional scenario analyses post EAG report production

The EAG also conducted additional scenario analyses on unscheduled follow-up visits i) for all devices except HeartLogic, assuming 50% of the alerts would result in face to face in-office follow-up visits and the remaining 50% will have remote non-face-face to consultation ii) for HeartLogic only based on the evidence from Baguda et al 2021, provided in stakeholder comments. The list price for HeartLogic is again used here.

Table 5: Additional scenario analyses based on stake holder comments

Label	Scenario	Device-Cost-effectiveness			
		CorVue	**HeartInsight**	**HeartLogic**	**TriageHF**
A	Assuming only 50% of the alerts in the intervention group require in-office follow-up visits and 50% of the alerts only require non-face to-face contacts	Cost saving	Cost increasing	-	Dominant
B	Using evidence from De Juan Baguda et al. (2021) suggested in consultation comments: 19% of the alerts in the intervention group require in-office	-	-	Dominant	-

	follow-up visits and 81% of the alerts only require non-face to-face contacts				

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices

External Assessment Report (EAR) and economic model – Collated Comments

Diagnostics Advisory Committee date 16 April 2024

Any confidential sections of the information provided should be underlined and highlighted. Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in blue and all that is 'academic in confidence' in yellow.

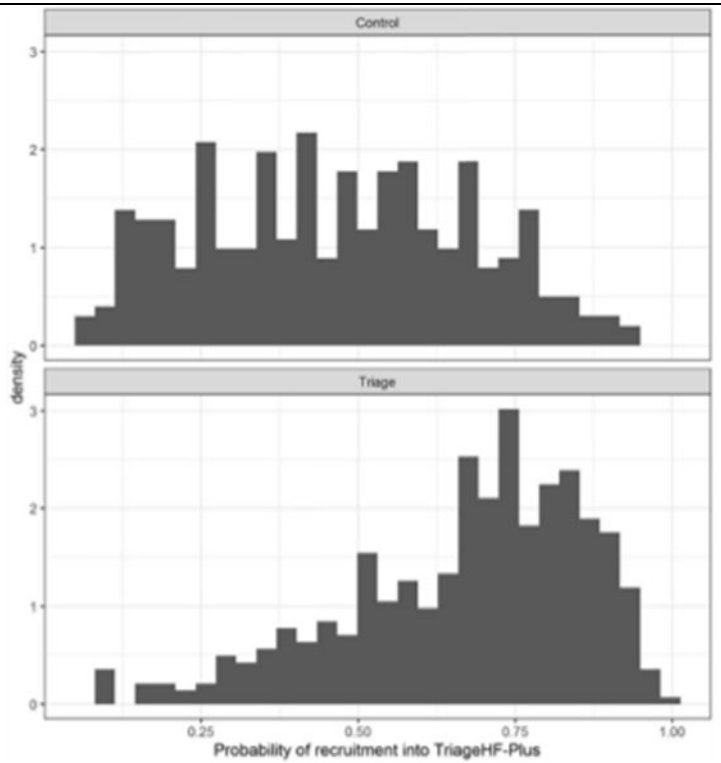
Comment no.	Name and Organisation	Page no.	Section no.	Comment	EAG Response
1	Ralphael Oghagbon Medtronic	All	All	We thank the assessment group for their comprehensive analysis and report, which came to similar conclusions regarding the cost-effectiveness of TriageHF as in our own evidence submission. TriageHF Plus is the only algorithm-based remote monitoring platform that has UK NHS real-world comparative evidence, and our over-arching comment on the EAR is we request more weighting should be given to the five UK studies which reported evidence for TriageHF implementation. We understand the NICE RWE framework recommendations are relevant to the assessment of this evidence, however, it is unclear how guidance from this framework has been applied in this assessment. We recognise the Assessment Group's concern with risk of bias due to the absence of randomised controlled trial data. We have provided further information to address concerns identified with the (non-randomised) comparative study for TriageHF in the UK.	We thank the company for their comments. Regarding the RWE framework, there is no recommendation regarding the evaluation based on location. In our review of the evidence we did not place weight on where the studies took place. It is mentioned in section 3.2 that the majority of TriageHF studies were conducted in the UK. We do agree that this is something that should be mentioned further. We have therefore added text to section 7.1.1 Clinical effectiveness to state this was the case: "It is worth noting that a number of studies evaluating TriageHF

					were undertaken in a UK setting (n = 5)." Regarding the bias, this was not solely due to the lack of RCT evidence. We appreciate there is RWE, however, there was still a lack of comparative studies (e.g. propensity matched cohorts).
2	Ralphael Oghagbon Medtronic	41, 47- 48 and 103	3.2, 3.4.4 and 3.7.8	It is unclear what weighting if any has been given to UK real-world vs. evidence from non-UK healthcare setting. A key strength of TriageHF Plus is that, compared to other studies submitted as supporting evidence within this DAP, it is a multicentre study conducted exclusively within the UK, specifically within an NHS setting; utilising real-world data to generate real world evidence. This distinction is important as international studies often fail to reflect the diverse demographics of the target population and overlook the importance of testing the intervention in a UK NHS setting. The current real-world study is also reflective of the diverse HF team structures that exist within the NHS, including community, integrated HF and hospital-based HF service. Five studies provide evidence in support of the successful implementation of TriageHF-enabled care pathways in the UK: Ahmed 2022 (Greater Manchester), Bachtiger 2021 (London), Debski 2021 (Blackpool), Garner 2022 (Merseyside) and Sammut-Powell 2022 (Manchester).	Please see the response to comment 2 regarding text highlighting the number of UK based studies. We feel this is sufficient.

				As TriageHF Plus is the only RM platform that has UK NHS real-world comparative evidence we would recommend that more weighting should be given to this as reflective of use and outcomes within the NHS which reflect the complexities unique to the this healthcare setting, in adherence with NICE RWE framework recommendations (Assessing data suitability section) It would be appropriate to cover this in Section 3.7 Implementation of outcome results and in Section 7 Discussion – Strengths and Limitations.	
3	Ralphael Oghagbon Medtronic	46 - 47 124	3.4.3 and Table 11 Table 32	One of the three comparative studies for HeartLogic is Treskes 2021. The ROBINS-I risk of bias assessment for this study is 'serious'. this was a pre-post study design in which 44 out of the 74 patients had a 'de novo' (initial) CRT-D implantation between the pre- and post- time period: CRT is proven to reduce mortality and HF hospitalisations, so a treatment effect of CRT should have been considered to have confounded the treatment effect of using HeartLogic. We believe this constitutes a 'critical' risk of bias. Secondly, Treskes (2021) reported patients were recruited between 3 January 2018 and 21 December 2019, and the study had pre-activation and post-activation periods of 12 months for usage of HeartLogic. The World Health Organisation declared the COVID-19 outbreak a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March 2020. The end date for follow-up of the HeartLogic post-activation is not reported, so it is unclear if 21 December 2019 is the end date, or if the follow-up period for some patients has overlapped with the COVID-19 pandemic. There would be a significant risk of confounding for a pre-post analysis of hospitalisation rates in which the 'post' time period overlapped with the COVID-19 pandemic. **On this basis we request that the EAG review and adjust the risk rating.** The treatment effect for HeartLogic from Treskes 2021 was used in the cost-effectiveness analysis for HeartLogic (rate ratio 0.282). It is implausible for the entire	We thank the company for their opinion on the risk of bias rating of this study. However, we are happy with our evaluation of the study. Critical appraisal such as this is subjective and we have followed standardised systematic review processes (i.e. two reviewers agreed on the rating and if required a third adjudicated). The treatment effect (rate ratio 0.282) was used in the

				treatment effect observed in Treskes 2021 to be attributed to HeartLogic considering a reduction in HF hospitalisations is expected due to de novo implantation of a CRT device in 59% (44/74) patients. **We strongly advise more appropriate reference sources used, please see comment in modelling section for more detail (Issue No.3, table 32)**	EAG model. It is correct that 59% of patients had a de novo implantation during the pre-activation period. Treskes et al. concluded that the majority of the reduction in hospitalisations was attributable to the algorithm activation. However, we conducted threshold analysis on this parameter and have reported that HeartLogic and TriageHF only needed to reduce hospitalisations by a few percent in order for them to be dominant (See section 7.1.2). Therefore, for example, whether the rate ratio is 0.282 or 0.6 makes no difference to the cost-effectiveness conclusions.
4	Ralphael Oghagbon Medtronic	48	3.4.4	Re: "*Ahmed et al., the only study to provide comparative data for Triage-HF is at critical risk of bias, due to missing information, including whether propensity score matching was successful and the majority of hospitalisations being unrelated to heart failure or cardiovascular disease*."	We thank the company for providing this extra information. Of course, the appraisal is based on available information. This information is helpful for

				We thank the EAG for raising this important point. First, our approach was to perform inverse probability of treatment weighting (IPTW) through the propensity score – we did not perform matching on the propensity score. Second, we include below a figure which shows the distribution of propensity score across both groups. As can be seen, there is overlap in the propensity score distribution across groups, which is a key assumption of the method. The propensity score models were fit conditional on several key variables, and we have no reason to expect there would be large differences across the groups in these variables after weighting on propensity score. We do, however, recognise that there may be differences in other variables not included (both observed and unobserved) and we recognise that the findings of this analysis are dependent on the validity of the assumptions underlying the analysis. Therefore, we would like to highlight that we performed the analysis in several ways, each making slightly different assumptions, and all of which led to the same overall conclusion. However, we currently do not have access to the data on residual differences in baseline characteristics post weighting due to a data breech lockdown. We will provide this information if possible during the appraisal.	context. We have adapted the phrasing to be: “Only a single study for TriageHF was comparative, providing **real-world** data on hospitalisations **in a UK setting**. However, this study was rated at critical risk of bias using ROBINS-I.”

				 Further, the EAG's comment on "a majority of hospitalisations being unrelated to heart failure or cardiovascular disease" raises a crucial point with respect to heart failure, and the management of heart failure patients with muti-parametric algorithms.	

				Previously published data has demonstrated the utility of device alerts to identify patients at elevated risk of non-heart failure events, such as exacerbations of COPD, respiratory infections, and arrhythmias. In particular, patients with a TriageHF alert have a 4.2 increased relative risk of 30-day all-cause hospitalisation. The leading cause for these admissions included respiratory infections and sepsis. Given that the TriageHF algorithm also includes some non-specific components (heart rate, physical activity) it is not surprising that a TriageHF alert preceded non-cardiovascular admission. Building on data from previous studies, the steering committee for TriageHF Plus deliberately chose all-cause hospitalisations as the endpoint to understand the utility of TriageHF Plus not just as an HF management tool, but more broadly as a patient management tool. People with HF often have multiple co-morbidities and identifying an exacerbation of COPD and avoiding any hospitalisation is beneficial to both patients and healthcare systems alike. Supporting the notion that TriageHF-based management can lead to a reduction in hospitalisations of non-HF and non-CV causes, clinicians in the AiC Ahmed study responded to alerts with a broad range of actions, including referral to other providers, a range of clinical investigation (blood tests, ECG, chest x-ray and echocardiogram), and lifestyle advice (see Table 3: Clinical actions undertaken as part of the TriageHF Plus pathway). Further, clinicians involved in TriageHF Plus study leveraged the TriageHF algorithm to identify patients for transition to palliative care. After this transition, patients received a different category of treatment, and thus also leading to avoided hospitalisations. **In summary, we request that the EAG considers these data holistically and provides a concluding statement that is more reflective of the nature of the**	

				evidence. Specifically, we request whether the EAG will consider re-wording this statement to: "***Ahmed et al., provide the only real-world comparative data with their TriageHF dataset, although these data are deemed to be at critical risk of bias due to missing information. Although the majority of hospitalisations were unrelated to heart failure or cardiovascular disease, all-cause hospitalisations is a relevant endpoint in examining the utility of a patient management tool in people with HF with multiple comorbidities, and the documented clinical actions taken in response to alerts were broader than only HF or CV disease."***	
5	Ralphael Oghagbon Medtronic	48-50	3.5.1	Standard epidemiological measures of algorithm accuracy (sensitivity, specificity, PPV, NPV) are routinely used to assess the accuracy of an algorithm. However, differences between studies in the definition of the event of interest are crucial to factor in when making comparisons of diagnostic performance (sensitivity, specificity, false positives) between studies and technologies. In section 3.5.1, the EAG summarised the evidence regarding the prognostic accuracy of each heart failure risk algorithm. We wish to highlight to the Committee that this section, and associated statements elsewhere in the document which assessed HeartLogic to have "the highest and most consistent accuracy measures (i.e. sensitivity of ≥70%)," (first paragraph page 10, second paragraph page 152, first paragraph page 154) may be invalid due to a lack of context given regarding: 1) **Differences in events included in the outcome definition**: The HeartLogic studies which characterised sensitivity had an "event" definition of either an inpatient hospitalisation or outpatient visit in which acute heart failure was treated, whereas the TriageHF studies more narrowly defined an "event" as	We agree that there is context required. Therefore, throughout the document we have included the caveat that this was accomplished using a composite outcome. While highlighting that TriageHF studies commonly utilised a single, non-combined, endpoint.

				only including inpatient hospitalisations. Applying a broader event criteria would increase the reported sensitivity of TriageHF. Regarding HeartLogic, MultiSENSE (Boehmer 2017) was the first study conducted and its definition of worsening HF events included outpatient visits as well as hospitalisations. This was copied by subsequent HeartLogic studies. From multiple studies we have checked, outpatient visits make up a majority of events in the HeartLogic studies (Boehmer 2017, Treskes 2021, Feijen 2023). Regarding TriageHF, the Assessment Group report rightly identified "substantial heterogeneity in TriageHF prognostic accuracy measures", however, we believe the report fails to explain the impact of these differences: the majority of TriageHF studies defined an event (for purposes of sensitivity or specificity) as a hospitalisation (all-cause, CV- or HF-related). The exclusion of the more numerically common occurrences of HF-related outpatient visits likely explains the lower sensitivity results reported. To illustrate, Table 15 in the Assessment Group's report summarises predictive accuracy results, and the sensitivity of TriageHF is reported as 87.9% (Bachtiger 2021) and 98.6% (Ahmed 2020) from the two studies which defined an event as 'worsening HF' based on the presence of symptoms (not solely hospitalisation). 2) **Differences in time window after high alert:** The TriageHF studies cited by the EAG as having "low sensitivity" (Reference #s: 33, 66, 67) examined HF, cardiovascular, and non-HF inpatient hospitalisation that occur *within 30 days of high risk alert*. While the time window for sensitivity assessment is not reported in the HeartLogic studies, the median time from high status alert to HF event was reported to be 34 days in Reference 56, and 38 days in	

				Reference 73. Thus, a broader event window was clearly applied in the HeartLogic studies. Therefore, given that less severe events were included in the criteria used to evaluate sensitivity of the HeartLogic algorithm, it is invalid to make a direct comparison to TriageHF. **Thus, we respectfully request that any language concluding HeartLogic to have "the highest and most consistent accuracy" to be removed accordingly.**	
6	Ralphael Oghagbon Medtronic	55	3.5.1 Table 15	Regarding the choice of endpoint for sensitivity and specificity results in a study for HeartLogic, it is reported that Treskes (2021) defined an event as hospital admission. However, our reading of the study identified "the same definitions were applied as in the MultiSENSE study.", meaning worsening HF events identified in hospitalisations or outpatient visits. This relates to an above comment: we identified only one study for HeartLogic that reported sensitivity and specificity for an endpoint of hospitalisation (Santobuono 2023), whereas the majority of TriageHF studies reported sensitivity and specificity for hospitalisation events only. **Please can the table 15 be corrected to reflect this.**	"the same definitions" is in reference to the sensitivity, specificity and unexplained alert rate. The primary endpoint was total number of hospital admissions for decompensated HF. We will therefore not be making this change.
7	Ralphael Oghagbon Medtronic	58, 60	3.5.2 and Table 16	It is reported that only 1 study reported information on false positives for TriageHF (Garner 2022). However, another study (Zile 2020, reference 74) used the term 'unexplained detection' interchangeably with the term false positive: "The computed unexplained detection rate was calculated as the FPs per year of patient monitoring across all patients". The rate of 0.5 alerts/patient/year is lower than the FP rates reported for other technologies. **Please can the EAG include the Zile paper, update table 16 and correct the report to reflect this.**	We thank the company for highlighting this information. This has been included in section 3.5.2 and table 16.

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8	Ralphael Oghagbon Medtronic	62	3.5.3	The statement that "No studies reported unexplained alert rates for the TriageHF algorithm" is incorrect. Zile 2020 (reference 74) reported an unexplained alert rate of 0.5 alerts/patient/year in a large population of TriageHF patients. Further, there appears to be no difference between 'unexplained alert rates', 'unexplained detection' and 'false positives' within these studies these are used interchangeably. **Please can the EAG consider merging these outcomes, and ensure the Zile 2020 study is included in the reporting?**	We have provided a sentence to state that Zile et al 2020 reported unexplained detections and false positive rates, using the term interchangeably. We agree that these terms have most likely being used interchangeably in places. However, as we have defined the unexplained alert rates and provide the evidence based on the available study descriptions, we will keep the sections separate.
9	Ralphael Oghagbon Medtronic	65, 69- 70	3.5.4 and Table 18	The comparative study for TriageHF (Ahmed et a, AiC) reported clinical actions taken in response to TriageHF alerts (see Table 3 of the AiC manuscript), however, this study appears to be omitted from Section 3.5.4. Changes to clinical management, including omission from Table 18. **We ask that the EAG include evidence from Ahmed AiC study in the text and table 18.**	Thank you for highlighting this, we have implemented this change to section 3.5.4 and table 18. We have added detail regarding device availability of the algorithms to section 7.2.2.

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10	Ralphael Oghagbon Medtronic	All 94	All 3.7.1	Informcation is included in the Assessment Group report about the compatible CIEDs for each algorithm-based remote monitoring system, however, an important omission elsewhere in the report is the point that HeartInsight (Biotronik) and HeartLogic (Boston Scientific) algorithms are not available on CRT-P devices currently, whereas the TriageHF algorithm is available on CRT-P, CRT-D and ICD devices. According to the most recent National Audit of Cardiac Rhythm Management implants in the UK (2021/22 data), there were 6,000 implants of ICDs, 5,309 implants of CRT-Ds and 5,694 implants of CRT-P devices. The NICE Technology appraisal guidance TA 314 recommends CRT-P as a treatment option for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less. In patients with NYHA Class IV heart failure, CRT-P is the only recommended device (not ICD or CRT-D). **Please may the EAG include the availability of the technology per CIED type (Section 3.7.1. seems an appropriate place). We believe this is so critical it should be highlighted in summary sections of the report as well.**	The EAG agree that this should be included. Added text to identify that TriageHF and CorVue are the only algorithms that can be used in CRT-P CIEDs: “The EAG also note that two of the alrogithms (HeartLogic and HeartInsight) are currently not available on all CIEDs. They are available on ICD and CRT-D devices, while TriageHF and CorVue are also available on CRT-P devices. Currently, only CRT-P devices are recommended for those with NYHA class IV HF.”
11	Ralphael Oghagbon Medtronic	150	7.1.1.	Wew have several requests regarding the summary paragraph about TriageHF, which is reproduced below for ease of understanding the comments: *There was substantial heterogeneity in TriageHF prognostic accuracy measures, estimates of sensitivity and specificity varied widely between studies. False positive rates were only reported in one study and were relatively low. Only a single study for TriageHF was comparative, providing data on hospitalisations. However, this study was rated at critical risk of bias using ROBINS-I. The remaining evidence was single cohort studies comparing risk status (high, medium and low). There is evidence for an increased risk of HF events when in high risk status compared to low risk status*	We thank the company for their feedback on the wording provided. However, we feel that the current wording reflects their concerns about the current evidence. We have therefore not implemented this change.

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				(e.g. hospitalisations). The lack of comparative data means we cannot draw conclusions on TriageHF use compared to standard care (i.e. no algorithm). As per Comment 6 above, we request a correction to the statement that false positive rates were only reported in one study. **We request the EAG or Committee to consider to amend the wording "lack of comparative data means we cannot draw conclusions on TriageHF use compared to standard care" to reflect Comments 2 and 3 provided above. In our opinion, a statement to reflect there is uncertainty about the magnitude of the treatment effect for TriageHF would be more appropriate than the current statement.**	
12	Sally Thompson Hilpert BIOTRONIK SE & Co KG	P3.	Abstract Results	*There was reasonable evidence to suggest HeartLogic and TriageHF can accurately predict heart failure events. There was only a single HeartInsight study, which suggested similar accuracy to the other algorithms.* BIOTRONIK requests to add the word '*published*' after the word "*single*" and before "*HeartInsight*". Reason: There was an additional META-COHORT submitted to NICE in 2023 as academic in confidence, which is planned for publication.	We have included the phrase "published" as requested.
13	Sally Thompson Hilpert BIOTRONIK SE & Co KG	P4	Abstract Conclusions	*Only a single study was identified for HeartInsight, therefore there is insufficient data to draw conclusions on prognostic accuracy and the benefits on clinical and intermediate outcomes.* BIOTRONIK requests to add the word '*published*' after the word "*single*" and before "*study was identified for HeartInsight*".	We thank the company for their comments and highlighting the meta-cohort data. We have included the term "published" as requested.

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				Reason: [redacted] This result is consistent with the secondary endpoint of the SELENE-HF study and underscores the prognostic accuracy of HeartInsight in a larger, mainly European, patient population. Furthermore, a recently published meta-analysis of 2,050 patients from nine previous trials has shed further light on the behaviour of the HeartInsight algorithm and its components before worsening of heart failure hospitalizations (WHFH) (Botto et al. 2024). Twelve-week trends before 369 WHFH were compared with trends in patients without WHFH. The HeartInsight HF Score was significantly higher 12 weeks before WHFH than in the no event group, and it further increased by 22% until the event. The seven algorithm components showed different behaviour and contribution, reflecting different mechanisms or different stages in the decompensation process.	
14	Sally Thompson Hilpert BIOTRONIK SE & Co KG	P4	Abstract Conclusions	Suggest to remove "*a*" after "*It is* …".	We have removed "a".
15	Sally Thompson Hilpert BIOTRONIK SE & Co KG	P10	Scientific summary	*HeartInsight reported comparable accuracy to HeartLogic and TriageHF (sensitivity of 65%); however, this was only based on one study, therefore it is uncertain whether further studies will replicate these findings.*	We have included "published" as requested.

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				BIOTRONIK requests to add the word '*published*' after the word "*one*" and before "*study was identified for HeartInsight*". Reason [redacted]	
16	Sally Thompson Hilpert BIOTRONIK SE & Co KG	P44	3.4.2 Risk of bias assessments for HeartInsight	*One prospective cohort evaluated the prognostic accuracy in the development (sensitivity, specificity) and validation (sensitivity, specificity, NPV and PPV) of HeartInsight. This study was judged to be at high risk of bias due to concerns around the conduct or reporting in the analysis (such as missing data and the statistical analysis) (Table 8).* BIOTRONIK would be happy to address any questions related to the original manuscript, providing they do not relate to topics protected by intellectual property laws.	Thank you for offering to provide additional information. Two reviewers followed a systematic process to assess the risk of bias using the recommended PROBAST tool. Based on the available information reported by D'Onofrio we were unable to ascertain appropriate handling of missing data, whether complexities in the data were accounted for, and lastly, if relevant performance measures were evaluated appropriately. The reviewers have confirmed high risk of bias but you may wish to

					discuss these factors at later stages with committee.
17	Sally Thompson Hilpert BIOTRONIK SE & Co KG			*The lack of hospitalisation outcome evidence for CorVue or HeartInsight means it is not possible to produce cost-effectiveness estimates for these technologies.* In the case of HeartInsight, we ask that the reporters consider extending this sentence to include … "*except under the assumption, with similar sensed components, that the clinical benefits are similar to TriageHF.*" It should be noted by the committee that at least one of the studies evaluated by the committee (Manage-HF, Hernandez et al) adopted a broad definition of HF hospitalization i.e. A HF hospitalization was defined as a Clinical Event Committee–adjudicated hospitalization with a primary or secondary cause of HF. Untangling whether HF is a primary or secondary reason for admission can be complex, so this is not an unusual approach to adopt. However, the definition adopted i.e. primary only or primary and secondary events will, of course, influence the findings. Furthermore, in the study by Treskes et al, it is our understanding that the patients included were not using prior remote monitoring and that the benefit demonstrated is a combination of the use of remote monitoring plus HeartLogic, not HeartLogic alone. The base rate of HFH prior to intervention were high in this study, suggesting focus on a patient population in most need of additional monitoring.	Thank you for the comment. The scope of this study includes evaluating the effectiveness and cost-effectiveness of each algorithm remote monitoring versus remote monitoring with no algorithm. It could not be assumed that different CIEDs had equal effectiveness. In the absence of evidence for hospitalisation for CorVue and HeartInsight, we made an assumption of no difference, for which threshold analysis was also conducted. We agree with your comment that a broad definition of HF hospitalisation was used, however, there was no evidence to untangle the HF

					hospitalisation as primary or secondary. Treskes et al 2021 reports that "All patients were provided remote monitoring of their ICD via LATITUDE (Boston Scientific) and signed an informed consent agreeing to undergo remote device monitoring. Furthermore, a technical service, organized by the company providing the remote monitoring system, was available in case of technical questions. Patients were followed via two ways. First, regularly scheduled outpatient clinic visits (standard care). Patients were treated and followed-up in accordance with ESC guidelines." From this it appears that remote monitoring was feasible prior to HeartLogic activation, and the text does

					not indicate that remote monitoring was not conducted prior to HeartLogic activation. To assess for the impact of any uncertainly in the evidence from Treskes et al, we conducted threshold analysis HF hospitalisation. (See the response to point 3 above), however the results indicated no change in conclusion of our economic evaluation for HeartLogic.
18	Sally Thompson Hilpert BIOTRONIK SE & Co KG	pp 54, 56, 60, 63, 97, 245		D'Onofrio (2022), 2nd column: *Prospective cohort (overall n = 744; validation n = 378)* Please, revise the numbers as they correspond to male patients only (see Table 2 in D'Onofrio publication). Numbers on *all* patients *analysed* are as follows (see Figure 1 in D'Onofrio publication): "*Prospective cohort (overall n = 912; validation n = 459)"*	We have corrected this error in reporting of the number of patients in the study.
19	Sally Thompson Hilpert BIOTRONIK SE & Co KG	P102	3.7.5 Software failure rate	*HeartInsight observed 39 of 918 patients, in a single cohort, had connection issues for home monitoring remote transmissions as they could not establish sufficient GSM (Global System for Mobile communication) coverage.*	We thank the company for this comment and agree that the information presented does not represent the whole picture. We have adapted to

				BIOTRONIK is of the opinion that this sentence alone could be misleading and requests that it be extended according to the manuscript. Suggestion is: *"The median remote monitoring rate was 91.3% of days (interquartile range, 83.5–95.8%) in the derivation cohort and 90.8% (83.1– 95.5%) in the validation cohort. In 39 of 918 patients (4.2%) connection for Home Monitoring remote transmissions could not be established due to insufficient GSM coverage."* It is also important for the committee to note that with the BIOTRONIK Home Monitoring system transmission occurs daily, whereas with the other technologies transmission occurs weekly (HeartLogic) or even less frequently (TriageHF). Therefore, the implications of a single missing transmission are likely to be different when it comes to the timely identification of patients at higher risk of worsening HF events.	include the median remote monitoring percentages as well. We also feel that highlighting the daily transmission is warranted. We have therefore included a statement in the discussion: "The EAG do note that HeartInsight is the only monitoring system that provides daily transmissions, whereas the other technologies occur less frequently. This could have implications for missing data."
19	Sally Thompson Hilpert BIOTRONIK SE & Co KG	P152	7.2.2 Limitations	*The evidence for HeartInsight suggests the accuracy of the algorithm is moderate but is yet to be further validated in external studies. The lack of evidence for this algorithm, both single cohort and comparative data, means that the EAG cannot provide any recommendations on its potential use in clinical practice*. BIOTRONIK proposes to modify this text to read as follows: *"Only one published validation study was found for HeartInsight, which suggests that the algorithm is capable of predicting worsening heart failure events but requires further validation in an independent patient population. The primary validation study*	We have included a statement that there is crossover of the prognostic values between the algorithms: "However, the one published study did provide similar prognostic accuracy measures to the other algorithms, as evidence by

				results in terms of sensitivity and specificity are within a similar range to alternative monitoring solutions." Reason: The sensed variables associated with HeartInsight are comparable to those included in TriageHF, although how the algorithm processes the information is different. All the technologies evaluated are applied in a similar manner in clinical practice i.e. the workflow following an alert is similar. Although the evidence underscoring the benefits of HeartInsight itself is limited, there exists a wide body of evidence to underscore the benefits of BIOTRONIK Home Monitoring (of which HeartInsight is an enhancement facilitating HF management) for patients, providers and the wider health care system, as captured in our responses to the earlier questions posed by NICE in 2023 (see text submitted in May 2023, copied below). Furthermore, BIOTRONIK Home Monitoring is the only remote monitoring system designed for alert-based care based on its continuous connectivity (Ferrick et al. 2023), which is facilitated by daily data transmission with minimum patient interaction and industry-leading patient compliance driven by our "plug-and-play" CardioMessenger. BIOTRONIK provides a clinically proven remote monitoring solution (Varma et al. 2021; Hindricks et al. 2017; Hindricks et al. 2014; García-Fernández et al. 2019) for optimising CIED management workflow and tailoring alerts to each patient's clinical needs, which are recommended to save time on non-clinical and non-actionable alerts. Adding the HeartInsight algorithm enhances this capability on BIOTRONIK Home Monitoring with a multiparametric predictor, allowing for earlier intervention on patients with compatible devices.	the crossover of confidence intervals."

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Diagnostics Advisory Committee date 16 April 2024

20	Sally Thompson Hilpert BIOTRONIK SE & Co KG			**Text submitted in May 2023** A key study highlighting the benefits of BIOTRONIK Home Monitoring is the IN-TIME study (Hindricks et al. 2014), the conclusions of which were supported in a later meta-analysis that included two additional pivotal BIOTRONIK studies, ECOST and TRUST (Hindricks et al. 2017). The IN-TIME trial was the first to demonstrate that automatic, daily, implant-based, multiparameter telemonitoring can significantly improve clinical outcomes for patients with heart failure and that such telemonitoring is feasible in clinical practice. In the pooled analysis, use of BIOTRONIK Home Monitoring with daily data transmission was shown to reduce all-cause mortality and the composite endpoint of all-cause mortality or WHF hospitalisation. It was concluded that similar magnitudes of absolute risk reductions for WHF and CV endpoints suggested that the benefit of Home Monitoring is driven by the prevention of heart failure exacerbation. The IN-TIME study was also the first to demonstrate the importance of a care pathway in using remote monitoring data to impact on patient outcomes. In the IN-TIME study, in parallel to patient level data being reviewed by study investigators according to their clinical routine, transmitted data were reviewed by a central monitoring unit composed of trained study nurses and supporting physicians, located at the Heart Center Leipzig (Germany). The role of this unit was to ensure the awareness of investigational sites to pre-defined medical events. A clinical response to telemonitoring observations was done at the discretion of investigators. **Literature** 1. Ferrick AM, Raj SR, Deneke T, Kojodjojo P, Lopez-Cabanillas N, Abe H et al. 2023 HRS/EHRA/APHRS/LAHRS expert consensus statement on practical management of the remote device clinic. Heart Rhythm 2023.	We thank the company for highlighting this information regarding home monitoring. However, the EAG only considered evidence for the algorithms and not home monitoring alone.

				2. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): A randomised controlled trial. The Lancet 2014; 384(9943):583–90. 3. Hindricks G, Varma N, Kacet S, Lewalter P, Soogard P, Guedon-Moreau L et al. Daily remote monitoring of implantable cardioverter-defibrillators: Insights from the pooled patient-level data from three randomised controlled trials (IN-TIME, ECOST, TRUST). European Heart Journal 2017; 38:1749–55. 4. Botto et al. Predicting worsening heart failure hospitalizations in patients with implantable cardioverter defibrillators: is it all about alerts? A pooled analysis of nine trials. 2024 Feb 1;26(2):euae032. doi: 10.1093. 5. Hernandez et al. Multiple cArdiac seNsors for mAnaGEment of Heart Failure (MANAGE-HF) – Phase I Evaluation of the Integration and Safety of the HeartLogic Multisensor Algorithm in Patients With Heart Failure. J Card Fail. 2022 Aug;28(8):1245-1254. doi: 10.1016. 6. Treskes et al. Clinical and economic impact of HeartLogic™ compared with standard care in heart failure patients. ESC Heart Fail. 2021 Apr;8(2):1541-1551. doi: 10.1002	
21	Claire Duxbury Boston Scientific	All	All	We thank the Newcastle Technology Assessment Review Group for their efforts in developing a useful summary of some key aspects of monitoring heart failure deterioration in patients with cardiac implantable electronic devices. We are pleased to see HeartLogic recognised for having the highest and most consistent accuracy measures, with adequate to high sensitivity and specificity for the prediction of heart failure events. For ease, we summarise our key issues highlighted in our section A comments below as follows: 2. Bias assessment for HeartLogic prognostic accuracy studies	The EAG thank the company for their feedback.

				3. Remote monitoring versus HF algorithms 4. Prognostic versus implementation outcomes 5. Missing & new evidence for HeartLogic 6. Errors in reporting of clinical data 7. Additional clinically relevant observations from HeartLogic real-world evidence a. HF events b. Hospitalisations c. Patient experience d. Changes to clinical management & interventions following an alert e. Alert response rates f. Number of monitoring reviews 8. Under-recognition of clinical benefits of prognostic accuracy 9. Assumptions on unscheduled follow-up visits 10. Description of HeartLogic technology 11. Incorrect brand name references 12. Device costs 13. Inequitable presentation of algorithms in scope	
22	Claire Duxbury Boston Scientific	45-47	3.4.3	**Bias assessment for HeartLogic prognostic accuracy studies.** We note that the EAR reports that all studies evaluating prognostic accuracy outcomes for HeartLogic were determined to be at high risk of bias due to "a lack of robust analysis, and small number of included participants with the outcome" (section 3.4.3, page 45). We would like to draw attention to some specific aspects of some of these studies: • We were particularly surprised to see the MultiSENSE study, the results of which are presented in Boehmer et al. 2017, was determined to be at high risk of bias. The MultiSENSE study was a multi-center, prospective study with pre-specified analyses and performance targets designed to develop	We thank the company for their insightful comments. Quality appraisal of studies is subjective. However, we have followed standard systematic review protocols and implemented the tools using the guidance available.

				and validate the multisensor HeartLogic algorithm. Due to the robustness of the study design, we can only assume that the primary concern lies in the number of subjects. The study included 900 patients (500 in the development set and 400 in the test set). The sample size was determined based on statistical calculations to provide 88% power for demonstrating for the sensitivity performance goal and 80% power for the unexplained alert rate performance goal. It is noted that the PROBAST tool emphasizes the importance of the number of subjects who experience an outcome event more so than the overall sample size. However, it should also be considered that in the context of heart failure, multiple HF hospitalizations may occur in the same patient during the course of follow-up, and given the negative prognosis associated with any HF hospitalisation, there is value in identifying all instances of worsening HF that a patient experiences. Therefore we think it is important for the EAR to take into account not just the number of patients experiencing HF events, but the total number of HF events that occurred during the study. Notably, in the development dataset, 64 patients experienced 127 HF events (with 96 of these events being usable for the analysis). In the test set, there were 65 HF events (with 50 being usable for analysis). • Given the emphasis on sample size, we were also surprised to see the analysis from Wariar et al. ranked at high risk of bias, as this analysis included 435 HF events. Table 15 of the EAR suggests that HF events were "undefined". This analysis used real-world Medicare claims data to identify HF events and these were defined as such: "Claims HF events were defined using primary HF diagnosis codes (DRG 291-3, I50.xx) and included inpatient events as well as outpatient events with intravenous diuretic therapy." The codes used to identify HF events would therefore be inclusive	As per PROBAST guidelines, if one domain is found to be at high risk of bias, the overall rating is also high. Two reviewers independently considered the available information reported by Boehmer et al., 2017 and Wariar, we found the model performance measures were not evaluated appropriately. We agree that the study reported by Wariar et al. had a reasonable number of participants with the outcome. Two reviewers undertook a quality appraisal of studies reported by Treskes and Feijen, and we found Treskes to be at serious risk of bias due to a lack of adjustments for confounding

				of HF hospitalisations as well as outpatient visits where IV diuretic therapy was administered. • We would also like to highlight a more recently published manuscript that was not included in the initial EAR which provides the results of our FDA-mandated post-approval analysis. This manuscript, submitted as supporting material to these comments, confirms the diagnostic performance of the HeartLogic algorithm in a dataset consisting of 1458 patients with ICDs or CRT-Ds. The analysis includes 302 HF events, and the results demonstrate sensitivity (74.5%) and false positive alert rate (1.48/pt-yr) in line with the original MultiSENSE validation study, meeting both pre-defined performance goals for these primary endpoints. While MultiSENSE only included CRT-D devices, this analysis includes both CRT-D and ICD devices. The study further validates the strong prognostic performance of HeartLogic for predicting heart failure events. • We would also like to address the bias assessment for two of the included studies that report comparative outcomes. The EAR indicates that the studies by Treskes et al. and Feijen et al. are at serious risk of bias due to classification of interventions and problems with uncontrolled confounding. Because Treskes et al. is a pre/post analysis, all patients received the intervention and served as their own controls in the "pre-activation" period. Therefore, there is no confounding of intervention effects. Time-varying confounding could be a concern for this study design; however, given the study only covers a 12-month pre-activation period and 12-month post-activation period, there were unlikely to be significant changes to clinical practice (background HF therapy and management) that would significantly impact the results. [redacted]	factors. Feijen was found to be at serious risk of bias due to its retrospective nature together with a lack of blinding of the outcome assessor. On balance, it was likely the collection of information at the time of intervention may not be sufficient to avoid bias. Thank you for raising the lack of risk of bias assessment for D'Onofrio 2023. Based on your comments, a ROBINS-I assessment has been included in the final report. Lastly, the ROBINS-I tool applied in this study was specifically developed to assess the risk of bias, in non-randomised studies of interventions. Likewise, the PROBAST tool was

				[redacted] hence the impact of the COVID-19 pandemic ought to be limited. The authors also performed a sub-analysis to address the fact that reverse remodeling due to de novo CRT could be responsible for the observed improvements. Comparing patients with de novo CRT in the pre-activation period vs those who had an ICD or CRT for >1 year prior to HL enablement, the significant reduction in HF admissions was maintained in both groups. Therefore the observed effect cannot be attributed to CRT alone. • Feijen et al. is a propensity-matched comparison. The EAR reports a serious risk score was assigned for bias in classification of interventions. Due to the retrospective nature of this analysis, it is understandable that there might be concern about bias. However, it should be noted that the inclusion criteria were broad (patients with HF, a device with telemonitoring, and 1 year of follow-up) and the intervention defined "as the HeartLogic algorithm's being switched on during the follow-up period". Thus the intervention assignment would not be impacted by knowledge of the outcome. The Treskes and Feijen studies complement each other because of their different designs. The Feijen study eliminates the bias inherent in a pre/post analysis and the Treskes paper uses the patients as their own controls, thus avoiding the limitations of having a separate control group. The studies included in the assessment should be considered not just individually, but also holistically. Taken together, these studies form a large body of evidence that generally supports the predictive accuracy of HeartLogic across heterogeneous populations. We would like to request the EAG considers commenting within the report on the significant challenges of obtaining bias-free data, particularly pertaining to HF interventions (CIED-related or not). This is adequately demonstrated by large	developed to assess the risk of bias and applicability of prediction models and can be applied to a wide range of study designs. Following standard guidance, both tools were applied to individual studies; the committee may wish to consider variations in the individual study designs and corresponding direction of effect across the complete body of evidence provided in the report.

				numbers of publications on differing innovations, technologies and remote approaches to HF management which have yielded conflicting results. Real-world evidence, being judged by rigid assessment tools designed principally for RCTs, should not discount showing positive outcomes in real world heart failure populations and healthcare system settings. • Lastly, we noted that the publication from D'Onofrio et al. (2023) titled "Predicting all-cause mortality by means of a multisensory implantable defibrillator algorithm for heart failure monitoring" is missing from the risk of bias assessment table. This paper should be assessed for bias as data is included in the report.	
23	Claire Duxbury Boston Scientific	All	All	**Remote monitoring versus HF algorithms.** We note multiple misleading references to remote monitoring through the report and subsequent errors in interpretation of clinical data. We also note the opposing responses from clinical advisors (section 6.4.3) regarding "remote monitoring systems" which may be the result of confusion as to what precisely is being asked of them. For clarity, we provide below a summary of these technologies: • **Remote monitoring (RM)** – also referred to as remote patient monitoring (RPM) or home monitoring – is the ability for a compatible cardiac implantable electronic device (CIED) to communicate wirelessly with a remote monitoring system. Patients implanted with CIEDs are required to be followed up by hospitals managing their care, which includes regular technical review of device function and monitoring of clinical events recorded by the device [1, 2]. With remote monitoring, these device data – in their discreet form without processing or analysis - can be transmitted wirelessly and automatically (both in real-time and at scheduled intervals) to the remote	Thank you for the comments. We have edited the text in Section 6.4.1 and have also removed the McGee et al 2022 reference. However, the EAG feels the terminologies used throughout the report are appropriate in the context of this study and in line with the study scope and protocol.

				monitoring system. Healthcare professionals can then access these data online, negating the need for the patient to be physically present. Remote monitoring systems are standard in all CIEDs and their use is recommended for all appropriate CIED patients [1,2]. The presence of RM is considered the comparator in this assessment. • **CIED-based heart failure (HF) algorithms** are software algorithms incorporated into CIEDs which analyse and collate different clinical data recorded by the device to detect gradual worsening of heart failure. These HF algorithms are present in addition to the software required for the devices to function. Dependent on the specific HF algorithm used, some HF algorithms (including HeartLogic) operate an alert-based system where deviation from a patients' own baseline collated values and/or specific absolute values in input clinical data will trigger an alert to be sent immediately to the healthcare professional managing the patient's care. They can then proactively investigate the cause of the suspected decompensation before the patient may even feel symptomatic. The transmission of outputs from these algorithms uses existing remote monitoring systems described above. We request the External Assessment Group make the following corrections in the EAR: • Replace references to "remote monitoring" or "CIED" to "HF algorithms" when discussing the intervention (Scientific Summary, section 6, section 8) • Replace references to "no remote monitoring" to "no HF algorithm" or "remote monitoring only" (Scientific Summary, section 6, section 8) • Remove the following erroneous text relating to McGee et al 2022 (page 122, section 6.4.1): "however, a systematic review and meta-analysis conducted	

				by McGee et al 2022 did not find any significant reduction in mortality (RR = 1.02, 95% CI 0.85 to 1.23, p=0.055) from remote monitoring in patients with heart failure with cardiac implantable electronic devices." – this study compared remote monitoring to no remote monitoring (i.e., the comparator here vs neither the comparator nor intervention) and the conclusions on the lack of relative mortality benefit shown are irrelevant to the decision problem. • Include a reference in section 6.4.1 (page 122) that while no direct comparative data is available – and hence the assumption is there is no difference in mortality – multiple HeartLogic studies reported increased hazard from HF related mortality when IN alert compared to OUT of alert. • Replace "CRM" acronym with more widely utilised acronyms "RPM" or "RM" to align with British Heart Rhythm Society, Heart Rhythm Society, American Heart Association and European Heart Rhythm Society terminology [1, 2] *[1] BHRS Clinical Standards and Guidelines for the follow up of Cardiac Implantable Electronic Devices (CIEDS) for Cardiac Rhythm Management 2022* *[2] HRS/EHRA/APHRS/LAHRS Expert Statement on Practical Management of the Remote Device Clinic 2023*	
24	Claire Duxbury Boston Scientific	42, 45-47, 65, 94	3.3, 3.4, 3.5.4, 3.7.2	**Prognostic versus implementation outcomes.** It seems there is some confusion in metrics that are cited as prognostic outcomes versus implementation outcomes. This reflects the fact that the interpretation of the data will differ depending on whether or not investigators have access to the HF diagnostic data and whether they are implementing changes in patient care in response to that data. • **Time between an alert and a heart failure event** is included as an implementation outcome. This makes sense in the context of studies where investigators have access to the algorithm data, because clinical actions	The EAG appreciates that there is crossover between the outcomes and that this format is not definitive. However, this was agreed upon with NICE input.

				taken in response to alerts could reduce the occurrence of HF events and thus increase time to an event. However, it is equally important to consider time from alert to HF event as a prognostic measure, especially in the context of blinded studies where the investigators do not have access to the HF diagnostic data. In these cases, the time from alert to event is an indicator of how far in advance the algorithm can predict a HF event, which has prognostic significance. o In the MultiSENSE study (Boehmer 2017), HeartLogic alerts occurred a median of 34 days before HF events. This would provide early warning for an impending decompensation and a window for clinical action to be taken to prevent further worsening. • **Changes to clinical management** is included as a prognostic measure, but not an implementation outcome. A change in clinical management can have multiple implications. 1) It could indicate that the managing clinician recognises worsening of their patient that requires some sort of action. This could confirm the validity of an alert, thus providing evidence of prognostic performance. 2) The change in clinical management could be in direct response to an alert, which would make this an implementation outcome.	
25	Claire Duxbury Boston Scientific	41, 105-116	3.2, 4	**Missing & new evidence for HeartLogic.** We note the absence of references to the following data in the report which may be of interest to consider here: • An abstract by Ahmad et al. 2020 (Ahmad et al. Heart, 2020;106(Suppl2):A1-A118. https://heart.bmj.com/content/heartjnl/106/Suppl_2/A78.full.pdf) contains an example of integration of HeartLogic into NHS practice. The	We thank the company for identifying this information. We have not included the information from Ahmad 2020 as this appears to be

				authors noted that alerts led to "early and increased frequency of HF nurse contact and significant intervention, possibly helping in prevention of hospitalization and in turn conservation of financial resources." • The initial abstract reporting MANAGE-HF results (Multiple cardiac sensors for management of heart failure (MANAGE-HF)- Phase I: ESC digital congress 2021. Dr. Adrian F. Hernandez – Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA) reported a 67% lower rate of HF hospitalisations during the study compared to the 12 months pre-study. This data point is not reported in the full manuscript publication. The abstract should be cited in the report in addition to the manuscript, given the unique data point. • In addition to the clinical outcomes reported in section 3, Treskes et al. 2021 also reported a health economic analysis comparing resource use between the 12-month pre-activation and post-activation periods for a subset of 30 patients from one of the four centres where the larger clinical study was performed. They estimated total costs per patient for those treated at this single centre. Key results included a substantial drop (-€298,746 including deceased patients; -€207,150 excluding deceased patients) in overall health economic costs and no significant increase in total ambulatory cost per patient (p=0.968). We would also like to highlight the following additional data that has been published since June 2023 which adds to the existing sizeable evidence base for HeartLogic: • Singh JP, Wariar R, Ruble S, et al. Prediction of Heart Failure Events With the HeartLogic Algorithm: Real-World Validation. J Card Fail. Published online November 14, 2023. doi:10.1016/j.cardfail.2023.10.478	the authors interpretation of the results. Originally, we did not include data from the abstract reported by Hernandez et al., 2021 as we assessed the information available in the linked full text. We have included the data from the abstract, see section 3.6.4 of the final report. The EAG strongly encourages developers to report key data in full-text, peer-reviewed publications. We have now summarised the findings from Treskes et al. 2011 in Section 4.2 and Table 29. We would also like to thank the company for highlighting new evidence that has been published since the EAG completed screening. Due to

				• Boriani G, Bertini M, Manzo M, et al. Performance of a multi-sensor implantable defibrillator algorithm for heart failure monitoring in the presence of atrial fibrillation. Europace. 2023;25(9):euad261. doi:10.1093/europace/euad261 • Feijen M, Egorova AD, Tops LF, et al. The Potential of the HeartLogic™ Algorithm in Patients with a Left Ventricular Assist Device, an Initial Report. J. Cardiovasc. Dev. Dis. 2024, 11(2), 51; https://doi.org/10.3390/jcdd11020051 • Feijen M, Egorova AD, Paghu AAS, et al. A multisensory algorithm for detection of upcoming congestion in chronic heart failure patients. European Heart Journal, Volume 44, Issue Supplement_2, November 2023. doi: 10.1093/eurheartj/ehad655.1012 • Pickett RA, Shannon E, Kaiser DW et al. Heart Logic Directed Uptitration of Guideline Directed Medical Therapy Improves EF Across All Device Categories. Circulation. 2023;148:A14302. doi: 10.1161/circ.148.suppl_1.14302 • Kataoka S, Morioka Y, Kanai M, et al. HeartLogic multisensor algorithm response prior to ventricular arrhythmia events. J Arrhythm. 2023;39(5):826-829. Published 2023 Sep 5. doi:10.1002/joa3.12913 • Kwon A and Denomme P. Impact of a pharmacist-managed remote heart failure program in patients with a multisensor-capable implanted device. American Journal of Health-System Pharmacy. Published online February 7, 2024. doi: 10.1093/ajhp/zxae028	time constraints, we are unable to include this information in the report.

				Lastly, the following abstracts were presented at the 2023 ESC Heart Failure Congress and published in a supplement of the European Journal of Heart Failure: • De Juan Baguda JJ, Cozar Leon R, Gavira Gomez JJ, et al. Clinical impact of remote heart failure management using a multiparametric implantable cardioverter-defibrillator alert: the multicentric Spanish RE-HEART Registry. Eur. J. Heart Fail. 2023; 25 (Suppl. S2), 3-457 (page 18). https://onlinelibrary.wiley.com/doi/epdf/10.1002/ejhf.2927 • De Juan Baguda JJ, Cozar Leon R, Garcia Bolao I, et al. Performance of a multiparametric implantable cardioverter-defibrillator algorithm for heart failure risk stratification and management: The multicentric Spanish RE-HEART Registry. Eur. J. Heart Fail. 2023; 25 (Suppl. S2), 3-457 (page 430). https://onlinelibrary.wiley.com/doi/epdf/10.1002/ejhf.2927	
26	Claire Duxbury Boston Scientific	8, 59, 85, 138	Scientific Summary, 3.5.2, 3.5.8, 3.7.2, 6.7.1	**Errors in reporting of clinical data.** There have been instances where key clinical data on the HeartLogic algorithm has been incorrectly reported. We would request that the following are corrected in the EAR: • References to the Vigdor 2020 study erroneous report 26 of 38 alerts as falsely positive. The study reports 26 patients experiencing false positive alerts out of 38 patients with at least 1 alert (of the total 80 patients). The number of false positive alerts and the total number of alerts are not reported in this abstract and the calculation by the EAG of a false positive rate of 68% is incorrect.	Regarding Vigor 2020, the results are reported as is from the abstract. This states “A total of 38 patients (48%) had at least one HeartLogic alert during the study period. Of these, 26 patients (**68%**) appeared to have false positive alerts…”. The calculation would also be correct if the EAG had calculated this. As 26 of 38 alerts were suggested to be

				• Table 42 erroneously sources a figure for unscheduled follow-up visits for HeartLogic as "company provided information". As highlighted in our communication with NICE, the 0.71 alerts per patient year figure was taken from Santobuono et al. 2023. • Section 3.7.2 refers to a study reporting on number of days from alert to first hospitalization: "Another study reported the median number of days from the first sensor alert to first hospitalisation was 145 (IQR: -1 to 380) for all causes, 63 (IQR: -26 to 229) for HF related, and 240 (147 to 497) for non-HF related." Not only is the citation unrelated to HeartLogic, we do not recognize this data and do not know where it came from. We ask that the External Assessment Group identify the correct citation and confirm or correct this data point.	a false positive. It would not be possible to calculate false positives from those who did not have an alert. We thank the company for noticing the erroneous reference. The reference is Table 42 has been updated. The citation in section 3.7.2 has been updated. This was incorrectly cited: Lerman et al 2023 The Use of the Multisensor HeartLogic Algorithm for Heart Failure Remote Monitoring in Patients With Left Ventricular Assist Devices. ASAIO Journal.
27	Claire Duxbury Boston Scientific	40-104	3	**Additional clinically relevant observations from HeartLogic real-world observations**. We note that the report focuses on quantitative data extracted for the SLR, but omits several clinically relevant observations from the studies. We have included below information we believe is relevant, grouped by topic, to the clinical effectiveness review results. Furthermore, to obtain additional information on the clinical and patient experience with HeartLogic in the NHS for this appraisal, we have carried out a clinician survey. 7 questionnaires were sent out to the relevant departments of NHS Trusts where	We thank the company for providing some clarification on points throughout the report. We have not included information from the clinician survey as this would not meet our inclusion criteria.

				HeartLogic use is highest. 5 have been returned to date; others are expected to be available for the consultation period. In the absence of published data, these responses provide valuable additional insight into the clinical impact of HeartLogic in NHS practice. The completed questionnaires have been supplied as a supporting document. We have included relevant key quotes from these questionnaires below, grouped by topic.	
28	Claire Duxbury Boston Scientific	87	3.6.1	**Additional clinically relevant observations from HeartLogic real-world observations: HF events.** • Page 76 (section 3.5.6): The following observation from Calo 2021 is also of value, illustrating that taking clinical actions as a result of alerts can lead to a reduction in HF events compared with not taking action: o The authors report that: “On comparing the event rate measured after HeartLogic alerts that were followed by clinical actions with the rate of events that were not followed by clinical actions, the hazard ratio was HR, 0.37 (95% CI, 0.14–0.99), P=0.047. A possible bias in this analysis could derive from the HF events occurred early after the alert, which may not have allowed any action to be taken. To account for this bias, a time window of 7 days was considered (data are transmitted weekly IN alert state), and a landmark analysis was performed starting at day 7. The result was confirmed, with a lower rate of events associated with alerts followed by clinical actions: HR, 0.34 (95% CI, 0.12–0.96), P=0.047.”	We appreciate the company highlighting this information and have included it in section 3.5.6.
29	Claire Duxbury Boston Scientific	89	3.6.4	**Additional clinically relevant observations from HeartLogic real-world observations: Hospitalisations.**	See reply to comment 27.

				The following quotes from the clinician survey provide supportive evidence on hospitalisations: • "No formal audit available, it feels like we do manage to intervene earlier and prevent some hospitalisations." [Cardiac Device Nurse, Blackpool Teaching Hospitals] • "Before HeartLogic was available, patients would either just be managed by their GP's or the Heart Failure Nurses (not all patients) and so in a sense they were 'forgotten'. The activation of the HeartLogic software means that the cardiology department is being proactive in managing their heart failure/LV systolic dysfunction, thus preventing hospital admissions" [Consultant Cardiologist, New Cross Hospital] • "likely reduction in HF admissions due to the ability to "catch" patients earlier in the HF cascade before they are symptomatic enough to become hospitalised" [Healthcare Professional, Manchester Royal Infirmary] • "In July 2021 at our centre, HeartLogic was initiated in 212 patients with CRT-D devices. Throughout the subsequent 12 months, 34 hospitalisations occurred, primarily due to heart failure (HF), with a median hospital stay of 5 days. The total outpatient visits numbered 37, with 22 visits attributable to HF decompensation. During this period, HeartLogic alerts were triggered 197 times, on average 0.95 alerts per patient-year, primarily signalling impending HF exacerbations. These alerts demonstrated a sensitivity of 100%, with all HF hospitalisations detected during alert states. Therapeutic actions were taken in response to 82 alerts, including medication adjustments, with 37% of alerts necessitating hospitalisation or outpatient visits for clinical management. Overall, HeartLogic significantly contributed to the early detection and management of HF events, potentially reducing unplanned hospital visits and improving patient outcomes." [Heart Failure Complex Device Clinical Lead Nurse Specialist, Liverpool Heart and Chest Hospital]	

30	Claire Duxbury Boston Scientific	93	3.7.7	**Additional clinically relevant observations from HeartLogic real-world observations: Patient experience.** Patient experience was addressed by 4 respondents to the clinician survey. Of those commenting, all stated patients have a positive experience of HeartLogic, particularly in relation to the reassurance of knowing that their condition is being monitored • Q: In your opinion, has using HeartLogic™ resulted in any changes to patients' quality of life? A: "Yes. It has become part of a patients routine care with heart failure that they are monitored by health professionals who alert if things change. Most patients report they feel safe knowing someone is keeping an eye on them. They can forget about their condition day to day and get on with living while we make sure things are stable." [Cardiac Device Nurse, Blackpool Teaching Hospitals] • "Patients using HeartLogic have provided positive feedback on its impact on their heart failure management. Many have expressed a sense of reassurance and empowerment knowing that their condition is continuously monitored remotely, allowing for early detection of potential exacerbations. This proactive approach has instilled a greater sense of confidence in managing their HF. Patient's appreciate the convenience of fewer clinic visits and the ability to maintain a more active role in their care while still receiving timely interventions when needed. Overall, feedback from patients indicates that HeartLogic has significantly improved their overall quality of life by providing peace of mind, enhancing convenience, and empowering them to	See reply to comment 27.

				better manage their heart failure condition." [Heart Failure and Complex Device Lead Clinical Nurse Specialist, Liverpool Heart and Chest Hospital] • "The objective data provided by HeartLogic enables more personalised and targeted therapies, optimising symptom management and enhancing overall well-being. Overall, the implementation of HeartLogic has undoubtedly contributed to a tangible improvement in the quality of life for patients living with heart failure." [Heart Failure and Complex Device Lead Clinical Nurse Specialist, Liverpool Heart and Chest Hospital] • "In addition to the above (being able to prevent decompensation and to improve prognostic medication) patients seem to find it psychologically beneficial to know someone is monitoring their condition. It allows us to explore the reasons for decompensation, some of which are lifestyle related, e.g. drinking lots of fluid or eating salty foods, and reiterate self care strategies." [Heart Failure and Complex Device Lead Clinical Nurse Specialist, Liverpool Heart and Chest Hospital] • "I was surprised by how positive they were about the system. They are very welcoming of phone calls even when ultimately they are deemed well and no action is taken. They seem reassured that they are still being monitored." [Heart Failure Nurse, NHS Trust in England] • "When performing telephone triage of HeartLogic compatible patients, we receive regular feedback that they are appreciative of the additional follow up and that we are keeping an eye on them alongside their routine HF clinic visits." [Healthcare Professional, Manchester Royal Infirmary]	
31	Claire Duxbury Boston Scientific	65, 94, 103	3.5.4, 3.5.6, 3.7.1, 3.7.2, 3.7.8	**Additional clinically relevant observations from HeartLogic real-world observations: Changes to clinical management & interventions following an alert.**	The EAG thank the company for highlighting some missing data. We have assessed each one and included where

				• Page 65 (section 3.5.4) & table 18: The following observation from Calo 2021 reports changes to clinical management triggered by a HeartLogic alert: o The authors report that: "Alert-triggered actions were reported in 117 (43%) cases. The most frequent actions taken to manage the HF condition detected by the alert were (multiple actions per alert): diuretic dosage increase in 77 (66%), other drug adjustment in 40 (34%), patient education on therapy adherence in 7 (6%), device reprogramming in 3 (3%)." • Page 94 (section 3.7.1): Intervention outcomes from the MANAGE-HF study (Hernandez 2022) study discuss the relevance of alerts in guiding intervention: o Hernandez 2022 reported "HF treatment augmentation within 2 weeks from an initial alert was associated with more rapid recovery of the HeartLogic Index" • Pages 94 (section 3.7.2), 103 (section 3.7.8): The following observation from Santini 2020 again illustrates that HeartLogic enables earlier intervention (usually treatment optimisation) in patients with clinically concerning markers, which is likely to prevent HF events in some patients. o Santini et al. 2020 reported that in 48 of the 60 clinically meaningful alerts the clinician was not previously aware of the condition; 43 of these 48 triggered clinical action. • Page 94 (section 3.7.1): The clinical significance of the application of "decongestive" treatments in the Guerra 2022 study should be highlighted. This study again shows that alerts can be used as an opportunity to optimise a patient's medication with the aim of preventing HF events – optimisation	appropriate. For Hernandez 2022, this provides no data and is only a comment, which has not been included in the report. The data in Calo 2021 has been added to section 3.5.4. Santini 2021 information does not appear to fit section 3.7.2 (time between an alert and a heart failure event). It is similar to information already provided in section 3.5.4 and has therefore not been included. Regarding the clinician survey see reply to comment 27.

				that would not have occurred as soon if patients had waited until a scheduled appointment and/or deterioration of symptoms. All three respondents to the clinician survey reported that HeartLogic enables them to intervene early to optimise patient's medication and/or offer lifestyle advice. • "With the introduction of HeartLogic, the management pathway for these patients has undergone a significant transformation. …. As a result [of early detection], healthcare providers can intervene promptly with targeted therapies or adjustments to medication regimens, potentially preventing or mitigating the severity of heart failure exacerbations." [Heart Failure and Complex Device Lead Clinical Nurse Specialist, Liverpool Heart and Chest Hospital] • With HeartLogic: "It's now a proactive pathway and will catch many patients who have been discharged from the community heart failure nurses and would otherwise have to try to obtain a GP appointment or present to secondary care via emergency pathways. Additionally this process allows us to pick up patients who may have been on optimal therapy when last seen by hospital or community specialist teams but could now be considered to be on sub-optimal therapy by current standards. We can therefore improve their medication in line with contemporary practice." [Heart Failure Nurse, NHS Trust in England] • "It's very early days yet but I have already made interventions to avert worsening heart failure symptoms and improved GDMT in patients who were no longer under ongoing specialist review." [Heart Failure Nurse, NHS Trust in England] • "By providing clinicians with real-time insights, HeartLogic facilitates the optimisation of oral medications, ensuring that treatment plans are tailored precisely to individual patient needs, thus maximising efficacy." [Heart Failure	

				and Complex Device Lead Clinical Nurse Specialist, Liverpool Heart and Chest Hospital] • "With adequate education and training, we found that our Cardiac Physiologists and Specialist Heart Failure Nurses had no objection in adopting and incorporating this technology into their normal day to day working." [Consultant Cardiologist, New Cross Hospital]	
32	Claire Duxbury Boston Scientific	94	3.7.2	**Time between an alert and a heart failure event** • De Juan Baguda (2022) reports a mean time from alert to HF hospitalization of 20 +/- 15 days during phase 2 & 3 of the study. This metric was erroneously reported in section 3.7.3 (Alert response rates) instead of Section 3.7.2 (Time between an alert and a heart failure event).	We have moved this information from section 3.7.3 to section 3.7.2.
33	Claire Duxbury Boston Scientific	95	3.7.3	**Additional clinically relevant observations from HeartLogic real-world observations: Alert response rates.** • Page 95-96 (section 3.7.3) & table 25: The following observations from De Juan Baguda 2022 are relevant here: o De Juan Baguda et al. 2022 reported "Of the 44 HeartLogic alerts reported in 32 patients during phase 2, 32 (73%) resulted in a consultation (in-person or telephone). During phase 3, consultations were more frequent, comprising 198 of the 233 alerts (85%, P = .047) in 130 patients". • Table 25 implies that the time from alert to review in the study by Pecora (2020) was 14 +/-8 days. In this study patients were followed via a standardized protocol that included remote reviews and phone contact every month *and* at the time of HeartLogic alerts. They report that the mean delay	See reply to comment 27.

				from alert to next monthly remote data review was 14 +/- 8 days. This indicates that had the clinician waited until the regular monthly review to check on the patient's data rather than upon receipt of the alert, there would be a 14 day delay (on average). It does not mean that clinicians took 8 days to review alerts. Rather, it should be taken to reflect the benefit of an alert-based approach on top of standard follow-up over monthly follow-up alone. According to clinician survey respondents, HeartLogic has enabled improvements in workflows and patient care. Improvements in workflows and efficiency are hugely valuable to the NHS, contributing to better service provision, better use of staff time and improved patient outcomes. • "Again early days … but it's allowed us to improve medical therapy for both short and long term clinical stability. Much better collaboration between HF team and physiologists and awareness of what each discipline can do to help patient outcomes." [Heart Failure Nurse, NHS Trust in England] • "Prior to HeartLogic, pacing team had to highlight any issues to heart failure team but now we have Heart Logic these alerts come direct to the HF teams to deal with reducing delay." [Cardiac Device Nurse, Blackpool Teaching Hospitals] • "Allows teams to see all patients device parameters to better manage patients in the clinic and remote settings." [Cardiac Device Nurse, Blackpool Teaching Hospitals] • "I find HeartLogic technology to be immensely beneficial in the management of heart failure patients. …. The convenience of remote monitoring and the potential for improved patient outcomes make a compelling case for HeartLogic to become the standard of care in heart failure management. Its integration into my routine clinical practice has optimised resource utilisation, improved patient outcomes, and ultimately enhances the overall quality of	

				care for heart failure patients. I firmly believe that HeartLogic should be embraced as a standard component of heart failure management protocols." [Heart Failure and Complex Device Lead Clinical Nurse Specialist, Liverpool Heart and Chest Hospital] • "Additionally, the use of HeartLogic reduces the reliance on subjective symptom reporting by patients, providing objective data to guide clinical decision-making. This objective data, combined with regular alerts and remote monitoring, enables a more proactive and personalised approach to managing heart failure. Consequently, patients may experience fewer unplanned hospital visits, reduced lengths of stay, and improved overall outcomes compared to the traditional management pathway." • "The management pathway for patients with heart failure has shifted from reactive and episodic care to proactive and continuous monitoring with the integration of HeartLogic technology." [Heart failure/ complex device lead clinical nurse specialist, Liverpool Heart and Chest Hospital] • "Utilisation of the HeartLogic algorithm witihin our physiologist-led service including review of HF diagnostic information and clinical assessment can shorten the time from patient presentation to HF review and therefore streamline the existing standard of care" [Healthcare Professional, Manchester Royal Infirmary	
34	Claire Duxbury Boston Scientific	102	3.7.6	**Additional clinically relevant observations from HeartLogic real-world observations: Number of monitoring reviews.** Three real-world observational studies on implementation of HeartLogic in clinical practice make observations that it can be effectively integrated into the care pathway without an increase in clinic workload. Ease and efficiency of implementation are very important aspects of the technology and provide important context when discussing	For Santini, the majority of this information is authors opinion based on their study, which we would not include in the report. The data pertaining to number of emergency or urgent care

				the literature on real-world clinical effectiveness. Furthermore, the early warning of a decompensation can be investigated with opportunity for drug optimisation, lifestyle advice and other factors e.g. presence of arrythmias, to be investigated, the opportunity for which wouldn't necessarily proactively occur without the alert. • Santini 2020 noted that: o "The HeartLogic algorithm allowed HF patients to be effectively and efficiently managed by means of a remote follow-up protocol." o "Out of 100 HeartLogic alerts, 16 required an in-office visit and 6 hospitalisations to manage the clinical condition". o "An alert-based management strategy seemed more efficient than a scheduled monthly remote follow-up scheme." • Calo 2021 reported that: o "Alerts may be safely managed remotely, without increasing the workload of the clinic. This, together with the possibility of relying on an alert-based remote review strategy, instead of a more burdensome scheduled remote review strategy, enables a very efficient protocol of patient follow-up management to be designed." o Rate of alerts was low (0.76 alerts/patient-year) and "would not generate high workload." o Of the 273 reported HeartLogic alerts, 204 (75%) did not require extra in-office visits and were managed remotely. Of the 69 in-office visits, 42 (61%) were scheduled examinations previously planned within 7 days from the alert. The median number of phone contacts per alert period was 1 [25th–75th percentile: 1–2]. o "Its adoption may enable an efficient use of healthcare resources for the management of patients with HF because the time IN alert state	visits was deemed not to be relevant for committee and was therefore not included. As per the sentence in section 3.7.4 for HeartLogic: "Four of the six studies for HeartLogic were single cohort study designs. These studies reported the number of emergency or urgent care visits." Regarding Calo 2021, the first point is author opinion and is not included in the report. The second report was not considered as an outcome in the report. Point four is also author opinion. The data from Calo 2021 and De Juan Baguda 2021 has been added to section 3.7.6 as requested. Regarding the clinical survey see reply to comment 27.

				(when more focus is required to mitigate any potential HF deterioration) is much shorter than that of OUT of alert state periods." • De Juan Baguda 2021 reported: o Of the 44 alerts in phase 2, 36 (82%) did not require in-person visits and could be remotely managed. During phase 3, remote consultations were used to manage 188 of the 233 alerts (81%;P = .861). The total numbers of telephone contacts with patients were 35 (0.65 contacts/patient-y) in phase 2 and 287 (1.12 contacts/patient-y) in phase 3 (P = .002). o Workload was estimated as 1 hour per week per 30 patients The following quotes from the clinician survey provide supportive evidence: • "Our experience [of HeartLogic] has shown us who we can leave alone and who we need to contact which helps when managing workload. It has also given teams more confidence to discharge patients from regular follow up as alerts highlight patients who are needing attention." [Cardiac Device Nurse, Blackpool Teaching Hospitals] • "Additionally, the decreased necessity for frequent clinic visits translates to a more convenient and less burdensome healthcare experience for patients, while simultaneously allowing healthcare providers to allocate their resources more efficiently towards those requiring heightened attention and care." [Heart Failure and Complex Device Lead Clinical Nurse Specialist, Liverpool Heart and Chest Hospital] • "We have used HeartLogic for the last 5 years and have a very good experience. We have analysed our experience of 143 patients between 2019 and 2021 who had their HeartLogic Alert switched 'on'. The median age of the cohort was 73 years and 74.1% were males. Roughly two thirds of the	

				patients had ischaemic cause of LV dysfunction. The follow-up period was a median of 459 days (range 215-994). there were a total of 1.17 alerts per patient per year. One alert was seen in 40.6% of patients and 2 alerts in 25.9% of patients. Less than 10 of the 143 patients had more than 4 alerts. We were also assured that 58.0% did not have any activations, suggesting stable heart failure. So, I would agree that the number of alerts that we get from HeartLogic certainly do not overwhelm our service" [Consultant Cardiologist, New Cross Hospital]	
35	Claire Duxbury Boston Scientific	All	All	**Under-recognition of clinical benefits of prognostic accuracy.** We note that while the EAR recognises HeartLogic has the "highest and most consistent accuracy measures… [with] adequate to high sensitivity and specificity for the prediction of heart failure events", the clinical benefit of these advantages are not well summarised either in the report nor are included in the economic model. For example, the cost-effectiveness model only takes into account one advantage of algorithms – reduced hospitalisations – and does not attempt to quantify the utility benefits arising from mitigation of these hospitalisations nor HF events. Hospitalisations and HF events are associated with important mortality implications and reduced quality of life, which are not taken into account, underestimating the potential benefit of HeartLogic (see also economic model comment 3 below). We would welcome reference to the clinical advantages associated with a diagnostic algorithm such as HeartLogic that can detect HF events early and accurately.	Thank you for the comment. The cost-effectiveness analysis is mainly driven by reduced hospitalisations. This is due to the limited evidence on any other outcome. There was no evidence for an effect of an algorithm on mortality, and the only effect of an algorithm on utility in the model was via reductions in hospitalisation. There was no evidence for an improvement in HRQoL for people living with HF due to the algorithm that we could use in the model.

36	Claire Duxbury Boston Scientific	125-126, 138	6.4.3, 6.7.1	**Assumptions on unscheduled follow-up visits.** We note that while not explicitly stated in the description of the modelling approach for unscheduled visits associated with HF algorithm use (section 6.4.3; see also comment 13), the assumption made by the EAG is that for HeartLogic the frequency of unscheduled follow-up visits for the intervention would be equal to the frequency of HeartLogic alerts. We believe this is an unreasonable assumption. Many alerts may be handled remotely without the patient coming into the clinic. For example, in the study by De Juan Baguda et al. (2021), 81% of alerts were managed remotely. In Calo et al. 2021, 75% of alerts were managed remotely. Furthermore, we note that the result of the above assumption on unscheduled follow-up visits is that there are a greater number of unscheduled follow up visits for the intervention than for the comparator. This contrasts with the published literature on HeartLogic: total follow up visits were shown to be statistically significantly reduced with HeartLogic in a propensity score matched retrospective cohort study described in Assessment Group's Report (Feijen et al. 2023). We recommend the addition of a sentence within the conclusions of the Assessment Group's Report mentioning that results are likely to be conservative for HeartLogic. We have also made a related comment below in the economic model section (comment 5) relating to this same point.	We would like to thank the company for the comment and acknowledge that the evidence from De Juan Baguda et al 2021 was not used for follow-up visit for HeartLogic. However, following the comment, we have now conducted an additional scenario analysis using the evidence from Baguda et al 2021 where 81% of alerts were managed remotely, and the remaining 19% only had a face to face in-office follow-up. Using this evidence did not change the conclusion of the study as HeartLogic remained dominant. We have now conducted an additional scenario analysis for CorVue, HeartInsight, and HeartLogic, assuming that only 50% of the alerts in the intervention group require in-office follow-up visits and

					25% of the alerts only require non-face to face contacts. (See Table 43). The conclusion of the study did not change in this scenario, except for CorVue which changed from being "cost increasing" in the basecase to "cost saving". Section 6.8.4 and Table 47 have been updated to report the additional scenario analysis. Further scenario analysis was conducted and included in the Addendum to the EAG report. This assumes 50% of alerts would need in-office follow up visits and the remaining 50% will have non-face to face contacts was modelled for CorVue, HeartInsight and TriageHF.
37	Claire Duxbury Boston Scientific	29-30	1.3.2	**Description of HeartLogic technology.** The current description of HeartLogic in section 1.3.2 is not fully representative of the technology. We propose alternative wording for section 1.3.2 as follows: HeartLogic is a diagnostic algorithm designed to monitor heart failure patients for early signs of worsening heart failure. It uses multiple sensors to track	The information from these sections is pre-published in the scoping and protocol documents, the EAG are therefore happy to keep the original wording.

					physiological signals in patients with CIEDs and identify changes that may indicate the onset of heart failure decompensation before symptoms become noticeable to the patient. HeartLogic is the only diagnostic heart failure system which compares these parameters against a personalised baseline of previous data collected from the same patient to detect personalised changes that may indicate worsening heart failure. By monitoring changes over time and comparing them to the patient's own historical data, HeartLogic can provide early alerts to clinicians about potential deterioration in heart function, allowing for proactive management and intervention. HeartLogic stands out in heart failure detection by uniquely leveraging both heart sounds and respiration (including respiratory rate and tidal volume) as key components of its algorithm. Heart sounds can detail valuable information about the functioning of the heart valves, chambers, and overall cardiac health. Its personalized monitoring and analysis of individual heart sound patterns enable more accurate and timely alerts. Given the significant association of worsening heart failure with increased respiratory rate, decreased tidal volume and patient subjective complaints of worsening dyspnoea, inclusion of measures of respiration such as respiratory rate and tidal volume in the HeartLogic algorithm provide added physiologic and prognostic insight into a heart failure patient's clinical status utilising highly relevant data. Boston Scientific's HeartLogic and Latitude NXT Patient Management System work together to provide advanced monitoring and management capabilities for heart failure patients with implantable cardiac devices. The Latitude NXT system is further described in the NICE Medtech innovation briefing MIB67. HeartLogic is currently in use in 13 NHS Trusts in England. HeartLogic detects early signs of worsening heart failure, while Latitude NXT	Table 14 has been updated as requested.

				facilitates remote monitoring, data transmission, and timely intervention by healthcare providers for all CIED alerts, ultimately enhancing patient care and outcomes. We also request that table 14 (page 49) is updated to more accurately reflect parameters which combine to form the HeartLogic Index: 1. Heart sounds (S1 & S3) 2. Thoracic impedance 3. Respiratory rate & tidal volume 4. Nocturnal heart rate 5. Activity level	
38	Claire Duxbury Boston Scientific	14, 28-30, 37, 105, 121, 124, 126, 128-130, 133	Table of contents, 1.3, 1.3.2, 2.1.2, 4, 6.2.2, 6.4.2, 6.4.3, 6.4.4, 6.6.1, 6.6.2, 6.7.1	**Incorrect brand name references.** We note incorrect references to Boston Scientific brand names throughout the document. We request that all such references are corrected to the following: • Latitude NXT Patient Management System (*not Heart Failure Management System*) • Latitude Communicator (*not Transmitter*) • HeartLogic (*not Heartlogic*; section 4 only) We also note that references to the HeartLogic "device" (section 3.6.5, page 92) are inaccurate – HeartLogic is a software algorithm, not a device in itself.	Brand names have been corrected. We have changed the sentence "… a HeartLogic device" to "… the HeartLogic algorithm"
39	Claire Duxbury Boston Scientific	128-129	6.6.1	**Device costs.** Further to our comment on the economic modelling below relating to incremental analysis, we note that the current analysis assumes that the algorithms cannot displace each other. However, while the algorithms are only compatible with	In the scope and protocol of this study, the effectiveness and cost-effectiveness of

				specific devices, the CIEDs on which the HF algorithms sit are integral to the functioning of the algorithms. As the price, longevity, etc. of each device differs, evaluating the algorithms as separate from devices does not reflect clinical practice, where the decisions are made for both the use of algorithm and the device with the algorithm, and not only the algorithms in isolation. Assuming equal efficacy for all devices as per prior NICE guidance, this would include consideration of the device costs (price, maintenance, replacement). Furthermore, the variable commercial models for these algorithms – e.g., availability of algorithms with specific tiers of CIEDs only, annual licensing fees, volume/commitment discounts – means the costs presented in table 38 are not reflective of the full relative acquisition costs for these algorithms. We request the External Assessment Group make the following amendments in the EAR: • Addition of the following footnote for table 138 (page 128-129): “Note: these costs are direct acquisition costs for HF algorithms and do not take into account other direct or indirect costs relating to compatible CIEDs, licensing fees and/or commercial discounts that may also apply.”20 [redacted]	each algorithm remote monitoring system was evaluated compared to no algorithm for the same CIED. It could not be assumed that each CIED was as effective as each other. This study comprises for separate technology appraisals, one for each algorithm remote monitoring system brand. For each economic evaluation, the cost of the device is the same with or without the algorithm activation. The cost of a device was therefore omitted from the analysis. The underlying assumption is that the algorithm is an optional extra for each device. The cost of the algorithm was modelled as a one-off cost or monthly according to the information supplied by the company. Often, free updates of an

					algorithm was quoted. There was no clear basis for assuming a useful life duration for an algorithm for the purpose of costing.
40	Claire Duxbury Boston Scientific	1, 2, 3, 5, 6, 23, 32, 35, 37, 48, 120, 121, 125, 148	Title, Abstract, Plain English Summary, Scientific Summary, 1.1, 1.5, 2.1.1, 2.1.2, 3.5.1, 6.4.3	**Inequitable presentation of algorithms in scope.** We note that a preferential presentation of one algorithm prevails in the EAR, likely as a result of the origins of this guidance as a single technology review. For example, there are multiple references to “risk data” in references to HF algorithms which is not broadly applicable to all algorithms. There are also references in the economic model outcome descriptions (section 6.4.3) to modelling approaches which are applicable to only one algorithm. The action performed by the HeartLogic algorithm is not one of risk assessment but rather computation of a composite index value to reflect underlying changes in physiologic measurements reflecting the variation in clinical status of a HF patient versus their own baseline values. In order to ensure the report remains an impartial evidence review as intended, we recommend the following amendments are made: • References to “heart failure risk data” be removed when used to refer to HF algorithms in scope of the assessment (Title, Abstract, Plain English Summary, Scientific Summary, sections 1.1, 1.5, 2.1.1, 2.1.2, 3.5.1, 6.1, 6.3, 6.9) and replaced with “worsening heart failure”. • Reference to “algorithm risk scores” (section 3.5.1) be replaced with “algorithm analytics” • Update of modelling approach description for unscheduled follow up visits for patients with HF algorithms (section 6.4.3) to acknowledge current assumptions around “high risk” patients receiving a follow up visit are not broadly applicable, and for most algorithms the assumption is that each alert	We feel the term heart failure risk data is adequate to represent the algorithms. As some of these sections are in pre-published documents (i.e. scoping and protocol), we feel this terminology can be used. We have updated section 3.5.1 to state algorithm analytics, as requested. Additional scenario analysis on assumptions of unscheduled follow up visits have been conducted. Please see response to point 36 above.

				will result in a follow up visit (modelled as incurring an outpatient appointment cost) also not necessarily reflective..	
41	Ross Wardle Abbott	93		In the report, it's explicitly stated: "Hospitalisations were statistically significantly reduced in those with a CorVue enabled device compared to those with no implanted device receiving standard home care." We believe the statistically significant reduction in hospitalisation should be implemented in the economic model, but it is not. Lead impedance monitoring via a CorVue ICD is statistically associated with lower readmission rates for patients with chronic HF, leading to lower health care costs. No patients with a CorVue ICD experienced a 30-day readmission. In contrast, 14 of 60 patients (23.3%) without the CorVue device experienced 30-day readmission. The $\chi 2$ test of independence show that non readmission is statistically associated with the CorVue ICD ($\chi 1 = 15.849$, $P < .001$).	Thank you for the comment. The comparative effectiveness evidence on hospitalisation from the Shapiro M. et al 2017 is for an algorithm enabled device compared to no device, as opposed to compared to a device without an enabled algorithm. Therefore, this evidence was not considered generalisable to the context in this economic evaluation.

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Table 21. 30-Day Readmission * CorVue/Study Crosstabulation Count
<table>
<tr><th></th><th colspan="2">CorVue/Study</th></tr>
<tr><th>Gender</th><th>No Device</th><th>CorVue ICD</th></tr>
<tr><td>Female</td><td></td><td></td></tr>
<tr><td>30-d readmission</td><td></td><td></td></tr>
<tr><td>No</td><td>11</td><td>13</td></tr>
<tr><td>Yes</td><td>7</td><td>0</td></tr>
<tr><td>Total</td><td>18</td><td>13</td></tr>
<tr><td>Male</td><td></td><td></td></tr>
<tr><td>30-d readmission</td><td></td><td></td></tr>
<tr><td>No</td><td>35</td><td>47</td></tr>
<tr><td>Yes</td><td>7</td><td>0</td></tr>
<tr><td>Total</td><td>42</td><td>47</td></tr>
</table>
Abbreviation: ICD, implantable cardioverter defibrillator.

Shapiro M, Bires AM, Waterstram-Rich K, Cline TW. Improving Clinical Outcomes for Patients With Class III Heart Failure. Crit Care Nurs Q. 2017 Apr/Jun;40(2):111-123. doi: 10.1097/CNQ.0000000000000148. PMID: 28240694.
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<tr>
<td>42</td>
<td>Ross Wardle Abbott</td>
<td>208</td>
<td></td>
<td>We do not believe that all the relevant evidence has been considered fully. We believe the LIMIT-CHF study by Domenichini et al. should be included in the assessment report and not excluded for wrong intervention. This study assesses the usefulness of</td>
<td>The EAG disagree with the inclusion of this study. This was identified as “wrong intervention” as the</td>
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				intrathoracic impedance measured by CorVue and is of particular interest to NICE because it is specific to the UK (Barts Health NHS Trust). *Domenichini G, Rahneva T, Diab IG, Dhillon OS, Campbell NG, Finlay MC, Baker V, Hunter RJ, Earley MJ, Schilling RJ. The lung impedance monitoring in treatment of chronic heart failure (the LIMIT-CHF study). Europace. 2016 Mar;18(3):428-35. doi: 10.1093/europace/euv293. Epub 2015 Dec 18. PMID: 26683599*.	intervention group includes those with Optivol (n = 13) or CorVue (n = 28). The only evidence reported individually was for sensitivity and PPV of the algorithms. However, we felt as all other outcomes and baseline characteristics were combined for reporting, it would be difficult to robustly assess the quality of the study for CorVue alone. Additionally, the sensitivity of 67% is within the range of the other identified studies (20-68%).
43	Ross Wardle Abbott	92		In the report, no studies for CorVue have been reported on health-related quality of life. However, the LIMIT-CHF study by Domenichini et al. shows that total Minnesota Living with Heart Failure (MLWHF) scores were significantly increased at the final follow-up in the control group (alarm turned off), whereas a trend towards reduction was observed in the active group (alarm turned on). Higher MLWHF scores indicate worse HRQoL.	Please see response to comment 42 regarding the inclusion of this data.
44	Ross Wardle Abbott	51		Table 15: Studies reporting predictive accuracy measures should also include the LIMIT-CHF study by Domenichini et Al. showing a sensitivity of 67%.	Please see response to comment 42 regarding the inclusion of this data.

DIAGNOSTICS ASSESSMENT PROGRAMME

Algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices

External Assessment Report (EAR) and economic model – Collated Comments

Diagnostics Advisory Committee date 16 April 2024

<table>
<tr><td>45</td><td>Ross Wardle Abbott</td><td>53</td><td></td><td>The low sensitivity (29%) in the Palfy et al. study (2018) should be disregarded because it’s not statistically significant.

TABLE 2 Subgroup analysis of CorVue™ specificity, sensitivity, PPV, and NPV according to CRT-D or ICD device and implantation localization
<table><tr><th></th><th>ICD</th><th>CRT-D</th><th>P-value</th><th>Submuscular</th><th>Subcutaneous</th><th>P-value</th></tr><tr><td>Sensitivity</td><td>0.13 (0.00–0.53)</td><td>0.29 (0.10–0.56)</td><td>0.624</td><td>0.10 (0.00–0.45)</td><td>0.33 (0.11–0.62)</td><td>0.345</td></tr><tr><td>Specificity</td><td>0.76 (0.69–0.82)</td><td>0.65 (0.57–0.72)</td><td>0.043</td><td>0.32 (0.25–0.40)</td><td>0.65 (0.57–0.72)</td><td>0.362</td></tr><tr><td>PPV</td><td>0.02 (0.00–0.13)</td><td>0.08 (0.03–0.18)</td><td>0.398</td><td>0.02 (0.00–0.11)</td><td>0.10 (0.03–0.21)</td><td>0.205</td></tr><tr><td>NPV</td><td>0.95 (0.90–0.98)</td><td>0.90 (0.83–0.95)</td><td>0.221</td><td>0.92 (0.85–0.96)</td><td>0.93 (0.87–0.96)</td><td>1.000</td></tr></table>CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter defibrillator; NPV = negative predictive value; PPV = positive predictive value.</td><td>This information is from a subgroup analysis, which compared the accuracy between ICD and CRT-D devices. We did include this data as we were concerned with the overall performance of the algorithm. The data extracted was the prognostic accuracy across both devices (i.e. 24% sensitivity, see table 15 in EAG report).</td></tr>
<tr><td>46</td><td>Ross Wardle Abbott</td><td>118</td><td></td><td>There’s a typo: ‘morality’ instead of ‘mortality’.</td><td>Thank you for pointing this out, we have made this change.</td></tr>
<tr><td>47</td><td>Ross Wardle Abbott</td><td>104</td><td></td><td>We believe the ‘Implementation outcomes’ are an important measure of how useful these algorithms are in practice. A key consideration is how the clinician will identify and treat the patients that are missed by the algorithms and if this additional work would identify all the patients anyway.</td><td>The EAG agree that these are important outcomes for consideration.</td></tr>
<tr><td>48</td><td>Ross Wardle Abbott</td><td>157</td><td></td><td>During section names ‘Implications for service provision’, the sensitivities of the algorithms are only compared with each other. Although it does make sense to compare the algorithms, we also believe it would be helpful to understand what level of sensitivity would be reliable enough to change service provision and therefore reduce workload in practice.</td><td>The EAG appreciate your comment. The focus on sensitivity was mainly based on it being consistently reported between the studies. However, we have not directly compared the studies within or between technologies. Whilst this was</td></tr>
</table>

					previously stated in section 3.5.8, based on this accumulative feedback we have made this more explicit throughout the report. Additionally, we have added in the section specified by the company the following sentence: "However, we did not perform any meta-analytical techniques and therefore, these quantifications are based on numerical trends only and should be interpreted with caution." The EAG could not provide comment on what level of sensitivity is required to alter clinical practice.
49	Chloe Nobel **British Society For Heart Failure**	Whole Document	Whole document	The BSH welcomes this report which has considered the available research into these remote algorithms. It is presented in uncomplicated language for the reader. The human resource and financial burden of unplanned hospitalizations for heart failure remain considerable and suggests that these remote algorithms are likely to be cost-effective. Improving outcomes for people with heart failure patients is of vital importance and endorsement of such technology could help overcome the perceived inertia in adopting these into clinical practice.	We thank the BSH for their positive comments.

50	Chloe Nobel **British Society For Heart Failure**	50	Whole Document	It is clear that considerable effort has been employed in putting this report together. However, there are a few typographical errors in this document (e.g. DRT-D rather than CRT-D on page 50). Before the final report is published, we would suggest further proof reading.	Again, we thank the BSH for their positive comments. We have endeavoured to correct such instances.

Model Comments

Name and Organisation	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG Response
Ralphael Oghagbon Medtronic	1) Hazard ratio for survival benefit	The EAG model samples the hazard ratio for mortality for TriageHF (which is set to 1 in the base-case) via a lognormal distribution based on an assumed standard error of 0.1, leading to a 95% confidence in the range (0.8, 1.2). This variability does not reflect the	As the key difference between the groups is the rate of hospitalisation (and the knock-on effect on cost and quality of life), we believe that modelling a difference in survival leads to a misleading picture of decision uncertainty (see the scatter plot and	We would anticipate that this leads to significantly less variability in incremental QALYs, with the scatter plot points being aligned more vertically and slightly to the right of the vertical axis. This would also increase the probability of TriageHF being cost-effective at a £20,000 threshold.	Thank you for raising this. The EAG acknowledges that assuming a 10% standard error in the mortality estimates could have led to wide variation in the expected QALYs differences between groups. Therefore, a scenario analysis excluding uncertainty in mortality from the probabilistic analysis was

		evidence and leads to wide varation in the expected QALY differences between TriageHF and the control group. While Figure 10 of the EAG report (the acceptability curve) suggrests ~80% chance of TriageHF being cost-effective at a threshold of £20,000 per QALY, we believe this should be considered a lower limit of this probability, given the minimal expected differences in mortality between the groups.	acceptability curve in Figures 9 and 10 of the EAG report) which clouds the true differences between the groups. While variation in outcomes between patients is to be expected, we would not anticipate such large QALY differences at a population level. If there are PSA replications in which TriageHF is predicted to be lower than the control, this should be driven by uncertainty in the distribution of the incidence rate ratio for hospitalisations in the TriageHF group. Our suggestion is therefore that the hazard ratio should be held constant at 1 in the PSA,		undertaken for HeartLogic and TriageHF (see Table 43) and the report section 6.8.4 and Table 47 has now been updated to explain the impact in results. Not modelling the uncertainty in the mortality parameter in the PSA did not change the overall conclusion for HeartLogic and TriageHF. However, it increased the probability of cost-effectiveness.

			as there is no evidence of a survival benefit in either direction.		
Ralphael Oghagbon Medtronic	2) Scenario analyses 6.8.2	One-way sensitivity analyses The EAG could not conduct a one-way sensitivity analysis for base case results because it was not feasible to derive an ICER when the results were either cost saving, cost increasing or dominant.	The Assessment Group report identified that the evidence for the treatment effect of TriageHF and other technologies is at risk of bias due to confounding. It may be informative to the Committee if sensitivity analyses had been conducted.	It has been observed by the EAG that “threshold analysis showed that HeartLogic and TriageHF only needed to reduce hospitalisations by a few percent in order for them to be dominant”.	Thank you for the comment. We acknowledge that because of the nature of the results for this evaluation, the one-way sensitivity analysis was not possible. However, we have conducted a number of scenario analyses (and threshold analysis) which the committee could find informative.
Ralphael Oghagbon Medtronic	3) Table 32	The treatment effect for HeartLogic from Treskes 2021 was used in the cost-effectiveness analysis for HeartLogic (rate ratio 0.282). It is implausible for the	One comparative study for HeartLogic utilised a propensity-matched retrospective cohort design (Feijen 2023) which appears to make this study a more suitable choice for inputs	Expected for HeartLogic to be dominant, as it has been observed by the EAG that “threshold analysis showed that HeartLogic and TriageHF only needed to reduce hospitalisations by a few percent in order for them to be dominant”.	Thank you for the comment. Please see the response to Report Comment 3. We report in Section (6.7.3, Table 43) that considering the potential biases in the evidence for

		entire treatment effect observed in Treskes 2021 to be attributed to HeartLogic considering a parallel reduction in HF hospitalisations is expected due to de novo implantation of a CRT device in 59% (44/74) patients.	to the cost effectiveness analysis. Alternatively, sensitivity analysis may be run with assumptions of a smaller treatment effect on HF hospitalisations than reported in Treskes 2021.		hospitalisation rates we changed the IRR of hospitalisation for HeartLogic from 0.282 to 0.641 as a scenario analyses. However, the result were generally similar to the one observed in basecase. We report this in section 6.8.4 and Table 47. In addition, in section 7.1.2. we also state "*Threshold analysis showed that HeartLogic and TriageHF only needed to reduce hospitalisations by a few percent in order for them to be dominant*."
Claire Duxbury Boston Scientific	1	**Absolute utilities/utility decrements incorporated in model as relative values** Currently absolute utility decrements are	Relative decrements should be estimated and used if the modeller wants to multiply the age relevant utilities. This could be done the following way:	The original model has underestimated the advantage of HeartLogic. With the corrections, HeartLogic remains a dominant alternative (i.e., more effective and less costly), however the QALY advantage of HeartLogic increases by 43%. **Incr. QALYs** / **Change from original**	The EAG acknowledges that there could be differences in the incremental QALYs because of calculating utility decrement as relative values instead of absolute differences.

<table>
<tr>
<td></td>
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<td>estimated for both HF utilities and for hospitalisations. However, in the model engine, the health state utilities for HF are estimated by using these absolute decrement as if they were relative decrements: age relevant general population utility values are multiplied by 1+the absolute decrement. Hospitalisation decrements are estimated similarly.

Absolute decrements should be subtracted from general population utilities and relative decrements should be multiplied by general population utilities.</td>
<td>• The relative individual NYHA values could be estimated as Modelled utility/Population utility (e.g., H7/G7 in Sheet ‘Utilities’), instead of Modelled utility-Population utility (e.g., H7-G7 in Sheet ‘Utilities’).

• QALYs are then estimated as age specific general population utilities multiplied by the weighted average of relative individual NYHA values and cycle length (e.g., Sheet ‘Intervention’, cell AG12 and sheet ‘Comparator’ cell AF12 =O12*INDEX(Utilities!$F$31:$F$116,MATCH(ROUND(D12,0)</td>
<td>
<table>
<tr><td>Original model</td><td>[redacted]</td><td>-</td></tr>
<tr><td>With correction for relative utilities</td><td>[redacted]</td><td>+43%</td></tr>
</table>
Please see changes in the submitted model:
• Relative utility/utility decrement calculations on Utilities sheet highlighted yellow
• QALY calculations on Comparator and Intervention sheet columns AG, AH, AI highlighted yellow
</td>
<td>The EAG conducted a scenario analysis using the relative utility decrements as suggested in the comments. Section 6.6, Table 43, Section 6.8.4 and Table 47 have now been updated to reflect this. The change in method of calculation changed the QALY gains as suggested in the comments for both HeartLogic and TriageHF. However, the difference is just minimal in real terms (about 2 days of additional life) and does not change the conclusion of the study.</td>
</tr>
</table>

			,Utilities!$C$31:$C$116),0)*relative utility*$C$13, and not multiplied by (1+absolute decrement) as in the current model • Relative hospitalisation individual decrements should be estimated Mean utility decrement/Modelled utility (e.g. D17/D7) (named as u_DecHosp) • QALY decrements are then estimated as age specific general population utilities multiplied by the weighted average of relative individual decrements and cycle length (e.g., Sheet 'Intervention',		

			cell AH12 and sheet 'Comparator' cell AG12= =S12*INDEX(Utilities !$F$31:$F$116,MAT CH(ROUND(D12,0), Utilities!$C$31:$C$1 16),0)*u_DecHosp*$ C$13, and not multiplied by (1+absolute decrement) as in the current model • Total QALYs then are NYHA QALYs minus hospitalisation decrements (e.g., AH12=AF12-AG12), as the relative decrement is given not as a negative, but as a positive proportion. In the Assessment Group's Report, this affects section 6.5, Table 41 and the results.		

DIAGNOSTICS ASSESSMENT PROGRAMME

Algorithm-based remote monitoring of heart failure risk data in people with cardiac implantable electronic devices

External Assessment Report (EAR) and economic model – Collated Comments

Diagnostics Advisory Committee date 16 April 2024

<table>
<tr>
<td>Claire Duxbury

Boston Scientific</td>
<td>2</td>
<td>Incremental analysis was not done

According to the NICE HTA Manual [1] “Economic evaluation results should be presented in a fully incremental analysis with technologies that are dominated [… and technologies that are extendedly dominated […] removed from the analysis. Pairwise comparisons may be presented when relevant and justified (for example, when the technology is expected to specifically displace individual comparators)”

The current analysis assumes that the technologies cannot displace each other.</td>
<td>1. As the algorithms are integral part of each device, assuming equal efficacy for all devices as per prior NICE guidance, this would include taking into account the device costs (price, maintenance, replacement).

2. Incremental analysis should be done as per NICE HTA Manual</td>
<td>The incremental analysis would result in HeartLogic being the only cost-effective algorithm.

Please see below the results using the original (not corrected) model. With the corrected analysis, the differences would be greater.
<table>
<tr><th></th><th>Incr. QALY</th><th>Incr. Costs</th><th>Dominance</th></tr>
<tr><td>comparator</td><td>[redacted]</td><td>[redacted]</td><td>-</td></tr>
<tr><td>CorVue</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr>
<tr><td>HeartInsight</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr>
<tr><td>HeartLogic</td><td>[redacted]</td><td>[redacted]</td><td>Dominant</td></tr>
<tr><td>TriageHF</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr>
</table>
</td>
<td>The same response given for Report Comment 39 is repeated here:

In the scope and protocol of this study, the effectiveness and cost-effectiveness of each algorithm remote monitoring system was evaluated compared to no algorithm for the same CIED. It could not be assumed that each CIED was as effective as each other. This study comprises four separate technology appraisals, one for each algorithm remote monitoring system brand.

For each economic evaluation, the cost of the device is the same with or without the algorithm activation. The cost of a device was therefore omitted from the analysis.</td>
</tr>
</table>

		However, while the algorithms are only compatible with specific devices, the algorithms are integral part of the devices, and the algorithms with their devices can displace each other. As the price, longevity, etc. of each device differs, evaluating the algorithms as separate from devices does not reflect clinical practice, where the decisions are made for both the use of algorithm and the device with the algorithm, and not in isolation just the algorithms. The separate analysis can also bias results.			The underlying assumption is that the algorithm is an optional extra for each device. The cost of the algorithm was modelled as a one-off cost or monthly according to the information supplied by the company. Often, free updates of an algorithm was quoted. There was no clear basis for assuming a useful life duration for an algorithm for the purpose of costing.

		[1] *NICE health technology evaluations: the manual. 31 October 2023.* https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation			
Claire Duxbury Boston Scientific	3	**Efficacy is limited to avoided hospitalisations, which could substantially underestimate the benefit of the algorithms** The cost-effectiveness model only takes into account one advantage of algorithms: reduced hospitalisations. However, there are additional,	1. The health benefit of avoiding HF can be quantified and should be included in the analysis by multiplying the benefit of avoiding a HF event with the probability of having an event with and without HeartLogic. This benefit can be explored for example by changing the hazard ratio on the Mortality sheet (cell D6).	The inclusion of the health benefit of avoiding HF would increase the QALY advantages for HeartLogic. E.g., just changing the hazard ratio from 1.00 to 0.99 increases the QALY benefit by 464% in the original model for HeartLogic.	Thank you for your comments. 1. We acknowledge that the economic evaluation was limited in terms of the parameter evidence. This has been stated in Section 7.2.2. 2. The EAG agrees that McGee et.al 2022 study looks at remote monitoring systems, and not HF algorithms. We have

		unaccounted for health benefits: 1. The mitigation of HF events are the main benefit of the algorithm. According to the Assessment Group's Report: "*The propensity-matched controlled study did show a statistically significant difference in HF events, with less events occurring in the HeartLogic intervention group compared to those without the algorithm*". This is supported by non-comparative studies: "*For non-comparative evidence using*	Some of the QoL benefit is difficult to quantify, however it should be mentioned as unaccounted for benefit for HeartLogic. We recommend adding a sentence to the conclusions of the Assessment Group's Report mentioning that results are potentially conservative for HeartLogic, as the cost-effectiveness model could not account for the benefit of the high accuracy.		now edited Section 6.4.1 to address this. 3. The EAG acknowleges that there could be other wider benefits such as increased patient satisfaction, improved QoL etc. however because of the limited evidence the impact on the wider benefits could not be considered in the economic evaluation. The limitations of the evaluation has already been highlighted in Section 7.2.2.

		HeartLogic there was evidence that when IN alert compared to OUT of alert related to increased risk of HF events occurring". HF hospitalisations are associated with important mortality and quality of life implications, which are not taken into account, underestimating the potential benefit of HeartLogic. For example, Zaca et al 2020 found an 11-fold increase in mortality risk for device patients with an occurrence of at least one heart			

		failure hospitalisation compared with patients without (95% CI: 5.9-20.5, P < 0.0001); an SLR from Di Tanna et al (2021) stated that "it is evident that a hospitalization event reduces utility"; McMurray et al (2018) reported a disutility of − 0.105 for patients hospitalized in the previous 30 days, which reduces to − 0.054 for patients hospitalized in the previous 30–90 days (UK value set). 2. The Assessment Group's Report			

		states, that the hazard ratio of 1 has been used for mortality as "*a systematic review and meta-analysis conducted by McGee et al 2022 did not find any significant reduction in mortality (RR= 1.02, 95% CI 0.85 to 1.23, p=0.055)) from remote monitoring in patients with heart failure with cardiac implantable electronic devices*" (page 122). However this study looks at remote monitoring systems, and not HF algorithms (please see comment 3 in the report section			

		above for further clarification). 3. According to the Assessment Group's Report, "*HeartLogic had the highest and most consistent accuracy measures*" (page 10), however the consequences of this on health benefit (e.g., increased mitigation, increased patient satisfaction, decreased QoL loss due to reduced false/non-clinically meaningful alerts) are not included, underestimating the potential benefit of HeartLogic.			

		Increased accuracy is only taken into account as potential extra cost (increased follow up for the increased number of alerts), but not potential health benefit, which disadvantages algorithms with higher sensitivity.			
Claire Duxbury Boston Scientific	4	**Baseline number of hospitalisations differs between interventions, underestimating the advantage of HeartLogic** The model assumes 48% higher hospitalisations for the comparator of TriageHF than for the comparator of HeartLogic (total hospitalisations: 6.31	As there is no reason to assume, that the populations differ for HeartLogic and TriageHF, the same baseline should be included. As discussed in section 6.4.1 of the Assessment Group's Report, McGee et al 2022, did not find significant difference between RMSs. As the model already uses IRRs to estimate	The original model has underestimated the advantage of HeartLogic. With the corrections, HeartLogic remains a dominant alternative (i.e., more effective and less costly), however the cost-savings increase. The monthly hospitalisation rates are redacted for TriageHF, but using the difference in the total number of hospitalisations, and increasing baseline (comparator) hospitalisations for HeartLogic by 48% results in: • The saved hospitalisations increasing by 48% with HeartLogic compared to the original model • Cost savings increasing by 76% with HeartLogic compared to the original model	Thank you for the comment. We have now removed the erroneous reference McGee et al 2022, which did not compare algorithm based RM with RM. However, the EAG is not convinced that the baseline population for HeartLogic would be same as TriageHF. Please see responses to Boston Scientific Model Comment 2 and Report

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<td>vs. 4.25 respectively). Unless there is a reason to assume that the population for HeartLogic is less ill than the population for TriageHF (which is currently not articulated in the report), there is no reason to use a different baseline.

The use of different baseline means, that despite the IRR (incidence relative ratio) for HeartLogic showing higher proportions of hospitalisations avoided than the IRR for TriageHF (0.282 vs. 0.42 respectively), with the much higher baseline, the number of hospitalisations saved is higher with TriageHF. This is due</td>
<td>hospitalisations for the interventions, the comparator or baseline hospitalisations need to be the same on the Resource use sheet, in cells C112:C171.

In the Assessment Group’s Report, this change affects section 6.6.3, Table 41 and the results.</td>
<td>
<table>
<tr><th></th><th>Incr. Hosp.</th><th>Change from original</th></tr>
<tr><td>Original model</td><td>-3.05</td><td>-</td></tr>
<tr><td>+ same hosp. baseline</td><td>-4.51</td><td>48%</td></tr>
<tr><th></th><th>Incr. costs</th><th>Change from original</th></tr>
<tr><td>Original model</td><td>-8,090</td><td>-</td></tr>
<tr><td>+ same hosp. baseline</td><td>-14,213</td><td>76%</td></tr>
</table>
Please see changes in the submitted model by toggling between the original calculations and the revised baseline on sheet Resource utilisation, in cell H7.
</td>
<td>Comment 39 regarding the appropriate comparators in this study.</td>
</tr>
</table>

		to being able to save more hospitalisations if the initial hospitalisations (the baseline) from which we are saving, is higher.			
Claire Duxbury Boston Scientific	5	**Not all cost-consequences are taken into account** Only hospitalisation and scheduled/unscheduled follow-up time is taken into account in the cost calculations. The following costs are not included in the model: 1. Clinic visits, which were shown to be statistically significantly reduced with HeartLogic in a propensity score	We recommend the addition of a sentence within the conclusions of the Assessment Group's Report mentioning that results are likely to be conservative for HeartLogic, as there are potential additional cost savings not accounted for in the cost-effectiveness model. These are due to the avoided HF events, reduced clinic visits and compared to other algorithms the less false/non-clinically meaningful alerts.	The original model has underestimated the advantage of HeartLogic.	Thank you for the comments. However, the EAG feels the current conclusion is appropriately worded. Please see responses to Boston Scientific Model Comment 2 and Report Comment 39 regarding the appropriate comparators in this study.

		matched retrospective cohort study described in Assessment Group's Report (Feijen et al. 2023). The model however assumes an increased number of visits (scheduled and unscheduled) with HeartLogic. 2. Cost of avoided HF events, other than hospitalisations (e.g., A&E visits, indirect costs (e.g. productivity), direct non-healthcare costs (e.g. travel)) According to the Assessment Group's Report, "*HeartLogic had the highest and*	We have also made a comment in the report section above (comment 9) relating to the assumptions around clinic visits.		

		most consistent accuracy measures" (page 10), however the consequences of reduced false/non-clinically meaningful alerts are not included, underestimating the potential benefit of HeartLogic.			
Ross Wardle Abbott	1	In the report, it's explicitly stated: "Hospitalisations were statistically significantly reduced in those with a CorVue enabled device compared to those with no implanted device receiving standard home care." We believe the statistically significant reduction in hospitalisation should	We believe the statistically significant reduction in hospitalisation should be implemented in the economic model	CorVue would be shown to be cost-effective	Thank you for the comment. However, the comparision for the economic evaluation was Algorithm based RMS versus RMS for a given device. The evidence you have stated here compared CorVue enabled device with standard care (with no device at all). Therefore, the evidence suggested does not apply.

		be implemented in the economic model, but it is not			