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Protocol and economic evaluation for Advanced Image Supported Lead Placement in Cardiac Resynchronization Therapy (ADVISE): a multicenter randomized controlled trial

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4 1 **Protocol and economic evaluation for Advanced Image Supported Lead**
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6 2 **Placement in Cardiac Resynchronization Therapy (ADVISE): a multicenter**
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8 3 **randomized controlled trial**

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26 **Abstract**

27 **Introduction:** Achieving optimal placement of the left ventricular (LV) lead in cardiac
28 resynchronization therapy (CRT) is a prerequisite in order to achieve maximum clinical
29 benefit, and is likely to help avoid non-response. Pacing outside scar tissue, as well as
30 targeting late activated segments, may improve outcome. The present study will be the first
31 randomized controlled trial to investigate the efficacy of *real-time* image-guided LV lead
32 delivery towards a pre-defined target, and compare this to conventional CRT implantation. In
33 addition, to estimate the cost-effectiveness of targeted lead implantation, a preliminary
34 decision analytic model was developed.

35 **Methods and analysis:** A multicenter, interventional, randomised controlled trial will be
36 conducted in a total of 130 patients with a class I or IIa indication for CRT implantation.
37 Patients will be stratified to heart failure aetiology and 1:1 randomized to either empirical lead
38 placement or live image-guided lead placement. Ultimate lead location and
39 echocardiographic assessment will be performed by core laboratories, blinded to treatment
40 allocation and patient information. Late gadolinium enhancement cardiac MRI (LGE-CMR)
41 and CINE-CMR with feature-tracking post processing software will be used to semi-
42 automatically determine myocardial scar and late mechanical activation. The subsequent
43 treatment file with optimal LV-lead positions will be fused with the fluoroscopy, resulting in
44 live projection of the overlay during the procedure. The primary endpoint is the difference in
45 percentage of successfully targeted LV-lead location. Secondary endpoints include relative
46 percentage reduction in indexed LV end-systolic volume and a hierarchical clinical endpoint.

47 **Ethics and dissemination:** In all patients, a standard CMR procedure and two
48 echocardiographic examinations are performed. Additionally, two questionnaires are
49 conducted at various time points until two year post-procedure. Lastly, a slightly prolonged
50 CRT implantation as a consequence of more specific guided LV-lead implantation may be
51 possible. The trial is registered at a Dutch trial register (Trial NL8666).

53 **Article Summary**

- 54 • First multicenter randomized controlled trial for CMR-guided lead placement in CRT.
- 55 • Live visualisation, fused with fluoroscopy, using accurate targeting model.
- 56 • Cost-effectiveness model of targeted implantation to predict economic benefit.
- 57 • CMR feature-tracking may be subject to noise and technical limitations.
- 58 • Limited power with respect to detecting differences in echocardiographic response.

59 **Keywords:** image-guided therapy; lead placement; cardiac resynchronization therapy; MRI
60

1. Introduction

Chronic heart failure is a major global health concern with a 5-year mortality rate of about 50%. In about one-third of these patients, heart failure is accompanied by left ventricular (LV) conduction delay (i.e. QRS-duration ≥ 130 ms), which is a predictor for worse prognosis [1,2]. Cardiac resynchronization therapy (CRT) greatly reduces morbidity and mortality in these patients, but the extent of response is inconsistent and highly dependent on adequate LV lead placement (LVLP). In-scar LVLP greatly increases risk of cardiovascular death and HF-hospitalisation [3], whereas pacing in an area of late activation is likely to improve outcome [4–6]. Moreover, a suboptimal lead position cannot be compensated by optimizing device programming [7], rendering adequate LVLP arguably the cornerstone of this device therapy.

Because the optimal location is highly variable and patient-specific, an individualised and targeted approach is often warranted [8]. Previous research has demonstrated the benefits of image-guided lead delivery as a mean of improving clinical outcome [8,9]. However, most studies did not allow for electrical guidance in the control group and allowed for only eight potential targets for lead deployment, thereby limiting the accuracy of lead deployment and increasing the odds of fortuitous “in-target” lead placement [10,11]. Moreover, no large studies allowed for real-time visualisation of optimal targets, and most of the image-guided studies were not conducted in a true multicenter setting. As such, the current evidence for image-guided LVLP has remained relatively limited, and contemporary LVLP is still largely based on an empirical strategy [1].

The present study protocol describes the first multicenter randomized controlled trial investigating advanced image supported lead placement in CRT (ADVISE-CRT). The primary aim of the study is to demonstrate the feasibility of reaching pre-defined segments through accurate image-guidance, using an 18-segment LV lateral wall model with live visual guidance. The secondary objective is to investigate the clinical efficacy by evaluating differences in the extent of reverse remodeling and a hierarchical clinical endpoint between both groups. Lastly, an early Health Technology Assessment (HTA) will be conducted to determine the expected cost-effectiveness of a patient-tailored approach for targeted lead placement.

2. Methods and analysis

The ADVISE-CRT trial is a multicenter, randomised controlled trial that is blinded to both patient and assessors of outcome (**Figure 1**). Assessment of LV dimension, LV function, and lead location will be performed by core laboratories. Patients will be stratified according to aetiology of heart failure in order to assure equal distribution of patients with ischemic cardiomyopathy (ICM) and non-ICM patients in both groups. All 130 patients will be 1:1 allocated to either image-guided or empirical LVLP using variable block-randomization:

- Intervention group: live visualised, fluoroscopy-fused, image-guided, lead placement on the basis of avoiding scar and targeting late mechanically activated segments.
- Control group: empirical standard-of-care lead placement in line with current CRT implantation guidelines with electrical guiding on the basis of Q-LV sense [4].

Patient involvement

Patients are part of our multidisciplinary consortium, both before and during the study, and are as such involved in the design and conduct of the study. The priority of the research question, patient communication, study logistics, and methods of recruitment have been informed by discussions with patients representing our study population.

Study population

Patients are prospectively enrolled in at least six Dutch academic and peripheral centres. Consecutive patients eligible for CRT with a class I or IIa indication, with or without defibrillator function, according to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure are considered. In addition, some additional criteria for study participation apply (**Table 1**). Informed consent will be obtained from willing participants by delegated study coordinators, prior to study procedures.

Overview of assessments

Prior to device implantation, all patients will undergo echocardiographic examination and cardiac magnetic resonance imaging (CMR). CMR feature-tracking (CMR-FT) analyses will be performed in both study groups, after which optimal LV-lead location will be determined. Randomization will occur after targets for lead deployment have been defined, after which targets cannot be altered. All patients will receive two quality of life questionnaires (EQ-5D-5L and Kansas City Cardiomyopathy Questionnaire) at four time-points: before implantation and at 6 months, 12 months, and 24 months after implantation. A 12-lead ECG will be

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4 130 performed before, directly after, and 6 months after implantation. During the procedure,
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6 131 various LV-paced effects will be measured. Ultimate lead location will be assessed on the
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8 132 basis of LAO40 and RAO30 fluoroscopy as described by Singh and colleagues [12]. A global
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10 133 schedule of all assessments is summarised (**Figure 2**).
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12 134

13 135 **CMR analysis and target allocation**

14 136 Clinical standard short axis CINE acquisitions with a minimum of 25 frames per R-R interval,
15
16 137 at max 8mm slice thickness and no slice gap, and LGE acquisitions at max 8mm slice
17
18 138 thickness will be performed in the participating hospitals. Post processing will be performed
19
20 139 in a centralized fashion using a dedicated software toolbox (CARTBox, CART-Tech B.V.,
21
22 140 Utrecht, The Netherlands). The CARTBox analysis results in a treatment file, which will be
23
24 141 used as an overlay with live fluoroscopy during the implantation procedure in the intervention
25
26 142 group. Semi-automated and deep-learning assisted contouring CMR-FT analysis will be
27
28 143 performed to quantify myocardial deformation and identify the tissue with the latest
29
30 144 mechanical contraction. Scar transmuralty will be identified based on the LGE acquisitions.
31
32 145 Three dimensional maps of mechanical activation and scar transmuralty are combined and
33
34 146 used to define the optimal tissue (targets) for the LV lead. Targets will then be allocated on
35
36 147 the basis of a pre-specified decision-model by two investigators, blinded to each other.
37
38 148 Segments that contain myocardial scar will be disregarded, whereas segments with latest
39
40 149 mechanical activation will be considered most appropriate.

41 150 Because multiple regions may be deemed suitable, a maximum of three of the most
42
43 151 suitable segments will be ranked and considered for implantation in that order of priority. In
44
45 152 the case of initial disagreement, consensus will follow after discussion. Of note, the original
46
47 153 unprocessed CMR will be available at the discretion of the implanting cardiologist, also in the
48
49 154 control group.
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51 155

52 156 **Echocardiography**

53 157 Transthoracic echocardiographic examinations will be performed at baseline and 6 months
54
55 158 after CRT implantation at each participating centre. A standard local protocol used for strain-
56
57 159 imaging in CRT candidates will be used, with special attention to high quality images of the
58
59 160 LV. To this end, each acquired image will include at least three separate beats, and LV strain
60
61 161 images will be frame-rate optimized by using the narrowest sector width possible. LV
62
63 162 volumes and function will be assessed using Simpson's bi-plane method [13]. Mechanical
64
65 163 dyssynchrony (apical rocking, septal flash) and discoordination (systolic rebound stretch of
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4 164 the septum, systolic stretch index) will be assessed as well. All examinations will be analysed
5
6 165 by an echocardiography core laboratory using vendor-independent software.
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9 167 **Randomization and blinding procedures**

11 168 After baseline assessments and subsequent identification of optimal targets for LVLP,
12
13 169 computer-generated variable block 1:1 randomization to either image-guided (intervention) or
14
15 170 empirical (control) implantation will be performed (Castor EDC, Amsterdam
16
17 171 the Netherlands). Randomization will be stratified according to ischemic or non-ischemic
18
19 172 heart failure etiology. Study data will be collected, recorded, logged and managed in
20
21 173 compliance with Good Clinical Practice guidelines. All study data are recorded in an
22
23 174 electronic case report form (eCRF), where any changes in data entry are logged. All data
24
25 175 entered, including perioperative data related to device implantation and optimization, are
26
27 176 collected and entered into the eCRF by either the coordinating investigator and/or research
28
29 177 nurse. External data validation will be managed by a study monitor, designated by a contract
30
31 178 research organization. Both the patient and core laboratories assessing endpoint data
32
33 179 (fluoroscopically determined LVLP and echocardiography) will be blinded to the intervention.
34
35 180 After 6 month follow-up has been completed by all patients, unblinding is allowed. After 6
36
37 181 months, no observer-dependent endpoint data remains to be collected, and electrode
38
39 182 reselection is allowed where indicated.
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41 183

42 184 **Device implantation**

43 185 Implantation of CRT, unrestricted by manufacturer or the presence or absence of defibrillator,
44
45 186 will occur under local anaesthesia and light intravenous sedation according to standard
46
47 187 procedure. In the control group, LVLP will occur at discretion of the physician but in line with
48
49 188 current guidelines (i.e. based on an empirical strategy, guided by Q-LV sense). Q-LV sense
50
51 189 is measured unipolar and defined as the time interval between QRS onset on the surface
52
53 190 ECG and the maximum voltage *change* over time (i.e. dV/dt), recorded on the
54
55 191 electrocardiogram. The LV electrode with the longest Q-LV sense in combination with
56
57 192 acceptable pacing threshold and without diaphragmatic stimulation will be selected. In the
58
59 193 image-guided intervention group, 2-dimensional fluoroscopic images are co-registered to the
60
194 previously derived CARTBox treatment file from CMR postprocessing, and visualised in real-
195 time in conjunction with the live fluoroscopy used during the implantation procedure (**Figure**
196 **3**). The LV-lead will be deployed on the basis of the pre-defined target. Only when multiple

1
2
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4 197 electrodes are within the target region, electrode selection based on electrical properties
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6 198 (e.g. Q-LV sense) is applied.

7 199 During the procedure, pacing capture thresholds, phrenic nerves stimulation, intrinsic
8
9 200 electrical delay (i.e. Q-LV sense) and various LV-paced effects (i.e. LV-pace to RV-sense
10
11 201 and RV-pace to LV-sense) will be determined for each electrode of the quadripolar lead
12
13 202 positions. When the ultimate lead position has been established, LAO40 and RAO 30
14
15 203 fluoroscopic imaging will be performed to determine the exact final lead location. Final LV
16
17 204 lead location will be determined by two investigators, blinded to outcome of each other, using
18
19 205 the method described by Singh and colleagues [12].
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21 206

207 **Endpoints**

22 208 The ability to achieve successful image-guidance will be based on differences in the
23
24 209 percentage of within, adjacent, or remote from the target(s) selected for lead placement.
25
26 210 Secondary outcomes include relative reduction in LV end-systolic volume indexed to body
27
28 211 surface area (LVESVi), proportional difference in volumetric response (> 15% LVESVi-
29
30 212 reduction), differences in quality of life, and differences in the CRT response score. The latter
31
32 213 is a hierarchical clinical endpoint based on HF-hospitalisation and/or death within 12 months,
33
34 214 relative LVESVi-change, and change in NYHA class [14]. Other secondary outcome
35
36 215 measures include the following: implantation procedure time, fluoroscopy time, contrast
37
38 216 dose, device or procedure-related complications, indices of mechanical resynchronisation
39
40 217 and recoordination, change in QRS duration and QRS_{AREA}, and LV-lead parameters (Q-LV
41
42 218 sense, pacing threshold, phrenic stimulation). Lastly, a Health Technology Assessment
43
44 219 (HTA) concerning the additional value of image-guided lead placement in terms of healthcare
45
46 220 expenditure revolving heart failure care will be performed. The HTA will be based on a
47
48 221 previously conducted preliminary economic analysis, which will be described in this article.
49
50 222

51 223 **Sample size**

52 224 When comparing image-guided and contemporary delivered of CRT, the proportional
53
54 225 difference in within-target LVLP ranges between 6 and 30%, and thus varies considerably
55
56 226 [8]. In contrast, ADVISE targets segments half the size of areas used in previous studies,
57
58 227 rendering the chance of fortuitously successful in-target implantation in either study group
59
60 228 much smaller.

229 We therefore hypothesized that image-guidance will result in a proportional difference in
230 within-target LVLP of at least 27% when compared to empirical lead placement. In order to

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4 231 demonstrate this proportional difference using a two-sided Fisher exact test with 80% power
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6 232 and $\alpha = 0.05$, a total of 114 successfully implanted patients are needed.

7 233 Concerning the secondary endpoint of reverse remodelling, given an expected standard
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9 234 deviation below 25%, a significant difference in LVESVi reduction between both groups of at
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11 235 least 13% can be detected in 116 patients. Accounting for failed implantations, loss to follow-
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13 236 up and incomplete (echocardiographic) data in about 10% of cases, total sample size
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15 237 necessary was set at 130 patients.

16 238

17 239 **Statistical analysis**

18 240 An intention-to-treat analysis will be performed to assess LV-lead location and
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20 241 echocardiographic response. In echocardiographic non-responders where electrode
21
22 242 reselection is feasible, transition of control patients towards the treatment group may occur
23
24 243 after 6 months. To account for this potential cross-over, an additional per-protocol analysis
25
26 244 may be performed with respect to long-term clinical endpoints and the HTA.

27 245 The primary endpoint concerning LV-lead location will be defined categorically as being
28
29 246 either within, adjacent, or remote from the pre-defined target. A two-tailed Fisher exact test
30
31 247 will be performed to assess differences in lead location between both groups. Because in
32
33 248 principle, the effect of a targeted approach is considered to result in a unidirectional change
34
35 249 in lead location, a one-tailed Fisher exact test may be performed as well.

36 250 Secondary endpoints will be analysed according to treatment allocation and lead location
37
38 251 using Student's *t*-test and one-way ANOVA, or the Wilcoxon's rank sum test and Kruskal-
39
40 252 Wallis wherever applicable. Lastly, intra- and inter-observer agreement of the
41
42 253 echocardiography core laboratory analysis of reverse remodelling will be demonstrated by
43
44 254 computing intraclass correlation coefficients in approximately 25 echocardiograms. A *p*-value
45
46 255 < 0.05 will be considered significant.

47 256

48 257 **3. Ethics and dissemination**

49 258 The ADVISE trial will be conducted according to the principles of the Helsinki Declaration II
50
51 259 and Good Clinical Practice guidelines. The protocol has been written in accordance with the
52
53 260 Standard Protocol Items: Recommendation For Interventional Trials (SPIRIT) checklist
54
55 261 (**Supplemental file 1**). The trial has been registered at the Dutch trial register (Trial NL8666),
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57 262 26 May 2020. Patients are currently being enrolled, with the first patient included in January
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59 263 2021. The study protocol has been approved by The Medical Ethical Committee at University
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61 264 Medical Centre Utrecht.

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266 **4. Preliminary economic evaluation**

267 To estimate the expected impact on cost and effects of image-guided lead placement in
268 CRT, a preliminary decision analytic model was developed using a Markov-model consisting
269 of seven mutually exclusive health states (**Figure 4**). These health states were identified in
270 collaboration with clinical experts and based on available literature. In brief, a group of 1.000
271 individuals with heart failure were simulated, receiving either contemporary or image-guided
272 LVLP. The analysis was performed from a societal perspective, including both direct
273 healthcare costs and productivity losses due to absence from work. Model cycle length was
274 one month, and model time horizon was 120 months. This model was developed in Microsoft
275 Excel, version 2010/2016 (Microsoft, Redmond, WA, USA).

277 **Treatment of patients/structure of the model**

278 Patients with heart failure enter the model after the index CRT procedure (4:1 CRT-D versus
279 CRT-P) where all patients are deemed to be in stable condition. After implantation,
280 sequentially patients may 'transition' towards various 'health states', namely: cardiac
281 decompensation (at most three times), Left Ventricle Assist Device (LVAD) implantation, or
282 heart transplant. Detailed overviews of healthcare provided for each of the health states are
283 found in appendix I. Each health state is assigned a different probability of all-cause
284 mortality.

286 **Input parameters**

287 Different sources were used to identify input parameters and parameter values. The majority
288 of parameter values were retrieved from existing scientific literature. Where data was not
289 publicly available, expert opinion and data from UMC Utrecht were used. Given the
290 preliminary nature of this analysis there is no definitive data available on clinical effects or
291 costs for Image-guided lead placement. Input values for effects and costs were therefore
292 estimated by experts.

294 **Clinical Outcomes & Image-guided lead placement effectiveness**

295 For standard care, an assumed percentage of responders (LVESV-reduction $\geq 15\%$) was set
296 at 60% (17). For the additional effects of image-guided lead placement the percentage of
297 responders was increased with steps of 2.5% to a maximum of 97.5%. We also analysed the
298 situation for when 70% of patients receiving standard care are responders. First
299 decompensation probability, the arrow from stable to first decompensation in **Figure 4**, was

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4 300 based on a weighted average for hospitalization probabilities for responders and non-
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6 301 responders (18). Transfer probabilities between other health states were assumed to be
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8 302 equal between standard care and care with image-guided lead placement and were based
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10 303 on clinical outcomes which were retrieved from literature (19-21). Most important index
11
12 304 procedure complications were pneumothorax, lead dislocation, bleeding and pocket infection.
13
14 305 Probabilities of these complications occurring were based on previous research conducted at
15
16 306 the UMCU and were assumed not to differ between image-guided lead placement and
17
18 307 standard care (22).
19 308

309 **Cost-effectiveness estimation for image-guidance**

20 310 Based on 10,000 Monte Carlo iterations in the probabilistic sensitivity analyses, **Figure 5A**
21
22 311 shows the cost-effectiveness plane. Here, the Monte Carlo iterations are represented by the
23
24 312 blue dots. Mean cost difference was found to be -€7.329 (95%-CI: -€15.760 to € 323) and
25
26 313 mean Quality Adjusted Life Year (QALY) gain was 0.17 (95%-CI: -0.02 to 0.40). The majority
27
28 314 of iterations (96%) resulted in cost saving and an incremental health gain for image-guided
29
30 315 lead placement, as compared to standard care.

31 316 When the effectiveness of standard care is considered to be 70%, and the effectiveness
32
33 317 of CMR guided LVLP is varied between 70% and 95%, the results shown in **Figure 5B** were
34
35 318 found. Even at relatively small improvements in the proportion of responders, image-guided
36
37 319 lead placement leads to cost savings ranging from € 317 to € 20.069.

321 **One-way sensitivity Analysis**

38 322 In the one-way sensitivity analysis, we varied input parameter value with -20% and +20%,
39
40 323 this means the values of all parameters were altered one-by-one. By doing this for all model
41
42 324 input parameters, the influence of each parameter on model outcome is demonstrated. The
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44 325 one-way sensitivity analysis showed that the parameters with the greatest influence on the
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46 326 outcomes of the economic evaluation were; i) the percentage of responders for standard
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48 327 care, and ii) the percentage of responders for care with image guided lead placement. This
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50 328 entails that changes in the value of these parameters will most likely change the outcomes of
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52 329 the economic evaluation the most.

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331 5. Discussion

332 Electrical versus image-guided strategy

333 Although the STARTER and TARGET study demonstrated the benefit of an image-guided
334 approach for lead placement, they were performed in a time where electrical guiding (using
335 QLV-sense) was not yet routinely performed [10,15]. However, QLV-guidance is nowadays
336 considered standard-of-care in most centres, and therefore, the results STARTER and
337 TARGET cannot be directly extrapolated to current practice [4,16].

338 It is therefore noteworthy that only one study carefully investigated both an
339 electrically guided approach (using QLV-sense) and an image-guided approach in a direct
340 comparison [17]. Although Stephansen et al., reported non-inferiority of an electrical
341 approach, we need to consider that these patients had typical LBBB with an average QRS-
342 duration of 169 ms. This is in contrast to patients with non-LBBB morphology, where a QLV-
343 guided approach fails to result in superior outcome when compared to contemporary lead
344 placement [18]. In these patients, an image-guided strategy appears to be more beneficial
345 [15]. Ultimately, electrically-guided and mechanically guided approaches each have their own
346 strengths and limitations, and both may have yet to reach their full potential [8].

348 Methods used for lead placement

349 Because in-scar pacing is associated with a 6-fold increased risk for cardiovascular death or
350 hospitalization for HF, avoiding in-scar pacing is of utmost importance [3]. We therefore used
351 CMR with late gadolinium enhancement, which is considered the gold-standard for detection
352 of myocardial scar and has a higher spatial resolution than ⁸²Rubidium positron emission
353 tomography [19]. In contrast, the utility of strain imaging using echocardiography for
354 detecting scar is poor with a sensitivity of only 33% [20].

355 In addition to avoiding scar, feature tracking is performed on CMR CINE
356 sequences in order to determine viable segments with late mechanical activation. Although
357 CMR has lower temporal resolution than speckle-tracking echocardiography, its benefits
358 include the ability to sequence the whole heart and the lack of need for adequate acoustic
359 windows. In addition, strain analysis from CMR is subject to less bias and variability and can
360 be done semi-automatically.

362 Live fusion and target visualisation

363 Regardless of the methods used, it is inevitable that there will always be patients in which a
364 target cannot be reached. In particular, the variability and difficulty of reaching a pre-defined

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4 365 target is evidenced by the wide range of remote-from-target lead location, as reported in
5 366 previous studies [8]. Although venous access is undoubtedly a limiting factor, visualizing
6 367 target for lead deployment *during* the procedure most likely enhances the proportion of
7 368 optimally placed leads, since the implanter strives to implant the LV lead as close as possible
8 369 to the target tissue in a patient specific fashion. Although the feasibility of live fusion has
9 370 been demonstrated in two previous studies [21,22], they were limited by a small sample size
10 371 and non-randomized design.
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17 373 **Limitations and strengths**

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19 374 Our study is primarily limited by its relatively small sample size, and as a consequence, lack
20 375 of primary *clinical* endpoint with sufficient power to detect differences in LVESVi-changes
21 376 below 13% between both groups. Regardless, the present study is the first *multicenter*
22 377 randomized controlled trial set out to investigate live CMR-guided LVLP in CRT, thereby
23 378 providing data in a real-world setting. CMR is however less suitable for patients with prior
24 379 device implantation due to magnetic field inhomogeneities, reducing image quality. Although
25 380 CMR-FT has a lower temporal resolution when compared to speckle-tracking
26 381 echocardiography, it may suffer from less noise and inter-observer dependence. Moreover,
27 382 our technique allows for gold-standard scar detection, accurate segmentation, and live
28 383 visualization of suitable targets for lead deployment.
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36 385 **Future perspectives**

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38 386 Previous studies were conducted without performing QLV-guidance in the control group, and
39 387 were limited by using at most two recruiting centres [10,15,17]. Moreover, to date, no studies
40 388 utilized *live* image-guidance in a randomized controlled design. Should our study be able to
41 389 detect more reverse remodelling and/or better clinical outcome, an important step has been
42 390 set towards more widespread adoption of image-guided strategies for optimized LVLP in
43 391 CRT.
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50 393 **Author contributions**

51 394 PCW was involved in the study design and drafting the manuscript. FJS was responsible for
52 395 technical and methodological aspects revolving image guidance. CL and GWJF were
53 396 responsible for execution of the preliminary economic analysis. FJS, MJC and MM were
54 397 involved in study design and critical revision of the manuscript.
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4 399 **Funding statement**

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6 400 This work was supported by ZonMW, grant number 404460098327.

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9 402 **Availability of data and materials**

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11 403 Data generated during the study will be pseudonymised, in agreement with national privacy
12 404 legislation. Datasets will be stored for 15 years after study completion, and can be made
13 405 available upon reasonable request. When consent was provided, trial participants will be
14 406 actively informed about study outcomes upon completion. Results will be published in peer-
15 407 reviewed international journals, regardless of the study outcome.

16 408

17 409 **Conflict of interests**

18
19 410 FJS is co-founder, chief technical officer, and shareholder of CART-Tech B.V. MM and FJS
20 411 are inventors and beneficiaries of a patent license arrangement between the University
21 412 Medical Center Utrecht and CART-Tech B.V. according to the rules of the University Medical
22 413 Center Utrecht. All other authors have reported that they have no relationships relevant to
23 414 the contents of this paper to disclose.

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521 **Tables**

522

523 **Table 1. ADVISE inclusion and exclusion criteria**

Inclusion criteria

- Heart failure with LVEF \leq 35%;
- NYHA class II, III, or IV (ambulatory);
- Optimal medical treatment that is tolerable;
- LBBB with QRS \geq 130 ms, *or* non-LBBB with QRS \geq 150 ms.

Exclusion criteria

- Age < 18 years or incapacitated adult;
- Contraindication for CMR (gadolinium; contrast agents; metal);
- Atrial fibrillation; either permanent or during CMR;
- Severe renal insufficiency (GFR < 30 ml/min/1.73 m²);
- Participation in other potentially confounding trials.

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4 544 **Figure legends**

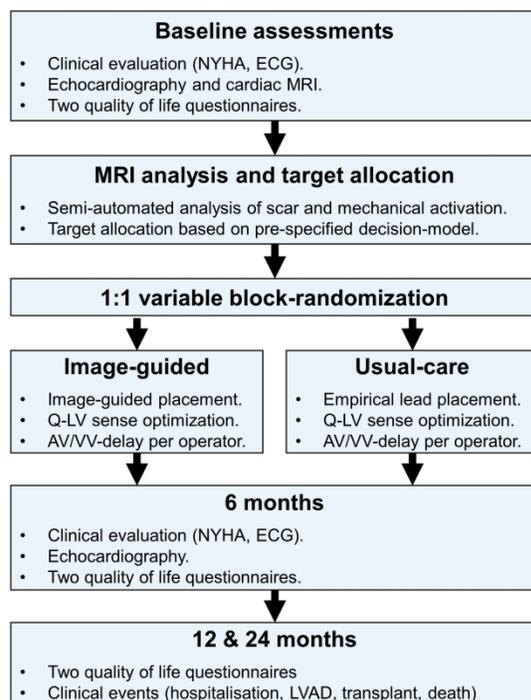
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6 545 **Figure 1.** Flow-chart presenting the course of the study.

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9 547 **Figure 2.** SPIRIT time schedule of enrolment, interventions, and assessments for the
10 548 ADVISE-CRT trial. ^a Includes implantation time, radiation exposure, and electrode
11 549 configurations; ^b e.g., indices of mechanical recoordination such as SRSsept.

12 550
13
14 551 **Figure 3.** Workflow for advanced image-guided LV-lead placement. CMR, cardiac magnetic
15 552 resonance imaging. LV, left ventricular.

16 553
17 554 **Figure 4.** Seven 'health states' (squares) were defined. Patients either remain in their state
18 555 during follow-up (inward arrows), or relocate towards the next sequential health state
19 556 (uninterrupted arrows). Each transition is assigned its own probability of occurrence. When
20 557 death occurs, other health states may be skipped (dashed arrows). Note that the assumption
21 558 was made that post-CRT patients with ≤ 2 decompensations will not receive LVAD or
22 559 transplantation. LVAD, Left Ventricle Assist Device.

23 560
24 561 **Figure 5. A:** Cost-Effectiveness Plane for image-guided lead placement. The graph shows
25 562 the iterations (blue dots) in comparison to the cost effectiveness thresholds for
26 563 €30.000/QALY and € 80.000/QALY (red and blue lines). B: Potential cost savings with
27 564 image-guided lead placement, based on the proportional difference in responders. Legend:
28 565 ICER, Incremental Cost Effectiveness Ratio ($\Delta\text{€}/\Delta\text{QALY}$); QALY, Quality Adjusted Life Year.



Flow-chart presenting the course of the study.

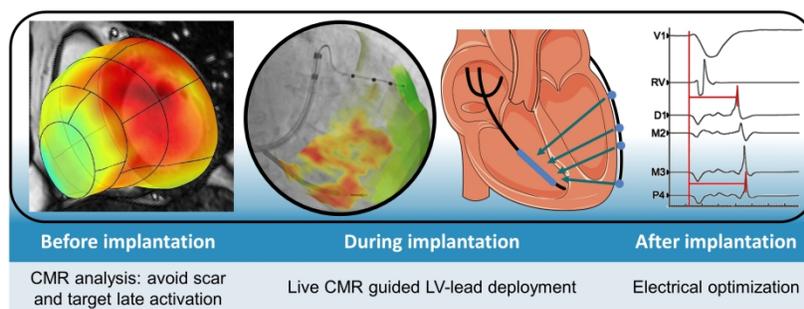
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Time point	Enrolment	Allocation	Post-allocation		Close-out
	-3 months	Day 0	Day 3	6 months	24 months
ENROLMENT					
Screening	X				
Informed consent	X				
Cardiac MRI	X				
Echocardiography	X			X	
Electrocardiogram	X		X	X	
NYHA class	X			X	
Questionnaires	X			X	X
Target allocation	X				
Treatment allocation		X			
INTERVENTIONS					
Image-guided		→			
Empirical		→			
ASSESSMENTS					
LV-lead location		X			
Procedural aspects ^a		X			
Technical aspects		X			
LVESVi- reduction	X			X	
Resynchronisation ^b	X			X	
QRS _{AREA}	X		X	X	
Mortality		X	X	X	X
HF Hospitalisation		X	X	X	X
Adverse events		X	X	X	X

SPIRIT time schedule of enrolment, interventions, and assessments for the ADVISE-CRT trial. a Includes implantation time, radiation exposure, and electrode configurations; b e.g., indices of mechanical recoordination such as SRSsept.

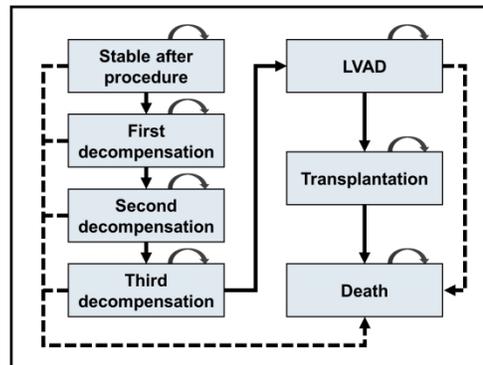
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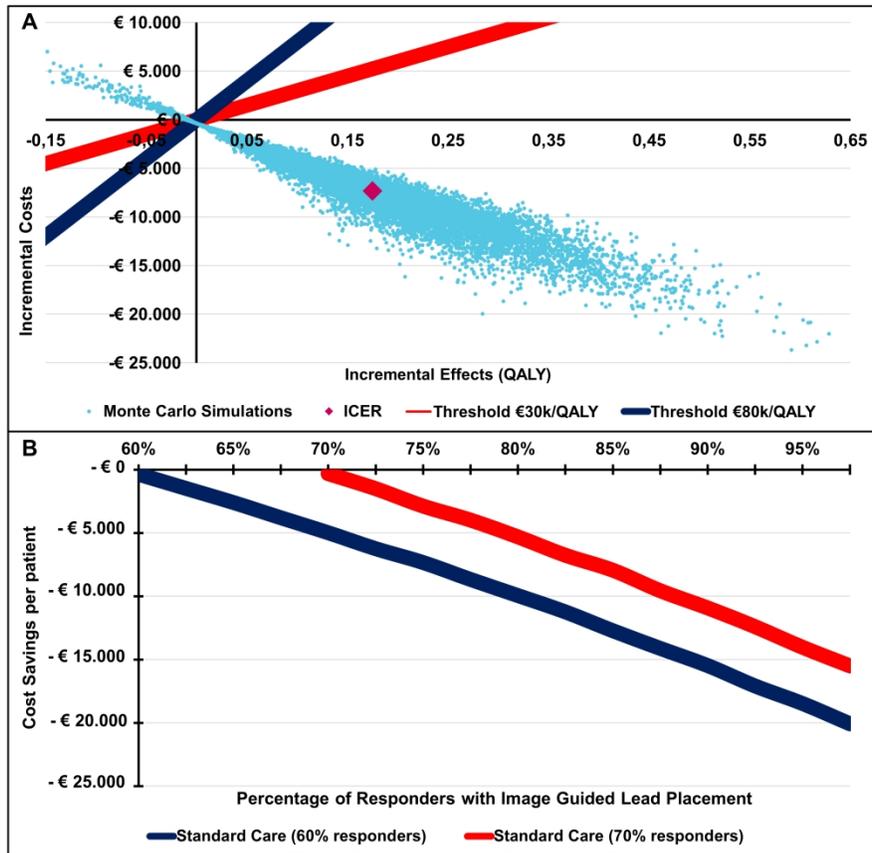
Workflow for advanced image-guided LV-lead placement. CMR, cardiac magnetic resonance imaging. LV, left ventricular.

250x338mm (300 x 300 DPI)



Seven 'health states' (squares) were defined. Patients either remain in their state during follow-up (inward arrows), or relocate towards the next sequential health state (uninterrupted arrows). Each transition is assigned its own probability of occurrence. When death occurs, other health states may be skipped (dashed arrows). Note that the assumption was made that post-CRT patients with ≤ 2 decompensations will not receive LVAD or transplantation. LVAD, Left Ventricle Assist Device.

250x338mm (300 x 300 DPI)



A: Cost-Effectiveness Plane for image-guided lead placement. The graph shows the iterations (blue dots) in comparison to the cost effectiveness thresholds for €30.000/QALY and € 80.000/QALY (red and blue lines).

B: Potential cost savings with image-guided lead placement, based on the proportional difference in responders. Legend: ICER, Incremental Cost Effectiveness Ratio ($\square\text{€}/\square\text{QALY}$); QALY, Quality Adjusted Life Year.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

	Reporting Item	Page Number
Administrative information		
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a Trial identifier and registry name. If not yet registered, name of intended registry	1, 8
Trial registration: data set	#2b All items from the World Health Organization Trial Registration Data Set	Trial NL8666
Protocol version	#3 Date and version identifier	Version 2.0, 29-07-2020
Funding	#4 Sources and types of financial, material, and other support	12
Roles and responsibilities:	#5a Names, affiliations, and roles of protocol contributors	1, 12

1	contributorship			
2	3	#5b	Name and contact information for the trial sponsor	12
4	responsibilities:			
5	sponsor contact			
6	information			
7				
8				
9	Roles and	#5c	Role of study sponsor and funders, if any, in study	NA
10	responsibilities:		design; collection, management, analysis, and	
11	sponsor and funder		interpretation of data; writing of the report; and the	
12			decision to submit the report for publication, including	
13			whether they will have ultimate authority over any of	
14			these activities	
15				
16				
17				
18	Roles and	#5d	Composition, roles, and responsibilities of the	NA
19	responsibilities:		coordinating centre, steering committee, endpoint	
20	committees		adjudication committee, data management team, and	
21			other individuals or groups overseeing the trial, if	
22			applicable (see Item 21a for data monitoring	
23			committee)	
24				
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29	Introduction			
30				
31	Background and	#6a	Description of research question and justification for	3
32	rationale		undertaking the trial, including summary of relevant	
33			studies (published and unpublished) examining benefits	
34			and harms for each intervention	
35				
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38	Background and	#6b	Explanation for choice of comparators	4, 5
39	rationale: choice of			
40	comparators			
41				
42				
43	Objectives	#7	Specific objectives or hypotheses	1
44				
45	Trial design	#8	Description of trial design including type of trial (eg,	2
46			parallel group, crossover, factorial, single group),	
47			allocation ratio, and framework (eg, superiority,	
48			equivalence, non-inferiority, exploratory)	
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52	Methods:			
53	Participants,			
54	interventions, and			
55	outcomes			
56				
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1	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
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8	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
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15	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4, 5
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20	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
21				
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27	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
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32	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
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36	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
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47	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
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54	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
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1	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	NA; consecutive patients
2				
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4				
5	Methods:			
6	Assignment of			
7	interventions (for			
8	controlled trials)			
9				
10				
11	Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
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23	Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
24				
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30	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
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35	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5, 6
36				
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40	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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46	Methods: Data collection, management, and analysis			
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52	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory	4-7
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1		tests) along with their reliability and validity, if known.	
2		Reference to where data collection forms can be found,	
3		if not in the protocol	
4			
5	Data collection plan:	#18b Plans to promote participant retention and complete	NA
6	retention	follow-up, including list of any outcome data to be	
7		collected for participants who discontinue or deviate	
8		from intervention protocols	
9			
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12	Data management	#19 Plans for data entry, coding, security, and storage,	6
13		including any related processes to promote data quality	
14		(eg, double data entry; range checks for data values).	
15		Reference to where details of data management	
16		procedures can be found, if not in the protocol	
17			
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20	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	7, 8
21		outcomes. Reference to where other details of the	
22		statistical analysis plan can be found, if not in the	
23		protocol	
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27	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	7, 8
28	analyses	adjusted analyses)	
29			
30			
31	Statistics: analysis	#20c Definition of analysis population relating to protocol	7, 8
32	population and	non-adherence (eg, as randomised analysis), and any	
33	missing data	statistical methods to handle missing data (eg, multiple	
34		imputation)	
35			
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37			
38	Methods:		
39	Monitoring		
40			
41			
42	Data monitoring:	#21a Composition of data monitoring committee (DMC);	All strategies used
43	formal committee	summary of its role and reporting structure; statement	during implantation
44		of whether it is independent from the sponsor and	are not known to be
45		competing interests; and reference to where further	associated with
46		details about its charter can be found, if not in the	additional risk.
47		protocol. Alternatively, an explanation of why a DMC	
48		is not needed	
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53	Data monitoring:	#21b Description of any interim analyses and stopping	NA
54	interim analysis	guidelines, including who will have access to these	
55		interim results and make the final decision to terminate	
56		the trial	
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1	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
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8	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
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13	Ethics and			
14	dissemination			
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17	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8
18				
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20				
21	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
22				
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29	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
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34	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
35				
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40	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
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46	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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50	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
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56	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
57				
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1	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	12
2	trial results		trial results to participants, healthcare professionals, the	
3			public, and other relevant groups (eg, via publication,	
4			reporting in results databases, or other data sharing	
5			arrangements), including any publication restrictions	
6				
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8				
9	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use	NA
10	authorship		of professional writers	
11				
12				
13	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	12
14	reproducible research		protocol, participant-level dataset, and statistical code	
15				
16				
17	Appendices			
18				
19	Informed consent	#32	Model consent form and other related documentation	NA; upon request.
20	materials		given to participants and authorised surrogates	
21				
22				
23	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage	NA
24			of biological specimens for genetic or molecular	
25			analysis in the current trial and for future use in	
26			ancillary studies, if applicable	
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Notes:

- 32 • 2b: Trial NL8666
- 34 • 3: Version 2.0, 29-07-2020
- 36 • 15: NA; consecutive patients
- 38 • 21a: All strategies used during implantation are not known to be associated with additional risk.
- 40 • 32: NA; upon request. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 01. June 2021 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

BMJ Open

Advanced image-supported lead placement in cardiac resynchronisation therapy: protocol for the multicenter, randomised controlled ADVISE trial and early economic evaluation

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4 1 **Advanced image-supported lead placement in cardiac resynchronisation**
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6 2 **therapy: protocol for the multicenter, randomised controlled ADVISE trial and**
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9 3 **early economic evaluation**

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Abstract

Introduction: Achieving optimal placement of the left ventricular (LV) lead in cardiac resynchronization therapy (CRT) is a prerequisite in order to achieve maximum clinical benefit, and is likely to help avoid non-response. Pacing outside scar tissue and targeting late activated segments may improve outcome. The present study will be the first randomized controlled trial to compare the efficacy of *real-time* image-guided LV lead delivery to conventional CRT implantation. In addition, to estimate the cost-effectiveness of targeted lead implantation, an early decision analytic model was developed, and described here.

Methods and analysis: A multicenter, interventional, randomised, controlled trial will be conducted in a total of 130 patients with a class I or IIa indication for CRT implantation. Patients will be stratified to ischemic heart failure aetiology and 1:1 randomized to either empirical lead placement or live image-guided lead placement. Ultimate lead location and echocardiographic assessment will be performed by core laboratories, blinded to treatment allocation and patient information. Late gadolinium enhancement cardiac MRI (LGE-CMR) and CINE-CMR with feature-tracking post processing software will be used to semi-automatically determine myocardial scar and late mechanical activation. The subsequent treatment file with optimal LV-lead positions will be fused with the fluoroscopy, resulting in live target-visualisation during the procedure. The primary endpoint is the difference in percentage of successfully targeted LV-lead location. Secondary endpoints are relative percentage reduction in indexed LV end-systolic volume, a hierarchical clinical endpoint, and quality of life. The early analytic model was developed using a Markov-model, consisting of seven mutually exclusive health states.

Ethics and dissemination: The protocol was approved by the Medical Research Ethics Committee Utrecht (NL73416.041.20). All participants are required to provide written informed consent. Results will be disseminated at various presentations and will be submitted to peer-reviewed journals.

Trial Registration: The trial is registered at a ClinicalTrials.gov (NCT05053568).

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61 **Strengths and limitations of this study**

- 62 • Real-time visualisation of targets for left ventricular lead implantation allows for user-
63 friendly and accurate guidance.
- 64 • Use of a specific model of the lateral wall with relatively small segments, which limits
65 fortuitous in-target lead placement.
- 66 • Health Technology Assessment offers better understanding of potential economic
67 benefits of targeted implantation.
- 68 • Cardiac MRI allows for observer independent image acquisition, but has relatively
69 limited temporal resolution.
- 70 • The study is limited in power to detect differences in clinical outcome, including
71 echocardiographic response.

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73 **Keywords:** image-guided therapy; lead placement; cardiac resynchronization therapy; MRI

94 1. Introduction

95 Chronic heart failure is a major global health concern with a 5-year mortality rate of about
96 50%. In about one-third of these patients, heart failure is accompanied by left ventricular (LV)
97 conduction delay (i.e. QRS-duration \geq 130 ms), which is a predictor for worse prognosis [1,2].
98 Cardiac resynchronization therapy (CRT) greatly reduces morbidity and mortality in these
99 patients, but the extent of response is inconsistent and highly dependent on adequate LV
100 lead placement (LVLP). In-scar LVLP greatly increases risk of cardiovascular death and HF-
101 hospitalisation [3], whereas pacing in an area of late activation is likely to improve outcome
102 [4–6]. Moreover, a suboptimal lead position cannot be compensated by optimizing device
103 programming [7], rendering adequate LVLP arguably the cornerstone of this device therapy.

104 Because the optimal location is highly variable and patient-specific, an individualised and
105 targeted approach is often warranted [8]. Previous research has demonstrated the benefits of
106 image-guided lead delivery as a mean of improving clinical outcome [8,9]. However, most
107 studies did not allow for electrical guidance in the control group and allowed for only eight
108 potential targets for lead deployment, thereby limiting the accuracy of lead deployment and
109 increasing the odds of fortuitous “in-target” lead placement [10,11]. Moreover, no large
110 studies allowed for real-time visualisation of optimal targets, and most of the image-guided
111 studies were not conducted in a true multicenter setting. As such, the current evidence for
112 image-guided LVLP has remained relatively limited, and contemporary LVLP is still largely
113 based on an empirical strategy [1].

114 The present study protocol describes the first multicenter randomized controlled trial
115 investigating advanced image supported lead placement in CRT (ADVISE). The primary aim
116 of the study is to demonstrate the feasibility of reaching pre-defined segments through
117 accurate image-guidance, using an 18-segment LV lateral wall model with live visual
118 guidance during the implantation. The secondary objective is to investigate the clinical
119 efficacy by evaluating differences in the extent of LV reverse remodeling, a hierarchical
120 clinical endpoint and quality of life between both groups. Lastly, a Health Technology
121 Assessment will be conducted to determine the expected cost-effectiveness of a patient-
122 tailored approach for targeted lead placement.

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2. Methods and analysis

The ADVISE-CRT trial is a multicenter, randomised, controlled trial that is blinded to the patient and assessors of outcome (**Figure 1**). Assessment of LV dimension, LV function, and lead location will be performed by core laboratories. Patients will be stratified according to aetiology of heart failure in order to assure equal distribution of patients with ischemic cardiomyopathy (ICM) and non-ICM patients in both groups. All 130 patients will be 1:1 allocated to either image-guided or empirical LVLP using variable block-randomization:

- Intervention group: live visualised, fluoroscopy-fused, image-guided, lead placement on the basis of avoiding scar and targeting late mechanically activated segments.
- Control group: empirical standard-of-care lead placement in line with current CRT implantation guidelines with electrical guiding on the basis of Q-LV sense [4].

Study population

Patients are prospectively enrolled in at least three, and at most six, Dutch academic and peripheral centres. Consecutive patients eligible for CRT with a class I or IIa indication, with or without defibrillator function, according to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure are considered. In addition, some additional criteria for study participation apply (**Table 1**).

Overview of assessments

Prior to device implantation, all patients will undergo echocardiographic examination and cardiac magnetic resonance imaging (CMR). CMR feature-tracking (CMR-FT) analyses will be performed in both study groups, after which optimal LV-lead location will be determined. Randomization will occur after targets for lead deployment have been defined, after which targets cannot be altered. All patients will receive two quality of life questionnaires (EQ-5D-5L and Kansas City Cardiomyopathy Questionnaire) at four time-points: before implantation and at six months, 12 months, and 24 months after implantation. A 12-lead ECG will be performed before, directly after, and six months after implantation. During the procedure, various LV-paced effects will be measured. Ultimate lead location will be assessed through registration of the 18-segment LV lateral wall model onto the LAO40 and RAO30 fluoroscopy images, similar to the method described by Singh and colleagues, [12]. A global schedule of all assessments is summarised (**Figure 2**).

161 **CMR analysis and target allocation**

162 Clinical standard short axis CINE acquisitions with a minimum of 25 frames per R-R interval,
163 at max 8mm slice thickness and no slice gap, and LGE acquisitions at max 8mm slice
164 thickness will be performed in the participating hospitals. Cardiac MRI scans may be
165 acquired at most six months before implantation, in case of no (suspicion of) recent
166 ischaemic events. Post processing will be performed in a centralized fashion using a
167 dedicated software toolbox (CARTBox, CART-Tech B.V., Utrecht, The Netherlands). The
168 CARTBox analysis results in a treatment file, which will be used as an overlay with live
169 fluoroscopy during the implantation procedure in the intervention group. Semi-automated and
170 deep-learning assisted contouring CMR-FT analysis will be performed to quantify myocardial
171 deformation and identify the tissue with the latest mechanical contraction. Scar transmural
172 will be identified based on the LGE acquisitions. Three dimensional maps of mechanical
173 activation and scar transmural are combined and used to define the optimal tissue
174 (targets) for the LV lead. Targets will then be allocated on the basis of a pre-specified
175 decision-model by two investigators, blinded to each other. Segments that contain
176 myocardial scar will be disregarded, whereas segments with latest mechanical activation will
177 be considered most appropriate. Because multiple regions may be deemed suitable, a
178 maximum of three of the most suitable segments will be ranked and considered for
179 implantation in that order of priority. In the case of initial disagreement, consensus will follow
180 after discussion. Of note, the original unprocessed CMR will be available at the discretion of
181 the implanting cardiologist, also in the control group.

183 **Echocardiography**

184 Transthoracic echocardiographic examinations will be performed at baseline and six months
185 after CRT implantation at each participating centre. A standard local protocol used for strain-
186 imaging in CRT candidates will be used, with special attention to high quality images of the
187 LV. To this end, each acquired image will include at least three separate beats, and LV strain
188 images will be frame-rate optimized by using the narrowest sector width possible. LV
189 volumes and function will be assessed using Simpson's bi-plane method [13]. Mechanical
190 dyssynchrony (e.g. apical rocking) will be assessed as well. All examinations will be analysed
191 by an echocardiography core laboratory using vendor-independent software.

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193 **Randomization and blinding procedures**

194 After baseline assessments and subsequent identification of optimal targets for LVLP,
195 computer-generated variable block 1:1 randomization to either image-guided (intervention) or
196 empirical (control) implantation will be performed (Castor EDC, Amsterdam
197 the Netherlands). Randomization will be stratified according to ischemic or non-ischemic
198 heart failure etiology. Study data will be collected, recorded, logged and managed in
199 compliance with Good Clinical Practice guidelines. All study data are recorded in an
200 electronic case report form (eCRF), where any changes in data entry are logged. All data
201 entered, including perioperative data related to device implantation and optimization, are
202 collected and entered into the eCRF by either the coordinating investigator and/or research
203 nurse. External data validation will be managed by a study monitor, designated by a contract
204 research organization. Both the patient and core laboratories assessing endpoint data
205 (fluoroscopically determined LVLP and echocardiography) will be blinded to the intervention.
206 After six month follow-up has been completed by all patients, unblinding is allowed. After six
207 months, no observer-dependent endpoint data remains to be collected, and electrode
208 reselection is allowed where indicated.

210 **Device implantation**

211 Implantation of CRT, unrestricted by manufacturer or the presence or absence of defibrillator,
212 will occur under local anaesthesia and light intravenous sedation according to standard
213 procedure. In the control group, LVLP will occur at discretion of the physician but in line with
214 current guidelines using quadripolar LV leads (i.e. based on an empirical strategy, guided by
215 Q-LV sense). Q-LV sense is measured unipolar and defined as the time interval between
216 QRS onset on the surface ECG and the maximum voltage *change* over time (i.e. dV/dt),
217 recorded on the electrocardiogram. The LV electrode with the longest Q-LV sense in
218 combination with acceptable pacing threshold and without diaphragmatic stimulation will be
219 selected. In the image-guided intervention group, 2-dimensional fluoroscopic images are co-
220 registered to the previously derived CARTBox treatment file from CMR postprocessing, and
221 visualised in real-time in conjunction with the live fluoroscopy used during the implantation
222 procedure (**Figure 3**). The LV-lead will be deployed on the basis of the pre-defined target.
223 Only when multiple electrodes are within the target region, electrode selection based on
224 electrical properties (e.g. Q-LV sense) is applied.

225 During the procedure, pacing capture thresholds, phrenic nerves stimulation, intrinsic
226 electrical delay (i.e. Q-LV sense) and various LV-paced effects (i.e. LV-pace to RV-sense
227 and RV-pace to LV-sense) will be determined for each electrode of the quadripolar lead

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4 228 positions. When the ultimate lead position has been established, LAO40 and RAO 30
5 229 fluoroscopic imaging will be performed to determine the exact final lead location. Final LV
6 230 lead location will be determined by two investigators, blinded to treatment group and
7 231 outcome of each other. LVLP will be determined through registration of the CMR-derived LV
8 232 lateral wall model onto the LAO40 and RAO30 fluoroscopy images, similar to the method
9 233 described by Singh and colleagues [12]. Adverse events which are possibly related to
10 234 CARTBox or the procedure, reported spontaneously by the subject or observed by the
11 235 investigator or his staff, will be recorded in an electronic database.
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19 237 **Endpoints**

20 238 The ability to achieve successful image-guidance will be based on differences in the
21 239 percentage of within, adjacent, or remote from the target(s) selected for lead placement.
22 240 Here, adjacent segments include diagonal segments. Secondary outcomes are relative
23 241 reduction in LV end-systolic volume indexed to body surface area (LVESVi), proportional
24 242 difference in volumetric response ($\geq 15\%$ LVESVi-reduction), differences in quality of life, and
25 243 differences in the CRT response score. The latter is a hierarchical clinical endpoint based on
26 244 HF-hospitalisation and/or death within 12 months, relative LVESVi-change, and change in
27 245 NYHA class (**Supplemental File 1**) [14]. Other outcome measures include the following:
28 246 implantation procedure time, fluoroscopy time, contrast dose, device or procedure-related
29 247 complications, change in QRS duration and QRS_{AREA} , indices of mechanical recoordination,
30 248 and LV-lead parameters (Q-LV sense, pacing threshold, phrenic stimulation). Lastly, a Health
31 249 Technology Assessment concerning the additional value of image-guided LVLP in terms of
32 250 healthcare expenditure revolving heart failure care will be performed. This assessment will
33 251 be based on a previously conducted early economic analysis, which is described in this
34 252 article.
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45 254 **Sample size**

46 255 When comparing image-guided and contemporary implantation of CRT, the proportional
47 256 difference in within-target LVLP ranges between 6 and 30%, and thus varies considerably
48 257 [8]. In contrast, ADVISE targets segments approximately half the size of areas used in
49 258 previous studies, rendering the chance of fortuitously successful in-target implantation in
50 259 either study group much smaller.

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55 260 We therefore hypothesized that image-guidance will result in a proportional difference in
56 261 within-target LVLP of at least 27% when compared to empirical lead placement. In order to
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4 262 demonstrate this proportional difference using a two-sided Fisher exact test with 80% power
5 263 and $\alpha = 0.05$, a total of 114 successfully implanted patients are needed.

7 264 Concerning the secondary endpoint of LV reverse remodelling, given an expected
8 265 standard deviation below 25%, a significant difference in LVESVi reduction between both
9 266 groups of at least 13% can be detected in 116 patients. Accounting for failed implantations,
10 267 loss to follow-up and incomplete (echocardiographic) data in about 10% of cases, total
11 268 sample size necessary was set at 130 patients.

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17 270 **Statistical analysis**

18 271 An intention-to-treat analysis will be performed to assess LV-lead location and
19 272 echocardiographic response. In echocardiographic non-responders where electrode
20 273 reselection is feasible, transition of control patients towards the treatment group may occur
21 274 after six months. To account for this potential cross-over, an additional per-protocol analysis
22 275 may be performed with respect to long-term clinical endpoints and the HTA.

26 276 The primary endpoint concerning LV-lead location will be defined categorically as being
27 277 within, adjacent, or remote from the pre-defined target. A two-tailed Fisher exact test will be
28 278 performed to assess differences in lead location between both groups. Because in principle,
29 279 the effect of a targeted approach is considered to result in a unidirectional change in lead
30 280 location, a one-tailed Fisher exact test may be performed as well.

34 281 Secondary endpoints will be analysed according to treatment allocation and lead location
35 282 using Student's *t*-test and one-way ANOVA, or the Wilcoxon's rank sum test and Kruskal-
36 283 Wallis wherever applicable. Lastly, intra- and inter-observer agreement of the
37 284 echocardiography core laboratory analysis of LV reverse remodelling will be demonstrated
38 285 by computing intraclass correlation coefficients in approximately 25 echocardiograms. A *p*-
39 286 value < 0.05 will be considered significant.

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46 288 **Patient and public involvement**

47 289 Patients are part of our multidisciplinary consortium, both before and during the study, and
48 290 are as such involved in the design and conduct of the study. The priority of the research
49 291 question, patient communication, study logistics, and methods of recruitment have been
50 292 informed by discussions with patients representing our study population.

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55 294 **3. Ethics and dissemination**

56 295 The ADVISE trial will be conducted according to the principles of the Helsinki Declaration II
57 296 and Good Clinical Practice guidelines. The protocol has been written in accordance with the

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4 297 Standard Protocol Items: Recommendation For Interventional Trials (SPIRIT) checklist [15].
5
6 298 The study protocol has been approved by the Medical Research Ethics Committee Utrecht
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8 299 (NL73416.041.20), and has been registered at ClinicalTrials.gov (NCT05053568). All
9
10 300 participants are required to provide written informed consent, prior to study procedures
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12 301 **(Supplemental File 2)**. Patients are currently being enrolled, with the first patient included in
13
14 302 February 2021. Results will be disseminated at various presentations and will be submitted
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16 303 to peer-reviewed journals.

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305 **4. Early economic evaluation**

306 To estimate the expected impact on cost and effects of image-guided LVLP in CRT, an early
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308 decision analytic model was developed using a Markov-model consisting of seven mutually
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310 exclusive health states **(Figure 4)**. These health states were identified in collaboration with
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312 clinical experts and based on available literature **(Supplemental File 3)**. In brief, a group of
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314 1.000 individuals with heart failure were simulated, receiving either contemporary or image-
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316 guided LVLP. The analysis was performed from a societal perspective, including both direct
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318 healthcare costs and, where applicable, productivity losses due to absence from work. Model
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320 cycle length was one month, and model time horizon was 120 months. This model was
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322 developed in Microsoft Excel, version 2010/2016 (Microsoft, Redmond, WA, USA).

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324 **Treatment of patients/structure of the model**

325 Patients with heart failure enter the model after the index CRT procedure (4:1 CRT-D versus
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327 CRT-P) where all patients are deemed to be in stable condition. After implantation,
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329 sequentially patients may 'transition' towards various 'health states', namely: cardiac
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331 decompensation (at most three times), Left Ventricle Assist Device (LVAD) implantation, or
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333 heart transplant. Detailed overviews of healthcare provided for each of the health states are
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335 found in **Supplemental File 2**. Each health state is assigned a different probability of all-
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337 cause mortality.

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339 **Input parameters**

340 Different sources were used to identify input parameters and parameter values. The majority
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342 of parameter values were retrieved from existing scientific literature. Where data was not
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344 publicly available, expert opinion and data from UMC Utrecht were used. Given the nature of
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346 this early analysis, no definitive data is currently available that combines clinical effects and
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4 330 costs for image-guided LVLP. Input values for effects and costs were therefore estimated by
5 331 experts.

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9 333 **Clinical Outcomes & image-guided lead placement effectiveness**

10 334 For standard care, an assumed percentage of responders (LVESV-reduction $\geq 15\%$) was set
11 335 at 60% (17). For the additional effects of image-guided LVLP the percentage of responders
12 336 was increased with steps of 2.5% to a maximum of 97.5%. We also analysed the situation for
13 337 when 70% of patients receiving standard care are responders. First decompensation
14 338 probability, the arrow from stable to first decompensation in **Figure 4**, was based on a
15 339 weighted average for hospitalization probabilities for responders and non-responders (18).
16 340 Transfer probabilities between other health states were assumed to be equal between
17 341 standard care and care with image-guided LVLP and were based on clinical outcomes which
18 342 were retrieved from literature (19-21). Most important index procedure complications were
19 343 pneumothorax, lead dislocation, bleeding and pocket infection. Probabilities of these
20 344 complications occurring were based on previous research conducted at the UMCU and were
21 345 assumed not to differ between image-guided LVLP and standard care (22).

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31 347 **Cost-effectiveness estimation for image-guidance**

32 348 Based on 10,000 Monte Carlo iterations in the probabilistic sensitivity analyses, **Figure 5A**
33 349 shows the cost-effectiveness plane. Here, the Monte Carlo iterations are represented by the
34 350 blue dots. Mean cost difference was found to be -€7.329 (95%-CI: -€15.760 to € 323) and
35 351 mean Quality Adjusted Life Year (QALY) gain was 0.17 (95%-CI: -0.02 to 0.40). The majority
36 352 of iterations (96%) resulted in cost saving and an incremental health gain for image-guided
37 353 LVLP, as compared to standard care.

38 354 When the effectiveness of standard care is considered to be 70%, and the effectiveness
39 355 of CMR guided LVLP is varied between 70% and 95%, the results shown in **Figure 5B** were
40 356 found. Even at relatively small improvements in the proportion of responders, image-guided
41 357 LVLP leads to cost savings ranging from € 317 to € 20.069.

42 358

51 359 **One-way sensitivity analysis**

52 360 In the one-way sensitivity analysis, we varied input parameter value with -20% and +20%,
53 361 this means the values of all parameters were altered one-by-one. By doing this for all model
54 362 input parameters, the influence of each parameter on model outcome is demonstrated. The
55 363 one-way sensitivity analysis showed that the parameters with the greatest influence on the

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4 364 outcomes of the economic evaluation were; i) the percentage of responders for standard
5 365 care, and ii) the percentage of responders for care with image guided LVLP. This entails that
6 366 changes in the value of these parameters will most likely change the outcomes of the
7 367 economic evaluation the most.
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12 369 **5. Discussion**

14 370 **Electrical versus image-guided strategy**

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16 371 Although the STARTER and TARGET study demonstrated the benefit of an image-guided
17 372 approach for LVLP, they were performed in a time where electrical guiding (using QLV-
18 373 sense) was not yet routinely performed [10,16]. However, QLV-guidance is nowadays readily
19 374 available in many centres, and therefore, the results STARTER and TARGET cannot be
20 375 directly extrapolated to current practice [4,17].
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24 376 It is therefore noteworthy that only one study carefully investigated both an
25 377 electrically guided approach (using QLV-sense) and an image-guided approach in a direct
26 378 comparison [18]. Although Stephansen et al., reported non-inferiority of an electrical
27 379 approach, we need to consider that these patients had typical LBBB with an average QRS-
28 380 duration of 169 ms. This is in contrast to patients with non-LBBB morphology, where a QLV-
29 381 guided approach fails to result in superior outcome when compared to contemporary lead
30 382 placement [19]. In these patients, an image-guided strategy appears to be more beneficial
31 383 [16]. Ultimately, electrically-guided and mechanically guided approaches each have their own
32 384 strengths and limitations, and both may have yet to reach their full potential [8].
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40 386 **Methods used for left ventricular lead placement**

41 387 Because in-scar pacing is associated with a six fold increased risk for cardiovascular death
42 388 or hospitalization for HF, avoiding in-scar pacing is of utmost importance [3]. We therefore
43 389 used CMR with late gadolinium enhancement, which is considered the gold-standard for
44 390 detection of myocardial scar and has a higher spatial resolution than ⁸²Rubidium positron
45 391 emission tomography [20]. In contrast, the utility of strain imaging using echocardiography for
46 392 detecting scar is poor with a sensitivity of only 33% [21].
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51 393 In addition to avoiding scar, feature tracking is performed on CMR CINE
52 394 sequences in order to determine viable segments with late mechanical activation. Although
53 395 CMR has lower temporal resolution than speckle-tracking echocardiography, its benefits
54 396 include the ability to sequence the whole heart and the lack of need for adequate acoustic
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4 397 windows. In addition, strain analysis from CMR is subject to less bias and variability and can
5 398 be done semi-automatically.

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8 9 400 **Live fusion and target visualisation**

10 401 Regardless of the methods used, it is inevitable that there will always be patients in which a
11 402 target cannot be reached. In particular, the variability and difficulty of reaching a pre-defined
12 403 target is evidenced by the wide range of remote-from-target lead location, as reported in
13 404 previous studies [8]. Although venous access is undoubtedly a limiting factor, visualizing
14 405 target for lead deployment *during* the procedure most likely enhances the proportion of
15 406 optimally placed leads, since the implanter strives to implant the LV lead as close as possible
16 407 to the target tissue in a patient specific fashion. Although the feasibility of live fusion has
17 408 been demonstrated in two previous studies [22,23], they were limited by a small sample size
18 409 and non-randomized design.

19 410

20 411 **Early economic analysis**

21 412 The analysis resulted in a robust model outcome for image-guided LVLP in CRT,
22 413 demonstrating a mean cost savings of approximately €7.000 with simultaneous incremental
23 414 health gain, relative to standard empirical LVLP. Although results are highly dependent on
24 415 proportional differences in response, cost-savings are likely feasible even at relatively small
25 416 clinical improvements. Because any decision analytic model is a simplified version of the
26 417 actual healthcare pathway, definitive clinical effectiveness must be awaited from data
27 418 gathered by the ADVISE trial. However, should the estimated mean cost savings hold, a
28 419 meaningful improvement in cost-effectiveness can be realised. This may be especially
29 420 valuable in low-to-middle income countries, where referral and implant rates are still relatively
30 421 lacking [24].

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32 423 **Strengths and limitations**

33 424 Our study is primarily limited by its relatively small sample size, and as a consequence, lack
34 425 of primary *clinical* endpoint with sufficient power to detect differences in LVESVi-changes
35 426 below 13% between both groups. Regardless, the present study is the first *multicenter*
36 427 randomized controlled trial set out to investigate live CMR-guided LVLP in CRT, thereby
37 428 providing data in a real-world setting. CMR is however less suitable for patients with prior
38 429 device implantation due to magnetic field inhomogeneities, reducing image quality. Although
39 430 CMR-FT has a lower temporal resolution when compared to speckle-tracking

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4 431 echocardiography, it may suffer from less noise and inter-observer dependence. Moreover,
5 432 our technique allows for gold-standard scar detection, accurate segmentation, and live
6 433 visualization of suitable targets for lead deployment. Lastly, although fluoroscopy-based
7 434 determination of LVLP has limited reproducibility, simultaneous co-registration with our MRI-
8 435 derived LV lateral wall model may improve its accuracy [25].
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14 437 **Future perspectives**

15 438 Previous studies were conducted without performing QLV-guidance in the control group, and
16 439 were limited by using at most two recruiting centres [10,16,18]. Moreover, to date, no studies
17 440 utilized *live* image-guidance in a randomized controlled design. Should our study be able to
18 441 detect more LV reverse remodelling and/or better clinical outcome, an important step has
19 442 been set towards more widespread adoption of image-guided strategies for optimized LVLP
20 443 in CRT.
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27 445 **Author contributions**

28 446 PCW was involved in the study design, drafting the manuscript, and acquisition, analysis and
29 447 interpretation of data. FJS was responsible for design and execution of the technical and
30 448 methodological aspects revolving image guidance. CL and GWJF were responsible for
31 449 design and execution of the early economic analysis. VFD, PPHMD, and MM were involved
32 450 in study design and data acquisition. PAFMD and MJC were involved in conception or design
33 451 of the work. All authors provided critical revision and final approval of the manuscript, and are
34 452 accountable for the work.
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42 454 **Funding statement**

43 455 This work was supported by ZonMW, grant number 404460098327.
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47 457 **Conflict of interests**

48 458 FJS is co-founder, chief technical officer, and shareholder of CART-Tech B.V. MM and FJS
49 459 are inventors and beneficiaries of a patent license arrangement between the University
50 460 Medical Center Utrecht and CART-Tech B.V. according to the rules of the University Medical
51 461 Center Utrecht. All other authors have reported that they have no relationships relevant to
52 462 the contents of this paper to disclose.
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569 **Tables**

570

571 **Table 1. ADVISE inclusion and exclusion criteria**

Inclusion criteria

- Heart failure with LVEF \leq 35%;
- NYHA class II, III, or IV (ambulatory);
- Optimal medical treatment that is tolerable;
- LBBB with QRS \geq 130 ms, *or* non-LBBB with QRS \geq 150 ms.

Exclusion criteria

- Age < 18 years or incapacitated adult;
 - Contraindication for CMR (gadolinium; contrast agents; metal);
 - Atrial fibrillation; either permanent or during CMR;
 - Severe renal insufficiency (GFR < 30 ml/min/1.73 m²);
 - Participation in other potentially confounding trials.
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4 **592 Figure legends**

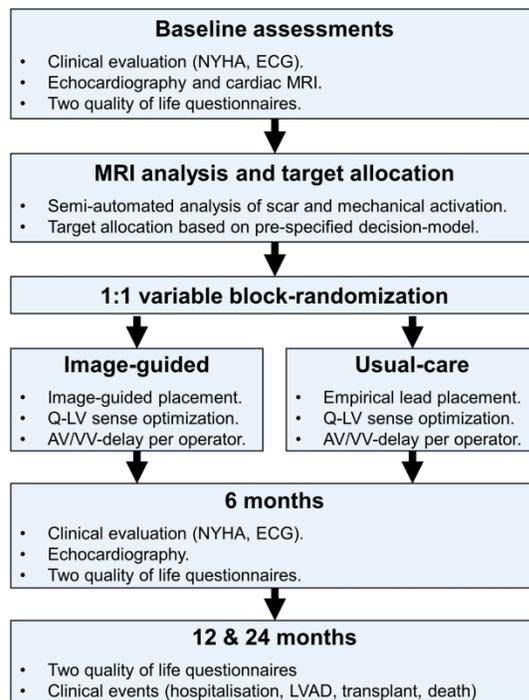
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6 **593 Figure 1.** Flow-chart presenting the course of the study.

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8 **594**
9 **595 Figure 2.** SPIRIT time schedule of enrolment, interventions, and assessments for the
10 **596 ADVISE-CRT trial.** ^a Includes implantation time, radiation exposure, and electrode
11 **597 configurations;** ^b e.g., indices of mechanical recoordination such as SRSsept.

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13 **598**
14 **599 Figure 3.** Workflow for advanced image-guided LV-lead placement. Adapted from Wouters
15 **600 et al [8].** CMR, cardiac magnetic resonance imaging. LV, left ventricular.

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17 **601**
18 **602 Figure 4.** Seven 'health states' (squares) were defined. Patients either remain in their state
19 **603 during follow-up** (inward arrows), or relocate towards the next sequential health state
20 **604 (uninterrupted arrows).** Each transition is assigned its own probability of occurrence. When
21 **605 death occurs,** other health states may be skipped (dashed arrows). Note that the assumption
22 **606 was made that post-CRT patients with ≤ 2 decompensations will not receive LVAD or**
23 **607 transplantation.** LVAD, Left Ventricle Assist Device.

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25 **608**
26 **609 Figure 5. A:** Cost-Effectiveness Plane for image-guided lead placement. The graph shows
27 **610 the iterations (blue dots) in comparison to the cost effectiveness thresholds for**
28 **611 €30.000/QALY and € 80.000/QALY (red and blue lines).** B: Potential cost savings with
29 **612 image-guided lead placement, based on the proportional difference in responders.** Legend:
30 **613 ICER, Incremental Cost Effectiveness Ratio ($\Delta\text{€}/\Delta\text{QALY}$); QALY, Quality Adjusted Life Year.**



45 Flow-chart presenting the course of the study.

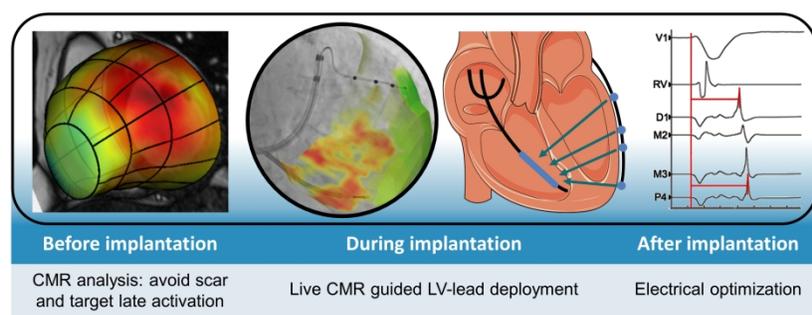
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Time point	Enrolment	Allocation	Post-allocation		Close-out
	-3 months	Day 0	Day 3	6 months	24 months
ENROLMENT					
Screening	X				
Informed consent	X				
Cardiac MRI	X				
Echocardiography	X			X	
Electrocardiogram	X		X	X	
NYHA class	X			X	
Questionnaires	X			X	X
Target allocation	X				
Treatment allocation		X			
INTERVENTIONS					
Image-guided		→			
Empirical		→			
ASSESSMENTS					
LV-lead location		X			
Procedural aspects ^a		X			
Technical aspects		X			
LVESVi- reduction	X			X	
Resynchronisation ^b	X			X	
QRS _{AREA}	X		X	X	
Mortality		X	X	X	X
HF Hospitalisation		X	X	X	X
Adverse events		X	X	X	X

SPIRIT time schedule of enrolment, interventions, and assessments for the ADVISE-CRT trial. a Includes implantation time, radiation exposure, and electrode configurations; b e.g., indices of mechanical recoordination such as SRSsept.

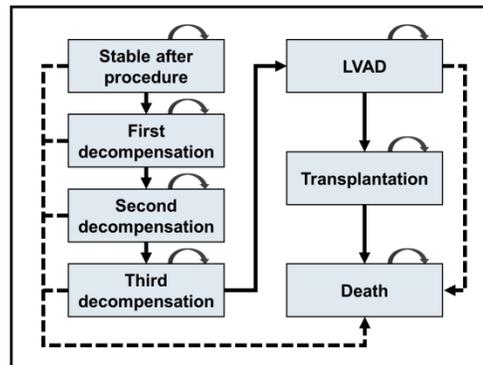
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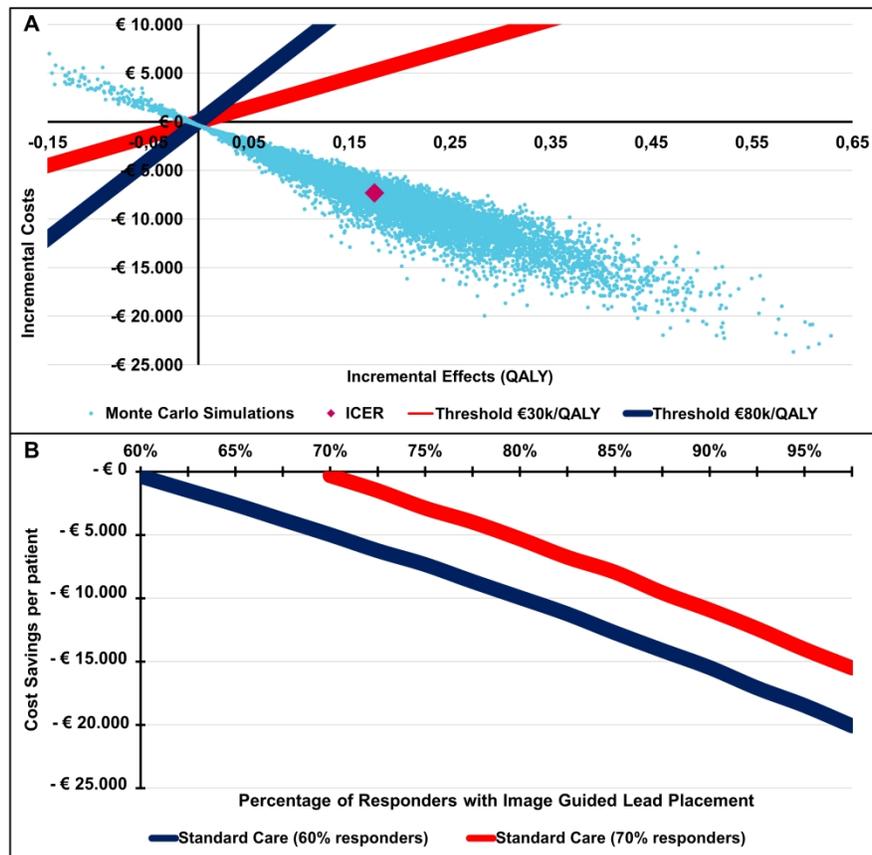
Workflow for advanced image-guided LV-lead placement. Adapted from Wouters et al [8]. CMR, cardiac magnetic resonance imaging. LV, left ventricular.

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Seven 'health states' (squares) were defined. Patients either remain in their state during follow-up (inward arrows), or relocate towards the next sequential health state (uninterrupted arrows). Each transition is assigned its own probability of occurrence. When death occurs, other health states may be skipped (dashed arrows). Note that the assumption was made that post-CRT patients with ≤ 2 decompensations will not receive LVAD or transplantation. LVAD, Left Ventricle Assist Device.

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A: Cost-Effectiveness Plane for image-guided lead placement. The graph shows the iterations (blue dots) in comparison to the cost effectiveness thresholds for €30.000/QALY and € 80.000/QALY (red and blue lines).

B: Potential cost savings with image-guided lead placement, based on the proportional difference in responders. Legend: ICER, Incremental Cost Effectiveness Ratio ($\square\text{€}/\square\text{QALY}$); QALY, Quality Adjusted Life Year.

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Explanation of the CRT Response Score

As opposed to a traditional Clinical Composite Score, the CRT response score is a hierarchical clinical endpoint that takes into account several parameters that have frequently been used in literature to assess response to CRT. As opposed to a more conventional time-to-event endpoint, the CRT response scores takes into account both the severity and frequency of endpoints.

In brief, physiological improvement is assessed at the 6 months follow-up visit, both in terms of *the extent of* reverse remodelling (i.e., LVESVi-reduction). Functional improvement is assessed using New York Heart Association (NYHA) classification. In addition, deaths and HF hospitalizations will be taken into account until 12 months after the initial CRT implantation procedure as hard clinical endpoints.

The CRT response score will be calculated as follows:

1. A patient who dies within 12 months after the initial implantation procedure will be assigned a score = 0.
2. All other patients will have a base score = 2, adapted with additive contributions for HF hospitalizations, relative LVESVi change, and (change in) NYHA class:
 - a) For each HF hospitalization within 12 months after the initial implantation procedure, 2 is subtracted.
 - b) Change in LVESVi at the 6 months visit compared to baseline will contribute:
 - +2 when there is $\geq 30\%$ reduction (i.e., super-response),
 - +1 when reduced $\geq 15\%$ but $< 30\%$ (i.e., response),
 - +0 when LVESVi is reduced but $< 15\%$ (i.e., non-response), or
 - -1 when LVESVi has increased (i.e., negative response).
 - c) NYHA class at the 6 months visit will contribute +1 when the patient is in Class I or has improved by at least 1 class compared to baseline; +0 when NYHA class is unchanged; or -1 when NYHA class has worsened.
3. A negative score is replaced by 0.

The change score will be determined for all patients, also in case of partially missing data. A patient without any follow-up data will get the base score = 2. The maximal score will be 5, which is achieved by patients who survive through 12 months without HF hospitalization and have $\geq 30\%$ reduction of LVESVi as well as improvement of NYHA class. The minimal score is 0, which can be achieved in several ways: including death, HF hospitalization and no improvement on LVESVi or NYHA class, multiple HF hospitalizations, or increase in LVESVi and NYHA class worsening.



UMC Utrecht

**Door beeldvorming gestuurde plaatsing van de linker kamerdraad bij
Cardiale Resynchronisatie Therapie III
ADVISE-CRT III**

Advanced Image Supported Left Ventricular Lead Placement in CRT III

Informatie voor deelname aan medisch-wetenschappelijk onderzoek

Geachte mevrouw/meneer,

Wij nodigen u uit om deel te nemen aan een wetenschappelijke onderzoek. Deelname aan dit onderzoek is vrijwillig. Om mee te doen is uw schriftelijke toestemming nodig.

U ontvangt deze brief omdat binnenkort een apparaat dat zorgt voor Cardiale Resynchronisatie Therapie (CRT) in uw lichaam wordt geplaatst. Een CRT-apparaat zorgt voor gelijktijdige activatie van uw hartkamers. Dit leidt tot een betere pompfunctie van het hart, en behandelt daarmee uw hartfalen. Voordat u beslist of u wil meedoen aan dit onderzoek, krijgt u van ons onderstaande uitleg over het onderzoek. Het is zeer belangrijk dat u deze informatie leest en begrijpt. Bespreek deze gerust met uw partner, vrienden of familie. Lees ook de Algemene Brochure ¹. Daarin staat algemene informatie over medisch-wetenschappelijk onderzoek.

Heeft u na het lezen van de informatie nog vragen? Dan kunt u terecht bij de onderzoeker. Op bladzijde 10 vindt u zijn contactgegevens. Ook staat daar een onafhankelijke arts vermeld, aan wie u ook vragen kan stellen over het onderzoek.

Als u na het lezen van alle informatie geen toestemming geeft voor deelname, om wat voor reden dan ook, zal dat geen effect hebben op uw verdere behandeling. De onderzoeker neemt zelf met u contact op.

1. Algemene informatie

Dit onderzoek wordt uitgevoerd door het UMC Utrecht. Voor dit onderzoek zijn in totaal 130 patiënten nodig uit minimaal drie Nederlandse ziekenhuizen. De medisch-ethische toetsingscommissie van het UMC Utrecht heeft het onderzoek goedgekeurd. Algemene informatie over de toetsing van onderzoek vindt u in de Algemene Brochure ¹. Bij deelname zullen studiehandelingen en de plaatsing van CRT enkel gebeuren in het centrum dat U heeft benaderd. Voor een volledige uitleg van de procedures tijdens het onderzoek is het van belang dat u dit gehele document met aandacht doorneemt.

¹ VWS brochure 'Medisch-wetenschappelijk onderzoek; Algemene informatie voor de proefpersoon'. Of op de website van de Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

2. Doel van het onderzoek

Het doel van het onderzoek is om te kijken naar de effectiviteit van een nieuwe technologie die we gebruiken tijdens de plaatsing van het CRT apparaat. Met deze technologie verwachten we de plaatsing van de linker kamerdraad bij een CRT apparaat te verbeteren. Met andere woorden: we kunnen de plek in het hart waar het apparaat moet worden geplaatst beter bepalen én dit tijdens de operatie zichtbaar maken voor de cardioloog. Hieronder vindt u uitgebreide informatie over de werking van CRT en de nieuwe technologie die we gebruiken om het CRT-apparaat mogelijk beter te plaatsen.

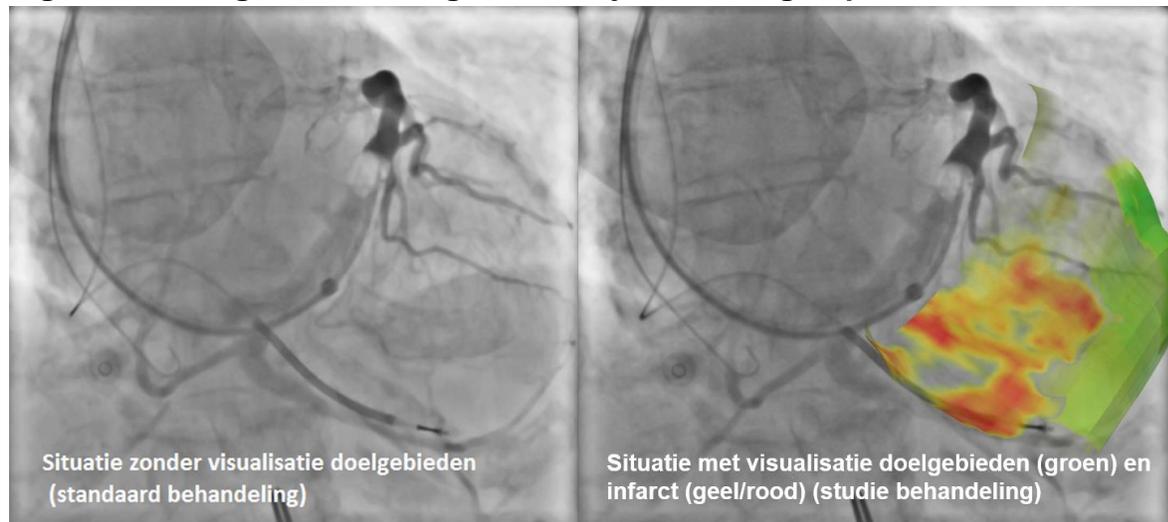
3. Achtergrond van het onderzoek

Uw behandelend arts heeft bij u vastgesteld dat het hart uw bloed niet effectief kan rondpompen in uw lichaam. Ondanks dat u behandeld wordt met medicijnen, houdt u een slechte pompfunctie van het hart. Dit wordt deels veroorzaakt doordat twee helften van het hart bij u niet gelijktijdig samentrekken. Dit speelt een rol in het ontstaan van klachten zoals kortademigheid, vermoeidheid en/of het vasthouden van vocht.

Daarom heeft uw cardioloog met u gesproken over behandeling door middel van zogenaamde Cardiale Resynchronisatie Therapie (CRT). Bij CRT wordt een pacemaker met of zonder defibrillator (ICD, 'klapkastje') onder de huid van uw borst geplaatst. Op dit apparaat worden drie draden aangesloten die de hartspier kunnen aansturen. Een daarvan wordt geplaatst in de rechter boezem, één in de rechter kamer en één in de linker kamer. De draden worden via de bloedvaten in het hart gebracht en geven elektrische signalen af waardoor beide hartkamers weer gelijktijdig gaan samentrekken. Het doel van CRT is een verbeterde pompfunctie van het hart, minder klachten van hartfalen, betere kwaliteit van leven en een betere levensverwachting. Dit is een gevolg van het meer synchron laten samentrekkende hartkamers (resynchronisatie therapie).

CRT is een techniek die standaard wordt toegepast in Nederland. De plek waar de linker kamerdraad wordt geplaatst is erg belangrijk voor het effect van CRT. De hartspier kan bijvoorbeeld beschadigd zijn door een hartinfarct. De linker kamerdraad moet niet in de buurt van beschadigd hartspierweefsel geplaatst worden. Daarnaast is het gebied in het hart dat het laatst samentrekt waarschijnlijk de meest gunstige plaats voor de linker kamerdraad. Plaatsing van deze draad op de meest gunstige plek kan leiden tot een grotere verbetering van de pompfunctie en een gunstiger effect van de behandeling.

Met de huidige manier van werken, waarbij de optimale plek voor de linker kamerdraad niet kan worden gezien tijdens de operatie, kunnen we helaas niet goed zien welke plek voor u het gunstigste is. Daardoor wordt de draad bij een deel van de patiënten niet optimaal geplaatst. Door technologische ontwikkelingen zijn we sinds kort in staat om de optimale plek wél zichtbaar te maken tijdens de operatie (Figuur 1).

Figuur 1: Weergave van doelgebieden tijdens de ingreep

Links: standaard röntgenopnames tijdens CRT-implantatie. Rechts: Röntgenopnames gecombineerd met informatie uit MRI-beelden. Littekenweefsel (rood) en doelgebieden (groen) worden nu weergegeven op de linker hartkamer, wat zorgt voor gerichte plaatsing van de linker kamerdraad.

Door vóór de CRT-implantatie een MRI-scan te maken kunnen we een 3D-plaatje van uw hart maken. De eerdergenoemde schade aan de hartspier en het laatst samentrekkende gebied kunnen hiermee goed in beeld worden gebracht. De nieuwe techniek van deze studie maakt het mogelijk om de informatie uit de MRI-te gebruiken. Daarnaast maakt het deze informatie zichtbaar voor de cardioloog tijdens de implantatie van het CRT-apparaat. Op deze manier kunnen we de plaats voor de linker kamerdraad waarvan we verwachten dat die optimaal is aangegeven tijdens de operatie. De cardioloog kan zo tijdens de operatie de linker kamerdraad naar deze plaatst leiden.

De techniek om MRI-beelden te combineren met de standaard röntgen beelden die gemaakt worden tijdens een CRT-implantatie is al onderzocht in twee eerdere patiëntonderzoeken. Daarbij is gebleken deze nieuwe technologie veilig en goed toepasbaar is. Ook waren er eerste aanwijzingen dat de procedure effectief kan zijn. In het huidige onderzoek willen we in een groter aantal patiënten uitgebreider naar de effectiviteit kijken. Daarbij gaan we kijken hoeveel patiënten baat hebben van het CRT-apparaat wanneer dit geplaatst wordt met behulp van de nieuwe technologie.

4. Wat meedoen inhoud

Om de effectiviteit van de nieuwe techniek zo betrouwbaar mogelijk aan te tonen, wordt u willekeurig ingedeeld in een groep. Dit betekent dat u bij deelname aan het onderzoek de plaatsing van het CRT-apparaat volgens de nieuwe techniek (studiegroep) of de gebruikelijke techniek (controlegroep) zult ondergaan. Dit noemt men randomisatie. Zowel uzelf als uw arts heeft geen invloed op de groep waar u in komt.

Als u meedoet duurt het onderzoek 2 jaar voor u, ongeacht van welke groep u krijgt toegedeeld. In deze 2 jaar moet u gedurende de eerste 6 maanden drie keer naar het ziekenhuis komen. U komt een keer vlak voordat de ingreep plaatsvindt voor extra beeldvorming van het hart. U komt een keer voor de ingreep zelf (CRT implantatie met ziekenhuisopname). Tot slot komt u 6 maanden na de implantatie voor de laatste keer terug om het effect van de behandeling te beoordelen. Als u niet meedoet met het onderzoek, komt u meestal twee keer naar het ziekenhuis in 6 maanden tijd (een keer voor de CRT plaatsing zelf en een keer voor een controle echo 6 maanden na de behandeling).

Daarnaast vragen wij uw toestemming om ná de CRT plaatsing uw medische gegevens te mogen inzien. Ook willen wij u op 1 en 2 jaar ná implantatie twee vragenlijsten sturen. Dit kan per post of digitaal. U hoeft dus niet naar het ziekenhuis te komen. Dit vragen wij zodat wij onder andere kunnen bepalen of de therapie heeft gezorgd voor minder ziekenhuisopnames en een betere kwaliteit van leven. Bij deelname kunt u er voor kiezen om toestemming te geven dat wij deze gegevens mogen opvragen en inzien. Dit gebeurt bij het ziekenhuis waar u bekend bent.

Wij gaan ervan uit dat uw cardioloog al uitleg heeft gegeven over het plaatsen van het CRT-apparaat. Als dat niet zo is, kunt u dit bespreken met uw cardioloog of met de hieronder genoemde arts/onderzoeker. Het plaatsen van het CRT-apparaat is een standaard operatie.

Anders dan bij gebruikelijke zorg

Hieronder leggen we uit wat we extra doen als u aan het onderzoek deelneemt (zie ook het stroomdiagram in bijlage I):

- Vóór de implantatie wordt een MRI-scan (45 minuten) en een echo van het hart (30 minuten) gemaakt. Mogelijk moet u hiervoor extra naar het ziekenhuis komen.
- Tijdens de CRT-implantatie wordt de linker kamerdraad geplaatst (Figuur 1). Dit gebeurt zoals gebruikelijk (controlegroep) of met behulp van de MRI-beelden (therapiegroep).
- Op 1 en 2 jaar ná implantatie ontvangt u twee vragenlijsten. Dit kan digitaal, u hoeft niet naar het ziekenhuis te komen. Ook ziet een onderzoeker uw medisch dossier in tot in ieder geval 2 jaar na implantatie.

MRI-scan

Bij het maken van een MRI-scan wordt gebruik gemaakt van een sterk magneetveld en radiogolven. Hiermee worden signalen in het lichaam opgewekt. Een antenne ontvangt de signalen en een computer zet deze om in een beeld. Zo wordt het hart afgebeeld terwijl het samentrekt. Er worden daarbij geen röntgenstralen gebruikt. Ook als u niet meedoet aan het onderzoek wordt soms er een MRI gemaakt voor de CRT implantatie. Als u meedoet aan het onderzoek worden er een aantal extra beelden gemaakt. Daardoor duurt de tijd dat u in de MRI-buis ligt enkele minuten langer.

Echo van het hart

Bij een echo wordt gebruik gemaakt van geluidsgolven. Er wordt geen gebruik gemaakt van Röntgenstraling. Een echo is veilig en niet pijnlijk. Met echo kan onder andere de pompfunctie van het hart worden beoordeeld. Door de pompfunctie voor én na CRT implantatie te meten op een hartecho, kunnen we het effect van CRT op de pompfunctie van uw hart beoordelen.

Vragenlijsten

- EQ-5D-5L is een maat voor de gezondheid. Deze vragenlijst bestaat uit 6 korte vragen op verschillende gezondheidsniveaus (mobiliteit, zelfzorg, dagelijkse activiteiten, ongemak en somberheid) waarop een score moet worden gegeven. Invullen duurt ongeveer 5 minuten.
- Kansas City Cardiomyopathy Questionnaire (KCCQ) is een vragenlijst ontwikkeld om de mate waarin hartfalen uw leven beïnvloedt te meten. Deze vragenlijst bestaat uit 15 items binnen verschillende domeinen. De vragenlijst richten zich met name op uw klachten en duurt ongeveer 5 minuten om in te vullen.

5. Wat wordt er van u verwacht?

Zoals hierboven uitgelegd moet u in ongeveer 6 maanden tijd in totaal drie keer naar het ziekenhuis komen (maximaal een keer vaker dan bij normale zorg). Om het onderzoek goed te laten verlopen is het belangrijk dat u afspraken voor bezoeken nakomt. Daarnaast is het belangrijk dat u contact opneemt met de onderzoeker:

- als u in een ziekenhuis wordt opgenomen of behandeld.
- als u plotseling gezondheidsklachten krijgt.
- als u niet meer wilt meedoen aan het onderzoek.
- als uw contactgegevens wijzigen.

6. Mogelijke bijwerkingen en andere nadelige effecten

Er zijn (geringe) risico's aan deelname aan het onderzoek.

MRI-scan

Een MRI-scan is niet schadelijk voor het menselijk lichaam. Het contrastmiddel dat bij MRI gebruikt wordt kan schadelijk zijn voor de nieren. Als u een slechte nierfunctie heeft, kunt u daarom niet deelnemen aan dit onderzoek. Ook kunt u allergisch reageren op het contrastmiddel. Dit komt zeer zelden voor (<1 per 1000 patiënten). Een nadeel voor u van de MRI is de tijdsinvestering en mogelijk een extra bezoek aan het ziekenhuis die wij u vragen. Verder ligt u tijdens het MRI-onderzoek in een kleine tunnel die aan het hoofd- en voeteneind open is. Als u niet in kleine ruimtes durft (claustrofobie), kunt u niet deelnemen aan dit onderzoek. Tot slot, omdat een MRI scanner werkt met een magnetisch veld kunt u niet meedoen als u metaal in uw lichaam heeft.

Mogelijke voor- en nadelen

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen. Bij deelname aan de studie kunt u in de onderzoeksgroep of de controlegroep worden geplaatst. De mogelijke voordelen zijn afhankelijk van in welke groep u krijgt toegewezen.

- Studiegroep: U hebt een mogelijk voordeel van deelname aan deze studie omdat we de optimale gebieden voor plaatsing van de linker kamerdraad zichtbaar maken. Plaatsing van de linker kamerdraad op de optimale plek kan leiden tot een verbeterde pompfunctie van het hart en daardoor minder klachten van hartfalen en een betere overleving. We weten dat er tussen patiënten grote verschillen bestaan en daarom kunnen we niet voorspellen of u met deze manier van plaatsen echt minder klachten krijgt van uw hartfalen. Er is een mogelijkheid dat de implantatie iets langer duurt doordat we gericht zoeken naar het optimale gebied. Er wordt dan een verwaarloosbare hoeveelheid extra straling gebruikt.
- Controlegroep: Er is ook een kans dat u in de controlegroep terechtkomt. Blijkt na afloop van de studie dat u als patiënt in de controlegroep onvoldoende baat van de pacemaker heeft gehad? Dan bestaat de mogelijkheid om de voor u specifieke studie-inzichten te gebruiken om de plaatsing van de linker kamerdraad bij u opnieuw te beoordelen met uw cardioloog. Daarnaast levert de studie nuttige wetenschappelijke gegevens voor de toekomst, maar daar heeft u niet direct baat bij.

Nadelen van meedoen aan het onderzoek zijn: 1) dat u extra tijd kwijt bent, en 2) dat u afspraken heeft waar u zich aan moet houden.

7. Als u niet wilt meedoen of wilt stoppen met het onderzoek

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. U hoeft niets te tekenen. U hoeft ook niet te zeggen waarom u niet wilt meedoen. U krijgt dan gewoon de behandeling die u anders ook zou krijgen. Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen. U mag uw deelname ook te allen tijde intrekken, ook gedurende het onderzoek. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan de onderzoeker.

Het onderzoek zal zo nauwkeurig mogelijk volgens plan worden uitgevoerd. Echter, de situatie kan veranderen, bijvoorbeeld door een reactie van uw lichaam, of door nieuwe informatie. Als dat zo is, bespreken we dat direct met u. U beslist dan zelf of u met het onderzoek wil stoppen of doorgaan. Als uw veiligheid of welbevinden in gevaar is, stoppen we direct met het onderzoek.

8. Einde van het onderzoek

Uw deelname aan het onderzoek stopt als

- alle bezoeken voorbij zijn
- u zelf kiest om te stoppen
- het einde van het hele onderzoek is bereikt
- de onderzoeker het beter voor u vindt om te stoppen
- de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Na het verwerken van alle gegevens informeert de onderzoeker u over de belangrijkste uitkomsten van het onderzoek. Dit gebeurt ongeveer 1-1.5 jaar na uw deelname. Als u dit niet wilt, dan kunt u dit tegen de onderzoeker zeggen. Hij/zij mag het u dan niet vertellen.

9. Gebruik en bewaren van uw gegevens

Voor dit onderzoek worden uw persoonsgegevens verzameld, gebruikt en bewaard. Het gaat om gegevens zoals uw naam, adres, geboortedatum en om gegevens over uw gezondheid. Het verzamelen, gebruiken en bewaren van uw gegevens is nodig om de vragen die in dit onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren. Wij vragen voor het gebruik van uw gegevens uw toestemming.

Vertrouwelijkheid van uw gegevens

Om uw privacy te beschermen krijgen uw gegevens een code. Uw naam en andere gegevens die u direct kunnen identificeren worden daarbij weggelaten. Alleen met de sleutel van de code zijn gegevens tot u te herleiden. De sleutel van de code blijft veilig opgeborgen in de lokale onderzoeksinstelling.

Voor dit onderzoek werken we samen met het bedrijf CART-Tech B.V. (Utrecht, Nederland). CART-Tech is een bedrijf dat voortkomt uit het UMC Utrecht en het heeft de

1 software voor het combineren van de Röntgen- en MRI-beelden ontwikkeld. De
2 gegevens die naar CART-Tech worden gestuurd bevatten alleen de code, maar niet uw
3 naam of andere gegevens waarmee u kunt worden geïdentificeerd

4 Ook in rapporten en publicaties over het onderzoek zijn de gegevens niet tot u te
5 herleiden.
6
7

8 9 **Toegang tot uw gegevens voor controle**

10 Sommige personen kunnen op de onderzoekslocatie toegang krijgen tot al uw
11 gegevens. Ook tot de gegevens zonder code. Dit is nodig om te kunnen controleren of
12 het onderzoek goed en betrouwbaar is uitgevoerd. Mensen die uw gegevens in kunnen
13 zien zijn een controleur/monitor die door het UMC Utrecht is ingehuurd, de Inspectie
14 Gezondheidszorg en Jeugd (IGJ) en het betrokken onderzoeksteam. Zij houden uw
15 gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.
16
17
18

19 **Bewaartermijn gegevens**

20 Uw gegevens moeten 15 jaar worden bewaarde op de onderzoekslocatie.
21
22
23

24 **Bewaren en gebruik van gegevens**

25 Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander
26 wetenschappelijk onderzoek op het gebied van CRT implantatie. Daarvoor zullen uw
27 gegevens 15 jaar worden bewaard. U kunt op het toestemmingsformulier aangeven of u
28 hier wel of niet mee instemt. Indien u hier niet mee instemt, kunt u gewoon deelnemen
29 aan het huidige onderzoek.
30
31
32

33 **Informatie over onverwachte bevindingen**

34 Tijdens dit onderzoek kan er bij toeval iets gevonden worden dat niet van belang is voor
35 het onderzoek maar wel voor u. Als dit belangrijk is voor uw gezondheid, dan zult u op
36 de hoogte worden gesteld [door de huisarts of medisch specialist]. U kunt dan met uw
37 huisarts of specialist bespreken wat er gedaan moet worden. Ook hiervoor geeft u
38 toestemming.
39
40
41

42 **Intrekken toestemming**

43 U kunt uw toestemming voor gebruik van uw persoonsgegevens altijd weer intrekken.
44 Dit geldt voor dit onderzoek en ook voor het bewaren en het gebruik voor het
45 toekomstige onderzoek. De onderzoeksgegevens die zijn verzameld tot het moment dat
46 u uw toestemming intrekt worden nog wel gebruikt in het onderzoek
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Meer informatie over uw rechten bij verwerking van gegevens

Voor algemene informatie over uw rechten bij verwerking van uw persoonsgegevens kunt u de website van de Autoriteit Persoonsgegevens raadplegen.

Bij vragen over uw rechten kunt u contact opnemen met de verantwoordelijke voor de verwerking van uw persoonsgegevens. Voor dit onderzoek is dat het UMC Utrecht. Zie bijlage A voor contactgegevens en website.

Bij vragen of klachten over de verwerking van uw persoonsgegevens raden we u aan eerst contact op te nemen met de onderzoekslocatie. U kunt ook contact opnemen met de Functionaris voor de Gegevensbescherming van de instelling [contactgegevens in bijlage A] of de Autoriteit Persoonsgegevens.

10. Verzekering proefpersonen

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt schade door het onderzoek. Niet alle schade is gedekt. In bijlage B vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

11. Informeren huisarts/behandelend cardioloog

Wij sturen uw huisarts/behandelend cardioloog altijd een brief om te laten weten dat u meedoet aan het onderzoek. Dit is voor uw eigen veiligheid. Als u dit niet goed vindt, kunt u niet meedoen aan dit onderzoek.

12. Vergoeding voor meedoen

Deelnemers aan dit onderzoek krijgen geen vergoeding.

13. Heeft u vragen?

Bij vragen kunt u contact opnemen met de onderzoekers. Voor onafhankelijk advies over meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke arts. Zij weet veel over het onderzoek, maar heeft niets te maken met dit onderzoek.

Indien u klachten heeft over het onderzoek, kunt u dit bespreken met de onderzoeker of uw behandelend arts. Wilt u dit liever niet, dan kunt u zich wenden tot de klachtenfunctionaris/klachtencommissie van uw ziekenhuis. Alle gegevens vindt u in bijlage A: Contactgegevens.

U heeft mogelijk al een telefonisch informatiegesprek gehad. Mocht u door omstandigheden geen telefonisch informatiegesprek hebben gehad, dan vindt er een gesprek met de arts-onderzoeker plaatst tijdens een ziekenhuisbezoek of tijdens de ziekenhuisopname. U heeft dan mogelijk een kortere bedenktijd voor studiedeelname maar deze is nooit korter dan 24 uur.

14. Ondertekening toestemmingsformulier (Informed Consent)

Wanneer u voldoende bedenktijd heeft gehad, wordt u gevraagd te beslissen over deelname aan dit onderzoek. Indien u toestemming geeft, zullen wij u vragen deze op de bijbehorende toestemmingsverklaring schriftelijk te bevestigen samen met de onderzoeker. Door uw schriftelijke toestemming geeft u aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek.

Zowel uzelf als de onderzoeker ontvangen een getekende versie van deze toestemmingsverklaring.

Dank voor uw aandacht.
Met vriendelijke groet,

Drs. P.C. Wouters, arts-onderzoeker cardiologie, UMC Utrecht
Dr. M. Meine, hoofdonderzoeker, cardioloog, UMC Utrecht

15. Bijlagen bij deze informatie

- A. Contactgegevens
- B. Informatie over de verzekering
- C. Schema onderzoekshandelingen
- D. Toestemmingsformulier
- E. Brochure "Medische-wetenschappelijk onderzoek. Algemene informatie voor proefpersoon"

Bijlage A: contactgegevens voor UMC Utrecht

Heeft u nog vragen of wilt u nadere informatie ontvangen dan kunt u altijd contact opnemen met één van onderstaande personen

Onderzoekers

Drs. P.C. Wouters
Arts-onderzoeker UMC Utrecht
Onderzoeker Advise-CRT
Telefoonnummer: 088-757 43 75
E-mail: p.wouters@umcutrecht.nl

Dr. M. Meine
Cardioloog UMC Utrecht
Hoofdonderzoeker Advise-CRT
Telefoonnummer: 088-755 61 84

Onafhankelijk arts

Als u er prijs op stelt informatie over dit onderzoek in te winnen bij een arts die niet bij de uitvoering van het onderzoek is betrokken maar wel over de gegevens ervan beschikt (een 'onafhankelijke arts') dan is Dr. Rittersma bereid uw vragen te beantwoorden (geldt voor alle deelnemende ziekenhuizen):

Dr. Z.H. Rittersma
Cardioloog UMC Utrecht
Onafhankelijk arts ADVISE-CRT III studie
Telefoonnummer: 088-755 61 76

Klachten

Als u klachten heeft kunt u dit melden aan de onderzoeker of aan uw behandelend arts. Mocht u ontevreden zijn over de gang van zaken bij het onderzoek en een klacht willen indienen dan kunt u contact opnemen met de klachtenbemiddelaars. Deze zijn bereikbaar via tel. 088-755 62 08. Of digitaal via:

<http://www.umcutrecht.nl/nl/Ziekenhuis/Ervaringen-van-patienten/Een-klachtindienen>.

Functionaris voor de Gegevensbescherming van de instelling: privacy@umcutrecht.nl

Raadpleeg de website van het UMC Utrecht voor meer informatie over uw rechten:
<https://www.umcutrecht.nl/nl/Ziekenhuis/In-het-ziekenhuis/Regels-en-rechten/Rechten>



UMC Utrecht

Bijlage B: Verzekeringsbijlage

INFORMATIE OVER DE VERZEKERING

Voor iedereen die meedoet aan dit onderzoek, heeft UMC Utrecht een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde ervan. Schade moet u binnen die vier jaar aan de verzekeraar hebben gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt.

Deze bepalingen staan in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Dit besluit staat op www.ccmo.nl, de website van de Centrale Commissie Mensgebonden Onderzoek (zie 'Bibliotheek' en dan 'Wet- en regelgeving').

Bij schade kunt u direct contact leggen met de verzekeraar.

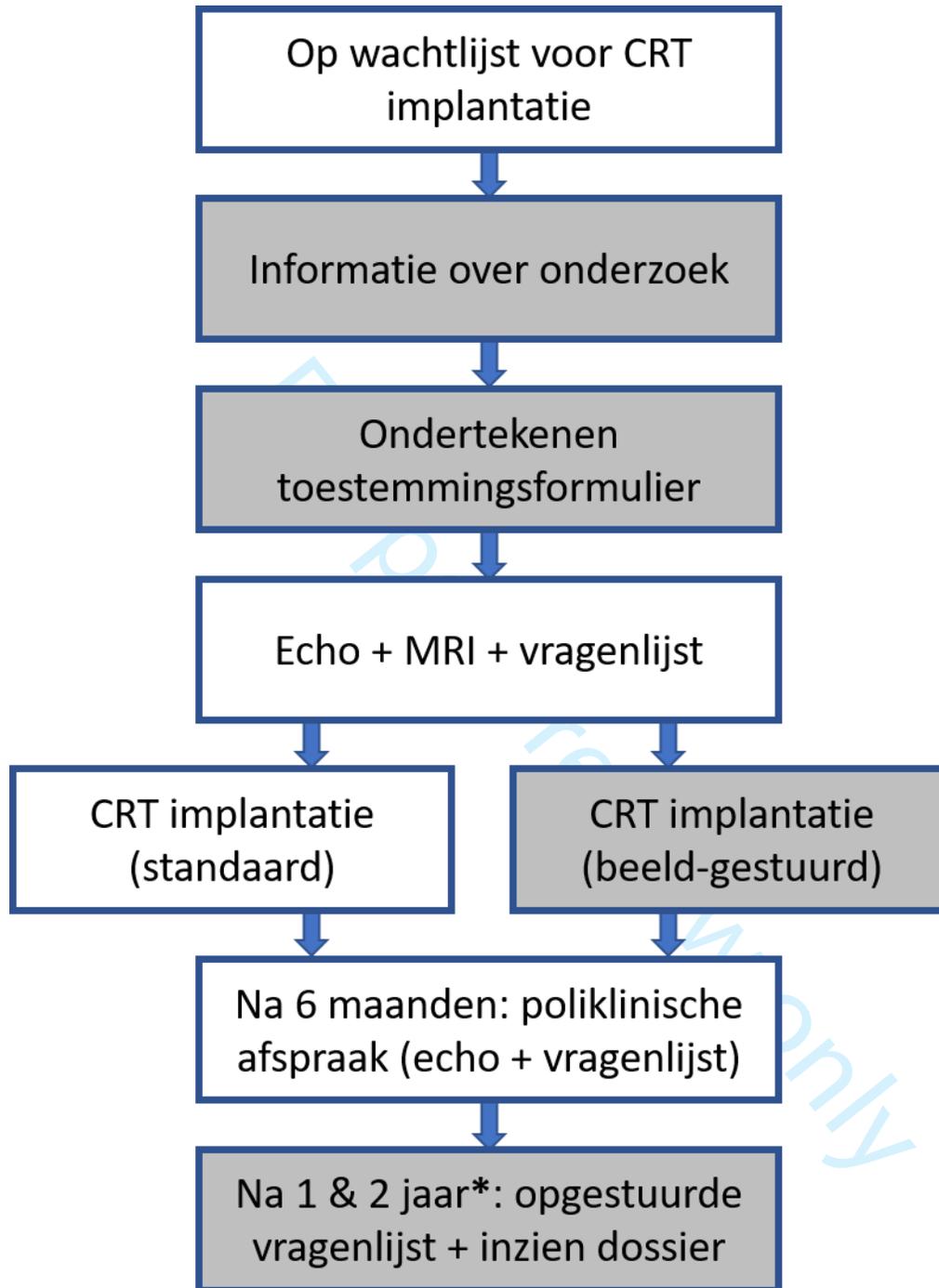
De verzekeraar van het onderzoek is:

Naam:	CNA Insurance Company Ltd
Adres:	Strawinskylaan 703, 1077 XX Amsterdam
Telefoonnummer:	020 – 57 37 274
Polisnummer:	10201366
Contactpersoon:	Mw. Esther van Herk

De verzekering biedt een dekking van € 650.000 per proefpersoon en maximaal € 5.000.000 voor het hele onderzoek en maximaal € 7.500.000 zijn per jaar voor alle onderzoeken van dezelfde opdrachtgever.

De verzekering dekt de volgende schade **niet**:

- schade door een risico waarover u in de schriftelijke informatie bent ingelicht. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
- schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan;
- schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
- schade aan uw nakomelingen, als gevolg van een negatief effect van het onderzoek op u of uw nakomelingen;
- schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.

Bijlage C: Schema onderzoekshandelingen

*Bijlage C: Stroomdiagram van het ADVISE-CRT III onderzoek. Grijs gekleurde blokken zijn extra handelingen behorende bij het onderzoek. Witte blokken worden vaak standaard verricht. Afkortingen: CRT: cardiale resynchronisatie therapie, MRI: magnetische resonantie scan. * Na 1 en 2 jaar moet u niet naar het ziekenhuis komen, deze stap kan online of per post.*



UMC Utrecht

Bijlage D: Toestemmingsformulier voor deelname aan het onderzoek

Advanced Image Supported Left Ventricular Lead Placement in Cardiac Resynchronization Therapy
Advise-CRT

Door beeldvorming gestuurde plaatsing van de linker kamerdraad bij CRT

Ik bevestig dat ik het informatieformulier voor de proefpersoon heb gelezen en dat ik ook mondeling informatie heb gekregen. Ik begrijp de informatie. Ik heb de gelegenheid gehad om aanvullende vragen te stellen. Deze vragen zijn in voldoende mate beantwoord. Ik heb voldoende tijd gehad om over deelname na te denken.

Ik weet dat mijn deelname geheel vrijwillig is en dat ik mijn toestemming op ieder moment kan intrekken zonder dat ik daarvoor een reden hoeft te geven en zonder dat dit een effect heeft op mijn medische behandeling.

Ik geef toestemming voor het informeren van mijn huisarts/behandelend Cardioloog.

Ik geef toestemming dat ten behoeve van het onderzoek medische gegevens bij mijn behandelend cardioloog worden opgevraagd.

Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens voor de beantwoording van de onderzoeksvraag in dit onderzoek.

Ik weet dat voor controle van het onderzoek sommige mensen toegang tot al mijn gegevens kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.

Ik geef toestemming voor het delen van mijn gecodeerde gegevens met CART-Tech.

Ik geef toestemming voor het informeren van mijn huisarts en/of behandelend specialist van onverwachte bevindingen die van belang (kunnen) zijn voor mijn gezondheid.

1 Ik geef toestemming voor het langer bewaren en gebruiken van gegevens voor
2 eventueel vervolgonderzoek op het gebied van CRT implantatie

- 3 ja
4 nee

6
7 Ik geef toestemming om benaderd te worden voor deelname aan eventueel
8 vervolgonderzoek.

- 9 ja
10 nee

12
13 Ik geef voor dit onderzoek toestemming om mijn zorggegevens op te vragen en in te
14 zien in andere ziekenhuizen waar ik bekend ben.

- 15 ja
16 nee

17
18 Ik weet dat mijn onderzoeksgegevens na het onderzoek nog 15 jaar bewaard worden en
19 daarna worden vernietigd.

20
21 Na afronding van het gehele onderzoek wil ik de uitslag van het onderzoek op
22 groepsniveau ontvangen.

- 23 ja
24 nee

25
26
27
28 Ik wil meedoen aan dit onderzoek.

29
30
31 Naam proefpersoon:

32
33
34 Handtekening:

Datum: __ / __ / __

35
36
37
38 -----
39 Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde
40 onderzoek.

41
42 Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de
43 proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de
44 hoogte.

45
46
47 Naam onderzoeker (of diens vertegenwoordiger):

48
49
50 Handtekening:

Datum: __ / __ / __

51
52
53
54
55 De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende
56 versie van het toestemmingsformulier.

Supplemental Table 1. Cost calculations for input parameters.

	Quantity	Unit Cost (€)	Total Cost (€)	Source
Index Procedure				
<i>Diagnostics</i>				
Cardiac MRI	1	376.91	376.91	(1)
Cardiac Ultrasound	1	139.49	139.49	(1)
Thorax X-Ray	1	61.27	61.27	(1)
Lab work	2	44.46	88.92	(1)
<i>CRT</i>				
Procedural Costs	1	1,432.74	1,432.74	(2)
Biventricular ICD	0.8	12,387.68	9,910.14	(2)
Biventricular Pacemaker	0.2	6,644.83	1,328.97	(2)
<i>Admission</i>				
General Ward Admission	2	668.24	1,336.48	(3)
			14,814.14	
Procedural Complications				
<i>Pocket Infection</i>				
PET/CT Thorax	1	850.99	850.99	(1)
Transesophageal Ultrasound	1	263.81	263.81	(1)
ICD Removal	1	1,039.19	1,039.19	(2)
Pocket Revision	1	956.46	956.46	(2)
ICD Implantation	1	1,045.41	1,045.41	(2)
ICD Device	1	11,594.87	11,594.87	(2)
General Ward Admission	7	668.27	4,677.89	(3)
			20,428.62	
<i>Pneumothorax</i>				
Thorax X-Ray	1	61.27	61.27	(1)
Thorax Drain	1	788.27	788.27	(1)
General Ward Admission	3	668.24	2,004.72	(3)
			2,854.26	
<i>Wire Dislocation</i>				
Thorax X-Ray	2	61.27	122.54	(1)
Replacement CRT Leads	1	600.75	600.75	(2)
General Ward Admission	2	668.24	1,336.48	(3)
			2,059.77	
Follow-up				
Outpatient Visit	1	169.86	169.86	(1)
Lab work	1	44.46	44.46	(1)
			214.32	

Supplemental Table 2. Cost calculations for various health states.

	Quantity	Unit Cost (€)	Total Cost (€)	Source
Additional Healthcare Costs Model Health States				
<i>Decompensation I</i>				
Cardiac Ultrasound	1	139.49	139.49	(1)
General Ward Admission	7	668.24	4,677.68	(3)
			4,817.17	
<i>Decompensation II</i>				
Cardiac Ultrasound	1	139.49	139.49	(1)
Central Venous Line	1	365.38	365.38	(1)
Cardiac Care Unit Admission	14	1,986.48	27,810.72	(3)
			28,316.59	
<i>Decompensation III</i>				
Cardiac Ultrasound	1	139.49	139.49	(1)
Central Venous Line	1	365.38	365.38	(1)
Implantation Ventricle Assist Device (LVAD)	1	5,388.58	5,388.58	(2)
Materials LVAD	1	87,292.15	87,292.15	(2)
Cardiac Care Unit Admission	28	1,986.48	55,621.44	(3)
			148,807.04	
<i>LVAD</i>				
Considered equal to Decompensation III	1	148,807.04	148,807.04	(1-3)
<i>Transplantation</i>				
Heart Transplantation including Admission	1	37,579.47	37,579.47	(4)

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4. Open data van de Nederlandse Zorgautoriteit [Internet]. Nederlandse Zorgautoriteit (Netherlands Healthcare Authority). 2020. Available from: www.opendisdata.nl

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Trial NL8666
Protocol version	#3	Date and version identifier	Version 2.0, 29-07-2020 Version 3.0, 15-09-2021
Funding	#4	Sources and types of financial, material, and other support	12

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1, 12
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	12
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
14	responsibilities:			
15	sponsor and funder			
16				
17				
18				
19				
20				
21				
22				
23	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
24	responsibilities:			
25	committees			
26				
27				
28				
29				
30				
31				
32				
33	Introduction			
34				
35	Background and	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
36	rationale			
37				
38				
39				
40				
41				
42				
43	Background and	#6b	Explanation for choice of comparators	4, 5
44	rationale: choice of			
45	comparators			
46				
47				
48	Objectives	#7	Specific objectives or hypotheses	1
49				
50				
51	Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	2
52				
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Methods:**Participants, interventions, and outcomes**

8	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
15	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
22	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4, 5
27	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
35	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
42	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
46	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
58	Participant timeline	#13	Time schedule of enrolment, interventions	4

(including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

1			
2			
3			
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7	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
8			
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14			
15	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size
16			NA; consecutive patients
17			
18			
19	Methods:		
20	Assignment of		
21	interventions (for		
22	controlled trials)		
23			
24			
25			
26	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
27	generation		
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39	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
40	concealment		
41	mechanism		
42			
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46			
47	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
48	implementation		
49			
50			
51			
52	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
53			5, 6
54			
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1	Blinding (masking):	#17b	If blinded, circumstances under which unblinding	6
2	emergency		is permissible, and procedure for revealing a	
3	unblinding		participant's allocated intervention during the	
4			trial	
5				
6				
7				
8	Methods: Data			
9	collection,			
10	management, and			
11	analysis			
12				
13				
14	Data collection plan	#18a	Plans for assessment and collection of outcome,	4-7
15			baseline, and other trial data, including any	
16			related processes to promote data quality (eg,	
17			duplicate measurements, training of assessors)	
18			and a description of study instruments (eg,	
19			questionnaires, laboratory tests) along with their	
20			reliability and validity, if known. Reference to	
21			where data collection forms can be found, if not	
22			in the protocol	
23				
24	Data collection plan:	#18b	Plans to promote participant retention and	NA
25	retention		complete follow-up, including list of any outcome	
26			data to be collected for participants who	
27			discontinue or deviate from intervention	
28			protocols	
29				
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36				
37	Data management	#19	Plans for data entry, coding, security, and	6
38			storage, including any related processes to	
39			promote data quality (eg, double data entry;	
40			range checks for data values). Reference to	
41			where details of data management procedures	
42			can be found, if not in the protocol	
43				
44				
45				
46				
47	Statistics: outcomes	#20a	Statistical methods for analysing primary and	7, 8
48			secondary outcomes. Reference to where other	
49			details of the statistical analysis plan can be	
50			found, if not in the protocol	
51				
52				
53				
54	Statistics: additional	#20b	Methods for any additional analyses (eg,	7, 8
55	analyses		subgroup and adjusted analyses)	
56				
57				
58	Statistics: analysis	#20c	Definition of analysis population relating to	7, 8
59				
60				

1 population and
2 missing data

protocol non-adherence (eg, as randomised
analysis), and any statistical methods to handle
missing data (eg, multiple imputation)

5 **Methods:**
6 **Monitoring**

9 Data monitoring:
10 formal committee

11 [#21a](#) Composition of data monitoring committee
12 (DMC); summary of its role and reporting
13 structure; statement of whether it is independent
14 from the sponsor and competing interests; and
15 reference to where further details about its
16 charter can be found, if not in the protocol.
17 Alternatively, an explanation of why a DMC is
18 not needed

All strategies used
during implantation
are not known to be
associated with
additional risk.

22 Data monitoring:
23 interim analysis

24 [#21b](#) Description of any interim analyses and stopping
25 guidelines, including who will have access to
26 these interim results and make the final decision
27 to terminate the trial

NA

29 Harms

30 [#22](#) Plans for collecting, assessing, reporting, and
31 managing solicited and spontaneously reported
32 adverse events and other unintended effects of
33 trial interventions or trial conduct

8

36 Auditing

37 [#23](#) Frequency and procedures for auditing trial
38 conduct, if any, and whether the process will be
39 independent from investigators and the sponsor

NA

41 **Ethics and**
42 **dissemination**

45 Research ethics
46 approval

47 [#24](#) Plans for seeking research ethics committee /
48 institutional review board (REC / IRB) approval

8

49 Protocol
50 amendments

51 [#25](#) Plans for communicating important protocol
52 modifications (eg, changes to eligibility criteria,
53 outcomes, analyses) to relevant parties (eg,
54 investigators, REC / IRBs, trial participants, trial
55 registries, journals, regulators)

NA

57 Consent or assent

58 [#26a](#) Who will obtain informed consent or assent from
59 potential trial participants or authorised

4

		surrogates, and how (see Item 32)	
1			
2	Consent or assent:	#26b Additional consent provisions for collection and	4
3	ancillary studies	use of participant data and biological specimens	
4		in ancillary studies, if applicable	
5			
6			
7	Confidentiality	#27 How personal information about potential and	12
8		enrolled participants will be collected, shared,	
9		and maintained in order to protect confidentiality	
10		before, during, and after the trial	
11			
12			
13			
14	Declaration of	#28 Financial and other competing interests for	13
15	interests	principal investigators for the overall trial and	
16		each study site	
17			
18			
19	Data access	#29 Statement of who will have access to the final	12
20		trial dataset, and disclosure of contractual	
21		agreements that limit such access for	
22		investigators	
23			
24			
25			
26	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial	NA
27	trial care	care, and for compensation to those who suffer	
28		harm from trial participation	
29			
30			
31	Dissemination	#31a Plans for investigators and sponsor to	12
32	policy: trial results	communicate trial results to participants,	
33		healthcare professionals, the public, and other	
34		relevant groups (eg, via publication, reporting in	
35		results databases, or other data sharing	
36		arrangements), including any publication	
37		restrictions	
38			
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43	Dissemination	#31b Authorship eligibility guidelines and any	NA
44	policy: authorship	intended use of professional writers	
45			
46			
47	Dissemination	#31c Plans, if any, for granting public access to the	12
48	policy: reproducible	full protocol, participant-level dataset, and	
49	research	statistical code	
50			
51			
52	Appendices		
53			
54	Informed consent	#32 Model consent form and other related	NA; upon request.
55	materials	documentation given to participants and	
56		authorised surrogates	
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1 Biological
2 specimens
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[#33](#)

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

NA

Notes:

- 2b: Trial NL8666
- 3: Version 2.0, 29-07-2020
- 15: NA; consecutive patients
- 21a: All strategies used during implantation are not known to be associated with additional risk.
- 32: NA; upon request. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 01. June 2021 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

BMJ Open

Advanced image-supported lead placement in cardiac resynchronisation therapy: protocol for the multicenter, randomised controlled ADVISE trial and early economic evaluation

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054115.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Oct-2021
Complete List of Authors:	Wouters, Philippe; Universitair Medisch Centrum Utrecht, Department of Cardiology van Lieshout, Chris; Universitair Medisch Centrum Utrecht, Department of Public Health, Healthcare Innovation & Evaluation and Medical Humanities (PHM) van Dijk, Vincent F.; Sint Antonius Ziekenhuis, Department of Cardiology Delnoy, Peter-Paul H.M.; Isala Zwolle Doevendans, Pieter; Universitair Medisch Centrum Utrecht cramer, maarten jan; Universitair Medisch Centrum Utrecht, Cardiology Frederix, Geert; Universitair Medisch Centrum Utrecht, Department of Public Health, Healthcare Innovation & Evaluation and Medical Humanities (PHM) van Slochteren, Frebus; Universitair Medisch Centrum Utrecht, Department of Cardiology Meine, Mathias; Universitair Medisch Centrum Utrecht, Department of Cardiology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Radiology and imaging, Patient-centred medicine, Health economics
Keywords:	Pacing & electrophysiology < CARDIOLOGY, Heart failure < CARDIOLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING

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4 1 **Advanced image-supported lead placement in cardiac resynchronisation**
5
6 2 **therapy: protocol for the multicenter, randomised controlled ADVISE trial and**
7
8
9 3 **early economic evaluation**

10
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39 16 **Word Count:** 4081 words (excluding title page, abstract, tables, contributions and refs)

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Abstract

Introduction: Achieving optimal placement of the left ventricular (LV) lead in cardiac resynchronization therapy (CRT) is a prerequisite in order to achieve maximum clinical benefit, and is likely to help avoid non-response. Pacing outside scar tissue and targeting late activated segments may improve outcome. The present study will be the first randomized controlled trial to compare the efficacy of *real-time* image-guided LV lead delivery to conventional CRT implantation. In addition, to estimate the cost-effectiveness of targeted lead implantation, an early decision analytic model was developed, and described here.

Methods and analysis: A multicenter, interventional, randomised, controlled trial will be conducted in a total of 130 patients with a class I or IIa indication for CRT implantation. Patients will be stratified to ischemic heart failure aetiology and 1:1 randomized to either empirical lead placement or live image-guided lead placement. Ultimate lead location and echocardiographic assessment will be performed by core laboratories, blinded to treatment allocation and patient information. Late gadolinium enhancement cardiac MRI (LGE-CMR) and CINE-CMR with feature-tracking post processing software will be used to semi-automatically determine myocardial scar and late mechanical activation. The subsequent treatment file with optimal LV-lead positions will be fused with the fluoroscopy, resulting in live target-visualisation during the procedure. The primary endpoint is the difference in percentage of successfully targeted LV-lead location. Secondary endpoints are relative percentage reduction in indexed LV end-systolic volume, a hierarchical clinical endpoint, and quality of life. The early analytic model was developed using a Markov-model, consisting of seven mutually exclusive health states.

Ethics and dissemination: The protocol was approved by the Medical Research Ethics Committee Utrecht (NL73416.041.20). All participants are required to provide written informed consent. Results will be submitted to peer-reviewed journals.

Trial Registration: The trial is registered at a ClinicalTrials.gov (NCT05053568) and Netherlands Trial Register (Trial NL8666).

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61 **Strengths and limitations of this study**

- 62 • Real-time visualisation of targets for left ventricular lead implantation allows for user-
63 friendly and accurate guidance.
- 64 • Use of a specific model of the lateral wall with relatively small segments, which limits
65 fortuitous in-target lead placement.
- 66 • Health Technology Assessment offers better understanding of potential economic
67 benefits of targeted implantation.
- 68 • Cardiac MRI allows for observer independent image acquisition, but has relatively
69 limited temporal resolution.
- 70 • The study is limited in power to detect differences in clinical outcome, including
71 echocardiographic response.

72
73 **Keywords:** image-guided therapy; lead placement; cardiac resynchronization therapy; MRI

94 1. Introduction

95 Chronic heart failure is a major global health concern with a 5-year mortality rate of about
96 50%. In about one-third of these patients, heart failure is accompanied by left ventricular (LV)
97 conduction delay (i.e. QRS-duration \geq 130 ms), which is a predictor for worse prognosis [1,2].
98 Cardiac resynchronization therapy (CRT) greatly reduces morbidity and mortality in these
99 patients, but the extent of response is inconsistent and highly dependent on adequate LV
100 lead placement (LVLP). In-scar LVLP greatly increases risk of cardiovascular death and HF-
101 hospitalisation [3], whereas pacing in an area of late activation is likely to improve outcome
102 [4–6]. Moreover, a suboptimal lead position cannot be compensated by optimizing device
103 programming [7], rendering adequate LVLP arguably the cornerstone of this device therapy.

104 Because the optimal location is highly variable and patient-specific, an individualised and
105 targeted approach is often warranted [8]. Previous research has demonstrated the benefits of
106 image-guided lead delivery as a mean of improving clinical outcome [8,9]. However, most
107 studies did not allow for electrical guidance in the control group and allowed for only eight
108 potential targets for lead deployment, thereby limiting the accuracy of lead deployment and
109 increasing the odds of fortuitous “in-target” lead placement [10,11]. Moreover, no large
110 studies allowed for real-time visualisation of optimal targets, and most of the image-guided
111 studies were not conducted in a true multicenter setting. As such, the current evidence for
112 image-guided LVLP has remained relatively limited, and contemporary LVLP is still largely
113 based on an empirical strategy [1].

114 The present study protocol describes the first multicenter randomized controlled trial
115 investigating advanced image supported lead placement in CRT (ADVISE). The primary aim
116 of the study is to demonstrate the feasibility of reaching pre-defined segments through
117 accurate image-guidance, using an 18-segment LV lateral wall model with live visual
118 guidance during the implantation. The secondary objective is to investigate the clinical
119 efficacy by evaluating differences in the extent of LV reverse remodeling, a hierarchical
120 clinical endpoint and quality of life between both groups. Lastly, a Health Technology
121 Assessment will be conducted to determine the expected cost-effectiveness of a patient-
122 tailored approach for targeted lead placement.

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2. Methods and analysis

The ADVISE-CRT trial is a multicenter, randomised, controlled trial that is blinded to the patient and assessors of outcome (**Figure 1**). Assessment of LV dimension, LV function, and lead location will be performed by core laboratories. Patients will be stratified according to aetiology of heart failure in order to assure equal distribution of patients with ischemic cardiomyopathy (ICM) and non-ICM patients in both groups. All 130 patients will be 1:1 allocated to either image-guided or empirical LVLP using variable block-randomization:

- Intervention group: live visualised, fluoroscopy-fused, image-guided, lead placement on the basis of avoiding scar and targeting late mechanically activated segments.
- Control group: empirical standard-of-care lead placement in line with current CRT implantation guidelines with electrical guiding on the basis of Q-LV sense [4].

Study population

Patients are prospectively enrolled in at least three, and at most six, Dutch academic and peripheral centres. Consecutive patients eligible for CRT with a class I or IIa indication, with or without defibrillator function, according to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure are considered. In addition, some additional criteria for study participation apply (**Table 1**).

Overview of assessments

Prior to device implantation, all patients will undergo echocardiographic examination and cardiac magnetic resonance imaging (CMR). CMR feature-tracking (CMR-FT) analyses will be performed in both study groups, after which optimal LV-lead location will be determined. Randomization will occur after targets for lead deployment have been defined, after which targets cannot be altered. All patients will receive two quality of life questionnaires (EQ-5D-5L and Kansas City Cardiomyopathy Questionnaire) at four time-points: before implantation and at six months, 12 months, and 24 months after implantation. A 12-lead ECG will be performed before, directly after, and six months after implantation. During the procedure, various LV-paced effects will be measured. Ultimate lead location will be assessed through registration of the 18-segment LV lateral wall model onto the LAO40 and RAO30 fluoroscopy images, similar to the method described by Singh and colleagues, [12]. A global schedule of all assessments is summarised (**Figure 2**).

161 **CMR analysis and target allocation**

162 Clinical standard short axis CINE acquisitions with a minimum of 25 frames per R-R interval,
163 at max 8mm slice thickness and no slice gap, and LGE acquisitions at max 8mm slice
164 thickness will be performed in the participating hospitals. Cardiac MRI scans may be
165 acquired at most six months before implantation, in case of no (suspicion of) recent
166 ischaemic events. Post processing will be performed in a centralized fashion using a
167 dedicated software toolbox (CARTBox, CART-Tech B.V., Utrecht, The Netherlands). The
168 CARTBox analysis results in a treatment file, which will be used as an overlay with live
169 fluoroscopy during the implantation procedure in the intervention group. Semi-automated and
170 deep-learning assisted contouring CMR-FT analysis will be performed to quantify myocardial
171 deformation and identify the tissue with the latest mechanical contraction. Scar transmural
172 will be identified based on the LGE acquisitions. Three dimensional maps of mechanical
173 activation and scar transmural are combined and used to define the optimal tissue
174 (targets) for the LV lead. Targets will then be allocated on the basis of a pre-specified
175 decision-model by two investigators, blinded to each other. Segments that contain
176 myocardial scar will be disregarded, whereas segments with latest mechanical activation will
177 be considered most appropriate. Because multiple regions may be deemed suitable, a
178 maximum of three of the most suitable segments will be ranked and considered for
179 implantation in that order of priority. In the case of initial disagreement, consensus will follow
180 after discussion. Of note, the original unprocessed CMR will be available at the discretion of
181 the implanting cardiologist, also in the control group.

183 **Echocardiography**

184 Transthoracic echocardiographic examinations will be performed at baseline and six months
185 after CRT implantation at each participating centre. A standard local protocol used for strain-
186 imaging in CRT candidates will be used, with special attention to high quality images of the
187 LV. To this end, each acquired image will include at least three separate beats, and LV strain
188 images will be frame-rate optimized by using the narrowest sector width possible. LV
189 volumes and function will be assessed using Simpson's bi-plane method [13]. Mechanical
190 dyssynchrony (e.g. apical rocking) will be assessed as well. All examinations will be analysed
191 by an echocardiography core laboratory using vendor-independent software.

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193 **Randomization and blinding procedures**

194 After baseline assessments and subsequent identification of optimal targets for LVLP,
195 computer-generated variable block 1:1 randomization to either image-guided (intervention) or
196 empirical (control) implantation will be performed (Castor EDC, Amsterdam
197 the Netherlands). Randomization will be stratified according to ischemic or non-ischemic
198 heart failure etiology. Study data will be collected, recorded, logged and managed in
199 compliance with Good Clinical Practice guidelines. All study data are recorded in an
200 electronic case report form (eCRF), where any changes in data entry are logged. All data
201 entered, including perioperative data related to device implantation and optimization, are
202 collected and entered into the eCRF by either the coordinating investigator and/or research
203 nurse. External data validation will be managed by a study monitor, designated by a contract
204 research organization. Both the patient and core laboratories assessing endpoint data
205 (fluoroscopically determined LVLP and echocardiography) will be blinded to the intervention.
206 After six month follow-up has been completed by all patients, unblinding is allowed. After six
207 months, no observer-dependent endpoint data remains to be collected, and electrode
208 reselection is allowed where indicated.

210 **Device implantation**

211 Implantation of CRT, unrestricted by manufacturer or the presence or absence of defibrillator,
212 will occur under local anaesthesia and light intravenous sedation according to standard
213 procedure. In the control group, LVLP will occur at discretion of the physician but in line with
214 current guidelines using quadripolar LV leads (i.e. based on an empirical strategy, guided by
215 Q-LV sense). Q-LV sense is measured unipolar and defined as the time interval between
216 QRS onset on the surface ECG and the maximum voltage *change* over time (i.e. dV/dt),
217 recorded on the electrocardiogram. The LV electrode with the longest Q-LV sense in
218 combination with acceptable pacing threshold and without diaphragmatic stimulation will be
219 selected. In the image-guided intervention group, 2-dimensional fluoroscopic images are co-
220 registered to the previously derived CARTBox treatment file from CMR postprocessing, and
221 visualised in real-time in conjunction with the live fluoroscopy used during the implantation
222 procedure (**Figure 3**). The LV-lead will be deployed on the basis of the pre-defined target.
223 Only when multiple electrodes are within the target region, electrode selection based on
224 electrical properties (e.g. Q-LV sense) is applied.

225 During the procedure, pacing capture thresholds, phrenic nerves stimulation, intrinsic
226 electrical delay (i.e. Q-LV sense) and various LV-paced effects (i.e. LV-pace to RV-sense
227 and RV-pace to LV-sense) will be determined for each electrode of the quadripolar lead

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4 228 positions. When the ultimate lead position has been established, LAO40 and RAO 30
5 229 fluoroscopic imaging will be performed to determine the exact final lead location. Final LV
6 230 lead location will be determined by two investigators, blinded to treatment group and
7 231 outcome of each other. LVLP will be determined through registration of the CMR-derived LV
8 232 lateral wall model onto the LAO40 and RAO30 fluoroscopy images, similar to the method
9 233 described by Singh and colleagues [12]. Adverse events which are possibly related to
10 234 CARTBox or the procedure, reported spontaneously by the subject or observed by the
11 235 investigator or his staff, will be recorded in an electronic database.
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19 237 **Endpoints**

20 238 The ability to achieve successful image-guidance will be based on differences in the
21 239 percentage of within, adjacent, or remote from the target(s) selected for lead placement.
22 240 Here, adjacent segments include diagonal segments. Secondary outcomes are relative
23 241 reduction in LV end-systolic volume indexed to body surface area (LVESVi), proportional
24 242 difference in volumetric response ($\geq 15\%$ LVESVi-reduction), differences in quality of life, and
25 243 differences in the CRT response score. The latter is a hierarchical clinical endpoint based on
26 244 HF-hospitalisation and/or death within 12 months, relative LVESVi-change, and change in
27 245 NYHA class (**Supplemental File 1**) [14]. Other outcome measures include the following:
28 246 implantation procedure time, fluoroscopy time, contrast dose, device or procedure-related
29 247 complications, change in QRS duration and QRS_{AREA} , indices of mechanical recoordination,
30 248 and LV-lead parameters (Q-LV sense, pacing threshold, phrenic stimulation). Lastly, a Health
31 249 Technology Assessment concerning the additional value of image-guided LVLP in terms of
32 250 healthcare expenditure revolving heart failure care will be performed. This assessment will
33 251 be based on a previously conducted early economic analysis, which is described in this
34 252 article.
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45 254 **Sample size**

46 255 When comparing image-guided and contemporary implantation of CRT, the proportional
47 256 difference in within-target LVLP ranges between 6 and 30%, and thus varies considerably
48 257 [8]. In contrast, ADVISE targets segments approximately half the size of areas used in
49 258 previous studies, rendering the chance of fortuitously successful in-target implantation in
50 259 either study group much smaller.

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55 260 We therefore hypothesized that image-guidance will result in a proportional difference in
56 261 within-target LVLP of at least 27% when compared to empirical lead placement. In order to
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4 262 demonstrate this proportional difference using a two-sided Fisher exact test with 80% power
5 263 and $\alpha = 0.05$, a total of 114 successfully implanted patients are needed.

7 264 Concerning the secondary endpoint of LV reverse remodelling, given an expected
8 265 standard deviation below 25%, a significant difference in LVESVi reduction between both
9 266 groups of at least 13% can be detected in 116 patients. Accounting for failed implantations,
10 267 loss to follow-up and incomplete (echocardiographic) data in about 10% of cases, total
11 268 sample size necessary was set at 130 patients.

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17 270 **Statistical analysis**

18 271 An intention-to-treat analysis will be performed to assess LV-lead location and
19 272 echocardiographic response. In echocardiographic non-responders where electrode
20 273 reselection is feasible, transition of control patients towards the treatment group may occur
21 274 after six months. To account for this potential cross-over, an additional per-protocol analysis
22 275 may be performed with respect to long-term clinical endpoints and the HTA.

26 276 The primary endpoint concerning LV-lead location will be defined categorically as being
27 277 within, adjacent, or remote from the pre-defined target. A two-tailed Fisher exact test will be
28 278 performed to assess differences in lead location between both groups. Because in principle,
29 279 the effect of a targeted approach is considered to result in a unidirectional change in lead
30 280 location, a one-tailed Fisher exact test may be performed as well.

34 281 Secondary endpoints will be analysed according to treatment allocation and lead location
35 282 using Student's *t*-test and one-way ANOVA, or the Wilcoxon's rank sum test and Kruskal-
36 283 Wallis wherever applicable. Lastly, intra- and inter-observer agreement of the
37 284 echocardiography core laboratory analysis of LV reverse remodelling will be demonstrated
38 285 by computing intraclass correlation coefficients in approximately 25 echocardiograms. A *p*-
39 286 value < 0.05 will be considered significant.

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46 288 **Patient and public involvement**

47 289 Patients are part of our multidisciplinary consortium, both before and during the study, and
48 290 are as such involved in the design and conduct of the study. The priority of the research
49 291 question, patient communication, study logistics, and methods of recruitment have been
50 292 informed by discussions with patients representing our study population.

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55 294 **3. Ethics and dissemination**

56 295 The ADVISE trial will be conducted according to the principles of the Helsinki Declaration II
57 296 and Good Clinical Practice guidelines. The protocol has been written in accordance with the

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4 297 Standard Protocol Items: Recommendation For Interventional Trials (SPIRIT) checklist [15].
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6 298 The study protocol has been approved by the Medical Research Ethics Committee Utrecht
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8 299 (NL73416.041.20), and has been registered at ClinicalTrials.gov (NCT05053568) and
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10 300 Netherlands Trial Register (Trial NL8666). All participants are required to provide written
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12 301 informed consent, prior to study procedures (**Supplemental File 2**). Patients are currently
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14 302 being enrolled, with the first patient included in February 2021. Results will be disseminated
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16 303 at various presentations and will be submitted to peer-reviewed journals.

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305 **4. Early economic evaluation**

306 To estimate the expected impact on cost and effects of image-guided LVLP in CRT, an early
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308 decision analytic model was developed using a Markov-model consisting of seven mutually
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310 exclusive health states (**Figure 4**). These health states were identified in collaboration with
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312 clinical experts and based on available literature (**Supplemental File 3**). In brief, a group of
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314 1.000 individuals with heart failure were simulated, receiving either contemporary or image-
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316 guided LVLP. The analysis was performed from a societal perspective, including both direct
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318 healthcare costs and, where applicable, productivity losses due to absence from work. Model
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320 cycle length was one month, and model time horizon was 120 months. This model was
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322 developed in Microsoft Excel, version 2010/2016 (Microsoft, Redmond, WA, USA).

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324 **Treatment of patients/structure of the model**

325 Patients with heart failure enter the model after the index CRT procedure (4:1 CRT-D versus
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327 CRT-P) where all patients are deemed to be in stable condition. After implantation,
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329 sequentially patients may 'transition' towards various 'health states', namely: cardiac
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331 decompensation (at most three times), Left Ventricle Assist Device (LVAD) implantation, or
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333 heart transplant. Detailed overviews of healthcare provided for each of the health states are
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335 found in **Supplemental File 2**. Each health state is assigned a different probability of all-
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337 cause mortality.

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339 **Input parameters**

340 Different sources were used to identify input parameters and parameter values. The majority
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342 of parameter values were retrieved from existing scientific literature. Where data was not
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344 publicly available, expert opinion and data from UMC Utrecht were used. Given the nature of
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346 this early analysis, no definitive data is currently available that combines clinical effects and
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4 330 costs for image-guided LVLP. Input values for effects and costs were therefore estimated by
5 331 experts.

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9 333 **Clinical Outcomes & image-guided lead placement effectiveness**

10 334 For standard care, an assumed percentage of responders (LVESV-reduction $\geq 15\%$) was set
11 335 at 60% (17). For the additional effects of image-guided LVLP the percentage of responders
12 336 was increased with steps of 2.5% to a maximum of 97.5%. We also analysed the situation for
13 337 when 70% of patients receiving standard care are responders. First decompensation
14 338 probability, the arrow from stable to first decompensation in **Figure 4**, was based on a
15 339 weighted average for hospitalization probabilities for responders and non-responders (18).
16 340 Transfer probabilities between other health states were assumed to be equal between
17 341 standard care and care with image-guided LVLP and were based on clinical outcomes which
18 342 were retrieved from literature (19-21). Most important index procedure complications were
19 343 pneumothorax, lead dislocation, bleeding and pocket infection. Probabilities of these
20 344 complications occurring were based on previous research conducted at the UMCU and were
21 345 assumed not to differ between image-guided LVLP and standard care (22).

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31 347 **Cost-effectiveness estimation for image-guidance**

32 348 Based on 10,000 Monte Carlo iterations in the probabilistic sensitivity analyses, **Figure 5A**
33 349 shows the cost-effectiveness plane. Here, the Monte Carlo iterations are represented by the
34 350 blue dots. Mean cost difference was found to be -€7.329 (95%-CI: -€15.760 to € 323) and
35 351 mean Quality Adjusted Life Year (QALY) gain was 0.17 (95%-CI: -0.02 to 0.40). The majority
36 352 of iterations (96%) resulted in cost saving and an incremental health gain for image-guided
37 353 LVLP, as compared to standard care.

38 354 When the effectiveness of standard care is considered to be 70%, and the effectiveness
39 355 of CMR guided LVLP is varied between 70% and 95%, the results shown in **Figure 5B** were
40 356 found. Even at relatively small improvements in the proportion of responders, image-guided
41 357 LVLP leads to cost savings ranging from € 317 to € 20.069.

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51 359 **One-way sensitivity analysis**

52 360 In the one-way sensitivity analysis, we varied input parameter value with -20% and +20%,
53 361 this means the values of all parameters were altered one-by-one. By doing this for all model
54 362 input parameters, the influence of each parameter on model outcome is demonstrated. The
55 363 one-way sensitivity analysis showed that the parameters with the greatest influence on the

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4 364 outcomes of the economic evaluation were; i) the percentage of responders for standard
5 365 care, and ii) the percentage of responders for care with image guided LVLP. This entails that
6 366 changes in the value of these parameters will most likely change the outcomes of the
7 367 economic evaluation the most.
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12 369 **5. Discussion**

14 370 **Electrical versus image-guided strategy**

15 371 Although the STARTER and TARGET study demonstrated the benefit of an image-guided
16 372 approach for LVLP, they were performed in a time where electrical guiding (using QLV-
17 373 sense) was not yet routinely performed [10,16]. However, QLV-guidance is nowadays readily
18 374 available in many centres, and therefore, the results STARTER and TARGET cannot be
19 375 directly extrapolated to current practice [4,17].

20 376 It is therefore noteworthy that only one study carefully investigated both an
21 377 electrically guided approach (using QLV-sense) and an image-guided approach in a direct
22 378 comparison [18]. Although Stephansen et al., reported non-inferiority of an electrical
23 379 approach, we need to consider that these patients had typical LBBB with an average QRS-
24 380 duration of 169 ms. This is in contrast to patients with non-LBBB morphology, where a QLV-
25 381 guided approach fails to result in superior outcome when compared to contemporary lead
26 382 placement [19]. In these patients, an image-guided strategy appears to be more beneficial
27 383 [16]. Ultimately, electrically-guided and mechanically guided approaches each have their own
28 384 strengths and limitations, and both may have yet to reach their full potential [8].
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40 386 **Methods used for left ventricular lead placement**

41 387 Because in-scar pacing is associated with a six fold increased risk for cardiovascular death
42 388 or hospitalization for HF, avoiding in-scar pacing is of utmost importance [3]. We therefore
43 389 used CMR with late gadolinium enhancement, which is considered the gold-standard for
44 390 detection of myocardial scar and has a higher spatial resolution than ⁸²Rubidium positron
45 391 emission tomography [20]. In contrast, the utility of strain imaging using echocardiography for
46 392 detecting scar is poor with a sensitivity of only 33% [21].

47 393 In addition to avoiding scar, feature tracking is performed on CMR CINE
48 394 sequences in order to determine viable segments with late mechanical activation. Although
49 395 CMR has lower temporal resolution than speckle-tracking echocardiography, its benefits
50 396 include the ability to sequence the whole heart and the lack of need for adequate acoustic
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4 397 windows. In addition, strain analysis from CMR is subject to less bias and variability and can
5 398 be done semi-automatically.
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400 **Live fusion and target visualisation**

401 Regardless of the methods used, it is inevitable that there will always be patients in which a
402 target cannot be reached. In particular, the variability and difficulty of reaching a pre-defined
403 target is evidenced by the wide range of remote-from-target lead location, as reported in
404 previous studies [8]. Although venous access is undoubtedly a limiting factor, visualizing
405 target for lead deployment *during* the procedure most likely enhances the proportion of
406 optimally placed leads, since the implanter strives to implant the LV lead as close as possible
407 to the target tissue in a patient specific fashion. Although the feasibility of live fusion has
408 been demonstrated in two previous studies [22,23], they were limited by a small sample size
409 and non-randomized design.
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411 **Early economic analysis**

412 The analysis resulted in a robust model outcome for image-guided LVLP in CRT,
413 demonstrating a mean cost savings of approximately €7.000 with simultaneous incremental
414 health gain, relative to standard empirical LVLP. Although results are highly dependent on
415 proportional differences in response, cost-savings are likely feasible even at relatively small
416 clinical improvements. Because any decision analytic model is a simplified version of the
417 actual healthcare pathway, definitive clinical effectiveness must be awaited from data
418 gathered by the ADVISE trial. However, should the estimated mean cost savings hold, a
419 meaningful improvement in cost-effectiveness can be realised. This may be especially
420 valuable in low-to-middle income countries, where referral and implant rates are still relatively
421 lacking [24].
422

423 **Strengths and limitations**

424 Our study is primarily limited by its relatively small sample size, and as a consequence, lack
425 of primary *clinical* endpoint with sufficient power to detect differences in LVESVi-changes
426 below 13% between both groups. Regardless, the present study is the first *multicenter*
427 randomized controlled trial set out to investigate live CMR-guided LVLP in CRT, thereby
428 providing data in a real-world setting. CMR is however less suitable for patients with prior
429 device implantation due to magnetic field inhomogeneities, reducing image quality. Although
430 CMR-FT has a lower temporal resolution when compared to speckle-tracking

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4 431 echocardiography, it may suffer from less noise and inter-observer dependence. Moreover,
5 432 our technique allows for gold-standard scar detection, accurate segmentation, and live
6 433 visualization of suitable targets for lead deployment. Lastly, although fluoroscopy-based
7 434 determination of LVLP has limited reproducibility, simultaneous co-registration with our MRI-
8 435 derived LV lateral wall model may improve its accuracy [25].
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14 437 **Future perspectives**

15 438 Previous studies were conducted without performing QLV-guidance in the control group, and
16 439 were limited by using at most two recruiting centres [10,16,18]. Moreover, to date, no studies
17 440 utilized *live* image-guidance in a randomized controlled design. Should our study be able to
18 441 detect more LV reverse remodelling and/or better clinical outcome, an important step has
19 442 been set towards more widespread adoption of image-guided strategies for optimized LVLP
20 443 in CRT.
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27 445 **Author contributions**

28 446 PCW was involved in the study design, drafting the manuscript, and acquisition, analysis and
29 447 interpretation of data. FJS was responsible for design and execution of the technical and
30 448 methodological aspects revolving image guidance. CL and GWJF were responsible for
31 449 design and execution of the early economic analysis. VFD, PPHMD, and MM were involved
32 450 in study design and data acquisition. PAFMD and MJC were involved in conception or design
33 451 of the work. All authors provided critical revision and final approval of the manuscript, and are
34 452 accountable for the work.
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47 457 **Conflict of interests**

48 458 FJS is co-founder, chief technical officer, and shareholder of CART-Tech B.V. MM and FJS
49 459 are inventors and beneficiaries of a patent license arrangement between the University
50 460 Medical Center Utrecht and CART-Tech B.V. according to the rules of the University Medical
51 461 Center Utrecht. All other authors have reported that they have no relationships relevant to
52 462 the contents of this paper to disclose.
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569 **Tables**

570

571 **Table 1. ADVISE inclusion and exclusion criteria**

Inclusion criteria

- Heart failure with LVEF \leq 35%;
- NYHA class II, III, or IV (ambulatory);
- Optimal medical treatment that is tolerable;
- LBBB with QRS \geq 130 ms, *or* non-LBBB with QRS \geq 150 ms.

Exclusion criteria

- Age < 18 years or incapacitated adult;
 - Contraindication for CMR (gadolinium; contrast agents; metal);
 - Atrial fibrillation; either permanent or during CMR;
 - Severe renal insufficiency (GFR < 30 ml/min/1.73 m²);
 - Participation in other potentially confounding trials.
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4 **592 Figure legends**

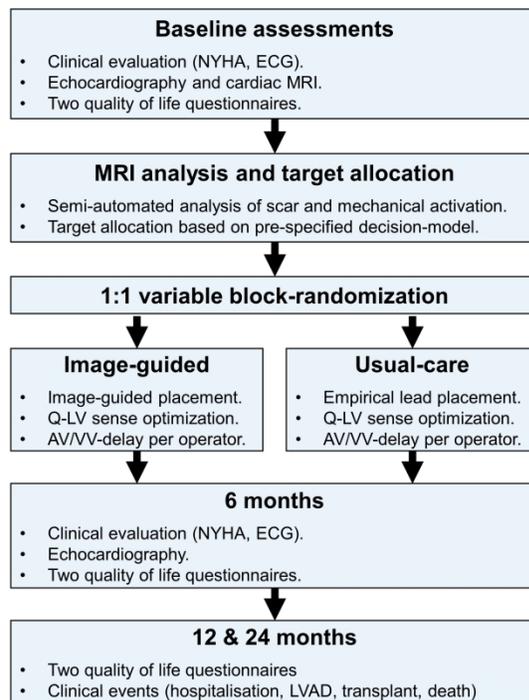
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6 **593 Figure 1.** Flow-chart presenting the course of the study.

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8 **594**
9 **595 Figure 2.** SPIRIT time schedule of enrolment, interventions, and assessments for the
10 **596 ADVISE-CRT trial.** ^a Includes implantation time, radiation exposure, and electrode
11 **597 configurations;** ^b e.g., indices of mechanical recoordination such as SRSsept.

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14 **598**
15 **599 Figure 3.** Workflow for advanced image-guided LV-lead placement. Adapted from Wouters
16 **600 et al [8].** CMR, cardiac magnetic resonance imaging. LV, left ventricular.

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19 **601**
20 **602 Figure 4.** Seven 'health states' (squares) were defined. Patients either remain in their state
21 **603 during follow-up** (inward arrows), or relocate towards the next sequential health state
22 **604 (uninterrupted arrows).** Each transition is assigned its own probability of occurrence. When
23 **605 death occurs,** other health states may be skipped (dashed arrows). Note that the assumption
24 **606 was made that post-CRT patients with ≤ 2 decompensations will not receive LVAD or**
25 **607 transplantation.** LVAD, Left Ventricle Assist Device.

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27 **608**
28 **609 Figure 5. A:** Cost-Effectiveness Plane for image-guided lead placement. The graph shows
29 **610 the iterations (blue dots) in comparison to the cost effectiveness thresholds for**
30 **611 €30.000/QALY and € 80.000/QALY (red and blue lines).** B: Potential cost savings with
31 **612 image-guided lead placement, based on the proportional difference in responders.** Legend:
32 **613 ICER, Incremental Cost Effectiveness Ratio ($\Delta\text{€}/\Delta\text{QALY}$); QALY, Quality Adjusted Life Year.**



45 Flow-chart presenting the course of the study.

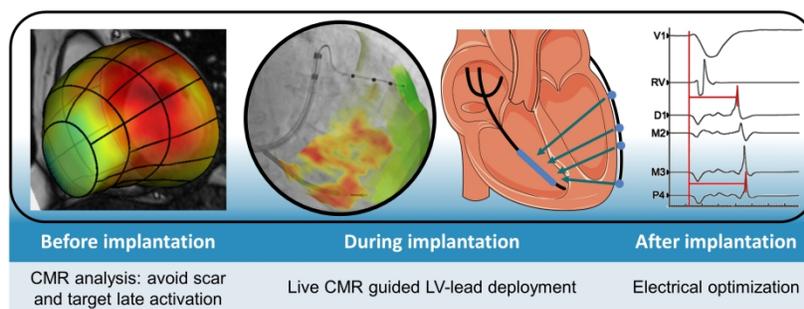
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Time point	Enrolment	Allocation	Post-allocation		Close-out
	-3 months	Day 0	Day 3	6 months	24 months
ENROLMENT					
Screening	X				
Informed consent	X				
Cardiac MRI	X				
Echocardiography	X			X	
Electrocardiogram	X		X	X	
NYHA class	X			X	
Questionnaires	X			X	X
Target allocation	X				
Treatment allocation		X			
INTERVENTIONS					
Image-guided		→			
Empirical		→			
ASSESSMENTS					
LV-lead location		X			
Procedural aspects ^a		X			
Technical aspects		X			
LVESVi- reduction	X			X	
Resynchronisation ^b	X			X	
QRS _{AREA}	X		X	X	
Mortality		X	X	X	X
HF Hospitalisation		X	X	X	X
Adverse events		X	X	X	X

SPIRIT time schedule of enrolment, interventions, and assessments for the ADVISE-CRT trial. a Includes implantation time, radiation exposure, and electrode configurations; b e.g., indices of mechanical recoordination such as SRSsept.

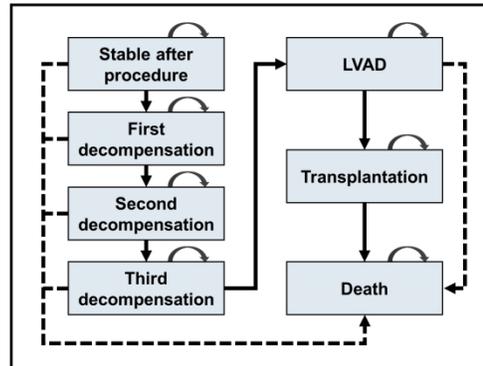
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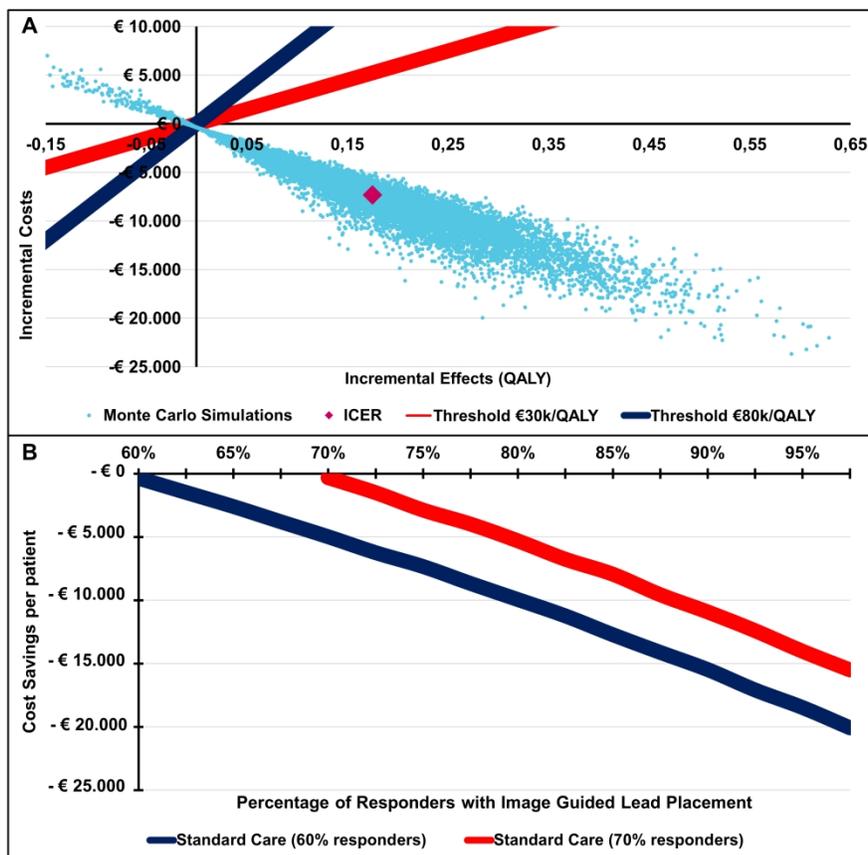
Workflow for advanced image-guided LV-lead placement. Adapted from Wouters et al [8]. CMR, cardiac magnetic resonance imaging. LV, left ventricular.

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Seven 'health states' (squares) were defined. Patients either remain in their state during follow-up (inward arrows), or relocate towards the next sequential health state (uninterrupted arrows). Each transition is assigned its own probability of occurrence. When death occurs, other health states may be skipped (dashed arrows). Note that the assumption was made that post-CRT patients with ≤ 2 decompensations will not receive LVAD or transplantation. LVAD, Left Ventricle Assist Device.

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A: Cost-Effectiveness Plane for image-guided lead placement. The graph shows the iterations (blue dots) in comparison to the cost effectiveness thresholds for €30.000/QALY and € 80.000/QALY (red and blue lines).

B: Potential cost savings with image-guided lead placement, based on the proportional difference in responders. Legend: ICER, Incremental Cost Effectiveness Ratio (€€/QALY); QALY, Quality Adjusted Life Year.

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Explanation of the CRT Response Score

As opposed to a traditional Clinical Composite Score, the CRT response score is a hierarchical clinical endpoint that takes into account several parameters that have frequently been used in literature to assess response to CRT. As opposed to a more conventional time-to-event endpoint, the CRT response scores takes into account both the severity and frequency of endpoints.

In brief, physiological improvement is assessed at the 6 months follow-up visit, both in terms of *the extent of* reverse remodelling (i.e., LVESVi-reduction). Functional improvement is assessed using New York Heart Association (NYHA) classification. In addition, deaths and HF hospitalizations will be taken into account until 12 months after the initial CRT implantation procedure as hard clinical endpoints.

The CRT response score will be calculated as follows:

1. A patient who dies within 12 months after the initial implantation procedure will be assigned a score = 0.
2. All other patients will have a base score = 2, adapted with additive contributions for HF hospitalizations, relative LVESVi change, and (change in) NYHA class:
 - a) For each HF hospitalization within 12 months after the initial implantation procedure, 2 is subtracted.
 - b) Change in LVESVi at the 6 months visit compared to baseline will contribute:
 - +2 when there is $\geq 30\%$ reduction (i.e., super-response),
 - +1 when reduced $\geq 15\%$ but $< 30\%$ (i.e., response),
 - +0 when LVESVi is reduced but $< 15\%$ (i.e., non-response), or
 - -1 when LVESVi has increased (i.e., negative response).
 - c) NYHA class at the 6 months visit will contribute +1 when the patient is in Class I or has improved by at least 1 class compared to baseline; +0 when NYHA class is unchanged; or -1 when NYHA class has worsened.
3. A negative score is replaced by 0.

The change score will be determined for all patients, also in case of partially missing data. A patient without any follow-up data will get the base score = 2. The maximal score will be 5, which is achieved by patients who survive through 12 months without HF hospitalization and have $\geq 30\%$ reduction of LVESVi as well as improvement of NYHA class. The minimal score is 0, which can be achieved in several ways: including death, HF hospitalization and no improvement on LVESVi or NYHA class, multiple HF hospitalizations, or increase in LVESVi and NYHA class worsening.



UMC Utrecht

**Door beeldvorming gestuurde plaatsing van de linker kamerdraad bij
Cardiale Resynchronisatie Therapie III
ADVISE-CRT III**

Advanced Image Supported Left Ventricular Lead Placement in CRT III

Informatie voor deelname aan medisch-wetenschappelijk onderzoek

Geachte mevrouw/meneer,

Wij nodigen u uit om deel te nemen aan een wetenschappelijke onderzoek. Deelname aan dit onderzoek is vrijwillig. Om mee te doen is uw schriftelijke toestemming nodig.

U ontvangt deze brief omdat binnenkort een apparaat dat zorgt voor Cardiale Resynchronisatie Therapie (CRT) in uw lichaam wordt geplaatst. Een CRT-apparaat zorgt voor gelijktijdige activatie van uw hartkamers. Dit leidt tot een betere pompfunctie van het hart, en behandelt daarmee uw hartfalen. Voordat u beslist of u wil meedoen aan dit onderzoek, krijgt u van ons onderstaande uitleg over het onderzoek. Het is zeer belangrijk dat u deze informatie leest en begrijpt. Bespreek deze gerust met uw partner, vrienden of familie. Lees ook de Algemene Brochure ¹. Daarin staat algemene informatie over medisch-wetenschappelijk onderzoek.

Heeft u na het lezen van de informatie nog vragen? Dan kunt u terecht bij de onderzoeker. Op bladzijde 10 vindt u zijn contactgegevens. Ook staat daar een onafhankelijke arts vermeld, aan wie u ook vragen kan stellen over het onderzoek.

Als u na het lezen van alle informatie geen toestemming geeft voor deelname, om wat voor reden dan ook, zal dat geen effect hebben op uw verdere behandeling. De onderzoeker neemt zelf met u contact op.

1. Algemene informatie

Dit onderzoek wordt uitgevoerd door het UMC Utrecht. Voor dit onderzoek zijn in totaal 130 patiënten nodig uit minimaal drie Nederlandse ziekenhuizen. De medisch-ethische toetsingscommissie van het UMC Utrecht heeft het onderzoek goedgekeurd. Algemene informatie over de toetsing van onderzoek vindt u in de Algemene Brochure ¹. Bij deelname zullen studiehandelingen en de plaatsing van CRT enkel gebeuren in het centrum dat U heeft benaderd. Voor een volledige uitleg van de procedures tijdens het onderzoek is het van belang dat u dit gehele document met aandacht doorneemt.

¹ VWS brochure 'Medisch-wetenschappelijk onderzoek; Algemene informatie voor de proefpersoon'. Of op de website van de Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

2. Doel van het onderzoek

Het doel van het onderzoek is om te kijken naar de effectiviteit van een nieuwe technologie die we gebruiken tijdens de plaatsing van het CRT apparaat. Met deze technologie verwachten we de plaatsing van de linker kamerdraad bij een CRT apparaat te verbeteren. Met andere woorden: we kunnen de plek in het hart waar het apparaat moet worden geplaatst beter bepalen én dit tijdens de operatie zichtbaar maken voor de cardioloog. Hieronder vindt u uitgebreide informatie over de werking van CRT en de nieuwe technologie die we gebruiken om het CRT-apparaat mogelijk beter te plaatsen.

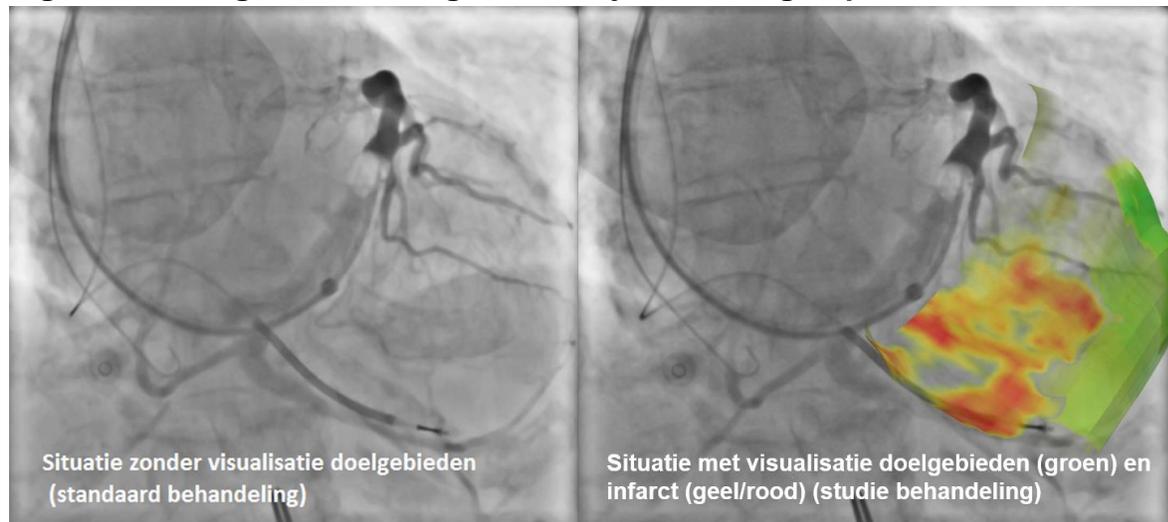
3. Achtergrond van het onderzoek

Uw behandelend arts heeft bij u vastgesteld dat het hart uw bloed niet effectief kan rondpompen in uw lichaam. Ondanks dat u behandeld wordt met medicijnen, houdt u een slechte pompfunctie van het hart. Dit wordt deels veroorzaakt doordat twee helften van het hart bij u niet gelijktijdig samentrekken. Dit speelt een rol in het ontstaan van klachten zoals kortademigheid, vermoeidheid en/of het vasthouden van vocht.

Daarom heeft uw cardioloog met u gesproken over behandeling door middel van zogenaamde Cardiale Resynchronisatie Therapie (CRT). Bij CRT wordt een pacemaker met of zonder defibrillator (ICD, 'klapkastje') onder de huid van uw borst geplaatst. Op dit apparaat worden drie draden aangesloten die de hartspier kunnen aansturen. Een daarvan wordt geplaatst in de rechter boezem, één in de rechter kamer en één in de linker kamer. De draden worden via de bloedvaten in het hart gebracht en geven elektrische signalen af waardoor beide hartkamers weer gelijktijdig gaan samentrekken. Het doel van CRT is een verbeterde pompfunctie van het hart, minder klachten van hartfalen, betere kwaliteit van leven en een betere levensverwachting. Dit is een gevolg van het meer synchron laten samentrekkende hartkamers (resynchronisatie therapie).

CRT is een techniek die standaard wordt toegepast in Nederland. De plek waar de linker kamerdraad wordt geplaatst is erg belangrijk voor het effect van CRT. De hartspier kan bijvoorbeeld beschadigd zijn door een hartinfarct. De linker kamerdraad moet niet in de buurt van beschadigd hartspierweefsel geplaatst worden. Daarnaast is het gebied in het hart dat het laatst samentrekt waarschijnlijk de meest gunstige plaats voor de linker kamerdraad. Plaatsing van deze draad op de meest gunstige plek kan leiden tot een grotere verbetering van de pompfunctie en een gunstiger effect van de behandeling.

Met de huidige manier van werken, waarbij de optimale plek voor de linker kamerdraad niet kan worden gezien tijdens de operatie, kunnen we helaas niet goed zien welke plek voor u het gunstigste is. Daardoor wordt de draad bij een deel van de patiënten niet optimaal geplaatst. Door technologische ontwikkelingen zijn we sinds kort in staat om de optimale plek wél zichtbaar te maken tijdens de operatie (Figuur 1).

Figuur 1: Weergave van doelgebieden tijdens de ingreep

Links: standaard röntgenopnames tijdens CRT-implantatie. Rechts: Röntgenopnames gecombineerd met informatie uit MRI-beelden. Littekenweefsel (rood) en doelgebieden (groen) worden nu weergegeven op de linker hartkamer, wat zorgt voor gerichte plaatsing van de linker kamerdraad.

Door vóór de CRT-implantatie een MRI-scan te maken kunnen we een 3D-plaatje van uw hart maken. De eerdergenoemde schade aan de hartspier en het laatst samentrekkende gebied kunnen hiermee goed in beeld worden gebracht. De nieuwe techniek van deze studie maakt het mogelijk om de informatie uit de MRI-te gebruiken. Daarnaast maakt het deze informatie zichtbaar voor de cardioloog tijdens de implantatie van het CRT-apparaat. Op deze manier kunnen we de plaats voor de linker kamerdraad waarvan we verwachten dat die optimaal is aangegeven tijdens de operatie. De cardioloog kan zo tijdens de operatie de linker kamerdraad naar deze plaatst leiden.

De techniek om MRI-beelden te combineren met de standaard röntgen beelden die gemaakt worden tijdens een CRT-implantatie is al onderzocht in twee eerdere patiëntonderzoeken. Daarbij is gebleken deze nieuwe technologie veilig en goed toepasbaar is. Ook waren er eerste aanwijzingen dat de procedure effectief kan zijn. In het huidige onderzoek willen we in een groter aantal patiënten uitgebreider naar de effectiviteit kijken. Daarbij gaan we kijken hoeveel patiënten baat hebben van het CRT-apparaat wanneer dit geplaatst wordt met behulp van de nieuwe technologie.

4. Wat meedoen inhoud

Om de effectiviteit van de nieuwe techniek zo betrouwbaar mogelijk aan te tonen, wordt u willekeurig ingedeeld in een groep. Dit betekent dat u bij deelname aan het onderzoek de plaatsing van het CRT-apparaat volgens de nieuwe techniek (studiegroep) of de gebruikelijke techniek (controlegroep) zult ondergaan. Dit noemt men randomisatie. Zowel uzelf als uw arts heeft geen invloed op de groep waar u in komt.

Als u meedoet duurt het onderzoek 2 jaar voor u, ongeacht van welke groep u krijgt toegedeeld. In deze 2 jaar moet u gedurende de eerste 6 maanden drie keer naar het ziekenhuis komen. U komt een keer vlak voordat de ingreep plaatsvindt voor extra beeldvorming van het hart. U komt een keer voor de ingreep zelf (CRT implantatie met ziekenhuisopname). Tot slot komt u 6 maanden na de implantatie voor de laatste keer terug om het effect van de behandeling te beoordelen. Als u niet meedoet met het onderzoek, komt u meestal twee keer naar het ziekenhuis in 6 maanden tijd (een keer voor de CRT plaatsing zelf en een keer voor een controle echo 6 maanden na de behandeling).

Daarnaast vragen wij uw toestemming om ná de CRT plaatsing uw medische gegevens te mogen inzien. Ook willen wij u op 1 en 2 jaar ná implantatie twee vragenlijsten sturen. Dit kan per post of digitaal. U hoeft dus niet naar het ziekenhuis te komen. Dit vragen wij zodat wij onder andere kunnen bepalen of de therapie heeft gezorgd voor minder ziekenhuisopnames en een betere kwaliteit van leven. Bij deelname kunt u er voor kiezen om toestemming te geven dat wij deze gegevens mogen opvragen en inzien. Dit gebeurt bij het ziekenhuis waar u bekend bent.

Wij gaan ervan uit dat uw cardioloog al uitleg heeft gegeven over het plaatsen van het CRT-apparaat. Als dat niet zo is, kunt u dit bespreken met uw cardioloog of met de hieronder genoemde arts/onderzoeker. Het plaatsen van het CRT-apparaat is een standaard operatie.

Anders dan bij gebruikelijke zorg

Hieronder leggen we uit wat we extra doen als u aan het onderzoek deelneemt (zie ook het stroomdiagram in bijlage I):

- Vóór de implantatie wordt een MRI-scan (45 minuten) en een echo van het hart (30 minuten) gemaakt. Mogelijk moet u hiervoor extra naar het ziekenhuis komen.
- Tijdens de CRT-implantatie wordt de linker kamerdraad geplaatst (Figuur 1). Dit gebeurt zoals gebruikelijk (controlegroep) of met behulp van de MRI-beelden (therapiegroep).
- Op 1 en 2 jaar ná implantatie ontvangt u twee vragenlijsten. Dit kan digitaal, u hoeft niet naar het ziekenhuis te komen. Ook ziet een onderzoeker uw medisch dossier in tot in ieder geval 2 jaar na implantatie.

MRI-scan

Bij het maken van een MRI-scan wordt gebruik gemaakt van een sterk magneetveld en radiogolven. Hiermee worden signalen in het lichaam opgewekt. Een antenne ontvangt de signalen en een computer zet deze om in een beeld. Zo wordt het hart afgebeeld terwijl het samentrekt. Er worden daarbij geen röntgenstralen gebruikt. Ook als u niet meedoet aan het onderzoek wordt soms er een MRI gemaakt voor de CRT implantatie. Als u meedoet aan het onderzoek worden er een aantal extra beelden gemaakt. Daardoor duurt de tijd dat u in de MRI-buis ligt enkele minuten langer.

Echo van het hart

Bij een echo wordt gebruik gemaakt van geluidsgolven. Er wordt geen gebruik gemaakt van Röntgenstraling. Een echo is veilig en niet pijnlijk. Met echo kan onder andere de pompfunctie van het hart worden beoordeeld. Door de pompfunctie voor én na CRT implantatie te meten op een hartecho, kunnen we het effect van CRT op de pompfunctie van uw hart beoordelen.

Vragenlijsten

- EQ-5D-5L is een maat voor de gezondheid. Deze vragenlijst bestaat uit 6 korte vragen op verschillende gezondheidsniveaus (mobiliteit, zelfzorg, dagelijkse activiteiten, ongemak en somberheid) waarop een score moet worden gegeven. Invullen duurt ongeveer 5 minuten.
- Kansas City Cardiomyopathy Questionnaire (KCCQ) is een vragenlijst ontwikkeld om de mate waarin hartfalen uw leven beïnvloedt te meten. Deze vragenlijst bestaat uit 15 items binnen verschillende domeinen. De vragenlijst richten zich met name op uw klachten en duurt ongeveer 5 minuten om in te vullen.

5. Wat wordt er van u verwacht?

Zoals hierboven uitgelegd moet u in ongeveer 6 maanden tijd in totaal drie keer naar het ziekenhuis komen (maximaal een keer vaker dan bij normale zorg). Om het onderzoek goed te laten verlopen is het belangrijk dat u afspraken voor bezoeken nakomt. Daarnaast is het belangrijk dat u contact opneemt met de onderzoeker:

- als u in een ziekenhuis wordt opgenomen of behandeld.
- als u plotseling gezondheidsklachten krijgt.
- als u niet meer wilt meedoen aan het onderzoek.
- als uw contactgegevens wijzigen.

6. Mogelijke bijwerkingen en andere nadelige effecten

Er zijn (geringe) risico's aan deelname aan het onderzoek.

MRI-scan

Een MRI-scan is niet schadelijk voor het menselijk lichaam. Het contrastmiddel dat bij MRI gebruikt wordt kan schadelijk zijn voor de nieren. Als u een slechte nierfunctie heeft, kunt u daarom niet deelnemen aan dit onderzoek. Ook kunt u allergisch reageren op het contrastmiddel. Dit komt zeer zelden voor (<1 per 1000 patiënten). Een nadeel voor u van de MRI is de tijdsinvestering en mogelijk een extra bezoek aan het ziekenhuis die wij u vragen. Verder ligt u tijdens het MRI-onderzoek in een kleine tunnel die aan het hoofd- en voeteneind open is. Als u niet in kleine ruimtes durft (claustrofobie), kunt u niet deelnemen aan dit onderzoek. Tot slot, omdat een MRI scanner werkt met een magnetisch veld kunt u niet meedoen als u metaal in uw lichaam heeft.

Mogelijke voor- en nadelen

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen. Bij deelname aan de studie kunt u in de onderzoeksgroep of de controlegroep worden geplaatst. De mogelijke voordelen zijn afhankelijk van in welke groep u krijgt toegewezen.

- Studiegroep: U hebt een mogelijk voordeel van deelname aan deze studie omdat we de optimale gebieden voor plaatsing van de linker kamerdraad zichtbaar maken. Plaatsing van de linker kamerdraad op de optimale plek kan leiden tot een verbeterde pompfunctie van het hart en daardoor minder klachten van hartfalen en een betere overleving. We weten dat er tussen patiënten grote verschillen bestaan en daarom kunnen we niet voorspellen of u met deze manier van plaatsen echt minder klachten krijgt van uw hartfalen. Er is een mogelijkheid dat de implantatie iets langer duurt doordat we gericht zoeken naar het optimale gebied. Er wordt dan een verwaarloosbare hoeveelheid extra straling gebruikt.
- Controlegroep: Er is ook een kans dat u in de controlegroep terechtkomt. Blijkt na afloop van de studie dat u als patiënt in de controlegroep onvoldoende baat van de pacemaker heeft gehad? Dan bestaat de mogelijkheid om de voor u specifieke studie-inzichten te gebruiken om de plaatsing van de linker kamerdraad bij u opnieuw te beoordelen met uw cardioloog. Daarnaast levert de studie nuttige wetenschappelijke gegevens voor de toekomst, maar daar heeft u niet direct baat bij.

Nadelen van meedoen aan het onderzoek zijn: 1) dat u extra tijd kwijt bent, en 2) dat u afspraken heeft waar u zich aan moet houden.

7. Als u niet wilt meedoen of wilt stoppen met het onderzoek

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. U hoeft niets te tekenen. U hoeft ook niet te zeggen waarom u niet wilt meedoen. U krijgt dan gewoon de behandeling die u anders ook zou krijgen. Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen. U mag uw deelname ook te allen tijde intrekken, ook gedurende het onderzoek. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan de onderzoeker.

Het onderzoek zal zo nauwkeurig mogelijk volgens plan worden uitgevoerd. Echter, de situatie kan veranderen, bijvoorbeeld door een reactie van uw lichaam, of door nieuwe informatie. Als dat zo is, bespreken we dat direct met u. U beslist dan zelf of u met het onderzoek wil stoppen of doorgaan. Als uw veiligheid of welbevinden in gevaar is, stoppen we direct met het onderzoek.

8. Einde van het onderzoek

Uw deelname aan het onderzoek stopt als

- alle bezoeken voorbij zijn
- u zelf kiest om te stoppen
- het einde van het hele onderzoek is bereikt
- de onderzoeker het beter voor u vindt om te stoppen
- de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Na het verwerken van alle gegevens informeert de onderzoeker u over de belangrijkste uitkomsten van het onderzoek. Dit gebeurt ongeveer 1-1.5 jaar na uw deelname. Als u dit niet wilt, dan kunt u dit tegen de onderzoeker zeggen. Hij/zij mag het u dan niet vertellen.

9. Gebruik en bewaren van uw gegevens

Voor dit onderzoek worden uw persoonsgegevens verzameld, gebruikt en bewaard. Het gaat om gegevens zoals uw naam, adres, geboortedatum en om gegevens over uw gezondheid. Het verzamelen, gebruiken en bewaren van uw gegevens is nodig om de vragen die in dit onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren. Wij vragen voor het gebruik van uw gegevens uw toestemming.

Vertrouwelijkheid van uw gegevens

Om uw privacy te beschermen krijgen uw gegevens een code. Uw naam en andere gegevens die u direct kunnen identificeren worden daarbij weggelaten. Alleen met de sleutel van de code zijn gegevens tot u te herleiden. De sleutel van de code blijft veilig opgeborgen in de lokale onderzoeksinstelling.

Voor dit onderzoek werken we samen met het bedrijf CART-Tech B.V. (Utrecht, Nederland). CART-Tech is een bedrijf dat voortkomt uit het UMC Utrecht en het heeft de

1 software voor het combineren van de Röntgen- en MRI-beelden ontwikkeld. De
2 gegevens die naar CART-Tech worden gestuurd bevatten alleen de code, maar niet uw
3 naam of andere gegevens waarmee u kunt worden geïdentificeerd

4 Ook in rapporten en publicaties over het onderzoek zijn de gegevens niet tot u te
5 herleiden.
6
7

8 9 **Toegang tot uw gegevens voor controle**

10 Sommige personen kunnen op de onderzoekslocatie toegang krijgen tot al uw
11 gegevens. Ook tot de gegevens zonder code. Dit is nodig om te kunnen controleren of
12 het onderzoek goed en betrouwbaar is uitgevoerd. Mensen die uw gegevens in kunnen
13 zien zijn een controleur/monitor die door het UMC Utrecht is ingehuurd, de Inspectie
14 Gezondheidszorg en Jeugd (IGJ) en het betrokken onderzoeksteam. Zij houden uw
15 gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.
16
17
18

19 **Bewaartermijn gegevens**

20 Uw gegevens moeten 15 jaar worden bewaarde op de onderzoekslocatie.
21
22
23

24 **Bewaren en gebruik van gegevens**

25 Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander
26 wetenschappelijk onderzoek op het gebied van CRT implantatie. Daarvoor zullen uw
27 gegevens 15 jaar worden bewaard. U kunt op het toestemmingsformulier aangeven of u
28 hier wel of niet mee instemt. Indien u hier niet mee instemt, kunt u gewoon deelnemen
29 aan het huidige onderzoek.
30
31
32

33 **Informatie over onverwachte bevindingen**

34 Tijdens dit onderzoek kan er bij toeval iets gevonden worden dat niet van belang is voor
35 het onderzoek maar wel voor u. Als dit belangrijk is voor uw gezondheid, dan zult u op
36 de hoogte worden gesteld [door de huisarts of medisch specialist]. U kunt dan met uw
37 huisarts of specialist bespreken wat er gedaan moet worden. Ook hiervoor geeft u
38 toestemming.
39
40
41

42 **Intrekken toestemming**

43 U kunt uw toestemming voor gebruik van uw persoonsgegevens altijd weer intrekken.
44 Dit geldt voor dit onderzoek en ook voor het bewaren en het gebruik voor het
45 toekomstige onderzoek. De onderzoeksgegevens die zijn verzameld tot het moment dat
46 u uw toestemming intrekt worden nog wel gebruikt in het onderzoek
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Meer informatie over uw rechten bij verwerking van gegevens

Voor algemene informatie over uw rechten bij verwerking van uw persoonsgegevens kunt u de website van de Autoriteit Persoonsgegevens raadplegen.

Bij vragen over uw rechten kunt u contact opnemen met de verantwoordelijke voor de verwerking van uw persoonsgegevens. Voor dit onderzoek is dat het UMC Utrecht. Zie bijlage A voor contactgegevens en website.

Bij vragen of klachten over de verwerking van uw persoonsgegevens raden we u aan eerst contact op te nemen met de onderzoekslocatie. U kunt ook contact opnemen met de Functionaris voor de Gegevensbescherming van de instelling [contactgegevens in bijlage A] of de Autoriteit Persoonsgegevens.

10. Verzekering proefpersonen

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt schade door het onderzoek. Niet alle schade is gedekt. In bijlage B vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

11. Informeren huisarts/behandelend cardioloog

Wij sturen uw huisarts/behandelend cardioloog altijd een brief om te laten weten dat u meedoet aan het onderzoek. Dit is voor uw eigen veiligheid. Als u dit niet goed vindt, kunt u niet meedoen aan dit onderzoek.

12. Vergoeding voor meedoen

Deelnemers aan dit onderzoek krijgen geen vergoeding.

13. Heeft u vragen?

Bij vragen kunt u contact opnemen met de onderzoekers. Voor onafhankelijk advies over meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke arts. Zij weet veel over het onderzoek, maar heeft niets te maken met dit onderzoek.

Indien u klachten heeft over het onderzoek, kunt u dit bespreken met de onderzoeker of uw behandelend arts. Wilt u dit liever niet, dan kunt u zich wenden tot de klachtenfunctionaris/klachtencommissie van uw ziekenhuis. Alle gegevens vindt u in bijlage A: Contactgegevens.

U heeft mogelijk al een telefonisch informatiegesprek gehad. Mocht u door omstandigheden geen telefonisch informatiegesprek hebben gehad, dan vindt er een gesprek met de arts-onderzoeker plaatst tijdens een ziekenhuisbezoek of tijdens de ziekenhuisopname. U heeft dan mogelijk een kortere bedenktijd voor studiedeelname maar deze is nooit korter dan 24 uur.

14. Ondertekening toestemmingsformulier (Informed Consent)

Wanneer u voldoende bedenktijd heeft gehad, wordt u gevraagd te beslissen over deelname aan dit onderzoek. Indien u toestemming geeft, zullen wij u vragen deze op de bijbehorende toestemmingsverklaring schriftelijk te bevestigen samen met de onderzoeker. Door uw schriftelijke toestemming geeft u aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek.

Zowel uzelf als de onderzoeker ontvangen een getekende versie van deze toestemmingsverklaring.

Dank voor uw aandacht.
Met vriendelijke groet,

Drs. P.C. Wouters, arts-onderzoeker cardiologie, UMC Utrecht
Dr. M. Meine, hoofdonderzoeker, cardioloog, UMC Utrecht

15. Bijlagen bij deze informatie

- A. Contactgegevens
- B. Informatie over de verzekering
- C. Schema onderzoekshandelingen
- D. Toestemmingsformulier
- E. Brochure "Medische-wetenschappelijk onderzoek. Algemene informatie voor proefpersoon"

Bijlage A: contactgegevens voor UMC Utrecht

Heeft u nog vragen of wilt u nadere informatie ontvangen dan kunt u altijd contact opnemen met één van onderstaande personen

Onderzoekers

Drs. P.C. Wouters
Arts-onderzoeker UMC Utrecht
Onderzoeker Advise-CRT
Telefoonnummer: 088-757 43 75
E-mail: p.wouters@umcutrecht.nl

Dr. M. Meine
Cardioloog UMC Utrecht
Hoofdonderzoeker Advise-CRT
Telefoonnummer: 088-755 61 84

Onafhankelijk arts

Als u er prijs op stelt informatie over dit onderzoek in te winnen bij een arts die niet bij de uitvoering van het onderzoek is betrokken maar wel over de gegevens ervan beschikt (een 'onafhankelijke arts') dan is Dr. Rittersma bereid uw vragen te beantwoorden (geldt voor alle deelnemende ziekenhuizen):

Dr. Z.H. Rittersma
Cardioloog UMC Utrecht
Onafhankelijk arts ADVISE-CRT III studie
Telefoonnummer: 088-755 61 76

Klachten

Als u klachten heeft kunt u dit melden aan de onderzoeker of aan uw behandelend arts. Mocht u ontevreden zijn over de gang van zaken bij het onderzoek en een klacht willen indienen dan kunt u contact opnemen met de klachtenbemiddelaars. Deze zijn bereikbaar via tel. 088-755 62 08. Of digitaal via:

<http://www.umcutrecht.nl/nl/Ziekenhuis/Ervaringen-van-patienten/Een-klachtindienen>.

Functionaris voor de Gegevensbescherming van de instelling: privacy@umcutrecht.nl

Raadpleeg de website van het UMC Utrecht voor meer informatie over uw rechten:
<https://www.umcutrecht.nl/nl/Ziekenhuis/In-het-ziekenhuis/Regels-en-rechten/Rechten>



UMC Utrecht

Bijlage B: Verzekeringsbijlage

INFORMATIE OVER DE VERZEKERING

Voor iedereen die meedoet aan dit onderzoek, heeft UMC Utrecht een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde ervan. Schade moet u binnen die vier jaar aan de verzekeraar hebben gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt.

Deze bepalingen staan in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Dit besluit staat op www.ccmo.nl, de website van de Centrale Commissie Mensgebonden Onderzoek (zie 'Bibliotheek' en dan 'Wet- en regelgeving').

Bij schade kunt u direct contact leggen met de verzekeraar.

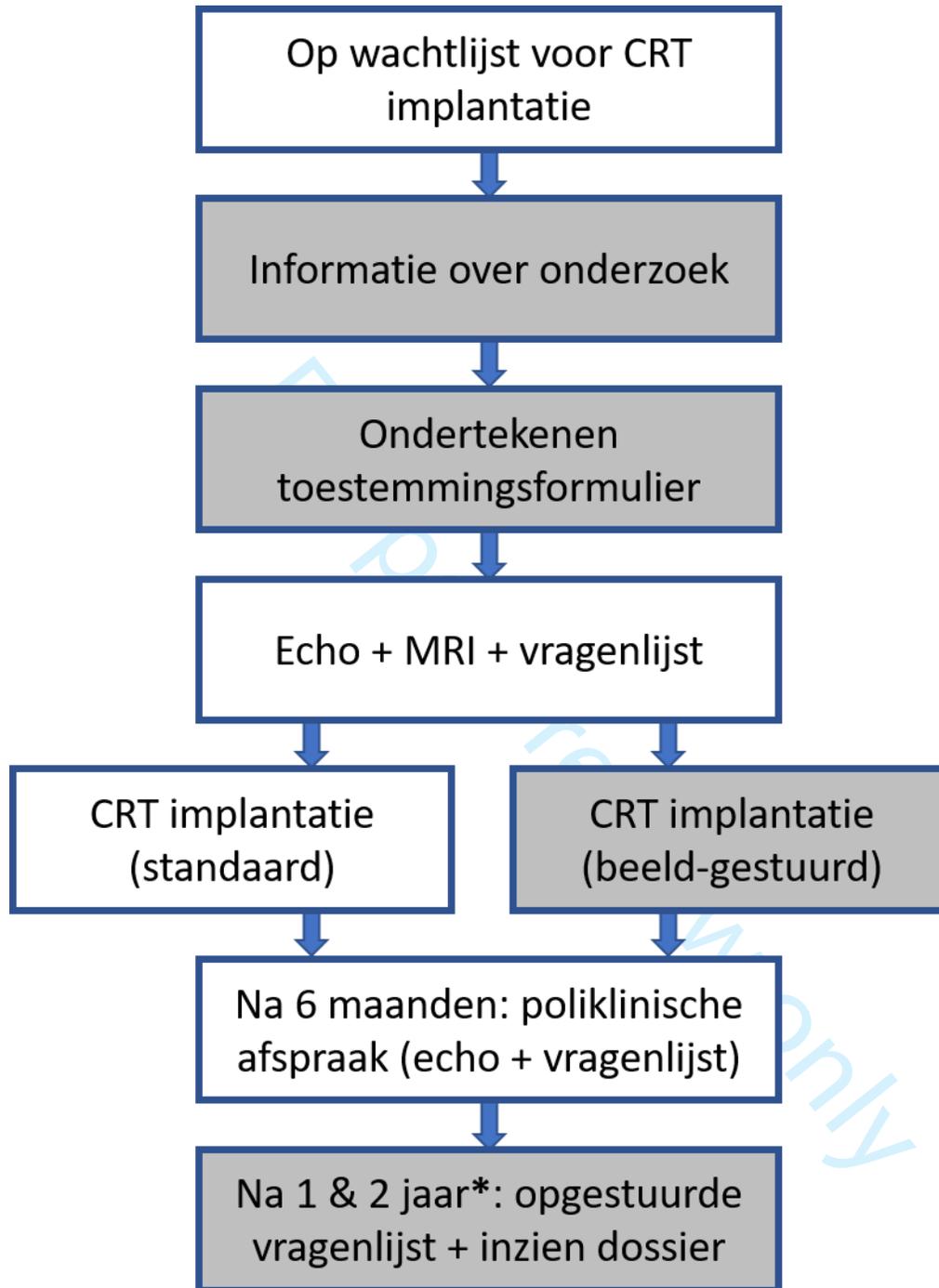
De verzekeraar van het onderzoek is:

Naam:	CNA Insurance Company Ltd
Adres:	Strawinskylaan 703, 1077 XX Amsterdam
Telefoonnummer:	020 – 57 37 274
Polisnummer:	10201366
Contactpersoon:	Mw. Esther van Herk

De verzekering biedt een dekking van € 650.000 per proefpersoon en maximaal € 5.000.000 voor het hele onderzoek en maximaal € 7.500.000 zijn per jaar voor alle onderzoeken van dezelfde opdrachtgever.

De verzekering dekt de volgende schade **niet**:

- schade door een risico waarover u in de schriftelijke informatie bent ingelicht. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
- schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan;
- schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
- schade aan uw nakomelingen, als gevolg van een negatief effect van het onderzoek op u of uw nakomelingen;
- schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.

Bijlage C: Schema onderzoekshandelingen

*Bijlage C: Stroomdiagram van het ADVISE-CRT III onderzoek. Grijs gekleurde blokken zijn extra handelingen behorende bij het onderzoek. Witte blokken worden vaak standaard verricht. Afkortingen: CRT: cardiale resynchronisatie therapie, MRI: magnetische resonantie scan. * Na 1 en 2 jaar moet u niet naar het ziekenhuis komen, deze stap kan online of per post.*



UMC Utrecht

Bijlage D: Toestemmingsformulier voor deelname aan het onderzoek

**Advanced Image Supported Left Ventricular Lead Placement in Cardiac
Resynchronization Therapy
Advise-CRT**

Door beeldvorming gestuurde plaatsing van de linker kamerdraad bij CRT

Ik bevestig dat ik het informatieformulier voor de proefpersoon heb gelezen en dat ik ook mondeling informatie heb gekregen. Ik begrijp de informatie. Ik heb de gelegenheid gehad om aanvullende vragen te stellen. Deze vragen zijn in voldoende mate beantwoord. Ik heb voldoende tijd gehad om over deelname na te denken.

Ik weet dat mijn deelname geheel vrijwillig is en dat ik mijn toestemming op ieder moment kan intrekken zonder dat ik daarvoor een reden hoeft te geven en zonder dat dit een effect heeft op mijn medische behandeling.

Ik geef toestemming voor het informeren van mijn huisarts/behandelend Cardioloog.

Ik geef toestemming dat ten behoeve van het onderzoek medische gegevens bij mijn behandelend cardioloog worden opgevraagd.

Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens voor de beantwoording van de onderzoeksvraag in dit onderzoek.

Ik weet dat voor controle van het onderzoek sommige mensen toegang tot al mijn gegevens kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.

Ik geef toestemming voor het delen van mijn gecodeerde gegevens met CART-Tech.

Ik geef toestemming voor het informeren van mijn huisarts en/of behandelend specialist van onverwachte bevindingen die van belang (kunnen) zijn voor mijn gezondheid.

1 Ik geef toestemming voor het langer bewaren en gebruiken van gegevens voor
2 eventueel vervolgonderzoek op het gebied van CRT implantatie

- 3 ja
4 nee

5
6
7 Ik geef toestemming om benaderd te worden voor deelname aan eventueel
8 vervolgonderzoek.

- 9 ja
10 nee

11
12
13 Ik geef voor dit onderzoek toestemming om mijn zorggegevens op te vragen en in te
14 zien in andere ziekenhuizen waar ik bekend ben.

- 15 ja
16 nee

17
18
19 Ik weet dat mijn onderzoeksgegevens na het onderzoek nog 15 jaar bewaard worden en
20 daarna worden vernietigd.

21
22 Na afronding van het gehele onderzoek wil ik de uitslag van het onderzoek op
23 groepsniveau ontvangen.

- 24 ja
25 nee

26
27
28 Ik wil meedoen aan dit onderzoek.

29
30
31 Naam proefpersoon:

32
33
34 Handtekening:

Datum: __ / __ / __

35
36
37
38 -----
39 Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde
40 onderzoek.

41
42 Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de
43 proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de
44 hoogte.

45
46
47 Naam onderzoeker (of diens vertegenwoordiger):

48
49
50 Handtekening:

Datum: __ / __ / __

51
52
53
54
55 De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende
56 versie van het toestemmingsformulier.

Supplemental Table 1. Cost calculations for input parameters.

	Quantity	Unit Cost (€)	Total Cost (€)	Source
Index Procedure				
<i>Diagnostics</i>				
Cardiac MRI	1	376.91	376.91	(1)
Cardiac Ultrasound	1	139.49	139.49	(1)
Thorax X-Ray	1	61.27	61.27	(1)
Lab work	2	44.46	88.92	(1)
<i>CRT</i>				
Procedural Costs	1	1,432.74	1,432.74	(2)
Biventricular ICD	0.8	12,387.68	9,910.14	(2)
Biventricular Pacemaker	0.2	6,644.83	1,328.97	(2)
<i>Admission</i>				
General Ward Admission	2	668.24	1,336.48	(3)
			14,814.14	
Procedural Complications				
<i>Pocket Infection</i>				
PET/CT Thorax	1	850.99	850.99	(1)
Transesophageal Ultrasound	1	263.81	263.81	(1)
ICD Removal	1	1,039.19	1,039.19	(2)
Pocket Revision	1	956.46	956.46	(2)
ICD Implantation	1	1,045.41	1,045.41	(2)
ICD Device	1	11,594.87	11,594.87	(2)
General Ward Admission	7	668.27	4,677.89	(3)
			20,428.62	
<i>Pneumothorax</i>				
Thorax X-Ray	1	61.27	61.27	(1)
Thorax Drain	1	788.27	788.27	(1)
General Ward Admission	3	668.24	2,004.72	(3)
			2,854.26	
<i>Wire Dislocation</i>				
Thorax X-Ray	2	61.27	122.54	(1)
Replacement CRT Leads	1	600.75	600.75	(2)
General Ward Admission	2	668.24	1,336.48	(3)
			2,059.77	
Follow-up				
Outpatient Visit	1	169.86	169.86	(1)
Lab work	1	44.46	44.46	(1)
			214.32	

Supplemental Table 2. Cost calculations for various health states.

	Quantity	Unit Cost (€)	Total Cost (€)	Source
Additional Healthcare Costs Model Health States				
<i>Decompensation I</i>				
Cardiac Ultrasound	1	139.49	139.49	(1)
General Ward Admission	7	668.24	4,677.68	(3)
			4,817.17	
<i>Decompensation II</i>				
Cardiac Ultrasound	1	139.49	139.49	(1)
Central Venous Line	1	365.38	365.38	(1)
Cardiac Care Unit Admission	14	1,986.48	27,810.72	(3)
			28,316.59	
<i>Decompensation III</i>				
Cardiac Ultrasound	1	139.49	139.49	(1)
Central Venous Line	1	365.38	365.38	(1)
Implantation Ventricle Assist Device (LVAD)	1	5,388.58	5,388.58	(2)
Materials LVAD	1	87,292.15	87,292.15	(2)
Cardiac Care Unit Admission	28	1,986.48	55,621.44	(3)
			148,807.04	
<i>LVAD</i>				
Considered equal to Decompensation III	1	148,807.04	148,807.04	(1-3)
<i>Transplantation</i>				
Heart Transplantation including Admission	1	37,579.47	37,579.47	(4)

References

1. Performance and Tariffs Specialist Medical Care (Prestaties en tarieven medisch-specialistische zorg) [Internet]. Nederlandse Zorgautoriteit (Netherlands Healthcare Authority) 2018 [cited 24-11-2020]. Available from: https://puc.overheid.nl/nza/doc/PUC_13408_22/.
2. Internal Calculation Department of Cardiology, UMC Utrecht
3. L. Hakkaart-van Roijen NvdL, C. Bouwmans, T. Kanters, S. Swan Tan. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg (Manual for cost analyses, methods and referenceprices for economic evaluations in healthcare). Diemen, the Netherlands: Zorginstituut Nederland (Netherlands National Healthcare Institute); 2016.
4. Open data van de Nederlandse Zorgautoriteit [Internet]. Nederlandse Zorgautoriteit (Netherlands Healthcare Authority). 2020. Available from: www.opendisdata.nl

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Trial NL8666
Protocol version	#3	Date and version identifier	Version 2.0, 29-07-2020 Version 3.0, 15-09-2021
Funding	#4	Sources and types of financial, material, and other support	12

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1, 12
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	12
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
14	responsibilities:			
15	sponsor and funder			
16				
17				
18				
19				
20				
21				
22				
23	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
24	responsibilities:			
25	committees			
26				
27				
28				
29				
30				
31				
32				
33	Introduction			
34				
35	Background and	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
36	rationale			
37				
38				
39				
40				
41				
42				
43	Background and	#6b	Explanation for choice of comparators	4, 5
44	rationale: choice of			
45	comparators			
46				
47				
48	Objectives	#7	Specific objectives or hypotheses	1
49				
50				
51	Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	2
52				
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59				
60				

Methods:**Participants, interventions, and outcomes**

8	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
15	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
22	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4, 5
27	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
35	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA
42	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
46	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
58	Participant timeline	#13	Time schedule of enrolment, interventions	4

(including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

1			
2			
3			
4			
5			
6			
7	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
8			
9			
10			
11			
12			
13			
14			
15	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size
16			NA; consecutive patients
17			
18			
19	Methods:		
20	Assignment of		
21	interventions (for		
22	controlled trials)		
23			
24			
25			
26	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
27	generation		
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
40	concealment		
41	mechanism		
42			
43			
44			
45			
46			
47	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
48	implementation		
49			
50			
51			
52	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
53			
54			
55			
56			
57			
58			
59			
60			

1	Blinding (masking):	#17b	If blinded, circumstances under which unblinding	6
2	emergency		is permissible, and procedure for revealing a	
3	unblinding		participant's allocated intervention during the	
4			trial	
5				
6				
7				
8	Methods: Data			
9	collection,			
10	management, and			
11	analysis			
12				
13				
14	Data collection plan	#18a	Plans for assessment and collection of outcome,	4-7
15			baseline, and other trial data, including any	
16			related processes to promote data quality (eg,	
17			duplicate measurements, training of assessors)	
18			and a description of study instruments (eg,	
19			questionnaires, laboratory tests) along with their	
20			reliability and validity, if known. Reference to	
21			where data collection forms can be found, if not	
22			in the protocol	
23				
24	Data collection plan:	#18b	Plans to promote participant retention and	NA
25	retention		complete follow-up, including list of any outcome	
26			data to be collected for participants who	
27			discontinue or deviate from intervention	
28			protocols	
29				
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37	Data management	#19	Plans for data entry, coding, security, and	6
38			storage, including any related processes to	
39			promote data quality (eg, double data entry;	
40			range checks for data values). Reference to	
41			where details of data management procedures	
42			can be found, if not in the protocol	
43				
44				
45				
46				
47	Statistics: outcomes	#20a	Statistical methods for analysing primary and	7, 8
48			secondary outcomes. Reference to where other	
49			details of the statistical analysis plan can be	
50			found, if not in the protocol	
51				
52				
53				
54	Statistics: additional	#20b	Methods for any additional analyses (eg,	7, 8
55	analyses		subgroup and adjusted analyses)	
56				
57				
58	Statistics: analysis	#20c	Definition of analysis population relating to	7, 8
59				
60				

1	population and		protocol non-adherence (eg, as randomised	
2	missing data		analysis), and any statistical methods to handle	
3			missing data (eg, multiple imputation)	
4				
5	Methods:			
6	Monitoring			
7				
8				
9	Data monitoring:	#21a	Composition of data monitoring committee	All strategies used
10	formal committee		(DMC); summary of its role and reporting	during implantation
11			structure; statement of whether it is independent	are not known to be
12			from the sponsor and competing interests; and	associated with
13			reference to where further details about its	additional risk.
14			charter can be found, if not in the protocol.	
15			Alternatively, an explanation of why a DMC is	
16			not needed	
17				
18	Data monitoring:	#21b	Description of any interim analyses and stopping	NA
19	interim analysis		guidelines, including who will have access to	
20			these interim results and make the final decision	
21			to terminate the trial	
22				
23	Harms	#22	Plans for collecting, assessing, reporting, and	8
24			managing solicited and spontaneously reported	
25			adverse events and other unintended effects of	
26			trial interventions or trial conduct	
27				
28	Auditing	#23	Frequency and procedures for auditing trial	NA
29			conduct, if any, and whether the process will be	
30			independent from investigators and the sponsor	
31				
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41	Ethics and			
42	dissemination			
43				
44	Research ethics	#24	Plans for seeking research ethics committee /	8
45	approval		institutional review board (REC / IRB) approval	
46				
47				
48	Protocol	#25	Plans for communicating important protocol	NA
49	amendments		modifications (eg, changes to eligibility criteria,	
50			outcomes, analyses) to relevant parties (eg,	
51			investigators, REC / IRBs, trial participants, trial	
52			registries, journals, regulators)	
53				
54				
55				
56				
57	Consent or assent	#26a	Who will obtain informed consent or assent from	4
58			potential trial participants or authorised	
59				
60				

		surrogates, and how (see Item 32)	
1			
2	Consent or assent:	#26b Additional consent provisions for collection and	4
3	ancillary studies	use of participant data and biological specimens	
4		in ancillary studies, if applicable	
5			
6			
7	Confidentiality	#27 How personal information about potential and	12
8		enrolled participants will be collected, shared,	
9		and maintained in order to protect confidentiality	
10		before, during, and after the trial	
11			
12			
13			
14	Declaration of	#28 Financial and other competing interests for	13
15	interests	principal investigators for the overall trial and	
16		each study site	
17			
18			
19	Data access	#29 Statement of who will have access to the final	12
20		trial dataset, and disclosure of contractual	
21		agreements that limit such access for	
22		investigators	
23			
24			
25			
26	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial	NA
27	trial care	care, and for compensation to those who suffer	
28		harm from trial participation	
29			
30			
31	Dissemination	#31a Plans for investigators and sponsor to	12
32	policy: trial results	communicate trial results to participants,	
33		healthcare professionals, the public, and other	
34		relevant groups (eg, via publication, reporting in	
35		results databases, or other data sharing	
36		arrangements), including any publication	
37		restrictions	
38			
39			
40			
41			
42			
43	Dissemination	#31b Authorship eligibility guidelines and any	NA
44	policy: authorship	intended use of professional writers	
45			
46			
47	Dissemination	#31c Plans, if any, for granting public access to the	12
48	policy: reproducible	full protocol, participant-level dataset, and	
49	research	statistical code	
50			
51			
52	Appendices		
53			
54	Informed consent	#32 Model consent form and other related	NA; upon request.
55	materials	documentation given to participants and	
56		authorised surrogates	
57			
58			
59			
60			

1 Biological
2 specimens
3

[#33](#)

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

NA

Notes:

- 2b: Trial NL8666
- 3: Version 2.0, 29-07-2020
- 15: NA; consecutive patients
- 21a: All strategies used during implantation are not known to be associated with additional risk.
- 32: NA; upon request. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 01. June 2021 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)