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# BMJ Open

## A tailored approach towards informing relatives at risk of inherited cardiac conditions: study protocol for a randomized controlled trial

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Complete List of Authors:	van den Heuvel, Lieke; Amsterdam University Medical Centres, Department of Clinical Genetics Hoedemaekers, Yvonne; University Medical Centre Groningen, Department of Clinical Genetics Baas, Annette; University Medical Center Utrecht, Department of Genetics van Tintelen, J; Amsterdam University Medical Centres, Department of Clinical Genetics Smets, Ellen; Amsterdam University Medical Centres, Department of Medical Psychology Christiaans, Imke; Amsterdam University Medical Centres, Clinical Genetics
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3 **A tailored approach towards informing relatives at risk of inherited cardiac conditions:**  
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5 **study protocol for a randomized controlled trial**  
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9 L.M. van den Heuvel<sup>1</sup>, Y.M. Hoedemaekers<sup>2</sup>, A.F. Baas<sup>3</sup>, J.P. van Tintelen<sup>1</sup>, E.M.A. Smets<sup>4</sup> & I.  
10 Christiaans<sup>1\*</sup>  
11

12  
13  
14 <sup>1</sup>Department of Clinical Genetics, Amsterdam University Medical Centres / University of  
15 Amsterdam, Amsterdam, the Netherlands;  
16

17  
18 <sup>2</sup>Department of Clinical Genetics, University Medical Centre Groningen / University of  
19 Groningen, Groningen, the Netherlands;  
20

21  
22 <sup>3</sup>Department of Genetics, University Medical Centre Utrecht / University Utrecht, Utrecht, the  
23 Netherlands;  
24

25  
26  
27 <sup>4</sup>Department of Medical Psychology, Amsterdam University Medical Centres / University of  
28 Amsterdam, Amsterdam, the Netherlands.  
29

30  
31  
32  
33 \* Corresponding author  
34

35 Department of Clinical Genetics,  
36

37  
38 Amsterdam University Medical Centre, location AMC  
39

40  
41 Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands  
42

43  
44 Telephone: +31 20-5667217  
45

46  
47 E-mail: i.christiaans@amc.nl  
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## Abstract

**Introduction** In current practice, probands are asked to inform relatives about the possibility of predictive DNA testing if a pathogenic variant causing an inherited cardiac condition (ICC) is identified. Previous research on uptake of genetic counselling and predictive DNA testing in relatives suggests that not all relatives are sufficiently informed. We developed a randomized controlled trial to evaluate the effectiveness of a tailored approach, in which probands, together with the genetic counsellor, decide which relatives they inform themselves and which relatives they prefer to be informed by the genetic counsellor. Here, we present the study protocol of this randomized controlled trial. **Methods** A multicentre randomized controlled trial with parallel-group design will be conducted, in which a tailored approach (i.e., intervention group) will be compared to a control group of usual care. Adult probands diagnosed with an ICC in whom a likely pathogenic or pathogenic variant is identified, will be randomly assigned to the intervention or control group (total sample n = 85 probands). The primary outcome is uptake of genetic counselling and predictive DNA testing in relatives (total sample n = 340 relatives). Secondary outcomes are appreciation of the used approach and impact on family- and psychological functioning, which will be assessed using questionnaires. Relatives of included probands who attend genetic counselling will be asked to fill out a questionnaire as well. **Ethics and dissemination** Ethical approval was obtained from the Medical Ethical Committee of the Amsterdam University Medical Centres (MEC 2017-145), the Netherlands. All participants provide informed consent prior to participation in this study. Results of the study on primary and secondary outcome measures will be published in peer-reviewed journals.

**Registration details** This trial is registered at the Netherlands Trial Register NTR6657.

**Key words** Inherited cardiac conditions, cardiogenetics, informing relatives at risk, family-mediated approach, tailored approach, randomized controlled trial

### Strengths and limitations of this study

*Strength:* To our knowledge, this is the first randomized controlled trial to evaluate a tailored intervention towards informing relatives at risk, compared to a control group of standard care.

*Strength:* This randomized controlled trial investigates the uptake of genetic counselling and predictive DNA testing, as well as the acceptance and impact on psychological and family functioning of the tailored versus the standard approach.

*Strength:* Both probands and relatives will be included in this study to assess their experiences with and their attitudes towards the used approach .

*Limitation:* In this randomized controlled trial, it is not possible to blind participants or genetic counsellors for the chosen intervention. Neither the executing investigator can be blinded for randomization.

*Limitation:* Only relatives of probands included in the study who attend genetic counselling can be approached for participation in the study.

## Introduction

Inherited cardiac conditions (ICCs), such as cardiomyopathies and primary arrhythmia syndromes, generally demonstrate an autosomal dominant inheritance pattern, and a wide variety of symptoms can manifest at any age (1, 2). A feared outcome is sudden cardiac death (SCD), often at young age, which can be the first symptom of disease (3, 4). With an incomplete penetrance and high variability in expression, even within families, carriers of the familial variant may remain undetected but can still be at risk for SCD, while treatment options are available to prevent disease progression or potential life-threatening arrhythmias (5).

Predictive DNA testing is therefore offered to first-degree relatives of probands (i.e., the first person in a family diagnosed with an ICC) in whom a pathogenic variant is identified, who are at 50% risk of inheriting the genetic variant (5, 6). Predictive DNA testing is offered in a stepwise manner (i.e., cascade screening), with the aim to identify asymptomatic carriers of the familial variant to facilitate timely treatment. Non-carriers of the familial variant generally do not need cardiac monitoring and can be reassured about their own risk and that of their offspring (6).

In current practice in the Netherlands, probands are asked to inform their relatives, supported by a family letter written by the genetic counsellor. This is referred to as the family-mediated approach (7). Previous research, however, shows that uptake (i.e., the number of relatives at risk attending genetic counselling and/or predictive DNA testing) is relatively low in ICCs, especially in cardiomyopathies. Reported uptakes are less than 50%, despite family letters being provided to a majority of relatives by the proband (8-10). Previous research in other genetic patient populations, such as hereditary types of cancer, shows similar percentages (11-13).

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3 Some relatives who do not attend genetic counselling will have deliberately decided  
4 against predictive DNA testing. However, these low uptake percentages also suggest that part  
5 of the relatives might be unaware or insufficiently aware of the risks involved and/or the  
6 possibilities for genetic counselling and subsequent surveillance and treatment. This is  
7 supported by research on family communication in ICCs. Patients are not always able to  
8 inform or correctly inform their relatives because of several reasons, including disengagement  
9 with relatives, lack of understanding of the importance of the information, preoccupation with  
10 their own grief, difficulties in conveying the complex information to relatives, or the wish to  
11 prevent burdening on relatives by informing them about genetic risks (8, 14-18).  
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22 A few studies have been published on more active approaches towards informing  
23 relatives at risk, in which HCPs directly contact at-risk relatives (19-22). These studies  
24 suggest that a more active approach can nearly double the uptake of genetic counselling and  
25 predictive DNA testing of relatives (19-22). However, these studies were performed in a  
26 research setting (e.g., in relatives already registered in research databases for the genetic  
27 disease), hampering direct translation of these results to a diagnostic setting. To our  
28 knowledge, more active approaches in patients with ICCs have not been studied so far.  
29 However, a study of Ormondroyd et al suggests that relatives eligible for predictive DNA  
30 testing for hypertrophic cardiomyopathy and long QT syndrome would support a more active  
31 approach to inform relatives at risk (15).  
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44 Although studies on more active approaches did not report any psychological harm in  
45 relatives on group level, these approaches could cause more unwarranted worries or pressure  
46 on relatives to opt for predictive DNA testing (19-21). An active approach towards informing  
47 relatives at risk could also breach the autonomy and confidentiality of probands, and may  
48 harm the right not to know of relatives (23-25). Furthermore, healthcare professionals (HCPs)  
49 are often unaware of interpersonal dynamics within families and personal circumstances of  
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3 relatives at risk. Active approaches may therefore have a negative impact on family  
4  
5 relationships or may cause psychological distress in both probands and relatives (26).  
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7 Because of this, a tailored approach in which probands may decide together with the  
8  
9 genetic counsellor which at-risk relatives they will inform themselves and which relatives  
10  
11 they prefer to be informed by the genetic counsellor, could be optimal. With this approach,  
12  
13 the probands' expert knowledge of relatives' functioning and family dynamics could be used  
14  
15 appropriately and the autonomy of the proband would be preserved. At the same time more  
16  
17 relatives at risk would be sufficiently informed (24, 26). Furthermore, probands for whom  
18  
19 informing relatives would be difficult or burdensome might be relieved or supported by this  
20  
21 approach (26).  
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### 26 *Objectives*

27  
28 The primary aim of this randomized controlled trial is to assess whether uptake of genetic  
29  
30 counselling and testing of relatives at risk of an ICC will be increased by using a tailored  
31  
32 approach of information provision for relatives, instead of usual care (i.e., family-mediated  
33  
34 approach). Secondary objectives are to evaluate how such a tailored approach is appreciated  
35  
36 by both probands and relatives, compared to usual care. In addition, this study aims to assess  
37  
38 the perceived impact on family relationships and psychological functioning of both probands  
39  
40 and relatives. The protocol presented here has been described on the basis of the SPIRIT  
41  
42 statement (27).  
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## 48 **Methods**

### 49 **Design**

50  
51 A multicentre randomized controlled trial with a parallel-group design will be conducted in  
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53 three university hospitals in the Netherlands (i.e., the Academic Medical Centre (AMC), the  
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3 University Medical Centre Utrecht (UMCU) and the University Medical Centre Groningen  
4 (UMCG)), comparing the effects of a tailored approach towards informing relatives at risk of  
5 ICCs to usual care in both probands and relatives.  
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## 10 11 **Participants**

12  
13 Probands aged 18 years or older with an ICC or suspicion thereof, attending pre-test genetic  
14 counselling at the cardiogenetics outpatient clinics will be asked to participate if they: (1) are  
15 the first of their family to visit the cardiogenetic outpatient clinic for counselling about  
16 genetic testing for ICCs; (2) they have at least one alive adult relative; and (3) are able to read  
17 and write Dutch. Only probands in whom a likely pathogenic or pathogenic variant (i.e., class  
18 4 - likely pathogenic - or class 5 - pathogenic variant) is detected will be definitively included.  
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26 In addition, eligible adult first- (or second-) degree relatives of enrolled probands who  
27 make an appointment at the cardiogenetic outpatient clinics will be invited to fill out a  
28 questionnaire to measure secondary outcomes. Inclusion criteria are defined as follows: (1)  
29 First-degree adult (i.e., 18 years or older) relatives, and second-degree adult relatives in case  
30 of a deceased connecting first-degree relative who was affected or suspected to be affected, of  
31 probands enrolled in the study; and (2) able to read and write Dutch.  
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## 41 **Procedure**

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43 Figure 1 shows a flow-chart of the study procedure.  
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### 48 *Recruitment & consent*

49  
50 During pre-test genetic counselling, the genetic counsellor will inform the probands about the  
51 study and will hand over an information letter. In addition, probands will be asked if the  
52 executing researcher can contact them to provide further information about the study.  
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3 Subsequently, probands will be contacted by telephone by the executing researcher. If  
4 probands are still interested in participation, written informed consent forms will be sent by  
5 post mail, including a return envelope. As described above, only probands in whom a likely  
6 pathogenic or pathogenic variant is detected, will be definitively included in the study.  
7  
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10  
11 Relatives at risk of enrolled probands attending pre-test genetic counselling in one of  
12 the participating centres, will be invited to participate in the study as well. The same  
13 recruitment procedure will be used.  
14  
15

### 16 17 18 19 20 *Randomization*

21  
22 Probands with an ICC in whom a likely pathogenic or pathogenic variant is identified, will be  
23 randomly assigned to either the intervention or the control group prior to receiving their test  
24 result. Block randomization will be used, with variable blocks ranging from size two to six.  
25  
26 Randomization will be stratified for gender, disease type (i.e., cardiomyopathies or primary  
27 arrhythmia syndromes) and hospital. To ensure allocation concealment, computer software  
28 will be used for randomization, with an allocation rate of 1:1 (28). Relatives of probands  
29 included in the study will be assigned to the group to which the proband was assigned.  
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37 Neither participants nor the genetic counsellors will and can be blinded for group  
38 assignment. The executing researcher cannot be blinded either, because of slight differences  
39 between questionnaires administered in the intervention- and control group. Part of the  
40 outcome data will be collected using telephone interviews. To minimize bias, these interviews  
41 will be conducted by a research assistant following a structured script.  
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### 50 Intervention group

51  
52 In the intervention group, a tailored approach towards informing relatives at risk, will be  
53 provided. In this approach, probands with a likely pathogenic or pathogenic variant will  
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2  
3 discuss with the genetic counsellor which relatives are at risk of inheriting the familial variant  
4 and are subsequently asked which of these relatives they prefer to inform themselves at first  
5 using a family letter written by the genetic counsellor, and which relatives they prefer to be  
6 directly informed by the genetic counsellor with a similar family letter.  
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11 In both cases, after one month the family letter will be sent directly by the genetic  
12 counsellor to all relatives at risk, for whom the proband has provided consent to contact them.  
13  
14 The proband will be asked to provide contact details of these relatives.  
15

16  
17 The family letter is standardised for all three participating centres. For the intervention  
18 group, the letter also includes a link to a website specifically designed for this study where  
19 relatives can find additional information ([www.familieleden.erfelijkehartziekten.nl](http://www.familieleden.erfelijkehartziekten.nl)). The  
20 information on this website is tailored to the relatives' situation (i.e., specified for disease  
21 type, hospital, whether they have a child wish and/or children, and which information they  
22 prefer to receive) by asking relatives at their first visit to the website to fill out a short  
23 questionnaire.  
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### 34 35 Control group

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37 In the control group, the standard care approach will be used. If a likely pathogenic or  
38 pathogenic variant is identified, probands assigned to the control group will be asked by the  
39 genetic counsellor to inform relatives at risk about the genetic test result, the consequences of  
40 this result for relatives and the advice regarding predictive DNA testing and/or cardiac  
41 monitoring. Probands will be supported in informing relatives at risk by a family letter  
42 written by the genetic counsellor. This family letter is also standardised for all three  
43 participating centres. However, this letter does not include the link to the specific website for  
44 tailored information, but includes a link to a general website on ICCs  
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60 (www.erfelijkehartziekten.nl).

### *Measurement time-points*

For secondary outcome measures, participating probands will be asked to complete a questionnaire one month after receiving the genetic test result (T1) and a questionnaire after nine months after the test result (T2). Before T1 and T2, a short structured telephone interview will be conducted about participants' knowledge of which relatives are at risk of ICCs and which relatives are informed, because these items are expected to be too complex to answer in a questionnaire (28). Participating relatives will complete one questionnaire after attending genetic counselling.

### **Measures**

#### *Primary outcome measure*

To assess the effect of a tailored approach towards informing relatives at risk, the difference between the intervention- and control group in uptake of genetic counselling and predictive DNA testing of relatives at risk will be measured. To do so, the number of relatives attending genetic counselling as well as the number of relatives that is genetically tested in the first year after detection of the likely pathogenic or pathogenic variant in the proband, will be collected in the laboratories of each participating centre. DNA test results of relatives counselled in non-participating centres are also taken into account, because in the Netherlands predictive DNA testing of relatives is always performed in the laboratory where the proband was tested.

The numbers of relatives attending genetic counselling and predictive DNA testing will be compared to the total number of relatives at risk of inheriting the variant eligible for genetic counselling and predictive DNA testing based on family pedigrees. For relatives who attended genetic counselling, but decided against predictive DNA testing, subsequent attendance of cardiac monitoring will be checked.

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3 Relatives at risk eligible for genetic counselling and predictive DNA testing are first-  
4 degree relatives, and second-degree relatives in case of a connecting deceased first-degree  
5 relative suspected of an ICC. For cardiomyopathies, relatives at risk are eligible for genetic  
6 counselling and predictive DNA testing from the age of 10 years and over, following Dutch  
7 clinical guidelines. For primary arrhythmias, depending on the specific arrhythmic disorder,  
8 relatives at risk are eligible for predictive DNA testing from birth.  
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15 Furthermore, conditional uptake of relatives at risk, defined as the number of relatives  
16 that is genetically tested relative to the number that attends genetic counselling, will be  
17 calculated. Uptake will be measured at randomisation condition (i.e., intervention- or control  
18 group) and family level.  
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### 26 *Secondary outcome measures*

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28 Secondary outcome measures will be conducted by using validated as well as self-constructed  
29 questionnaire items. An overview of these items is shown in the Supplementary Material.  
30

31  
32 Secondary outcome measures include the following:  
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- 34  
35 - Appreciation of the used information provision strategy and preferences regarding the  
36 approach used to inform relatives at risk: This will be evaluated in both probands and  
37 relatives by using self-constructed items on a 5 point Likert scale (i.e., 1 = ‘Totally  
38 disagree’ to 5 = ‘Totally agree’) in a questionnaire (probands 5 items, range 5-25;  
39 relatives 6 items, range 6-30). Probands will be asked to answer an additional self-  
40 constructed item during the structured telephone interview on whether they preferred to  
41 inform their relatives differently. In the intervention group, two additional self-constructed  
42 items will be administered to assess decisional conflict in probands, including whether  
43 probands thought it was hard to choose whether they wanted to inform their relatives  
44 themselves or by the counsellor, and whether they were satisfied by their decision on a 5  
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3 point Likert scale (i.e., 1 = ‘Totally disagree’ to 5 = ‘Totally agree’; range 2-10). Probands  
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5 will be asked to fill out these items at T1. At T2, a self-constructed item will be  
6  
7 administered whether their opinion regarding the used approach has changed. Finally,  
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9 probands (i.e., T1 and T2) and relatives will be asked whether they visited the website  
10  
11 www.erfelijkehartziekten.nl and if yes, how they evaluated this website, using four self-  
12  
13 constructed items on a 5 point Likert scale (i.e., 1 = ‘Totally disagree’ to 5 = ‘Totally  
14  
15 agree’; range 4-20).

- 16  
17  
18 - Impact on family communication: To assess the impact on family functioning of the  
19  
20 tailored approach versus the usual care approach, probands (i.e., on T1 and T2) and  
21  
22 relatives will be asked to fill out an adapted version of the Openness to Discuss Cancer in  
23  
24 the Family (ODCF) scale, assessing communication about genetic risks within families  
25  
26 with nine items on a 5 point Likert scale (i.e., 1 = ‘Totally disagree’ to 5 = ‘Totally agree’;  
27  
28 range 9-45) (29). Psychometric characteristics of the original ODCF scale are satisfactory  
29  
30 (29). In addition, a self-constructed item will be administered asking whether probands  
31  
32 and relatives experienced changes in their relationships with relatives as a consequence of  
33  
34 the information process.  
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- 37 - Impact on psychological functioning: To assess the impact on psychological functioning,  
38  
39 two validated questionnaires will be administered in both probands (i.e., T1 and T2) and  
40  
41 relatives. Participants will be asked to fill out an adapted version of the Cancer Worry  
42  
43 Scale (CWS) (30). The CWS was developed and previously used in studies with patients  
44  
45 with hereditary types of cancer. It consists of eight items on a 4 point Likert scale (i.e., 1=  
46  
47 ‘Almost never’ to 4 = ‘Almost always’; range 8-32). Psychometric characteristics were  
48  
49 assessed in a sample of breast cancer survivors, which supported the reliability and  
50  
51 validity of the CWS (30).  
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3 In addition, the Hospital Anxiety and Depression Scale (HADS) will be  
4 administered to assess whether participants experience anxious or depressed feelings after  
5 being informed about the hereditary disease (31). The HADS contains two 7-item  
6 subscales on a 4 point Likert scale with diverse answer options, assessing anxiety and  
7 depression both with a score range of 0-21. Psychometric characteristics were assessed as  
8 good (31).  
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### 18 *Participants' characteristics*

19 To assess whether randomization succeeded and whether characteristics of participating  
20 probands and relatives influence primary and secondary outcome measures,  
21 sociodemographic and clinical factors will be collected, including gender, education level,  
22 ethnicity, living situation and parenthood, family history and diagnosis of the probands at T1.  
23  
24 Relatives will be asked additionally what their degree of kinship is with the proband.  
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30 For the same reason, psychosocial and personality factors will be assessed in both  
31 probands (i.e., at T1) and relatives as well. Coping style will be assessed by using the  
32 shortened version of the Threatening Medical Situations Inventory (TMSI) (32, 33). This  
33 questionnaire assesses a monitoring and a blunting coping style related to a medical threat and  
34 is previously evaluated in an oncogenetic patient population (32, 34). The shortened version  
35 of the TMSI contains two subscales, both consisting of six items on a 5 point Likert scale (i.e.,  
36 1 = 'Totally not applicable' to 5 = 'Totally applicable'; range 6-30). Reliability and validity  
37 are satisfactory (32, 33).  
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48 The Trait subscale of the State Trait Anxiety Inventory (STAI) will be administered to  
49 assess trait anxiety in both probands and relatives. The STAI is a frequently used  
50 questionnaire in research settings, and consists of 20 items on a 4 point Likert scale (i.e., 1 =  
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3 'Not at all' to 4 = 'Very much so'; range 20-80) (35). The reliability and validity for the  
4  
5 Dutch translation of the STAI are assessed as good (36).

6  
7 Self-efficacy, and perceived motivators and barriers regarding informing relatives at  
8  
9 risk will be assessed by using an adapted version of the 'motivation' and 'self-efficacy'  
10  
11 subscales of the Informing Relatives Inventory (IRI) (37). The IRI was developed and  
12  
13 evaluated in an oncogenetic patient population, showing satisfactory reliability and validity  
14  
15 (37). The 'motivation' subscale consists of 30 items on a 5 point Likert scale (i.e., 'No role' to  
16  
17 'A large role'; range 30-150); the 'self-efficacy' subscale of 7 items on a 4 point Likert scale  
18  
19 (i.e., 1= 'Not sure at all' to 4 = 'Very sure'; range 7-21).

20  
21  
22 Risk perception regarding the risk of relatives carrying the variant and developing the  
23  
24 disease will be assessed by using self-constructed items. These items ask participants to rate  
25  
26 the perception of the risk of relatives on carrying the variant and on developing the disease, on  
27  
28 a scale from 1 (lowest risk) to 10 (highest risk) as well as from 0% (lowest risk) to 100%  
29  
30 (highest risk).

31  
32  
33 Health literacy, defined as the ability to obtain, process and understand basic health  
34  
35 information and services, will be assessed in probands and relatives, using the items on the  
36  
37 'functional health literacy' and 'communicative health literacy' subscales of the 3HL  
38  
39 questionnaire (38). Both subscales contain five items on a 4 point Likert scale (i.e., 1 =  
40  
41 'Never' to 4 = 'Often'; range per subscale 5-20). The reliability for both scales was assessed  
42  
43 as high and the validity as satisfactory (38).

#### 44 45 46 47 48 **Sample size calculation**

49  
50 The study aims to detect a difference of 15% in uptake of genetic counselling of relatives  
51  
52 between the control (i.e., usual care, 50%) and the intervention group (i.e., tailored approach,  
53  
54 65%). Assuming a two-sided 5% significance level and a power of 80%, a number of 340



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3 relatives (170 in each group) would be required to participate in this study. On average, a  
4  
5 number of six relatives per proband is at 50% risk of inheriting the variant, including children  
6  
7 and adults (9). With a conservative estimate of four eligible adult relatives per proband at risk,  
8  
9 85 probands with an ICC and an identified likely pathogenic or pathogenic (i.e., class 4 or 5)  
10  
11 variant will be required to include in this study to reach 340 relatives. In on average 20%  
12  
13 (lower margin) of all probands with a suspected ICC a likely pathogenic or pathogenic variant  
14  
15 is found. With an expected response rate of 70% and a drop-out rate of 20%, approximately  
16  
17 759 probands will be approached to participate in the study.  
18  
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21

## 22 **Data analysis**

23  
24 Sociodemographic, clinical, psychosocial and personality variables will be analysed using  
25  
26 descriptive and frequency statistics. An intention-to-treat approach will be used. SPSS version  
27  
28 24.0 will be used to perform statistical analyses (39). An  $\alpha$  level of  $p < .05$  will be used.  
29  
30

31 Student t-tests and chi-square tests will be used to assess differences (i) on  
32  
33 sociodemographic, clinical, psychosocial and personality characteristics between the  
34  
35 intervention- and control group, and (ii) participants and non-participants. Descriptive and  
36  
37 frequency statistics will be used to describe the primary outcome: uptake of genetic  
38  
39 counselling and of predictive DNA testing. Student t-tests and non-parametric statistics will  
40  
41 be used to assess differences between the intervention- and control group on the primary  
42  
43 outcome, as appropriate. Appreciation of the used approach will be described by using  
44  
45 frequency statistics.  
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47

48 Multilevel analyses will be performed to assess whether the intervention has an impact  
49  
50 on family and psychological functioning. The two measurement time-points will be treated as  
51  
52 nested within probands. Regression analyses will be conducted as well to assess the influence  
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2  
3 on the primary and secondary outcomes of sociodemographic, clinical, psychological and  
4  
5 personality characteristics. Open questions will be analysed using thematic analysis.  
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### 8 9 **Patient and public involvement**

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11 Prior to this randomized controlled trial, face-to-face interviews were conducted with  
12  
13 probands and counselled relatives (both carriers and non-carriers) to explore their experiences  
14  
15 with and preferences regarding informing at-risk relatives (unpublished). In addition, online  
16  
17 focus groups with HCPs were conducted. Based on the findings of both these interviews and  
18  
19 focus groups, this randomized controlled trial was designed. Since this study is part of the  
20  
21 eDETECT research consortium (CVON2015-12), several patient representative groups (i.e.,  
22  
23 PLN foundation; Harteraad, Hartz) participate in the user committee and scientific meetings  
24  
25 and thereby gave input to this research proposal. Patients are not involved in the recruitment  
26  
27 to and conduct of the study.  
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30  
31 During patient seminars, patients will be updated on the progression and results of this  
32  
33 study. In addition, during the eDETECT scientific meetings, all participants of the eDETECT  
34  
35 consortium (including representatives of the aforementioned patient organisations) will be  
36  
37 informed. After completion of the study, group results will be disseminated by e-mail to study  
38  
39 participants who indicated during informed consent to be interested. Furthermore, a summary  
40  
41 of the results will be posted on the website on inherited cardiac  
42  
43 conditions ([www.erfelijkehartziekten.nl](http://www.erfelijkehartziekten.nl)).  
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46  
47 The burden of the intervention was not assessed because this is an intrinsic part of the  
48  
49 outcome measures of this study. The patients themselves were involved in pilot testing of the  
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51 questionnaires used to assess these outcome measures.  
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### **Ethics and dissemination**

Approval of the study design has been obtained by the Medical Ethical Committee of the AMC (MEC 2017-145). Subsequently, additional approval of regional Medical Ethical Committees of the other participating academic centres has been obtained. Informed consent is required from each participant. Participants who provided written informed consent can withdraw from the study at any time, without providing a reason.

After receiving informed consent, a unique research ID will be assigned to the participant. Only this ID will be used to identify research documents. Each research document will be saved on a secured server. The principal investigator, coordinating investigator and executing investigator have access to this secured server. Research documents will be saved for a period of 15 years. This randomized controlled trial is registered at the Netherlands Trial Register NTR6657. Separate manuscripts with findings on respectively the primary and secondary outcomes will be published in peer-reviewed journals.

### **Trial status**

Recruitment of probands during pre-test genetic counselling for this randomized controlled trial started in November 2017. In total, recruitment of probands will last one year. Subsequently, uptake of genetic counselling and predictive DNA testing will be measured until one year after the detection of a pathogenic variant in the proband. Therefore, data collection will continue until January 2020 taking into account a duration of on average three months for the DNA-test result in the proband to be available.

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#### 28 **Authors contributions**

29  
30 LvdH and IC designed the intervention. LvdH, IC, ES and PvT were involved in conception  
31 and design of the protocol. LvdH was involved in drafting the manuscript. IC, ES, PvT, YH  
32 and AB critically revised the manuscript. All authors were involved in the final approval of  
33 the manuscript.  
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40  
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43 eDETECT and CVON2017-10 DOLPHIN-GENESIS.  
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#### 50 **Competing interests statement**

51  
52 All authors declare they have no competing interests.  
53  
54

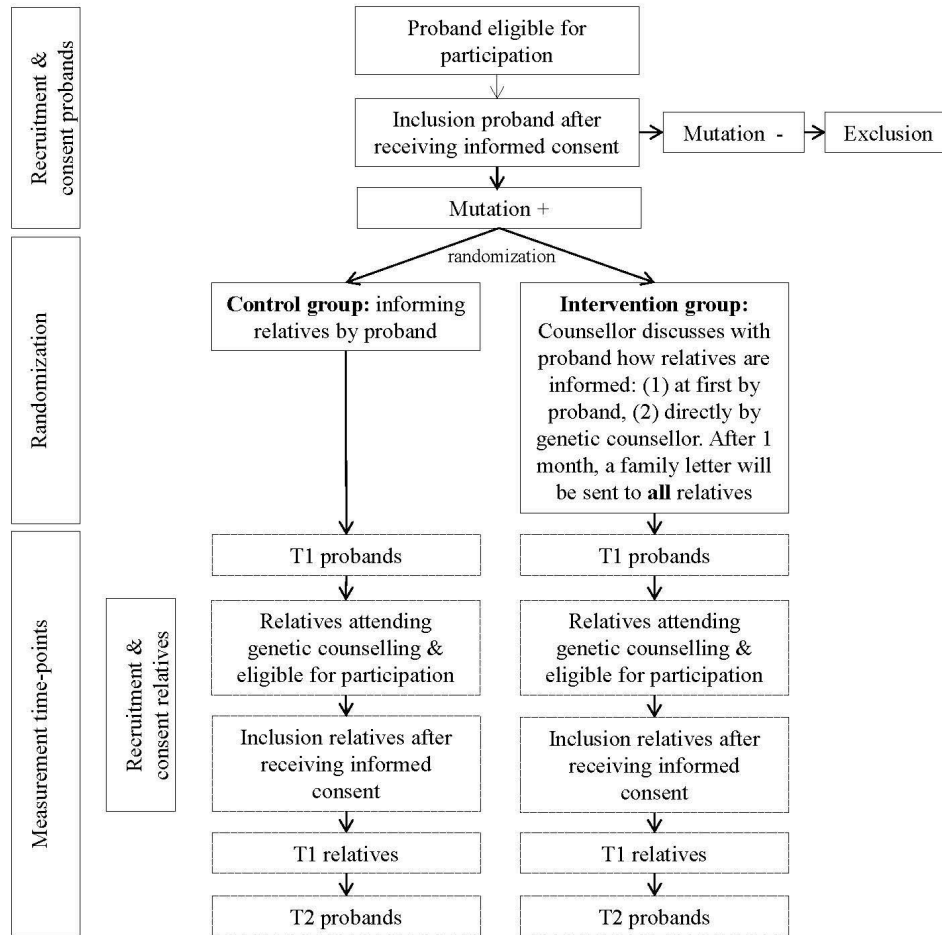
#### 55 **Acknowledgements**



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Patient advisors are acknowledged for their input regarding the design of this randomized controlled trial.

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**Figure 1** Study procedure

126x130mm (300 x 300 DPI)

## Supplementary material

### Supplementary material 1: Overview of questionnaire-items to assess secondary outcomes per time-point

**Table 1** Questionnaire items probands per time-point

Questionnaire time-point	Items	Questionnaires
T1	Sociodemographic, clinical, family and personality factors	Self-constructed items; trait scale of STAI; shortened version of TMSI
	Advices for relatives at risk, eligible relatives at risk, the number of informed relatives at risk, risk perception and experiences with informing relatives at risk	Eleven self-constructed items
	Evaluation of used approach (incl. website)	Thirteen self-constructed items
	Perceived impact on family communication with relatives at risk	Adapted version of ODCF; one self-constructed item
	Impact on psychological functioning of proband	HADS; adapted version of CWS
T2	Number of informed relatives at risk, risk perception and experiences with informing relatives at risk	Three self-constructed items
	Evaluation of used approach	One self-constructed item
	Perceived impact on family communication with relatives at risk	Adapted version of ODCF; one self-constructed item
	Impact on psychological functioning of proband	HADS; adapted version of CWS

**Table 2** Questionnaire items relatives

Questionnaire time-point	Items	Questionnaires
T1	Sociodemographic, family and personality factors	Eight self-constructed items; trait scale of STAI; shortened version of TMSI
	Evaluation of used approach (incl. website), risk perception	Thirteen self-constructed items
	Perceived impact on family communication with index patient	Adapted version of ODCF; one self-constructed item
	Impact on psychological functioning of family member	HADS; adapted version of CWS

### Supplementary material 2: Self-constructed items administered in probands and relatives

**Table 3** Self-constructed items (telephone interview) - Experiences with informing relatives at risk (probands)

1. Did the genetic counsellor give you an advice for your relatives? 2. What was this advice? (open question) 3. For which relatives was this advice meant? (open question)	Yes/No
4. Have relatives at risk been informed about the advice of the genetic counsellor? If yes, which relatives have been informed? 5. Who informed your relatives?	Yes/No

**Table 4** Self-constructed items (telephone interview) - Risk perception (probands)

1. How do you consider the risk of your relatives on being a carrier of the familial variant?	0% - 100% 1-10
2. How do you estimate the risk of your relatives on developing symptoms of the ICC?	0% - 100% 1-10

**Table 5** Self-constructed items - Evaluation of the used approach (probands)

<i>T1</i>	<p><i>Closed questions</i></p> <p><i>Below you can see statements regarding your experiences with how your relatives have been informed. Please rate each statement on a scale of 1-5 (1 totally disagree to 5 totally agree) how much each statement applies to you.</i></p> <p>1. I feel supported by the genetic counsellor in informing my relatives</p> <p>2. I think the used approach to inform relatives at risk is acceptable</p> <p>3. I felt a little coerced to inform my relatives</p> <p>4. The way my relatives are informed, can be improved</p> <p>5. I am satisfied with the way my relatives are informed</p> <p>Other: _____</p>	<p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p>
<i>T2</i>	<p>1. Did your opinion regarding the used approach change?</p> <p>a. Yes, my opinion regarding the used approach became more positive</p> <p>b. Yes, my opinion regarding the used approach became more negative</p> <p>c. No, my opinion regarding the used approach is still positive</p> <p>d. No, my opinion regarding the used approach is still negative</p> <p>e. No, my opinion regarding the used approach is still neutral</p>	
<i>T1/T2</i>	<p>1. Do you think another approach to inform relatives at risk would have been better?</p> <p>2. Are there relatives for which you would have preferred another approach to inform them?</p>	<p>Yes/No</p> <p>Yes/No</p>
<i>T1/T2</i>	<p><i>Open questions</i></p> <p>1. What are advantages of the approach used to inform your relatives?</p>	

2. What are disadvantages of the approach used to inform your relatives?

**Table 6** Self-constructed items - Impact on family relationships (probands)

1. Are there relatives with whom your relationship has changed after they are informed about their risk on the inherited cardiac disease?
  - a. Yes, our relationship improved
  - b. Yes, our relationship worsened
  - c. No, our relationship is still not good/not bad
  - d. No, our relationship is still good
  - e. No, our relationship is still bad

**Table 7** Self-constructed items - Evaluation of the used approach (relatives)

<i>Closed questions</i>	
<i>Below you can see statements regarding your experiences with how you have been informed about the inherited cardiac disease in your family. Please rate each statement on a scale of 1-5 (1 totally disagree to 5 totally agree) how much each statement applies to you.</i>	
1. I appreciated to be informed about my risk on the inherited cardiac disease	1 2 3 4 5
2. I am satisfied with the way I have been informed	1 2 3 4 5
3. I preferred to have received more information before I contacted the clinical genetic centre	1 2 3 4 5
4. I understand why I have been informed	1 2 3 4 5
5. The way I have been informed, can be improved	1 2 3 4 5
6. I felt free to decide myself whether I wanted to contact the clinic genetic centre	1 2 3 4 5
7. I would have preferred not to be informed about my risk on the inherited cardiac disease in my family	1 2 3 4 5
8. I would have preferred to not know about the inherited cardiac disease in my family	1 2 3 4 5
Other: _____	
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1. Do you think another approach to be informed would have been better?	Yes/No
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<i>Open questions</i>	
1. What are advantages of the way you have been informed?	
2. What are disadvantages of the way you have been informed?	

**Table 8** Self-constructed items - Impact on family relationships (relatives)

1. Did your relationship with your relative change after they were informed about their risk on the inherited cardiac disease?
  - a. Yes, our relationship improved
  - b. Yes, our relationship worsened
  - c. No, our relationship is still not good/not bad

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|---------------------------------------|
| d. No, our relationship is still good |
| e. No, our relationship is still bad  |

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page no
<b>Administrative information</b>			
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	6-17
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	-
	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	-
	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)	-
<b>Introduction</b>			
Background and rationale	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	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6

1				
2	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, noninferiority, exploratory)	6
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6				
7	<b>Methods: Participants, interventions, and outcomes</b>			
8				
9	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	6
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13	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)	7
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17	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9, 10
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21		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)	17
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25		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
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29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
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32	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	11-14
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39	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)	8, 11, 17
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44	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	15, 16
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48	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
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#### Methods: Assignment of interventions (for controlled trials)

Allocation:



1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	9
3	generation		generated random numbers), and list of any factors for stratification.	
4			To reduce predictability of a random sequence, details of any	
5			planned restriction (eg, blocking) should be provided in a separate	
6			document that is unavailable to those who enrol participants or	
7			assign interventions	
8				
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	9
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
11	mechanism		describing any steps to conceal the sequence until interventions are	
12			assigned	
13				
14	Implementation	16c	Who will generate the allocation sequence, who will enrol	9
15			participants, and who will assign participants to interventions	
16				
17	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial	9
18			participants, care providers, outcome assessors, data analysts),	
19			and how	
20				
21				
22		17b	If blinded, circumstances under which unblinding is permissible, and	9
23			procedure for revealing a participant's allocated intervention during	
24			the trial	
25				
26	<b>Methods: Data collection, management, and analysis</b>			
27				
28	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	11-15
29	methods		other trial data, including any related processes to promote data	
30			quality (eg, duplicate measurements, training of assessors) and a	
31			description of study instruments (eg, questionnaires, laboratory	
32			tests) along with their reliability and validity, if known. Reference to	
33			where data collection forms can be found, if not in the protocol	
34				
35		18b	Plans to promote participant retention and complete follow-up,	-
36			including list of any outcome data to be collected for participants	
37			who discontinue or deviate from intervention protocols	
38				
39	Data management	19	Plans for data entry, coding, security, and storage, including any	17
40			related processes to promote data quality (eg, double data entry;	
41			range checks for data values). Reference to where details of data	
42			management procedures can be found, if not in the protocol	
43				
44				
45	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes.	16, 17
46			Reference to where other details of the statistical analysis plan can	
47			be found, if not in the protocol	
48				
49		20b	Methods for any additional analyses (eg, subgroup and adjusted	16, 17
50			analyses)	
51				
52		20c	Definition of analysis population relating to protocol non-adherence	16, 17
53			(eg, as randomised analysis), and any statistical methods to handle	
54			missing data (eg, multiple imputation)	
55				
56				
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58				
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**Methods: Monitoring**

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
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	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

**Ethics and dissemination**

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
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)	-
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
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

1	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	17
2	policy		participants, healthcare professionals, the public, and other relevant	
3			groups (eg, via publication, reporting in results databases, or other	
4			data sharing arrangements), including any publication restrictions	
5				
6				
7		31b	Authorship eligibility guidelines and any intended use of	18
8			professional writers	
9				
10		31c	Plans, if any, for granting public access to the full protocol,	-
11			participant-level dataset, and statistical code	
12				

### Appendices

13				
14				
15	Informed consent	32	Model consent form and other related documentation given to	-
16	materials		participants and authorised surrogates	
17				
18	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
19	specimens		specimens for genetic or molecular analysis in the current trial and	
20			for future use in ancillary studies, if applicable	
21				

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## A tailored approach towards informing relatives at risk of inherited cardiac conditions: study protocol for a randomised controlled trial

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Keywords:	Inherited cardiac conditions, Cardiogenetics, Informing relatives at risk, Family-mediated approach, Tailored approach, Randomized controlled trial

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Manuscripts

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3 **1 A tailored approach towards informing relatives at risk of inherited cardiac conditions:**  
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5 **2 study protocol for a randomised controlled trial**  
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10 4 L.M. van den Heuvel<sup>1</sup>, Y.M. Hoedemaekers<sup>2</sup>, A.F. Baas<sup>3</sup>, J.P. van Tintelen<sup>1</sup>, E.M.A. Smets<sup>4</sup>&  
11  
12 5 I. Christiaans<sup>1\*</sup>  
13  
14

15 6 <sup>1</sup>Department of Clinical Genetics, Amsterdam University Medical Centres / University of  
16  
17 Amsterdam, Amsterdam, the Netherlands  
18

19 8 <sup>2</sup>Department of Genetics, University of Groningen, University Medical Centre Groningen,  
20  
21 Groningen, the Netherlands  
22  
23

24 10 <sup>3</sup>Department of Genetics, University Medical Centre Utrecht / University Utrecht, Utrecht, the  
25  
26 Netherlands  
27  
28

29 12 <sup>4</sup>Department of Medical Psychology, Amsterdam University Medical Centres / University of  
30  
31 Amsterdam, Amsterdam, the Netherlands  
32  
33

34 14  
35  
36 15 \* Corresponding author  
37

38 16 Department of Clinical Genetics,  
39

40  
41 17 Amsterdam University Medical Centre, location AMC  
42

43  
44 18 Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands  
45  
46

47  
48 19 Telephone: +31 20-5667217  
49

50  
51 20 E-mail: i.christiaans@amc.nl  
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## Abstract

**Introduction** In current practice, probands are asked to inform relatives about the possibility of predictive DNA testing when a pathogenic variant causing an inherited cardiac condition (ICC) is identified. Previous research on the uptake of genetic counselling and predictive DNA testing in relatives suggests that not all relatives are sufficiently informed. We developed a randomised controlled trial to evaluate the effectiveness of a tailored approach in which probands decide together with the genetic counsellor which relatives they inform themselves and which relatives they prefer to have informed by the genetic counsellor. Here, we present the study protocol of this randomised controlled trial. **Methods** A multicentre randomised controlled trial with parallel-group design will be conducted in which an intervention group receiving the tailored approach will be compared to a control group receiving usual care. Adult probands diagnosed with an ICC in whom a likely pathogenic or pathogenic variant is identified, will be randomly assigned to the intervention or control group (total sample: n = 85 probands). Primary outcomes are uptake of genetic counselling and predictive DNA testing by relatives (total sample: n = 340 relatives). Secondary outcomes are appreciation of the approach used and impact on familial and psychological functioning, which will be assessed using questionnaires. Relatives who attend genetic counselling will be asked to fill out a questionnaire as well. **Ethics and dissemination** Ethical approval was obtained from the Medical Ethical Committee of the Amsterdam University Medical Centres (MEC 2017-145), the Netherlands. All participants will provide informed consent prior to participation in the study. Results of the study on primary and secondary outcome measures will be published in peer-reviewed journals. **Registration details** This trial is registered at the Netherlands Trial Register NTR6657.

**Key words** Inherited cardiac conditions, cardiogenetics, informing relatives at risk, family-mediated approach, tailored approach, randomised controlled trial

### Strengths and limitations of this study

- This randomised controlled trial investigates both the uptake of genetic counselling and of predictive DNA testing, as well as the acceptance and impact on psychological and family functioning in the tailored versus the standard approach, in probands and relatives.
- This study will be conducted in three clinical genetics clinics with expertise on cardiogenetics, which will facilitate participant inclusion.
- In this trial, evaluation of the effect on outcome of the different components of the intervention is not possible, due to limited power.
- In this randomised controlled trial it is not possible to blind participants, genetic counsellors or the executing investigator for the chosen intervention.
- Because a baseline measure for the secondary outcomes is not possible, we cannot control for likely confounding factors, such as intention to inform at-risk relatives, and family and psychological functioning at baseline.

## Introduction

Inherited cardiac conditions (ICCs) such as cardiomyopathies and primary arrhythmia syndromes generally demonstrate an autosomal dominant inheritance pattern and a wide variety of symptoms that can manifest at any age [1, 2]. One feared outcome is sudden cardiac death (SCD), which can occur at a young age and be the first symptom of disease [3, 4]. With an incomplete penetrance and high variability in expression even within families, carriers of a familial variant may remain undetected but still be at risk for SCD even though treatment options are available that prevent disease progression or potentially life-threatening arrhythmias [5]. Predictive DNA testing is therefore offered to first-degree relatives of probands (the first person in a family diagnosed with an ICC) in whom a pathogenic variant is identified because these relatives are at 50% risk of also having inherited the genetic variant [5, 6]. Predictive DNA testing is offered to relatives in a stepwise manner (cascade screening), with the aim of identifying asymptomatic carriers of the familial variant to facilitate timely treatment. Non-carriers of the familial variant generally do not need cardiac monitoring and can be reassured about their own risk and that of their offspring [6].

In current practice in the Netherlands, probands are asked to inform their relatives, supported by a family letter written by the genetic counsellor. This is referred to as the family-mediated approach [7]. Previous research, however, shows that uptake (the number of relatives at risk attending genetic counselling and/or undergoing predictive DNA testing) is relatively low in ICCs, particularly for cardiomyopathies. Reported uptakes are around 50% despite family letters being provided to a majority of relatives by the proband [8-10]. Previous research in other genetic patient populations, such as hereditary types of cancer, shows similar uptake percentages [11-13].

Some relatives who do not attend genetic counselling will have deliberately decided against predictive DNA testing. However, the low uptake percentages also suggest that many



1  
2  
3 1 relatives may be unaware, or insufficiently aware, of the risks involved and/or the possibilities  
4  
5 2 for genetic counselling and subsequent surveillance and treatment. This is supported by  
6  
7 3 research on family communication in ICCs. Patients are not always able to inform or correctly  
8  
9 4 inform their relatives for a number of reasons, including disengagement with relatives, lack of  
10  
11 5 understanding of the importance of the information, preoccupation with their own grief,  
12  
13 6 difficulties in conveying the complex information to relatives, or a wish to prevent burdening  
14  
15 7 relatives by informing them about genetic risks [8, 14-18].  
16  
17  
18

19 8 Previous studies assessing interventions to enhance family communication in  
20  
21 9 hereditary diseases showed that some interventions are effective in increasing the uptake of  
22  
23 10 genetic counselling [19-21]. An intervention trial aimed at improving family communication  
24  
25 11 in specifically dilated cardiomyopathy is still ongoing [22]. A few studies have been  
26  
27 12 published on more active approaches to informing relatives at risk in which healthcare  
28  
29 13 professionals (HCPs) contact at-risk relatives directly [23-26]. These studies suggest that a  
30  
31 14 more active approach can almost double the uptake of genetic counselling and predictive  
32  
33 15 DNA testing by relatives (23-26) However, some of these studies were performed in a  
34  
35 16 research setting (e.g. in relatives already registered in research databases for the genetic  
36  
37 17 disease), hampering direct translation of these results to a diagnostic setting. To our  
38  
39 18 knowledge, more active approaches in patients with ICCs have not been studied thus far.  
40  
41 19 However, a study by Ormondroyd et al [14] suggests that relatives eligible for predictive  
42  
43 20 DNA testing for hypertrophic cardiomyopathy and long QT syndrome would support a more  
44  
45 21 active approach to informing relatives at risk.  
46  
47  
48  
49

50  
51 22 Although studies on more active approaches did not report any psychological harm in  
52  
53 23 relatives at group level, these approaches could cause more unwarranted worry or pressure on  
54  
55 24 relatives to opt for predictive DNA testing [23-25]. An active approach to informing relatives  
56  
57 25 at risk could also breach the autonomy and confidentiality of probands, and may harm  
58  
59  
60

1  
2  
3 1 relative's right not to know [27-29]. Furthermore, HCPs are often unaware of interpersonal  
4  
5 2 dynamics within families and the personal circumstances of relatives at risk. Active  
6  
7 3 approaches may therefore have a negative impact on family relationships or may cause  
8  
9 4 psychological distress in both probands and relatives [30].  
10  
11

12 5 Because of this, a tailored approach in which a proband decides together with the  
13  
14 6 genetic counsellor which at-risk relatives he or she will inform and which relatives he or she  
15  
16 7 prefers to be informed by the genetic counsellor could be optimal. With this approach, the  
17  
18 8 probands expert knowledge of a relative's functioning and of family dynamics could be used  
19  
20 9 appropriately, and the autonomy of the proband preserved. At the same time, more relatives at  
21  
22 10 risk would be sufficiently informed [28, 30]. Furthermore, probands for whom informing  
23  
24 11 relatives is difficult or burdensome might be relieved or supported by this approach [30].  
25  
26  
27  
28  
29  
30

### 31 *Objectives*

32  
33 14 The primary aim of this randomised controlled trial is to assess whether uptake of genetic  
34  
35 15 counselling and testing of relatives at risk of an ICC will be increased by using a tailored  
36  
37 16 approach to information provision for relatives, instead of usual care (i.e. the family-mediated  
38  
39 17 approach). Secondary objectives are to evaluate how such a tailored approach is appreciated  
40  
41 18 by both probands and relatives as compared to usual care. In addition, this study aims to  
42  
43 19 assess the perceived impact on family relationships and psychological functioning of both  
44  
45 20 probands and relatives. The protocol presented here has been described based on the SPIRIT  
46  
47 21 statement [31]  
48  
49  
50

## 51 **Methods**

### 52 **Design**

53  
54 23 A multicentre randomised controlled trial with a parallel-group design will be conducted in  
55  
56 24 three university hospitals in the Netherlands (the Amsterdam University Medical Centres  
57  
58 25  
59  
60

1  
2  
3 1 (Amsterdam UMC), the University Medical Centre Utrecht (UMCU) and the University  
4  
5 2 Medical Centre Groningen (UMCG)) to compare the effects of a tailored approach to  
6  
7 3 informing relatives at risk of ICCs to usual care in both probands and relatives.  
8  
9  
10 4

## 11 5 **Participants**

12  
13  
14 6 All probands aged 18 years or older with an ICC, or suspicion thereof, attending pre-test  
15  
16 7 genetic counselling at the cardiogenetics outpatient clinics during the inclusion period will be  
17  
18 8 asked to participate if they: (1) are the first member of their family to visit the cardiogenetics  
19  
20 9 outpatient clinic for counselling about genetic testing for ICCs; (2) they have at least one  
21  
22 10 living adult relative; and (3) are able to read and write Dutch. Only probands in whom a likely  
23  
24 11 pathogenic or pathogenic variant is detected (class 4 - likely pathogenic or class 5 -  
25  
26 12 pathogenic variant) will be definitively included.  
27  
28  
29

30  
31 13 In addition, eligible adult first- (or second-) degree relatives of enrolled probands who  
32  
33 14 make an appointment at the cardiogenetics outpatient clinics will be invited to fill out a  
34  
35 15 questionnaire to measure secondary outcomes. Inclusion criteria are defined as follows: (1)  
36  
37 16 first-degree adult (18 years or older) relatives of probands enrolled in the study or second-  
38  
39 17 degree adult relatives in case of a deceased connecting first-degree relative who was affected  
40  
41 18 or suspected to be affected, and (2) able to read and write Dutch.  
42  
43  
44  
45  
46

## 47 20 **Procedure**

48  
49 21 Figure 1 shows a flowchart of the study procedure.  
50

### 51 22 *Recruitment & consent*

52  
53 23 During pre-test genetic counselling, the genetic counsellor will inform the probands about the  
54  
55 24 study and provide an informational letter (see Supplementary Material S1). In addition,  
56  
57 25 probands will be asked if the executing researcher can contact them to provide further  
58  
59  
60

1  
2  
3 1 information about the study. Subsequently, probands will be contacted by telephone by the  
4  
5 2 executing researcher. If probands are still interested in participation, written informed consent  
6  
7 3 forms will be sent by post, including a return envelope. As described above, only probands in  
8  
9 4 whom a likely pathogenic or pathogenic variant is detected will be definitively included in the  
10  
11 5 study.  
12  
13

14 6 Relatives of enrolled probands attending pre-test genetic counselling in one of the  
15  
16 7 participating centres who are also at risk will also be invited to participate in the study. The  
17  
18 8 same recruitment procedure will be used.  
19  
20  
21 9

### 22 23 24 10 *Randomisation*

25  
26 11 Prior to receiving their test result, probands with an ICC in whom a likely pathogenic or  
27  
28 12 pathogenic variant is identified will be randomly assigned to either the intervention or control  
29  
30 13 group. Block randomisation will be used, with variable blocks ranging from size two to six.  
31  
32 14 Randomisation will be stratified for gender, disease type (cardiomyopathies or primary  
33  
34 15 arrhythmia syndromes) and hospital. To ensure allocation concealment, computer software  
35  
36 16 will be used for randomisation, with an allocation rate of 1:1 [32]. Relatives of probands  
37  
38 17 included in the study will be assigned to the group to which the proband was assigned.  
39  
40

41  
42 18 Neither participants nor genetic counsellors will or can be blinded for group  
43  
44 19 assignment. The executing researcher also cannot be blinded because of slight differences  
45  
46 20 between the questionnaires administered in the intervention- and control groups. Part of the  
47  
48 21 outcome data will be collected using telephone interviews. To minimize bias, these interviews  
49  
50 22 will be conducted by a research assistant following a structured script.  
51  
52  
53  
54 23

### 55 56 24 Intervention group

57  
58  
59  
60

1  
2  
3 1 In the intervention group, a tailored approach to informing relatives at risk will be provided.  
4  
5 2 In this approach, probands with a likely pathogenic or pathogenic variant will discuss with the  
6  
7 3 genetic counsellor which relatives are at risk of inheriting the familial variant. They will then  
8  
9 4 be asked which of these relatives they prefer to inform themselves at first using a family letter  
10  
11 5 written by the genetic counsellor, and which relatives they prefer to be directly informed by  
12  
13 6 the genetic counsellor with a similar family letter. This will be discussed during routine post-  
14  
15 7 test counselling. In both cases, after one month, the genetic counsellor will send the family  
16  
17 8 letter directly to all relatives at risk for whom the proband has provided consent to contact.  
18  
19 9 The proband will be asked to provide contact details of these relatives.  
20  
21  
22

23  
24 10 The family letter is standardised for all three participating centres. For the intervention  
25  
26 11 group, the letter also includes a link to a website specifically designed for this study where  
27  
28 12 relatives can find additional information ([www.familieleden.erfelijkehartziekten.nl](http://www.familieleden.erfelijkehartziekten.nl)). The  
29  
30 13 information on this website will be tailored to relative's situations (i.e. specified for disease-  
31  
32 14 type, hospital, parenthood, whether relatives have a desire to have children in the future, and  
33  
34 15 which information relatives prefer to receive) by asking them to fill out a short questionnaire  
35  
36 16 on their first visit to the website.  
37  
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39

40 17

#### 41 42 18 Control group

43  
44 19 In the control group, the standard care approach will be used. If a likely pathogenic or  
45  
46 20 pathogenic variant is identified, probands assigned to the control group will be asked by the  
47  
48 21 genetic counsellor to inform relatives at risk about the genetic test result, the consequences of  
49  
50 22 this result for relatives and the advice regarding predictive DNA testing and/or cardiac  
51  
52 23 monitoring. This will be discussed during routine post-test counselling. Probands will be  
53  
54 24 supported in informing relatives at risk by a family letter written by the genetic counsellor.  
55  
56 25 This family letter is also standardised for all three participating centres. However, this letter  
57  
58  
59  
60

1  
2  
3 1 does not include the link to the website with tailored information described above, but does  
4  
5 2 include a link to a general website on ICCs ([www.erfelijkehartziekten.nl](http://www.erfelijkehartziekten.nl)).

### 3 *Measurement time-points*

4 For secondary outcome measures, participating probands will be asked to complete a  
5 questionnaire one month after receiving the genetic test result (T1) and to complete a second  
6 questionnaire nine months after the test result (T2). Before T1 and T2, a short structured  
7 telephone interview will be conducted about participant's knowledge of which relatives are at  
8 risk of ICCs and which relatives are informed, because these items are expected to be too  
9 complex to answer in a questionnaire [33]. Participating relatives will complete one  
10 questionnaire after attending genetic counselling.

## 12 **Measures**

### 13 *Primary outcome measures*

14 To assess the effect of a tailored approach to informing relatives at risk, the difference  
15 between the intervention and control groups in uptake of (1) genetic counselling, and (2)  
16 predictive DNA testing of relatives at risk will be measured. To do this, the number of  
17 relatives attending genetic counselling and the number of relatives who are genetically tested  
18 in the first year after detection of the likely pathogenic or pathogenic variant in the proband  
19 will be collected in the laboratories of each participating centre. DNA test results of relatives  
20 counselled in non-participating centres will also be taken into account because, in the  
21 Netherlands, predictive DNA testing of relatives is always performed in the same laboratory  
22 where the proband was tested.

23 The number of relatives attending genetic counselling and undergoing predictive DNA  
24 testing will be compared to the total number of relatives at risk of inheriting the variant who  
25 are eligible for genetic counselling and predictive DNA testing based on family pedigrees. For

1  
2  
3 1 relatives who attend genetic counselling but decide against predictive DNA testing,  
4  
5 2 subsequent attendance of cardiac monitoring will be checked.  
6

7  
8 3 Relatives at risk who are eligible for genetic counselling and predictive DNA testing  
9  
10 4 are first-degree relatives and second-degree relatives if there is a connecting deceased first-  
11  
12 5 degree relative suspected of having an ICC. Following the Dutch clinical guidelines for  
13  
14 6 cardiomyopathies, relatives at risk are eligible for genetic counselling and predictive DNA  
15  
16 7 testing from the age of 10 years. For primary arrhythmias, depending on the specific  
17  
18 8 arrhythmic disorder, relatives at risk are eligible for predictive DNA testing from birth.  
19  
20

21 9 Furthermore, conditional uptake of relatives at risk, defined as the number of relatives  
22  
23 10 who are genetically tested relative to the number who attend genetic counselling, will be  
24  
25 11 calculated. Uptake will be measured at randomisation condition (intervention or control  
26  
27 12 group) and family level.  
28  
29

30  
31 13

#### 32 33 14 *Secondary outcome measures*

34  
35 15 Secondary outcome measures will be measured using both validated and self-constructed  
36  
37 16 questionnaire items. An overview of these items is shown in the Supplementary Material S2.

38  
39  
40 17 Secondary outcome measures include the following:

- 41  
42 18 - Appreciation of the information provision strategy used and preferences regarding the  
43  
44 19 approach used to inform relatives at risk: This will be evaluated in both probands and  
45  
46 20 relatives using self-constructed items on a 5 point Likert scale (1 = 'Totally disagree' to 5  
47  
48 21 = 'Totally agree') in a questionnaire (probands: 5 items, range 5-25; relatives: 6 items,  
49  
50 22 range 6-30). Probands will be asked to answer an additional self-constructed item during  
51  
52 23 the structured telephone interview about whether they would have preferred to inform  
53  
54 24 their relatives differently. Two additional self-constructed items will be administered in  
55  
56 25 the intervention group to assess decisional conflict in probands, including whether  
57  
58  
59  
60

1 probands thought it was difficult to choose to inform their relatives themselves or have  
2 them informed by the counsellor, and whether they were satisfied by their decision, on a 5  
3 point Likert scale (1 = 'Totally disagree' to 5 = 'Totally agree'; range 2-10). Probands will  
4 be asked to fill out these items at T1. At T2, a self-constructed item will be administered  
5 to assess whether their opinion regarding the approach used has changed. Finally,  
6 probands (at T1 and T2) and relatives will be asked whether they visited the website  
7 www.erfelijkehartziekten.nl and, if yes, how they evaluated the website, using four self-  
8 constructed items on a 5 point Likert scale (1 = 'Totally disagree' to 5 = 'Totally agree';  
9 range 4-20).

10 - Impact on family communication: To assess the impact of the tailored approach versus the  
11 usual care approach on family functioning, probands (at T1 and T2) and relatives will be  
12 asked to fill out an adapted version of the Openness to Discuss Cancer in the Family  
13 (ODCF) scale, which assesses communication about genetic risks within families with  
14 nine items on a 5 point Likert scale (1 = 'Totally disagree' to 5 = 'Totally agree'; range 9-  
15 45) [34]. Psychometric characteristics of the original ODCF scale are satisfactory [34]. In  
16 addition, a self-constructed item will be administered asking about the nature of regular  
17 communication with relatives and whether probands and relatives experienced changes in  
18 their relationships with relatives as a consequence of the information provision process.

19 - Impact on psychological functioning: To assess the impact on psychological functioning,  
20 two validated questionnaires will be administered in probands (at T1 and T2) and  
21 relatives. Participants will be asked to fill out an adapted version of the Cancer Worry  
22 Scale (CWS) [35]. The CWS was developed and validated in Dutch patients with  
23 hereditary types of cancer [35]. Because it was validated in a Dutch patient population and  
24 is previously used in a genetic patient population, it was considered the most appropriate  
25 scale for this randomised controlled trial. The CWS consists of eight items on a 4 point



1  
2  
3 1 Likert scale (1 = ‘Almost never’ to 4 = ‘Almost always’; range 8-32). Psychometric  
4  
5 2 characteristics of the CWS have been assessed in a sample of breast cancer survivors, and  
6  
7 3 support its reliability and validity [35].  
8  
9

10 4 In addition, the Hospital Anxiety and Depression Scale (HADS) will be  
11  
12 5 administered to assess whether participants experience anxious or depressed feelings after  
13  
14 6 being informed about the hereditary disease [36]. The HADS contains two 7-item  
15  
16 7 subscales on a 4 point Likert scale with diverse answer options that assess both anxiety  
17  
18 8 and depression with a score range of 0-21. Psychometric characteristics of the HADS were  
19  
20 9 assessed as good [36].  
21  
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24 10

### 25 26 11 *Participants’ characteristics*

27  
28 12 To assess whether randomisation succeeded and whether characteristics of participating  
29  
30 13 probands and relatives have influenced the primary and secondary outcome measures,  
31  
32 14 sociodemographic and clinical factors will be collected, including gender, education level,  
33  
34 15 ethnicity, living situation and parenthood, family history and the diagnosis of the probands at  
35  
36 16 T1. Relatives will additionally be asked what their degree of kinship is with the proband.  
37  
38  
39

40 17 For the same reason, psychosocial and personality factors will be assessed in both  
41  
42 18 probands (at T1) and relatives. Coping style will be assessed by using the shortened version of  
43  
44 19 the Threatening Medical Situations Inventory (TMSI) [37, 38]. The TMSI assesses a  
45  
46 20 “monitoring” versus “blunting” coping style related to a medical threat, and it was previously  
47  
48 21 evaluated in an oncogenetic patient population [37, 39]. The shortened version of the TMSI  
49  
50 22 contains two subscales, both consisting of six items on a 5 point Likert scale (1 = ‘Totally not  
51  
52 23 applicable’ to 5 = ‘Totally applicable’; range 6-30). Reliability and validity are satisfactory  
53  
54 24 [37, 38]. The Trait subscale of the State Trait Anxiety Inventory (STAI) will be administered  
55  
56 25 to assess trait anxiety in both probands and relatives [40]. The STAI is frequently used in  
57  
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60

1 research settings and consists of 20 items on a 4 point Likert scale (1 = 'Not at all' to 4 =  
2 'Very much so'; range 20-80) [40]. The reliability and validity for the Dutch translation of the  
3 STAI are assessed as good [41].

4 Self-efficacy and perceived motivators and barriers regarding informing relatives at  
5 risk will be assessed using an adapted version of the 'motivation' and 'self-efficacy' subscales  
6 of the Informing Relatives Inventory (IRI) [42]. The IRI was developed and evaluated in an  
7 oncogenetic patient population, and showed satisfactory reliability and validity [42]. The  
8 'motivation' subscale consists of 30 items on a 5 point Likert scale (1 = 'No role' to 5 = 'A  
9 large role'; range 30-150); the 'self-efficacy' subscale of 7 items on a 4 point Likert scale (1 =  
10 'Not sure at all' to 4 = 'Very sure'; range 7-21). Probands will also be asked to answer a self-  
11 constructed item during the telephone interviews regarding whether relatives were informed  
12 and whether probands intended to inform (remaining) at-risk relatives.

13 Risk perception regarding the risk of relatives carrying the variant and developing the  
14 disease will be assessed by using self-constructed items. These items ask participants to rate  
15 the perception of the risk of relatives carrying the variant and developing the disease on a  
16 scale from 1 (lowest risk) to 10 (highest risk) as well as from 0% (lowest risk) to 100%  
17 (highest risk).

18 Health literacy – defined as the ability to obtain, process and understand basic health  
19 information and services – will be assessed in probands and relatives using the items on the  
20 'functional health literacy' and 'communicative health literacy' subscales of the 3HL  
21 questionnaire [43]. Both subscales contain five items on a 4 point Likert scale (1 = 'Never' to  
22 4 = 'Often'; range per subscale 5-20). The reliability for both scales was assessed as high and  
23 the validity as satisfactory [43].

## 24 **Sample size calculation**

1  
2  
3 1 The study aims to detect a difference of 15% in uptake of genetic counselling by relatives  
4  
5 2 between the control (usual care, 50%) and intervention groups (tailored approach, 65%).  
6  
7 3 Assuming a two-sided 5% significance level and a power of 80%, 340 relatives (170 in each  
8  
9 4 group) would be required to participate in this study. On average, six relatives per proband are  
10  
11 5 at 50% risk of inheriting the variant, including children and adults [9]. With a conservative  
12  
13 6 estimate of four eligible adult relatives per proband at risk, 85 probands with an ICC and an  
14  
15 7 identified likely pathogenic or pathogenic (class 4 or 5) variant will need to be included in this  
16  
17 8 study to reach 340 relatives. A likely pathogenic or pathogenic variant is found in, on average,  
18  
19 9 20% (lower margin) of all probands with a suspected ICC. With an expected response rate of  
20  
21 10 70% and a drop-out rate of 20%, approximately 759 probands will be approached to  
22  
23 11 participate in the study.  
24  
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### 31 **Data analysis**

#### 32 *Statistical analysis*

33 Sociodemographic, clinical, psychosocial and personality variables will be analysed using  
34  
35 15 descriptive and frequency statistics. An intention-to-treat approach will be used. SPSS version  
36  
37 16 24.0 will be used to perform statistical analyses [44]. An  $\alpha$  level of  $p < .05$  will be used.  
38  
39 17 Analysis of Variance and chi-square tests will be used to assess differences (i) in  
40  
41 18 sociodemographic, clinical and psychological characteristics between the intervention- and  
42  
43 19 control group and (ii) in participants and non-participants, as appropriate. Descriptive and  
44  
45 20 frequency statistics will be used to describe the primary outcomes: (1) uptake of genetic  
46  
47 21 counselling and (2) uptake of predictive DNA testing. Logistic regression analysis will be  
48  
49 22 conducted to assess differences between the intervention- and control group on the primary  
50  
51 23 outcomes. Multilevel analyses will be performed to assess whether the intervention has an  
52  
53 24 impact on family and psychological functioning. The two measurement time-points will be  
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1 treated as nested within probands. To prevent influence of potential confounding factors,  
2 analysis will be adjusted for covariates (i.e., sociodemographic, clinical and psychological  
3 variables). Participant appreciation of the approach used will be described using frequency  
4 statistics.

### 6 *Qualitative analysis*

7 Open questions will be analysed using thematic analysis based on the principles of Braun and  
8 Clarke [45]. Analysis software for qualitative data, MAXQDA version 12, will be used [46].  
9 Coding analysis will be conducted by two trained coders independently. The codes will be  
10 analysed and interpreted to create a structure of themes and subthemes. The qualitative results  
11 will be used to supplement the questionnaire data.

### 13 **Patient and public involvement**

14 Prior to this randomised controlled trial, face-to-face interviews were conducted with  
15 probands and counselled relatives (both carriers and non-carriers) to explore their experiences  
16 with and preferences regarding informing at-risk relatives (unpublished). In addition, online  
17 focus groups were conducted with HCPs. The randomised controlled trial was then designed  
18 based on the findings of both these interviews and focus groups. Since this study is part of the  
19 eDETECT research consortium (CVON2015-12), several patient representative groups (the  
20 PLN foundation; Harteraad, Hertz) participated in the user committee and scientific meetings  
21 and thereby gave input to this research proposal. Patients are not involved in the recruitment  
22 and conduct of the study.

23 During patient seminars, patients will be updated on the progress and results of the  
24 study. In addition, during the eDETECT scientific meetings, all participants of the eDETECT  
25 consortium (including representatives of the aforementioned patient organisations) will be

1 informed. After completion of the study, group results will be disseminated by e-mail to study  
2 participants who indicated their interest in the outcome during informed consent. A summary  
3 of the results will also be posted on the ICCs website ([www.erfelijkehartziekten.nl](http://www.erfelijkehartziekten.nl)).

4 The burden of the intervention was not assessed because this is an intrinsic part of the  
5 outcome measures of this study. The patients themselves were involved in pilot testing the  
6 questionnaires used to assess these outcome measures.

### 8 **Ethics and dissemination**

9 The Medical Ethical Committee of the Amsterdam UMC has approved the study design  
10 (MEC 2017-145). Additional approval of regional Medical Ethical Committees of the other  
11 participating academic centres has also been obtained. Informed consent is required from each  
12 participant. Participants who provide written informed consent can withdraw from the study at  
13 any time, without providing a reason.

14 After receiving informed consent, a unique research ID will be assigned to the  
15 participant. Only this ID will be used to identify research documents. Each research document  
16 will be saved on a secured server. The principal investigator, coordinating investigator and  
17 executing investigator have access to this secured server. Research documents will be saved  
18 for a period of 15 years. This randomised controlled trial is registered at the Netherlands Trial  
19 Register NTR6657. Separate manuscripts with findings on, respectively, the primary and  
20 secondary outcomes will be published in peer-reviewed journals.

### 22 **Trial status**

23 Recruitment of probands during pre-test genetic counselling for this randomised controlled  
24 trial started in November 2017. In total, recruitment of probands will last one year.

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2  
3 1 Subsequent uptake of genetic counselling and predictive DNA testing will be measured until  
4  
5 2 one year after the detection of a pathogenic variant in the proband. Data collection will  
6  
7 3 therefore continue until January 2020, taking into account a duration of, on average, three  
8  
9 4 months for the DNA-test result in the proband to be available. To date, 68 probands have been  
10  
11 5 included and randomised to either the intervention or the control group. In addition, 49  
12  
13 6 relatives consented to participate.  
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#### 18 **Authors contributions**

19 LvdH and IC designed the intervention. LvdH, IC, ES and PvT were involved in conception  
20 and design of the protocol. LvdH was involved in drafting the manuscript. IC, ES, PvT, YH  
21 and AB critically revised the manuscript. All authors were involved in the final approval of  
22 the manuscript.

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#### 5 **Competing interests statement**

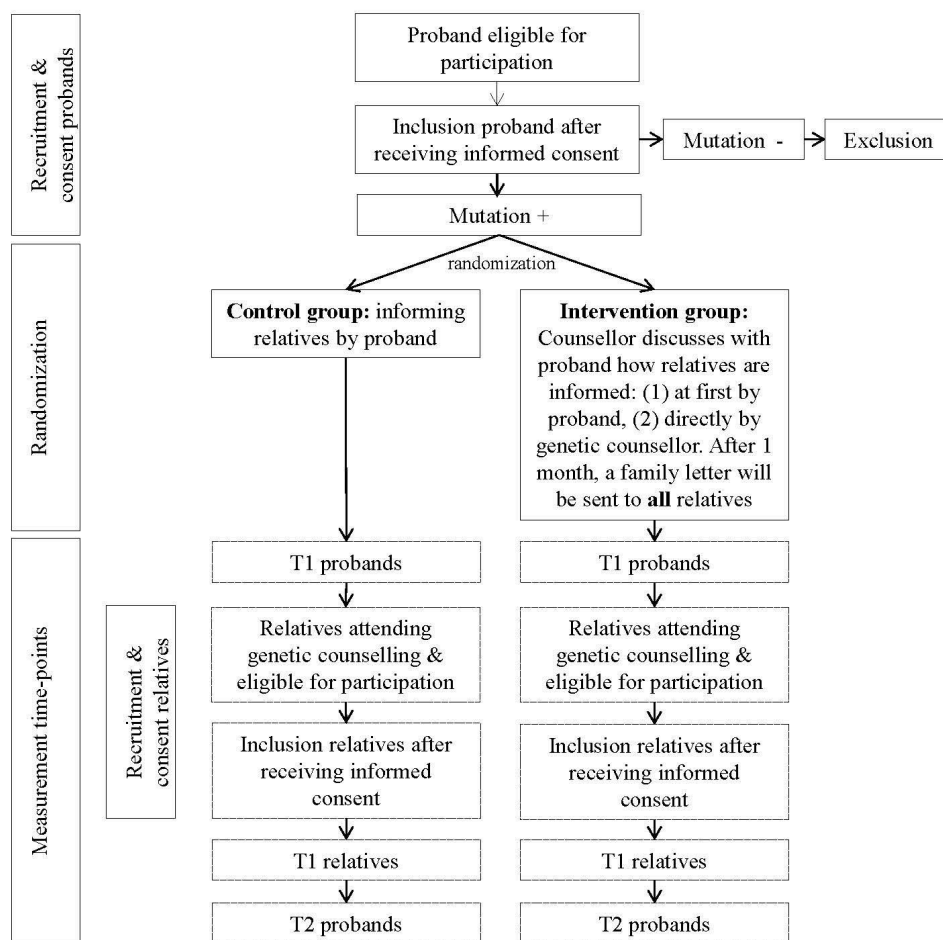
6 All authors declare they have no competing interests.

#### 8 **Acknowledgements**

9 Patient advisors are acknowledged for their input regarding the design of this randomised  
10 controlled trial.

#### 12 **Figures**

13 **Figure 1** Flow-chart of the study procedure



**Figure 1** Study procedure

126x130mm (300 x 300 DPI)

## Supplementary Material S1

**Supplementary material S1:** Information letter and informed consent form probands and relatives

umcg

Amsterdam UMC  
Universitair Medische Centra

UMC Utrecht

Dear Sir or Madam,

Recently you visited the department of Clinical Genetics for genetic counselling concerning a possible inherited cardiac disease in your family. A clinical geneticist or genetic counsellor informed you about participation in a research study examining how to inform relatives at risk of inheriting the genetic predisposition. In this letter, we would like to inform you about this research study.

*What is the goal of this research study?*

At the current moment, we ask people in whom a genetic cause for a cardiac disease is identified to inform their relatives about the possibility of genetic testing, supported by a letter written by the clinician. This research study aims to investigate whether another approach to informing relatives would be more effective. Using this approach, people who are the first in their family in whom the hereditary predisposition is identified can decide which relatives they prefer to inform themselves and which relatives they prefer to have contacted directly by the clinician. In addition, a website will be used to further inform relatives. This research study will investigate which approach is the most effective.

*Who is conducting the study?*

This research study will be conducted by the department of Clinical Genetics and the department of Medical Psychology of the Amsterdam UMC, in collaboration with the department of Clinical Genetics of the University Medical Centre Groningen (UMCG) and the University Medical Centre Utrecht (UMCU). The study is funded by the Dutch Heart Foundation.

*What does study participation involve?*

If the DNA test shows that no genetic variant causing the disease is identified, no further activity is needed for this study. If the DNA test shows that a genetic variant causing the disease is identified, the clinician will inform you about advice for your relatives. To investigate what the most effective approach is, one group of participants will be asked to inform relatives using the approach that is currently used, while the other group of participants will be asked to inform relatives using the other approach. Which group you are part of will be determined randomly.

## Supplementary Material S1

In addition, we will ask you to fill out two questionnaires. These questionnaires can be administered online or by mail. If you prefer to receive the questionnaire by mail, the questionnaire can be returned using the provided return envelope. These questionnaires ask you for some general information, such as your age and gender, and about your experiences with informing relatives and your opinion regarding the approach that was used. You will receive the first questionnaire two months after you receive the DNA test result. The second questionnaire will be sent to you after nine months.

### *What are advantages and disadvantages of study participation?*

There will be no direct benefit to you for your participation in this study. We hope that the information obtained from this study may contribute to research on improving approaches to informing relatives at risk of inherited cardiac diseases. Participation in this research study will take time: we will ask you to fill out two questionnaires. We expect that this will cost you 20 to 30 minutes per questionnaire. In addition, we will ask questions regarding personal information, such as the disease in your family and your opinion and feelings concerning informing your relatives about this disease. You will not receive an incentive for study participation.

### *What if I do not want to participate anymore?*

Your participation in this research is entirely voluntary. There are no consequences if you decide not to participate. You may also change your mind later and stop participating during the study even if you earlier agreed to do so. If you decide to stop participation, please let us know. The data collected up to that moment will be used for the research study. The researcher will inform you if there is new information about the study that might be important for you. In that case, you will be asked if you still consent to participate in the study.

### *How will my personal data be handled?*

By participating in this study, you will provide us personal data. This data will be collected for the research study. A research code will be assigned to all research documents. This means that your name and other personal data are not visible on research documents. Only the researchers know which research code belongs to you. Some institutes (the Safety Committee and the Health Care Inspectorate) are allowed to look into your clinical and personal data. These institutes are allowed to do this to control whether the research study is conducted in a proper and reliable manner. They will treat your data confidentially. If you sign the informed consent form, you will provide consent for collection, storage and inspection of your medical and personal data. Your data will be stored for 15 years.

### *Do you have any further questions regarding this research study?*

If you have any questions about this research study or about study participation, please contact the executing researcher Lieke van den Heuvel by telephone (<telephone number>) or e-mail (<e-mail address>). If you prefer to discuss study participation with an independent clinician, or if you would like additional information, advice or support, please contact the independent expert (see attachment).

### *What if I want to participate?*

## Supplementary Material S1

The researcher, Lieke van den Heuvel, will contact you by telephone to provide further information about the research study. If you decide to participate in this study after this telephone contact, a consent form will be sent to you by mail. You can return this consent form by using the attached return envelope. A postage stamp is not necessary.

Thank you for your time!

Sincerely,

Lieke van den Heuvel, MSc

Also on behalf of the research team and all the clinical geneticists and genetic counsellors involved from Amsterdam UMC, University Medical Centre Utrecht and University Medical Centre Groningen

**Attachment:** Information about your hospital 'UMCG/Amsterdam UMC/UMCU'

### **Questions, suggestions or complaints**

If you have any questions, suggestions or a complaint about this research study, please contact Lieke van den Heuvel. She will conduct this research study. She can be contacted by telephone (<telephone number>) or by e-mail (<e-mail address>).

### **Independent advice or support**

If you prefer to discuss study participation with someone who is not involved in this research study, because you need further information or advice, you may contact <independent researcher> (<e-mail address>). He/she is a clinical geneticist at the department of Clinical Genetics at UMCG/Amsterdam UMC/UMCU.



## Supplementary Material S1

**Certificate of consent****For participation in a research study regarding informing relatives at risk of an inherited cardiac disease**

- I am satisfied about the information I received about this research study. I have had sufficient time to consider participation in this study. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.
- I can stop study participation at any time, without providing any reason and without any consequences.

**By signing this form, I provide consent for:**

1. Informing my clinician (clinical geneticist/genetic counselor) about my participation in this research study.
2. Collecting of data using questionnaire(s), and inspection of my medical record until 12 months after signing this consent form and the use of these data for the research study described in this letter.
3. Being approached for other research projects in the future.
4. Storing of my research data for 15 years after the research study has been finished
5. Inspection of the research data by the Safety Committee and the Dutch Health Care Inspectorate

**I want to participate in this research study**

Name of participant: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of participant: \_\_\_\_\_

I would like to be informed about the group results of this research study:

- Yes
- No

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**Statement by the researcher:** I have accurately informed this person about the aforementioned research project. The person may stop participating at any time during the study without any consequences. Any questions from the person about study participation were answered sufficiently

Name of researcher: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of researcher: \_\_\_\_\_

## Supplementary Material S1



umcg

Amsterdam UMC  
Universitair Medische Centra

UMC Utrecht

Dear Sir or Madam,

Recently you visited the department of Clinical Genetics for genetic counselling concerning an inherited cardiac disease in your family. A clinical geneticist or genetic counsellor informed you about participation in a research study examining how to inform relatives at risk of inheriting the genetic predisposition. In this letter, we would like to inform you about this research study.

*What is the goal of this research study?*

At the current moment, we ask people in whom a genetic cause for a cardiac disease is identified to inform their relatives about the possibility of genetic testing, supported by a letter written by the clinician. This research study aims to investigate whether another approach to informing relatives would be more effective. Using this approach, people who are the first in their family in whom the hereditary predisposition is identified can decide which relatives they prefer to inform themselves and which relatives they prefer to have contacted directly by the clinician. In addition, a website will be used to further inform relatives. This research study will investigate which approach is the most effective.

*Who is conducting the study?*

This research study will be conducted by the Department of Clinical Genetics and the Department of Medical Psychology of the Amsterdam UMC, in collaboration with the Departments of Clinical Genetics of the University Medical Centre Groningen (UMCG) and the University Medical Centre Utrecht (UMCU). The study is funded by the Dutch Heart Foundation.

*What does study participation involve?*

For this research study, we ask you to fill out a questionnaire. This questionnaire can be administered online or by mail. If you prefer to receive the questionnaire by mail, the questionnaire can be returned by using the provided return envelope. These questionnaires ask you for some general information, such as your age and gender, and about your experiences with being informed about the inherited cardiac disease in your family and your opinion regarding the approach that was used. This questionnaire will also ask you some questions about how you feel, at the current moment and in general, and how you generally cope with complex situations.

In addition, it is important for this research study to receive some information about your medical background. Because of this, we ask you to provide consent to inspect your medical record up to 12 months after completion of this research study. Important information includes, for example, the inherited cardiac disease diagnosed in your family and information

## Supplementary Material S1

1  
2  
3 about your family history regarding cardiac diseases. This information will be handled  
4 confidentially.  
5

6 Your clinician (the clinical geneticist/genetic counsellor) will be informed if you decide to  
7 participate in this study. You might be approached for other research studies in the future.  
8  
9

### *What are advantages and disadvantages of study participation?*

10  
11 There will be no direct benefit to you for your participation in this study. We hope that the  
12 information obtained from this study will contribute to research on improving approaches to  
13 inform relatives at risk of inherited cardiac diseases. Participation in this research study will  
14 take time: we will ask you to fill out two questionnaires. We expect that this will cost you 20  
15 to 30 minutes per questionnaire. In addition, we will ask questions regarding personal  
16 information, such as the disease in your family and your opinion and feelings concerning  
17 informing your relatives about this disease. You will not receive an incentive for study  
18 participation.  
19  
20  
21  
22

### *What if I do not want to participate anymore?*

23  
24 Your participation in this research is entirely voluntary. There are no consequences if you  
25 decide not to participate. You may also change your mind later and stop participating during  
26 the study even if you earlier agreed to do so. If you decide to stop participation, please let us  
27 know. The data collected up to that moment will be used for the research study. The  
28 researcher will inform you if there is new information about the study that might be important  
29 for you. In that case, you will be asked if you still consent to participate in the study.  
30  
31  
32

### *How will my personal data be handled?*

33  
34 By participating in this study, you will provide us personal data. This data will be collected  
35 for the research study. A research code will be assigned to all research documents. This means  
36 that your name and other personal data are not visible on research documents. Only the  
37 researchers know which research code belongs to you. Some institutes (the Safety Committee  
38 and the Health Care Inspectorate) are allowed to look into your clinical and personal data.  
39 These institutes are allowed to do this to control whether the research study is conducted in a  
40 proper and reliable manner. They will treat your data confidentially. If you sign the informed  
41 consent form, you will provide consent for collection, storage and inspection of your medical  
42 and personal data. Your data will be stored for 15 years.  
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45  
46

### *Do you have any further questions regarding this research study?*

47  
48 If you have any questions about this research study or about study participation, please  
49 contact the executing researcher Lieke van den Heuvel by telephone (<telephone number>) or  
50 e-mail (<e-mail address>). If you prefer to discuss study participation with an independent  
51 clinician, or if you would like additional information, advice or support, please contact the  
52 independent expert (see attachment).  
53  
54  
55

### *What if I want to participate?*

56  
57 The researcher, Lieke van den Heuvel, will contact you by telephone to provide further  
58 information about the research study. If you decide to participate in this study after this  
59 telephone contact, a consent form will be sent to you by mail. You can return this consent  
60

## Supplementary Material S1

form using the attached return envelope. A postage stamp is not necessary. Subsequently, you will receive the questionnaire online or by mail.

Thank you for your time!

Sincerely,

Lieke van den Heuvel, MSc

Also on behalf of the research team and all the clinical geneticists and genetic counsellors involved from Amsterdam UMC, University Medical Centre Utrecht and University Medical Centre Groningen

**Attachment:** Information about your hospital 'UMCG/Amsterdam UMC/UMCU'

### **Questions, suggestions or complaints**

If you have any questions, suggestions or a complaint about this research study, please contact Lieke van den Heuvel. She will conduct this research study. She can be contacted by telephone (<telephone number>) or by e-mail (<e-mail address>).

### **Independent advice or support**

If you prefer to discuss study participation with someone who is not involved in this research study, because you need further information or advice, you may contact <independent researcher> (<e-mail address>). He/she is a clinical geneticist at the department of Clinical Genetics at UMCG/Amsterdam UMC/UMCU.

## Supplementary Material S1

**Certificate of consent****For participation in a research study regarding informing relatives at risk of an inherited cardiac disease**

- I am satisfied about the information I received about this research study. I have had sufficient time to consider participation in this study. I have had the opportunity to ask questions about it, and any questions that I have asked have been answered to my satisfaction.
- I can stop study participation at any time, without providing any reason and without any consequences.

**By signing this form, I provide consent for:**

6. Informing my clinician (clinical geneticist/genetic counselor) about my participation in this research study.
7. Collection of data using questionnaire(s), and inspection of my medical record until 12 months after signing this consent form and the use of these data for the research study described in this letter.
8. Being approached for other research projects in the future.
9. Storage of research data for 15 years after the research study has been finished
10. Inspection of the research data by the Safety Committee and the Dutch Health Care Inspectorate

**I want to participate in this research study**

Name of participant: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of participant: \_\_\_\_\_

I would like to be informed about the group results of this research study:

- Yes
- No

-----

**Statement by the researcher:** I have accurately informed this person about the aforementioned research project. The person may stop participating at any time during the study without any consequences. Any questions from the person about study participation were answered sufficiently

Name of researcher: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of researcher: \_\_\_\_\_

## Supplementary Material S2

**Supplementary material S2:** Overview of questionnaire items to assess secondary outcomes per time-point

**Table 1** Questionnaire items probands per time-point

Questionnaire time-point	Items	Questionnaires
T1	Sociodemographic, clinical, family and personality factors	Self-constructed items Trait scale of STAI Shortened version of TMSI
	Advices for relatives at risk, eligible relatives at risk, the number of informed relatives at risk, risk perception and experiences with informing relatives at risk	Eleven self-constructed items
	Evaluation of used approach (incl. website)	Thirteen self-constructed items
	Perceived impact on family communication with relatives at risk	Adapted version of ODCF One self-constructed item
	Impact on psychological functioning of proband	HADS  Adapted version of CWS
T2	Number of informed relatives at risk, risk perception and experiences with informing relatives at risk	Three self-constructed items
	Evaluation of approach used	One self-constructed item
	Perceived impact on family communication with relatives at risk	Adapted version of ODCF One self-constructed item
	Impact on psychological functioning of proband	HADS Adapted version of CWS

**Table 2** Questionnaire items relatives

Questionnaire time-point	Items	Questionnaires
T1	Sociodemographic, family and personality factors	Eight self-constructed items Trait scale of STAI Shortened version of TMSI
	Evaluation of used approach (incl. website), risk perception	Thirteen self-constructed items
	Perceived impact on family communication with index patient	Adapted version of ODCF One self-constructed item
	Impact on psychological functioning of family member	HADS Adapted version of CWS

**Table 3** Self-constructed items (telephone interview) - Experiences with informing relatives at risk (probands)

1. Did the genetic counsellor give you an advice for your relatives?	Yes/No
2. What was this advice? (open question)	
3. For which relatives was this advice meant? (open question)	

## Supplementary Material S2

4. Have relatives at risk been informed about the advice of the genetic counsellor? If yes, which relatives have been informed? 5. Who informed your relatives?	Yes/No
--	--------

**Table 4** Self-constructed items (telephone interview) - Risk perception (probands)

1. How do you consider the risk of your relatives on being a carrier of the familial variant?	0% - 100% 1-10
2. How do you estimate the risk of your relatives on developing symptoms of the ICC?	0% - 100% 1-10

**Table 5** Self-constructed items - Evaluation of the used approach (probands)

<i>T1</i>	<p><i>Closed questions</i></p> <p><i>Below you can see statements regarding your experiences with how your relatives have been informed. Please rate each statement on a scale of 1-5 (1 totally disagree to 5 totally agree) how much each statement applies to you.</i></p> <p>1. I feel supported by the genetic counsellor in informing my relatives</p> <p>2. I think the used approach to inform relatives at risk is acceptable</p> <p>3. I felt a little coerced to inform my relatives</p> <p>4. The way my relatives are informed, can be improved</p> <p>5. I am satisfied with the way my relatives are informed</p> <p>Other: _____</p>	<p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p>
<i>T2</i>	<p>1. Did your opinion regarding the used approach change?</p> <p>a. Yes, my opinion regarding the used approach became more positive</p> <p>b. Yes, my opinion regarding the used approach became more negative</p> <p>c. No, my opinion regarding the used approach is still positive</p> <p>d. No, my opinion regarding the used approach is still negative</p> <p>e. No, my opinion regarding the used approach is still neutral</p>	
<i>T1/T2</i>	<p>1. Do you think another approach to inform relatives at risk would have been better?</p> <p>2. Are there relatives for which you would have preferred another approach to inform them?</p>	<p>Yes/No</p> <p>Yes/No</p>
<i>T1/T2</i>	<p><i>Open questions</i></p> <p>1. What are advantages of the approach used to inform your relatives?</p> <p>2. What are disadvantages of the approach used to inform your relatives?</p>	

**Table 6** Self-constructed items - Impact on family relationships (probands)

1. Are there relatives with whom your relationship has changed after they are informed about their risk on the inherited cardiac disease?
---

Supplementary Material S2

- a. Yes, our relationship improved
- b. Yes, our relationship worsened
- c. No, our relationship is still not good/not bad
- d. No, our relationship is still good
- e. No, our relationship is still bad

**Table 7** Self-constructed items - Evaluation of the used approach (relatives)

<i>Closed questions</i>	
<i>Below you can see statements regarding your experiences with how you have been informed about the inherited cardiac disease in your family. Please rate each statement on a scale of 1-5 (1 totally disagree to 5 totally agree) how much each statement applies to you.</i>	
1. I appreciated to be informed about my risk on the inherited cardiac disease	1 2 3 4 5
2. I am satisfied with the way I have been informed	1 2 3 4 5
3. I preferred to have received more information before I contacted the clinical genetic centre	1 2 3 4 5
4. I understand why I have been informed	1 2 3 4 5
5. The way I have been informed, can be improved	1 2 3 4 5
6. I felt free to decide myself whether I wanted to contact the clinic genetic centre	1 2 3 4 5
7. I would have preferred not to be informed about my risk on the inherited cardiac disease in my family	1 2 3 4 5
8. I would have preferred to not know about the inherited cardiac disease in my family	1 2 3 4 5
Other: _____	
-----	
1. Do you think another approach to be informed would have been better?	Yes/No
-----	
<i>Open questions</i>	
1. What are advantages of the way you have been informed?	
2. What are disadvantages of the way you have been informed?	

**Table 8** Self-constructed items - Impact on family relationships (relatives)

1. Did your relationship with your relative change after they were informed about their risk on the inherited cardiac disease?
<ul style="list-style-type: none"> <li>a. Yes, our relationship improved</li> <li>b. Yes, our relationship worsened</li> <li>c. No, our relationship is still not good/not bad</li> <li>d. No, our relationship is still good</li> <li>e. No, our relationship is still bad</li> </ul>





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page no
<b>Administrative information</b>			
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	6-17
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	-
	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	-
	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)	-
<b>Introduction</b>			
Background and rationale	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	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6

1				
2	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, noninferiority, exploratory)	6
3				
4				
5				
6				
7	<b>Methods: Participants, interventions, and outcomes</b>			
8				
9	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	6
10				
11				
12				
13	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)	7
14				
15				
16				
17	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9, 10
18				
19				
20		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)	17
21				
22				
23				
24		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
25				
26				
27				
28				
29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
30				
31				
32	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	11-14
33				
34				
35				
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38				
39	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)	8, 11, 17
40				
41				
42				
43				
44	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	15, 16
45				
46				
47				
48	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
49				
50				

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	9
3	generation		generated random numbers), and list of any factors for stratification.	
4			To reduce predictability of a random sequence, details of any	
5			planned restriction (eg, blocking) should be provided in a separate	
6			document that is unavailable to those who enrol participants or	
7			assign interventions	
8				
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	9
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
11	mechanism		describing any steps to conceal the sequence until interventions are	
12			assigned	
13				
14	Implementation	16c	Who will generate the allocation sequence, who will enrol	9
15			participants, and who will assign participants to interventions	
16				
17	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial	9
18			participants, care providers, outcome assessors, data analysts),	
19			and how	
20				
21				
22		17b	If blinded, circumstances under which unblinding is permissible, and	9
23			procedure for revealing a participant's allocated intervention during	
24			the trial	
25				
26	<b>Methods: Data collection, management, and analysis</b>			
27				
28	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	11-15
29	methods		other trial data, including any related processes to promote data	
30			quality (eg, duplicate measurements, training of assessors) and a	
31			description of study instruments (eg, questionnaires, laboratory	
32			tests) along with their reliability and validity, if known. Reference to	
33			where data collection forms can be found, if not in the protocol	
34				
35		18b	Plans to promote participant retention and complete follow-up,	-
36			including list of any outcome data to be collected for participants	
37			who discontinue or deviate from intervention protocols	
38				
39				
40	Data management	19	Plans for data entry, coding, security, and storage, including any	17
41			related processes to promote data quality (eg, double data entry;	
42			range checks for data values). Reference to where details of data	
43			management procedures can be found, if not in the protocol	
44				
45	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes.	16, 17
46			Reference to where other details of the statistical analysis plan can	
47			be found, if not in the protocol	
48				
49		20b	Methods for any additional analyses (eg, subgroup and adjusted	16, 17
50			analyses)	
51				
52		20c	Definition of analysis population relating to protocol non-adherence	16, 17
53			(eg, as randomised analysis), and any statistical methods to handle	
54			missing data (eg, multiple imputation)	
55				
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**Methods: Monitoring**

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
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	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

**Ethics and dissemination**

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
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)	-
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
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

1				
2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	17
3	policy		participants, healthcare professionals, the public, and other relevant	
4			groups (eg, via publication, reporting in results databases, or other	
5			data sharing arrangements), including any publication restrictions	
6				
7		31b	Authorship eligibility guidelines and any intended use of	18
8			professional writers	
9				
10		31c	Plans, if any, for granting public access to the full protocol,	-
11			participant-level dataset, and statistical code	
12				
13	<b>Appendices</b>			
14				
15	Informed consent	32	Model consent form and other related documentation given to	-
16	materials		participants and authorised surrogates	
17				
18	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
19	specimens		specimens for genetic or molecular analysis in the current trial and	
20			for future use in ancillary studies, if applicable	
21				

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## A tailored approach towards informing relatives at risk of inherited cardiac conditions: study protocol for a randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025660.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Feb-2019
Complete List of Authors:	van den Heuvel, Lieke; Amsterdam University Medical Centres, Department of Clinical Genetics Hoedemaekers, Yvonne; University Medical Centre Groningen, Department of Clinical Genetics Baas, Annette; University Medical Center Utrecht, Department of Genetics van Tintelen, J; Amsterdam University Medical Centres, Department of Clinical Genetics Smets, Ellen; Amsterdam University Medical Centres, Department of Medical Psychology Christiaans, Imke; Amsterdam University Medical Centres, Clinical Genetics
<b>Primary Subject Heading</b>:	Genetics and genomics
Secondary Subject Heading:	Communication, Ethics, Genetics and genomics, Cardiovascular medicine, Health policy
Keywords:	Inherited cardiac conditions, Cardiogenetics, Informing relatives at risk, Family-mediated approach, Tailored approach, Randomized controlled trial

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Manuscripts

1  
2  
3 **1 A tailored approach towards informing relatives at risk of inherited cardiac conditions:**  
4  
5 **2 study protocol for a randomised controlled trial**  
6  
7

8 3  
9  
10 4 L.M. van den Heuvel<sup>1</sup>, Y.M. Hoedemaekers<sup>2</sup>, A.F. Baas<sup>3</sup>, J.P. van Tintelen<sup>1</sup>, E.M.A. Smets<sup>4</sup>&  
11  
12 5 I. Christiaans<sup>1\*</sup>  
13  
14

15 6 <sup>1</sup>Department of Clinical Genetics, Amsterdam University Medical Centres / University of  
16  
17 Amsterdam, Amsterdam, the Netherlands  
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19  
20 8 <sup>2</sup>Department of Genetics, University of Groningen, University Medical Centre Groningen,  
21  
22 Groningen, the Netherlands  
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24  
25 10 <sup>3</sup>Department of Genetics, University Medical Centre Utrecht / University Utrecht, Utrecht, the  
26  
27 Netherlands  
28

29  
30 12 <sup>4</sup>Department of Medical Psychology, Amsterdam University Medical Centres / University of  
31  
32 Amsterdam, Amsterdam, the Netherlands  
33

34 14  
35  
36 15 \* Corresponding author  
37

38 16 Department of Clinical Genetics,  
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40  
41 17 Amsterdam University Medical Centre, location AMC  
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43  
44 18 Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands  
45

46  
47 19 Telephone: +31 20-5667217  
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49  
50  
51 20 E-mail: i.christiaans@amc.nl  
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## Abstract

**Introduction** In current practice, probands are asked to inform relatives about the possibility of predictive DNA testing when a pathogenic variant causing an inherited cardiac condition (ICC) is identified. Previous research on the uptake of genetic counselling and predictive DNA testing in relatives suggests that not all relatives are sufficiently informed. We developed a randomised controlled trial to evaluate the effectiveness of a tailored approach in which probands decide together with the genetic counsellor which relatives they inform themselves and which relatives they prefer to have informed by the genetic counsellor. Here, we present the study protocol of this randomised controlled trial. **Methods** A multicentre randomised controlled trial with parallel-group design will be conducted in which an intervention group receiving the tailored approach will be compared to a control group receiving usual care. Adult probands diagnosed with an ICC in whom a likely pathogenic or pathogenic variant is identified, will be randomly assigned to the intervention or control group (total sample: n = 85 probands). Primary outcomes are uptake of genetic counselling and predictive DNA testing by relatives (total sample: n = 340 relatives). Secondary outcomes are appreciation of the approach used and impact on familial and psychological functioning, which will be assessed using questionnaires. Relatives who attend genetic counselling will be asked to fill out a questionnaire as well. **Ethics and dissemination** Ethical approval was obtained from the Medical Ethical Committee of the Amsterdam University Medical Centres (MEC 2017-145), the Netherlands. All participants will provide informed consent prior to participation in the study. Results of the study on primary and secondary outcome measures will be published in peer-reviewed journals. **Registration details** This trial is registered at the Netherlands Trial Register NTR6657.

**Key words** Inherited cardiac conditions, cardiogenetics, informing relatives at risk, family-mediated approach, tailored approach, randomised controlled trial



### Strengths and limitations of this study

- This randomised controlled trial investigates both the uptake of genetic counselling and of predictive DNA testing, as well as the acceptance and impact on psychological and family functioning in the tailored versus the standard approach, in probands and relatives.
- This study will be conducted in three clinical genetics clinics with expertise on cardiogenetics, which will facilitate participant inclusion.
- In this trial, evaluation of the effect on outcome of the different components of the intervention is not possible, due to limited power.
- In this randomised controlled trial it is not possible to blind participants, genetic counsellors or the executing investigator for the chosen intervention.
- Because a baseline measure for the secondary outcomes is not possible, we cannot control for likely confounding factors, such as intention to inform at-risk relatives, and family and psychological functioning at baseline.

## Introduction

Inherited cardiac conditions (ICCs) such as cardiomyopathies and primary arrhythmia syndromes generally demonstrate an autosomal dominant inheritance pattern and a wide variety of symptoms that can manifest at any age [1, 2]. One feared outcome is sudden cardiac death (SCD), which can occur at a young age and be the first symptom of disease [3, 4]. With an incomplete penetrance and high variability in expression even within families, carriers of a familial variant may remain undetected but still be at risk for SCD even though treatment options are available that prevent disease progression or potentially life-threatening arrhythmias [5]. Predictive DNA testing is therefore offered to first-degree relatives of probands (the first person in a family diagnosed with an ICC) in whom a pathogenic variant is identified because these relatives are at 50% risk of also having inherited the genetic variant [5, 6]. Predictive DNA testing is offered to relatives in a stepwise manner (cascade screening), with the aim of identifying asymptomatic carriers of the familial variant to facilitate timely treatment. Non-carriers of the familial variant generally do not need cardiac monitoring and can be reassured about their own risk and that of their offspring [6].

In current practice in the Netherlands, probands are asked to inform their relatives, supported by a family letter written by the genetic counsellor. This is referred to as the family-mediated approach [7]. Previous research, however, shows that uptake (the number of relatives at risk attending genetic counselling and/or undergoing predictive DNA testing) is relatively low in ICCs, particularly for cardiomyopathies. Reported uptakes are around 50% despite family letters being provided to a majority of relatives by the proband [8-10]. Previous research in other genetic patient populations, such as hereditary types of cancer, shows similar uptake percentages [11-13].

Some relatives who do not attend genetic counselling will have deliberately decided against predictive DNA testing. However, the low uptake percentages also suggest that many

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2  
3 1 relatives may be unaware, or insufficiently aware, of the risks involved and/or the possibilities  
4  
5 2 for genetic counselling and subsequent surveillance and treatment. This is supported by  
6  
7 3 research on family communication in ICCs. Patients are not always able to inform or correctly  
8  
9 4 inform their relatives for a number of reasons, including disengagement with relatives, lack of  
10  
11 5 understanding of the importance of the information, preoccupation with their own grief,  
12  
13 6 difficulties in conveying the complex information to relatives, or a wish to prevent burdening  
14  
15 7 relatives by informing them about genetic risks [8, 14-18].  
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19 8 Previous studies assessing interventions to enhance family communication in  
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21 9 hereditary diseases showed that some interventions are effective in increasing the uptake of  
22  
23 10 genetic counselling [19-21]. An intervention trial aimed at improving family communication  
24  
25 11 in specifically dilated cardiomyopathy is still ongoing [22]. A few studies have been  
26  
27 12 published on more active approaches to informing relatives at risk in which healthcare  
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29 13 professionals (HCPs) contact at-risk relatives directly [23-26]. These studies suggest that a  
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31 14 more active approach can almost double the uptake of genetic counselling and predictive  
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33 15 DNA testing by relatives (23-26) However, some of these studies were performed in a  
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35 16 research setting (e.g. in relatives already registered in research databases for the genetic  
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37 17 disease), hampering direct translation of these results to a diagnostic setting. To our  
38  
39 18 knowledge, more active approaches in patients with ICCs have not been studied thus far.  
40  
41 19 However, a study by Ormondroyd et al [14] suggests that relatives eligible for predictive  
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43 20 DNA testing for hypertrophic cardiomyopathy and long QT syndrome would support a more  
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45 21 active approach to informing relatives at risk.  
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51 22 Although studies on more active approaches did not report any psychological harm in  
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53 23 relatives at group level, these approaches could cause more unwarranted worry or pressure on  
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55 24 relatives to opt for predictive DNA testing [23-25]. An active approach to informing relatives  
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57 25 at risk could also breach the autonomy and confidentiality of probands, and may harm  
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3 1 relative's right not to know [27-29]. Furthermore, HCPs are often unaware of interpersonal  
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5 2 dynamics within families and the personal circumstances of relatives at risk. Active  
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7 3 approaches may therefore have a negative impact on family relationships or may cause  
8  
9 4 psychological distress in both probands and relatives [30].  
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12 5 Because of this, a tailored approach in which a proband decides together with the  
13  
14 6 genetic counsellor which at-risk relatives he or she will inform and which relatives he or she  
15  
16 7 prefers to be informed by the genetic counsellor could be optimal. With this approach, the  
17  
18 8 probands expert knowledge of a relative's functioning and of family dynamics could be used  
19  
20 9 appropriately, and the autonomy of the proband preserved. At the same time, more relatives at  
21  
22 10 risk would be sufficiently informed [28, 30]. Furthermore, probands for whom informing  
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24 11 relatives is difficult or burdensome might be relieved or supported by this approach [30].  
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### 31 *Objectives*

32  
33 14 The primary aim of this randomised controlled trial is to assess whether uptake of genetic  
34  
35 15 counselling and testing of relatives at risk of an ICC will be increased by using a tailored  
36  
37 16 approach to information provision for relatives, instead of usual care (i.e. the family-mediated  
38  
39 17 approach). Secondary objectives are to evaluate how such a tailored approach is appreciated  
40  
41 18 by both probands and relatives as compared to usual care. In addition, this study aims to  
42  
43 19 assess the perceived impact on family relationships and psychological functioning of both  
44  
45 20 probands and relatives. The protocol presented here has been described based on the SPIRIT  
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47 21 statement [31]  
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## 51 **Methods**

### 52 **Design**

53  
54 23 A multicentre randomised controlled trial with a parallel-group design will be conducted in  
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56 24 three university hospitals in the Netherlands (the Amsterdam University Medical Centres  
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3 1 (Amsterdam UMC), the University Medical Centre Utrecht (UMCU) and the University  
4  
5 2 Medical Centre Groningen (UMCG)) to compare the effects of a tailored approach to  
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7 3 informing relatives at risk of ICCs to usual care in both probands and relatives.  
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## 11 5 **Participants**

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14 6 All probands aged 18 years or older with an ICC, or suspicion thereof, attending pre-test  
15  
16 7 genetic counselling at the cardiogenetics outpatient clinics during the inclusion period will be  
17  
18 8 asked to participate if they: (1) are the first member of their family to visit the cardiogenetics  
19  
20 9 outpatient clinic for counselling about genetic testing for ICCs; (2) they have at least one  
21  
22 10 living adult relative; and (3) are able to read and write Dutch. Only probands in whom a likely  
23  
24 11 pathogenic or pathogenic variant is detected (class 4 - likely pathogenic or class 5 -  
25  
26 12 pathogenic variant) will be definitively included.  
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30  
31 13 In addition, eligible adult first- (or second-) degree relatives of enrolled probands who  
32  
33 14 make an appointment at the cardiogenetics outpatient clinics will be invited to fill out a  
34  
35 15 questionnaire to measure secondary outcomes. Inclusion criteria are defined as follows: (1)  
36  
37 16 first-degree adult (18 years or older) relatives of probands enrolled in the study or second-  
38  
39 17 degree adult relatives in case of a deceased connecting first-degree relative who was affected  
40  
41 18 or suspected to be affected, and (2) able to read and write Dutch.  
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## 47 20 **Procedure**

48  
49 21 Figure 1 shows a flowchart of the study procedure.

### 50 51 22 *Recruitment & consent*

52  
53 23 During pre-test genetic counselling, the genetic counsellor will inform the probands about the  
54  
55 24 study and provide an informational letter (see Supplementary Material S1). In addition,  
56  
57 25 probands will be asked if the executing researcher can contact them to provide further  
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1  
2  
3 1 information about the study. Subsequently, probands will be contacted by telephone by the  
4  
5 2 executing researcher. If probands are still interested in participation, written informed consent  
6  
7 3 forms will be sent by post, including a return envelope. As described above, only probands in  
8  
9 4 whom a likely pathogenic or pathogenic variant is detected will be definitively included in the  
10  
11 5 study.  
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14 6 Relatives of enrolled probands attending pre-test genetic counselling in one of the  
15  
16 7 participating centres who are also at risk will also be invited to participate in the study. The  
17  
18 8 same recruitment procedure will be used.  
19  
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21 9

### 22 23 24 10 *Randomisation*

25  
26 11 Prior to receiving their test result, probands with an ICC in whom a likely pathogenic or  
27  
28 12 pathogenic variant is identified will be randomly assigned to either the intervention or control  
29  
30 13 group. Block randomisation will be used, with variable blocks ranging from size two to six.  
31  
32 14 Randomisation will be stratified for gender, disease type (cardiomyopathies or primary  
33  
34 15 arrhythmia syndromes) and hospital. To ensure allocation concealment, computer software  
35  
36 16 will be used for randomisation, with an allocation rate of 1:1 [32]. Relatives of probands  
37  
38 17 included in the study will be assigned to the group to which the proband was assigned.  
39  
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42 18 Neither participants nor genetic counsellors will or can be blinded for group  
43  
44 19 assignment. The executing researcher also cannot be blinded because of slight differences  
45  
46 20 between the questionnaires administered in the intervention- and control groups. Part of the  
47  
48 21 outcome data will be collected using telephone interviews. To minimize bias, these interviews  
49  
50 22 will be conducted by a research assistant following a structured script.  
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### 55 56 24 Intervention group

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3 1 In the intervention group, a tailored approach to informing relatives at risk will be provided.  
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5 2 In this approach, probands with a likely pathogenic or pathogenic variant will discuss with the  
6  
7 3 genetic counsellor which relatives are at risk of inheriting the familial variant. They will then  
8  
9 4 be asked which of these relatives they prefer to inform themselves at first using a family letter  
10  
11 5 written by the genetic counsellor, and which relatives they prefer to be directly informed by  
12  
13 6 the genetic counsellor with a similar family letter. This will be discussed during routine post-  
14  
15 7 test counselling. In both cases, after one month, the genetic counsellor will send the family  
16  
17 8 letter directly to all relatives at risk for whom the proband has provided consent to contact.  
18  
19 9 The proband will be asked to provide contact details of these relatives.  
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23  
24 10 The family letter is standardised for all three participating centres. For the intervention  
25  
26 11 group, the letter also includes a link to a website specifically designed for this study where  
27  
28 12 relatives can find additional information ([www.familieleden.erfelijkehartziekten.nl](http://www.familieleden.erfelijkehartziekten.nl)). The  
29  
30 13 information on this website will be tailored to relative's situations (i.e. specified for disease-  
31  
32 14 type, hospital, parenthood, whether relatives have a desire to have children in the future, and  
33  
34 15 which information relatives prefer to receive) by asking them to fill out a short questionnaire  
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36 16 on their first visit to the website.  
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#### 40 17 41 42 18 Control group

43  
44 19 In the control group, the standard care approach will be used. If a likely pathogenic or  
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46 20 pathogenic variant is identified, probands assigned to the control group will be asked by the  
47  
48 21 genetic counsellor to inform relatives at risk about the genetic test result, the consequences of  
49  
50 22 this result for relatives and the advice regarding predictive DNA testing and/or cardiac  
51  
52 23 monitoring. This will be discussed during routine post-test counselling. Probands will be  
53  
54 24 supported in informing relatives at risk by a family letter written by the genetic counsellor.  
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56 25 This family letter is also standardised for all three participating centres. However, this letter  
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3 1 does not include the link to the website with tailored information described above, but does  
4  
5 2 include a link to a general website on ICCs ([www.erfelijkehartziekten.nl](http://www.erfelijkehartziekten.nl)).  
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#### 10 4 *Measurement time-points*

11  
12 5 For secondary outcome measures, participating probands will be asked to complete a  
13  
14 6 questionnaire one month after receiving the genetic test result (T1) and to complete a second  
15  
16 7 questionnaire nine months after the test result (T2). Before T1 and T2, a short structured  
17  
18 8 telephone interview will be conducted about participant's knowledge of which relatives are at  
19  
20 9 risk of ICCs and which relatives are informed, because these items are expected to be too  
21  
22 10 complex to answer in a questionnaire [33]. Participating relatives will complete one  
23  
24 11 questionnaire after attending genetic counselling.  
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#### 33 13 **Measures**

##### 34 14 *Primary outcome measures*

35 15 To assess the effect of a tailored approach to informing relatives at risk, the difference  
36  
37 16 between the intervention and control groups in uptake of (1) genetic counselling, and (2)  
38  
39 17 predictive DNA testing of relatives at risk will be measured. To do this, the number of  
40  
41 18 relatives attending genetic counselling and the number of relatives who are genetically tested  
42  
43 19 in the first year after detection of the likely pathogenic or pathogenic variant in the proband  
44  
45 20 will be collected in the laboratories of each participating centre. DNA test results of relatives  
46  
47 21 counselled in non-participating centres will also be taken into account because, in the  
48  
49 22 Netherlands, predictive DNA testing of relatives is always performed in the same laboratory  
50  
51 23 where the proband was tested.  
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56 24 The number of relatives attending genetic counselling and undergoing predictive DNA  
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58 25 testing will be compared to the total number of relatives at risk of inheriting the variant who  
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3 1 are eligible for genetic counselling and predictive DNA testing based on family pedigrees. For  
4  
5 2 relatives who attend genetic counselling but decide against predictive DNA testing,  
6  
7 3 subsequent attendance of cardiac monitoring will be checked.  
8  
9

10 4 Relatives at risk who are eligible for genetic counselling and predictive DNA testing  
11  
12 5 are first-degree relatives and second-degree relatives if there is a connecting deceased first-  
13  
14 6 degree relative suspected of having an ICC. Following the Dutch clinical guidelines for  
15  
16 7 cardiomyopathies, relatives at risk are eligible for genetic counselling and predictive DNA  
17  
18 8 testing from the age of 10 years. For primary arrhythmias, depending on the specific  
19  
20 9 arrhythmic disorder, relatives at risk are eligible for predictive DNA testing from birth.  
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23  
24 10 Furthermore, conditional uptake of relatives at risk, defined as the number of relatives  
25  
26 11 who are genetically tested relative to the number who attend genetic counselling, will be  
27  
28 12 calculated. Uptake will be measured at randomisation condition (intervention or control  
29  
30 13 group) and family level.  
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### 33 14

#### 35 15 *Secondary outcome measures*

36  
37 16 Secondary outcome measures will be measured using both validated and self-constructed  
38  
39 17 questionnaire items. An overview of these items is shown in the Supplementary Material S2.

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41  
42 18 Secondary outcome measures include the following:

- 43  
44 19 - Appreciation of the information provision strategy used and preferences regarding the  
45  
46 20 approach used to inform relatives at risk: This will be evaluated in both probands and  
47  
48 21 relatives using self-constructed items on a 5 point Likert scale (1 = 'Totally disagree' to 5  
49  
50 22 = 'Totally agree') in a questionnaire (probands: 5 items, range 5-25; relatives: 6 items,  
51  
52 23 range 6-30). Probands will be asked to answer an additional self-constructed item during  
53  
54 24 the structured telephone interview about whether they would have preferred to inform  
55  
56 25 their relatives differently. Two additional self-constructed items will be administered in  
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3 1 the intervention group to assess decisional conflict in probands, including whether  
4  
5 2 probands thought it was difficult to choose to inform their relatives themselves or have  
6  
7 3 them informed by the counsellor, and whether they were satisfied by their decision, on a 5  
8  
9 4 point Likert scale (1 = 'Totally disagree' to 5 = 'Totally agree'; range 2-10). Probands will  
10  
11 5 be asked to fill out these items at T1. At T2, a self-constructed item will be administered  
12  
13 6 to assess whether their opinion regarding the approach used has changed. The  
14  
15 7 questionnaire for relatives also includes a self-constructed item on how they were  
16  
17 8 informed (i.e., by whom they were informed and what information was provided). Finally,  
18  
19 9 probands (at T1 and T2) and relatives will be asked whether they visited the website  
20  
21 10 www.erfelijkehartziekten.nl and, if yes, how they evaluated the website, using four self-  
22  
23 11 constructed items on a 5 point Likert scale (1 = 'Totally disagree' to 5 = 'Totally agree';  
24  
25 12 range 4-20).

26  
27 13 - Impact on family communication: To assess the impact of the tailored approach versus the  
28  
29 14 usual care approach on family functioning, probands (at T1 and T2) and relatives will be  
30  
31 15 asked to fill out an adapted version of the Openness to Discuss Cancer in the Family  
32  
33 16 (ODCF) scale, which assesses communication about genetic risks within families with  
34  
35 17 nine items on a 5 point Likert scale (1 = 'Totally disagree' to 5 = 'Totally agree'; range 9-  
36  
37 18 45) [34]. Psychometric characteristics of the original ODCF scale are satisfactory [34]. In  
38  
39 19 addition, a self-constructed item will be administered asking about the nature of regular  
40  
41 20 communication with relatives and whether probands and relatives experienced changes in  
42  
43 21 their relationships with relatives as a consequence of the information provision process.

44  
45 22 - Impact on psychological functioning: To assess the impact on psychological functioning,  
46  
47 23 two validated questionnaires will be administered in probands (at T1 and T2) and  
48  
49 24 relatives. Participants will be asked to fill out an adapted version of the Cancer Worry  
50  
51 25 Scale (CWS) [35]. The CWS was developed and validated in Dutch patients with

1 hereditary types of cancer [35]. Because it was validated in a Dutch patient population and  
2 is previously used in a genetic patient population, it was considered the most appropriate  
3 scale for this randomised controlled trial. The CWS consists of eight items on a 4 point  
4 Likert scale (1 = ‘Almost never’ to 4 = ‘Almost always’; range 8-32). Psychometric  
5 characteristics of the CWS have been assessed in a sample of breast cancer survivors, and  
6 support its reliability and validity [35].

7 In addition, the Hospital Anxiety and Depression Scale (HADS) will be  
8 administered to assess whether participants experience anxious or depressed feelings after  
9 being informed about the hereditary disease [36]. The HADS contains two 7-item  
10 subscales on a 4 point Likert scale with diverse answer options that assess both anxiety  
11 and depression with a score range of 0-21. Psychometric characteristics of the HADS were  
12 assessed as good [36].

#### 13 *Participants’ characteristics*

14 To assess whether randomisation succeeded and whether characteristics of participating  
15 probands and relatives have influenced the primary and secondary outcome measures,  
16 sociodemographic and clinical factors will be collected, including gender, education level,  
17 ethnicity, living situation and parenthood, family history and the diagnosis of the probands at  
18 T1. Relatives will additionally be asked what their degree of kinship is with the proband.

19 For the same reason, psychosocial and personality factors will be assessed in both  
20 probands (at T1) and relatives. Coping style will be assessed by using the shortened version of  
21 the Threatening Medical Situations Inventory (TMSI) [37, 38]. The TMSI assesses a  
22 “monitoring” versus “blunting” coping style related to a medical threat, and it was previously  
23 evaluated in an oncogenetic patient population [37, 39]. The shortened version of the TMSI  
24 contains two subscales, both consisting of six items on a 5 point Likert scale (1 = ‘Totally not  
25

1 applicable' to 5 = 'Totally applicable'; range 6-30). Reliability and validity are satisfactory  
2 [37, 38]. The Trait subscale of the State Trait Anxiety Inventory (STAI) will be administered  
3 to assess trait anxiety in both probands and relatives [40]. The STAI is frequently used in  
4 research settings and consists of 20 items on a 4 point Likert scale (1 = 'Not at all' to 4 =  
5 'Very much so'; range 20-80) [40]. The reliability and validity for the Dutch translation of the  
6 STAI are assessed as good [41].

7 Self-efficacy and perceived motivators and barriers regarding informing relatives at  
8 risk will be assessed using an adapted version of the 'motivation' and 'self-efficacy' subscales  
9 of the Informing Relatives Inventory (IRI) [42]. The IRI was developed and evaluated in an  
10 oncogenetic patient population, and showed satisfactory reliability and validity [42]. The  
11 'motivation' subscale consists of 30 items on a 5 point Likert scale (1 = 'No role' to 5 = 'A  
12 large role'; range 30-150); the 'self-efficacy' subscale of 7 items on a 4 point Likert scale (1 =  
13 'Not sure at all' to 4 = 'Very sure'; range 7-21). Probands will also be asked to answer a self-  
14 constructed item during the telephone interviews regarding whether relatives were informed  
15 and whether probands intended to inform (remaining) at-risk relatives.

16 Risk perception regarding the risk of relatives carrying the variant and developing the  
17 disease will be assessed by using self-constructed items. These items ask participants to rate  
18 the perception of the risk of relatives carrying the variant and developing the disease on a  
19 scale from 1 (lowest risk) to 10 (highest risk) as well as from 0% (lowest risk) to 100%  
20 (highest risk).

21 Health literacy – defined as the ability to obtain, process and understand basic health  
22 information and services – will be assessed in probands and relatives using the items on the  
23 'functional health literacy' and 'communicative health literacy' subscales of the 3HL  
24 questionnaire [43]. Both subscales contain five items on a 4 point Likert scale (1 = 'Never' to

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2  
3 1 4 = 'Often'; range per subscale 5-20). The reliability for both scales was assessed as high and  
4  
5 2 the validity as satisfactory [43].  
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#### 4 **Sample size calculation**

5 The study aims to detect a difference of 15% in uptake of genetic counselling by relatives  
6 between the control (usual care, 50%) and intervention groups (tailored approach, 65%).  
7 Assuming a two-sided 5% significance level and a power of 80%, 340 relatives (170 in each  
8 group) would be required to participate in this study. On average, six relatives per proband are  
9 at 50% risk of inheriting the variant, including children and adults [9]. With a conservative  
10 estimate of four eligible adult relatives per proband at risk, 85 probands with an ICC and an  
11 identified likely pathogenic or pathogenic (class 4 or 5) variant will need to be included in this  
12 study to reach 340 relatives. A likely pathogenic or pathogenic variant is found in, on average,  
13 20% (lower margin) of all probands with a suspected ICC. With an expected response rate of  
14 70% and a drop-out rate of 20%, approximately 759 probands will be approached to  
15 participate in the study.  
16

#### 17 **Data analysis**

##### 18 *Statistical analysis*

19 Sociodemographic, clinical, psychosocial and personality variables will be analysed using  
20 descriptive and frequency statistics. An intention-to-treat approach will be used. SPSS version  
21 24.0 will be used to perform statistical analyses [44]. An  $\alpha$  level of  $p < .05$  will be used.  
22 Analysis of Variance and chi-square tests will be used to assess differences (i) in  
23 sociodemographic, clinical and psychological characteristics between the intervention- and  
24 control group and (ii) in participants and non-participants, as appropriate. Descriptive and  
25 frequency statistics will be used to describe the primary outcomes: (1) uptake of genetic

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3 1 counselling and (2) uptake of predictive DNA testing. Logistic regression analysis will be  
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5 2 conducted to assess differences between the intervention- and control group on the primary  
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7 3 outcomes, with the randomisation group as the main exploratory variable. Two logistic  
8  
9 4 regression models will be used, with the first model including only the randomisation group  
10  
11 5 and the second model also including the potential covariates (i.e., sociodemographic, clinical  
12  
13 6 and psychological variables). Multilevel analyses will be performed to assess whether the  
14  
15 7 randomisation group, i.e., the independent variable, has an impact on family and  
16  
17 8 psychological functioning, i.e., the secondary outcome variables. The two measurement time-  
18  
19 9 points in probands will be treated as nested within probands. To prevent influence of potential  
20  
21 10 confounding factors, multilevel analysis will be adjusted for covariates as well. Participant  
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23 11 appreciation of the approach used will be described using frequency statistics.  
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### 31 *Qualitative analysis*

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33 14 Open questions will be analysed using thematic analysis based on the principles of Braun and  
34  
35 15 Clarke [45]. Analysis software for qualitative data, MAXQDA version 12, will be used [46].  
36  
37 16 Two trained coders will conduct the coding analysis of open answer options independently.  
38  
39 17 Codes will be discussed and modified by the two coders until agreement is met. Subsequently,  
40  
41 18 the coders will analyse and interpret the codes to create a structure of main themes and  
42  
43 19 subthemes. The qualitative results will be used to supplement the questionnaire data.  
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### 49 **Patient and public involvement**

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51 22 Prior to this randomised controlled trial, face-to-face interviews were conducted with  
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53 23 probands and counselled relatives (both carriers and non-carriers) to explore their experiences  
54  
55 24 with and preferences regarding informing at-risk relatives (unpublished). In addition, online  
56  
57 25 focus groups were conducted with HCPs. The randomised controlled trial was then designed  
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1 based on the findings of both these interviews and focus groups. Since this study is part of the  
2 eDETECT research consortium (CVON2015-12), several patient representative groups (the  
3 PLN foundation; Harteraad, Hartz) participated in the user committee and scientific meetings  
4 and thereby gave input to this research proposal. Patients are not involved in the recruitment  
5 and conduct of the study.

6 During patient seminars, patients will be updated on the progress and results of the  
7 study. In addition, during the eDETECT scientific meetings, all participants of the eDETECT  
8 consortium (including representatives of the aforementioned patient organisations) will be  
9 informed. After completion of the study, group results will be disseminated by e-mail to study  
10 participants who indicated their interest in the outcome during informed consent. A summary  
11 of the results will also be posted on the ICCs website ([www.erfelijkehartziekten.nl](http://www.erfelijkehartziekten.nl)).

12 The burden of the intervention was not assessed because this is an intrinsic part of the  
13 outcome measures of this study. The patients themselves were involved in pilot testing the  
14 questionnaires used to assess these outcome measures.

### 15 16 **Ethics and dissemination**

17 The Medical Ethical Committee of the Amsterdam UMC has approved the study design  
18 (MEC 2017-145). Additional approval of regional Medical Ethical Committees of the other  
19 participating academic centres has also been obtained. Informed consent is required from each  
20 participant. Participants who provide written informed consent can withdraw from the study at  
21 any time, without providing a reason.

22 After receiving informed consent, a unique research ID will be assigned to the  
23 participant. Only this ID will be used to identify research documents. Each research document  
24 will be saved on a secured server. The principal investigator, coordinating investigator and

1  
2  
3 1 executing investigator have access to this secured server. Research documents will be saved  
4  
5 2 for a period of 15 years. This randomised controlled trial is registered at the Netherlands Trial  
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7 3 Register NTR6657. Separate manuscripts with findings on, respectively, the primary and  
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9 4 secondary outcomes will be published in peer-reviewed journals.  
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### 6 **Trial status**

7 Recruitment of probands during pre-test genetic counselling for this randomised controlled  
8 trial started in November 2017. In total, recruitment of probands will last one year.  
9 Subsequent uptake of genetic counselling and predictive DNA testing will be measured until  
10 one year after the detection of a pathogenic variant in the proband. Data collection will  
11 therefore continue until January 2020, taking into account a duration of, on average, three  
12 months for the DNA-test result in the proband to be available. To date, 68 probands have been  
13 included and randomised to either the intervention or the control group. In addition, 49  
14 relatives consented to participate.  
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### Authors contributions

LvdH and IC designed the intervention. LvdH, IC, ES and PvT were involved in conception and design of the protocol. LvdH was involved in drafting the manuscript. IC, ES, PvT, YH and AB critically revised the manuscript. All authors were involved in the final approval of the manuscript.

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### Competing interests statement

All authors declare they have no competing interests.

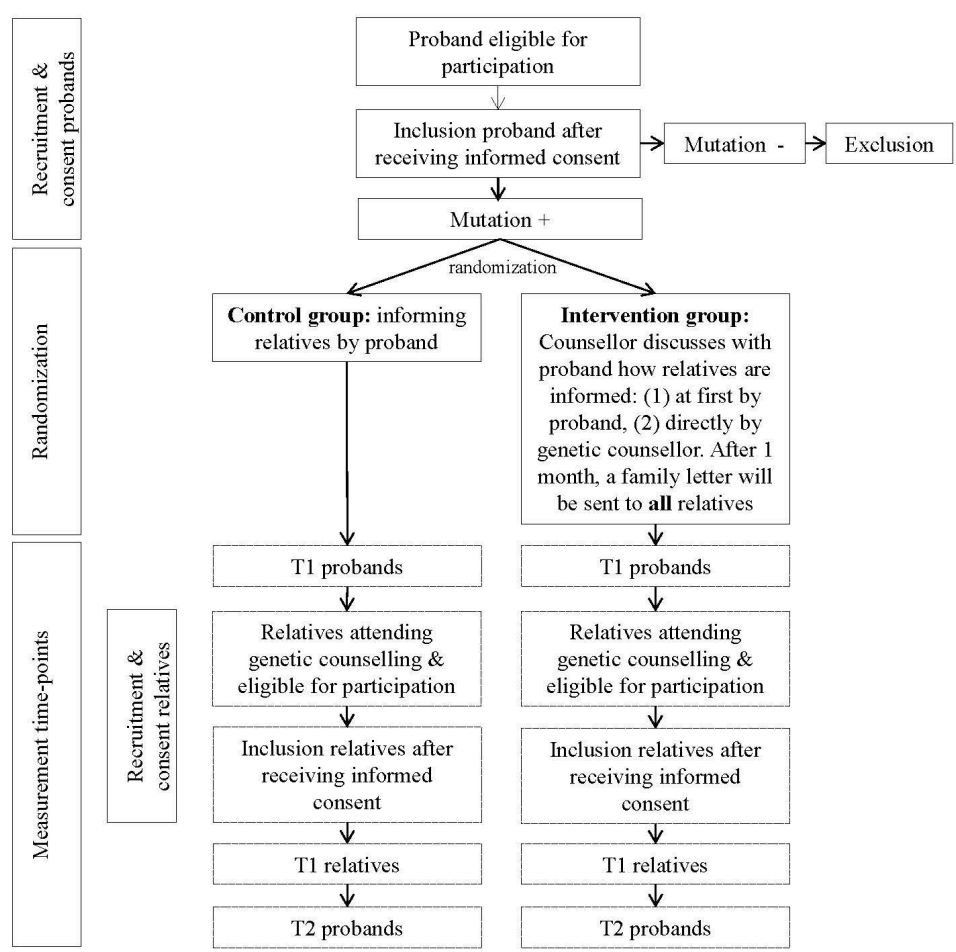
### Acknowledgements

Patient advisors are acknowledged for their input regarding the design of this randomised controlled trial.

### Figures

**Figure 1** Flow-chart of the study procedure

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**Figure 1** Study procedure

126x130mm (300 x 300 DPI)

## Supplementary Material S1

**Supplementary material S1:** Information letter and informed consent form probands and relatives

umcg

Amsterdam UMC  
Universitair Medische Centra

UMC Utrecht

Dear Sir or Madam,

Recently you visited the department of Clinical Genetics for genetic counselling concerning a possible inherited cardiac disease in your family. A clinical geneticist or genetic counsellor informed you about participation in a research study examining how to inform relatives at risk of inheriting the genetic predisposition. In this letter, we would like to inform you about this research study.

*What is the goal of this research study?*

At the current moment, we ask people in whom a genetic cause for a cardiac disease is identified to inform their relatives about the possibility of genetic testing, supported by a letter written by the clinician. This research study aims to investigate whether another approach to informing relatives would be more effective. Using this approach, people who are the first in their family in whom the hereditary predisposition is identified can decide which relatives they prefer to inform themselves and which relatives they prefer to have contacted directly by the clinician. In addition, a website will be used to further inform relatives. This research study will investigate which approach is the most effective.

*Who is conducting the study?*

This research study will be conducted by the department of Clinical Genetics and the department of Medical Psychology of the Amsterdam UMC, in collaboration with the department of Clinical Genetics of the University Medical Centre Groningen (UMCG) and the University Medical Centre Utrecht (UMCU). The study is funded by the Dutch Heart Foundation.

*What does study participation involve?*

If the DNA test shows that no genetic variant causing the disease is identified, no further activity is needed for this study. If the DNA test shows that a genetic variant causing the disease is identified, the clinician will inform you about advice for your relatives. To investigate what the most effective approach is, one group of participants will be asked to inform relatives using the approach that is currently used, while the other group of participants will be asked to inform relatives using the other approach. Which group you are part of will be determined randomly.



## Supplementary Material S1

In addition, we will ask you to fill out two questionnaires. These questionnaires can be administered online or by mail. If you prefer to receive the questionnaire by mail, the questionnaire can be returned using the provided return envelope. These questionnaires ask you for some general information, such as your age and gender, and about your experiences with informing relatives and your opinion regarding the approach that was used. You will receive the first questionnaire two months after you receive the DNA test result. The second questionnaire will be sent to you after nine months.

### *What are advantages and disadvantages of study participation?*

There will be no direct benefit to you for your participation in this study. We hope that the information obtained from this study may contribute to research on improving approaches to informing relatives at risk of inherited cardiac diseases. Participation in this research study will take time: we will ask you to fill out two questionnaires. We expect that this will cost you 20 to 30 minutes per questionnaire. In addition, we will ask questions regarding personal information, such as the disease in your family and your opinion and feelings concerning informing your relatives about this disease. You will not receive an incentive for study participation.

### *What if I do not want to participate anymore?*

Your participation in this research is entirely voluntary. There are no consequences if you decide not to participate. You may also change your mind later and stop participating during the study even if you earlier agreed to do so. If you decide to stop participation, please let us know. The data collected up to that moment will be used for the research study. The researcher will inform you if there is new information about the study that might be important for you. In that case, you will be asked if you still consent to participate in the study.

### *How will my personal data be handled?*

By participating in this study, you will provide us personal data. This data will be collected for the research study. A research code will be assigned to all research documents. This means that your name and other personal data are not visible on research documents. Only the researchers know which research code belongs to you. Some institutes (the Safety Committee and the Health Care Inspectorate) are allowed to look into your clinical and personal data. These institutes are allowed to do this to control whether the research study is conducted in a proper and reliable manner. They will treat your data confidentially. If you sign the informed consent form, you will provide consent for collection, storage and inspection of your medical and personal data. Your data will be stored for 15 years.

### *Do you have any further questions regarding this research study?*

If you have any questions about this research study or about study participation, please contact the executing researcher Lieke van den Heuvel by telephone (<telephone number>) or e-mail (<e-mail address>). If you prefer to discuss study participation with an independent clinician, or if you would like additional information, advice or support, please contact the independent expert (see attachment).

### *What if I want to participate?*

## Supplementary Material S1

The researcher, Lieke van den Heuvel, will contact you by telephone to provide further information about the research study. If you decide to participate in this study after this telephone contact, a consent form will be sent to you by mail. You can return this consent form by using the attached return envelope. A postage stamp is not necessary.

Thank you for your time!

Sincerely,

Lieke van den Heuvel, MSc

Also on behalf of the research team and all the clinical geneticists and genetic counsellors involved from Amsterdam UMC, University Medical Centre Utrecht and University Medical Centre Groningen

**Attachment:** Information about your hospital 'UMCG/Amsterdam UMC/UMCU'

### **Questions, suggestions or complaints**

If you have any questions, suggestions or a complaint about this research study, please contact Lieke van den Heuvel. She will conduct this research study. She can be contacted by telephone (<telephone number>) or by e-mail (<e-mail address>).

### **Independent advice or support**

If you prefer to discuss study participation with someone who is not involved in this research study, because you need further information or advice, you may contact <independent researcher> (<e-mail address>). He/she is a clinical geneticist at the department of Clinical Genetics at UMCG/Amsterdam UMC/UMCU.

## Supplementary Material S1

**Certificate of consent****For participation in a research study regarding informing relatives at risk of an inherited cardiac disease**

- I am satisfied about the information I received about this research study. I have had sufficient time to consider participation in this study. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.
- I can stop study participation at any time, without providing any reason and without any consequences.

**By signing this form, I provide consent for:**

1. Informing my clinician (clinical geneticist/genetic counselor) about my participation in this research study.
2. Collecting of data using questionnaire(s), and inspection of my medical record until 12 months after signing this consent form and the use of these data for the research study described in this letter.
3. Being approached for other research projects in the future.
4. Storing of my research data for 15 years after the research study has been finished
5. Inspection of the research data by the Safety Committee and the Dutch Health Care Inspectorate

**I want to participate in this research study**

Name of participant: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of participant: \_\_\_\_\_

I would like to be informed about the group results of this research study:

- Yes
- No

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**Statement by the researcher:** I have accurately informed this person about the aforementioned research project. The person may stop participating at any time during the study without any consequences. Any questions from the person about study participation were answered sufficiently

Name of researcher: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of researcher: \_\_\_\_\_

## Supplementary Material S1



umcg



Dear Sir or Madam,

Recently you visited the department of Clinical Genetics for genetic counselling concerning an inherited cardiac disease in your family. A clinical geneticist or genetic counsellor informed you about participation in a research study examining how to inform relatives at risk of inheriting the genetic predisposition. In this letter, we would like to inform you about this research study.

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*What does study participation involve?*

For this research study, we ask you to fill out a questionnaire. This questionnaire can be administered online or by mail. If you prefer to receive the questionnaire by mail, the questionnaire can be returned by using the provided return envelope. These questionnaires ask you for some general information, such as your age and gender, and about your experiences with being informed about the inherited cardiac disease in your family and your opinion regarding the approach that was used. This questionnaire will also ask you some questions about how you feel, at the current moment and in general, and how you generally cope with complex situations.

In addition, it is important for this research study to receive some information about your medical background. Because of this, we ask you to provide consent to inspect your medical record up to 12 months after completion of this research study. Important information includes, for example, the inherited cardiac disease diagnosed in your family and information

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1  
2  
3 about your family history regarding cardiac diseases. This information will be handled  
4 confidentially.  
5

6 Your clinician (the clinical geneticist/genetic counsellor) will be informed if you decide to  
7 participate in this study. You might be approached for other research studies in the future.  
8  
9

### *What are advantages and disadvantages of study participation?*

10  
11 There will be no direct benefit to you for your participation in this study. We hope that the  
12 information obtained from this study will contribute to research on improving approaches to  
13 inform relatives at risk of inherited cardiac diseases. Participation in this research study will  
14 take time: we will ask you to fill out two questionnaires. We expect that this will cost you 20  
15 to 30 minutes per questionnaire. In addition, we will ask questions regarding personal  
16 information, such as the disease in your family and your opinion and feelings concerning  
17 informing your relatives about this disease. You will not receive an incentive for study  
18 participation.  
19  
20  
21  
22

### *What if I do not want to participate anymore?*

23  
24 Your participation in this research is entirely voluntary. There are no consequences if you  
25 decide not to participate. You may also change your mind later and stop participating during  
26 the study even if you earlier agreed to do so. If you decide to stop participation, please let us  
27 know. The data collected up to that moment will be used for the research study. The  
28 researcher will inform you if there is new information about the study that might be important  
29 for you. In that case, you will be asked if you still consent to participate in the study.  
30  
31  
32

### *How will my personal data be handled?*

33  
34 By participating in this study, you will provide us personal data. This data will be collected  
35 for the research study. A research code will be assigned to all research documents. This means  
36 that your name and other personal data are not visible on research documents. Only the  
37 researchers know which research code belongs to you. Some institutes (the Safety Committee  
38 and the Health Care Inspectorate) are allowed to look into your clinical and personal data.  
39 These institutes are allowed to do this to control whether the research study is conducted in a  
40 proper and reliable manner. They will treat your data confidentially. If you sign the informed  
41 consent form, you will provide consent for collection, storage and inspection of your medical  
42 and personal data. Your data will be stored for 15 years.  
43  
44  
45  
46

### *Do you have any further questions regarding this research study?*

47  
48 If you have any questions about this research study or about study participation, please  
49 contact the executing researcher Lieke van den Heuvel by telephone (<telephone number>) or  
50 e-mail (<e-mail address>). If you prefer to discuss study participation with an independent  
51 clinician, or if you would like additional information, advice or support, please contact the  
52 independent expert (see attachment).  
53  
54  
55

### *What if I want to participate?*

56  
57 The researcher, Lieke van den Heuvel, will contact you by telephone to provide further  
58 information about the research study. If you decide to participate in this study after this  
59 telephone contact, a consent form will be sent to you by mail. You can return this consent  
60

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form using the attached return envelope. A postage stamp is not necessary. Subsequently, you will receive the questionnaire online or by mail.

Thank you for your time!

Sincerely,

Lieke van den Heuvel, MSc

Also on behalf of the research team and all the clinical geneticists and genetic counsellors involved from Amsterdam UMC, University Medical Centre Utrecht and University Medical Centre Groningen

**Attachment:** Information about your hospital 'UMCG/Amsterdam UMC/UMCU'

### **Questions, suggestions or complaints**

If you have any questions, suggestions or a complaint about this research study, please contact Lieke van den Heuvel. She will conduct this research study. She can be contacted by telephone (<telephone number>) or by e-mail (<e-mail address>).

### **Independent advice or support**

If you prefer to discuss study participation with someone who is not involved in this research study, because you need further information or advice, you may contact <independent researcher> (<e-mail address>). He/she is a clinical geneticist at the department of Clinical Genetics at UMCG/Amsterdam UMC/UMCU.

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**Certificate of consent****For participation in a research study regarding informing relatives at risk of an inherited cardiac disease**

- I am satisfied about the information I received about this research study. I have had sufficient time to consider participation in this study. I have had the opportunity to ask questions about it, and any questions that I have asked have been answered to my satisfaction.
- I can stop study participation at any time, without providing any reason and without any consequences.

By signing this form, I provide consent for:

6. Informing my clinician (clinical geneticist/genetic counselor) about my participation in this research study.
7. Collection of data using questionnaire(s), and inspection of my medical record until 12 months after signing this consent form and the use of these data for the research study described in this letter.
8. Being approached for other research projects in the future.
9. Storage of research data for 15 years after the research study has been finished
10. Inspection of the research data by the Safety Committee and the Dutch Health Care Inspectorate

**I want to participate in this research study**

Name of participant: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of participant: \_\_\_\_\_

I would like to be informed about the group results of this research study:

- Yes
- No

-----

**Statement by the researcher:** I have accurately informed this person about the aforementioned research project. The person may stop participating at any time during the study without any consequences. Any questions from the person about study participation were answered sufficiently

Name of researcher: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature of researcher: \_\_\_\_\_

## Supplementary Material S2

**Supplementary material S2:** Overview of questionnaire items to assess secondary outcomes per time-point

**Table 1** Questionnaire items probands per time-point

Questionnaire time-point	Items	Questionnaires
T1	Sociodemographic, clinical, family and personality factors	Self-constructed items Trait scale of STAI Shortened version of TMSI
	Advices for relatives at risk, eligible relatives at risk, the number of informed relatives at risk, risk perception and experiences with informing relatives at risk	Eleven self-constructed items
	Evaluation of used approach (incl. website)	Thirteen self-constructed items
	Perceived impact on family communication with relatives at risk	Adapted version of ODCF One self-constructed item
	Impact on psychological functioning of proband	HADS  Adapted version of CWS
T2	Number of informed relatives at risk, risk perception and experiences with informing relatives at risk	Three self-constructed items
	Evaluation of approach used	One self-constructed item
	Perceived impact on family communication with relatives at risk	Adapted version of ODCF One self-constructed item
	Impact on psychological functioning of proband	HADS Adapted version of CWS

**Table 2** Questionnaire items relatives

Questionnaire time-point	Items	Questionnaires
T1	Sociodemographic, family and personality factors	Eight self-constructed items Trait scale of STAI Shortened version of TMSI
	Evaluation of used approach (incl. website), risk perception	Thirteen self-constructed items
	Perceived impact on family communication with index patient	Adapted version of ODCF One self-constructed item
	Impact on psychological functioning of family member	HADS Adapted version of CWS

**Table 3** Self-constructed items (telephone interview) - Experiences with informing relatives at risk (probands)

1. Did the genetic counsellor give you an advice for your relatives?	Yes/No
2. What was this advice? (open question)	
3. For which relatives was this advice meant? (open question)	



## Supplementary Material S2

4. Have relatives at risk been informed about the advice of the genetic counsellor? If yes, which relatives have been informed? 5. Who informed your relatives?	Yes/No
--	--------

**Table 4** Self-constructed items (telephone interview) - Risk perception (probands)

1. How do you consider the risk of your relatives on being a carrier of the familial variant?	0% - 100% 1-10
2. How do you estimate the risk of your relatives on developing symptoms of the ICC?	0% - 100% 1-10

**Table 5** Self-constructed items - Evaluation of the used approach (probands)

<i>T1</i>	<p><i>Closed questions</i></p> <p><i>Below you can see statements regarding your experiences with how your relatives have been informed. Please rate each statement on a scale of 1-5 (1 totally disagree to 5 totally agree) how much each statement applies to you.</i></p> <p>1. I feel supported by the genetic counsellor in informing my relatives</p> <p>2. I think the used approach to inform relatives at risk is acceptable</p> <p>3. I felt a little coerced to inform my relatives</p> <p>4. The way my relatives are informed, can be improved</p> <p>5. I am satisfied with the way my relatives are informed</p> <p>Other: _____</p>	<p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p> <p>1 2 3 4 5</p>
<i>T2</i>	<p>1. Did your opinion regarding the used approach change?</p> <p>a. Yes, my opinion regarding the used approach became more positive</p> <p>b. Yes, my opinion regarding the used approach became more negative</p> <p>c. No, my opinion regarding the used approach is still positive</p> <p>d. No, my opinion regarding the used approach is still negative</p> <p>e. No, my opinion regarding the used approach is still neutral</p>	
<i>T1/T2</i>	<p>1. Do you think another approach to inform relatives at risk would have been better?</p> <p>2. Are there relatives for which you would have preferred another approach to inform them?</p>	<p>Yes/No</p> <p>Yes/No</p>
<i>T1/T2</i>	<p><i>Open questions</i></p> <p>1. What are advantages of the approach used to inform your relatives?</p> <p>2. What are disadvantages of the approach used to inform your relatives?</p>	

**Table 6** Self-constructed items - Impact on family relationships (probands)

1. Are there relatives with whom your relationship has changed after they are informed about their risk on the inherited cardiac disease?
---

Supplementary Material S2

- a. Yes, our relationship improved
- b. Yes, our relationship worsened
- c. No, our relationship is still not good/not bad
- d. No, our relationship is still good
- e. No, our relationship is still bad

**Table 7** Self-constructed items - Evaluation of the used approach (relatives)

<i>Closed questions</i>	
1. How were you informed about the hereditary predisposition in your family?	
a. With an information letter from the hospital, received from a relative	
b. With a letter written by a relative	
c. In person by a relative	
d. With an information letter from the hospital, received from a genetic counsellor/clinical geneticist	
e. In person by a genetic counsellor/clinical geneticist	
2. What information did you receive (multiple answers are possible)?	
a. The risk to be a carrier of the hereditary predisposition for the inherited cardiac disease in my family	
b. The possibility to make an appointment for predictive DNA testing at an outpatient clinic Clinical Genetics	
c. The advice to be regularly monitored by a cardiologist in the hospital	
d. Something else, namely _____	
-----	
<i>Below you can see statements regarding your experiences with how you have been informed about the inherited cardiac disease in your family. Please rate each statement on a scale of 1-5 (1 totally disagree to 5 totally agree) how much each statement applies to you.</i>	
1. I appreciated to be informed about my risk on the inherited cardiac disease	1 2 3 4 5
2. I am satisfied with the way I have been informed	1 2 3 4 5
3. I preferred to have received more information before I contacted the clinical genetic centre	1 2 3 4 5
4. I understand why I have been informed	1 2 3 4 5
5. The way I have been informed, can be improved	1 2 3 4 5
6. I felt free to decide myself whether I wanted to contact the clinic genetic centre	1 2 3 4 5
7. I would have preferred not to be informed about my risk on the inherited cardiac disease in my family	1 2 3 4 5
8. I would have preferred to not know about the inherited cardiac disease in my family	1 2 3 4 5
Other: _____	
-----	
1. Do you think another approach to be informed would have been better?	Yes/No
-----	
<i>Open questions</i>	

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- |  |  |
|--|--|
| 1. What are advantages of the way you have been informed?    |  |
| 2. What are disadvantages of the way you have been informed? |  |

**Table 8** Self-constructed items - Impact on family relationships (relatives)

- |  |
|--|
| 1. Did your relationship with your relative change after they were informed about their risk on the inherited cardiac disease?<br>a. Yes, our relationship improved<br>b. Yes, our relationship worsened<br>c. No, our relationship is still not good/not bad<br>d. No, our relationship is still good<br>e. No, our relationship is still bad |
|--|



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page no
<b>Administrative information</b>			
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	6-17
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	-
	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	-
	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)	-
<b>Introduction</b>			
Background and rationale	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	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6

1				
2	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, noninferiority, exploratory)	6
3				
4				
5				
6				
7	<b>Methods: Participants, interventions, and outcomes</b>			
8				
9	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	6
10				
11				
12				
13	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)	7
14				
15				
16				
17	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9, 10
18				
19				
20		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)	17
21				
22				
23				
24		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
25				
26				
27				
28				
29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
30				
31				
32	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	11-14
33				
34				
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38				
39	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)	8, 11, 17
40				
41				
42				
43				
44	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	15, 16
45				
46				
47				
48	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
49				
50				

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	9
3	generation		generated random numbers), and list of any factors for stratification.	
4			To reduce predictability of a random sequence, details of any	
5			planned restriction (eg, blocking) should be provided in a separate	
6			document that is unavailable to those who enrol participants or	
7			assign interventions	
8				
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	9
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
11	mechanism		describing any steps to conceal the sequence until interventions are	
12			assigned	
13				
14	Implementation	16c	Who will generate the allocation sequence, who will enrol	9
15			participants, and who will assign participants to interventions	
16				
17	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial	9
18			participants, care providers, outcome assessors, data analysts),	
19			and how	
20				
21		17b	If blinded, circumstances under which unblinding is permissible, and	9
22			procedure for revealing a participant's allocated intervention during	
23			the trial	
24				
25				
26	<b>Methods: Data collection, management, and analysis</b>			
27				
28	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	11-15
29	methods		other trial data, including any related processes to promote data	
30			quality (eg, duplicate measurements, training of assessors) and a	
31			description of study instruments (eg, questionnaires, laboratory	
32			tests) along with their reliability and validity, if known. Reference to	
33			where data collection forms can be found, if not in the protocol	
34				
35		18b	Plans to promote participant retention and complete follow-up,	-
36			including list of any outcome data to be collected for participants	
37			who discontinue or deviate from intervention protocols	
38				
39	Data management	19	Plans for data entry, coding, security, and storage, including any	17
40			related processes to promote data quality (eg, double data entry;	
41			range checks for data values). Reference to where details of data	
42			management procedures can be found, if not in the protocol	
43				
44				
45	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes.	16, 17
46			Reference to where other details of the statistical analysis plan can	
47			be found, if not in the protocol	
48				
49		20b	Methods for any additional analyses (eg, subgroup and adjusted	16, 17
50			analyses)	
51				
52		20c	Definition of analysis population relating to protocol non-adherence	16, 17
53			(eg, as randomised analysis), and any statistical methods to handle	
54			missing data (eg, multiple imputation)	
55				
56				
57				
58				
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60				

**Methods: Monitoring**

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
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	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

**Ethics and dissemination**

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
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)	-
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
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

1	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	17
2	policy		participants, healthcare professionals, the public, and other relevant	
3			groups (eg, via publication, reporting in results databases, or other	
4			data sharing arrangements), including any publication restrictions	
5				
6				
7		31b	Authorship eligibility guidelines and any intended use of	18
8			professional writers	
9				
10		31c	Plans, if any, for granting public access to the full protocol,	-
11			participant-level dataset, and statistical code	
12				

### Appendices

13				
14				
15	Informed consent	32	Model consent form and other related documentation given to	-
16	materials		participants and authorised surrogates	
17				
18	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
19	specimens		specimens for genetic or molecular analysis in the current trial and	
20			for future use in ancillary studies, if applicable	
21				

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.