Protocol for diagnostics and follow-up of PLN mutation carriers

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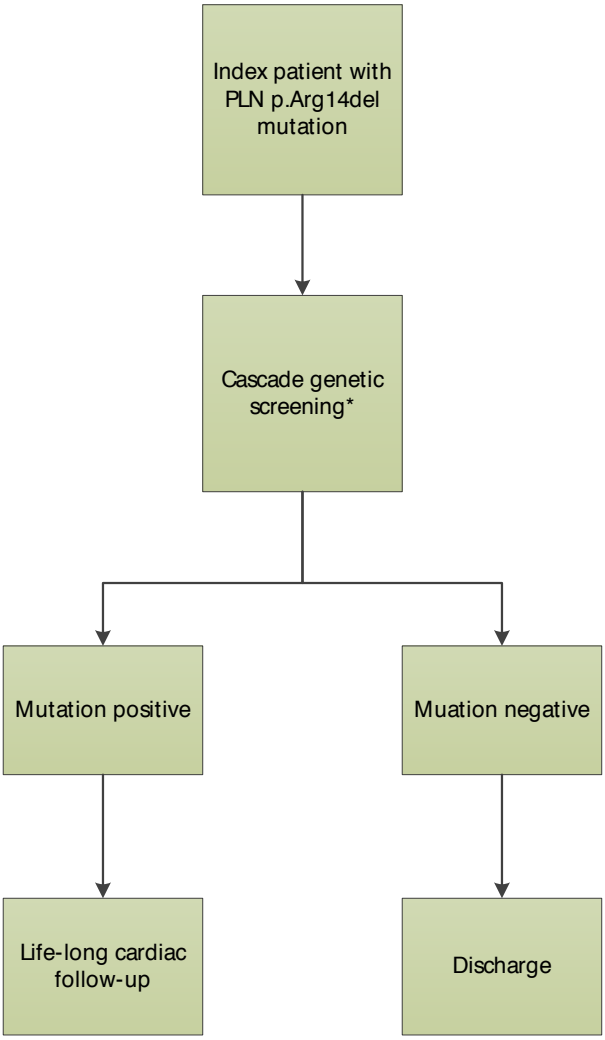
Background

Pathogenic mutations in the phospholamban (PLN) gene may cause cardiomyopathies which are characterized by a high frequency of ventricular arrhythmias and early-onset heart failure.[1] Several mutations have been described in the PLN gene, of which the p.Arg14del mutation is a founder mutation that originates from the northern part of the Netherlands.[2] This mutation has been found in 12% of patients diagnosed with arrhythmogenic cardiomyopathy (ACM) and 15% of patients with dilated cardiomyopathy (DCM).[3] Due to genetic cascade screening, over 1000 carriers of this mutation have currently been identified.

Aim

This protocol is designed for physicians and researchers. It describes the diagnostic process, follow-up strategies and the collection of research data in carriers of a PLN mutation. The aim of this protocol is to standardize clinical care in PLN mutation carriers and to uniformly collect high-quality data for future research.

Genetic and clinical screening process



*Cascade screening implies genetic screening of first-degree relatives of mutation carriers for having the same mutation as their relative. Relatives who are not willing to undergo genetic screening should have life-long cardiac follow-up.

Baseline cardiac screening

Comprehensive cardiac screening should be performed in **index patients, mutation positive relatives and in relatives with an unknown mutation status**. The first screening should at least include:

- Electrocradiography (ECG)
- Exercise tolerance testing (X-ECG)
- Cardiac imaging (echocardiography and cardiac MRI)*
- Holter monitoring

*Echocardiography and cardiac MRI should preferably both be performed during the first screening. Echocardiography should not be replaced with cardiac MRI because it may provide additional information on diastology, valvular disease and cardiac mechanics. Also, for follow-up screenings it is important to have a baseline echocardiogram for comparability. Echo and MRI protocols are added in the appendix.

Biobanking

If available at the local institute, blood samples should be drawn and stored for future research, as well as remnant body material.

For blood sample biobanking, the following blood tubes should at least be collected:

- 1 citrate (blue) – 4,5 mL
- 1 without additives (red) – 10 mL
- 1 sodium-heparin (green/black) – 9 mL
- 1 EDTA (lavender) – 2 mL
- 1 EDTA (purple) – 10 mL

The full SOP for blood sample biobanking can be found on https://www.unravelrdp.nl/.

Follow-up strategy

Follow-up cardiac screenings are advised in **index patients, mutation positive relatives and in relatives with an unknown mutation status.** The follow-up strategy relies on the presence of a clinical phenotype during baseline cardiac screening.

The following follow-up scheme is advised in relatives with a mutation (or first-degree relatives with an unknown mutation status)

	Baseline visit	Repeating frequency
ECG	+	1x p/2 years
X-ECG	+	Guided by clinical indication
Echocardiogram*	+	1x p/2 years
MRI**	+	1x p/3-5 years
Holter	+	1x p/2 years
Blood analysis	Guided by clinical indication	

*Preferably with a GE machine to allow standardized strain analysis (SOP added in appendix)
**Hematocrit value should be determined on the day of MRI to enable calculation of extracellular volume (SOP MRI added in appendix)

In index patients or relatives with a clinical phenotype, a similar follow-up scheme can be applied. Specific examinations can be performed more frequently depending on symptoms or clinical disease signs.

Research electronic data capture

All baseline and follow-up data regarding medical history, performed examinations and clinical outcomes are collected on a research electronic data capture (REDCap) platform in which every participating centre has its own restricted data access group.[4] The variables that are collected in this platform are added in the appendices (REDCap data dictionary).

Literature references

1 Hof IE, van der Heijden JF, Kranias EG, et al. Prevalence and cardiac phenotype of patients with a phospholamban mutation. Neth Heart J. 2019;27:64-69.

2 Van der Zwaag PA, van Rijsingen IA, de Ruiter R, et al. Recurrent and founder mutations in the Netherlands-Phospholamban p.Arg14del mutation causes arrhythmogenic cardiomyopathy. Neth Heart J. 2013;21:286–93.

3 Van der Zwaag PA, van Rijsingen IA, Asimaki A, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. Eur J Heart Fail. 2012;14:1199–207.

4 Bosman LP, Verstraelen TE, van Lint FHM, et al. The Netherlands Arrhythmogenic Cardiomyopathy Registry: design and status update. Neth Heart J. 2019 [Epub ahead of print].

Appendices

- Echocardiography protocol
- MRI protocol
- REDCap data dictionary

Echocardiography protocol

University Medical Center Utrecht, February 2019

Abbreviations

AV	Aortic valve
CW	Continuous wave Doppler
FR	Frame rate
LA	Left atrium
LV	Left ventricle
LVOT	Left ventricular outflow tract
MV	Mitral valve
PV	Pulmonary valve
PW	Pulsed wave Doppler
RA	Right atrium
RV	Right ventricle
RVOT	Right ventricular outflow tract
TDI	Tissue Doppler imaging
TV	Tricuspid valve

Acquisition

Echocardiograms should preferably be acquired with a GE machine for standardization of strain analysis. Height and weight of the patient should be registered. All echocardiograms should go along with appropriate ECG recording. At least 3 cardiac cycles should be acquired per view. For patients with atrial fibrillation, at least 5 cardiac cycles should be acquired per view. Doppler recordings should be acquired during end-expiration.

Views and measurements

Parasternal long-axis view	2D/M-Mode Color Doppler MV/AV 2D focused on RVOT for measurement diameter
Parasternal RV inflow view (RV 2-chamber view) **(figure 1A)**	2D (for assessment RV wall motion, **figure 3**) Color Doppler TV CW TV
Parasternal short-axis view	
Apical level	2D
Mid-papillary level	2D (FR >55/sec)
MV level	2D Color Doppler MV
AV level	2D Color Doppler AV Color Doppler PV PW RVOT Color Doppler TV CW TV 2D focused image of RVOT for measurement diameters
RV-focused short axis view	2D (for assessment RV wall motion abnormalities) **(figure**

	1B and figure 3)
Apical 4-chamber view	2D LV/LA 2D LV focused view (FR >55/sec), **(figure 2A)** Color Doppler MV PW MV inflow TDI PW medial annulus TDI PW lateral annulus
Apical 5-chamber view	2D LV/LA Color Doppler AV PW LVOT CW AV
RV-focused apical 4 chamber	2D RV/RA 2D RV focused view (FR >55/sec) 2D Narrow-angle, RV free wall (FR>80/sec) **(figure 1C)** M-mode tricuspid annulus TDI PW tricuspid annulus Color Doppler TV CW TV
Apical 2-chamber view	2D LV/LA 2D LV focused view (FR >55/s), **(figure 2B)** Color Doppler MV
Apical 3-chamber view	2D LV/LA 2D LV focused view (FR >55/s), **(figure 2C)** Color Doppler MV/AV
Apical 3D view	LV focused (FR >20)
Subcostal 4-chamber view	2D (assessment RV wall motion abnormalities, **figure 3**)
Subcostal vena cava inferior	2D/M-mode (with sniff)

Figure 1: RV-specific views. A = Parasternal RV-inflow view; B = RV-focused short-axis view; C = RV-focused apical 4-chamber view.

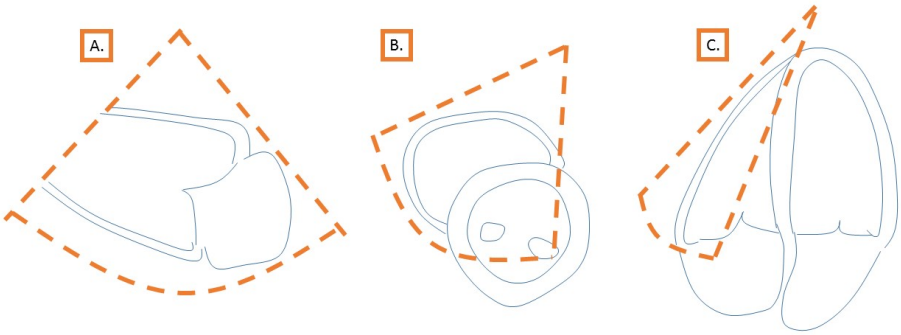


Figure 2: LV-focused views. A = apical 4-chamber view; B = Apical 2-chamber view; C= Apical 3-chamber view.

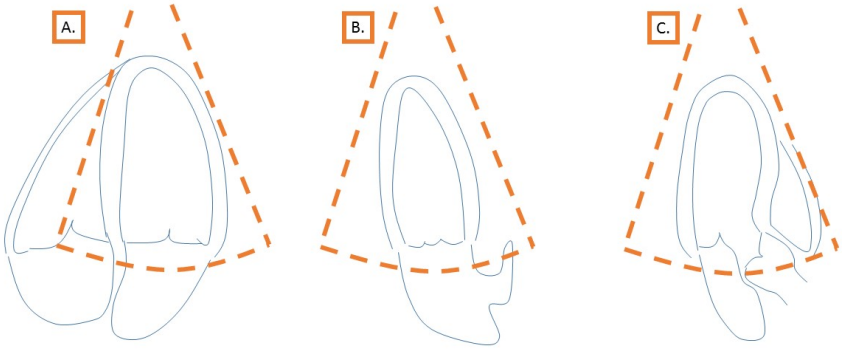
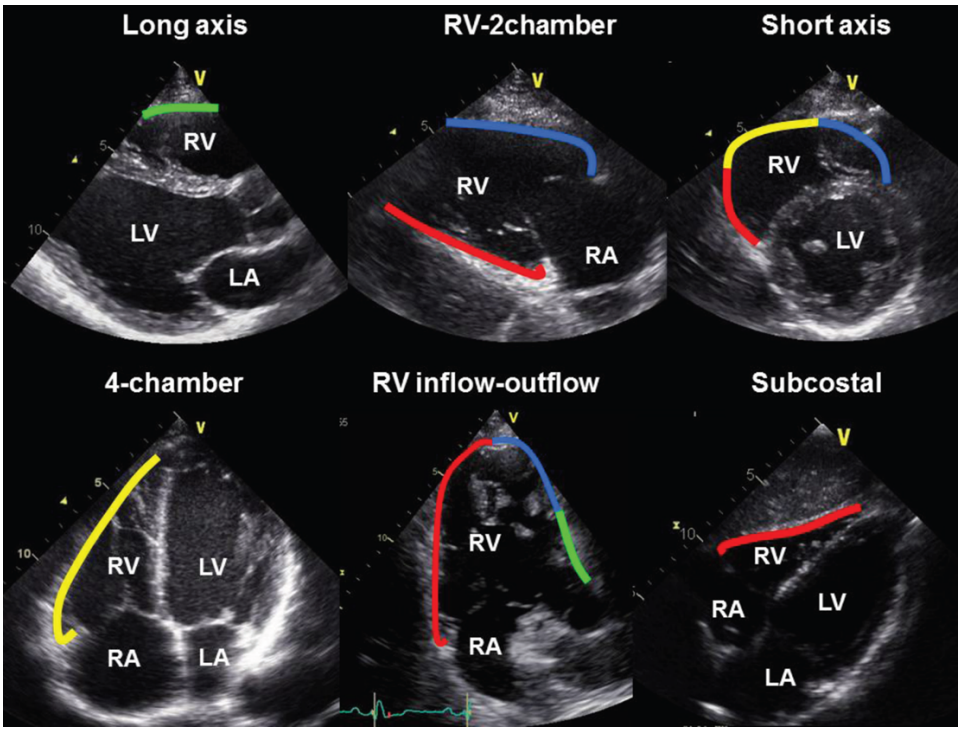


Figure 3: Wall motion assessment RV. Green = RVOT anterior wall; blue = RV anterior wall; yellow = RV lateral wall; red = RV inferior wall.



MRI protocol

CMR ARVC/PLN protocol on 1.5 Tesla (Philips scanner)
UMC Utrecht, Radiology department Last version: 2-7-'18 Version 46.0

Cardiovascular Magnetic Resonance (CMR)
ARVC/PLN protocol
Scanned Sequences
1. Survey for determination of the cardiac position – Balanced Fast Field Echo (BFFE) – expiration

2. t T1 weighted Black Blood
Plan on coronal plane

3. Balanced Turbo Field Echo (BTFE/RETR) 2 chamber left
Cine images of the 2 chamber view
Plan parallel to the septum, in the middle of the mitral valve

4. BTFE/RETR short axis
Plan perpendicular to the 2 chamber left view, about 1/3 to the apex

5. BTFE/RETR 4 chamber 50 phases
Cine images of the 4 chamber view: plan on the short axis

6. Native T1 mapping in short axis (3 slices) (MOLLI sequence)
Three slices of the short axis: between mitral valve and apex. Three times in one breath hold.
Administer a double dose of contrast (0.2 cc gadovist/kg) for the late enhancement images

7. 3D whole heart breath hold
Transversal non-angulated image of the whole heart

8. BTFE/RETR short axis view
Functional images of the short axis, parallel to mitral valve
Between mitral valve and apex ±12-15 slices
Always check on the end diastolic phase

9. BTFE/RETR left ventricular outflow tract (LVOT) view
Cine images of the LVOT, angulate through the mitral- and aortic valve

10. BTFE/RETR 2 chamber right view
Plan on the 4 chamber view, through the tricuspid valve and parallel to the septum.
It is important that the tricuspid valve is clearly visible.

11. BFFE/RETR Right Ventricular Outflow Tract (RVOT)
Cines of the RVOT. These are sagittal views through the RVOT

12. Look Locker 2 beats
Determine the optimal inversion time (=highest blood/muscle contrast)
Use the inversion delay table and use these values for the 3D short axis views
Add +85 and use this value for the 2D Phase-Sensitive Inversion Recovery (PSIR) images.

13. Viability 2D 4 chamber

14. Multiple 2D slices (M2D)/ 4 chamber PSIR
Viability of 4 chamber

15. M2D/short axis PSIR
Viability of the short axis view, number is the same as the number of slices used for the cine short axis images

16. M2D/RVOT PSIR
Viability of RVOT

17. M2D/ 2 chamber right PSIR
Viability of the 2 chamber right view
Make sure that at least 15 minutes have past between contrast injection and T1 mapping sequence

18. T1 mapping enhanced short axis, 3 slices
Three slices of the short axis view conform native T1 mapping.

Important notes
It is important that the blood draw for determination of the hematocrit value will be performed on the same day of the CMR. Hematocrit is necessary for the calculation of the extracellular volume from the T1 mapping sequence.

REDCap Data dictionary

Demographics		
Country	Free text	*Country of residence*
Centre	Free text	*Centre of enrolment*
Year of birth	YYYY	*Year in which the patient was born*
Sex	• Female • Male	*Sex of the patient*
Pedigree	• Proband • Family member	*Proband ('index patient') is defined as the first affected family member seeking medical attention for ACM-related complaints in whom the diagnosis was confirmed (i.e. an individual ascertained independently of family history).*
Ethnicity	• Caucasian • Asian • African (-American) • Hispanic • Mixed	*Ethnicity of the patient*

Presentation & symptoms		
Date of presentation	DD/MM/YYYY	
Type of presentation	• Sudden cardiac death • Symptomatic and living • Resuscitated sudden cardiac arrest • Abnormal test • Family history	*Symptomatic is defined as having symptoms attributed to ACM (syncope, pre-syncope, palpitations, chest pain).*
Ventricular arrhythmia	Duration; morphology; cycle length.	
Symptoms	• Cardiac syncope • Presyncope • Palpitations • Dyspnoea • Chest pain	*Cardiac syncope is defined as transient loss of consciousness and postural tone with spontaneous recovery with a likely arrhythmic mechanism.*
NYHA class	I - IV	*Functional classification as defined by the New York Heart Association.*
Comorbidities	• Hypertension • Diabetes Mellitus • Dyslipidaemia • Myocardial infarction • Peripheral vascular disease • Cerebrovascular accident / Transient ischemic attack • COPD • Sarcoidosis	

Family history		
Date of ascertainment of family history	DD/MM/YYYY	
Degree of relatedness to the index patient	• First degree • Second degree	*First degree is defined as family members with 50% relatedness (i.e. parents, siblings and children).*

		Second degree is defined as family members with 25% relatedness (i.e. grandparents, grandchildren, aunts, uncles, nephews, nieces, etc.)

Family history of heart disease	• ACM/ARVC
	  ○ Task force diagnosis
	  ○ Autopsy diagnosis
	  ○ Assumed diagnosis
	• DCM
	• HCM
	• Other (specify)
		Assumed diagnosis is defined as diagnosis not confirmed by Task Force criteria or autopsy

Genetics		
Date of genetic testing	DD/MM/YYYY	
Type of analysis	• Sanger sequencing • Gene panel(s) • CNV detection software • Multiplex ligation-dependent probe amplification	
Gene tested	• Plakophilin-2 *(PKP2)* • Desmoplakin *(DSP)* • Junctional plakoglobin (*JUP*) • Desmoglein-2 (*DSG2*) • Desmocolin-2 (*DSC2*) • Transmembrane protein 43 (*TMEM43*) • Transforming growth factor β3 (*TGFβ3*) • Phospholamban (*PLN*) • Titin (*TTN*) • Desmin (*DES*) • Lamin A/C (*LMNA*) • Ryanodine receptor 2 (*RYR2*) • Voltage-gated sodium channel α-subunit 5 (*SCN5A*) • N-cadherin (*CDH2*) • Catenin α3 (*CTNNA3*) • Other variants found (specify)	
If variant found:	• Reference sequence number • Nucleotide variant • Amino acid change • Homozygous, heterozygous, compound heterozygous • Pathogenicity classification	*Pathogenicity classification as per ACMG guidelines. Nonsense, frameshift, splice site mutations and exon deletions are considered proven pathogenic unless previously identified as polymorphism. Missense mutations are considered pathogenic when 1) minor allele frequency in Exome Sequencing Project (ESP) was ≤0.05%, (NHLBI 6500 Exome data sets; EVS; http://evs.gs.washington.edu/EVS/) and 2) in silico prediction programs predicted the variant to affect protein function by score <0.02 (SIFT) and >0.900 (Polyphen2).*

Exercise history		
Endurance athlete	Yes/no	*Defined as Bethesda class C (High dynamic component >70% max O_2)*
Types of sport	Free text	*E.g. Soccer, tennis, basketball, etc.*
Activity level	Low Moderate High	
Competitive athlete	Yes/no	

Medication		
Date of medication log	DD/MM/YYYY	
Beta-blockers	• Yes (specify name + dose) • No	
Anti-arrhythmic drugs	• Class 1A (specify name + dose) • Class 1B (specify name + dose) • Class 1C (specify name + dose) • Class 3 (specify name + dose) • Class 4 (specify name + dose)	*NB Sotalol classified as class 3 anti-arrhythmic drug irrespective of dose*
Diuretics	• Yes (specify name + dose) • No	
ACE-inhibitors / ARBs	• Yes (specify name + dose) • No	

Electrocardiogram		
Date of ECG	DD/MM/YYYY	
Upload anonymized ECG	Upload button	*Anonymization facilitated by automatic redaction tool*
Medication used during recording	Free text	
Rhythm	• Sinus rhythm • Atrial pacing • (Atrial-)ventricular pacing • Other (free text)	
Heart rate frequency	(bpm)	*Allowed range 10 - 400*
QRS duration	(ms)	*Maximal QRS duration on ECG* *Allowed range 20-400*
R-axis	(degrees)	*Allowed range -90 - 270*
PQ duration	(ms)	*Allowed range 20-400*
QT interval	(ms)	*Allowed range 100-700*
Bundle branch block	• Complete RBBB • Atypical complete RBBB • Complete LBBB • Non-specific intraventricular conduction delay	*Criteria for typical right and left bundle branch block criteria as per WHO criteria*
Terminal activation duration	• >55 ms (Yes/No) • Absolute duration (ms)	*TAD is defined as the longest duration in V1-3, from the nadir of the S wave to the end of all depolarization deflections including R', in the absence of typical complete right bundle-branch block*
Epsilon wave	• Yes • No	*Distinct waves of small amplitude within the ST segment in the right precordial leads (V1-3) which are distinct from the QRS complex.*

T-wave inversion	• V1 • V2 • V3 • V4 • V5 • V6 • II • III • aVF	*Inverted T-waves are recorded per lead.* *T-waves are considered inverted if amplitude ≥ 1 mV.*
Presence of PVC(s)	Yes/No; number; morphology.	
Low QRS voltage	• Leads I, II and III all <0.5 mV • Leads I+II+III <1.5 mV • Leads V1-6 all <1.0 mV • Other (free text)	

Signal-averaged Electrocardiogram (SAECG)		
Date of SAECG	DD/MM/YYYY	
Upload anonymized SAECG	Upload button	*Anonymization facilitated by automatic redaction tool*
Filtered QRS duration	(ms)	*Allowed range 60-300*
Duration of terminal QRS <40mV	(ms)	*Allowed range 0-100*
Root mean square voltage of terminal 40ms	(mV)	*Allowed range 0-100*

Holter monitoring		
Date of Holter monitor	DD/MM/YYYY	
Upload copy of Holter monitor report	Upload button	*Anonymization facilitated by automatic redaction tool*
Use of cardiac medication during recording	Free text	
Monitoring time	hours	*Allowed range 12-50*
Total PVC count	number	*Allowed range 0-200000*
Ventricular arrhythmia	Duration; morphology; cycle length.	

Exercise tolerance test		
Date of exercise tolerance test	DD/MM/YYYY	
Upload anonymized exercise tolerance test	Upload button	*Anonymization facilitated by automatic redaction tool*
Cardiac medication during test	Free text	
Baseline blood pressure	(mmHg)	*Allowed range 40-250 / 20-180*
Maximum blood pressure	(mmHg)	*Allowed range 40-250 / 20-180*
Ventricular tachycardia	Duration; morphology; cycle length.	
PVC(s)	Presence; morphology.	
Other arrhythmia(s)	Free text	

Electrophysiology study (EPS)		
Date of EPS	DD/MM/YYYY	
Upload copy of EPS report	Upload button	*Anonymization facilitated by automatic redaction tool*
Cardiac medication during EPS	Free text	
Ventricular arrhythmia	Duration; morphology; cycle length.	

induced at stimulation		
Induction method	• Programmed ventricular stimulation • Isoproterenol infusion	
Late potentials	• Yes • No	*Considered positive if potentials are recorded on intracardiac electrogram after the end of the QRS-complex on the surface ECG.*
Ablation performed	• Yes • No If yes: • Endocardial location(s) • Epicardial location(s) • Both endo- and epicardial location(s)	

Magnetic resonance imaging (MRI)		
Date of MRI	DD/MM/YYYY	
Upload copy of MRI report	Upload button	*Anonymization facilitated by automatic redaction tool*
Body surface area at time of test	(m^2)	*As calculated by DuBois formula (height^0.725)*(length^0.425)*0.007184*
Global RV dilatation	• Mild • Moderate • Severe	*Qualitative assessment* *Mild: RV diameter < LV diameter* *Moderate: RV diameter = LV diameter* *Severe: RV diameter > LV diameter*
Global RV dysfunction	• Mild • Moderate • Severe	*Qualitative assessment*
Regional RV wall motion abnormalities	• Hypokinesia (specify region) • Akinesia (specify region) • Dyskinesia (specify region) • Aneurysm (specify region)	*Qualitative assessment*
RV measurements	• End-diastolic volume (mL) • End-systolic volume (mL) • Ejection fraction (%)	
Global LV dilatation	• Mild • Moderate • Severe	*Qualitative assessment*
Global LV dysfunction	• Mild • Moderate • Severe	*Qualitative assessment*
Regional LV wall motion abnormalities	• Hypokinesia (specify region) • Akinesia (specify region) • Dyskinesia (specify region) • Aneurysm (specify region)	*Qualitative assessment*
LV measurements	• End-diastolic volume (mL) • End-systolic volume (mL) • Ejection fraction (%)	
Dyssynchronous movement	• Dyssynchronous contraction • Dyssynchronous relaxation	*Qualitative assessment*
Fatty infiltration	• Yes (specify region)	*Qualitative assessment*

	• No	
Late gadolinium enhancement	• Yes (specify region) • No	*Qualitative assessment*
Atrial dilatation	• Left • Right • Both	*Qualitative assessment*
Abnormal feature tracking	• Yes (specify region) • No	
T1 mapping performed	• Yes • No	
Signs of non-compaction	• RV • LV • Both	

Echocardiogram		
Date of echocardiogram	DD/MM/YYYY	
Upload copy of echocardiogram report	Upload button	*Anonymization facilitated by automatic redaction tool*
Body surface area at time of test	(m^2)	*Calculated by DuBois formula (height^0.725)*(length^0.425)*0.007184*
Global RV dilatation	• Mild • Moderate • Severe	*Qualitative assessment* *Mild: RV diameter < LV diameter* *Moderate: RV diameter = LV diameter* *Severe: RV diameter > LV diameter*
Global RV dysfunction	• Mild • Moderate • Severe	*Qualitative assessment of RV function*
Regional RV wall motion abnormalities	• Hypokinesia (specify region) • Akinesia (specify region) • Dyskinesia (specify region) • Aneurysm (specify region)	*Qualitative assessment*
RV measurements	• Fractional area change (%) • Tricuspid annular plane systolic excursion (mm) • Outflow tract (PLAX)(mm) • Outflow tract (PSAX)(mm)	
Global LV dilatation	• Mild • Moderate • Severe	*Qualitative assessment*
Global LV dysfunction	• Mild • Moderate • Severe	*Qualitative assessment*
LV measurements	• Ejection fraction (%) • Fractional shortening (%) • End-diastolic volume (mL)	
Abnormal deformation imaging	• Yes (specify region) • No	
Atrial dilatation	• Left • Right • Both	
Signs of non-compaction	• RV • LV	

	• Both	

Angiogram		
Date of angiogram	DD/MM/YYYY	
Upload copy of angiogram report	Upload button	*Anonymization facilitated by automatic redaction tool*
Global RV dilatation	• Yes • No	*Qualitative assessment*
Regional RV regional wall motion abnormalities	• Akinesia, dyskinesia or aneurysm (specify region) • Hypokinesia (specify region) • No	*Qualitative assessment*
Global LV dilatation	• Yes • No	*Qualitative assessment*
Regional LV regional wall motion abnormalities	• Akinesia, dyskinesia or aneurysm (specify region) • Hypokinesia (specify region) • No	*Qualitative assessment*
Coronary artery disease	• Yes • No	*Defined as >=75% stenosis in a major epicardial coronary artery*

Tissue histology		
Date that specimen is obtained	DD/MM/YYYY	
Upload copy of pathology report	Upload button	*Anonymization facilitated by automatic redaction tool*
Source of tissue	• Biopsy • Autopsy • Transplantation • Other	
Fulfilment of Arrhythmogenic Cardiomyopathy diagnostic criteria	• Major • Minor • None	*As defined by the 2010 TFC: Major if < 60% residual myocytes by morphometric analysis (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium >=1 sample, with or without fatty replacement of tissue on endomyocardial biopsy; Minor if 60% to 75% residual myocytes by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in >=1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.*

Device implantation		
Date of implantation	DD/MM/YYYY	
Copy of device readouts / settings summary	Upload button	*Anonymization facilitated by automatic redaction tool*
Type of device	• ICD: Single chamber • ICD: Dual chamber or CRT-D • S-ICD • Pacemaker: single chamber	*RV lead only = single chamber. RV and RA lead = dual chamber. RA, RV and LV lead = CRT-(D), subcutaneous ICD = S-ICD.*

	• Pacemaker: dual chamber • Pacemaker: leadless • Other (specify)	
Type of implantation	• New implantation • Generator replacement • Lead revision • Other (specify)	
Defibrillator indication	• Primary prevention • Secondary prevention	*Secondary prevention if previously documented sustained VT/VF. If the ICD indication is based on syncope without registration of a ventricular arrhythmia it is regarded as primary prevention.*
Defibrillator settings	• Rate cut-off for anti-tachycardia pacing or shock • Rate cut-off for monitoring window	*For anti-tachycardia pacing or shock, note lowest rate at which device provides therapy.* *For rate cut-off specify cycle lengths in ms.*

Arrhythmic event / ICD intervention		
Date of arrhythmic event	DD/MM/YYYY	
Upload copy of event registration	Upload button	*Anonymization facilitated by automatic redaction tool*
Documentation type	• ECG recording • ICD recording • Other (specify)	
Cardiac medication at time of event	Free text	
Event type	• Spontaneous VT/VF • Appropriate ICD intervention (anti-tachycardia pacing or shock) • VT-storm / electrical storm • Aborted SCD	*VT storm is defined by >2 sustained arrhythmias (or appropriate ICD interventions) within 24h.*
Ventricular tachycardia or ICD intervention	Duration; morphology; cycle length	*Ventricular tachycardia is considered sustained if lasting 30 seconds or more, or less than 30 seconds when terminated electrically or pharmacologically*
Type of ICD intervention	• Anti-tachy-pacing (ATP) • Shock	
Circumstances event	• Routine activity • Rest • Sleep • Exercise	

Inappropriate ICD intervention		
Date of inappropriate ICD intervention	DD/MM/YYYY	
Upload copy of event registration	Upload button	*Anonymization facilitated by automatic redaction tool*
Type of intervention	• Anti-tachycardia pacing (ATP) • Shock	
Cause	• Atrial arrhythmia • Sinus tachycardia • Lead or device malfunction	

	• Other (specify)	

Atrial arrhythmia		
Date of atrial arrhythmia	DD/MM/YYYY	
Upload copy of event registration	Upload button	*Anonymization facilitated by automatic redaction tool*
Type	• Atrial fibrillation • Atrial flutter • Other (specify)	
Documentation type	• ECG recording • ICD recording • Holter recording • Exercise test • Other (specify)	

Pregnancy		
Number of pregnancies	Number; date of delivery	
Cardiac complications associated with pregnancy	• Yes (specify) • No • Unknown	*E.g. symptoms of heart failure or arrhythmia in the mother, obstetric complications in the child*

Heart failure		
Date of onset heart failure	DD/MM/YYYY	*Defined as a clinical syndrome with symptoms as dyspnoea, fatigue, limited exercise tolerance, and/or fluid retention caused by a structural and/or functional cardiac abnormality. (Definitions from: ACCF/AHA 2013, ESC 2016).*
Date of first hospitalization for heart failure	DD/MM/YYYY	

Heart transplantation / ventricular assist device		
Date of transplantation / VAD implantation	DD/MM/YYYY	
Type	• Heart transplantation • LVAD • RVAD • BiVAD • Other	
Indication	• Incessant ventricular arrhythmia • RV failure • LV failure • Biventricular failure • Other (specify)	

Death		
Date of death	DD/MM/YYYY	

Cause	• Cardiovascular
	  ○ Sudden cardiac death
	  ○ Heart failure / shock
	  ○ Other (specify)
	• Non-cardiovascular (specify)	

Diagnostic criteria		
Fulfilment of criteria for ARVC	Total TFC score; automatically calculated by software based on previous entry sheets	*Definite diagnosis ≥ 4 TFC criteria* *Borderline diagnosis: 3 TFC criteria* *Possible diagnosis: 2 TFC criteria*
Fulfilment of criteria for ARVC; by category	• Family history / genetics • Depolarization • Repolarization • Arrhythmia • Structural (imaging) • Tissue Automatically calculated by software based on previous entry sheets	
Fulfilment of criteria for DCM	Automatically calculated by software based on previous entry sheets	*If LVEDD>117% of the predicted value, and a reduced LV function (EF< 45% or FS< 35%)*
Coronary artery disease	Automatically calculated by software based on previous entry sheets	*If CTA calcium score >10 and/or CAG stenosis >= 75%*
Fulfilment of criteria for non-compaction	Automatically calculated by software based on previous entry sheets	*If non-compacted / compacted layer ratio on MRI is >2.3, or the end systolic non-compacted / compacted layer ratio in echocardiogram is >2.0*