SUPPLEMENTAL FILE 1: Centre Inclusion Criteria

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SUPPLEMENTAL FILE 1: Centre Inclusion Criteria

All participating centres in the pilot phase should have dedicated cardiomyopathy clinics staffed by experienced medical and nursing teams. All participants should have access to facilities for genetic testing of the main genes implicated in cardiomyopathy and demonstrable experience in the interpretation of the results.

Mandatory criteria:

1. European centre with expertise in diagnosis and management of cardiomyopathies.
2. Dedicated outpatient clinic(s) for cardiomyopathies (HCM, DCM, ARVC, RCM).
3. More than 100 new index cases per year, or a total of more than 500 new cases within the last 10 years.
4. Established cooperation with a paediatric cardiac department experienced in family screening, diagnosis and management of cardiomyopathies.
5. Access to a high volume echocardiography laboratory with experience in diagnosis of typical and atypical phenotypes of cardiomyopathies.
6. Exercise testing facilities with experience in physical evaluation of cardiomyopathies (stress echo, exercise echo).
7. Non invasive electrophysiology: Holter-ECG, Signal Average ECG analysis

8. Genetic Unit (on site or close collaboration) with expertise in the study of the most prevalent genes (sarcomeric, desmosomal, cytoskeletal, etc.) and experience in the interpretation of the results (geneticists).
9. Cardiac Magnetic Resonance Imaging Lab with experience in diagnosis of typical and atypical cardiomyopathies.
10. Interventional Cardiology Unit with experience on haemodynamic studies, myocardial biopsies and specific therapies (e.g. alcohol septal ablation).
11. Electrophysiology and Devices Units with experience in diagnosis and invasive treatment of supra and ventricular arrhythmias in patients with cardiomyopathies.
12. Collaboration with cardiac surgical teams with experience in management of cardiomyopathies (myectomy, heart transplantation etc.).
13. Pathology department with experience on typical and atypical histology of cardiomyopathies

SUPPLEMENTAL FILE 2: Cardiomyopathy Definitions

Dilated Cardiomyopathy

Dilated cardiomyopathy is a heart muscle disorder defined by dilatation and impaired systolic function of the left ventricle or both ventricles, in the absence of coronary artery disease, valvular abnormalities or pericardial disease.

Diagnostic criteria:

1. Ejection fraction of the left ventricle <0·45 (>2 SD) and/or factional shortening <25% (>2 SD), as ascertained by echocardiography radionucliide scanning angiography or cardiac magnetic resonance imaging.
2. Left ventricular end-diastolic diameter >117% of the predicted value corrected for age and body surface area[Henry formula], which corresponds to 2 SD of the predicted normal limit +5%.

{Henry equation: (45·3(BSA)1/3"0·03(age)"7·2)}

Ref: (See ref: Mestroni L et al. *European Heart Journal* (1999) **20,** 93–102)

Familial Disease:

The diagnosis of familial dilated cardiomyopathy is made:

3. In the presence of two or more affected individuals in a single family OR
4. In the presence of a first-degree relative of a patient that has dilated cardiomyopathy with well-documented, unexplained sudden death [1] at <35 years of age

Diagnostic Criteria in Relatives

Affected

- The presence of the major criteria (left ventricular dilatation and systolic dysfunction) OR
- Left ventricular dilatation (>117%)+one minor criterion OR
- Three minor criteria.

Unknown

The presence of one or two minor criteria.

Unaffected

- Individuals with normal hearts.
- The presence of other causes of myocardial disease.

Major criteria	**Minor criteria**
A reduced ejection fraction of the left ventricle (< 45%) and/or fractional shortening (< 25%) as assessed by echocardiography, radionuclide scanning, or angiography.	- Unexplained supraventricular or ventricular arrhythmia. - Ventricular dilatation (> 112% of the predicted value). - An intermediate impairment of left ventricular dysfunction.
An increased left ventricular end-diastolic diameter corresponding to > 117% of the predicted value corrected for age and body surface area (Manolio et al.	- Conduction defects. - Segmental wall motion abnormalities in the absence of intraventricular conduction defect or ischaemic heart disease.

1992)*.	- Unexplained sudden death of a first-degree relative or stroke before 50 years of age.

*Manolio TA, Baughman KL, Rodeheffer R et al. Prevalence and etiology of idiopathic dilated cardiomyopathy (summary of a National Heart, Lung and Blood Institute Workshop). Am J Cardiol 1992; 69: 1459–66

Hypertrophic cardiomyopathy

Definition: left ventricular hypertrophy in the absence of loading conditions to account for the observed degree of hypertrophy.

The diagnosis for HCM in an index case is a a maximum left ventricular wall thickness of ≥ 15 mm in one or more myocardial segments.

For the clinical diagnosis of HCM to be established in a first degree relative one of the following requirements needs to be satisfied (see table):

- One major criterion, OR
- Two minor echocardiographic criteria, OR
- One minor echocardiographic plus 2 minor ECG criteria.

Criteria for HCM in first degree relatives. (modified from McKenna et al. Heart 1997;77:130-132.)	
Major criteria	**Minor criteria**

LV wall thickness >13mm in the anterior septum or posterior wall or >15mm in the posterior septum or lateral free wall	LV wall thickness >12mm in the anterior septum or posterior wall or >14mm in the posterior septum or lateral free wall
Severe SAM with septal contact	Moderate SAM with no septal contact
	Redundant MV leaflets.
LVH and repolarisation changes (Romhilt & Estes)	Complete BBB or (minor) interventricular conduction defect (in LV leads)
Abnormal Q (> 40 ms or >25% R wave) in at least 2 leads from II, III, aVF (in absence of left anterior hemiblock), V1-V4; or I, aVI, V5-V6	Deep S V2 (> 25mm)
T wave inversion in leads I and aVL (> 3mm) (with QRS-T wave axis difference > 30°), V3-V6 (> 3 mm) or II and III and aVF (> 5 mm)	Minor repolarisation changes in LV leads

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease characterised by:

- Myocyte loss with fatty or fibro-fatty replacement predominately of the right ventricle (30 % also have left ventricular involvement)
- Ventricular arrhythmias
- Congestive heart failure and sudden cardiac death

Diagnostic criteria

The criteria for ARVC are based on the identification of:

- Right ventricular functional and structural abnormalities
- Fibro-fatty replacement of the right ventricular myocardium
- Electrocardiographic repolarization abnormalities
- Electrocardiographic depolarization abnormalities
- Arrhythmias of right ventricular origin
- Familial disease
- Genetic mutations

Diagnostic criteria are classified as **major or minor**, according to their specificity for the disease. The diagnostic terminology is:

Definite diagnosis: two major, or one major and two minor or four minor criteria from different categories

Borderline diagnosis: one major and one minor or three minor criteria from different categories

Possible diagnosis: one major or two minor criteria from different categories

Table 3: 2010 Task force criteria for the diagnosis of ARVC (Modifi ed from Marcus F.I., McKenna W.J. *et al. Eur Heart J* 2010; **31** : 806–814.)

I Global and/or regional dysfunction and structural alterations

<u>Major</u>

By 2D echo: regional RV akinesia, dyskinesia, or aneurysm *and* 1 of the following (end diastole):

- PLAX RVOT ≥ 32 mm (corrected for body size [PLAX/BSA] ≥ 19mm/m 2).
- PSAX RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥ 21mm/m 2) OR
- Fractional area change ≤ 33%.

By MRI: regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following:

- Ratio of RV end-diastolic volume to BSA ≥ 110mL/m 2 (male) or ≥ 100mL/m 2 (female) OR
- RV ejection fraction ≤ 40%.

By RV angiography: regional RV akinesia, dyskinesia, or aneurysm.

Minor

By 2D echo: regional RV akinesia or dyskinesia *and* 1 of the following (end diastole):

- PLAX RVOT ≥ 29 to <32mm (corrected for body size [PLAX/BSA] ≥ 16 to <19mm/m 2).
- PSAX RVOT ≥ 32 to <36mm (corrected for body size [PSAX/BSA] ≥ 18 to <21mm/m 2) OR
- Fractional area change > 33 % to ≤ 40 %.

By MRI: regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following:

- Ratio of RV end-diastolic volume to BSA ≥ 100 to <110mL/m 2 (male) or ≥ 90 to <100mL/m 2 (female) OR
- RV ejection fraction > 40 % to ≤ 45 %.

II Tissue characterization of walls

Major

Residual myocytes <60 % by morphometric analysis (or <50 % if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.

Minor

Residual myocytes 60–75 % by morphometric analysis (or 50–65 % if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.

III Repolarization abnormalities

Major

Inverted T waves in right precordial leads (V 1, V 2, and V 3) or beyond in individuals > 14 years of age (in the absence of complete right bundle-branch block QRS ≥ 120ms).

Minor

Inverted T waves in leads V 1 and V 2 in individuals > 14 years of age (in the absence of complete right bundle-branch block) or in V 4, V 5, or V 6 Inverted T waves in leads V1, V2, V3 and V4 in individuals > 14 years of age in the presence of complete right bundle-branch block).

IV Depolarisation/conduction abnormalities

Major

Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V 1 to V 3).

Minor

Late potentials by SAECG in ≥ 1 of 3 parameters in the absence of a QRS duration of ≥ 110ms on the standard ECG:

- Filtered QRS duration (fQRS)
- ≥ 114ms; duration of terminal QRS <40μV (low-amplitude signal duration)

- ≥ 38ms; root-mean-square voltage of terminal 40ms ≤ 20μV
- Terminal activation duration of QRS ≥ 55ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2 or V3, in the absence of complete right bundle-branch block.

V Arrhythmias

Major

Non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III and aVF and positive in lead aVL).

Minor

Non-sustained or sustained ventricular tachycardia of RV outfl ow confi guration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis > 500 ventricular extrasystoles per 24 hours (Holter).

VI Family history

Major

- ARVC/D confi rmed in a first-degree relative who meets current Task Force criteria.
- ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative.
- Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation.

Minor

- History of ARVC/D in a fi rst-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
- Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative
- ARVC/D confirmed pathologically or by current Task Force Criteria in a second-degree relative
- PLAX, parasternal long-axis view; RV, right ventricular; RVOT, right ventricular outflow tract.
- BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar.
- left foot lead; aVL, augmented voltage unipolar left arm lead.

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is the least common of all the cardiomyopathies. It is characterised by increased stiffness of the myocardium which causes ventricular pressure to rise steeply with small increases in volume in the presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes and normal ventricular wall thickness.

Restrictive ventricular physiology also occurs in other cardiomyopathies including HCM and DCM. In this registry, RCM should be diagnosed only when there is objective evidence for elevated left ventricular filling pressure, based on conventional echocardiographic Doppler or invasive haemodynamic measurements in patients with a left ventricular ejection fraction > 0.45, normal left ventricular wall thickness (corrected for geneder and body size) and no evidence of pericardial constriction

SUPPLEMENTAL FILE 3: Definitions of subgroups of patients

Some subgroups analyses were performed according to the following definitions.

Proband was defined as the first patient identified in the family with a diagnosis of a cardiomyopathy and a relative was defined as a relative of this proband, who should also have a diagnosis of a cardiomyopathy to be able to be enrolled.

Incident patient was defined as a patient with a first evaluation less than one year before date of inclusion, and prevalent patient as a patient with a first evaluation more than one year before date of inclusion.

Pilot phase was defined as patients enrolled during the first phase of the project (inclusion between 1th December 2012 and 30th November 2013 in preselected referral highly expert centers) and Long term phase was defined as patients enrolled during the second phase of the study (inclusion between 06thJune 2014 and 30th December 2016 in centers with more variable expertise).

Geographical areas were defined as North vs South vs East vs West Europe vs North Africa according to United Nations geoscheme for Europe (https://unstats.un.org/unsd/methodology/m49/). East Europe: Belarus, Czech Republic, Hungary, Poland, Romania; North Europe: Denmark, Finland, Great Britain, Lithuania, Sweden; South Europe: FYR Macedonia, Greece, Italy, Portugal, Serbia, Spain, Turkey; West Europe: Austria, France, Germany, Netherlands; North Africa: Egypt.