PROFID EHRA

profid-project.eu

PRevention Of sudden cardiac death aFter myocardial Infarction by Defibrillator implantation

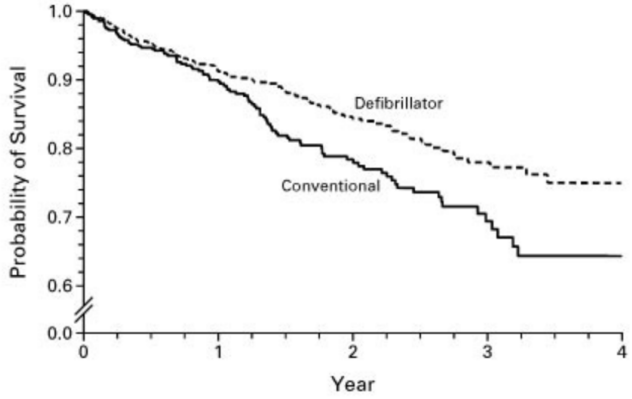
28 June 2024

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847999

PROFID EHRA TRIAL: BACKGROUND

- **Evidence basis for current strategy**

MADIT-II

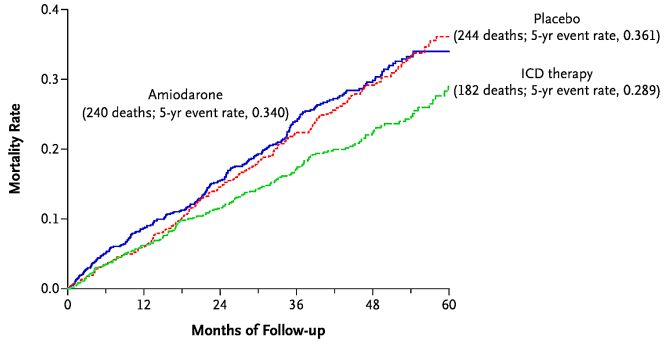


No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Moss A et al. N Engl J Med. **2002**

SCD-HeFT

	Hazard Ratio (97.5% CI)	P Value
Amiodarone vs. placebo	1.06 (0.86–1.30)	0.53
ICD therapy vs. placebo	0.77 (0.62–0.96)	0.007



No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD therapy	829	778	733	501	304	103

Bardy G et al, N Engl J Med. **2005**

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ICD for primary prevention of SCD

	ESC Guidelines	US Guidelines
Ischaemic HF		
LVEF <35% + NYHA Class II–III	Recommendation: Class I Level of evidence: A	Recommendation: Class I Level of evidence: A
LVEF <30% + NYHA Class I	Not recommended	Recommendation: Class I Level of evidence: A
LVEF <40% + NSVT + inducible VTA	Not recommended	Recommendation: Class I Level of evidence: B
Time after MI	≥6 weeks	≥40 days ≥3 months if patients underwent cor ≥4 days if NSVT + inducible VT/VF
Non-ischaemic HF		
LVEF <35% + NYHA Class II–III	Recommendation: Class I Level of evidence: B	Recommendation: Class I Level of evidence: B
LVEF <35% + NYHA Class I	Not recommended	Recommendation: Class IIb Level of evidence: C
Time on OMT	≥3 months	≥3 months

PROFID EHRA TRIAL: BACKGROUND

- **Evidence basis for current strategy**

  Reduced LVEF is risk marker for:

  – Total mortality

  – Cardiac mortality

  – Sudden cardiac death

  => Non-specific risk marker for sudden and non-sudden cardiac death

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PROFID EHRA TRIAL: BACKGROUND

- **Changes in treatment in the last 25 years**
  - Beta blockers
  - Mineralocorticoid antagonists
  - ARNI
  - SGLT2 inhibitors
  - Statins
  - Primary recanalization
  - Cardiac resynchronization therapy
  - …

  Most of these reduce not only mortality but ***specifically sudden cardiac death***

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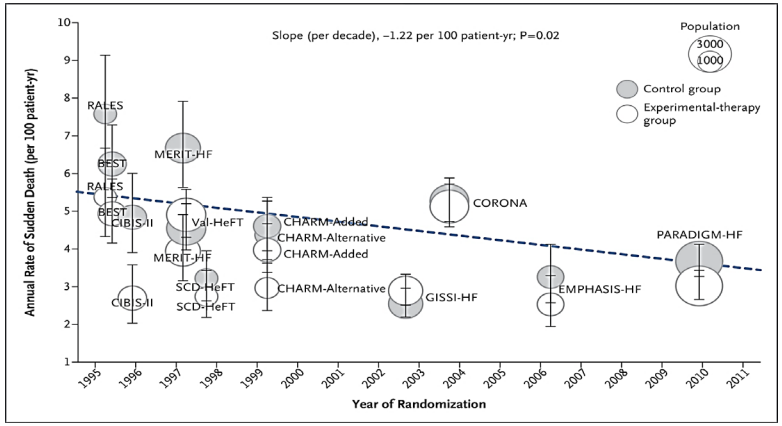
PROFID EHRA TRIAL: RATIONALE

- **Reduced SCD risk** over the last two decades.
- Decreased annual shock rate.



Shen L et al. N Engl J Med **2017**;377:41-51

Trial	Year	Average duration (mo)	Average annual rate of appropriate shock, %
MADIT II	2002	24	17
SCD-HeFT	2005	45.5	5
PREPARE	2008	12	5.4
MADIT-RIT	2012	16	3
ICD Registry	2014	20	1

Sabbag A et al. Heart Rhythm **2015**;12:2426–33

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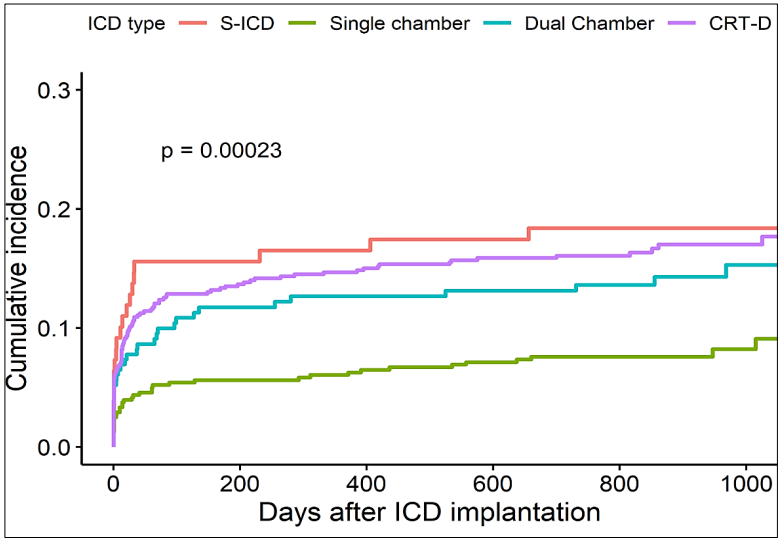
PROFID EHRA TRIAL: RATIONALE

- **Substantial complication rates** of ICD therapy exceeding 10%.



van Barreveld M, et al.
J Am Heart Assoc. 2021;10(7):e018063.

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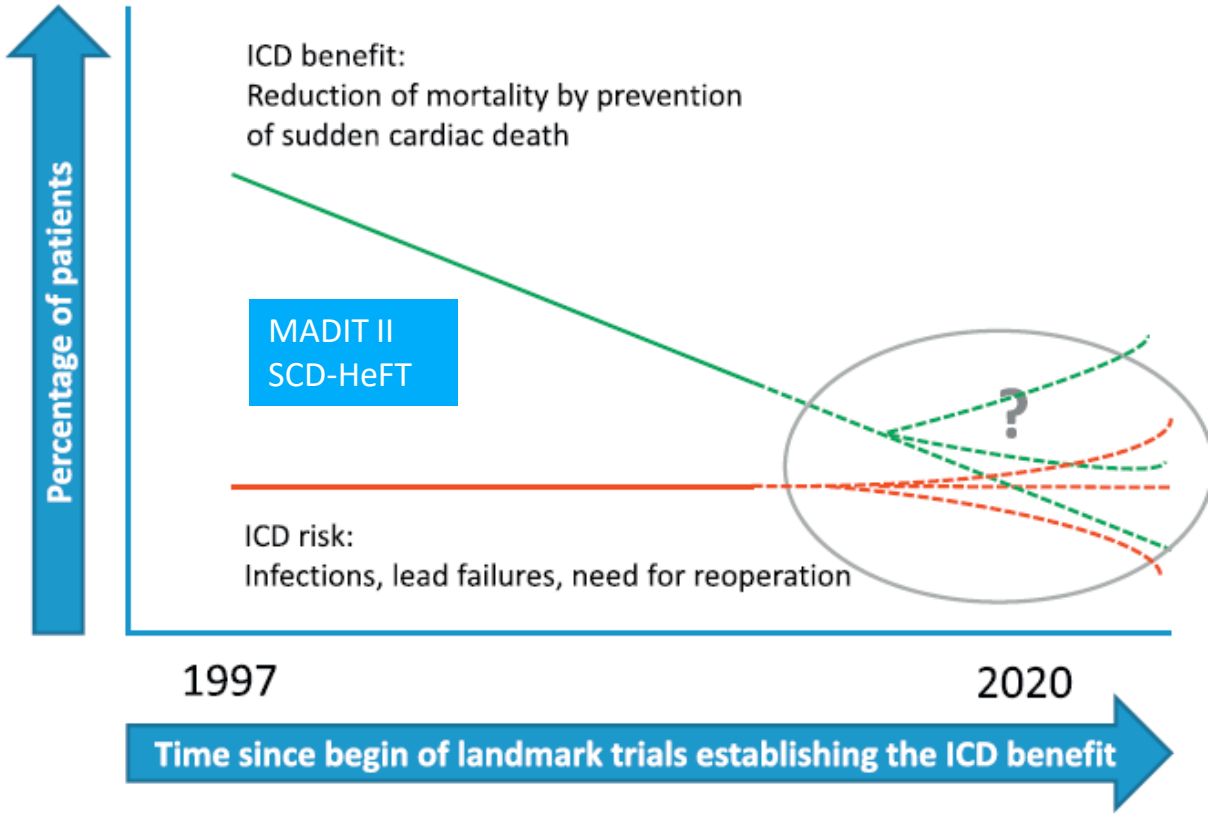
Projection of the benefit-risk ratio of the ICD



PROFID EHRA TRIAL: RATIONALE

- **Existing data is outdated** and does not represent current therapies.
- **New evidence** is necessary to define future strategy for primary prevention ICD implantation.
- A **novel randomized, adequately powered assessment** of the role of the defibrillator under contemporary optimal medical therapy is imperative.
- **EHRA and ESC strong supporters (PROFID EHRA trial)** to close the evidence gap.

EHRA
European Heart
Rhythm Association

ESC
European Society
of Cardiology

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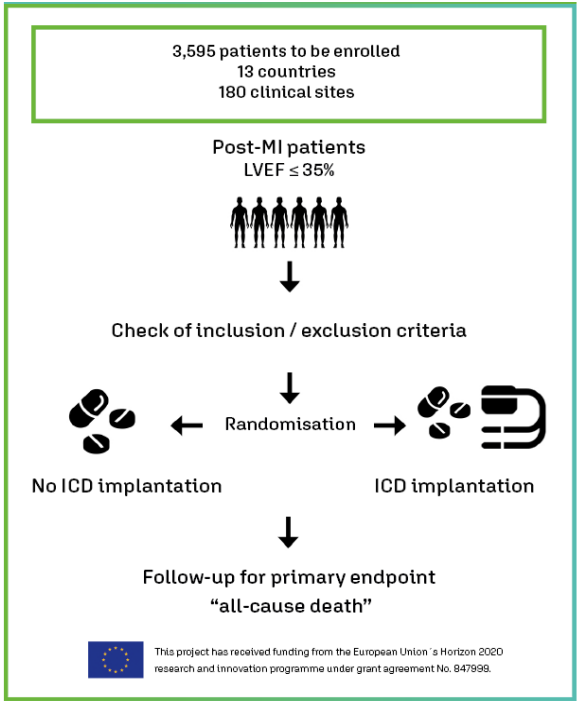
PROFID EHRA TRIAL: OBJECTIVES

Study population: **3,595 post-MI patients with symptomatic heart failure and reduced LVEF ≤35%,** all receive optimal medical therapy (OMT) for this condition

1. Demonstrate that **OMT without ICD implantation** (index group) is **not inferior to OMT with ICD implantation** (control group) with respect to **all-cause mortality** within about 2.5 years of observation.



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PROFID EHRA TRIAL: OBJECTIVES

2. Explore the potential of **novel and promising risk markers for personalised risk prediction of SCD**.
    - **Artificial intelligence(AI)-based analysis** of the body-surface Electrocardiograms (**ECGs**) collected at baseline and at follow-ups.
    - **Two sub-studies for personalised risk markers:**
        a. Cardiac Magnetic Resonance Imaging (cMRI)
        b. Genomics

>> Designed to be as close to routine clinical care as possible

>> Optional, thus only applicable for interested study sites

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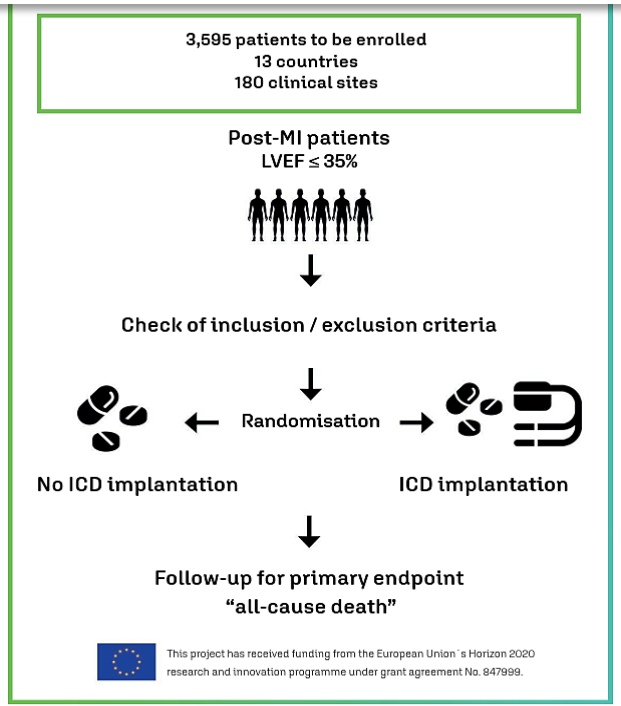
PROFID EHRA TRIAL: KEY FACTS

Reassess the role of routine prophylactic ICD implantation for primary prevention of SCD and change medical guidelines

Study design	Proof of strategy, event-driven, randomised, non-inferiority trial
Random groups	Index: OMT; Control: OMT+ICD
Objectives	(1) Demonstrate that OMT is not inferior to OMT+ICD within 2.5yrs of observation reg. all-cause mortality (2) Explore risk markers for personalised risk prediction – AI-based analysis of 12-lead ECG at BL and FU – **Optional sub-studies**: cMRI and genomics
Prim. Endpoint	(1) All-cause death (n=374)
Sec. Endpoints	(2) Death from cardiovasc. causes (3) First hospital readmissions for cardiovascular causes after randomisation. (4) Average length of stay in hospital during the study period. (5) QoL (EQ-5D-5L) trajectories over time at BL and 12-month intervals thereafter.
Duration	30 months enrolment, total study duration~49 months



PROFID EHRA TRIAL: PARTICIPATING COUNTRIES

Country*		National Coordinators (natCos)	Planned number of sites**
	DE	Prof. Philipp Sommer	85
	ES	Prof. José L. Merino	20
	FR	Prof. Serge Boveda	15
	AT	Prof. Helmut Pürerfellner	10
	NL	Prof. Kevin Vernooy	15
	PL	Prof. Radosław Lenarczyk	8
	HU	Prof. Béla Merkely	7
	DK	Prof. Jens Cosedis Nielsen	6
	BE	Prof. Tom De Potter	5
	CZ	Prof. Miloš Táborský	5
	SE	Prof. Frieder Braunschweig	5
	UK	Prof. Chris P. Gale	5
	IL	Dr. Mahmoud Suleiman	tbc

* Sorted acc. to the number of planned sites.
** Planned number of sites does not represent a fixed number.

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PROFID EHRA TRIAL: STUDY DESIGN

Key inclusion criteria	▪ Documented history of MI either as STEMI or as NSTEMI at least 3 months prior to enrolment. ▪ Symptomatic heart failure with NYHA class II or III. ▪ On OMT for at least 3 months prior to enrolment. ▪ LVEF ≤35% (at TTE or CMR at least 3 months after MI).
Key exclusion criteria	▪ Class I or IIa indication for an **ICD implantation for secondary prevention** of SCD and ventricular tachycardia. ▪ Ventricular tachycardia induced in an electrophysiologic study. ▪ Unexplained syncope when ventricular arrhythmia is suspected as the cause of syncope. ▪ Class I or IIa indication for **Cardiac Resynchronization Therapy (CRT)**. ▪ Acute coronary syndrome or coronary angioplasty or CABG within 6 weeks prior to enrolment. ▪ Cardiac valve surgery or percutaneous cardiac valvular intervention within 6 weeks prior to enrolment. ▪ On the waiting list for heart transplantation.

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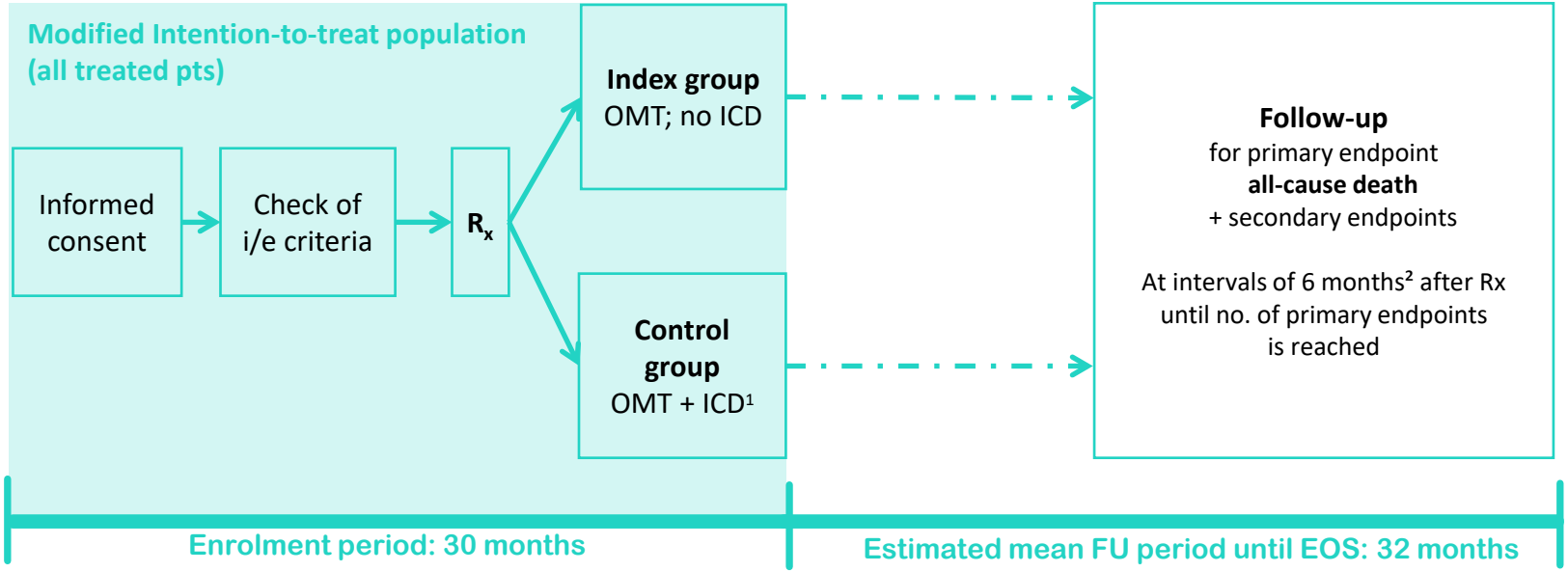
PROFID EHRA TRIAL: STUDY FLOW CHART



[1]Selection of adequate marketed devices is the responsibility of the treating physician and follows local policies
[2]Clinical visits at the study site at month 12 and 24 + FU questionnaires sent to patients at 6 month intervals in between clinical visits and thereafter
i/e: inclusion/exclusion; Rx: Randomisation; OMT: Optimal medical therapy; ICD Implantable cardioverter defibrillator

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PROFID EHRA TRIAL: VISIT SCHEDULE

Assessments **(FU visit schedules are aligned to date of randomisation)**	**Baseline**	**ICD implantation**	**FU at site month 12 + 24**	**cFU month 6 + 18 + 30** **(+ 6 month intervals thereafter)**	**Final FU**
Signed Informed Consent Form (ICF)	x				
Check of inclusion & exclusion criteria	x				
Randomisation	x				
Medical history assessment	x				
Physical examination	x		x		
Laboratory parameters	x				
12 lead Electrocardiogram (ECG), digital transfer	x		x		
Transthoracic echocardiography (TTE) or cardiac MRI according to local policy in routine clinical care	x				
Documentation of OMT & other concomitant medication	x		x		x
Quality of life questionnaires (EQ-5D-5L)	x		x	(x)[1]	
Documentation of ICD implantation		x			
Documentation and print-out of programmed settings of ICD		x	x		
Assessment of recorded events in memory of ICD			x		
SAEs		x	x	x	x

[1] *EQ-5D-5L will only be provided in 12-month intervals, i.e. 36 months and 48 months etc.*

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PROFID EHRA TRIAL: INVESTIGATOR FEE PAYMENTS

Visits to be compensated are:

- **Baseline Visit** with an amount of **600 €**
- **Implantation Visit** with an amount of **300 €**
- **Clinical Follow-up Visits** with an amount of **250 €** (=at study site, month 12 and 24)
- **Final Visit** with an amount of **100 €**

per patient
with/without ICD implantation:
1.500 €/1.200 €

Prerequisites for payment beyond others:

- Full documentation, adequate reply to all corresponding data queries, investigator's signature in the e-CRF

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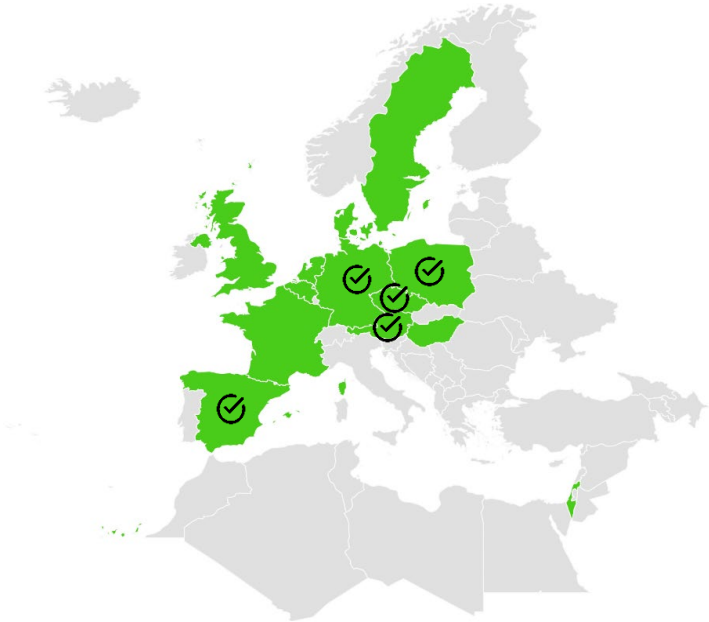
PROFID EHRA TRIAL: STATUS (25.06.2024)

PARTICIPATING SITES

- Initiated sites: 27
- Sites open for recruitment (OFR): 23
  - Austria: 2
  - Czech Republic: 1
  - Germany: 19
  - Poland: 0
  - Spain: 1
- Total goal: 180

ENROLLMENT STATUS

- Randomized patients: 58
  - Austria: 8
  - Czech Republic: 38
  - Germany: 12
  - Poland: 0
  - Spain: 0
- Total randomization goal: 3,595



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PROFID EHRA TRIAL: MORE INFORMATION

PROFID project website

PROFID EHRA trial website

PROFID EHRA trial flyer

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PRevention Of sudden cardiac death aFter myocardial Infarction by Defibrillator implantation

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Deutsches Herzzentrum der Charité

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