


# STereotactic Arrhythmia Radioablation (STAR): the Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary consortium (STOPSTORM.eu) and review of current patterns of STAR practice in Europe

Melanie Grehn <sup>1†</sup>, Stefano Mandija <sup>2†</sup>, Marcin Miszczyk <sup>3</sup>, David Krug <sup>1</sup>, Bartłomiej Tomasik <sup>4,5</sup>, Kristine E. Stickney<sup>6</sup>, Pino Alcantara <sup>7</sup>, Filippo Alongi<sup>8</sup>, Matteo Anselmino <sup>9,10</sup>, Ricardo Salgado Aranda <sup>11</sup>, Brian V. Balgobind<sup>12</sup>, Judit Boda-Heggemann<sup>13</sup>, Leif-Hendrik Boldt<sup>14</sup>, Nicola Bottoni<sup>15</sup>, Jakub Cvek <sup>16</sup>, Olgun Elicin <sup>17</sup>, Gaetano Maria De Ferrari <sup>9</sup>, Rutger J. Hassink <sup>18</sup>, Colien Hazelaar<sup>19</sup>, Gerhard Hindricks <sup>20</sup>, Coen Hurkmans <sup>21</sup>, Cinzia Iotti <sup>22</sup>, Tomasz Jadczyk <sup>23,24</sup>, Otakar Jiravsky <sup>25</sup>, Raphaël Jumeau <sup>26</sup>, Steen Buus Kristiansen<sup>27</sup>, Mario Levis <sup>28</sup>, Manuel Algara López <sup>29</sup>, Julio Martí-Almor <sup>30</sup>, Felix Mehrhof <sup>31</sup>, Ditte Sloth Møller <sup>32</sup>, Giulio Molon <sup>33</sup>, Alexandre Ouss <sup>34</sup>, Petr Pechl <sup>35</sup>, Jiri Plasek<sup>36</sup>, Pieter G. Postema <sup>37</sup>, Aurelio Quesada <sup>38</sup>, Tobias Reichlin <sup>39</sup>, Roberto Rordorf <sup>40</sup>, Boris Rudic <sup>41</sup>, Ardan M. Saguner<sup>42</sup>, Rachel M.A. ter Bekke <sup>43</sup>, José López Torrecilla <sup>44</sup>, Esther G. C. Troost<sup>45,46,47</sup>, Viviana Vitolo <sup>48</sup>, Nicolaus Andratschke <sup>49</sup>, Katja Zeppenfeld <sup>50</sup>, Slawomir Blamek <sup>4</sup>, Martin Fast <sup>2</sup>, Ludovica de Panfilis <sup>51</sup>, Oliver Blanck<sup>1</sup>, Etienne Pruvot <sup>52‡</sup>, and Joost J. C. Verhoeff <sup>2\*‡</sup>

<sup>1</sup>Department of Radiation Oncology, University Medical Center Schleswig-Holstein, Arnold-Heller-Strasse 3, Kiel 24105, Germany; <sup>2</sup>Department of Radiotherapy, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands; <sup>3</sup>Illrd Radiotherapy and Chemotherapy Department, Maria Skłodowska-Curie National Research Institute of Oncology, Ul. Wyrbrzeze Armii Krajowej, Gliwice 44102, Poland; <sup>4</sup>Department of Radiotherapy, Maria Skłodowska-Curie National Research Institute of Oncology, Ul. Wyrbrzeze Armii Krajowej, Gliwice 44102, Poland; <sup>5</sup>Department of Oncology and Radiotherapy, Faculty of Medicine, Medical University of Gdansk, M. Skłodowskiej-Curie 3a, Gdansk 80210, Poland; <sup>6</sup>Research Support Office, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands; <sup>7</sup>Department of Radiation Oncology, Hospital Clínico San Carlos, Faculty of Medicine, University Complutense of Madrid, Profesor Martin Lagos, Madrid 28040, Spain; <sup>8</sup>Department of Advanced Radiation Oncology, IRCCS Sacro Cuore Don Calabria Hospital, University of Brescia, Via San Zeno in Monte 23, Verona 37129, Italy; <sup>9</sup>Division of Cardiology, Cardiovascular and Thoracic Department, 'Città della Salute e della Scienza' Hospital, Via Giuseppe Verdi 8, Torino 10124, Italy; <sup>10</sup>Department of Medical Sciences, University of Turin, Via Verdi 8, Torino 10124, Italy; <sup>11</sup>Electrophysiology Unit, Department of Cardiology, Hospital Clínico San Carlos Madrid, Professor Martin Lagos, Madrid 28040, Spain; <sup>12</sup>Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Meibergdreef 15, Amsterdam 1105AZ, The Netherlands; <sup>13</sup>Department of Radiation Oncology, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, Mannheim 68167, Germany; <sup>14</sup>Department of Rhythmology, Charité—University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany; <sup>15</sup>Cardiology Arrhythmology Center, AUSL-IRCCS di Reggio Emilia, Via Amendola 2, Reggio Emilia 42100, Italy; <sup>16</sup>Department of Oncology, University Hospital and Faculty of Medicine, Listopadu 1790, Ostrava Poruba 70852, Czech Republic; <sup>17</sup>Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, Bern 3010, Switzerland; <sup>18</sup>Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands; <sup>19</sup>Department of Radiation Oncology (Maastr), GROW School for Oncology and Reproduction, Maastricht University Medical Centre+, P. Debyeilaan 25, Maastricht 6229 HX, The Netherlands; <sup>20</sup>Department of

\* Corresponding author. Tel: +3188-7558800, E-mail address: [j.j.c.verhoeff-10@umcutrecht.nl](mailto:j.j.c.verhoeff-10@umcutrecht.nl)

† Co-equal first authorship.

‡ Co-equal last authorship.

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

Electrophysiology, Heart Center Leipzig, University of Leipzig, Struempellstrasse 39, Leipzig 04289, Germany; <sup>21</sup>Department of Radiation Oncology, Catharina Hospital, Michelangelolaan 2, Eindhoven 5623 EJ, The Netherlands; <sup>22</sup>Radiation Oncology Unit, Clinical Cancer Centre, AUSL-IRCCS di Reggio Emilia, Via Amendola 2, Reggio Emilia 42100, Italy; <sup>23</sup>Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Ul. Poniatowskiego 15, Katowice 40055, Poland; <sup>24</sup>Interventional Cardiac Electrophysiology Group, International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic; <sup>25</sup>Cardiocenter, Hospital Agel Trinec Podlesi and Masaryk University, Kanska 453, Trinec 73961, Czech Republic; <sup>26</sup>Department of Radio-Oncology, Lausanne University Hospital, Rue du Bugnon 21, Lausanne 1011, Switzerland; <sup>27</sup>Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus 8200, Denmark; <sup>28</sup>Department of Oncology, University of Torino, Via Giuseppe Verdi 8, Torino 10124, Italy; <sup>29</sup>Department of Radiation Oncology, Hospital del Mar, Universitat Pompeu Fabra, Institut Hospital del Mar d'Investigacions Mèdiques, Paseo Maritim 25-29, Barcelona 08003, Spain; <sup>30</sup>Department of Cardiology, Hospital del Mar, Universitat Pompeu Fabra, Institut Hospital del Mar d'Investigacions Mèdiques, Paseo Maritim 25-29, Barcelona 08003, Spain; <sup>31</sup>Department for Radiation Oncology, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; <sup>32</sup>Department of Oncology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus 8200, Denmark; <sup>33</sup>Department of Cardiology, IRCCS Sacro Cuore Don Calabria Hospital, Via San Zeno in Monte 23, Verona 37129, Italy; <sup>34</sup>Department of Cardiology, Catharina Hospital, Michelangelolaan 2, Eindhoven 5623 EJ, The Netherlands; <sup>35</sup>Department of Cardiology, Institute for Clinical and Experimental Medicine, Videnska 9, Prague 14000, Czech Republic; <sup>36</sup>Department of Cardiovascular Medicine, University Hospital Ostrava, Listopadu 1790, Ostrava Poruba 70852, Czech Republic; <sup>37</sup>Department of Cardiology, Amsterdam UMC, University of Amsterdam, Meibergdreef 15, Amsterdam 1105AZ, The Netherlands; <sup>38</sup>Arrhythmia Unit, Department of Cardiology, Consorcio Hospital General Universitario de Valencia, Av Tres Cruces 2, Valencia 46014, Spain; <sup>39</sup>Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, Bern 3010, Switzerland; <sup>40</sup>Cardiac Intensive Care Unit, Arrhythmia and Electrophysiology and Experimental Cardiology, Fondazione IRCCS Policlinico San Matteo, Camillo Golgi Avenue 5, Pavia 27100, Italy; <sup>41</sup>Department of Medicine I, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, Mannheim 68167, Germany; <sup>42</sup>Arrhythmia Unit, Department of Cardiology, University Hospital Zurich, Ramistrasse 71, Zurich 8006, Switzerland; <sup>43</sup>Department of Cardiology, Maastricht University Medical Center, P. Debyealaan 25, Maastricht 6229 HX, The Netherlands; <sup>44</sup>Department of Radiation Oncology, Hospital General Valencia, Av Tres Cruces 2, Valencia 46014, Spain; <sup>45</sup>Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstraße 74, Dresden 01307, Germany; <sup>46</sup>OncoRay—National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Fetscherstrasse 74, Dresden 01307, Germany; <sup>47</sup>Institute of Radiooncology - OncoRay, Helmholtz-Zentrum Dresden-Rossendorf, Bautzner Landstr. 400, Dresden 01328, Germany; <sup>48</sup>National Center of Oncological Hadrontherapy (Fondazione CNAO), Strada Campeggi 53, Pavia PV27100, Italy; <sup>49</sup>Department of Radiation Oncology, University Hospital of Zurich, Ramistrasse 71, Zurich 8006, Switzerland; <sup>50</sup>Unit of Clinical Electrophysiology, Leiden University Medical Center, Albinusdreef 2, Leiden 2333 ZA, The Netherlands; <sup>51</sup>Bioethics Unit, Azienda Unità Sanitaria Locale—IRCCS, Via Amendola 2, Reggio Emilia 42100, Italy; and <sup>52</sup>Heart and Vessel Department, Service of Cardiology, Lausanne University Hospital and University of Lausanne, Rue du Bugnon 21, Lausanne 1011, Switzerland

Received 4 August 2022; accepted after revision 18 November 2022

## Abstract

The EU Horizon 2020 Framework-funded Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary (STOPSTORM) consortium has been established as a large research network for investigating STereotactic Arrhythmia Radioablation (STAR) for ventricular tachycardia (VT). The aim is to provide a pooled treatment database to evaluate patterns of practice and outcomes of STAR and finally to harmonize STAR within Europe. The consortium comprises 31 clinical and research institutions. The project is divided into nine work packages (WPs): (i) observational cohort; (ii) standardization and harmonization of target delineation; (iii) harmonized prospective cohort; (iv) quality assurance (QA); (v) analysis and evaluation; (vi, ix) ethics and regulations; and (vii, viii) project coordination and dissemination. To provide a review of current clinical STAR practice in Europe, a comprehensive questionnaire was performed at project start. The STOPSTORM Institutions' experience in VT catheter ablation (83%  $\geq$  20 ann.) and stereotactic body radiotherapy (59% > 200 ann.) was adequate, and 84 STAR treatments were performed until project launch, while 8/22 centres already recruited VT patients in national clinical trials. The majority currently base their target definition on mapping during VT (96%) and/or pace mapping (75%), reduced voltage areas (63%), or late ventricular potentials (75%) during sinus rhythm. The majority currently apply a single-fraction dose of 25 Gy while planning techniques and dose prescription methods vary greatly. The current clinical STAR practice in the STOPSTORM consortium highlights potential areas of optimization and harmonization for substrate mapping, target delineation, motion management, dosimetry, and QA, which will be addressed in the various WPs.

## Keywords

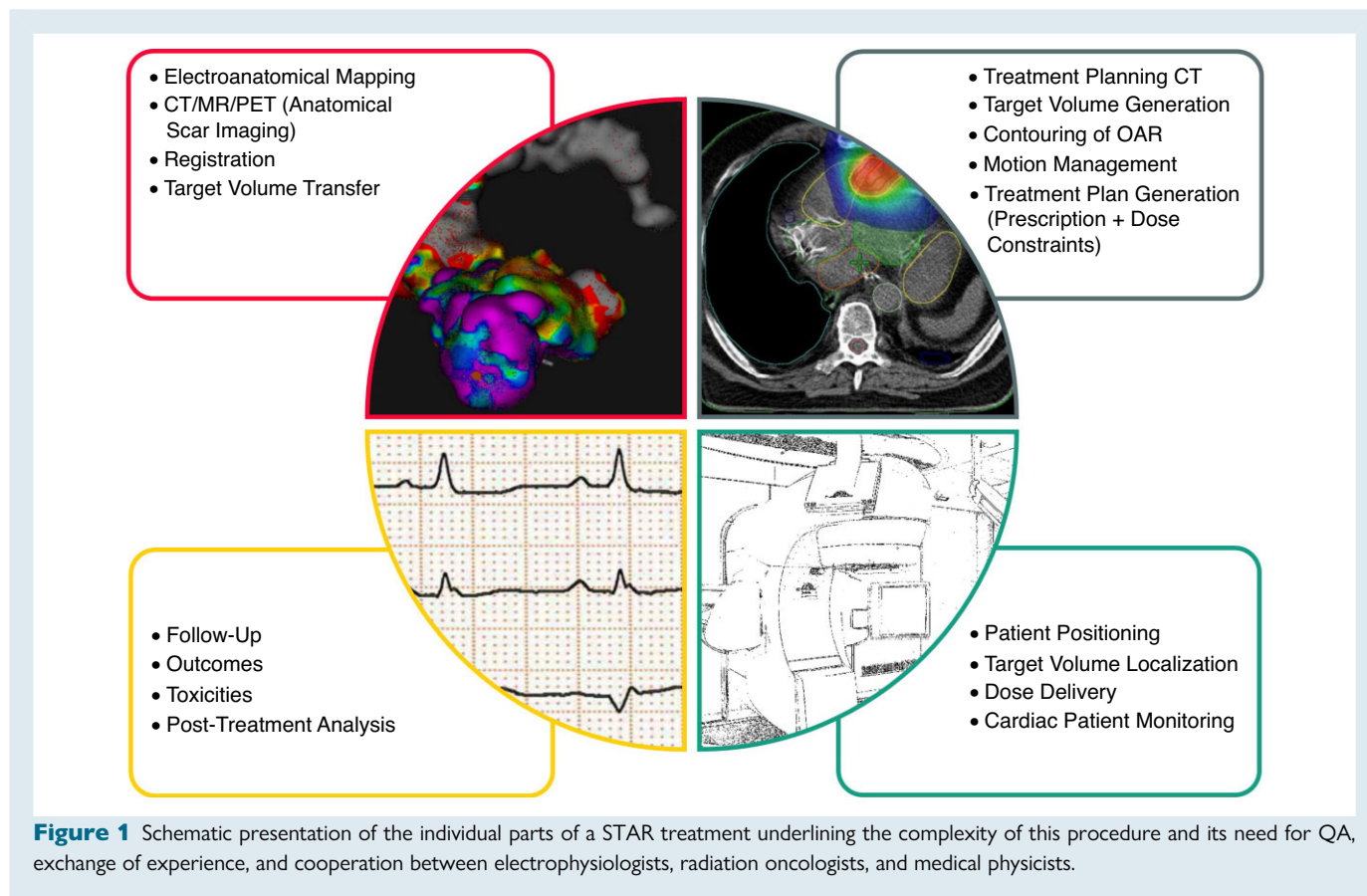
Stereotactic arrhythmia radioablation • Ventricular tachycardia • Cardiac arrhythmias • Stereotactic body radiotherapy • Consortium • EU Horizon 2020

## Introduction

Cardiovascular disease is one of the leading causes of death in Europe (45%).<sup>1</sup> In patients with structural heart disease (SHD), ventricular tachycardia (VT) and ventricular fibrillation play a decisive role in sudden cardiac death, and anti-arrhythmic medication and implantable cardioverter-defibrillators (ICDs) are used to minimize the risks.<sup>2</sup> Patients with refractory VT often undergo minimally invasive catheter ablation. However, many patients with advanced heart disease have secondary diagnoses that make invasive procedures difficult or impossible. Another limitation for performing ablation is the accessibility of the corresponding VT region. Deep intramural areas or subepicardial locations, especially in the vicinity of structures such as coronary arteries, make effective ablation difficult so that ~20–50% of the patients develop recurrent VT after catheter ablation.<sup>3,4</sup> For refractory VT

patients without other interventional options, cardiac stereotactic body radiation therapy (SBRT), called STereotactic Arrhythmia Radioablation (STAR), is now a new promising form of therapy.<sup>5,6</sup>

Preclinical studies on STAR were already realized in 2010,<sup>7</sup> while the first clinical STAR treatments for VT were accomplished as early as 2012<sup>8</sup> and 2014.<sup>9</sup> STAR treatments are based on a complex, interdisciplinary interaction of various diagnostic procedures, as well as quality assurance (QA) methods, and require a great amount of clinical experience in the respective areas.<sup>10</sup> A schematic presentation of the STAR process is shown in *Figure 1*. First, pre-planning takes place, in which an electrophysiologist defines the VT substrate. This is usually done based on electroanatomical mapping (EAM) data, which can be obtained, for example, from previous ablation procedures or dedicated non-invasive mapping systems, combined with anatomical scar imaging. The latter is performed through the assessment of echocardiography,



computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET)/scintigraphy imaging. The defined VT substrate must then be transferred to the contrast-enhanced cardiac CT and the planning CT for delineation of the target volume (TV) by the radiation oncologists for treatment planning.<sup>11–13</sup> Radiotherapy treatment delivery is another challenge in the case of STAR treatments because of respiratory and cardiac motion of the target area.<sup>13</sup> Furthermore, the indication for STAR treatment is often given at a short notice due to incessant VT or electrical storm.

Little is currently known about the possible acute and late radiation-related effects of STAR on the whole heart or on individual substructures. Furthermore, the exact radiobiological processes in healthy as well as diseased cardiac tissue are also not yet fully understood, though recent data suggest that STAR at lower doses (20–25 Gy) may quickly induce reprogramming of cardiac conduction, whereas radioablation at higher doses (> 30 Gy) may induce scar formation.<sup>14–17</sup> These different mechanisms further complicate accurate recommendations for the prescription dose, desired dose (in)homogeneity, and the maximum dose. Nevertheless, the first clinical data for STAR showed promising results with markedly reduced VT burden after treatment.<sup>10,18–21</sup> The first prospective clinical trial by Robinson *et al.* (NCT 02919618) evaluated the safety and efficacy of STAR. Limited acute toxicities were observed, with a 1-year survival rate which is comparable with survival rates of similar patients and an improvement in quality of life (QoL) over time with a marked reduction in VT burden.<sup>20</sup>

That said, the complexity of STAR with regard to substrate identification by EAM, target volume delineation, cardiac and respiratory motion management, and the application of high-dose single-fraction irradiation requires a high-quality standard for optimal safety and efficacy. Further multi-centre evaluation of this novel procedure is urgently needed,<sup>22,23</sup> despite several ongoing clinical trials for STAR currently

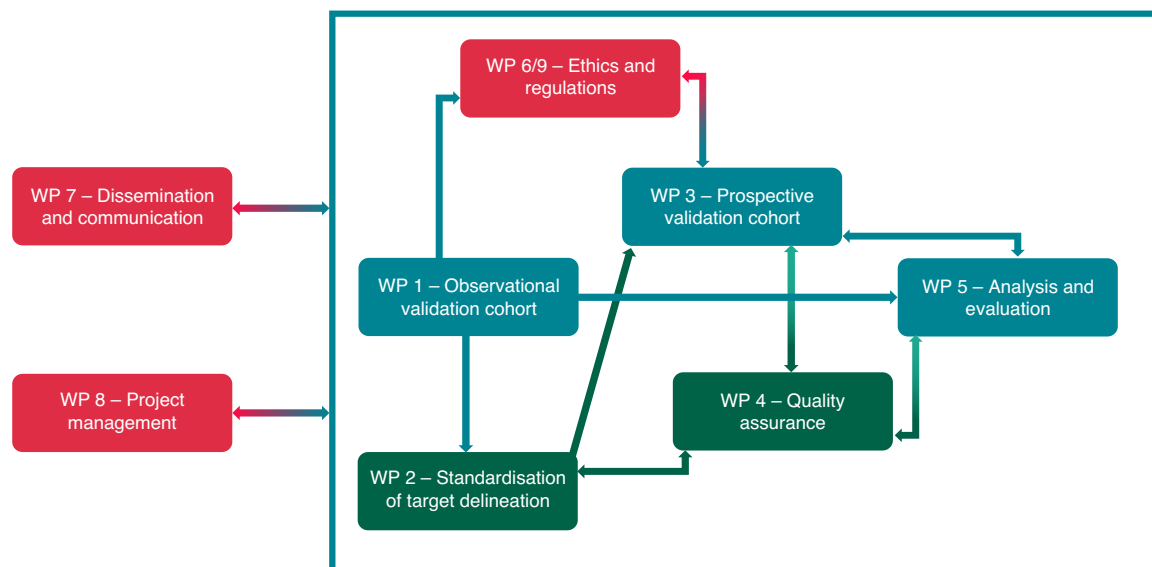
recruiting in Europe (e.g. NCT 03867747,<sup>23</sup> NCT 04642963,<sup>24</sup> and NCT 04066517<sup>25</sup>). A novel programme investigating STAR is the EU-funded Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary project (STOPSTORM consortium, Horizon 2020, GA No. 945119). The aim of this project is to establish a pooled STAR treatment database to evaluate efficacy and safety and to eventually harmonize STAR within Europe. Herein, in the first part of the article, we present an outline of the STOPSTORM project, followed by a review of current clinical STAR practice in Europe based on a comprehensive survey of the participating centres.

## STOPSTORM consortium

The STOPSTORM consortium comprises 31 clinical and research institutes in Europe (see <https://stopstorm.eu/en/consortium>). These include 24 electrophysiology (EP) and 22 radiation oncology (RO) departments. Additionally, five institutes have recently joined the consortium as participating centres, and participation remains open throughout the project to all centres in the European Union that want to or are already performing STAR treatments.

The main objectives of the STOPSTORM consortium project are as follows:

- (1) To implement a European registry infrastructure for collecting STAR data from all patients treated non-invasively for refractory VT:
  - (a) Observational data collection from patients who have been treated before the launch of the prospective validation cohort and from patients treated throughout the project who do not meet the selection and quality criteria of the prospective validation cohort.



**Figure 2** Presentation of the different WPs in the STOPSTORM project and their relationships. The early retrospective data collected in WP 1 will serve as base for several other WPs in order to develop workflows and guidelines in WP 2 and sequentially WP 4 and WP 6/9 and sequentially WP 3. WPs 2 and 4 are responsible for benchmarks and audits, credentialing and centralized treatment reviews for QA, while the fully clinical data collected and analysed in WP 1, 3, and 5 are used to establish harmonized quality criteria for STAR in Europe. WP 6–9 are responsible for project management and communication and for clinical and project ethics and other regulatory needs for the prospective validation cohort (WP3) and the accompanying national clinical trials.

- (b) Prospective data collection within the prospective validation cohort of the consortium that meets the selection and quality criteria evaluated by the credentialing and audit committee of the STOPSTORM consortium.
- (2) To harmonize, standardize, and optimize STAR treatment across Europe.
- (3) To validate the safety and efficacy of STAR in a larger patient cohort, while also:
  - (a) Deriving predictive factors for efficacy and outcome;
  - (b) Learning which patients benefit most from STAR (e.g. impact of underlying heart diseases, stage of heart failure, size, and type of VT substrate); and
  - (c) Modelling radiation dose–volume–response and deriving recommendations for optimal target delineation, dose prescription, critical structures selection, and their respective dose constraints.
 Where the following endpoints are analysed:
  - (i) Efficacy: 6-month survival free from VT storm and incessant VT (binary endpoint) including an initial blanking period of 8 weeks (primary project endpoint) and short- and long-term arrhythmic events/burden, medication, further treatments, QoL, and mortality (secondary analysis).
  - (ii) Safety: measured by registered adverse events using the CTCAE v5 system (primary endpoint), ‘early’ (up to 30 days), ‘intermediate’ (30–90 days), and ‘late’ (>90 days after treatment), and pattern-of-failure analysis (secondary analysis).
- (4) To work towards a consensus statement and multidisciplinary guidelines for the clinical implementation of STAR, regarding external audit and end-to-end treatment protocols for the procedure, which will improve the QoL of VT patients.

To meet these goals, the project is divided into nine work packages (WPs) (Figure 2) in order to work on optimal solutions for certain aspects of STAR: (i) observational validation cohort; (ii) standardization of target delineation; (iii) prospective validation cohort; (iv) QA of clinical structure delineation, treatment planning, and treatment delivery; (v)

analysis and evaluation; (vi) clinical ethics and regulations; (vii) dissemination, exploitation, and communication; (viii) project coordination and management; and (ix) EU project ethics requirements. Within the framework of WP 1 and 3, comprehensive patient data will be collected using an electronic data capture database (Castor EDC, Ciwit B.V., Amsterdam, The Netherlands) either retrospectively or prospectively of all STAR treatments performed by the consortium member institutions. For this purpose, regulatory and infrastructure prerequisites based on a definition of harmonized methods (STOPSTORM protocol) and parameters (electronic case report forms) are derived and used for setting up national prospective clinical trials and the STOPSTORM database. The full cohort will be split into two cohorts by the credentialing and audit committee based on a detailed treatment review audit of each case (WP 4) and based on defined selection and quality criteria (see the next section) and specified STAR quality guidelines from WP 2 and WP 4. In WP 2 (EP, target delineation) and WP 4 (RO, treatment delivery), dedicated benchmark studies and audits for target delineation based on invasive and non-invasive mapping, target transport methods from mapping to RO systems, critical structure contouring, radiation treatment planning, and radiation dose delivery (including an assessment on the impact of target motion) will be established and used as a base for early STAR quality guidelines and for accreditation of each participating centre in order to be enabled to submit data into the project database. Furthermore, WP 2 and WP 4 also contain the development of a dedicated STAR software solution to perform the standardized, centralized multi-centre multi-platform case review of the credentialing and audit committee and to facilitate a secondary independent means of treatment QA for each centre. Finally, the main implementation of harmonizing and optimizing STAR in Europe will come from the patient data evaluation of the two cohorts including dose–effect and outcome modelling in WP 5, where we hypothesize that the prospective cohort would demonstrate superior outcomes in terms of safety and efficacy. The result at the end of the project



will be a patterns-of-care analysis and according to consensus recommendations for STAR based on the collected clinical data and its analysis. Supporting the project, WP 6–9 are responsible for project organization, clinical and project ethical guidance, patient involvement, and other regulatory needs including the establishment of national observer groups.

## STAR treatment registry

At the time of the project start in May 2021, many patients have already been treated within the STOPSTORM consortium.<sup>10,19,21</sup> Based on previous STAR treatments and ongoing clinical trials in Europe, at least 317 patients are expected to be observationally/retrospectively ( $n=100$ ) and prospectively ( $n=217$ ) entered into the STAR treatment registry over the project period. All VT patients of age  $\geq 18$  treated with STAR at the consortium member institutions will be included in the registry, which comprises retrospective cases treated before the project start (observational validation cohort) as well as prospectively treated cases ideally included in ongoing approved local/national clinical trials with their trial protocols harmonized with the STOPSTORM consortium registry protocol (protocol number BASEC-2021-01730, approved by the Medical Ethical Committee of the Canton Zurich, Switzerland, 14 December 2021). The STOPSTORM consortium registry has been designed to include as many patients as possible, while allowing for data set uniformity and sufficient analytical power to determine the safety and efficacy of STAR. For this purpose, a specific set of selection criteria for the harmonized prospective validation cohort has been set for the STOPSTORM consortium registry, while all other cases that do not meet the following criteria will be added to the observational cohort:

- SHD: ischaemic cardiomyopathy (ICM) and/or non-ischaemic cardiomyopathy (dilatative cardiomyopathy/hypertrophic cardiomyopathy).
- Implantable cardioverter-defibrillator (ICD) and/or cardiac resynchronization therapy defibrillator.
- At least one sustained monomorphic VT recurrence under optimized anti-arrhythmic medication without demonstration of
  - acute myocardial infarction,
  - primary electrical disease (channelopathy),
  - reversible and treatable cause (e.g. drug-induced or intoxication) that can be adequately addressed otherwise.
- Prior  $\geq 1$  failed the catheter ablation procedure to control  $\geq 1$  sustained monomorphic VT or catheter ablation not feasible based on currently recommended mapping and ablation techniques.
- No evidence of active systemic, pulmonary, or pericardial inflammation that has required systemic treatment during the past 6 months (e.g. treatment with disease-modifying agents, corticosteroids, or immunosuppressive drugs).
- No uncontrolled cancer or chemo/immune therapy, either during the past month or planned within 1 month.
- Data acquisition performed prospectively (ideally within a prospective national clinical trial) with the
  - Target precisely defined based on the STOPSTORM quality requirements for STAR and
  - Target safely treated based on established STOPSTORM dose constraints and planning guidelines.

For the prospective cohort, all patients meeting the selection and quality criteria that signed written consent for pseudonymized data sharing in agreement with the European Union's General Data Protection Regulation will be registered in the STOPSTORM consortium STAR treatment registry before treatment and will undergo harmonized diagnostics, pre-treatment imaging, and at least 24 months of follow-up (Table 1). In addition, dedicated questionnaires before and after treatment, comprehensive treatment documentation, and data collection will enrich the STOPSTORM consortium database.

## National clinical trials

The STOPSTORM consortium comprises a STAR treatment registry but is not an actual interventional clinical trial. However, the project specifically supports national clinical trials through a dedicated STOPSTORM consortium ethics advisory board and through ethical and regulatory guidelines for STAR. Furthermore, in order to assign a STAR case to the harmonized prospective treatment registry, treatment within a clinical trial or according to a quality-assured STAR protocol with prospective registration and follow-up according to the standards of the STOPSTORM protocol is mandated. An overview of ongoing clinical trials for STAR in participating STOPSTORM centres is provided in Table 2.

## Quality assurance

To enable harmonization, standardization, and optimization of STAR treatments within the STOPSTORM consortium, a comprehensive QA programme including mandatory benchmark studies (target definition and contouring of cardiac substructures, treatment planning, and delivery) and audits (treatment unit quality audits and STAR case audits) and a dedicated STAR case review software for secondary QA has been established within the project, with detailed results being reported with the progress of the project. The QA programme and a case-by-case audit of each prospective STAR case are steered by an elected credentialing and audit expert committee. Due to the heterogeneity within the STOPSTORM consortium with varying expertise in STAR treatments in various countries in Europe, we performed a comprehensive survey through a questionnaire on patterns of practice for STAR. The QA programmes regarding catheter ablation and stereotactic radiotherapy were enquired at the beginning of the project, and the results are presented and discussed in the following sections.

## Patterns of practice for STAR

### STOPSTORM consortium survey

For the survey on the patterns of practice of STAR, a comprehensive questionnaire was developed which was divided into three sections: cardiology/EP (18 items), RO (24 items), and medical physics (23 items). The cardiology/EP section included questions about the organization, experience, and technical equipment of the departments for catheter ablation of VT, as well as specific inquiries on STAR (patient selection, mapping, and imaging techniques). The RO section consisted of questions on organization, experience with SBRT,<sup>26</sup> as well as specific inquiries on STAR (number of treatments performed, ongoing clinical trials, contouring, TV definition, treatment specifications, and delivery). Questions about radiotherapy equipment, corresponding quality controls, dosimetry, and QA were clarified in the medical physics section of the questionnaire. The full questionnaire can be found in [Supplementary material online, Appendix S1](#). The survey was developed by the management board of the consortium consisting of 17 electrophysiologists, radiation oncologists, and medical physicists using a three-staged agreement process. The survey was then sent to the representatives of each STOPSTORM partner site at the beginning of the project to be filled out by the site's specialists. The evaluation was done using Excel and descriptive statistics (Version 2207, Microsoft 365, Microsoft Corporation, Redmond, USA).

### Cardiology/electrophysiology

The majority of the STOPSTORM consortium cardiology/EP departments are participating in multi-centre clinical trials for VT ablation (23/24, 96%), and more than two-thirds perform 20–100 VT ablations per year (17/24, 71%), while three centres (3/24, 13%) perform annually more than 100 ablations in SHD. Also, more than two-thirds of the

**Table 1** STOPSTORM.eu data collection theme

Clinical examination ECG	Data uploaded to STOPSTORM.eu Registry	Pre-RT	RT	Day	Week	Month	Month	Month	Month	Month	Month
			1	1	1	3	6	9	12	18	24
	No	M	—	M	M	M	M	M	M	M	M
	Yes	M	—	—	—	M	M	M	M	M	M
EP map (invasive/ non-invasive)	Screenshots (M), full data (optional)	M (at least one of the two)	—	—	—	—	—	—	—	—	—
Lung Function	No	O	—	—	—	O	—	—	O	—	O
FDG-PET	Yes	O	—	—	—	O	—	—	O	—	O
SPECT	Yes	O	—	—	—	O	—	—	O	—	O
MRI	Yes	O	—	—	—	O	—	—	O	—	O
Cardiac CT (+contrast)	Yes	M	—	—	—	O	—	—	O	—	—
RT Planning CT	Yes	M	—	—	—	—	—	—	—	—	—
(RT) plan + delivery	Yes	—	M	—	—	—	—	—	—	—	—
NIPS	No	O	—	—	—	—	O	—	O	—	—
Transthoracic Echocardiography	No	M	—	—	—	M	—	—	M	—	M
ICD readout	Yes	M	—	O	O	M	M	M	M	M	M
Medications	No	M	M	M	M	M	M	M	M	M	M
Blood samples	No	M	—	O	O	O	—	—	O	—	O
Chest X-Ray	No	O	—	—	—	O	—	—	O	—	O
Transoesophageal echocardiography	No	O	—	O	O	O	O	O	O	O	O
CTCAE v5	Optional	M	—	M	M	M	M	M	M	M	M
PROMS	Optional	M	—	—	O	M	M	M	M	M	M
EQ5D	Optional	M	—	M	M	M	M	M	M	M	M
Physician Reported Quality of Life	Optional	M	—	M	M	M	M	M	M	M	M

RT, radiotherapy; M, mandatory; O, optional; ECG, electrocardiography; EP, electrophysiology; FDG, fludeoxyglucose; PET, positron emission tomography; SPECT, single photon emission computed tomography; MRI, magnetic resonance imaging; CT, computed tomography; NIPS, non-invasive programmed stimulation; ICD, implantable cardioverter-defibrillator; CTCAE, Common Terminology Criteria for Adverse Events; PROMS, patient-recorded outcome measures; EQ5D, standardized measure of health-related quality of life.

departments use EAM for preprocedural imaging of the VT substrate for STAR within their institutional protocol (17/24, 71%). In contrast, non-invasive ECG-based mapping (ECGI)<sup>18,20</sup> so far found little use clinically (3/24, 13%), for research purposes (2/24, 8%), and for evaluation of the STAR procedure (1/24, 4%). Nuclear imaging has little application within the consortium (PET: 8/24, 33%; single photon emission CT SPECT: 3/24, 13%). General quality audits for ablation are rarely implemented in the participating centres (9/24, 37%). Detailed information on the cardiology/EP in the questionnaire can be found in [Supplementary material online, Tables S1 and S2](#).

## Radiation oncology and medical physics

More than three-quarters of the RO departments have more than 10 years of experience in SBRT (18/22, 82%), and the majority have already participated in multi-centre clinical trials (21/22, 95%). About three-quarters of the radiotherapy systems are calibrated according to small-field dosimetry guidelines (17/22, 77%), mainly in reference to the International Atomic Energy Agency (IAEA) report 483 (11/17, 65%).<sup>27</sup> Furthermore, more than half of these centres perform small-

field dosimetry for absolute dose calibration (10/17, 59%). External audits and dosimetry audits are not yet performed in all departments (13/22, 59%; and 16/22, 73%, respectively). In three-quarters of participating sites, end-to-end tests are integrated specifically for SBRT (17/22, 77%). Detailed information on the RO and medical physics sections of the questionnaire can be found in [Supplementary material online, Tables S3–S6](#).

## STAR treatment

At the start of the STOPSTORM project in May 2021, almost three-quarters of the STOPSTORM consortium members reported having already performed STAR (16/22, 73%), with a total number of 84 patients treated. For more than two-thirds of the centres performing STAR, treatments were based on a dedicated STAR protocol or on a running clinical trial (11/16, 69%). Prerequisites as indication and contraindications for STAR treatments of the STOPSTORM consortium members are shown in [Table 3](#).

Most of the centres perform dedicated EAM procedures before STAR treatments (17/24, 71%) while almost two-thirds merge their

**Table 2** Overview of ongoing and planned national clinical trials for STAR in the STOPSTORM.eu consortium

Name Clinical Trial	Identifier	Start	Origin Country	Status	Estimated Enrollment	Trial Method
Noninvasive Radiosurgical Ablation of Ventricular Tachycardia (NIRA-VT)	NCT03601832	08/2018	Czech Republic	Discontinued after six patients	10	Prospective interventional single-arm Stage I/II Study
STereotactic Arrhythmia Radiotherapy Netherlands (STARNL-1)	NL7510	04/2019	The Netherlands	Complete	6	Prospective interventional single-arm Stage I/II feasibility and safety study
STereotactic RadioAblation by Multimodal Imaging for VT (STRA-MI-VT)	NCT04066517	09/2019	Italy	Actively recruiting	15	Prospective interventional single-arm Stage I/II Study safety and efficacy study
Mapping guided Stereotactic ablative Radiotherapy	NL7950	09/2019	The Netherlands	Actively recruiting	12	Prospective interventional single-arm Stage I/II feasibility and safety study <sup>a</sup>
Radiotherapy for the Treatment of Refractory Ventricular Extrasystoles and Tachycardias (RAVENTA)	NCT03867747	12/2019	Germany	Actively recruiting	20	Prospective, multi-centre, multi-platform interventional single-arm Stage I/II feasibility and safety study <sup>a</sup>
Stereotactic Management of Arrhythmia—Radiotherapy in Treatment of Ventricular Tachycardia (SMART-VT)	NCT04642963	09/2020	Poland	Actively recruiting	11	Prospective interventional single-arm Stage I/II safety study <sup>a</sup>
STereotactic Ablative Radiotherapy of Recurrent Ventricular Tachycardia in Structural Heart Disease (STAR VT)	NCT04612140	10/2020	Czech Republic	Actively recruiting	100	Multi-centre inclusion, single-centre STAR prospective interventional, randomized two-arm study on clinical effects
PROspective feasibility study of STereotactic Arrhythmia Radioablation (PRO-STAR)	NL9752	11/2021	The Netherlands	Actively recruiting	11	Prospective interventional single-arm Stage I/II safety and efficacy study <sup>a</sup>
Electroanatomic substrate-guided STereotactic Ablative Radiotherapy for refractory Ventricular Tachycardia (ELSTAR-VT)	NL9339	02/2022	The Netherlands	Actively recruiting	23	Prospective, multi-centre, single-arm, interventional single-arm Stage I/II study
RANIT	2019/8857/1	02/2020	Spain	Actively recruiting	5–7/year	Prospective, multi-centre, STAR treatment register with dedicated treatment protocol <sup>a</sup>
POP-STAR	tbd	tbd	Italy	Planned	5–7/year	Prospective, multi-centre, STAR treatment register with dedicated treatment protocol <sup>a</sup>

<sup>a</sup>Harmonized with the STOPSTORM protocol.

**Table 3** Prerequisites and contraindications for STAR treatments indicated by the electrophysiology/cardiology departments of the STOPSTORM consortium

		# Centres	# In percent
Prerequisites	Structural heart disease	16	67%
	Presence of ICD	17	71%
	Recurrent sustained monomorphic	19	79%
	Electrical storm	12	50%
	Optimal anti-arrhythmic and heart failure medication	21	88%
	One or more previous failed catheter ablations	22	92%
	Contraindications to invasive catheter ablation	15	63%
Contraindications	Polymorphic VT	10	42%
	Ventricular fibrillation	10	42%
	Temporary causes of VT	22	92%
	Channelopathies	18	75%
	Eligibility for invasive catheter ablation	2	8%
	Advanced heart failure NYHA IV	9	38%
	ICD malfunction	14	58%
	Prior chest irradiation	3	13%
	Life expectancy < 6 months	13	54%
	Pregnancy	24	100%
	Young age (e.g. < 60 years)	4	17%
	Breastfeeding	20	83%
	VT region directly adjacent to risk structure	7	29%

A total number (#) of 24 centres were asked. ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; NYHA, New York Heart Association (classification of heart disease).

mapping data with CT or MRI images during the procedures (15/24, 63%). Furthermore, three-quarters of the centres perform motion compensation during EAM (18/24, 75%), while only few departments implemented QA methods for these processes (5/18, 28%).

For TV definition for the VT substrate, dedicated interdisciplinary STAR teams are installed in all centres. However, the methods of TV delineation and transport from the EAM to the radiotherapy planning systems vary greatly. The basis for TV delineation is mainly mapping during VT (23/24, 96%), and also pace mapping (18/24, 75%), reduced voltage mapping (15/24, 63%), late ventricular potentials/fragmented potentials mapping (18/24, 75%), and other methods (5/24, 21%) such as scar imaging on CT/MRI (1/5, 20%), presumable channels on CT/MRI wall-thinning maps (1/5, 20%), evoked delayed potentials (2/5, 40%), and isochronal late activation mapping (1/5, 20%). Almost half of the centres include only the specific clinical VT areas in the TV (10/24, 42%), while the same number always includes the whole arrhythmogenic substrate. Over half of the centres perform the TV transfer to the radiotherapy treatment planning systems (TPSs) manually by visual matching (12/22, 55%, e.g. <sup>12</sup>), while others use a combination of manual transport and software-aided data review tools (4/22, 18%, e.g. STOPSTORM consortium review software), or use the American Heart Association (AHA) 17-segment model for atlas-based TV definition (1/22, 5%, e.g. <sup>28,29</sup>) or use in-house or open-source 3D data matching software only (2/22, 9%, e.g. <sup>11,30–32</sup>).

For radiotherapy treatment planning imaging (TPI), most centres use 4D CT for respiratory motion assessment (18/22, 82%), while the rest uses breath-hold techniques in inspiration and/or expiration. Less than half of the centres use additional ECG-triggered cardiac CT for patient-specific cardiac motion assessment.

Different definitions are used for organs at risk (OAR) contouring of cardiac substructures.<sup>33–36</sup> For example, 63% (12/19) contour the whole ventricle including the blood pool, while 21% (4/19) contour

the ventricle wall. For the coronary arteries, typically only one structure is contoured including proximal, mid, and distal parts (12/20, 60%). Treatment uncertainty margins to generate the planning target volume (PTV) for radiotherapy treatment planning range between 0 and 5 mm, with 5 mm being the most common (10/22, 45%). The dose prescription for STAR is predominately 25 Gy in a single session (21/22, 95%). However, the method of dose prescription, the desired PTV dose coverage, and the dose (in)homogeneity in the PTV vary greatly. Only few centres allow or specifically desire stronger dose inhomogeneities to the TV area (6/22, 27%), while all centres allow underdosage in the PTV for sparing critical structures such as the stomach or oesophagus. The most commonly used radiation technique is intensity-modulated arc therapy (16/22, 73%) with standard c-arm linear accelerators (linac) or MRI linacs, followed by robotic-based CyberKnife radiosurgery (5/22, 23%) and intensity-modulated particle therapy with protons (1/22, 5%).

## Discussion

### STOPSTORM consortium

Reports on STAR for patients with refractory VT with limited treatment options so far demonstrated high efficacy in terms of reduction of VT burden and associated ICD interventions, with low toxicity in the majority. However, these reports are mostly small single-centre experiences with varying methods and techniques, relatively short follow-up, and the overall number of treated patients is still low in Europe and worldwide.<sup>10,19,21</sup> To optimize this novel treatment modality early on despite the limited number of patients, the STOPSTORM consortium was successfully founded to create a Europe-wide pooled STAR treatment database with accompanying harmonization and QA projects.



The founding STOPSTORM consortium members represent a large variety of experienced research and treatment institutions for VT ablation, SBRT, and STAR across Europe. Most importantly, the project is open for further centres for participation. With 84 STAR treatments and several ongoing national clinical trials at project start, the STOPSTORM consortium has a solid basis for high-quality scientific analysis and clinical evaluation of STAR. Besides having established the observational and harmonized prospective treatment registry, we also present the most comprehensive review of the current patterns of STAR practice which will serve as a baseline for further harmonization and standardization of this novel treatment. In the following sections, we will discuss the current STAR practice in terms of treatment indications and technical considerations.

## Patterns of STAR practice in Europe

### Cardiology/electrophysiology

One of the major challenges of novel treatments is patient selection, and not surprisingly, the survey showed significant heterogeneity in terms of patient selection for STAR across Europe. Recently, a modified Delphi process from selected German and Swiss centres on recommendations for STAR practice was published.<sup>37</sup> Comparing these recommendations ( $\geq 20\%$  difference = distinct,  $< 15\%$  difference = agreement), distinctly fewer STOPSTORM consortium members consider SHD to be a prerequisite as an indication for STAR (67% vs. 100% of the survey and Delphi consensus participants, respectively). This is in stark contrast to the selection criteria for the prospective STOPSTORM cohort and could potentially originate from differences in experience and availability of catheter ablation, radiation therapy, and STAR in each centre and the very early stage of the STOPSTORM project where no consensus discussions have been performed. The different opinions on STAR prerequisites are also distinct on electrical storm (50% vs. 85%), contraindications to catheter ablation (63% vs. 100%), and the presence of an ICD (71% vs. 92%), while agreement seems to be on one or more previous failed catheter ablations (92% vs. 100%), optimal anti-arrhythmic and heart failure medication (88% vs. 100%), and recurrent sustained monomorphic VT (79% vs. 85%) as a prerequisite. There is also a distinct difference between the Delphi recommendations and the STOPSTORM consortium members on contraindications for STAR, predominantly on polymorphic VT/ventricular fibrillation (42% vs. 62%) and life expectancy  $< 6$  months (54% vs. 15%). On the other hand, there was an agreement with respect to channelopathies/genetic causes (75% vs. 77%), eligibility for catheter ablation (83% vs. 77%), pregnancy (100% vs. 85%), temporary causes for VT (92% vs. 77%), and breastfeeding (83% vs. 85%). Interestingly, advanced heart failure (NYHA Class IV; 38% vs. 15%) and prior chest irradiation (13% vs. 31%) seem not to be a major contraindication in both the consensus statement and the STOPSTORM consortium (albeit differently weighted), although this was defined as an exclusion criterion for the harmonized prospective cohort.

While there are, of course, significant differences between a multidisciplinary Delphi consensus process with four discussion rounds<sup>37</sup> and a comprehensive survey with a single-disciplinary, uni-directional questionnaire with prior knowledge of and partly participation in the consensus recommendations, we still find some differences in preferences of the prerequisite and contraindication worthwhile highlighting. It seems that within the STOPSTORM consortium, STAR is used less in more severe or terminal patients (e.g. with limited life expectancy or advanced heart failure), while patients without an SHD may also be considered for STAR. This is interesting inasmuch, as patients with severe conditions such as electrical storm do seem to benefit from STAR as the last resort bail-out procedure.<sup>38,39</sup> Nevertheless, it should be mentioned that specific inclusion/exclusion criteria for current clinical trials are considerably stricter than the answers of the

presented survey may imply.<sup>23,24,37</sup> Further pooled treatment data analysis will hopefully shed some light on optimal patient selection.

Another challenge for STAR is the paradigm change between catheter ablation and the specific TV definition of the underlying VT substrate for stereotactic radiotherapy treatment planning. Functional information through EAM in combination with anatomical imaging is most often used for STAR. Interestingly, non-invasive ECGI is rarely used within the STOPSTORM consortium at the time, potentially due to limited availability, despite well-documented clinical evidence from the worldwide first case series and the first clinical trial on STAR.<sup>18,20</sup> The STOPSTORM consortium members predominantly use invasive EAM for TV definition. However, the specifics of the EAM procedures including image integration or even the EAM data format itself are very heterogeneous in clinical practice.

The more data are available, the more likely an estimation of which patients benefit most from STAR, and thus a better definition of the prerequisites and contraindications can be made. Also, more data and additional longer follow-up times will show what needs to be defined as TV. Hence, one of the major WPs 2 of the STOPSTORM consortium project is designated to the harmonization of TV definition as this is currently the largest uncertainty of STAR.<sup>10,13,16,17</sup>

Functional imaging such as PET and SPECT, which can easily be co-registered to the radiotherapy planning CT, might be helpful to characterize the VT substrate in patients with non-ICM or show derived scar maps that correlate with the voltage maps.<sup>40,41</sup> Additionally, scar imaging derived from CT or MRI may also be helpful to further increase the TV delineation accuracy for STAR<sup>42</sup> as additional information from functional imaging has demonstrated knowledge increase about the pathophysiology of ventricular arrhythmias and improvement in the outcomes of catheter ablation.<sup>40,41</sup> The STOPSTORM consortium is split between the question of either targeting the whole scar substrate or solely the re-entrant VT channels if specifically identifiable. In the aforementioned consensus recommendations for STAR, functional imaging was not judged to be a minimum requirement for STAR<sup>37</sup> and STOPSTORM consortium members rarely perform PET/SPECT. If available though, most if not all clinicians would use the data additionally alongside the EAM.

Another aspect of the STOPSTORM consortium project is the establishment of QA measures for STAR. In our survey, we found that general audits for EP and especially EAM are not common within the STOPSTORM consortium (EP: 38%, EAM: 28%), although they would enhance the development of standards and increase the treatment quality.<sup>43</sup> Furthermore, the clinical practice guidelines of the European Society of Cardiology for ventricular arrhythmias and the prevention of sudden cardiac death do also not contain any recommendations regarding QA or audits,<sup>44</sup> although the benefits of audits have already indeed been demonstrated in other cardiological indications<sup>45,46</sup> or for imaging and image registration procedures by other societies.<sup>47</sup>

### Radiation oncology

One of the crucial aspects of stereotactic radiotherapy is the precise definition and delineation of gross tumour volume (GTV) and clinical tumour volume (CTV), internal target volume, and OAR on time-resolved (respiratory and cardiac motion)<sup>13</sup> contrast- and non-contrast-enhanced TPI.<sup>26,48</sup> Contrary to RO treatments, there is generally no visible tumour on the TPI (MRI, CT) for STAR except for scar visualization in a subset of patients. Thus, the GTV/CTV is mainly defined based on the invasive or non-invasive EAM within dedicated EP mapping systems whose data formats are incompatible with current radiotherapy TPSs. A standardized and quality-controlled transfer method between the two working spaces is urgently needed, which is one of the major challenges for STAR.<sup>10,12</sup> A clinical-validated software specifically for this task currently does not exist. The EAM-to-TPS TV transfer is predominantly carried out manually via visually and anatomically assisted transfer

of the surface-based EAM-determined TV to the cross-sectional TPI in the TPS. Unfortunately, such approach undoubtedly introduces a major potential for inaccuracies and target misses.<sup>12</sup> Several approaches are already under development; however, due to the novelty of STAR, this issue remains to be resolved.<sup>29</sup>

Customized, in-house or open-source, software-aided tools for this process are hence investigated in many centres, which may have the potential to reduce user-dependent variability in the transfer and interpretation of the TV in the TPS. That said, these tools are used heterogeneously throughout the STOPSTORM consortium creating an environment where treatments would not be reproducible and difficult to compare. Two approaches have been reported so far: (i) anatomical cardiology presentation of the left ventricle in the TPS and (ii) joint EAM-TPI data presentation in tertiary software. The first is achieved by overlaying the commonly used AHA 17-segment model over the left ventricle in the TPS.<sup>28,29</sup> The benefit is that this method is well standardized even allowing the estimation of the target region based on ECG. The downside is that the larger segments may create unnecessary large treatment volumes, despite a higher technical accuracy in terms of dose delivery with SBRT. The second approach is the specific EAM data representation in either in-house or open-source software.<sup>11,30–32</sup> The data formats are mostly specific to the software versions used in each centre and hence limiting broad dissemination. Furthermore, the EAM and TPS data may be also not easily registered, and validation of those methods has only just begun.<sup>11</sup> Hence, we urge to use such software with great care and only as additional QA tools. The upside, however, is the joint display of EP and RO data. A platform-independent joint EAM-TPS data display tool will be developed within the STOPSTORM consortium to enable standardized display and evaluation of TV determination for STAR treatments.

Besides TV definition, OAR delineation and dose constraints are heterogeneous within the STOPSTORM consortium. While large efforts are being made for harmonization of OAR delineation<sup>49</sup> and dose constraints<sup>50</sup> for SBRT, only limited information exists on cardiac substructures for STAR.<sup>51</sup> Contouring, as well as dosimetry for OARs, is already being harmonized through ongoing consensus-oriented benchmarks. Similarly, respiratory and cardiac motion compensation strategies for STAR and their comparability will be addressed. Cardiac and respiratory motion can be larger than 1 and 2 cm, respectively,<sup>13</sup> and the lack of motion compensation and possible interplay effects may blur and reduce the actual radiation dose to the TV significantly as compared with active motion compensation techniques with tracking and gating.<sup>48,52</sup>

These points automatically lead to the question of how much dose is needed for a therapeutic effect. Almost all centres use a single dose of 25 Gy at the time, while some centres began looking into dose modification based on recent findings from radiation biology studies.<sup>14,15,17</sup> However, the methods of planning margins, dose prescription, target coverage, dose (in)homogeneity, and treatment duration vary greatly. Inconsistent documentation further complicates comparability between institutions and even systems. Many questions on STAR techniques such as degree of dose homogeneity (27.5–35 Gy maximum dose), treatment duration (10–120 min), and active vs. passive motion compensation (tracking, gating, motion margins) within complex functional and pathological dose responses between 25 and 30 Gy remain unanswered.<sup>13–17</sup> Consistent treatment documentation according to the International Commission on Radiation Units and Measurements (ICRU) report 91<sup>53</sup> and accurate dose calculation methods including specific motion management concepts will be important steps towards inter-system and inter-institutional comparability for STAR.

## Medical physics

Finally, differences are also observed regarding the overall system calibration and QA, especially in the regularity of audits. The functionality of the radiation therapy devices is only audited in 59% of the

STOPSTORM consortium members, although strongly recommended by many international guidelines.<sup>54,55</sup> Furthermore, only three-quarters of the centres calibrate their machines according to small-field dosimetry guidelines,<sup>27,48</sup> while for regular dosimetry quality audits we find higher rates in the STOPSTORM consortium than reported in a recently published European Federation Of Medical Physics (EFOMP) survey (73% vs. 58%,<sup>56</sup>). Nevertheless, this clearly demonstrates variability in national guidelines for basic calibration and system audits even in a supposedly harmonized (European) Union.

Other important QA methods for stereotactic radiotherapy comprise regular complete radiotherapy treatment chain tests, called end-to-end tests, which are not performed in almost 25% of the centres on a routine basis despite being highly recommended.<sup>57</sup> Hardly performed in the STOPSTORM consortium, however, are specific end-to-end tests using moving phantoms,<sup>48</sup> which seem highly relevant for complex moving targets such as for STAR.<sup>58</sup> The transformation of international guidelines into national laws would favour harmonization, for example the performance of external audits and the implementation of small-field dosimetry. We also recommend the initiation of external audits, especially for small fields due to their complexity. We need an establishment of regular E2E tests for non-moving and above all for moving phantoms that seem highly relevant for complex moving targets such as in STAR. Implementing QA standards for STAR will be a key aspect of WP 4 in the consortium.

STOPSTORM provides the necessary basics to answer the open questions regarding STAR. Simply more patient data are needed in many cases, which can be collected via the STOPSTORM registry.

## Limitations

The limitation of the questionnaires and their representation of European EP and RO departments is that only consortium members were surveyed without prior consensus discussion and with varying clinical expertise in catheter ablation, radiation therapy, and STAR. Thus, the results cannot be considered as a general measure of the quality and experience of all European facilities. The guidelines developed through the survey and subsequently in the STOPSTORM project over the next few years can serve as a recommendation for departments worldwide and thus bring harmonization to a larger number of users.

## Conclusion

The experience in catheter ablation, stereotactic radiotherapy, and STAR within the STOPSTORM consortium is adequate, while the survey clearly showed areas of harmonization and optimization need for substrate mapping, target delineation, motion management, dosimetry, and QA, which will be addressed in the respective STOPSTORM project WPs. The STOPSTORM project is also open for new participating centres within the European Union.

## Supplementary material

Supplementary material is available at *Europace* online.

## Data availability

Detailed survey data is available upon reasonable request to the lead authors.

## Acknowledgements

The authors would like to thank all members of the STOPSTORM consortium (see <https://stopstorm.eu/en/consortium>). Special thanks to Marcus Both and the advisory board members Matthew Bates, Matthew Hatton,

Phillip Cuculich, Clifford Robinson, Paul C. Zei, Jan Smook, Reinier Versluis, Annette Rogge, Rieke van der Graaf, Dick Enge, Juan Carlos Miembro, Stephanie Hellwig, and Denis Janssen. The following STOPSTORM participants were part of the Delphi consensus<sup>37</sup>: David Krug, Oliver Blanck, Nicolaus Andratschke, Raphael Jumeau, Felix Mehrhof, Judit Boda-Heggemann, Etienne Pruvot, Ardan M. Saguner, Boris Rudic, and Leif-Hendrik Boldt. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 945119.

**Conflict of interests:** D.K. has received honoraria from Merck Sharp & Dohme and Pfizer, as well as research funding from Merck KGaA, all outside of the submitted work. M.A. is a consultant for Biosense Webster and Boston Scientific, has received educational grants from Abbott, and is a proctor for Medtronic. J.B.-H. received personal fees from EBAMed SA, Switzerland, outside the submitted work. O.E. received honoraries for participation on advisory board meetings from Merck Serono, MSD, and AstraZeneca concerning oncologic treatments and also received project funding for clinical trials from non-profit organizations, all outside of the submitted work. T.R. gets research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, and the Sitem Insel support fund. Speaker/consulting honoraria or travel support from Abbott/SJM, Bayer, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Farapulse, Medtronic, and Pfizer-BMS. Support for the institution's fellowship programme from Abbott/SJM, Biosense Webster, Biotronik, Boston Scientific and Medtronic. A.S. received educational grants through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, BMS/Pfizer, and Medtronic; and speaker/advisory board fees from Abbott, Bayer Healthcare, Daiichi Sankyo, Medtronic and Novartis. All other authors declare no conflict of interests.

## References

- Movsisiyan NK, Vinciguerra M, Medina-Inojosa JR, Lopez-Jimenez F. Cardiovascular diseases in central and Eastern Europe: a call for more surveillance and evidence-based health promotion. *Ann Glob Health* 2020;**86**:1–10.
- Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N et al. HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. *Heart Rhythm* 2019; **21**(8): 1143–4.
- Tung R, Vaseghi M, Frankel DS, Vergara P, Di Biase L, Nagashima K et al. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: an international VT ablation center collaborative group study. *Heart Rhythm* 2015;**12**:1997–2007.
- Fernandez-Armenta J, Soto-Iglesias D, Silva E, Penela D, Jáuregui B, Linhart M et al. Safety and outcomes of ventricular tachycardia substrate ablation during sinus rhythm: a prospective multicenter registry. *JACC Clin Electrophysiol* 2020;**6**:1435–48.
- Jumeau R, Ozsahin M, Schwitzer J, Elicin O, Reichlin T, Roten L et al. Stereotactic radiotherapy for the management of refractory ventricular tachycardia: promise and future directions. *Front Cardiovasc Med* 2020;**7**:108.
- Whitaker J, Mak RH, Zei PC. Non-invasive ablation of arrhythmias with stereotactic ablative radiotherapy. *Trends Cardiovasc Med* 2022;**32**(5):287–296.
- Sharma A, Wong D, Weidlich G, Fogarty T, Jack A, Sumanaweera T et al. Noninvasive stereotactic radiosurgery (CyberHeart) for creation of ablation lesions in the atrium. *Heart Rhythm* 2010;**7**:802–10.
- Loo BW Jr, Soltys SG, Wang L, Lo A, Fahimian BP, Lagaru A et al. Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. *Circ Arrhythm Electrophysiol* 2015;**8**:748–50.
- Cvek J, Neuwirth R, Knybel L, Molenda L, Otahal B, Pindor J et al. Cardiac radiosurgery for malignant ventricular tachycardia. *Cureus* 2014;**6**:e190.
- Miszczuk M, Jadczyk T, Golba K, Wojakowski W, Wita K, Bednarek J et al. Clinical evidence behind stereotactic radiotherapy for the treatment of ventricular tachycardia (STAR)—A comprehensive review. *J Clin Med* 2021;**10**:1238.
- Abdel-Kafi S, Sramko M, Omara S, de Riva M, Cvek J, Peichl P et al. Accuracy of electro-anatomical mapping-guided cardiac radiotherapy for ventricular tachycardia: pitfalls and solutions. *Europace* 2021;**23**(12):1989–1997.
- Boda-Heggemann J, Blanck O, Mehrhof F, Ernst F, Buergy D, Fleckenstein J et al. Interdisciplinary clinical target volume generation for cardiac radioablation: multicenter benchmarking for the RADIOSURGERY for VENTricular TACHycardia (RAVENTA) trial. *Int J Radiation Oncol Biol Phys* 2021;**110**:745–56.
- Lydiard S, Blanck O, Hugo G, O'Brien R, Keall P. A review of cardiac radioablation (CR) for arrhythmias: procedures, Technology, and future opportunities. *Int J Radiation Oncol Biol Phys* 2020;**109**:783–800.
- Zhang DM, Navara R, Yin T, Szymanski J, Goldsztejn U, Kenkel C et al. Cardiac radiotherapy induces electrical conduction reprogramming in the absence of transmural fibrosis. *Nat Commun* 2021;**12**:5558.
- Kim JS, Choi SW, Park Y, Kim SJ, Choi CH, Cha M et al. Impact of high-dose irradiation on human iPSC-derived cardiomyocytes using multi-electrode arrays: implications for the antiarrhythmic effects of cardiac radioablation. *Int J Mol Sci* 2021;**23**:351.
- Kautzner J, Jedlickova K, Sramko M, Peichl P, Cvek J, Knybel L et al. Radiation-induced changes in ventricular myocardium after stereotactic body radiotherapy for recurrent ventricular tachycardia. *JACC Clin Electrophysiol* 2021;**7**:1487–92.
- Blanck O, Boda-Heggemann J, Hohmann S, Mehrhof F, Krug D. [Cardiac stereotactic radiotherapy induces electrical conduction reprogramming]. *Strahlenther Onkol* 2022;**198**:209–11.
- Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. *N Engl J Med* 2017;**377**:2325–36.
- Kovacs B, Mayingier M, Schindler M, Steffel J, Andratschke N, Saguner AM. Stereotactic radioablation of ventricular arrhythmias in patients with structural heart disease—A systematic review. *Radiother Oncol* 2021;**162**:132–9.
- Robinson CG, Samson PP, Moore KMS, Hugo GD, Knutson N, Mutic S et al. Phase I/II trial of electrophysiology-guided noninvasive cardiac radioablation for ventricular tachycardia. *Circulation* 2019;**139**:313–21.
- van der Ree MH, Blanck O, Limpens J, Lee CH, Balgobind BV, Dieleman EMT et al. Cardiac radioablation—A systematic review. *Heart Rhythm* 2020;**17**:1381–92.
- Krug D, Blanck O, Demming T, Dottermusch M, Koch K, Hirt M et al. Stereotactic body radiotherapy for ventricular tachycardia (cardiac radiosurgery). *Strahlenther Onkol* 2020;**196**:23–30.
- Blanck O, Buergy D, Vens M, Eidinger L, Zaman A, Krug D et al. Radiosurgery for ventricular tachycardia: preclinical and clinical evidence and study design for a German multi-center multi-platform feasibility trial (RAVENTA). *Clin Res Cardiol* 2019;**109**: 1319–32.
- Miszczuk M, Jadczyk T, Tomasiak B, Latusek T, Bednarke J, Kurzelowski R et al. Stereotactic management of arrhythmia—radiosurgery in treatment of ventricular tachycardia (SMART-VT)—clinical trial protocol and study rationale. *OncoReview* 2020;**10**:123–9.
- Carbucicchio C, Jereczek-Fossa BA, Andreini D, Catto V, Piperno G, Conte E et al. STRA-MI-VT (STereotactic RadioAblation by multimodal imaging for ventricular tachycardia): rationale and design of an Italian experimental prospective study. *J Interv Card Electrophysiol* 2020;**61**:585–93.
- Guckenberger M, Baus WW, Blanck O, Combs SE, Debus J, Engenhart-Cabillic R et al. Definition and quality requirements for stereotactic radiotherapy: consensus statement from the DEGRO/DGMP working group stereotactic radiotherapy and radiosurgery. *Strahlenther Onkol* 2020;**196**:417–20.
- IAEA. Dosimetry of Small Static Fields Used in External Beam Radiotherapy, An International Code of Practice for Reference and Relative Dose Determination. Technical Reports Series 2017 No. 483. ISBN: 978-92-0-105916-1. [https://www-pub.iaea.org/MTCD/Publications/PDF/D483\\_web.pdf](https://www-pub.iaea.org/MTCD/Publications/PDF/D483_web.pdf).
- Brownstein J, Afzal M, Okabe T, Harfi T, Tong MS, Thomas E et al. Method and atlas to enable targeting for cardiac radioablation employing the American heart association segmented model. *Int J Radiat Oncol Biol Phys* 2021;**111**:178–85.
- van der Ree MH, Visser J, Planken N, Dieleman EMT, Boekholdt SM, Balgobind BV et al. Standardizing the cardiac radioablation targeting workflow: enabling semi-automated angulation and segmentation of the heart according to the American heart association segmented model. *Adv Radiat Oncol* 2022;**7**(4):100928.
- Hohmann S, Henkenberens C, Zormpas C, Christiansen H, Bauersachs J, Duncker D et al. A novel open-source software-based high-precision workflow for target definition in cardiac radioablation. *J Cardiovasc Electrophysiol* 2020;**31**:2689–95.
- Brett CL, Cook JA, Aboud AA, Karim R, Shinohara ET, Stevenson WG. Novel workflow for conversion of catheter-based electroanatomic mapping to DICOM imaging for non-invasive radioablation of ventricular tachycardia. *Pract Radiat Oncol* 2021;**11**:84–8.
- Lee J, Bates M, Shepherd E, Riley S, Henshaw M, Metherall P et al. Cardiac stereotactic ablative radiotherapy for control of refractory ventricular tachycardia: initial UK multicentre experience. *Open Heart* 2021;**8**:e001770.
- Duane F, Aznar MC, Bartlett F, Cutter DJ, Darby SC, Jaggi R et al. A cardiac contouring atlas for radiotherapy. *Radiother Oncol* 2017;**122**:416–22.
- Milo MLH, Offersen BV, Bechmann T, Diederichsen ACP, Hansen CR, Holtved E et al. Delineation of whole heart and substructures in thoracic radiation therapy: national guidelines and contouring atlas by the danish multidisciplinary cancer groups. *Radiother Oncol* 2020;**150**:121–7.
- Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys* 2011;**79**:10–8.
- Loap P, Serois V, Dhonneur G, Kirov K, Fourquet A, Kirova Y. A radiation therapy contouring atlas for cardiac conduction node delineation. *Pract Radiat Oncol* 2021;**11**: e434–7.

37. Krug D, Blanck O, Andratschke N, Guckenberger M, Jumeau R, Mehrhof F et al. Recommendations regarding cardiac stereotactic body radiotherapy for treatment refractory ventricular tachycardia. *Heart Rhythm* 2021;**18**:2137–45.
38. Scholz EP, Seidensaal K, Naumann P, André F, Katus HA, Debus J. Risen from the dead: cardiac stereotactic ablative radiotherapy as last rescue in a patient with refractory ventricular fibrillation storm. *HeartRhythm Case Rep* 2019;**5**:329–32.
39. Jumeau R, Ozsahin M, Schwitter J, Vallet V, Duclos F, Zeverino M et al. Rescue procedure for an electrical storm using robotic non-invasive cardiac radio-ablation. *Radiother Oncol* 2018;**128**:189–91.
40. Kuo L, Liang JJ, Nazarian S, Marchlinski FE. Multimodality imaging to guide ventricular tachycardia ablation in patients with non-ischaeamic cardiomyopathy. *Arrhythm Electrophysiol Rev* 2019;**8**:255–64.
41. Duell J, Dilsizian V, Smith M, Chen W, Dickfeld T. Nuclear imaging guidance for ablation of ventricular arrhythmias. *Curr Cardiol Rep* 2016;**18**:19.
42. Qian PC, Quadros K, Aguilar M, Wie C, Boeck M, Bredfeldt J et al. Substrate modification using stereotactic radioablation to treat refractory ventricular tachycardia in patients with ischemic cardiomyopathy. *JACC Clin Electrophysiol* 2022;**8**:49–58.
43. Zhao M, Vaartjes I, Klipstein-Grobusch K, Kotseva K, Jennings C, Grobbee DE et al. Quality assurance and the need to evaluate interventions and audit programme outcomes. *Eur J Prev Cardiol* 2017;**24**:123–8.
44. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J et al. ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart* 2015;**36**:2793–867.
45. Sawhney V, Volkova E, Shaikat M, Khan F, Segal O, Ahsan S et al. Impact of attributed audit on procedural performance in cardiac electrophysiology catheter laboratory. *J Interv Card Electrophysiol* 2019;**56**:199–203.
46. Bhattacharyya S, James R, Rimington H, Allen J, Lee L, Fox K et al. Development of a national echocardiography quality improvement programme: insights into feasibility, uptake, and clinical utility. *Eur Heart* 2014;**15**:747–52.
47. Brock KK, Mutic S, McNutt TR, Li H, Kessler ML. Use of image registration and fusion algorithms and techniques in radiotherapy: report of the AAPM radiation therapy committee task group No. 132. *Med Phys* 2017;**44**:e43–76.
48. Schmitt D, Blanck O, Gauer T, Fix MK, Brunner TB, Fleckenstein J et al. Technological quality requirements for stereotactic radiotherapy: expert review group consensus from the DGMP working group for physics and technology in stereotactic radiotherapy. *Strahlenther Onkol* 2020;**196**:421–43.
49. Mir R, Kelly SM, Xiao Y, Moore A, Clark CH, Clementel E et al. Organ at risk delineation for radiation therapy clinical trials: global harmonization group consensus guidelines. *Radiother Oncol* 2020;**150**:30–9.
50. Timmerman R. A story of hypofractionation and the table on the wall. *Int J Radiat Oncol Biol Phys* 2022;**112**:4–21.
51. Knutson NC, Samson PP, Hugo GD, Goddu SM, Reynoso FJ, Kavanaugh JA et al. Radiation therapy workflow and dosimetric analysis from a phase 1/2 trial of noninvasive cardiac radioablation for ventricular tachycardia. *Int J Radiat Oncol Biol Phys* 2019;**104**:1114–23.
52. Gauer T, Sothmann T, Blanck O, Petersen C, Werner R. Under-reported dosimetry errors due to interplay effects during VMAT dose delivery in extreme hypofractionated stereotactic radiotherapy. *Strahlenther Onkol* 2018;**194**:570–9.
53. Seuntjens J, Lartigau EF, Cora S, Ding GX, Goetsch S, Nuyttens J et al. ICRU Report 91. Prescribing, recording, and reporting of stereotactic treatments with small photon beams. *J ICRU* 2014;**14**:1–160.
54. IAEA. Comprehensive Audits of Radiotherapy Practices: A Tool for Quality Improvement. Quality Assurance Team for Radiation Oncology (QUATRO). ISBN 92–0–103707–4. 2007.
55. European Commission. Guideline on Clinical Audit for Medical Radiological Practices (Diagnostic Radiology, Nuclear Medicine, and Radiotherapy. Radiation Protection No. 159. ISBN 978-92-79-14281-9. 2009.
56. Casares-Magaz O, Marcu LG, Prezado Y, Koutsouveli E, Brambilla M. EFOMP Survey results on national radiotherapy dosimetry audits. *Phys Med* 2021;**84**:10–4.
57. Benedict SH, Yenice KM, Followill D, Hinson VV, Kavanagh B, Keall P et al. Stereotactic body radiation therapy: the report of AAPM task group 101. *Med Phys* 2010;**37**(8):4078–101.
58. Akdag O, Borman PTS, Woodhead P, Uijtewaal P, Mandija S, Van Asselen B et al. First experimental exploration of real-time cardiorespiratory motion management for future stereotactic arrhythmia radioablation treatments on the MR-linac. *Phys Med Biol* 2022;**67**:065003.