DELIVERABLE

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D7.3 – Design specifications of an API for DSS algorithms

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Revision History, Status, Abstract, Keywords, Statement of Originality

Revision History

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0.01	29/08/24	Agakov, Pekkanen-Mattila, Valtonen, Ahola, Faiem, Bartolucci, Severi, Coleman, Le Rolle, Forouzandehmehr, Taconne, Mainardi, Moreno-Sanchez, McCarthy, Baretta, Schneider, Garcia-Cabrera, Bueno-Orovio, Hyttinen, van Gils	Pharmatics, TAU, UNIBO, UOXF, UNIVREN, POLIMI, UCD, IST, MDT	Aggregated inputs from WP3-7 included in Sec 3.
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Abstract (for dissemination)	This document presents the initial technical specifications for an Application Programming Interface (API) designed to support clinical decisions and scientific research related to HCM. The API will ensure consistent access to data, models, and algorithms developed in work packages WP3-WP6 by harmonising data structures, processes, variable names, measurement units, and references, while also ensuring model utility and accessibility both within and beyond the consortium. Key components include a standardised template for model specifications, clear definitions of inputs/outputs, and comprehensive documentation of each model's background and use cases. As the API specification is in its early stage, it is expected to evolve throughout the project. Ultimately, the specification aims to enhance research collaboration and improve clinical decision-making for HCM.
Keywords	API, technical specification, data harmonisation, model standardisation, clinical decision support.

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

Executive Summary

This report, deliverable D7.3 of the SMASH-HCM Project, outlines the development of technical specifications for the Application Programming Interface (API) to support clinical decisions and scientific investigations focused on hypertrophic cardiomyopathy (HCM). The goal of the report is to create a unified development framework that will enable consistent and straightforward access to research results from work packages WP3-WP6 for HCM researchers and clinicians.

By following the proposed framework, we will address the following requirements:

- Harmonisation of data, models, and processes:
  - Standardisation and incorporation of all data, algorithms, and models developed in WP3-WP6.
  - Harmonisation of variable names and conversion of measurement units to a consistent canonical form.
  - Development of auxiliary utilities for handling outliers, missing data, and error logging to ensure robust data management.
- Harmonisation of API references to enable the use of models and algorithms:
  - Utilisation of a detailed template to gather comprehensive specifications for each function or model.
  - Clear definition of model names, types, inputs, and outputs, including data types, units, descriptions, and plausible ranges.
  - Provision of detailed descriptions of models, including theoretical background, methodologies, and references to data sources and evaluation methods.
- Model utility and accessibility:
  - Specification of software environments, including necessary programming languages, libraries, and configurations.
  - Consideration of licensing agreements and contextual information regarding the clinical applications of each function/model.
  - Documentation of known limitations and practical use cases for each function or model.

The report begins with an overview of work packages WP3-6, which will develop research results for integration within the API. This is followed by an explanation of the standardised template for collecting model information and concludes with considerations for software environment and usability. To illustrate the approach, the report summarises the structure of some of the models that are being developed in SMASH-HCM by following the proposed framework. This structured approach ensures that functions and models included in the final API will be called, integrated within workflows, shared, documented, and supported in a harmonised way, which will facilitate research and support effective clinical decision-making for HCM using results of the SMASH-HCM project.

Since we are at an early stage of development, the report should be viewed as an *initial* set of technical design specifications for API developers that may evolve over time; thus, sections 2, 3, and 4 of this report are live documents that will be continuously updated throughout the project. Once the API is developed and the specifications are clearly defined and consistently followed, it will become a powerful tool for supporting research by providing access to harmonised models and algorithms. It will also help clinicians make informed decisions using the models developed within SMASH-HCM, validated both in the pilot trial in WP8 and in clinical studies outside the project. By gathering detailed information and ensuring the research results are standardised and programmatically accessible, our API will facilitate better collaboration among researchers and may improve the effectiveness of clinical decision-making for hypertrophic cardiomyopathy.

1 Model Overview

1.1 WP3: In vitro HCM and patient models

WP3 focuses on developing in vitro models to study hypertrophic cardiomyopathy (HCM), including:

1. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and their monolayers/ clusters.
2. Engineered cardiac tissue (EHT), using the hiPSC-CMs.
3. Adult HCM patient ex-vivo cardiac tissues, both stored and fresh.

The work will involve assessing existing HCM cell lines and selecting new patient samples to create hiPSC-CMs and EHTs, followed by characterising these cells and tissues through mechanical, electrophysiological, and structural measurements, along with mitochondrial respiration studies. Protocols for differentiation, maturation, and purification of cells and tissues will be standardised among partners. WP3 will develop tools for in vitro organ-on-a-chip models to explore HCM phenotypes, providing cell- and tissue-level features for in silico heart models in WP4, multi-organ models in WP5, and machine learning models in WP6.

The tasks of in vitro modelling include:

1. **Patient selection** and generation of cardiomyocytes and EHTs by identifying patient cell lines with common HCM mutations, differentiating them into hiPSC-CMs and EHTs, comparing them with healthy control cell lines, and expanding the cardiac tissue repository with new samples.
2. **Mechanical characterisation** and **pharmacological treatment** of hiPSC-CMs by studying the mechanical properties and contraction dynamics of EHTs, using video microscopes to monitor contractions over time, performing mechanical studies using imposed pacing frequencies and various calcium levels, testing EHTs with drugs commonly used to manage HCM as well as emerging myosin inhibitors (such as mavacamten and aficamten), and validating the results against native adult human myocardium for HCM patients in our tissue repository.
3. **Electrophysiological characterisation** and **pharmacological treatment** of hiPSC-CMs and EHTs, including measuring contraction and beat regularity using video optical systems, assessing response to stimulants like catecholamines, recording action potentials with microelectrodes, analysing extracellular field potentials, evaluating the inducibility of arrhythmias in cellular and tissue models by applying blockers and stimulants, and validating electrophysiological data against native adult human myocardium for HCM patients in our repository.
4. **Mitochondrial respiration studies**, including measuring mitochondrial function in long-term matured hiPSC-CMs; analysing the effects of mutations on oxygen consumption rates, and studying the impact of established drugs and the emerging myosin inhibitors on mitochondrial respiration of hiPSC-CMs.

The models created in WP3, together with their computational surrogates, will be accessed programmatically via an application programming interface (API) in WP7. This will enable the use of the cell- and tissue-level simulations as priors, constraints, or features in other computational models, supporting research and development efforts within and outside the SMASH-HCM consortium. The API will harmonise access to documented research results and help researchers and clinicians make informed decisions about HCM treatments, offering personalised medicine options based on in vitro predictions. This may enhance cardiac and multi-organ modelling, facilitates the development of new therapeutic strategies and treatment regimens for both established and emerging therapies such as myosin inhibitors, and enhance decision-making capabilities based on in vitro modelling.

1.2 WP4: Validated in silico heart models in HCM

WP4 focuses on developing multiscale heart models and simulation tools to explore pathophysiology and efficacy in HCM by focusing on deep phenotyping and stratification at the cellular, tissue, and whole-heart levels, along with predicting therapy response to established and emerging medications in HCM. The work involves closely integrated multiscale modelling and simulation studies to investigate how different genetic mutations in HCM affect phenotypes. These models will be used for high-throughput studies to investigate how different drugs impact the disease, with the aim of developing optimal, patient-specific treatment strategies for HCM. Additionally, these models will be used for generating synthetic training and validation datasets for the AI- and machine-learning- (ML) based tools in WP6.

The tasks of in silico modelling include:

1. At the **cellular level**, adapting electromechanical models of hiPSC-CM cells to include the effects of specific HCM mutations, which involves modelling the effects of mutations on electrophysiology, mechanobiology, and energetics, as well as secondary changes in ion channels and calcium handling due to disease progression; developing baselines for control and mutation-specific Populations of Models (POMs) that reflect variability in cellular function; using POMs in studies with known pro-arrhythmic factors in HCM (e.g., fast pacing, calcium overload, sympathetic stimulation) to serve as in-silico stratification tools based on genetic variants; assessing pro-arrhythmic phenotypes, identifying key mechanisms behind arrhythmia risk, and suggesting mutation-specific treatments for specific genotypes in HCM.
2. At the **tissue level**, simulating POMs for each phenotypic variant per HCM mutation, informed by imaging and in vitro histology data from 2D cardiomyocyte sheet models and 3D EHTs produced from patients' hiPSC-CMs from WP3, as well as clinical data on structural effects of HCM mutations; describing conduction using bidomain equations; developing tissue models with increasing complexity that reflect the structural effects of mutations to identify disease markers of impaired cardiac conduction and mechanical disfunction not visible at the cellular level; and uncovering key structural mechanisms that influence the risk of arrhythmias based on individual HCM genetic variants, which are difficult to study in human tissue.
3. At the **whole-heart level**, integrating cellular and tissue data into personalised HCM heart models using automated 3D reconstruction, including myocardial fibre orientation, regional fibrosis, ischemic scarring, and regional mechanical properties from cardiac magnetic resonance (CMR) imaging; personalising functional heart models using patient-specific cell models and ECG data to refine activation sequences and electrophysiological gradients; using longitudinal patient data to personalise anatomical and functional heart models during disease progression and enable investigations of personalised arrhythmic risk and genotype-specific ECG manifestations; simulating heart models in response to ectopic triggers to study arrhythmia risk, including modelling acute myocardial ischemia as a comorbidity and assessing whether personalised arrhythmic risks are driven by anatomical structure or cellular function; using these personalised whole-heart models to inform the development of ECG scores associated with disease progression and to guide AI/ML research on stratification and personalised arrhythmic risks.
4. For **precision therapy response prediction** in HCM, integrating POMs and personalised models linked to clinical data within a three-level (cell-to-organ) platform for systematic simulation studies on the response of human HCM electromechanical cardiac function to drug action for disease management; testing established (e.g., β-blockers, diltiazem, verapamil, disopyramide, amiodarone, ranolazine) and emerging HCM therapies (e.g., novel myosin inhibitors like mavacamten and aficamten); modelling the impact of central nervous system agents (e.g., anti-depressants) on electromechanical function in HCM, based on their inhibitory profiles and in-vitro data from WP3; testing therapies in virtual populations that mimic clinical protocols, specifically exploring different drug dosages and combinations; identifying likely

therapy outcomes and divergent responses across different mutations, including investigations of their underlying mechanisms; laying the foundation for linking molecular events to whole organ level and thereby assisting the interpretation of ECG signatures in response to therapy, and enabling patient stratification for disease management according to the optimal choice of therapy.

The models and simulation results developed in WP4 will be accessible programmatically via the research and development API developed in WP7. This API will enable researchers in WP5 and WP6 to use the results of simulations for research and development (R&D), including the use of the results during data augmentation during AI/ML training and validation. Characterisation of treatment response may potentially guide clinical decision support for identifying optimal treatment regimens based on personalised whole-heart models. The models developed in WP4 wrapped in the API will assist in understanding the impacts of different genetic mutations; enhance the prediction of treatment outcomes for individual patients; support the development of personalised treatment plans and interventions; and provide additional data sources for AI and machine learning models.

1.3 WP5: Integrated multiscale vascular and multi-organ modelling

WP5 focuses on developing multiscale dynamic vascular and multiorgan modelling and simulation tools. These tools aim to augment datasets; link clinical, cellular, molecular, and gene variant effects; and capture vascular and multiorgan mechanisms for deep phenotyping in HCM. We will model multiorgan function in HCM by integrating knowledge from various domains, including cellular electro-mechano energetics (focusing on smooth muscle and cardiomyocytes), cardiac function, the dynamics of the circulatory system (from smooth muscle cells to system level), and autonomic nervous system (ANS) regulation. The work will include simulations of vascular smooth muscle and vascular wall phenotypes, multilevel cardiovascular and autonomic in-silico modelling, and multiorgan hybrid modelling for risk stratification and therapy response prediction in HCM.

The outcomes of WP5 include the development of multiscale dynamic multiorgan modelling and simulation tools for novel personalised model-based biomarkers related to cardiac, vascular, and autonomic functions. These tools will help to identify the most relevant features for AI-based stratification and prediction tools to be developed in WP6. They will also produce panels of putative predictors for optimal treatment options, including ICD implantation and drug therapy, as well as predictors of optimal lifestyle choices such as physical exercises, assessing their risks and prognosis. Additionally, WP5 will explore genotype-phenotype responses to investigate how specific genetic mutations impact HCM at the cardiovascular and multiorgan levels, enabling the prediction of adverse events and prognostic outcomes and ultimately improving therapeutic choices for HCM patients.

The tasks of multi-scale multi-organ modelling include:

1. **Vascular wall and smooth muscle simulation in HCM**, by integrating the effects of HCM variants into in-silico models of smooth muscle cellular electrophysiology, contractility, and energetics based on domain knowledge and data from clinical and in-vitro sources (WP2-3), starting with existing models and using expertise in cardiomyocyte (CM) electromechanical modelling; investigating phenotypic variability using population of models (POMs) to serve as in-silico stratification tools for characterising adverse phenotypes and drug effects emerging from each genotype; deriving features from POMs on contractility and vascular tone control for data augmentation in AI/ML techniques (WP6); simulating models of each phenotype per HCM mutation at the cellular level and translating them to 2D/3D vascular wall finite element models (FEM), calibrating wall biomechanics using cardiovascular function data (WP2); providing genotypic parameters for vascular system models, including changes in vascular

resistance, compliance, and dynamic responses to autonomic nervous system (ANS) control; and using POM-derived features on the effects of cellular contractility on ANS control dynamics for data augmentation in WP6 to inform personalised vascular systemic and multiorgan models.

2. **Multilevel cardiovascular and autonomic multi-organ models**, by integrating interactions between vascular, systemic, and pulmonary systems, including a multi-segment representation of cardiac cavities and autonomic modulations through sympathetic and parasympathetic pathways; adapting state-of-the-art models of cardiovascular and autonomic regulation to include autonomic dysfunction and altered vascular responses during exercise; accounting for physiological mechanisms specific to HCM by coupling vascular wall cellular-, tissue-, and system-level models that incorporate HCM mutations, and integrating electrical activation sequences from WP4 whole-heart models; considering specific myocardial contraction patterns in HCM by simulating mechanical and temporal heterogeneities in the deformation of the left ventricle (LV) and its interaction with vascular loading conditions to reproduce LV strains for detecting ventricular arrhythmias in HCM patients; personalising the multi-organ system-level model using parameters identified via evolutionary algorithms from clinical data in WP2, which includes analyses of autonomic modulations during stress tests, baseline, effort echocardiography, and vascular responses due to orthostatic challenges.
3. **Multi-organ hybrid modelling for risk stratification and therapy response prediction in HCM**, by exploiting multiple integrated in-silico models of HCM vascular systems (including heart, vascular tone control, and vascular system-level models) in sensitivity analysis. This includes local and screening methods, to provide key information for dealing with the complexity of physiological mechanisms underlying HCM risk; using in-silico patient-specific model-based features to propose a pheno-mapping of HCM patient profiles and passing the most relevant and predictive model-based features to WP6 to improve AI-based prediction and stratification tools, ensuring appropriate explainability through the direct physiological meaning of the identified model-based features; investigating HCM treatment options, including drug therapy and ICD implantation, by utilising the integrated and multiorgan model-based approaches; using the models to simulate the effects of drugs such as beta-blockers and vasodilators and to predict and explain their safety and efficacy across different HCM variants; testing established and emerging therapies in virtual populations, specifically examining drug dosages and combinations; deriving novel in-silico biomarkers and synthesised data to identify high-risk patients who may benefit from an ICD or an insertable cardiac monitor for intermediate risk; evaluating the risk of multiorgan and cardiovascular adverse events for ICD implantation and its related settings; based on in-silico biomarkers and simulations of lifestyle conditions (such as exercise), using personalised risk profiles to identify key factors that empower patients to take an active role in their care; and integrating molecular events at the multiorgan level to provide insights for biomarker interpretation for treatment response and patient stratification according to optimal therapy choices; and offering lifestyle guidance.

The tools, models, and simulation results developed in WP5 will be accessible programmatically via both the research and development and clinical decision support API, facilitating the use of simulation results and predictors for data-efficient machine learning modelling in WP6. Additionally, the API-enabled access to WP5 models will assist in predicting treatment outcomes and identifying optimal treatment options based on personalised multiorgan models. This approach will enhance our understanding of the impacts of different genetic mutations, improve the prediction of treatment outcomes for individual patients, assist in developing personalised treatment plans, and provide additional data sources for AI and machine learning models based on findings from multiorgan models. Ultimately, this will improve therapy and decision-making in HCM.

1.4 WP6: Data-based modelling and integration

WP6 focuses on developing new data- and knowledge-driven AI/ML models to predict HCM outcomes from heterogeneous data sources, including scientific biomedical literature, patient demographics, health records, ECG signals, CMR and echocardiography images, and multiorgan data. It involves developing novel multilevel clustering and prediction methods for stratification, prognosis of disease progression, and prediction of treatment response by combining machine learning models with computational and mechanistic models developed in WP3-5. The models will be validated and refined both internally and externally using accessible retrospective datasets. The outputs of WP6 will include a set of validated, robust AI/ML tools for data-driven patient stratification and prediction of HCM progression and treatment response, accessible via an API for both research and medical use. Additionally, WP6 will identify a subset of methods to be included in the clinical decision support software in WP7 and inform a pilot clinical trial based on interim evaluation results.

The tasks of data-based modelling and integration include:

1. **Knowledge- and data-driven predictive modelling**, by using various data sources for predicting HCM-related risks, progression, and treatment response; synthesising knowledge-based predictive models and risk scores from scientific biomedical publications by combining natural language processing with information extraction; predicting treatment response in new HCM populations by utilising population and intervention features extracted from published trials using large language models; developing a cost-effective approach to interpretable risk stratification in HCM by using routinely collected clinical variables and referring higher-risk patients to extended data collection when required; developing novel markers for HCM stratification, prognosis, and response by analysing ECG signals, CMR and echocardiography images, and multi-organ data from WP5, including novel biomarkers of ventricle vulnerability and handcrafted, window-based morphology features with Heart Rate Variability indices; exploring features from hidden layers of neural networks, including the bottleneck-layer of long short-term memory (LSTM) networks, transformer networks, or convolutional neural network (CNN) autoencoders; enhancing the current state-of-the-art in interpretability of CMR biomarkers by integrating interpretable designs with deep learning, and applying these models to both cardiac MRI segmentation and prediction of HCM outcomes in accessible patient datasets.
2. **Multilevel model integration**, by developing a multilayer approach to combine multiple predictive models for monitoring HCM and comorbidities; pooling patient-specific information from in-silico simulations of cells, tissues, whole-heart, and multiple organs, as well as ECG-, CMR-, and echocardiography-based biomarkers to identify HCM patients at risk of adverse outcomes and improve their management and treatment response; enriching the stratification tool by incorporating in-vitro hiPSC-CM models to unveil HCM mechanisms and inform personalised therapies; utilising ensemble methods, including stacking classifiers and multi-fidelity modelling, to fuse detailed, computationally expensive models and data with less costly models and data; applying explainable AI techniques to unveil the relevance of input features for prediction and clustering; providing a platform for personalised HCM management through multiple models of HCM phenotype-genotype associations and comorbidities, including multiscale and spatiotemporal descriptions of the cardiovascular system with multilevel biomarker discovery methods; enabling the identification of optimal therapy options, including ICD implantation and pharmacological treatment, based on personalised risk scores and identified mechanisms of safety and efficacy of interventions across different disease variants.
3. **Technical validations and model refinement** by evaluating methods internally and externally across cohorts for common performance criteria of regression and classification models, robustness under unexpected conditions, reliability for multiple subgroups, generalisability to new populations, reproducibility of predictions, trustworthiness (including explainability and

trust by domain experts), bias, and fairness by assessing performance across different datasets; generating clinical vignettes for difficult cases, adversarial perturbations, and data poisoning; evaluating data, design, and outcome fairness by assessing relevance and fitness-for-purpose of models for disparate populations; detecting and mitigating biases in datasets, algorithms, and model architectures; assessing parity/equitability for individuals and groups defined by sensitive/protected attributes; using evaluation results to generate augmented datasets iteratively to improve model performance; informing development of clinician- and patient-facing software and development of trial protocols; assessing model performance according to traditional performance criteria or problem-specific metrics informed by with larger penalties for wrong predictions resulting in incorrect or unnecessary therapeutic actions or other health-economic criteria; performing retrospective validation on separate datasets to provide feedback and refine prediction and integration models.

All the models developed in WP6 will be accessible programmatically and included in the research and development (R&D) API developed in WP7. A selected number of models demonstrating the most promise for addressing real clinical challenges in terms of performance and health economics will also be included in the clinical decision support API. This API-enabled access will facilitate the use of AI/ML models for predicting treatment outcomes, identifying optimal treatment options, and integrating findings from *in vitro* (WP3), *in silico* (WP4), multi-organ (WP5), and machine learning modelling (WP6) into personalised strategies, ranging from preclinical discovery to clinical decision support. By providing programmatic access to these models, we aim to enhance the understanding of HCM, improve identification of patients at risk of adverse predictions or poor treatment response, and support the development of personalised treatment plans.

2 Technical Specification Template for SMASH-HCM API

We have developed the initial API Technical Specification Template aimed at harmonising model and algorithm descriptions; function and model documentation; and specification of hardware and software requirements needed for using the models at both training and inference.

The main purpose of this template is to collect information from model developers to facilitate the use of the models by multiple groups within the consortium. Partners were asked to add, remove, or modify fields in the meta-data template, or provide their comments. They were also instructed to continuously track their changes to the template as the models and functions are being developed. After reviewing the initial template, partners were requested to fill it in with their additions and modifications for the different models they were working on or intended to work on. They were allowed to copy the template as many times as needed, providing 20 exemplar descriptions in total.

The current template, which includes the aggregated and reviewed additions from the project partners, is summarised in Table 1. This should be viewed as a live document, as additional requirements may become clearer as the models are developed and tested.

Table 1 Technical Specification Template for the SMASH-HCM API.

Field	Explanation
Function/model name	The unique identifier or title of the function/model. This should be descriptive enough to convey the purpose or role of the function/model.
Function/model type	The category or nature of the function/model, such as whether it is an AI/ML regression model, a classification model, a survival regression model, a numerical model based on FEM modelling, ODEs, stochastic differential equations, etc.
Function/model's short description	A concise summary of the function/model, including its main purpose or intended use. This description may be one or two sentences long and will appear in the header of the models and functions in the SMASH-HCM model browser.
Function/model inputs	Details about what the function/model needs as input, including: • **Name:** The identifiers for each input variable. • **Type:** The data type of each input (e.g., integer, float, string, dictionary, vector, matrix, tensor, etc.), or format of input files if applicable. • **Unit:** The measurement unit of each input (e.g., ms, µmol/L, mg/dL, kg/m^2, ml/min/1.73m^2, etc.) • **Description:** A brief explanation of what each input variable represents. • **Range:** The range of plausible values each input can take. In case of categorical variables, define all categories the input might have and their meaning.
Function/model outputs	Details about what the function/model produces as output, including: • **Name:** The identifier for the output variable. • **Type:** The data type of the output (e.g., integer, float, string, dictionary, vector, matrix, tensor, etc.), or format of output files if applicable. • **Unit:** The measurement unit of the output (e.g., ms, µmol/L, mg/dL, kg/m^2, ml/min/1.73m^2, etc.) • **Description:** A brief explanation of what the output represents.

	• **Range:** The range of plausible values an output can take. In case of categorical variables, define all categories the output might have and their meaning.
Function/model's extended description	A more detailed explanation of the function/model, including its theoretical background, underlying algorithms, assumptions, relevant mathematical formulations, or clinical evidence. This description may be similar to the method paragraph in the abstract of a scientific publication and include multiple sentences. It will appear under the function description tag in the API reference if an investigator decides to examine a specific model in more detail.
Function/model's version	Version number of the function/model.
References to data sources	Links to publications or other online resources describing datasets or data collection protocols used in the development or evaluation of the function/model, including version numbers or dates if applicable, and data credibility evaluations (assessment of measurement errors, data provenance, quality, metrological properties, instrument or software certifications) if applicable.
References to labels	Information on the labels or definitions of the output variables that the model is designed to estimate, including references to sources, protocols, or definitions if applicable.
References to methods	Links to publications or other online resources describing the methods, algorithms, architectures, learning or inference techniques used in the development of the function/model, including academic papers, documentation, or other resources.
Software	Details about the software environment required to run the function/model: • **Programming language:** The programming languages used (e.g., Python, R, C++). • **Required packages/Libraries:** The packages or libraries needed, including specific versions (e.g., NumPy 1.19.2, TensorFlow 2.3.0). • **Configurations:** Configuration files or settings required for running the function/model, if applicable. • **Environment variables:** Any necessary environment variables that need to be set for the function/model to run correctly, if applicable. • **Licensing agreements:** Any licenses or terms of use associated with the software or model. • **Installation instructions:** Any relevant instructions.
System and computing requirements	• **Operating system:** Windows, Linux, Mac OS, others. • **Hardware:** minimum hardware required (e.g., CPUs, GPUs, RAM, etc.) • **Batch mode:** if the simulation can or needs to be launched in batch mode • **Execution:** parallel execution, single-/multi-threading • **Running times:** expected duration of simulations
Intended use	Intended use of the model, such as preclinical or clinical, including optional details about the intended use.
Detailed clinical use (optional)	Clarification of the clinical question that may be addressed by using the model, including the population being studied, the predictors or

	interventions being analysed, the comparison or reference group (if applicable), and the outcomes being predicted or evaluated. • **Population:** The specific demographic or clinical group for which the model is intended. • **Intervention:** The specific treatment, device, or action that the model is designed to predict or inform. • **Comparison**: Any comparative metrics, control groups, or baseline metrics used in the model, if relevant. • **Outcome / Clinical Endpoint:** The primary results or endpoints the model is designed to predict or improve. • **Inclusion:** detailed patient characteristics required for eligibility to use the function, model, or resulting intervention. • **Exclusion:** specific characteristics that disqualify patients from using the function, model, or resulting intervention.
Methodological limitations	Any known constraints or weaknesses of the function/model, including conditions under which it may not perform well, or specific scenarios where its predictions may be inaccurate.
Example of use (optional)	An example of a function/model call, or a brief description of a specific instance or scenario in which the function/model could be applied. This might help users understand practical applications and the context of usage.
Additional Information	Any other relevant details that might explain the use of the function/model or affect its performance or outputs. This may include information about local or cloud-based deployment environments; additional recommended technical or hardware specifications; best practices for using the function/model; considerations for handling missing or noisy data; interoperability requirements; compliance with standards or regulations; or any legal restrictions, if applicable.
Reference to evaluation	Links to publications or other online resources describing the performance of the function or model in any scientific channel, including descriptions of the datasets used for evaluations, if applicable. (Note: initially, this field is likely to be empty for most models.)
Support team contact details	Contact details of a support team that can provide further details and information, process bug reports, and address complaints.

While preparing our initial technical specifications in this Deliverable 7.3, we discussed the need to detail intellectual property (IP) issues related to model development. We concluded that although IP issues are undoubtedly important, they do not form part of the *technical* specifications for the library of predictive models. Nevertheless, we fully acknowledge the importance of IP considerations. To address this, IP strategy will be clarified as part of our work on "Business model planning, sustainability, and commercialisation strategy" in Task 9.4, as detailed in Section 2.2 "Measures to Maximise Impact - Dissemination, Exploitation, and Communication" of the SMASH-HCM Project Proposal, including deliverables 9.3 (Exploitation and Business Plan) and 9.4 (Final Business Model Planning). Those deliverables will clarify crucial IP aspects, including ownership and, where applicable, commercial and academic licensing agreements covering the use of mathematical or computational models developed in SMASH-HCM, including modelling parameters and hyper-parameters, auxiliary tools, as well as the modelling data used for training and both internal and external validations.

3 Exemplar API Specifications

This section provides an example of the initial API reference produced by following the methodology summarised in the template in Section 2. For some functions and models, many fields are yet to be defined, as these functions and models are in the early stages of development. This section should be viewed as a live document, where information about validations, performance, some additional inputs and outputs, minimal hardware and software requirements, and detailed use is subject to change based on the upcoming experiments and evaluations.

D7.3 Table WP3.1. Information given by: Pekkanen-Mattila, Valtonen, Ahola [TAU] [WP3].	
Field	**Explanation**
Function/model name	hiPSC-CM monolayer
Function/model type	Monolayer, physical in-vitro model.
Function/model's short description	Spontaneously contracting hiPSC-derived cardiac sheets or aggregates.
Function/model inputs	TBD.
Function/model outputs	• **Name:** Conduction velocity. • **Type:** float. • **Unit:** um/ms. • **Description:** TBD. • **Range:** [0.1-1].
	• **Name:** Mitochondrial respiration. • **Type:** Oxygen Consumption Rate (OCR). • **Unit:** pmol/min. • **Description:** Basal respiration, maximal respiration, ATP-linked respiration, spare respiratory capacity. • **Range:** [0-2000].
	• **Name:** Video microscopy. • **Type:** vector. • **Unit:** ms, AU. • **Description:** BPM, Relaxation time, Contraction time, contraction amplitude. • **Range:** [0-5000].
	• **Name:** micro electrode array (MEA). • **Type:** float. • **Unit:** ms. • **Description:** field potential duration, depolarisation time, BPM, depolarisation amplitude. • **Range:** [0-1000]
Function/model's extended description	For extracellular field potential measures (FP) of iPSC cardiomyocyte populations, spontaneously contracting cardiac sheets/aggregates are plated on micro electrode arrays (MEA). Contraction will be measured by a video optical system and beating regularity will be assessed.

	Mitochondrial respiration of iPSC-derived cardiomyocytes (M1-M36) (TAU-lead). Automated SeaHorse XFe platform will be used to assess mitochondrial function of single long-term matured iPSC cardiomyocytes and the effect of different mutations on oxygen consumption rate (OCR). Automated assay will be carried out and the measurement of the OCR will enable calculation of basal and maximal respiration rates during sequential addition of electron transport chain inhibitors. Addition of standardised drugs and myosin inhibitors to the sequence will elucidate their effect on mitochondrial function of the cardiomyocytes. Role of participants in WP3: UNIFI (lead) will provide electrophysiological and mechanical data from HCM patients; characterise hiPSC-derived cardiomyocytes for action potential and ion channels and engineered heart tissues for mechanical analysis and drug testing; generation novel hiPSC lines. UKE will provide electrophysiological and mechanical data from EHT based on hiPSC-CM from patients with HCM and their respective controls under baseline conditions and after challenge to catecholamines and to drugs clinically used in HCM. TAU will provide electrophysiological and mitochondrial respiration data collected for the in silico and tissue simulation; characterise hiPSC-derived HCM cardiomyocytes for action potential, field potential, and ion channels, in addition to mitochondrial respiration; generation novel hiPSC lines from patients with frequent HCM mutations.
Function/model's version	Ver 0.01.
References to data sources	N/A.
References to labels	N/A.
References to methods	Häkli et al, 2022 Stem Cell int. doi: 10.1155/2022/9438281 Ahola et al, 2018 Ann Biomed Eng. doi: 10.1007/s10439-017-1933-2
Software	• CellVisus (in-house software based on MATLAB R2021a). • Musclemotion. • Cardio PyMEA (Python 3.10). • MATLAB. • Multi Channel Experimenter (version 2.17.5.21056, Multi Channel Systems MCS GmbH). • Multi Channel Analyzer. • Agilent Seahorse XF Pro analyzer. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** minimum hardware TBD. • **Batch mode:** batch mode. • **Execution:** single- or multi-threading. • **Running times:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 4-6.
Detailed clinical use (optional)	TBD.

Methodological limitations	• Variability between iPS-cell lines and differentiation patches. • Low maturation status of hiPS-CMs.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP3.2. Information given by: Pekkanen-Mattila, Valtonen, Ahola [TAU] [WP3]	
Field	**Explanation**
Function/model name	hiPSC-CM engineered heart tissue.
Function/model type	Engineered Heart Tissue (EHT), physical in-vitro model.
Function/model's short description	Spontaneously contracting and paced hiPSC-derived cardiac engineered heart tissue constructs. Micropillar measurement of generated force. Contractility and contraction duration measurements using video image correlation-based methods. Oxygen lifetime measurement using 50 µM CPOx beads and SPIM-FLIM imaging system.
Function/model inputs	TBD.
Function/model outputs	• **Name:** Force. • **Type:** float. • **Unit:** µN. • **Description:** Force generated by the EHT. • **Range:** [0, 1000].
	• **Name:** Video microscopy. • **Type:** float. • **Unit:** ms, AU, mN. • **Description:** BPM, Relaxation time, Contraction time, contraction amplitude, relative force. • **Range:** [0, 5000]
	• **Name:** Oxygen lifetime measurement. • **Type:** float. • **Unit:** ms. • **Description:** Oxygen consumption. • **Range:** [0, 5000].
	• **Name:** Sharp needle measurement • **Type:** float. • **Unit:** ms. • **Description:** APD90, APD50, ADP10. • **Range:** [0, 5000].

Function/model's extended description	Contraction-frequency relationship will be determined in field-stimulated EHT. Response to catecholamines (positive inotropy but also arrhythmias) will be measured. Action potentials (AP) will be recorded by sharp microelectrodes and analysed. EHTs mechanics and excitation-contraction coupling will be tested for tension and kinetics of contraction. After EHT synthesis, auxotonic spontaneous contractions and their frequency will be regularly estimated over a long-term period (40-60 days) in culture by recording the deflection of individual posts using an inverted video-microscope with on-stage incubation. At the end of maturation, mechanical studies in isometric conditions with imposed pacing frequencies and precise length control will be used for a detailed characterisation of EHT mechanics. EHTs fixed-end twitch contractions at various Ca2+ levels and different pacing protocols (Krebs Henseleit (KH) solution, 37°C) will be measured. Skinned EHTs and individual myofibrils will be used for dissecting crossbridge mechanics and ATPase activity and determine myofilament calcium sensitivity. EHTs will be tested with standardised drugs in the clinical management of HCM (e.g., β-blockers, diltiazem, verapamil, disopyramide, amiodarone, ranolazine), the new generation of emerging myosin inhibitors (e.g., mavacamten, aficamten), and novel sodium-glucose cotrasporter-2 (SGLT-2) inhibitors (dapaglifozin, empaglifozin), used for the therapy of heart failure. The EHT data be validated against native adult human myocardium from HCM patients at the UNIFI tissue and data repository. Short-term variability of APD in paced EHT will be used as an index of electrical stability. EHTs and cultures will be challenged to hERG blockers and APD prolongation and occurrence of afterdepolarisation will be measured to determine repolarisation capacity. Inducibility of arrhythmias will be tested by burst stimulation. Patch-clamp studies on single long-term matured iPSC-CMs will be performed to evaluate the effects of different mutations measuring single currents in voltage-clamp mode and divided by cell capacitances pA/pF. The effects of specific treatments/drugs on ion currents and FPD will also be evaluated. The obtained data be validated against native adult human myocardium from HCM patients at the UNIFI tissue and data repository.
Function/model's version	Ver 0.01.
References to data sources	N/A.
References to labels	N/A.
References to methods	Mannhardt et al. 2016 Stem Cell Reports DOI: 10.1016/j.stemcr.2016.04.011
Software	• CellVisus (in-house software based on MATLAB R2021a) • Lab-Chart (ADInstruments) • **Installation instructions:** TBD.

System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** minimum hardware TBD. • **Batch mode:** TBD. • **Execution:** single- or multi-threading. • **Running times:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 4-6.
Detailed clinical use (optional)	TBD.
Methodological limitations	• Variability between individual EHTs • Variability between cell lines
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP4.1. Information given by: Stefano Severi and Chiara Bartolucci [UNIBO] [WP3-4]	
Field	**Explanation**
Function/model name	HCM mutation-specific cardiac tissue model
Function/model type	ODEs / PDEs
Function/model's short description	*Models of each phenotype HCM mutation will be simulated in virtual 2D/3D tissue models produced from patients' hiPSC-CMs and tissue samples*
Function/model inputs	Time course of the stimulus current • **Name:** Stimulation protocol. • **Type:** integer • **Unit:** none • **Description:** the variable will represent a flag for the choice of stimulation protocol (e.g. basal rate, rate dependence, EADs, DADs, alternans etc). • **Range:** none.
Function/model outputs	• **Name:** Conduction velocity (CV). • **Type:** float • **Unit:** cm/s or m/s • **Description:** Conduction velocity in cardiac cells refers to the speed at which an electrical impulse, or action potential, propagates through the heart's tissue. • **Range:** 0.3 to 1 m/s.
	• **Name:** Contraction markers, e.g. Amplitude, Time-to-peak, Relaxation time. • **Type:** float • **Unit:** kPa or μN/mm², ms or s

	• **Description:** *Amplitude* refers to the maximum force or extent of contraction that a cardiac muscle cell or tissue achieves during the contraction phase. *Time-to-peak* is the duration it takes for the contraction to reach its maximum amplitude from the onset of the contraction. *Relaxation time* is the time it takes for the heart muscle to return from peak contraction back to its resting state, or baseline, during diastole. • **Range:** 30 to 70µN/mm², 150 to 300ms, 100 to 300ms (under normal condition).
	• **Name:** EADs, DADs, Alternans, Reentry inducibility. • **Type:** integer • **Unit:** none • **Description:** Flag that gives the information of the presence of Early Afterdepolarisations (EADs), Delayed Afterdepolarisations (DADs), alternans, or reentry inducibility. • **Range:** 0 or 1
Function/model's extended description	Representative models of each phenotypic variant per HCM mutation will be simulated in tissue models, which can then later be translated to whole-heart models. We will hence identify key structural mechanisms responsible for modulating the pro-arrhythmic substrate according to individual HCM genetic variants, which would otherwise be difficult to isolate and study in human tissue.
Function/model's version	Ver 0.01.
References to data sources	Links to publications or other online resources describing datasets or data collection protocols used in the development or evaluation of the function/model, including version numbers or dates if applicable.
References to labels	Information on the labels or definitions of the output variables that the model is designed to estimate, including references to sources, protocols, or definitions if applicable.
References to methods	1. M. Forouzandehmehr, J. T. Koivumäki, J. Hyttinen, and M. Paci, "A mathematical model of hiPSC cardiomyocytes electromechanics," Physiol Rep, vol. 9, no. 22, Nov. 2021, doi: 10.14814/phy2.15124. 2. C. Bartolucci, M. Forouzandehmehr, S. Severi, and M. Paci, "A Novel In Silico Electromechanical Model of Human Ventricular Cardiomyocyte," Front Physiol, vol. 13, Jun. 2022, doi: 10.3389/fphys.2022.906146 3. Mazhar F, Bartolucci C, Regazzoni F, Paci M, Dedè L, Quarteroni A, Corsi C, Severi S. A detailed mathematical model of the human atrial cardiomyocyte: Integration of electrophysiology and cardiomechanics. Vascul Pharmacol. 2024 Jun;155:107330. doi: 10.1016/j.vph.2024.107330. PMID: 38985637.

	4. Jæger KH, Trotter JD, Cai X, Arevalo H, Tveito A. Evaluating computational efforts and physiological resolution of mathematical models of cardiac tissue. Sci Rep. 2024 Jul 23;14(1):16954. doi: 10.1038/s41598-024-67431-w. PMID: 39043725; PMCID: PMC11266357.
Software	Details about the software environment required to run the function/model: • **Programming language:** The programming languages used (e.g., Matlab). • **Required packages/Libraries:** • **Configurations:** Configuration files or settings required for running the function/model, if applicable. • **Environment variables:** Any necessary environment variables that need to be set for the function/model to run correctly, if applicable. • **Licensing agreements:** Any licenses or terms of use associated with the software or model. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** minimum hardware TBD. • **Batch mode:** TBD. • **Execution:** single- or multi-threading. • **Running times:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 5-6.
Detailed clinical use (optional)	Contextual information about the function/model's application in clinical care or self-management: • **Population:** HCM patients. • **Intervention:** TBD, with the intend of identifying key mechanisms underlying adverse outcomes and pro-arrhythmic risk according to genetic variants, suggesting potential mutation-specific treatments, and providing refined computational models for further investigations in human cardiac diseases. • **Comparison:** Healthy individuals. • **Outcome / Clinical Endpoint:** TBD, so as to support tightly coupled multi-scale modelling and simulation studies for mechanistic investigations of genotype-phenotype stratification in HCM. • **Inclusion and exclusion:** TBD.
Methodological limitations	Computational resources available for running the simulations and time for them.
Example of use	An example of a function/model call, or a brief description of a specific instance or scenario in which the function/model could be applied. This might help users understand practical applications and the context of usage.

Additional Information	Any other relevant details that might explain the use of the function/model or affect its performance or outputs. This may include information about local or cloud-based deployment environments; recommended hardware specifications; best practices for using the function/model; considerations for handling missing or noisy data; interoperability requirements; compliance with standards or regulations; or any legal restrictions due to IP rights or licenses, if applicable.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP4.2. Information given by: Amin Forouzandehmehr [TAU] [WP4]	
Field	**Explanation**
Function/model name	Mutation-specific HCM cellular model of hiPSC cardiomyocytes: *electro-mechano-energetics.*
Function/model type	ODEs.
Function/model's short description	*Models of each phenotype HCM mutation will be simulated in virtual cellular models following in vitro data on the mutations.*
Function/model inputs	Time course of the stimulus current • **Name:** Stimulation protocol. • **Type:** integer • **Unit:** none • **Description:** the variable will represent a flag for the choice of stimulation protocol (e.g. basal rate, rate dependence, EADs, DADs, alternans etc). • **Range:** none.
Function/model outputs	• **Name:** Action Potential (AP). • **Type:** float • **Unit:** mV or V • **Description:** Electrical signals that propagate through the heart muscle, triggering the contraction and relaxation of the heart. • **Range:** -75 to 28 mV (control).

	• **Name:** Intracellular Ca^{2+} transient (CaT) + all CaT biomarkers:
	  ○ *DURATION: duration of the transient,*
	  ○ *tRise10, peak: time to peak,*
	  ○ *tRise10, 50 and tRise10, 90: rise time from 10 to 50% and 90% of maximum threshold, respectively*
	  ○ *tDecay90,10: decay time from 90 to 10%.*
	• **Type:** float
	• **Unit:** mM or M, ms or s.
	• **Description:** Dynamic concentration of total cytosolic Ca^{2+}.
	• **Range:** 0.02 to 0.19 M (control).

	• **Name:** Contraction markers, e.g. Active Tension (AT), Time-to-peak, time from peak tension to 50% of Relaxation (CRT50), percent of fractional shortening, contractile ATPase rate. • **Type:** float. • **Unit:** kPa or µN/mm², ms or s, % or µm. • **Description:** *Amplitude* refers to the maximum force or extent of contraction that a cardiac muscle cell or tissue achieves during the contraction phase. *Time-to-peak* is the duration it takes for the contraction to reach its maximum amplitude from the onset of the contraction. *CRT50* is the time it takes for the heart muscle to return from peak contraction back to 50% resting state, or baseline, during diastole. Rate of ATP consumption in myofilament crossbridge cycling (mM/s) • **Range:** AT = 0 to 0.0557 kPa, CRT50=154 ms, contractile ATPase: 0.013 mM/s.
	• **Name:** Dynamic extracellular O^2 concentration, Oxygen consumption rate (OCR) • **Type:** float • **Unit:** mM, mM/s. • **Description:** The model links the cellular ionic and contractile ATPase rate changes to extracellular O_2 concentration. • **Range:** 0.129 to 0.133 mM (control).
	• **Name:** Mechanosensitive channel Piezo1, Piezo1 Ca^{2+} flux • **Type:** float • **Unit:** A/F, mM/s. • **Description:** A Piezo1 model with a tension/stretch-gated activation and voltage-dependent inactivation parametrised based on indentation (poking) protocol of *in vitro* data on Piezo1. • **Range:** -2 to 0 A/F (control).
	• **Name:** EADs, DADs, Alternans due to protocol or ischemia • **Type:** integer • **Unit:** none

	• **Description:** >= 85% IKr and/or IKs block leading to Early Afterdepolarisations (EADs), Delayed Afterdepolarisations (DADs), alternans, simulations. • **Range:** 0 or 1.
Function/model's extended description	Representative models of each phenotypic variant per HCM mutation will be simulated in cellular electro-mechano-energetic models, which can then later be translated to whole-heart models. We will hence identify key structural mechanisms responsible for modulating the pro-arrhythmic substrate according to individual HCM genetic variants, which would otherwise be difficult to isolate and study in human tissue. A detailed mitochondria submodel is available to be integrated into the whole cell model offering insight upon the metabolic molecular mechanisms underlying HCM mutations pathophysiology. ATP-sensitive I_{NaK} current is a promising future addition to the current framework.
Function/model's version	Ver 0.01.
References to data sources	Links to publications or other online resources describing datasets or data collection protocols used in the development or evaluation of the function/model: Tables 1-6 in https://doi.org/10.3389/fphys.2022.1010786, Table 1 and Supplementary Materials in: https://doi.org/10.1242/dmm.050365, Tables 1&2 in: https://doi.org/10.22489/CinC.2023.359
References to labels	Information on the labels or definitions of the output variables that the model is designed to estimate, including references to sources, protocols, or definitions if applicable.
References to methods	1. M. Forouzandehmehr, J. T. Koivumäki, J. Hyttinen, and M. Paci, "A mathematical model of hiPSC cardiomyocytes electromechanics," Physiol Rep, vol. 9, no. 22, Nov. 2021, doi: 10.14814/phy2.15124. 2. M. Forouzandehmehr, M. Paci, J.T. Koivumäki, J. Hyttinen, Altered contractility in mutation-specific hypertrophic cardiomyopathy: A mechano-energetic in silico study with pharmacological insights, Front. Physiol. 13 (2022). doi:10.3389/fphys.2022.1010786 3. M. Forouzandehmehr, S. Ghosi, M. Paci, J. Hyttinen, J. Koivumäki, Mechanosensitive Channel Piezo1 in R403Q Hypertrophic Cardiomyopathy: A Computational Study, in: 2023 Computing in Cardiology (CinC), 2023: pp. 1–4. https://doi.org/10.22489/CinC.2023.359. 4. M. Forouzandehmehr, M. Paci, J. Hyttinen, J.T. Koivumäki, In silico study of the mechanisms of hypoxia and contractile dysfunction during ischemia and reperfusion of hiPSC cardiomyocytes, Disease Models & Mechanisms 17 (2024) dmm050365. https://doi.org/10.1242/dmm.050365.

Software	Details about the software environment required to run the function/model: • **Programming language:** Currently MATLAB. • **Required packages/Libraries:** TBD. • **Configurations:** TBD. • **Environment variables:** TBD. • **Licensing agreements:** Any licenses or terms of use associated with the software or model TBD. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** minimum hardware TBD. • **Batch mode:** TBD. • **Execution:** TBD. • **Running times:** TBD. • **Installation instructions:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 5-6.
Detailed clinical use (optional)	Information about the function/model's clinical application: • **Population:** HCM patient. • **Intervention:** identify key mechanisms underlying adverse outcomes and pro-arrhythmic risk according to genetic variants, suggest potential mutation-specific treatments, and provide refined computational models for further investigations in human cardiac diseases. • **Comparison:** Control and diseased *in vitro*. • **Outcome / Clinical Endpoint:** tightly coupled multi-scale modelling and simulation studies for mechanistic investigations of genotype-phenotype stratification in HCM.
Methodological limitations	Neglecting spatial heterogeneity in excitation contraction coupling as the model is based on ODEs (not PDEs). Computational resources available for running the simulations and time for them.
Example of use	TBD.
Additional Information	**hiMCES model outputs**: Relaxation dysfunction in ischemia (CRT50s and active tension amplitude) and altered SERCA phosphorylation due to change in MgATP, MgADP, and Pi. Altered oxygen dynamics due to change in INaK, IpCa, and contractile ATPase. 0.3 and 2 uM of Levosimendan effect in ischemia and reperfusion: Mapping Levosimendan molecular mechanism of action: Ca2+ bound Troponin affinity, Ca2+ flux to the myofilament, Potential contributions for HCM: altered oxygen consumption rate prediction for mutation-specific HCM and sarcomere-targeting drugs. **hiMCE and hiPSC-CM-CE output**: A metabolite-sensitive parameter space of myofilament crossbridge cycling for $MYH7^{R403Q/+}$ HCM and Mavacamten: altered kinetics between non-permissive, permissive, and force-generating states of actomyosin

	interactions. 0.5 uM Mavacamten, on MYH7$^{R403Q/+}$ HCM simulated. Also: 1 uM Omecamtive (OM) and 5 uM Blebbistatin (BLEB), dose-dependent inotropic effect of OM and BLEB was parametrised, 90 mM Verapamil. **hiMCES+Piezo1 output**: Altered active tensions, fractional cell shortenings, Piezo1 tension sensitivity, altered or healthy Piezo1 Ca^{2+} influx contribution to Ca^{2+} homeostasis in MYH7$^{R403Q/+}$ HCM.
Reference to evaluation (future)	[1] N. M. Blythe et al., "Mechanically activated Piezo1 channels of cardiac fibroblasts stimulate p38 mitogenactivated protein kinase activity and interleukin-6 secretion," Journal of Biological Chemistry, vol. 294, no. 46, pp. 17395–17408, Nov. 2019, doi: 10.1074/jbc.RA119.009167. [2] Z.-Y. Yu et al., "Piezo1 is the cardiac mechanosensor that initiates the cardiomyocyte hypertrophic response to pressure overload in adult mice," Nat Cardiovasc Res, vol. 1, no. 6, Art. no. 6, Jun. 2022, doi: 10.1038/s44161-022- 00082-0 [3] Toepfer C. N., Wakimoto H., Garfinkel A. C., McDonough B., Liao D., Jiang J., et al. (2019). Hypertrophic cardiomyopathy mutations in MYBPC3 dysregulate myosin. *Sci. Transl. Med.* 11, eaat1199. doi:10.1126/scitranslmed.aat1199 [4] Sarkar S. S., Trivedi D. V., Morck M. M., Adhikari A. S., Pasha S. N., Ruppel K. M., et al. (2020). The hypertrophic cardiomyopathy mutations R403Q and R663H increase the number of myosin heads available to interact with actin. *Sci. Adv.* 6, eaax0069. doi:10.1126/sciadv.aax0069 [5] Kampourakis T., Zhang X., Sun Y.-B., Irving M. (2018). Omecamtiv mercabil and blebbistatin modulate cardiac contractility by perturbing the regulatory state of the myosin filament. *J. Physiol.* 596, 31–46. doi:10.1113/JP275050.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP4.3. Information given by: James Coleman [UOXF] [WP4]	
Field	**Explanation**
Function/model name	reconstruct_biventricular_anatomy_from_cmr_images
Function/model type	Pre-processing step for patient-specific multiscale cardiac electrophysiology simulations.
Function/model's short description	Used to reconstruct patient-specific biventricular anatomy from clinical CMR images, and generate fields required for simulation such as fibres, apex-to-base gradients and transmural gradients.
Function/model inputs	• **Name:** cmr_data. • **Type:** DICOM files. • **Description:** patient CMR images.
Function/model outputs	• **Name:** biventricular_anatomy. • **Type:** array of vector coordinates. • **Unit:** µm.

	• **Description:** each element of the output array represents a hexahedral mesh element centre.
	• **Name:** fibres_field. • **Type:** array of 3x3 float matrices. • **Description:** each element of the output array contains information about local myocardial orientation (fibre, sheet, sheet-normal unit vectors) corresponding to each biventricular mesh element.
	• **Name:** apex_base_field. • **Type:** array of floats. • **Unit:** TBD. • **Description:** each element of the output array describes how far the corresponding biventricular mesh element is from the apex (0 at the apex, 1 at the base).
	• **Name:** transmural_field. • **Type:** array of floats. • **Description:** each element of the output array describes how far the corresponding biventricular mesh element is from the endocardium (0 at the endocardium, 1 at the epicardium).
Function/model's extended description	TBD.
Function/model's version	Ver 0.01.
References to data sources	TBD.
References to labels	TBD.
References to methods	A. Banerjee et al: "A completely automated pipeline for 3D reconstruction of human heart from 2D cine magnetic resonance slices" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8543046/
Software	TBD.
System and computing requirements	• **Operating system:** Windows, Linux, or Mac OS. • **Hardware:** TBD. • **Batch mode:** TBD. • **Execution:** parallel execution enabled. • **Running times:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 5-6.
Detailed clinical use (optional)	TBD.
Methodological limitations	TBD.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation (future)	TBD.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP4.4. Information given by: James Coleman [UOXF] [WP4]

Field	Explanation
Function/model name	qrs_personalisation
Function/model type	Pre-processing step for patient-specific multiscale cardiac electrophysiology simulations.
Function/model's short description	Bayesian inference using simplified wavefront propagation models and pseudo-ECG to infer activation properties for a patient-specific biventricular anatomy with a fibres field, using patient ECG.
Function/model inputs	• **Name:** ecg_data. • **Type:** csv. • **Description:** patient ECG data.
	• **Name:** biventricular_anatomy. • **Type:** array of vector coordinates. • **Unit:** µm. • **Description:** each element of the output array represents a hexahedral mesh element centre.
	• **Name:** fibres_field. • **Type:** array of 3x3 float matrices. • **Description:** each element of the output array contains information about local myocardial orientation (fibre, sheet, sheet-normal unit vectors) corresponding to each biventricular mesh element.
Function/model outputs	• **Name:** endo_activation_times. • **Type:** array of floats. • **Unit:** ms. • **Description:** each element of the output array describes an endocardial activation time for an element on the endocardial surface of the biventricular mesh.
Function/model's extended description	TBD.
Function/model's version	Ver 0.01.
References to data sources	TBD.
References to labels	TBD.
References to methods	J. Camps et al: "Digital twinning of the human ventricular activation sequence to Clinical 12-lead ECGs and magnetic resonance imaging using realistic Purkinje networks for in silico clinical trials" https://pubmed.ncbi.nlm.nih.gov/38447244/
Software	TBD.
System and computing requirements	• **Operating system:** Windows, Linux, or Mac OS. • **Hardware:** TBD. • **Batch mode:** TBD. • **Execution:** parallel execution enabled.

	• **Running times:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 5-6.
Detailed clinical use (optional)	TBD.
Methodological limitations	TBD.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation (future)	TBD.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP4.5. Information given by: James Coleman [UOXF] [WP4]	
Field	**Explanation**
Function/model name	monoalg3d_main_simulator
Function/model type	Multiscale cardiac electrophysiology simulation.
Function/model's short description	GPU-enabled monodomain simulations of cardiac electrophysiology, for the biventricular_anatomy mesh, stimulated according to endo_activation_times, with myocardial fibres set by fibres_field, apex-to-base IKs gradients set by apex_base_field, and endo/epicardial cell types set by transmural_field.
Function/model inputs	• **Name:** config. • **Type:** ini. • **Description:** MonoAlg3D configuration file, which specifies simulation parameters such as the total simulation time, ODE/PDE solving parameters, ECG electrode positions, output directories, conductivities and anisotropy.
	• **Name:** biventricular_anatomy. • **Type:** array of vector coordinates. • **Unit:** µm. • **Description:** each element of the output array represents a hexahedral mesh element centre.
	• **Name:** endo_activation_times. • **Type:** array of floats. • **Unit:** ms. • **Description:** each element of the output array describes an endocardial activation time for an element on the endocardial surface of the biventricular mesh.
	• **Name:** fibres_field. • **Type:** array of 3x3 float matrices. • **Description:** each element of the output array contains information about local myocardial orientation (fibre,

	sheet, sheet-normal unit vectors) corresponding to each biventricular mesh element.
	• **Name:** apex_base_field. • **Type:** array of floats. • **Description:** each element of the output array describes how far the corresponding biventricular mesh element is from the apex (0 at the apex, 1 at the base).
	• **Name:** transmural_field. • **Type:** array of floats. • **Description:** each element of the output array describes how far the corresponding biventricular mesh element is from the endocardium (0 at the endocardium, 1 at the epicardium).
Function/model outputs	• **Name:** vms. • **Type:** 2D array of floats. • **Unit:** mV. • **Description:** each element of the output array describes a membrane potential for an element of the biventricular mesh for a given time.
	• **Name:** ecg. • **Type:** 2D array of floats. **Description:** each element of the output array describes an electrical potential for an ECG electrode for a given time.
Function/model's extended description	TBD.
Function/model's version	Ver 0.01.
References to data sources	TBD.
References to labels	TBD.
References to methods	R. Oliveira et al: "Performance evaluation of GPU parallelisation, space-time adaptive algorithms, and their combination for simulating cardiac electrophysiology" https://pubmed.ncbi.nlm.nih.gov/28636811/ MonoAlg3D source code is publicly available at https://github.com/rsachetto/MonoAlg3D_C
Software	• C. • Nvidia Driver. • CUDA library. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Linux. • **Hardware:** TBD. • **Batch mode:** TBD. • **Execution:** parallel execution enabled. • **Running times:** TBD.

Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 5-6.
Detailed clinical use (optional)	TBD.
Methodological limitations	TBD.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation (future)	TBD.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP4.6. Information given by: James Coleman [UOXF] [WP4]	
Field	**Explanation**
Function/model name	arrhythmic_risk_protocol
Function/model type	Function that initiates many patient-specific multiscale cardiac electrophysiology simulations.
Function/model's short description	Makes many calls to monoalg3d_main_simulator, where each simulation involves an S1-S2 pacing protocol used to attempt arrhythmia induction in the patient-specific biventricular model.
Function/model inputs	• **Name:** ectopic_position. • **Type:** array of floats. • **Description:** position of the ectopic stimulus (S2) used to attempt re-entry induction in the patient-specific biventricular model.
	• **Name:** s1_s2_range. • **Type:** array of floats. • **Description:** times at which the ectopic stimulus (S2) is activated, following sinus rhythm (S1).
	• **Name:** config_base. • **Type:** ini. • **Description:** MonoAlg3D configuration base file, which is then slightly modified to facilitate the S1-S2 protocol.
	• **Name:** biventricular_anatomy. • **Type:** array of vector coordinates. • **Unit:** µm. • **Description:** each element of the output array represents a hexahedral mesh element centre.
	• **Name:** endo_activation_times. • **Type:** array of floats. • **Unit:** ms. • **Description:** each element of the output array describes an endocardial activation time for an element on the endocardial surface of the biventricular mesh.

	• **Name:** fibres_field. • **Type:** array of 3x3 float matrices. • **Description:** each element of the output array contains information about local myocardial orientation (fibre, sheet, sheet-normal unit vectors) corresponding to each biventricular mesh element.
	• **Name:** apex_base_field. • **Type:** array of floats. • **Description:** each element of the output array describes how far the corresponding biventricular mesh element is from the apex (0 at the apex, 1 at the base).
	• **Name:** transmural_field. • **Type:** array of floats. • **Description:** each element of the output array describes how far the corresponding biventricular mesh element is from the endocardium (0 at the endocardium, 1 at the epicardium).
Function/model outputs	Many instances of the outputs from monoalg3d_main_simulator • **Name:** vms. • **Type:** 2D array of floats. • **Unit:** mV. • **Description:** each element of the output array describes a membrane potential for an element of the biventricular mesh for a given time.
	• **Name:** ecg. • **Type:** 2D array of floats. • **Description:** each element of the output array describes an electrical potential for an ECG electrode for a given time.
Function/model's extended description	TBD.
Function/model's version	Ver 0.01.
References to data sources	TBD.
References to labels	TBD.
References to methods	J. Coleman et al: "Effects of ranolazine on the arrhythmic substrate in hypertrophic cardiomyopathy" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11039821/

Software	• Python + MonoAlg3D software:
	  ○ C
	  ○ Nvidia Driver
	  ○ CUDA library
	• **Installation instructions:** TBD.

System and computing requirements	• **Operating system:** Linux. • **Hardware:** TBD. • **Batch mode:** TBD. • **Execution:** parallel execution enabled. • **Running times:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 5-6.
Detailed clinical use (optional)	TBD.
Methodological limitations	TBD.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation (future)	TBD.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP4.7. Information given by: James Coleman [UOXF] [WP4]	
Field	**Explanation**
Function/model name	alya_main_simulator
Function/model type	Multiscale cardiac electromechanical simulation
Function/model's short description	Simulations of cardiac electromechanics.
Function/model inputs	• **Name:** config. • **Type:** ini. • **Description:** Alya configuration file.
	• **Name:** biventricular_anatomy. • **Type:** array of vector coordinates. • **Unit:** µm. • **Description:** each element of the output array represents a hexahedral mesh element centre.
	• **Name:** endo_activation_times. • **Type:** array of floats. • **Unit:** ms. • **Description:** each element of the output array describes an endocardial activation time for an element on the endocardial surface of the biventricular mesh.
	• **Name:** fibres_field • **Type:** array of 3x3 float matrices • **Description:** each element of the output array contains information about local myocardial orientation (fibre, sheet, sheet-normal unit vectors) corresponding to each biventricular mesh element.
	• **Name:** apex_base_field. • **Type:** array of floats.

	Description: each element of the output array describes how far the corresponding biventricular mesh element is from the apex (0 at the apex, 1 at the base).
	• **Name:** transmural_field. • **Type:** array of floats. • **Description:** each element of the output array describes how far the corresponding biventricular mesh element is from the endocardium (0 at the endocardium, 1 at the epicardium).
Function/model outputs	• **Name:** vms • **Type:** 2D array of floats • **Unit:** mV • **Description:** each element of the output array describes a membrane potential for an element of the biventricular mesh for a given time
	• **Name:** cell_positions. • **Type:** 2D array of float tuples. • **Unit:** µm. • **Description:** each element of the output array describes the position for an element of the biventricular mesh for a given time.
	• **Name:** ecg. • **Type:** 2D array of floats. • **Description:** each element of the output array describes an electrical potential for an ECG electrode for a given time.
	• **Name:** pressure. • **Type:** array of floats. • **Unit:** mmHg. • **Description:** each element of the output array describes myocardial pressure for a given time.
	• **Name:** volume. • **Type:** array of floats. • **Unit:** mL. • **Description:** each element of the output array describes myocardial pressure for a given time.
Function/model's extended description	TBD.
Function/model's version	Ver 0.01.
References to data sources	TBD.
References to labels	TBD.
References to methods	Zhou et al: "Clinical phenotypes in acute and chronic infarction explained through human ventricular electromechanical modelling and simulations"

	https://elifesciences.org/reviewed-preprints/93002
Software	TBD.
System and computing requirements	• **Operating system:** Windows, Linux, or Mac OS. • **Hardware:** TBD. • **Batch mode:** TBD. • **Execution:** parallel execution enabled. • **Running times:** TBD.
Intended use	Preclinical and research, including generation of synthetic data and prior knowledge for WP 5-6.
Detailed clinical use (optional)	TBD.
Methodological limitations	TBD.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation (future)	TBD.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP5.1. Information given by: Virginie Le Rolle [UNIVREN] [On behalf of WP5]	
Field	**Explanation**
Function/model name	SCVmodel_HCM_strain.
Function/model type	Personalised Model of the cardiovascular system.
Function/model's short description	Computational model of the cardiovascular system including: i) Multi-segment representation of left and right ventricles, ii) left and right atria, iii) systemic and pulmonary circulations and iv) Left ventricular outflow tract (LVOT).
Function/model's inputs	• **Name:** Clinical strains. • **Type:** float. • **Unit:** %. • **Description:** Myocardial strains obtained from echocardiography. • **Range:** [-25, 10].
	• **Name:** Pressures • **Type:** float. • **Unit:** mmHg. • **Description:** LVOT pressure gradient, systolic pressure, diastolic pressure **Range:** [0, 70], [90, 180], [50, 100].
Function/model outputs	• **Name:** Simulated strains. • **Type:** float. • **Unit:** %. • **Description:** Simulation of myocardial strains.

	• **Range:** [-25, 10].
	• **Name:** Patient-specific parameters. • **Type:** float. • **Description:** Identified parameters according to clinical data: level of contractility, stiffness, systolic and diastolic properties.
Function/model's extended description	The computational model of SCV could be personalised according to clinical data by identifying model parameters. A database of 201 HCM patients, from Rennes hospital, could be used to access myocardial strains from echocardiography.
Function/model's version	Ver 0.01.
References to data sources	The study involved 201 adult HCM patients with a diagnosis established according to current guidelines. All patients underwent standard and 2D-speckle-tracking transthoracic echocardiography at baseline. Left ventricle longitudinal strains by speckle tracking echocardiography were obtained from 2D apical four (4ch), two (2ch), and three (3ch) chamber views. See more details in https://doi.org/10.1016/j.ijcard.2024.132167
References to labels	TBD.
References to methods	The data used will be a subset of: • https://doi.org/10.1016/j.ijcard.2024.132167 The model was adapted from: • https://doi.org/10.3389/fams.2022.833003 • https://doi.org/10.1093/ehjci/jeac046 • https://doi.org/10.1371/journal.pone.0258225
Software	Details about the software environment required to run the model: • **Programming language:** C++ • **Required packages/Libraries:** M2SL • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** open license.
	Details about the software environment required to run the parameters identification: • **Programming language:** python 3.8 or later. • **Required packages/Libraries:** pagmo 2.19.0 or pymoo library • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** custom proprietary license. • **Installation instructions:** TBD.

System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** TBD. • **Batch mode:** batch mode supported. • **Execution:** single- or multi-threading. • **Running times:** TBD.
Intended use	Preclinical and clinical research, including generation of synthetic data and prior knowledge for WP 6.
Detailed clinical use (optional)	• **Population:** HCM patients with different levels of risks of ventricular arrhythmia (VA). • **Intervention:** None • **Comparison:** None. • **Outcome:** TBD, with the view of exploring whether automatic extraction and analysis of LV strain parameters improves the risk stratification for VA in HCM patients. • **Inclusion and exclusions:** details to be defined.
Methodological limitations	The model has several limitations: it does not include the HCM mutation, it includes high levels description of cardiac mechanics. Further limitations will be investigated.
Example of use	Not yet available.
Additional Information	Personalised parameters identified with the model could help to improve risk stratification.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP5.2. Information given by: Virginie Le Rolle [UNIVREN] [On behalf of WP5]	
Field	**Explanation**
Function/model name	IntegratedModel_HCM.
Function/model type	Integrated physiological model.
Function/model's short description	Computational model including: i) Smooth muscle cell, ii) cardiac cavities, ii) coronary circulation, and iii) systemic and pulmonary circulations.
Function/model inputs	Should be defined.
Function/model outputs	• **Name:** Simulated pressures. • **Type:** float. • **Unit:** mmHg and ml/s. • **Description:** Simulation of hemodynamic variables. • **Range:** [0, 180].
	• **Name:** Smooth muscle tension.

	• **Type:** float. • **Unit:** TBD. • **Description:** TBD. • **Range:** TBD.
Function/model's extended description	The integrated model of SCV could be analysed using sensitivity analysis to provide insights concerning HCM.
Function/model's version	Ver 0.01.
References to data sources	TBD.
References to labels	TBD.
References to methods	TBD.
Software	Details about the software environment required to run the model: • **Programming language:** C++ • **Required packages/Libraries:** M2SL • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** open license. • **Installation instructions:** TBD.
	Details about the software environment required to run the model: • **Programming language:** Matlab/Python • **Required packages/Libraries:** TBD. • **Configurations:** TBD. • **Environment variables:** TBD. • **Licensing agreements:** TBD. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** TBD. • **Batch mode:** batch mode supported. • **Execution:** single- or multi-threading. • **Running times:** TBD.
Intended use	Preclinical and clinical research, including generation of synthetic data and prior knowledge for WP 6.
Detailed clinical use (optional)	• **Population:** TBD. • **Intervention:** None (exploratory observational). • **Comparison:** None (single arm). • **Outcome:** TBD. • **Inclusion and exclusion:** TBD.
Methodological limitations	Not yet available.
Example of use	Not yet available.
Additional Information	Not yet available.

Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP5.3. Information given by: Virginie Le Rolle [UNIVREN] [On behalf of WP5]	
Field	**Explanation**
Function/model name	SMC_HCM (contributors 8 & 13 of WP5 deliverables)
Function/model type	SMC electrophysiological and contractile model
Function/model's short description	Smooth muscle cell and tissue model
Function/model inputs	• **Name:** Simulated local pressure, all electrophysiological initial conditions, Ca ion concentration, initial tone, HCM variation • **Type:** float. • **Unit:** (kPa, M) • **Description:** details to be defined.
Function/model outputs	• **Names:** output_vector containing the estimates of passive and active force, tension, compliance/elastance, resistance, state variables (AP, contractility, Ca ion concentrations, potassium and calcium currents, membrane potential) • **Type:** array of float. • **Unit:** (N, mL/kPa, M) • **Description:** Calcium, electrophysiology, contractility, estimates of the vascular wall tone, compliance effects on resistance.
Function/model's extended description	To be analysed using sensitivity analysis to provide insights concerning HCM.
Function/model's version	Ver 0.01.
References to data sources	• DOI: 10.1007/s11538-011-9681-1 • DOI: 10.1016/j.jtbi.2011.11.012
References to labels	N/A
References to methods	• SMC base model adapted from: doi:10.1016/j.jtbi.2008.03.004 and doi.org/10.1080/19336950.2017.1293220 • SMC contractile element from: doi:10.1152/ajpcell.1988.254.1.C99 (Hai) • doi: 10.1016/j.jtbi.2011.11.012 (Murtada) • doi: 10.1038/s41598-018-27069-x (Testrow)

Software	Details about the software environment required to run the model: • **Programming language:** MATLAB/Python • **Required packages/Libraries:** • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** MATLAB. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** TBD. • **Batch mode:** batch mode supported. • **Execution:** single- or multi-threading. • **Running times:** TBD.
Intended use	Preclinical and clinical research, including generation of synthetic data and prior knowledge for WP 6.
Detailed clinical use (optional)	• **Population:** TBD. • **Intervention:** None (observational). • **Comparison:** None (single arm). • **Outcome:** TBD. • **Inclusion and exclusion:** TBD.
Methodological limitations	No studies on HCM specific mutation changes, only secondary factors (changes in pressure, tone, calcium sensitivity, etc) considered.
Example of use	Not yet available.
Additional Information	Not yet available.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP6.1. Information given by: Agakov [Pharmatics] [WP6]	
Field	**Explanation**
Function/model name	HCM_RVADAfterLVAD_001.
Function/model type	Binary classifier.
Function/model's short description	Prediction of the need for right ventricular assist device (RVAD) support after left ventricular assist device (LVAD) implantation in patients with LVAD using transient elastography. This model is based on multivariate logistic regression analysis.
Function/model inputs	• **Name:** lvef. • **Type:** float. • **Unit:** none (%). • **Description:** left ventricular ejection fraction. • **Range:** 5-70%.
	• **Name:** liver_stiffness.

	• **Type:** float. • **Unit:** kPa. • **Description:** liver stiffness in kPa. • **Range:** 2 - 75 kPa.
Function/model outputs	• **Name:** RVAD_after_LVAD. • **Type:** float. • **Unit:** none. • **Description:** Need for RVAD after LVAD implantation. • **Range:** [0, 1].
Function/model's extended description	This binary machine learning classifier predicts the need for right ventricular assist device (RVAD) support after left ventricular assist device (LVAD) implantation based on the left ventricular ejection fraction (LVEF) and liver stiffness (measured in kPa). The model parameters are derived from a cohort of 55 patients with LVAD implantation as a bridge to transplantation, assessed using transient elastography.
Function/model's version	Ver 0.02.
References to data sources	The study analysed 55 of 82 LVAD implantations performed at Osaka University Hospital from August 2011 to October 2015. Exclusions included 15 patients without pre-LVAD liver stiffness assessments and 12 requiring temporary LVAD, as most needed extracorporeal membrane oxygenation, affecting liver stiffness measurements. See more details in PMC:5400022.
References to labels	The target variable is the need for RVAD support after LVAD implantation.
References to methods	The model employs multivariate logistic regression to estimate the probability of RVAD support.
Software	Details about the software environment required to run the function/model: • **Programming language:** python 3.8 or later. • **Required packages/Libraries:** numpy 1.19.0 or later, scikit-learn 0.24.0 or later. • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** custom proprietary license. • **Installation instructions:** no installation required (API keys will be provided for the cloud access).
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** single CPU core. • **Running time:** TBD.
Intended use	Clinical research or clinical decision support.
Detailed clinical use (optional)	• **Population:** patients who underwent LVAD implantation for advanced HF as bridge to transplantation. The pathohistological diagnoses prior to LVAD implantation included idiopathic dilated cardiomyopathy (DCM), dilated phase of hypertrophic cardiomyopathy (d-HCM), secondary DCM,

	adriamycin-induced cardiomyopathy, DCM secondary to Becker muscular dystrophy, or ischaemic cardiomyopathy. • **Intervention:** The institutional heart team determined surgical strategies and device types based on patients' conditions and body size (details available). Various LVAD devices were used, with some patients undergoing additional cardiac procedures during implantation. • **Comparison:** none. • **Outcome:** Need for RVAD support after LVAD implantation. • **Inclusion:** HCM patients with LVAD implantation. • **Exclusion:** Individuals who do not satisfy the inclusion criterion.
Methodological limitations	The model is based on data from a specific patient cohort and may not generalise well to other populations. The predictions are dependent on the accuracy of LVEF and liver stiffness measurements. The model assumes a generalised linear relationship between the predictors and the log odds of the outcome, which may not hold true in complex settings.

Example of use	`curl -X POST https://hcm.predict-medai.uk/call_func.php \`
	`-H "Content-Type: application/json" \`
	`-H "Accept: application/json; charset=UTF-8" \`
	`-d '{`
	`"method": "HCM_RVADAfterLVAD_001",`
	`"params": [`
	`{`
	`"$LVEF": 68.68,`
	`"$LiverStiffness": {"value": 5.915, "unit": "kPa"}`
	`}`
	`],`
	`"jsonrpc": "2.0",`
	`"id": 0`
	`}'`

Additional Information	After validation, the model can potentially be used in a clinical setting to predict the need for RVAD support in patients who have undergone LVAD implantation, helping clinicians improve decision-making and preparedness for potential RVAD in patients with cardiomyopathies. Additionally, the model may be used as a feature for predicting other HCM outcomes, including complications arising from the right ventricle struggling to handle the increased blood flow resulting from the improved left ventricular function facilitated by the LVAD. Some of the likely complications may include right ventricular failure, systemic congestion, or low cardiac output syndrome. In its current form, this unvalidated model can be used for research and development and is not intended for medical use.
Reference to evaluation (future)	Not yet available.

Support team contact details	SMASH-HCM support for general enquiries: https://smash-hcm.eu/contact/ Pharmatics MedAI technical support for technical enquiries: support@pharmaticsltd.com

D7.3 Table WP6.2. Information given by: Pedro Moreno-Sanchez [TAU] [WP6]

Field	Explanation
Function/model name	Heart Failure_Survival_001.
Function/model type	Survival model.
Function/model's short description	Prediction of the risk score of death after any-cause Heart Failure based on a Survival gradient boosting model that tackles a balance between accuracy and explainability.
Function/model inputs	<table><tr><th>Id</th><th>Feature (units)</th><th>Range (mean ± std)/ binary values (number of instances per class)</th></tr><tr><td>1</td><td>Age (years)</td><td>40–95 (60.83 ± 11.89)</td></tr><tr><td>2</td><td>Anaemia (boolean)</td><td>0 (170) or 1 (129)</td></tr><tr><td>3</td><td>High Blood Pressure (boolean)</td><td>0 (194) or 1 (105)</td></tr><tr><td>4</td><td>Creatinine phosphokinase-CPK (mcg/L)</td><td>23–7,861 (581.83 ± 970.29)</td></tr><tr><td>5</td><td>Diabetes (boolean)</td><td>0 (174) or 1 (125)</td></tr><tr><td>6</td><td>Ejection fraction (percentage)</td><td>14–80 (38.08 ± 11.83)</td></tr><tr><td>7</td><td>Sex (boolean)</td><td>0 (194-Men) or 1 (105-Women)</td></tr><tr><td>8</td><td>Platelets (kiloplatelets/ml)</td><td>25,100–8,50,000 (2,63,358.03 ± 97,804.23)</td></tr><tr><td>9</td><td>Serum creatinine (mg/dl)</td><td>0.50–9.40 (1.39 ± 1.03)</td></tr><tr><td>10</td><td>Serum sodium (mEq/L)</td><td>113–148 (136.62 ± 4.41)</td></tr><tr><td>11</td><td>Smoking (boolean)</td><td>0 (203) or 1 (96)</td></tr><tr><td>12</td><td>Time-Follow up period (days)</td><td>4–285 (130.26 ± 77.61)</td></tr></table>
Function/model outputs	• **Name:** death_by_HF_risk. • **Type:** float. • **Unit:** none. • **Description:** death by HF risk score • **Range:** [0, 1].
Function/model's extended description	Heart Failure survival prediction models using a dataset with 299 patients who have experienced HF. The model considers death events and time as target features. The model employs an optimisation data workflow pipeline capable of selecting the best machine learning algorithm as well as the optimal collection of features. Additionally, the model shows an explainability-driven approach to select the best HF survival prediction model balancing prediction performance and explainability.
Function's version	Ver 1.00.
References to data sources	The dataset employed in this paper, released by Ahmad et al. (52), consist of the medical records of 299 patients (194 men and 105 women) who suffered an HF episode. The dataset was collected from April to December 2015 at the Faisalabad Institute of Cardiology and at the University Allied Hospital in Faisalabad (Punjab, Pakistan) See more details in: https://doi.org/10.1371/journal.pone.0181001.

References to labels	The model considers death events and time as target features.
References to methods	The model employs a Survival Gradient boosting technique to estimate the risk to death.
Software	Details about the software environment required to run the function/model: • **Programming language:** python 3.10 or later. • **Required packages/Libraries:** numpy 1.24.3 or later, scikit-learn 1.2.2 or later, scikit-survival 0.21.0 • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** custom proprietary license. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** single CPU core. • **Running time:** TBD.
Intended use	Research or clinical decision support.
Detailed clinical use (optional)	• **Population:** patients who have undergone heart failure. • **Intervention:** none • **Comparison:** none. • **Outcome:** Risk of death after undergoing a heart failure. • **Inclusion:** patients with history of HF. • **Exclusion:** patients not satisfying the inclusion criterion.
Methodological limitations	The model is based on data from a specific patient cohort and may not generalise well to other populations. As the population is any-cause Heart Failure, the model could not serve for the specific characteristic of HCM population that underwent a HF.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation	Number of features: 4 out of 12. C-index: 0.714 (0.018); C-index IPWC (concordance index inverse probability of censoring weights): 0.754; AUCD_ROC (area under the cumulative/dynamic ROC): 0.733. For more info, see the reference: https://doi.org/10.3389/fcvm.2023.1219586
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP6.3. Information given by: Pedro Moreno-Sanchez [TAU] [WP6]	
Field	**Explanation**
Function/model name	Arrhythmia_classifier_001.
Function/model type	Classifier model for 8 classes of arrhythmia.
Function/model's short description	Prediction of the following classes of arrhythmias: Atrial Fibrillation (AF), intrinsic paroxysmal atrioventricular block (I-AVB), left bundle branch block (LBBB), normal heartbeat (SNR), premature atrial contraction (PAC), premature ventricular contraction (PVC), right bundle branch block (RBBB), ST-segment depression (STD), and ST-segment elevation (STE).

Function/model inputs	• **Name:** ECG raw signal. • **Type:** array (one per ECG leads). • **Unit:** seconds. • **Description:** 12 lead ECG raw signal sampled at 500 Hz • **Range:** 6 to 60 seconds of duration.
Function/model outputs	• **Name:** arrhythmia classifier • **Type:** float. • **Unit:** unitless (probability). • **Description:** Arrhythmia classification of 8 classes: • **Range:** [0, 1].
Function/model's extended description	This study introduces an explainable DL-based prediction model using ECG signals to classify nine distinct arrhythmia categories. We evaluated various DL architectures, including ResNet, DenseNet, and VGG16, using raw ECG data. The ResNet34 model emerged as the most effective, achieving an Area Under the Receiver Operating Characteristic (AUROC) of 0.98 and an F1-score of 0.826.
Function/model's version	Ver 1.00.
References to data sources	We utilised the 'China Physiological Signal Challenge 2018 (CPSC 2018)' dataset to investigate arrhythmia predictions [21]. This dataset also comprises 12 lead ECG recordings and was sourced through collaboration with 11 hospitals in China. CPSC 2018 includes a total of 6,877 individual data samples, with a gender distribution of 3,178 females and 3,699 males. The ECG recordings are sampled at a frequency of 500 Hz, and they vary in length, ranging from 6 to 60 s. The distribution across the arrhythmia categories is as follows: AF: 1098 recordings, I-AVB: 704 recordings, LBBB: 207 recordings, SNR with 918 recordings, PAC with 574, PVC with 653 recordings, RBBB with 1695 recordings, STD with 826 recordings, and STE with 202 recordings. It's worth noting that among the 6,877 recordings, 476 of them have two or three different labels, indicating their complexity. For more information, see: https://doi.org/10.1166/jmihi.2018.2442
References to labels	Each instance in the database is annotated with (at least one) arrhythmia categories.
References to methods	The best performing model employs a ResNet-34 architecture
Software	Details about the software environment required to run the function/model: • **Programming language:** python 3.10 or later. • **Required packages/Libraries:** numpy 1.24.3 or later, scikit-learn 1.2.2 or later, pythorch, restnet • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** custom proprietary license. • **Installation instructions:** TBD.
Intended use	Research or clinical decision support.
System and computing requirements	• **Operating system:** Windows or Linux. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** single CPU core. • **Running time:** TBD.
Detailed clinical use (optional)	• **Population:** patients with a diagnosed arrhythmia from ECG inspection.

	• **Intervention:** none • **Comparison:** none. • **Outcome:** Probability of undergoing an arrhythmia. • **Inclusion:** HCM patients with diagnosed arrhythmia. • **Exclusion:** Opposite to inclusion.
Methodological limitations	The model is based on data from a specific patient cohort and may not generalise well to other populations.
Example of use	TBD.
Additional Information	TBD.
Reference to evaluation	<table><tr><th>Arrhythmia category</th><th>Accuracy</th><th>Precision</th><th>Recall</th><th>F1-Score</th><th>AUC</th></tr><tr><td>SNR</td><td>0.96</td><td>0.77</td><td>0.84</td><td>0.80</td><td>0.98</td></tr><tr><td>AF</td><td>0.98</td><td>0.94</td><td>0.93</td><td>0.94</td><td>0.99</td></tr><tr><td>IAVB</td><td>0.98</td><td>0.96</td><td>0.90</td><td>0.93</td><td>0.99</td></tr><tr><td>LBBB</td><td>0.99</td><td>0.95</td><td>0.83</td><td>0.88</td><td>1.00</td></tr><tr><td>RBBB</td><td>0.96</td><td>0.93</td><td>0.94</td><td>0.94</td><td>0.99</td></tr><tr><td>PAC</td><td>0.95</td><td>0.66</td><td>0.71</td><td>0.68</td><td>0.96</td></tr><tr><td>PVC</td><td>0.97</td><td>0.87</td><td>0.86</td><td>0.87</td><td>0.99</td></tr><tr><td>STD</td><td>0.96</td><td>0.84</td><td>0.85</td><td>0.85</td><td>0.97</td></tr><tr><td>STE</td><td>0.97</td><td>0.63</td><td>0.50</td><td>0.56</td><td>0.95</td></tr><tr><td>Average</td><td>0.97</td><td>0.84</td><td>0.82</td><td>0.83</td><td>0.98</td></tr></table> For more info, see the reference: https://doi.org/10.1007/978-3-031-59091-7_16
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP6.4. Information given by: Nabid Faiem [TAU] [WP6]	
Field	**Explanation**
Function/model name	HCM_MultimodalPerceiver_001.
Function/model type	Binary or Multiclass classifier or Regression
Function/model's short description	Detection or stratification of HCM using multimodal data. This model uses genetic profile, ECG, medical image and biomarkers derived from these modalities.
Function/model inputs	• **Name:** 12-Lead ECG signal. • **Type:** array of floats. • **Unit:** mV. • **Description:** 10 second timeseries signal, 12 channels. • **Range:** TBD.
	• **Name:** CMR. • **Type:** image, multi-dimensional array of floats. • **Unit:** N/A. • **Description:** Cardiac Magnetic Resonance imaging. • **Range:** 0-255 (intensities).
	• **Name:** Features.

	• **Type:** array. • **Unit:** TBD. • **Description:** Important Features from demographic, anthropometry, biochemistry, medications, lifestyles clinical history and measurements (will be determined after availability of dataset). • **Range:** TBD.
Function/model outputs	• **Name:** NOHCM/HCM, Normal/NOHCM/HCM or HCM RISK Scores. • **Type:** float. • **Unit:** none. • **Description:** Need for the detection of HCM patients. • **Range:** [0, 1], [0, 1, 2]. 0: Normal, 0: Normal 1: HCM 1: LVH 2: HCM
Function/model's extended description	This model is a multimodal classifier/regression model that leverages multiple health data modalities to enhance the accuracy of diagnosis and stratification of HCM. This multimodal machine learning model is designed using the Perceiver architecture from Google's DeepMind, which is fundamentally based on the Transformer network. This multimodal model is capable of processing and analysing different health data modalities simultaneously such as ECG signals, medical images, and other data types for the detection or stratification of HCM.
Function/model's version	Ver 0.02.
References to data sources	This study will use timeseries signal from 12-Lead ECG, medical imaging data and relevant features from structured EHR data from SMASH-HCM project. The relevant features will be determined when the dataset becomes available.
References to labels	The target variable is the normal, Left Ventricle hypertrophy (LVH), Hypertrophic cardiomyopathy (HCM).
References to methods	Perceiver: General Perception with Iterative Attention, Assessment of Parkinson's Disease Severity Using Gait Data: A Deep Learning-Based Multimodal Approach.
Software	Details about the software environment required to run the function/model: • **Programming language:** python 3.8 or later. • **Required packages/Libraries:** numpy 1.19.0 or later, scikit-learn 0.24.0 or later. • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** MIT Licence. • **Installation instructions:** TBD.

System and computing requirements	• **Operating system:** Windows, Linux, or MacOS. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** multiple CPUs recommended. • **Running time:** TBD.
Intended use	Research or clinical decision support.
Detailed clinical use (optional)	• **Population:** TBD according to the data collection protocols for SMASH-HCM project datasets. • **Intervention:** N/A • **Comparison:** N/A • **Outcome:** Endpoints quantifying detection and stratification of HCM. • **Inclusion/exclusion:** to be defined.
Methodological limitations	The model is based on data from a specific patient cohort and may not generalise well to other populations.

Example of use	`curl -X POST https://hcm.predict-medai.uk/call_func.php \`
	`-H "Content-Type: application/json" \`
	`-H "Accept: application/json; charset=UTF-8" \`
	`-d '{`
	`"method": " HCM_MultimodalPerceiver_001 ",`
	`"params": [`
	`{`
	`"$ECG": array(),`
	`"$CMR": array(),`
	`"$Features": array()`
	`}`
	`],`
	`"jsonrpc": "2.0",`
	`"id": 0`
	`}'`

Additional Information	Not yet available.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP6.5. Information given by: McCarthy, Garcia-Cabrera [UCD] [WP6]	
Field	**Explanation**
Function/model name	HCM_Segmentation_001
Function/model type	Deep Learning Convolutional Neural Network (CNN) - Segmentation Model.
Function/model's short description	This model automatically segments the ventricles from cardiac MRI images to assist in the diagnosis and monitoring of Hypertrophic Cardiomyopathy (HCM). By computing the volumes at the specific time frames, it would be possible to obtain metrics such as the Ejection Fraction. Additionally, this could be the baseline towards further functional analysis.

Function/model inputs	• **Name**: MRI Image Slice. • **Type**: Tensor (3D Matrix). • **Unit**: uint8. • **Description**: 2d stack from a cardiac MRI scan. • **Range**: Pixel intensity values typically range from 0 to 255.
Function/model outputs	• **Name**: seg-mask. • **Type**: Tensor (3D Matrix). • **Unit**: uint8. • **Description**: mask of the segmented ventricles from MRI slices. • **Range**: 0 (Left Ventricle), 1 (Myocardium), 2 (Right Ventricle), 4 (background).
Function/model's extended description	The segmentation model is built using a U-Net architecture, optimised for cardiac MRI data. The model is trained on a diverse dataset of annotated HCM cases to ensure robust performance across varying morphologies. This model is intended to assist clinicians in identifying and quantifying the extent of ventricular hypertrophy, which is critical for the management and treatment planning of HCM patients. Validation includes cross-validation with manual segmentations by expert cardiologists. Extensive MRI-specific data augmentation is performed during training. Data normalisation includes processing of slices to canonical orientations, histogram normalisation and intensity normalisation.
Function/model's version	Ver 0.02.
References to data sources	SMASH-HCM Data-bank - "Cardiac MRI Dataset for HCM"
References to labels	Manual segmentations by expert cardiologists, following the guidelines provided by the American Heart Association (AHA) for cardiac MRI segmentation in HCM. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging, Cerqueira et al. "Standardised myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association." Circulation 105.4 (2002): 539-542. O. Bernard et al., "Deep Learning Techniques for Automatic MRI Cardiac Multi-Structures Segmentation and Diagnosis: Is the Problem Solved?", in IEEE Transactions on Medical Imaging, vol. 37, no. 11, pp. 2514-2525, Nov. 2018, doi: 10.1109/TMI.2018.2837502.
References to methods	1. Ronneberger, O., Fischer, P., Brox, T. (2015). U-Net: Convolutional Networks for Biomedical Image Segmentation. In: Navab, N., Hornegger, J., Wells, W.,

	Frangi, A. (eds) Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015. MICCAI 2015. Lecture Notes in Computer Science(), vol 9351. Springer, Cham. https://doi.org/10.1007/978-3-319-24574-4_28 2. Chen, L.-C., Papandreou, G., Schroff, F., & Adam, H. (2017). Rethinking Atrous Convolution for Semantic Image Segmentation. arXiv [Cs.CV]. Retrieved from http://arxiv.org/abs/1706.05587 3. Roy, S. et al. (2023). MedNeXt: Transformer-Driven Scaling of ConvNets for Medical Image Segmentation. In: Greenspan, H., et al. Medical Image Computing and Computer Assisted Intervention – MICCAI 2023. MICCAI 2023. Lecture Notes in Computer Science, vol 14223. Springer, Cham. https://doi.org/10.1007/978-3-031-43901-8_39
Software	Details about the software environment required to run the function/model: ● **Programming language:** Python 3.8+ ● **Required packages/Libraries:** NumPy, OpenCV, pytorch, torchio. ● **Configurations:** GPU with CUDA support recommended. ● **Environment variables:** None required. ● **Licensing agreements:** MIT Licence. ● **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows, Linux, or MacOS. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** GPU recommended. • **Running time:** TBD.
Intended use	Clinical research or clinical decision support.
Detailed clinical use (optional)	● **Population**: Adult patients diagnosed or suspected of HCM. ● **Intervention**: Non-invasive imaging with cardiac MRI. ● **Outcome / Clinical Endpoint**: Accurate assessment of ventricular hypertrophy extent. ● **Inclusion/exclusion:** details to be defined.
Methodological limitations	The model may perform suboptimally in cases with extremely poor image quality or in the presence of significant motion artefacts. Additionally, the model is trained primarily on adult populations and may require retraining for paediatric cases.

Example of use	`curl -X POST https://hcm.predict-medai.uk/call_func.php \`
	`-H "Content-Type: multipart/form-data" \`
	`-H "Accept: application/json; charset=UTF-8" \`
	`-F "method=HCM_Segmentation_001" \`
	`-F "id=0" \`
	`-F "DICOM=@/path/to/DICOM"`

	Note: This is for reference with a single DICOM file only, many methods work with a 2D stack / 3D volume of DICOM files and actual functioning may depend on API design.
Additional Information	**Deployment**: The model can be deployed on a local workstation with a CUDA-enabled GPU for real-time segmentation, or as part of a cloud-based PACS system for integration into clinical workflows. Recommended minimum hardware includes a 4GB VRAM GPU and 16GB RAM.
Reference to evaluation (future)	Evaluation planned as part of the SMASH-HCM consortium's ongoing research into AI-driven cardiac imaging tools. Future publication to follow.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP6.6. Information given by: Marion Taconne [POLIMI] [WP6]	
Field	**Explanation**
Function/model name	HCM_ECG_LVH_RVHClassifier_001.
Function/model type	Classifier.
Function/model's short description	LVH and RVH classifiers using biomarkers derived from ECG and if available other clinical features.
Function/model inputs	• **Name:** 12-Lead ECG signal. • **Type:** array of floats. • **Unit:** mV. • **Description:** 10 second time series signal, 12 channels. • **Range:** TBD.
	• **Name:** Features. • **Type:** array. • **Unit:** TBD. • **Description:** Important Features from demographic, anthropometry, biochemistry, medications, lifestyles clinical history and measurements (will be determined after availability of dataset). • **Range:** TBD.

Function/model outputs	• **Name:** LVH, RVH Classifier.
	• **Type:** float.
	• **Unit:** none.
	• **Description: D**etection of hypertrophic HCM patients.
	• **Range:** [0, 1], with
	  ○ 0: Control, 1: LVH, or
	  ○ 0: Control, 1: RVH

Function/model's extended description	This model is left and right ventricular hypertrophy classifier model based on ECG to enhance the diagnosis and stratification of HCM.

Function/model's version	Ver 0.02.
References to data sources	This study will use timeseries signal from 12-Lead ECG, and relevant features from structured EHR data from SMASH-HCM project. The relevant features will be determined when the dataset becomes available.
References to labels	The target variable is left ventricular hypertrophy (LVH), right ventricular hypertrophy (RVH) and no hypertrophy (control).
References to methods	Classical supervised ML methods.
Software	Details about the software environment required to run the function/model: • **Programming language:** python 3.8 or later. • **Required packages/Libraries:** numpy 1.19.0 or later, scikit-learn 0.24.0 or later. • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** MIT License. • **Installation instructions:** TBD.
System and computing requirements	• **Operating system:** Windows, Linux, or MacOS. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** multiple CPUs recommended. • **Running time:** TBD.
Detailed clinical use (optional)	• **Population:** TBD according to the data collection protocols for SMASH-HCM project datasets. • **Intervention:** N/A (observational). • **Comparison:** N/A (single arm). • **Outcome:** Markers or diagnosis of hypertrophy of the ventricle. • **Inclusion/exclusion:** TBD.
Methodological limitations	The model is based on data from a specific patient cohort and may not generalise well to other populations.

Example of use	`curl -X POST https://hcm.predict-medai.uk/call_func.php \`
	`-H "Content-Type: application/json" \`
	`-H "Accept: application/json; charset=UTF-8" \`
	`-d '{`
	`  "method": " HCM_ECG_LVH_RVHClassifier_001",`
	`  "params": [`
	`  {`
	`  "$ECG": array(),`
	`  "$Features": array()`
	`  }`
	`  ],`
	`  "jsonrpc": "2.0",`
	`  "id": 0`
	`}'`

Additional Information	TBD.

Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

Information given by: [Luca Mainardi] [POLIMI] [Work Package 6]

D7.3 Table WP6.7. Information given by: Luca Mainardi [POLIMI] [WP6]	
Field	**Explanation**
Function/model name	HCM_ECGbased_predictor_001.
Function/model type	Binary classifier or a regression model.
Function/model's short description	Detection of patients with positive response to treatment options using ECG data. Stratification of HCM patients against adverse cardiovascular events.
Function/model inputs	• **Name:** 12-Lead ECG signal. • **Type:** array or float. • **Unit:** mV. • **Description:** 10 second ECG signal, 12 channels. • **Range:** TBD.
	• **Name:** Features. • **Type:** array. • **Unit:** TBD. • **Description:** Important features from demographic, anthropometry, biochemistry, medications, lifestyles clinical history and measurements (will be determined after availability of dataset). • Range: TBD.
Function/model outputs	• **Name:** Treatment response scores, risk score for adverse cardiovascular events. • **Type:** float. • **Unit:** none. • **Description:** Need for evaluating patient responses to treatment and related risk scores. • **Range:** [0 1] (continuous range).
Function/model's extended description	This model is a classifier/regression model that leverages ECG and multiple health data modalities to enhance the prognostic stratification of HCM patients. This multimodal machine learning model will process the ECG data through a combined end-to-end and feature based AI approach.
Function/model's version	Ver 0.02.
References to data sources	This study will use signal from 12-Lead ECG and relevant features from structured EHR data from SMASH-HCM project. The relevant features will be determined when the dataset becomes available.

References to labels	The target variable are discrete or continuous variables used to define the patient's treatment response and the risk of adverse cardiovascular events.
References to methods	Guadalupe Garcia-Isla, Federico M Muscato, Andrea Sansonetti, Stefano Magni, Valentina DA Corino, Luca T Mainardi "Ensemble classification combining ResNet and handcrafted features with three-steps training", Physiological measurement 43 (9), 094003.
Software	Details about the software environment required to run the function/model: • **Programming language:** python 3.8 or later. • **Required packages/Libraries:** numpy 1.19.0 or later, scikit-learn 0.24.0 or later. • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** MIT License.
System and computing requirements	• **Operating system:** Windows, Linux, or MacOS. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** multiple CPUs recommended. • **Running time:** TBD.
Intended use	Clinical research and decision support.
Detailed clinical use (optional)	• **Population:** Datasets from the SMASH-HCM projects (patients with diagnosis of HCM only, no controls) • **Intervention:** Multiple treatment options, as defined in the SMASH-HCM datasets. • **Comparison:** N/A (single arm). • **Outcome:** TBD, to quantify the safety and efficacy of HCM stratification. • **Inclusion/exclusion:** to be defined according to the SMASH-HCM data protocols.
Methodological limitations	The model is based on data from a specific patient cohort and may not generalise well to other populations.

Example of use	`curl -X POST https://hcm.predict-medai.uk/call_func.php \`
	`-H "Content-Type: application/json" \`
	`-H "Accept: application/json; charset=UTF-8" \`
	`-d '{`
	`"method": "HCM_ECGbased_predictor_001",`
	`"params": [`
	`{`
	`"$ECG": array(),`
	`"$Features": array()`
	`}`
	`],`
	`"jsonrpc": "2.0",`

	<pre> "id": 0 }'</pre>
Additional Information	None
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP6.8. Information given by: Marion Taconne [POLIMI] [WP6]	
Field	**Explanation**
Function/model name	HCM_ECGRiskClassifier_001.
Function/model type	Classifier.
Function/model's short description	Risk stratification of HCM using ECG, and/or biomarkers derived from this modality and classical clinical features (depending on the availability).
Function/model inputs	• **Name:** 12-Lead ECG signal. • **Type:** array of floats. • **Unit:** mV. • **Description:** 10 second timeseries signal, 12 channels. • **Range:** TBD.
	• **Name:** Features. • **Type:** array. • **Unit:** TBD for each considered feature. • **Description:** Important Features from demographic, anthropometry, biochemistry, medications, lifestyles clinical history and measurements (will be determined after availability of dataset). • **Range:** TBD for each considered feature

Function/model outputs	• **Name:** HCM Risk Scores.
	• **Type:** float.
	• **Unit:** none.
	• **Description:** Probability of elevated risk.
	• **Range:** [0, 1]
	  ○ 0: No risk (no event)
	  ○ 1: High risk of event

Function/model's extended description	This model is a risk classifier model based on ECG to enhance the stratification of HCM.
Function/model's version	Ver 0.02.
References to data sources	This study will use timeseries signal from 12-Lead ECG, and relevant features from structured EHR data from SMASH-HCM project. The relevant features will be determined when the dataset becomes available.

References to labels	The target variable is no risk (of event), risk of event.
References to methods	Classical supervised ML methods.
Software	• **Programming language:** python 3.8 or later. • **Required packages/Libraries:** numpy 1.19.0 or later, scikit-learn 0.24.0 or later. • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements:** MIT License.
System and computing requirements	• **Operating system:** Windows, Linux, or MacOS. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** GPU recommended. • **Running time:** TBD.
Intended use	Clinical research and decision support.
Detailed clinical use (optional)	• **Population:** Datasets from the SMASH-HCM projects (patients with diagnosis of HCM only, no controls) • **Intervention:** Multiple treatment options, as defined in the SMASH-HCM datasets. • **Comparison:** N/A (single arm). • **Outcome:** TBD, to quantify the safety and efficacy of HCM stratification. • **Inclusion/exclusion:** to be defined according to the SMASH-HCM data protocols.
Methodological limitations	The model is based on data from a specific patient cohort and may not generalise well to other populations.

Example of use	`curl -X POST https://hcm.predict-medai.uk/call_func.php \`
	`-H "Content-Type: application/json" \`
	`-H "Accept: application/json; charset=UTF-8" \`
	`-d '{`
	`  "method": " HCM_ECGRiskClassifier_001",`
	`  "params": [`
	`  {`
	`  "$ECG": array(),`
	`  "$Features": array()`
	`  }`
	`  ],`
	`  "jsonrpc": "2.0",`
	`  "id": 0`
	`}'`

Additional Information	Not yet available.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

D7.3 Table WP6.9. Information given by: Luca Mainardi [POLIMI] [WP6]	
Field	**Explanation**

Function/model name	HCM_Model_integrator_001.
Function/model type	Multimodal classifier or Regression.
Function/model's short description	Combination of SMASH-HCM models. Detection of patients with positive response to treatment options using SMASH-HCM models. Stratification of HCM patients against adverse cardiovascular events.
Function/model inputs	Name: SMASH_HCM_Model_Ensemble (HCM_ECGbased_predictor_001+ HCM_ECGbased_predictor_002 + HCM_ECGbased_predictor_003 + HCM_ECGbased_predictor_004 + …) • **Type:** array or float. • **Unit:** various. • **Description:** SMASH_HCM Models' outputs. • **Range:** various.
	• **Population:** Datasets from the SMASH-HCM projects (patients with diagnosis of HCM only, no controls) • **Intervention:** Multiple treatment options, as defined in the SMASH-HCM datasets. • **Comparison:** N/A (single arm). • **Outcome:** TBD, to quantify the safety and efficacy of HCM stratification. • **Inclusion/exclusion:** to be defined according to the SMASH-HCM data protocols.
Function/model outputs	• **Name:** HCM patients' stratification, treatment response scores, risk score for adverse cardiovascular events. • **Type:** float. • **Unit:** none. • **Description:** Evaluating patient responses to treatment and related risk scores. • **Range:** [0 1] (continuous range)
Function/model's extended description	This model is a multimodal classifier/regression model that leverages on SMASH-HCM models output and parameters. This multimodal machine learning model is based on Ensemble Models or Hybrid Models tools.
Function/model's version	Ver 0.02.
References to data sources	Sources are constituted by SMASH-HCM models and SMASH-HCM data.
References to labels	The target variable are discrete or continuous variables used to define the patient's treatment response and the risk of adverse cardiovascular events.
References to methods	Ensemble/stacking/hybrid models methods.

Software	Details about the software environment required to run the function/model: • **Programming language:** python 3.8 or later. • **Required packages/Libraries:** numpy 1.19.0 or later, scikit-learn 0.24.0 or later. • **Configurations:** none. • **Environment variables:** none. • **Licensing agreements**: MIT Licence.
System and computing requirements	• **Operating system:** Windows, Linux, or MacOS. • **Hardware:** minimal requirements TBD. • **Batch mode:** batch or online use. • **Execution:** GPU recommended. • **Running time:** TBD.
Intended use	Clinical research and decision support.
Detailed clinical use (optional)	• **Population:** Datasets from the SMASH-HCM projects (patients with diagnosis of HCM only, no controls) • **Intervention:** Multiple treatment options, as defined in the SMASH-HCM datasets. • **Comparison:** N/A (single arm). • **Outcome:** TBD, to quantify the safety and efficacy of HCM stratification. • **Inclusion/exclusion:** to be defined according to the SMASH-HCM data protocols.
Methodological limitations	The model is based on data/models derived from the specific patient cohort of SMASH-HCM and may not generalise well to other populations.

Example of use	`curl -X POST https://hcm.predict-medai.uk/call_func.php \`
	`-H "Content-Type: application/json" \`
	`-H "Accept: application/json; charset=UTF-8" \`
	`-d '{`
	`  "method": "HCM_Model_integrator_001",`
	`  "params": [`
	`  {`
	`  $variable arguments as input: array(),`
	`  …`
	`  }`
	`  ],`
	`  "jsonrpc": "2.0",`
	`  "id": 0`
	`}'`

Additional Information	Not yet available.
Reference to evaluation (future)	Not yet available.
Support team contact details	https://smash-hcm.eu/contact/

4 Linking it all - DSS software architecture view

The SMASH-HCM software architecture will be designed with best practices in software engineering to ensure a modular, scalable, and maintainable system. Central to this architecture will be the use of Docker for containerisation, which encapsulates each software module within isolated program environments and standardised communication protocols like REST and JSON-RPC. This approach minimises dependencies and conflicts, thereby simplifying deployment across varied computing environments and deployment scenarios. The use of Docker aligns with the software engineering principle of separation of concerns, where each container is dedicated to specific tasks, such as data storage, processing, or user interaction, promoting modularity and ease of management. Figure 1 illustrates the component-based architecture, highlighting how different *dockerised* modules communicate over REST interfaces.

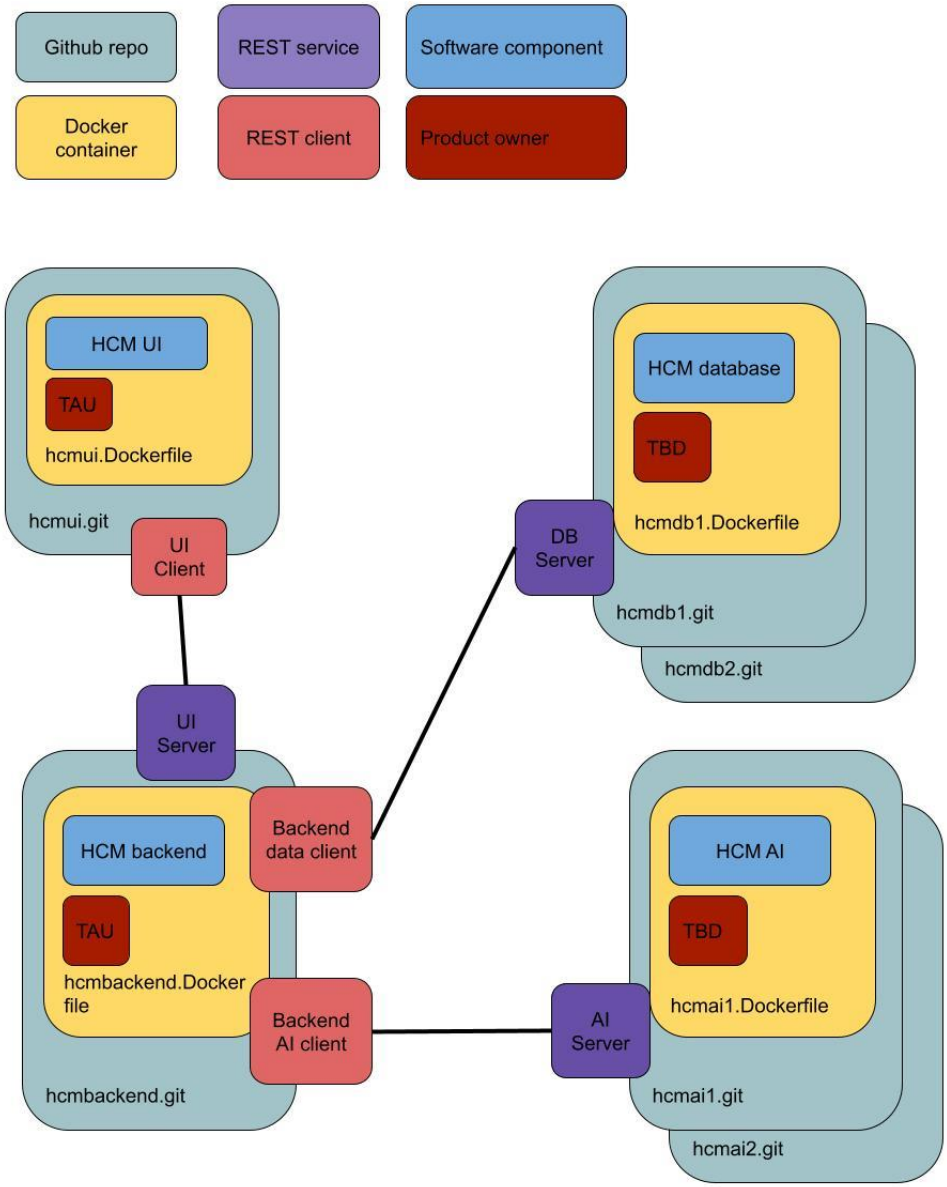

Figure 1: Containerised architecture

To accommodate the diverse programming languages used by consortium members, Docker templates for commonly used languages will be provided. Languages used in the different WPs by the different research groups have been identified, and at the moment of writing this document, templates for

Python, Matlab, and R have been developed. Templates for C and C++ support are going to be considered next. This standardises the setup process and allows developers to leverage language-specific libraries and frameworks, enhancing the flexibility and innovation potential of the project. Communication between modules is handled via REST or JSON-RPC, selected based on the specific requirements for statefullness, performance, and operation type. This ensures that communication remains independent of the underlying technology.

The project's codebase, documentation, and Docker recipes are centralised in a GitHub repository, enabling collaborative development. An Agile methodology is recommended for the project, emphasising iterative development, frequent updates, and adaptability to evolving requirements. This approach ensures continuous feedback and iterative improvement suitable for a complex project like SMASH-HCM.

In terms of data flow and system design, the architecture adheres to the Model-View-Controller (MVC) pattern. This design pattern divides the application into three interconnected components: Model, View, and Controller. Each of these handling distinct aspects of the application. The *Model* manages data and business logic, residing within containers that handle database operations, computations, and machine learning tasks. The *View* manages the user interface, housed in containers that serve web or desktop applications, translating data into user-friendly formats. The *Controller* acts as a mediator, processing user inputs and coordinating the interactions between the *Model* and *View*, typically within an API or middleware container. Figure 2 depicts how SMASH-HCM components and data flows are organised according to the MVC principle, ensuring clear separation of concerns, enhanced modularity and maintainability.

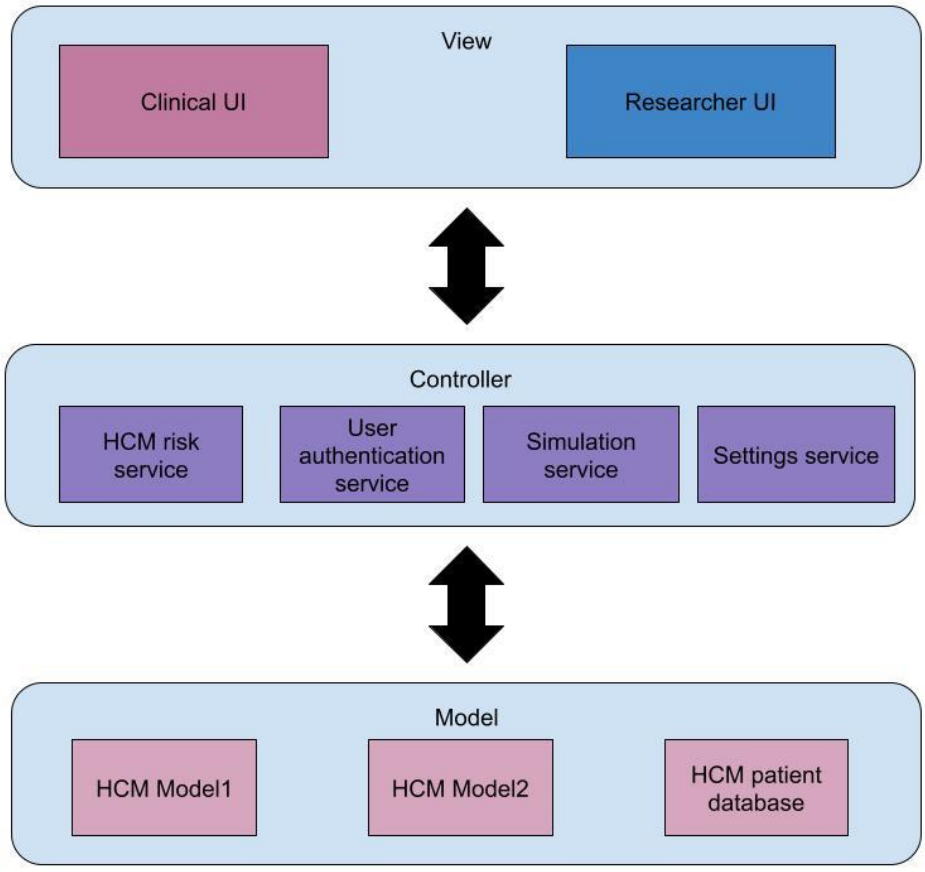

Figure 2: Containerised MVC communication

The suggested initial Software Architecture for implementing and hosting the clinical decision support system will be continuously reviewed to ensure optimal performance, scalability, and security. This ongoing review process will incorporate feedback from stakeholders and users, as well as developments in standards for software-based medical devices and medical artificial intelligence, to adapt and improve the system over time. By doing so, we shall maintain a robust and adaptable architecture that meets the evolving needs of healthcare providers, patients, and regulators. A small subset of models will be made compatible with FHIR (Fast Healthcare Interoperability Resources) to ensure seamless interoperability with existing health IT systems. The exploration of this compatibility will be further detailed in Task 7.4 (Integration, Deployment, and Post-Project Availability) and Deliverable 7.5 (Integrated DSS for HCM stratification and disease management - initial). Furthermore, models intended for research and development will be hosted using the *InSilicoTrials*' IT infrastructure, which will be enhanced to support preclinical drug discovery and clinical development of new HCM medications. Additionally, a small subset of risk prediction and stratification models for HCM will be explored for integration with the *Medtronic* platform for clinical decision support, to ensure availability of the results to the wider community of international stakeholders after the end of the project. This integration effort will be further investigated and detailed in Deliverable 7.8 (Integrated DSS for HCM stratification and disease management - final).

5 Conclusions

In conclusion, deliverable D7.3 of the SMASH-HCM Project outlines the initial framework for defining the technical specifications of the API for both research and clinical decision support in hypertrophic cardiomyopathy (HCM). By prioritising harmonisation and integration of diverse variables, models, and algorithms from WP3-WP6, we have proposed a unified framework to ensure consistency and accessibility of research results for scientific investigators and clinicians. Additionally, we have defined a detailed template that enables the systematic gathering of comprehensive specifications for each function or model, including their inputs, outputs, theoretical backgrounds, and methodologies. Furthermore, we have specified the hardware and software environments and considered licensing agreements, while documenting known limitations and practical use cases of the models that are being developed in SMASH-HCM. This approach will enhance research capabilities within and outside the consortium and may additionally support more effective clinical decision-making for HCM, paving the way for improved patient outcomes and advancing the field of cardiology.