DELIVERABLE

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D6.1 – Requirement specifications for predictive/clustering tool for HCM patient stratification.

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Revision History

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Abstract (for dissemination)	This document outlines the requirements specifications for the methods and algorithms developed under WP6 and adopted, as tools, for HCM patient stratification and clustering within the SMASH-HCM Project. The document is especially intended as reference for developers of data-driven models, but also relevant for the wider consortium.
Keywords	Data-driven models; AI/ML tools; Specifications

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This deliverable contains original unpublished work except where clearly indicated otherwise.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.

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Executive Summary

This report, deliverable D6.1 of SMASH-HCM Project, outlines the requirements specifications for the methods and algorithms developed under WP6 that are adopted, as tools, for HCM patient stratification and clustering within the SMASH-HCM Project. Considering that WP6 focuses on data-driven model discovery, development and integration with mechanistic models developed in WPs 3-5, the following requirements are addressed in detail:

- **Model Input-Output Data Definition:**
  - Clarification of input-output data for both the learning and inference stages of the models developed in tasks 6.1, 6.2, and 6.3. This encompasses specifying the type of data, labelling conventions, and establishing the minimum data requirements essential for effective model tuning.
  - Definition of target outcomes for tasks such as stratification, prevention, or treatment monitoring, shaping the output of the model.
  - Integration of contributions from mechanistic *in vitro* and *in silico* models developed in WP3, WP4, and WP5 within task 6.4, elucidating data and information from these models.
- **Model Design Concepts:**
  - Formulation of design concepts guiding model development, including the adoption of reusable and accessibility concepts.
  - In-depth consideration of accessibility, reproducibility, trustworthiness, and explainability aspects as integral components of the SMASH-HCM model design concepts.
- **Model deployment and integration:**
  - Definition of specifications for model deployment and integration of tools within the SMASH-HCM infrastructure, specifically addressing their incorporation into the Decision Support System (DSS) developed in WP7.

The report is structured as follows: it firstly introduces the tools to be developed and their data needs, then it identifies the design requirements for these tools considering different issues (accessibility and reproducibility, trustworthy and explainability aspects), and finally it describes the minimal software and hardware requirements needed to incorporate the tools into the final SMASH-HCM solution.

This document deeply considers the vision, recommendations and terminology proposed by the Deliverable 3.2, “First draft of the VHT roadmap” prepared by the EDITH consortium[1] and by the position paper on “Paper from the Digital Twins in Healthcare to the Virtual Human Twin”[2].

[1] https://www.edith-csa.eu/materials/

[2] https://ieeexplore.ieee.org/document/10278402

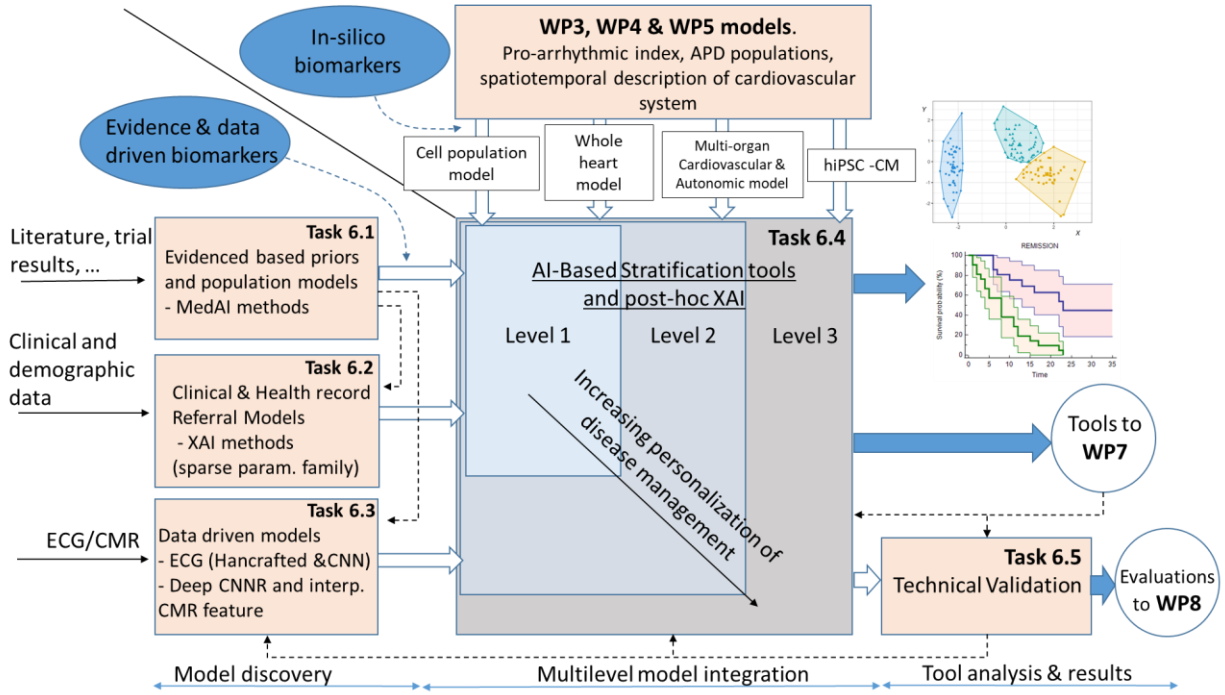
1 Description of the models and data requirements

This section describes the types of models to be developed in WP6 with the objective to identify model requirements in terms of **Input-Output data definition and needs**. This is "*a key factor for model development process that must be performed with the highest possible quality assurance efficiency, which requires availability of accurate input data to build benchmark problems used in the verification of the solvers*" ("First draft of the VHT roadmap", Deliverable 3.2, EDITH Consortium). Identification of data and their use is also to be considered as part of the recently issued TRIOPOD+AI statement for reporting clinical prediction models.[3]

Models to be developed will encompass: 1) new data-driven predictive models at the patient and population levels using heterogeneous data sources (such as literature results, patient electronic health records (EHR), electrocardiogram (ECG) signals, cardiac magnetic resonance (CMR) and echocardiography images, and multi-organ data) using artificial intelligence/machine learning (AI/ML) approaches and informative priors synthesized from published evidence; 2) multilevel clustering and prediction methods for patient stratification, prediction of disease progression, and treatment response, by combining models developed in WP6 with computational/mechanistic models developed in WP 3-5. A schematic view of WP6 tasks organization and interaction is shown in Figure 1.

This deliverable deals with data-driven model development (task from 6.1 to 6.3) and integration (task 6.4). They have diverse data requirements and specifications which will be detailed separately in the following subsections.

Figure 1 – Tasks organization and interactions in WP6



1.1 Task 6.1 Evidence-based Modelling

Task 6.1 will develop evidence-based models and provide priors and features accessible as a software library. These evidence-based models will be developed using an extension of Pharmatics' MedAI method, which combines natural language processing and information extraction algorithms with text embeddings to identify systematic reviews, reports on randomized controlled trials, and primary

[3] https://www.bmj.com/content/bmj/385/bmj-2023-078378.full.pdf

research articles that are most relevant to targeted tasks. The approach subsequently synthesizes predictive models and risk scores from quantitative tabular information automatically extracted and harmonized from the identified relevant publications.

1.1.1 Task 6.1 Data requirements for evidence-based models

Pharmatics' MedAI approach[4] constructs evidence-based models from information extracted from scientific articles and harmonizes it, **without the need for accessing individual-level datasets.** Additionally, unlike the construction of data-driven models using a predefined set of covariates (inputs) and outcomes (outputs) of discriminative models, the MedAI approach may result in multiple models using a variety of structured data sources for predicting multiple outcomes that cannot be easily summarized prior to carrying out an extensive literature search. **The only data requirement for the MedAI approach used in Task 6.1 is access to full texts of scientific biomedical publications with statistical results**, such as model coefficients, confidence intervals of individual covariates, and model descriptions, which can be extracted, analysed, and integrated based on published information.

A preliminary application of the MedAI pipeline to the set of openly accessible scientific biomedical publications from the PMC repository identified around 90 candidate predictive models relevant to HCM patients. These models aim to assess HCM risks for primary prevention, enabling early detection and facilitating screening. Additionally, they aim to evaluate risks of potential HCM-related complications including sudden cardiac death (SCD), heart failure (HF), atrial fibrillation (AF) for secondary prevention to minimize the risk of patients' developing complications. Furthermore, a small set of models can be used to predict treatment response and the progression of complications for tertiary prevention to optimize treatment and minimize further deterioration of the conditions. This list may contract or expand based on the further processing of the aggregated results from the constantly evolving literature and based on the granularity of the extracted statistical information.

Instead of summarizing the details of approximately 90 specific models in terms of model types, inputs, and outputs, we will highlight only high-level details of the likely outputs of the MedAI approach in the table below:

Table 1 – Data requirements for Pharmatics' MedAI approach-

#	Model Type	Model input	Model output	Requested data source	Requested labels
1-90	Dozens (possibly hundreds) of parametric classification and regression models synthesized from scientific biomedical literature on HCM and its common complications	Multiple structured inputs including demography, family history, patient-reported variables, information from health records including primary care, blood tests, ECG and imaging biomarkers	Multiple outcomes relevant for primary, secondary, and tertiary prevention, including NOHCM *vs* OHCM, HCMpos *vs* HCMneg; complications (incident MACE, AF, HF, stroke, NSCD, SCD); markers of complications or functional decline (RV-EF, RV-GCS, FFA levels, apelin levels, prolonged QT, LGE, LVH, LAE, MPRI, LVOTO, LVOTG, LVMI, EF)	No access to individual-level data is required. However, data providers are encouraged to submit a ***data dictionary*** describing the available measurements in a *natural language* to assess whether evidence-based models can be applied to their datasets	*Diagnostic codes*, such as ICD-10, or descriptions in a natural language; *therapeutic codes* or descriptions in a natural language

[4] https://pharmaticsltd.com/MedAI/Pharmatics-MedAI-leaflet-2023.pdf

1.2 Task 6.2 Interpretable referral models using routinely collected data

The primary objective of T6.2 is to improve referrals of high-risk individuals to specialist tests. Such tests may include lab measurements, multimodality imaging, genetic testing, endomyocardial biopsy, or collection of novel markers. The aim is to enhance the evaluation and management of cardiomyopathies by developing machine learning models that use only routinely collected or easily accessible non-invasive measurements. These models will identify HCM patients who may require second-level tests to identify specific aetiologies, as well as those at risk of poor prognosis or inadequate response to standard care. Such patients will then undergo extended data collection for diagnosis confirmation, prognosis evaluation, and treatment selection using models from Tasks 6.3-6.4 and WP3-5. Through this task, our goal is to speed up referrals and enhance targeted management.

Additionally, T6.2 may uncover the relationships between routinely collected variables from patient electronic health records (EHRs) and demographic data to provide a low-cost stratification of HCM patients. Evidence-based models from T6.1 will act as additional inputs for models in T6.2. The required data sources will be integrated, documented, and made available using the data and knowledge infrastructure of WP2.

1.2.1 Data requirements for EHR-based models.

Below is a non-exhaustive list of the models that could be developed in T6.2 based on the possible inputs provided by WP2. The inputs detailed in the table can be combined to produce more accurate models. These models will not only target the screening of HCM patients but also stratify the risk level to identify high-risk individuals for extended data collection and enhanced management using the models developed in T6.3 and T.6.4. Here we will prioritize the use of interpretable methods for structured data to ensure that both providers and patients can easily understand the predictions, to increase acceptance and uptake of the methods in practice.

Table 2 – Input-output relationship and data requirements for EHR-based models.

<table>
<tr><th>#</th><th>Model Type</th><th>Model input</th><th>Model output</th><th>Requested data source</th><th>Requested labels</th></tr>
<tr><td>1</td><td rowspan="2">Parametric classifiers (Logistic/Linear Regression and Naive Bayes Classifier), and Non-parametric classifiers (Support Vector Machines, Ensemble Trees methods)</td><td>•Demographic information (e.g. age, gender, socioeconomic status, educational level, etc.).
•Anthropometry (e.g. height, weight, BMI, waist-to-hip ratio, body fat percentage, etc.)</td><td rowspan="2">Screening (HCM vs. normal)
HCM risk stratification (low vs medium vs high risk)
HCM cardiomiopathies.</td><td>Patient registry information/EHR</td><td rowspan="2">Different cardiomiopathies labels (Normal, LVH, HCM, etc…)</td></tr>
<tr><td>2</td><td>•Biochemistry (e.g., cholesterol, glycated hemoglobin, uric acid, serum creatinine, Cardiac troponin-T, etc.)
•Clinical Measurements (e.g., blood pressure, ankle-brachial index,</td><td>EHR</td></tr>
</table>

		Heart Rate variability) • **Clinical history** (e.g., diseases, chronic diseases, comorbidities, clinical procedures) • **Medications** (e.g., antihypertensive, anticoagulants, antiplatelet, beta-blockers, diuretics, etc.)			
3		**Lifestyle** (e.g., smoking, physical activity, dietary habits, alcohol consumption, sleep patterns, stress levels)		Patient Questionnaires	
4	Categorical or multi-label parametric classifiers.	T6.1 models used as additional predictors alongside demography, signs and symptoms, and primary care data	Suspected cardiomyopathy; recommended morphological and functional assessments	Inputs needed for using T6.1 models (TBC); symptoms, primary care EHRs, demography	Referrals to ECG, genetic, lab, imaging tests; diagnosis of cardiomyopathy
5	Parametric classifiers; ordinal and survival regression models	As in the model above (#4), with the results of ECGs, imaging, genetic, or lab tests; morphological or functional traits	Cardiomyopathy phenotypes (HCM types, DCM, ARVC, NDLVC); disease severity; risk of complications including secondary disfunction	As in the model above (#4), with linked secondary care EHRs	Cardiomyopathy phenotypes; traits derived from test results; outcomes at follow-up

1.3 Task 6.3 Data-driven biomarker discovery and prediction

Task 6.3 will focus on deriving novel biomarkers for HCM stratification, prognosis, and personalized treatment by analysing ECG signals, CMR and echocardiography images, and multi-organ data from WP5, via discovery of data-driven biomarkers.[5] The characteristics of each model and the requirements are detailed separately for the different data sources.

1.3.1 Data requirements for ECG-based models

The following table (Table 1Table 3) describes the ECG-based approaches proposed in the literature that will be initially considered in SMASH-HCM project. Models are detailed in the following table in terms of modal input/outputs relationships and data needs. We expect the models to target at least the following needs: patient screening, phenotyping and risk stratification, and monitoring of treatment responses.

[5] Note: Model-driven and mechanistic-based biomarkers will be part of specific WP5 deliverables and will not be discussed here.

Table 3 – Input-output relationship and data needs for ECG-based models

#	Model Type	Model input	Model output	Requested data source	Requested labels
1	Logistic Regression[6]	30 ECG features computed from wave duration and amplitude.	Screening (HCM vs. normal)	12- Leads ECG or measures contained in EHR.	Patient labels (normal, LVH, HCM, etc…)
2	Convolutional Neural-Network (CNN)[7]	12-Lead ECG signals	Screening (HCM vs. normal)	12-Lead ECG (10s)	Patient labels (normal, LVH, HCM, etc…)
3	CNN+Gradient Boosting[8]	725 ECG Features computed after automatic waveform segmentation	Screening (HCM detection)	12-Lead ECG (10s)	Patient labels (normal, LVH, HCM, etc…)
4	Random forest or SVM[9]	504 morphological and temporal ECG features	Screening (HCM vs. normal)	12-Lead ECG (10s)	Patient labels (normal, LVH, HCM, etc…)
5	Logistic Regression[10]	30 ECG features computed from wave duration and amplitude.	Phenotyping (OHCM vs. NOHCM)	12- Lead ECG or measures contained in HER.	Phenotype labels (OHCM vs. NOHCM)
6	Unsupervised clustering[11]	4 QRS features by signal decomposition, T-wave biomarkers + CMR images.	Phenotyping (Arrhythmic risks)	12-Leads ECG (30 min) and eventually CMR images for a deeper patient phenotyping.	Risk factors scores (i.e. HCM Risk, SCD events, time-to-event)
7	CNN[12]	12-lead ECG signals	Treatment response monitoring	12-Lead ECG (10s) recorded at different time-points.	Indicator of responses (LVOT gradient, NT-proBNP levels)

All the models require 12-Lead ECG recordings (>10s duration, >125Hz sampling rate) or, in case models use a few standard ECG features, those features could be retrieved from the EHR. Digital ECG signals are required but, as a suboptimal alternative, ECG traces could be digitalized from printed paper-ECG scans or PDF files, with extra work. The columns of label requirements indicate the minimum information requested to be able to train the models, which might be extended if a deeper characterization of the HCM patients is required.

In terms of requirements on the minimal amount of data for training we observe that: a) models #1 and #5 do not need any training as authors have provided the regression coefficients and the relevant parameters (model is fully disclosed); b) model #6 describes the relevant features obtained by signal decomposition but their combination is not fully published so that training data is needed (estimated approximatively in 50 samples/risk class). Model #3 and #4 use hundreds of features, which can be

[6] Guo L, et al. Derivation and Validation of a Screening Model for Hypertrophic Cardiomyopathy Based on Electrocardiogram Features. Front Cardiovasc Med. 2022 May 24;9:889523. doi: 10.3389/fcvm.2022.889523.

[7] Ko WY, et al. Detection of Hypertrophic Cardiomyopathy Using a Convolutional Neural Network-Enabled Electrocardiogram. J Am Coll Cardiol. 2020 Feb 25;75(7):722-733. doi: 10.1016/j.jacc.2019.12.030

[8] Tison et al. Automated and Interpretable Patient ECG Profiles for Disease Detection, Tracking, and Discovery. Circ Cardiovasc Qual Outcomes. 2019 Sep;12(9):e005289. doi: 10.1161/CIRCOUTCOMES.118.00528

[9] Rahman QA, et al. Utilizing ECG-Based Heartbeat Classification for Hypertrophic Cardiomyopathy Identification. IEEE Trans Nanobioscience. 2015 Jul;14(5):505-12. doi: 10.1109/TNB.2015.2426213. Epub 2015 Apr 24. PMID: 25915962

[10] Guo L, et al.. Identifying Obstructive Hypertrophic Cardiomyopathy from Nonobstructive Hypertrophic Cardiomyopathy: Development and Validation of a Model Based on Electrocardiogram Features. Glob Heart. 2023 Aug 4;18(1):40. doi: 10.5334/gh.1250

[1111] Lyon A, et al. Distinct ECG Phenotypes Identified in Hypertrophic Cardiomyopathy Using Machine Learning Associate with Arrhythmic Risk Markers. Front Physiol. 2018 Mar 13;9:213. doi: 10.3389/fphys.2018.00213

[12] Risk Markers. Front Physiol. 2018 Mar 13;9:213. doi: 10.3389/fphys.2018.00213.

Tison and PIONEER-OLE Investigators. Assessment of Disease Status and Treatment Response With Artificial Intelligence-Enhanced Electrocardiography in Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2022 Mar 15;79(10):1032-1034. doi: 10.1016/j.jacc.2022.01.005. PMID: 35272798

reduced to a few tens by feature selection methods, but model details are not available: data need for the retraining of these models is expected to be in the range of a few hundreds of examples/classes. Finally, Model #2 and #7 provide a description of the CNN structure but not the pre-trained version of the CNN. Thus >1K cases are expected to be necessary to retrain it.

The demand for ECG training data can be alleviated by using synthetic examples provided by WP4 or by data augmentation techniques which generate synthetic data, for example by GAN[13].

1.3.2 Data requirements for image based (CMR and echocardiography) models

In the following table, we describe the diverse approaches to the segmentation of CMR and Echocardiography. These approaches will generate biomarkers for HCM phenotyping, stratification, and monitoring.

Table 4 – Data requirements for Image based models

#	Model Type	Model input	Model output	Requested data source	Requested labels
1	CNN[14][15]	Long axis and short axis CMR	Segmentation Masks	Short axis and long axis CMR	Contours or segmentation masks. Patient labels. Phenotype labels.
2	Conv-NeXt[16]	Long axis and short axis CMR	Segmentation Masks	Short axis and long axis CMR	Contours or segmentation masks. Patient labels. Phenotype labels.
	CNN[8][9]	Echocardiography	Segmentation Masks	Echocardiography	Tracings and EF. Patient labels. Phenotype labels.
	Conv-NeXt[10]	Echocardiography	Segmentation Masks	Echocardiography	Tracings and EF. Patient labels. Phenotype labels.

The models involved in CMR data processing require a minimum of 200 patients with contours. Similarly, in the echocardiography analysis, the necessary tracings and EF measurements of a similar number of patients is required for prospective biomarker identification. Additional information on patient type and phenotype labels directly impacts the performance of data subsets, especially in uncommon diseases or patients.

The above-mentioned models, combined with data augmentation techniques, and specific strategies to enhance the performance on smaller dataset subsets, are crucial for minimizing errors in CMR

[13] https://doi.org/10.1016/j.artmed.2023.102489

[14] 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

[15] 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

[16] 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

analysis[17][18]. In the case of echocardiography, ensuring temporal consistency and selecting the correct heartbeat will play a crucial role in the precision of the extracted features[19][20].

In both imaging modalities, the importance is placed on having diverse data over quantity of data. Therefore, a lower but representative amount of each phenotype and patients is preferred over larger but less diverse cohort.

1.3.3 Data requirements for data-driven biomarker discovery in multi-organ models

The following table describes the approaches, based on the analysis of myocardial strains and heart rate variability features, proposed in the literature for the prediction of cardiovascular events and risks stratifications. These approaches will be considered in the SMASH-HCM project in the context of HCM for risk stratification. The text describes the activities which are pertinent to WP6, more details on the multi-organ models will be in a specific deliverable of WP5.

Table 5- Data requirements for multi organs, data-driven models

#	Model input	Model output	Requested data source	Requested labels
1	Time-frequency heart rate variability (HRV) feature[21]	HCM risk stratification (low vs high risk)	Stress test 12-lead ECG	Type of ventricular arrhythmias
2	Integral-based features[22][23]	HCM risk stratification (low vs high risk)	Myocardial strains	Type of ventricular arrhythmias
3	Strain-volume loops features[24]	HCM risk stratification (low vs high risk)	Myocardial strains	Type of ventricular arrhythmias

1.4 Task 6.4 Multilevel stratification and prediction for disease management

Task 6.4 will develop a multilayer approach that progressively combines disparate models to create increasingly personalized prediction and stratification methods for monitoring progression of HCM and comorbidities. These predictions are constitutive parts of the SMASH-HCM three-level, digital-twin, deep phenotyping platform which is designed to maximize the stratification power of the data available. In terms of data-driven models this is translated into tools which: at Level 1 (see Figure 1), stratification will be based on low-cost clinical or demographic data along with simple in-silico biomarkers derived by cell-population models (i.e., pro-arrhythmic index, APD curves and derived metrics). For a more detailed stratification (Level 2 in Figure 1), information will be pooled from additional sources providing patient-specific details such as in-silico models including single cells,

[17] C. Martín-Isla et al., "Deep Learning Segmentation of the Right Ventricle in Cardiac MRI: The M&Ms Challenge," in IEEE Journal of Biomedical and Health Informatics, vol. 27, no. 7, pp. 3302-3313, July 2023, doi: 10.1109/JBHI.2023.3267857

[18] V. M. Campello et al., "Multi-Centre, Multi-Vendor and Multi-Disease Cardiac Segmentation: The M&Ms Challenge," in IEEE Transactions on Medical Imaging, vol. 40, no. 12, pp. 3543-3554, Dec. 2021, doi: 10.1109/TMI.2021.3090082

[19] N. Painchaud, N. Duchateau, O. Bernard and P. -M. Jodoin, "Echocardiography Segmentation with Enforced Temporal Consistency," in IEEE Transactions on Medical Imaging, vol. 41, no. 10, pp. 2867-2878, Oct. 2022, doi: 10.1109/TMI.2022.3173669

[20] Ouyang, D., He, B., Ghorbani, A. et al. Video-based AI for beat-to-beat assessment of cardiac function. Nature 580, 252–256 (2020). https://doi.org/10.1038/s41586-020-2145-8

[21] Calvo M, et al (2018) Multivariate classification of Brugada syndrome patients based on autonomic response to exercise testing. PLoS ONE 13(5): e0197367

[22] Gallard A et al. (2021) Echocardiographic view and feature selection for the estimation of the response to CRT. PLoS ONE 16(6): e0252857

[23] Gallard A et al. Characterization of Responder Profiles for Cardiac Resynchronization Therapy through Unsupervised Clustering of Clinical and Strain Data J Am Soc Echocardiogr. 2021;34(5):483-493. doi: 10.1016/j.echo.2021.01.019

[24] Hubert A. et al. New expectations for diastolic function assessment in transthoracic echocardiography based on a semi-automated computing of strain-volume loops. European Heart Journal - Cardiovascular Imaging. 2020 Dec 1 ;21(12) :1366-1371. doi: 10.1093/ehjci/jeaa123

tissues, whole-heart simulations (with patient-specific geometry), and vascular simulations; at Level 3 the most complete phenotyping is obtained combining biomarkers derived from ECGs, CMR and echocardiography images, and multiorgan simulations with the above (Level1 and 2) models.

The increasingly level of personalization, required by the models in Task 6.4, needs inputs and contributes from the mechanistic models developed in WPs 3-5. The following tables list the contributions by those WPs which task 6.4 models will integrate.

Table 6 – Data contributes from WP3-5.

#	WP	Model type	Model output	Model scale	Expected cases/simulation
1	WP3	iPSC-derived cardiomyocytes from HCM patient specific lines	Action potentials -Ion currents (patch clamp) -Calcium transients -Unloaded shortening -Expression of proteins/ biomarkers	Single cardiomyocytes	Characterization of 8-10 different patient-specific lines and the respective isogenic controls in 3 centers (UNIFI, TAU, UKE)
2	WP3	iPSC-derived engineered heart tissues (EHTs)	-Action potentials -Calcium transients -Fine mechanical measurements, contractility by video analysis -Structural and functional biomarkers	Engineered Myocardial Tissue (cardiomyocytes, fibroblasts, endothelial cells)	8-10 different patient-specific lines and the respective isogenic controls
3	WP3	Patch-clamp data of cardiomyocytes isolated from myectomy samples of HCM patients	-Action potentials -Arrhythmic events (afterdepolarizations) -Ion currents (patch clamp) -Calcium transients -Unloaded shortening -Expression of proteins/ biomarkers	Single cardiomyocytes	Electrophysiological data from >100 HCM patient samples and from >40 non-HCM patient-samples (to be used as controls)
4	WP3	Mechanical data of intact trabeculae	-Fine mechanical measurements (systolic and diastolic function) -Arrhythmic events (aftercontractions)	Native Myocardial-Tissue	Mechanical data from trabeculae of >50 HCM patient samples and from >25 non-HCM patient-samples (to be used as controls)
5	WP3	Mechanical data of demembranated trabeculae or single myofibrils	-Fine mechanical measurements of cross bridge mechanics -ATP consumption and tension cost	Subcellular (myofibrils)	Myofibril data from >40 HCM patient samples and from >20 non-HCM patient-samples (to be used as controls)
6	WP3	Digital structural staining	Distributions of myofibrillar orientations and nuclei shape/size/orientation r	Structural staining model of hiPSC-CM monolayer	n.a.
7	WP4	hiPSC-derived cardiomyocyte model	All the state variables (action potential, active tension, fractional shortening, intracellular ion concentrations, ion currents, energy consumption, etc.) saved to plain ascii/txt-files	Cell	single AP cycle (at dynamic steady-state) and long-term simulations adapting to changing inputs for each phenotype, databases from parameter screenings in virtual cell cohorts (N ~10^3). Selected drug effects on populations of genotypes.
8	WP5	SMC	All the state variables (AP, contractility, Ca ion concentrations, potassium and calcium currents),	1-D population of smooth muscle cells.	AP cycle and Ca concentration (at dynamic steady-state) and long-term simulations adapting to changing inputs for each phenotype, databases from

			estimates of the HCM effects on the vascular tone, compliance.		parameter screenings in virtual cell cohorts (N ~10^3). Selected drug effects on populations of genotypes.
9	WP4	Cardiac tissue model	Simulated: Conduction velocity, Effective refractory period, Re-entry inducibility and sustainability	Tissue	– Each protocol will be simulated for each mutation that will be modelled in T4.1 and compared to control tissue. – Selected drug effects on populations of genotypes. – Simulations will be performed in a 2D rectangular tissue domain of dimensions comparable with a substantial portion of the ventricle wall with and without an anatomical obstacle. – Simulation will be also performed in ETH type 3D tissues domain to mimic the in-vitro culture information – Protocols: Stimulated propagation at different rates, S1-S2, programmed ventricular stimulation protocol, Unstimulated evolution from initial conditions including a phase singularity Population of models (N≧100) will be built and simulated for each mutation
9	WP4	Whole heart model (electro-physiology)	Simulated: - Activation maps - APD maps - Voltage maps - ECG signals (these can be complemented with extra electrode for uncertainty in their positions, and with physiologically compatible translations and rotations of the heart within the torso, to act as data augmentation techniques). Activation/APD/Voltage maps: written in table format (easily convertible to txt). Also, option to provide these in either Ensight or VTK formats.	Organ	Simulations will be performed in anatomical reconstructions of the patient's ventricles (from MRI), with EP personalised to the patient's ECG (likely multiple EP substrates per anatomy). Models will be simulated under different protocols (sinus rhythm, exercise, ischaemia) based on specific research questions. Cases in 2 years: 20-40 maximum.
11	WP4	Whole heart model (electro-mechanics)	Simulated: Same as before (ECG, activation/APD/voltage maps), plus: - myocardial displacements - pressure-volume loops (from the latter, any related clinical biomarker can be computed: ejection fraction, end systolic / end diastolic volumes, etc).	Organ	Same considerations as before. Cases in 2 years: 10-20 maximum.
12	WP5	SMC tissue level models	Simulated: Calcium, electrophysiology, contractility, estimates of the vascular wall tone, compliance effects on resistance	2D and 3f tissue level	AP cycle and Ca concentration (at dynamic steady-state) and long-term simulations adapting to changing inputs for each phenotype, databases from parameter screenings in virtual cells tissue cohorts (N ~10^2)

13	WP5	Integrated cardiovascular model : i) multi-segment ventricles, ii) systemic and pulmonary circulation iii) autonomic nervous system.	State variables and model outputs: myocardial strains, left ventricular pressure and volume, arterial pressure, heart rate, vagal and sympathetic modulations. Patient-specific parameters: myocardial contractility and stiffness levels, electrical activation delays, vagal and sympathetic gains, contractility regulation gains.	Multi-organ	Several conditions could be simulated: i) steady-state, ii) cardiovascular and autonomic response to stress test. Sensitivity analysis: provide most influent parameter on cardiovascular and autonomic output. Patient-specific parameter: identified from clinical data.

The analysis of the Table above shows that mechanistic models can contribute with mainly 3 types of inputs: multiple models of HCM phenotype-genotype associations; ii) simulated heart and vascular system parameters and iii) simulated data (such as ECG, APs, etc…) which will serve as data augmentation for model training.

Models should consider the need for integration of those multi-factorial information sources which will be pursued by combinations of AI/ML models which mimic the decision taken by a pool of experts using techniques such as model ensembles, stacking of classifiers, or the theory of multi-fidelity modelling. As we are not expecting to have all reliably measurements/simulations for any of the cases, attention must be paid to developing methods that account for missing data and data imputation techniques including generative AI imputations. Post-hoc eXplainable AI (XAI) techniques will be used to unveil relevance of input features for prediction and clustering. This last aspect will be discussed further in the next section.

2 Design Requirements

This section describes the design principles to adhere to when developing the SMASH-HCM data driven models. This document shares the vison of models as *data transformation services* indicated in the deliverable 3.2 by the EDITH project. The vision considers the model as software components which must consider the following aspects to face the current barriers to the adoption of Digital Twin models in healthcare:

- Model reuse and reproducibility (see section 2.1).
- Model credibility and trustworthiness (see section 2.2).
- Model compartmentation and interoperability (see section 3.1)
- Identification of Regulatory frameworks (see section 3.2)
- Identification of necessary pre/post-processing tools and dependency (see section 3.3)

2.1 Accessibility/Reproducibility of the AI/ML models

To improve accessibility and reproducibility, we will consider the following aspects:

- **Code and model sharing**: where this is possible, we will encourage all project partners to share the source code, or the complete codebase used for developing and training the AI models. Where sharing the code or the codebase is not possible (for example, due to data privacy or commercial sensitivity), we will encourage sharing the trained models, such as model coefficients or executables implementing inference procedures with the trained models to ensure transparency and enable independent verification and replication of the results in new datasets.
- **Documentation**: for all new models, detailed documentation should be provided, covering the following aspects:
    - Intended use.
    - Detailed explanations of the algorithms employed, including references to descriptions of mathematical formulations and theoretical foundations where that is relevant.
    - Model specification, including model types, architectures, and/or objective functions, where relevant. The specification should provide enough detail for other developers to recreate the model structure without ambiguity.
    - Documentation of preprocessing techniques, including feature engineering, normalization, handling missing values, data transformations, data augmentation, etc. The specification should provide enough detail for other developers to recreate preprocessing.
    - Detailed explanations of the training process, including optimization algorithms, regularization techniques, initializations, seed fixation, learning rates, annealing schedules, batch sizes, numbers of iterations, early stopping criteria. The specification should provide enough details for other developers to recreate the training process without ambiguity.
    - Documentation of hyperparameters used for model specification and training, including details about how hyperparameters were selected, including details of searches employed.
    - Explanations of how the trained models are used for inference, including input preprocessing, output post-processing, and details of any model combinations applied.

- Implementation details: Detailed logs of all experiments, including hyperparameter configurations, random seed values, training/validation data splits, performance metrics, or

similar characteristics should be maintained and shared to enable reproducibility and facilitate comparisons with future experiments. A version control system should be used to track changes in the codebase, ensuring reproducibility and enabling replication of specific model iterations or results. Any licenses, libraries, or dependencies used in the development process should be clearly documented to ensure that the results can be replicated by other model developers. Optionally, additional information regarding the suggested hardwire requirements for using the models for both learning and inference should be internally shared to ensure that researchers and developers meet the recommended equipment requirements.

2.2 Trustworthy and explainability aspects

The definition of the trustworthy and explainability aspects in the design requirements for the data-driven model developed in WP6 will comply with the Ethical Guidelines for Trustworthy AI published by the HLEG-AI of the European Commission[25]. The guidelines establish a set of key requirements (Figure 2) that apply to any phase of the project cycle. Within these 7 requirements, the guidelines define various sub-requirements that allow data scientists, developers, and other stakeholders that interact with the AI models to achieve trustworthiness.

Figure 2 – Trustworthy AI requirements

The AI models developed in SMASH-HCM will be aligned with the requirements defined by the EC HLEG-AI. The table below describes an exhaustive list of potential characteristics that SMASH-HCM models should have to meet such requirements. Due to the general comprehensiveness of the list, it might not be required to adopt all the characteristics by all the specific models. Therefore, once the different uses-cases to be implemented in the project are defined, the specific group of characteristics to be addressed in the models will be identified. This selection process will be achieved through collaborative discussions between our clinical partners and AI development teams.

[25] https://ec.europa.eu/futurium/en/ai-alliance-consultation.1.html.

Table 7 – SMASH-HCM compliance to Trustworthy AI requirements

#	Trustworthy AI requirements	Trustworthy AI sub-requirements	SMASH-HCM data-driven models characteristics
1	Human agency and oversight	i. Fundamental rights ii. Human agency iii. Human oversight	1) SMASH_HCM models aligned with fundamental rights: a) The patient has control over her/his privacy (what data are fit to the model for training/prediction). b) The cardiologist/physician (C/P) feels autonomous and is aware of the limitation of his/her freedom when using the system (what can/can't be done and/or allowed) c) The dignity of the patient must be preserved. No action is allowed on patient's data without his/her consent. d) Ensure C/P is not affected by unfair manipulation, deception, or conditioning when using the models that would affect his/her autonomy. 2) A continuous risk assessment of the models from the fundamental rights perspective should be enabled. 3) C/P should be able to interact with the decision support tool that deploys the models. 4) Improves C/P's agency and intuition in the decision-making by offering sandbox options in the models' input to test new ad-hoc use cases. 5) Offer information about the HCM models/architecture that allows users (C/P and patients) to comprehend the system. 6) The output provided by models would enhance the decision-making process on the HCM screening but the C/P must be independent to decide autonomously on the results. 7) C/P uses the system in a human-in-command (HIC) approach, by deciding when to apply the models' decision when, for instance, there is a non-clear case of HCM diagnosis/screening. 8) Offering the C/P a human-in-the-loop (HITL) approach where he/she can decide which models and inputs to employ. This may vary depending on the decision goal i.e. screening, HCM risk estimation, etc. 9) Extend the HITL approach to the design phase where C/P can collaborate in the models building by specifying the type of data, the inputs, or the features to use.
2	Technical robustness and safety	i. Resilience to attack and security, ii. Fall back plan and general safety iii. Accuracy, iv. Reliability and reproducibility	1) Vulnerabilities protection measures: a) *Data poisoning*: To ensure that spurious instances do not get into the models use mechanisms such as out-of-range values filtering, outliers management, ad-hoc preprocessing of ECG signal and medical images. b) *Model Leakage*: The sets for training/validation/test should be clearly identified. Avoid the use of test set in any training/validation phase. If possible, use an independent dataset different from train/val dataset to test the model. Otherwise, a thorough inspection of the test set must be made to avoid data leakage, i.e. different records from the same patients are used simultaneously in train/val and test set. The train/val and test split should be made initially and leave out the test set's instances untouched, even at the preprocessing phase. If needed, through harmonization procedures, ensure that features employed to train/validate the models are the same as included in the test set. c) *For hardware vulnerabilities*, the SMASH-HCM models will follow persistence approaches to guarantee a rapid replacement in case the machine where they are primarily deployed is affected by an adversarial attack. 2) In case a problem is detected, fallback strategies should be defined to recover the last stable releases of the model. To that end, a version control system (e.g. GitHub) during the model

			development must be implemented with clear documentation for every commit to the main repository branch. 3) Employ strategies such as hold-out test sets (see above model leakage), or different kinds of cross-validation (k-fold CV, Nested CV, Leave-one-out CV) to ensure generalization capabilities and avoid overfitting and other inaccuracies. Performance results must be given with confidence intervals and statistical significance indicators that allow the selection of the best-performing model and prevent the C/P from misunderstanding any inaccurate predictions that might occur. 4) The target performing levels should be discussed and agreed upon with C/P in order to indicate which are performing metrics of interest (sensitivity, specificity, accuracy, auroc) according to the clinical prediction goal. 5) To ensure the reliability of the SMASH-HCM models, as many situations/contexts as possible in terms of patients phenotypes, clinical data available, etc. should be reflected in the training/validation/sets by creating a wide range of inputs. Handling fluctuation of input data through appropriate preprocessing (see above data poisoning) might be useful to avoid model drifting performance. 6) The model should offer mechanisms for continuous monitoring and improvement, i.e. update the models with new data, evaluate their performance, and improve algorithms to improve accuracy and dependability. 7) To allow the reproducibility of SMASH-HCM models, different strategies should be adopted such as a thorough benchmark of our modes with different variations of data (clinical data, ECG signals, medical images) to ensure consistent performance across a wide range of values. 8) In addition, embracing open science directives where the code of AI models will be available for other researchers will improve their reproducibility over other datasets owned by external research groups or 3rd-parties.
3	Privacy and data governance	i. Respect for privacy, ii. Quality and integrity of data iii. Access to data	1) The privacy and data protection, especially concerning patients' information, must be guaranteed at any time of the SMASH-HCM models lifecycle, i.e. from design and development to their eventual deployment in clinical routine. 2) The privacy measures adopted must comply with GDPR and other data security regulations. 3) All data regardless of their type (demographics, EHR, ECG, or medical image) used to train and test the models must be completely anonymized and/or pseudonymized impeding the identification of the individual using direct identifiers (e.g., names, social security numbers) and indirect identifiers (e.g., combination of zip code, gender, and age) 4) Inference of sensitive personal information that might be subject to discrimination and does not provide predictive usefulness to the models, should be restricted (e.g. economic level, study level, sexual orientation, etc.). 5) The process of data collection or retrieving from different databases and sources should be carefully carried out to avoid socially constructed biases, inaccuracies, errors, and mistakes. To this end, an appropriate research data management plan must be defined and followed before the training phase of the models. The measures taken to avoid data poisoning are also valid to ensure data quality and integrity. 6) Exploratory data analysis prior to training models can support the quality of data, particularly concerning those sensitive features that might compromise user privacy. 7) An exhaustive documentation of the datasets employed in each SMASH-HCM model's lifecycle phases as well as privacy-preserving measures must be maintained.

			8) Protocols to govern data access must be developed encompassing access rights either for models' users (C/Ps) or users affected (patients). These protocols should detail who can access the data and under which circumstances, as well as secure methods of data collection, processing, and deletion, ensuring maximum privacy and data minimization. 9) Incorporating differential privacy mechanisms to add noise to the training data or the model's outputs, would ensure that the model's predictions do not compromise patient privacy. However, the level of noise added should sufficiently protect individual data points without significantly degrading the model's predictive accuracy. 10) Ensure that model training and testing are carried out in secure, controlled environments to prevent unauthorized access to sensitive data. 11) Implement mechanisms of continuous privacy monitoring to allow adjusting privacy parameters to be adapted to different deployment environments.
4	Transparency	i. Traceability, ii. Explainability iii. Communication	1) The process of the SMASH-HCM models' development (including data gathering and labelling) should be documented to allow traceability of the different components and stages. 2) The models must provide explainable information about how they produce their prediction output. This explainable info can be defined at various levels user-wise: a more technical explainability for AI researchers and developers, and another more non-expert (human-centered) explainability to allow C/Ps and patients to understand the model's decision-making logic. 3) The explainable information provided by the models about the prediction as well as the documentation of their other components (source code, data use, model's internal parameters, type of outputs provided) must allow their audit by different stakeholders of the model (C/Ps, patients, healthcare providers, regulators, etc.) 4) The explainability information should be given globally and individually, i.e. global explainability by showing the models' whole functioning towards their prediction; and individual explainability by showing how the model predicts a specific instance. 5) The trade-off between model performance and model interpretability should be adequately addressed considering the user's (C/Ps, patient) requirements for the different use cases. 6) The C/Ps' acceptability of the explanations provided should be assessed in order to refine or adapt the prediction outputs and make them clinically useful. 7) The SMASH-HCM model's users or any other individual affected by the decision-making must be informed that they are interacting with an AI system. The AI model's capabilities and limitations should also be communicated to avoid misunderstandings that might negatively impact the diagnosis/prognosis. This requirement is aligned with the human oversight and fundamental rights subprinciples.
5	Diversity, non-discrimination, and fairness	i. Avoidance of unfair bias, ii. Accessibility and universal design iii. Stakeholder participation	1) An initial exploration and pre-assessment of the collected data should be carried out to detect the existence of identifiable and discriminatory bias before model training. If possible, the data over which the models are trained should be diverse and representative. 2) A thorough assessment of the model performance should be tackled by inspecting the influence that some sensitive variables might have on the model decisions. The insights obtained from those variables' influence must be discussed concerning unintended (in)direct prejudice and discrimination occurrences against certain groups of individuals considering the model's purposes and requirements.

			3) The decision support tools that would employ models' decisions must tackle a user-centric design that allows all users to use them regardless of their abilities. Tackling universal design principles and accessibility standards will allow for providing accessibility features to the models. By doing so, equitable access and active participation is offered. 4) The users that may be directly (patients) or indirectly (C/Ps) affected by the AI models should be consulted throughout the lifecycle to receive their feedback about the models' design and development. 5) The SMASH-HCM models and the tools that use them must preserve and promote justice for the users by using technical standards, monitoring and auditing mechanisms, and allowing the right to appeal, recourse, redress, or remedy the decisions made.
6	Societal and environmental wellbeing	i. Sustainability and environmental friendliness, ii. Social impact, iii. Society and democracy	1) The model's development and deployment must be carried out via a critical examination of resource usage. If possible, to save computing resources make use of energy-saving training approaches such as transfer learning or ensemble of pretraining models. 2) The physical and mental well-being of the potential users (patients and C/Ps) should be monitored when interacting with the models to prevent any harmful effects that might occur at a societal level. 3) SMASH-HCM models should be aligned with the UN Sustainable Development Goals.
7	Accountability	i. Auditability, ii. Minimisation and reporting of negative impact, iii. Trade-offs iv. Redress.	1) SMASH-HCM models should allow the audit of their algorithms, data and design process whenever there is no IP conflict. This will ease the evaluation by internal and external auditors, who could make the evaluation reports available to increase the trustworthiness of the system. 2) Any potential negative impact that models could generate has to be identified, assessed, monitored, documented, and eventually minimized. Tools such as Algorithmic Impact Assessment can be helpful to minimize the negative impact. 3) Potential trade-offs between these requirements (e.g. accuracy vs explainability) must be assessed rationally and methodologically considering ethical risks to their users (either C/Ps or patients). The user responsible of the decision-making process (i.e. C/Ps) should be accountable for the way that trade-off is managed. 4) Redress mechanisms should be available when an adverse impact occurs (specially to vulnerable groups, i.e. patients). Prioritizing the patient's safety and dignity through redress approach will reinforce the SMASH-HCM models' trustworthiness.

3 Software Requirements

This section identifies the requirements for software development in view of a model deployment in the SMASH-HCM Decision Support System (DSS). The section will start with the technical requirements for model deployment provided by WP7, describes the standards to adhere and finally analysis the licence constrains of the developed models.

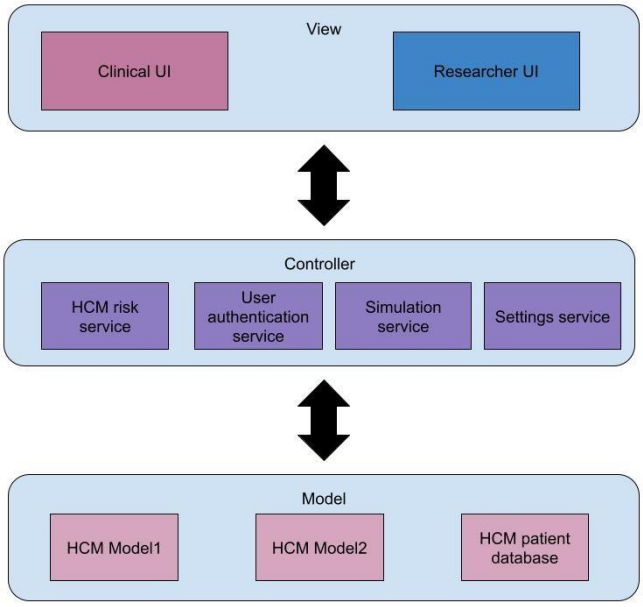
3.1 Technical Requirements for model deployment

Models developed in WP6 must be integrated into the final SMASH-HCM DSS software solution (WP7). Model developers must be aware, at high level, of the software architecture and requirements imposed to model development to facilitate model deployment and integration. They are described in the following sections.

3.1.1 SMASH-HCM architecture

The SMASH-HCM software architecture leverages *Docker* for containerizing each software module, ensuring consistent, isolated environments that minimize dependencies and conflicts. This facilitates deployment across varied computing environments and simplifies development. To support diverse programming languages used by consortium members, *Docker container* templates for commonly used programming languages in the consortium will be provided, streamlining module setup. The architecture supports development in multiple programming languages, enabling consortium members to select the most appropriate languages for their modules' needs. This approach allows leveraging language-specific libraries and frameworks, enhancing the project's innovation and adaptability. Docker is a platform as a service product that uses OS-level virtualization to deliver software in packages called containers. Containers are isolated from one another and bundle their own software, libraries, and configuration files; they can communicate with each other through well-defined channels. All containers are run by a single operating system kernel and are thus more lightweight than traditional virtual machines.

Figure 3 – Example of possible SMASH-HCM components and data flows according to MVC principle



Data flow between components will be arranged according to Model-View-Controller (MVC) principle, where the individual containers should be storing data, transforming data or representing data to the

end user. The MVC principle is a software design pattern that separates an application into three main components: Model, View, and Controller, each responsible for different aspects of the application. This separation helps manage complexity, enhance modularity, and facilitate scalable and maintainable code development. Figure 3 shows an example distribution of SMASH-HCM components and data flows according to the MVC principle.

Below is a brief description of the SMASH-HCM components (from bottom upward in Figure 3)

- **Model:** Represents the data and business logic of the application. It directly manages the data of the application. In a Dockerized environment, the Model would reside in a container that could include the application's database and any related data-processing services. This container would be responsible for accessing and storing data, performing computations, and executing machine learning models. These can also be nested in a way that there are pure data containers that provide data, and machine learning model containers that use the provided data. *Docker Implementation:* A container running a database and possibly another process for handling business logic and communicating with the database.
- **Controller**: Acts as an intermediary between the Model and the View. It receives user input from the View, processes it, and returns the output display to the View. Essentially, the Controller translates user actions into operations on the Model and updates the View accordingly. The Controller can also call other components, such as prediction containers to get the prediction results of a machine learning model. *Docker Implementation:* A container running the application logic that interacts with both the Model and View containers. This could involve API services, middleware that handles requests from the View, processes them, and then sends data back to the View.
- **View:** Represents the user interface of the application. It displays data to the user and sends user commands to the Controller. The View is responsible for the look and feel of the application, translating data from the Model into a form that users can interact with. *Docker Implementation:* A container serving the frontend, which could be a web server hosting HTML pages or a Desktop application.

3.1.2 Requirements for model developers

HCM models must be encapsulated into a Docker container, which puts no constrains for the developers on the selection of computing environments and programming languages. The container must contain all the settings, library and data needed to run the model and provide the model outputs. This **compartmentalization** allows for the decoupling of the complexity of the workflow and its usability in complex use cases. Likewise, these containers facilitate benchmarks of different tools aimed at the same or similar tasks.

At least the following elements are supposed to exist in the SMASH-HCM model component:

- Docker file
  - Container setup file that describes the used software packages and versions and initializes the software environment
- Readme file
  - Description and example usage of the component, including API definitions
- Software binaries
  - Actual component code to be run in the container

For details on Docker reference, please visit: https://docs.docker.com/get-started/overview/

3.2 Regulations & Standards for Software as a Medical Device

Throughout the project, the various software components will be developed and validated to prepare the SMASH-HCM DSS solution for future regulatory acceptability and commercial strategy. This section identifies the main applicable regulatory and standard requirements and guidelines for a Software as Medical Device to receive CE marking before being legally placed on the market.

The regulatory requirements will be further explored in the dedicated Task 8.3 "Preparatory work for market access and EU Medical Device Regulation (MDR) (M6—M48)", which will focus on obtaining guidance on approval under the current regulatory framework for MDR and IVDR, ensuring that the pilot study data collection (Task 8.6) and software validations will be performed in compliance for later CE marking application.

Table 8 – Main Regulation and Standards for SMASH-HCM

Document class	References
Regulations	• Regulation (EU) 2017/745 on medical devices (MDR)
Guidelines	• MDCG 2019-11 Qualification and classification of software - Regulation (EU)2017/745 and Regulation (EU) 2017/746 • MDCG 2020-1 - Guidance on clinical evaluation (MDR) / Performance evaluation (IVDR) of medical device software
Standards	• ISO 13485:2016 Medical devices — Quality management systems — Requirements for regulatory purposes • IEC 62304:2006/AMD 1:2015 Medical device software — Software life cycle processes — Amendment 1 • ISO 14971:2019 Medical devices — Application of risk management to medical devices • BS/ AAMI TIR 34971:2023 Application of ISO 14971 to machine learning in artificial intelligence—Guide • ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice
United States Food and Drug Administration (FDA):	• https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices • https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device • https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles
International Medical Device Regulators Forum (IMDRF) Software as a Medical Device Working Group (WG):	• https://www.imdrf.org/documents/software-medical-device-possible-framework-risk-categorization-and-corresponding-considerations • https://www.imdrf.org/documents/software-medical-device-samd-application-quality-management-system • https://www.imdrf.org/documents/software-medical-device-samd-clinical-evaluation

SMASH-HCM will follow closely the future developments on how the use of artificial intelligence in the EU will be regulated by the AI Act, the world's first comprehensive AI law:

Table 9 - EU AI acts

Type	Documents
EU Artificial Intelligence Act	• https://www.europarl.europa.eu/doceo/document/TA-9-2024-0138_EN.pdf

3.3 Dependency constraints

In view of a market placement of the SMASH-HCM solution, including the models developed in WP6, model dependency has been carefully analysed. The result of this analysis is reported in the following table.

Table 10 – Model dependency

#	Task	Model	Analysis	Solution	Licence
1	T6.3	ECG-based model	ECG needs to be elaborated for feature extraction	Proprietary algorithms will be used or publicly available library implementations (e.g. ECGPUWAVE)	GNU General Public License (GPL)
2	T6.3	Image-based models	CMR and Echocardiography images requires pre-processing augmentation for feature extraction.	Publicly available library implementations (e.g. TorchIO)	Apache-2, GNU, MIT
3	T6.4	Integrated cardiovascular model	Simulation and synthetized data	Simulation Library: Multi-formalism modeling and simulation library (M2SL)	CeCILL 2 (compatible with GNU)

4 Conclusions

A comprehensive overview of models' requirements, implementation constrains, and guidelines has been provided within this document. It serves as reference for WP6 model developers and for other project's WP (WP3-5,7).

The content of this report is based on the information/knowledge on patient, as well as simulation and modelling data or software/hardware architecture available at M4 of the SMASH-HCM project. It may be therefore subjected to amendments if new information (or constraints) emerges during the development of the SMASH-HCM project.