



DELIVERABLE

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D1.4 – Risk Assessment Report

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Authors and Contributors	Annariina Koivu (TAU), Antti Ahola (TAU), Jari Hyttinen (TAU), Mark van Gils (TAU), Malte von Tottleben (EMP), Nicholas McCarthy (UCD), Kathleen Curran (UCD), Katriina Aalto-Setälä (TAU), Luca Mainardi (POLIMI), Virginie Le Rolle (UNIVREN), Alfonso Bueno Orovio (UOXF)		
Responsible Author	Jari Hyttinen	Email	jari.hyttinen@tuni.fi
	Beneficiary TAU	Phone	+358504793743

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Abstract (for dissemination)	This deliverable, D1.4 provides a comprehensive snapshot of the project's evolving risk profile at month 18. Twenty-two risks are reviewed (18 identified at project launch, 3 added following the integration of a new partner and one unforeseen risk identified during the General Assembly September 2024).
Keywords	Risk Assessment

Statement of originality

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List of Abbreviations

API	Application Programming Interface
CM	Cardiomyocyte
EHT	Engineered Heart Tissue
GMLP	Good Machine Learning Practice
HCM	Hypertrophic Cardiomyopathy
iPSC-CM	Induced Pluripotent Stem Cell Derived Cardiomyocyte
MTA	Material Transfer Agreement
MVP	Minimum Viable Product
POM	Populations of Models
RWD	Real-World Data
WP	Work Package
XAI	Explainable Artificial Intelligence

Executive Summary

SMASH-HCM is an interdisciplinary research and innovation project developing advanced technologies to improve patient stratification and disease management for hypertrophic cardiomyopathy (HCM). This Risk Assessment Report, submitted at Month 18, provides a comprehensive snapshot of the project's evolving risk profile.

A total of 22 risks are reviewed in this report. 18 were identified at project launch, and 3 were added following the integration of a new partner, reflecting the consortium's proactive and adaptive approach to risk identification. In addition, one unforeseen risk—identified during the General Assembly on 27 September 2024—is added to the EU Funding & Tenders Portal.

Out of the 22 risks, 3 have materialised during the first 18 months of implementation. Each of these has been promptly addressed through appropriate mitigation measures, ensuring continuity and minimal disruption to project progress.

Risk management is a core part of the SMASH-HCM governance framework, given the project's reliance on in-depth understanding of a multifaceted topic, complex technologies, multi-sectoral collaboration, and high standards of scientific and operational quality. Risks—both technical and managerial—are reviewed regularly to support early detection and timely response, thus safeguarding the effective delivery of project goals.

This report outlines the identification, status, materialisation, and mitigation actions for each risk, in alignment with updates simultaneously submitted to the EU portal. It serves as both a formal checkpoint and a tool for continuous improvement in project execution.

1 Introduction

SMASH-HCM is conducting research and developing innovative technologies to improve the stratification and disease management of patients with hypertrophic cardiomyopathy (HCM). This Risk Assessment Report, submitted at month 18 of the SMASH-HCM project, provides a comprehensive overview of the project's current risk landscape. A total of 22 risks are reviewed: 18 were identified at project launch, and 3 additional risks were added following the entry of a new partner Novamechanics Monoprosopi Ite (NovaM) through the EC HORIZON-WIDERA-2023-ACCESS-06 (HopOn) program reflecting the consortium's adaptive and evolving risk awareness. In this report, we also discuss one unforeseen risk—identified during the General Assembly on 27 September 2024—and add also that to the EU Funding & Tenders Portal.

Risk management and mitigation are essential components of the SMASH-HCM project, given its interdisciplinary nature and reliance on cutting-edge technologies, multi-sectoral collaboration, and coordination across diverse partners. Both technical and management risks—along with their corresponding mitigation strategies—have been identified, discussed and documented at key time points (project launch, General Assembly on 27.9.2024 and presently) while remaining under continuous review throughout the project lifecycle.

By systematically monitoring risks, the SMASH-HCM consortium ensures a proactive response to emerging challenges, safeguarding the timely and effective implementation of project activities. This structured approach also reinforces consortium's commitment to maintaining high standards of quality, transparency, and accountability in both research outputs and project management.

The risks are grouped under corresponding Work Packages (WP). While a risk may be related to several WPs, they are only listed once under the first WP to which it corresponds. For each risk, this report outlines the current state of play, evaluates whether it has materialised, and describes any mitigation actions taken—based on information concurrently submitted to the EU Funding & Tenders Portal. The report thus serves both as a formal checkpoint and a tool for continuous improvement and alignment with project goals.

2 Work Package 1 risks: State of the play at month 18

Risk#, Risk Description	1. Default or withdrawal of partner	WP1
Likelihood / Severity	Low likelihood/High severity	
Proposed risk mitigation measures	The consortium has been assembled so backup is possible in most areas. If needed, alternative partner(s) may be recruited.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	None of the partners defaulted or withdrew from the consortium, hence no need to add new partner for that reason. The assembly of the consortium has remained such as back-up arrangements can be made if needed.	

Additional information: None of the partners defaulted or withdrew from the consortium during the first 18 months of the project. One partner was added, but not as a back-up, but additional resource followed by successful HORIZON-WIDERA-2023-ACCESS-06 “Hop-On” funding decision.

3 Work Package 2 risks: State of the play at month 18

Risk#, Risk Description	2. Data transfer delays due to ethics challenges	WP2
Likelihood / Severity	(Medium likelihood/High severity)	
Proposed risk mitigation measures	Involve ethics advisory board early and then annually to review and advise on emerging issues; use anonymized de-identified data if possible.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	YES	
Comments	There have been some data transfer delays, mainly due to legal delays, but they have been addressed with prompt action including meetings of legal teams, developing the of data storage, access and transfer mechanisms prior the data was available. The Ethics Advisory Board has convened, too. We assess that the delays have not caused serious harm on the project nor its deliverable and milestone timetables. The Data Transfer Agreement is in place now.	

Additional information: N/A

Risk#, Risk Description	3. Failure to fulfil data transfer commitments	WP2
Likelihood / Severity	(Low likelihood/High severity)	
Proposed risk mitigation measures	Outline responsibilities and deadlines, monitor progress, and proactively communicate with institutional signatories to address problems early.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	NO	
Comments	While all partners have been able to fulfil the key data transfer commitments, additional CMR imaging data was requested, which is still undergoing collection at site. Other data mentioned in the original project plan (e.g. Echocardiograms) were deemed unusable, or had a technical or ethical barriers to transfer and have been removed from the data transfer process upon discussion with all partners.	

Additional information:

Risk#, Risk Description	4. Delays in annotating patient CMR data	WP2
Likelihood / Severity	(Low likelihood/High severity)	
Proposed risk mitigation measures	Allocate budgets/resources for dedicated radiologist/cardiologist panel; use annotation tools; prioritize the most clinically relevant samples.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	YES	
Comments	We are in negotiating phase with a company with state-of-the-art CRM annotation tool that will speed up the annotation process and provide more comprehensive biomarker space of cardiac function than originally planned.	

Additional information: Delays in CMR annotation materialized due to negotiation and licensing of appropriate annotation tools, as well as various technical challenges. We have a draft Collaborator Agreement between UCD and MEDIS for acquiring a licence to use MEDIS software for CMR annotation. This is currently (6/2025) under review by UCD legal.

4 Work Package 3 risks: State of the play at month 18

Risk#, Risk Description	5. iPSC multiline culture exceeds resources	WP3
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	TAU, UNIFI, UKE send frozen iPSC-CMs for recovery as single cells or EHTs after rapid thawing post-differentiation; optimize protocols.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	NO	
Comments	We plan to extend WP3 also to 4 th year to have the time to fully characterize the selected HCM mutation lines. No additional budgetary resources are needed.	

Additional information: At the time of this report, we have just received approval from the Project Officer and from the SMASH General Assembly to extend the WP3 with additional 12 months.

5 Work Package 4 risks: State of the play at month 18

Risk#, Risk Description	6 Insufficient data availability for modeling and validation	WP4
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Use rich data/samples available to partners; access data from existing and new collaborations; use data-/parameter-efficient methods that need less data (evidence priors, transfer learning); collect or synthesize new data.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	YES	
Comments	Delays in MTAs have led to delayed availability of data, however we have used data from existing collaborations with project partners. Also new mitigation measures have been identified: using surrogate data from our state of the art in-silico simulations, or access of data from other projects are also on negotiation phase as additional data source	

Additional information: N/A

Risk#, Risk Description	7 Computational models omit physiological responses in the experimental data	WP4
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Use populations of models to explore physiological responses; recalibrate or reformulate underlying models to correct inaccuracies or mismatches with experiments; engage with other experts in physiological data modeling to include additional data. (Strong consortium expertise).	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	NO	
Comments	We have developed as part of D5.1 a software platform to facilitate efficient population of models' development.	

Additional information: N/A

Risk#, Risk Description	8 Model predictions of drug action do not match experimental observations	WP4
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Use established drug action models conforming with pharma data; correct possible mismatches by recalibration of underlying electromechanical models or alternative drug models; engage with other experts to get additional data. (Strong consortium expertise in drug action modeling).	

Risk State of Play: Did you apply risk mitigation measures?	YES
Did your risk materialise?	NO
Comments	This risk might emerge later the in the project. However, it is mitigated already by including new partner NovaMechanics which has excellent track record on molecular level drug simulations.

Additional information: N/A

6 Work Package 5 risks: State of the play at month 18

Risk#, Risk Description	10 Insufficient genotype and drug effect data on smooth muscle responses preventing accurate simulation	WP5
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Use estimates from CM electromechanical machinery in smooth muscle cell POMs for HCM effect estimation; simulate system-level drug effect by modifying systemic mechanisms (e.g. decreasing parasympathetic tone for simulating beta-blockers); explore alternative data sources.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	Not applicable at the moment; the risk may materialise later in the project.	

Additional information: N/A

Risk#, Risk Description	11 Unsuccessful translation of information from vascular cell level phenomena to tissue and system level	WP5
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Ensure transition via tissue-level contractions for vessel compliance and sympathetic drive at systemic level; use phenomenological effects to improve vascular resistance modeling; conduct additional experimental studies; consider further robust computational modeling techniques.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	NO	
Comments	Models of systemic and vessel/cellular level are done by different partners. We have already first joint papers appearing at IEEE/EMBS conference July 2025, and in 2025 summer a three-month researcher exchange is planned from UNIVREN to TAU to ensure smooth and intense collaboration on this topic.	

Additional information: N/A

Risk#, Risk Description	12 Integrated multiorgan model fails to represent clinical HCM phenotypes	WP5
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Use sensitivity analysis to generate different types of BP responses to exercise by integrating interactions between circulatory, cardiac, nervous systems; refine models using additional experiments and simulations.	

Risk State of Play: Did you apply risk mitigation measures?	YES
Did your risk materialise?	NO
Comments	Not applicable at the moment. However, new clinical series with selected HCM patients undergoing also exercise is planned at Rennes Hospital to facilitate deeper model parameter specifications and is starting in autumn 2025.

Additional information: N/A

7 Work Package 6 risks: State of the play at month 18

Risk#, Risk Description	9 Lower accuracy than state-of-art HCM patient profiling or standard	WP6,7
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Mitigate using multilayer AI stratification combining various biomarkers and published evidence; include state-of-the-art predictions as priors or features in AI/ML models; collect/synthesize data for complex cases.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	Not applicable at the moment	

Additional information: N/A

Risk#, Risk Description	13 Available patient data is too noisy to train robust AI models	WP6
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Use synthetic data generated by in silico models for training AI/ML models; preprocess data to reduce noise; adopt data-efficient models; incorporate evidence-based models generated from literature as priors or in transfer learning; consider Bayesian models to handle data uncertainty.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	Not applicable at the moment	

Additional information: N/A

Risk#, Risk Description	14 End-users (professionals, patients) have low trust in AI-based stratification and decision support tools	WP6,7
Likelihood / Severity	Medium likelihood/Low severity	
Proposed risk mitigation measures	Involve end-users in the development from the very start and integrate user feedback; rigorously validate in diverse datasets and in real-world testing; use interpretable methods and XAI for transparent explanations; use tailored interfaces and explanations for different end-users; follow GMLP and guidelines for responsible AI development and monitoring.	
Risk State of Play: Did you apply risk mitigation measures?	NO	

Did your risk materialise?	NO
Comments	Not applicable at the moment

Additional information: N/A

8 Work Package 7 risks: State of the play at month 18

Risk#, Risk Description	15 Decision support solution too complex to be used in clinical practice	WP7,8
Likelihood / Severity	Low likelihood/Medium severity	
Proposed risk mitigation measures	Involve end-users and integrate requirements for clinical meaningfulness, understandability, usability throughout; simplify the interfaces; offer training; implement refinements based on usability study; monitor use.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	NO	
Comments	Not applicable at the moment, however, several meetings with clinicians and patient organizations have been conducted to gather data on the needs and possibilities for the solution. These “functional requirements” are presented in deliverables D7.1 and D7.2.	

Additional information: This risk can only materialise once the support solution is complete.

D7.1 Requirements SMASH-HCM solution in clinical practice - initial

D7.2 = Requirements for disease patients self-management

9 Work Package 8 risks: State of the play at month 18

Risk#, Risk Description	16 Industries may be vulnerable to economic fluctuations due to funding pressures and investor obligations	WP8,1
Likelihood / Severity	Medium likelihood/Low severity	
Proposed risk mitigation measures	Ensure that the CA outlines the financial responsibilities; use staged payments aligning to milestones (already in place); maintain regular communications to address financial concerns; work collaboratively on contingency plans to address potential disruption.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	NO	
Comments	Not applicable at the moment	

Additional information: N/A

Risk#, Risk Description	17 At the end of the project, we may not achieve high accuracy from an algorithm standpoint. In addition, we may not get solid enough clinical evidence from an efficacy standpoint.	WP8
Likelihood / Severity	Medium likelihood/Medium severity	
Proposed risk mitigation measures	Define an MVP with diverse levels of accuracy that would be minimally acceptable for a basic clinical application by physicians in clinical practice and for commercialization at secondary research and development markets.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	Not applicable at the moment	

Additional information: This risk can materialise at the end of the project.

Risk#, Risk Description	18 The approach may not be cost-effective, so we would not be able to commercialize the solution as there would be no reimbursement.	WP8
Likelihood / Severity	Medium likelihood/Medium severity	
Proposed risk mitigation measures	Arrange advisory boards with health insurance providers and other payers to determine evidence requirements (i.e. guideline recommendation levels) to identify current or define new reimbursement codes. Pursue commercialization in secondary R&D markets.	

Risk State of Play: Did you apply risk mitigation measures?	NO
Did your risk materialise?	NO
Comments	Not applicable at the moment

Additional information: This risk can materialise at the end of the project.

10 Work Package 10 risks: State of the play at month 18

Risk#, Risk Description	19 Failure to identify effective drug candidates for repurposing	WP10
Likelihood / Severity	Medium likelihood/High severity	
Proposed risk mitigation measures	1. Pre-analysis to ensure data and algorithm quality. 2. Mid-term review to assess and adjust approach. 3. Implement a backup analysis pipeline.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	The WP lead Novamechanics has just been added to the consortium and the respective WP10 has just started.	

Additional information: N/A

Risk#, Risk Description	21 Unforeseen data inconsistencies or inaccuracies in real-world data (RWD) used for repurposing	WP10,11
Likelihood / Severity	Low likelihood/high severity	
Proposed risk mitigation measures	1. Enforce strict data validation and cleaning. 2. Cross-validate RWD with multiple sources. 3. Conduct regular audits to maintain data integrity.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	WP10 has just started.	

Additional information: N/A

11 Work Package 11 risks: State of the play at month 18

Risk#, Risk Description	20 Delays in integration of APIs and microservices into the Digital Twin DSS	WP11
Likelihood / Severity	Medium likelihood/Medium severity	
Proposed risk mitigation measures	1. Early collaboration with WP7 developers for API compatibility. 2. Regular checkpoints and testing. 3. Allocate extra resources for integration if delayed.	
Risk State of Play: Did you apply risk mitigation measures?	NO	
Did your risk materialise?	NO	
Comments	Not applicable at the moment.	

Additional information: N/A

12 Discussion on risks at General Assembly at Month 9

Discussion on potential risks in the current project phase was held as part of the SMASH-HCM General Assembly on 27.9.2024, as summarised below.

- Risk 2 (Data transfer delays) was discussed, Kathleen Curran informed that UCD now has the Data Transfer Agreement (DTA) from all partners. The coordinator continues to follow any emerging issues regarding this risk.
- Risk 6 (Insufficient data availability for modeling and validation) was discussed. Mitigation measures that are currently reported in Funding and Tenders Portal are: Use rich data/samples available to partners; access data from existing and new collaborations; use data-/parameter-efficient methods that need less data (evidence priors, transfer learning); collect or synthesize new data. New mitigation ideas emerged, e.g., Luca Mainardi identified an additional data source. Using surrogate data, or data from other projects were also suggested as additional data source. If this risk materialises, coordinator can update the mitigation section in the portal in reporting phase. Coordinator continues to follow any emerging issues regarding this risk.
- A new risk was identified, inadequate continuation of exploitation on results (tools, methods) after project end. Mitigation: beginning to involve companies before the project end. This is embedded at least partially in some WPs (e.g. WP9). Other suggestions: initial clinical trial to convince the companies, applying other EU funding for commercialising results, considering requirements that companies might have already now in the developing phase. The Coordinator can update this risk on to the portal in reporting phase.

This will be added as Unforeseen Risk

Risk#, Risk Description	22 inadequate continuation of exploitation on results (tools, methods) after the project end	WP9
Likelihood / Severity	Medium likelihood/Low severity	
Proposed risk mitigation measures	Beginning to involve companies before the project end.	
Risk State of Play: Did you apply risk mitigation measures?	YES	
Did your risk materialise?	NO	
Comments	Collaborations with InSilico Trials have potential to exploit the project outcomes, models and tools beyond the integrated SMASH-HCM approach. Monitoring measures are planned to identify such outcomes.	

13 Conclusions

At Month 18, SMASH-HCM has demonstrated strong and proactive risk management across its technical and administrative activities. Out of 22 identified risks, 3 have materialised and were effectively addressed through timely mitigation measures. The addition of 3 new risks, as well as one unforeseen risk identified during the General Assembly, highlights the consortium's commitment to continuous monitoring and responsiveness.

The structured and ongoing assessment of risks—conducted at key project milestones and in coordination with updates to the EU Funding & Tenders Portal—ensures that the project remains on track, maintains high quality standards, and is prepared to manage emerging challenges. Risk management will continue to be an integral part of project governance, supporting the successful and timely delivery of SMASH-HCM's objectives.