# DELIVERABLE

Project Acronym: **SMASH-HCM**

Grant Agreement number: **101137115**

Project Title: **Stratification, Management, and Guidance of Hypertrophic Cardiomyopathy Patients using Hybrid Digital Twin Solutions**

## D8.5 – PILOT Submission Package

Revision: 1.0.


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| Dissemination Level | | |
| PU | Public, fully open | X |
| CO | Confidential, restricted under conditions set out in Model Grant Agreement | |
| CI | Classified, information as referred to in Commission Decision 2001/844/EC | |

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

**Revision History**

| Revision | Date | Author | Organisation | Description |
|---|---|---|---|---|
| 0.1 | 16.6.25 | AK | TAU | Initial version |
| 0.2 | 18.6.25 | KAS | TAU | Included missing details |
| 0.3 | 19.6.25 | AK | TAU | Revisions |
| 0.4 | 20.6.25 | FB | UNIFI | Review, details added on hospital |
| 1.0 | 26.6.25 | AK | TAU | Final version |

| Date of delivery | Contractual: | 30.06.2025 | Actual: | 29.6.2025 |
|---|---|---|---|---|
| Status | Final ☒ / draft ☐ | | | |

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| Abstract (for dissemination) | PILOT is an open, uncontrolled study designed to test the software developed by the SMASH-HCM project. Individuals with stable HCM during the 5-10 year follow-up period will be compared to those reaching a particular composite endpoint during this time, to see whether the software can predict from the initial information the progress of the disease. This deliverable, D8.4, "PILOT Submission Package" documents the key aspects of the PILOT study, including the inclusion and exclusion criteria for the participants, and the collected data variables. The retrospective PILOT will inform future, prospective studies in HCM cohorts. |
| Keywords | Hypertrophic Cardiomyopathy; Decision Support System; Digital Twin |

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This deliverable contains original unpublished work except where clearly indicated otherwise.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

**Table of Content**



Abbreviations:

| | |
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| AI | Artificial Intelligence |
| DSS | Decision Support Solution |
| HCM | Hypertrophic Cardiomyopathy |
| ML | Machine Learning |
| MRI | Magnetic Resonance Imaging |
| NYHA | New York Heart Association functional class |
| TIA | Transient Ischemic Attack |
| VUS | Variant of Uncertain Significance |

# Executive Summary

SMASH-HCM is conducting research and developing innovative technologies to improve the stratification and disease management of patients with hypertrophic cardiomyopathy (HCM). The SMASH-HCM PILOT study is an open, retrospective, uncontrolled study designed to validate the decision support software developed within the project. It compares patients with stable HCM over 5-10 years to those reaching a particular composite endpoint during this time assessing whether the software can accurately predict disease progression from initial clinical data. PILOT will inform the feasibility and clinical value of the SMASH-HCM solution, setting the stage for future large-scale, prospective evaluations.

# 1 Introduction

The purpose of SMASH-HCM (https://smash-hcm.eu/) is to develop a human digital-twin-based platform to dramatically improve HCM stratification and disease management, both for clinicians and patients. SMASH-HCM combines clinical research, cardiology, radiology, cell biology, -omics tools, biophysical computational modelling, artificial intelligence (AI) and machine learning (ML), biomedical signal and image processing, clinical decision support software development, innovation management, and social sciences to address unmet clinical, societal and psychological needs. The results of the project - new insights into HCM, improved patient care and guidance, validated preclinical tools, and above all, a first HCM stratification and management strategy are validated in a PILOT clinical study. In other words, the PILOT will demonstrate whether the decision support solution (DSS) enhances patient stratification for improved prognosis and treatment of HCM.

PILOT will be carried out as specified in Task 8.6. of the SMASH-HCM Grant Agreement "Pilot clinical study (PILOT) of the DSS software" (M6-M48). Ethical approval for the PILOT study has been amended for the SMASH-HCM ethical approval. The PILOT will be conducted according to the ISO 14155 requirements for CE marking and future validation, regulation, and commercial strategy. Following the protocol specification in T8.7, a selected component of the DSS will be evaluated for a set of recruited patients from SMASH-HCM participant hospitals with known genetic and /or clinical phenotypes, and a few with hypertrophy due to severe training to distinguish benign hypertrophy from the diseased condition. The selection of primary, secondary, and exploratory endpoints will be guided by Task 8.7, also taking into consideration usability and clinical acceptability. The PILOT will include a social science component aimed at evaluating, through surveys and interviews, the empowerment capability and acceptance of the technology by patients and their caregivers. The results of PILOT will inform future large-scale multi-centre prospective evaluations outside the SMASH-HCM and set the basis to outline plans for a larger clinical study with an increased number of involved stakeholders.

The progress towards completing PILOT is documented in deliverables D8.5, D8.7, D8.10 and D8.12, the current report being the first (Figure 1).

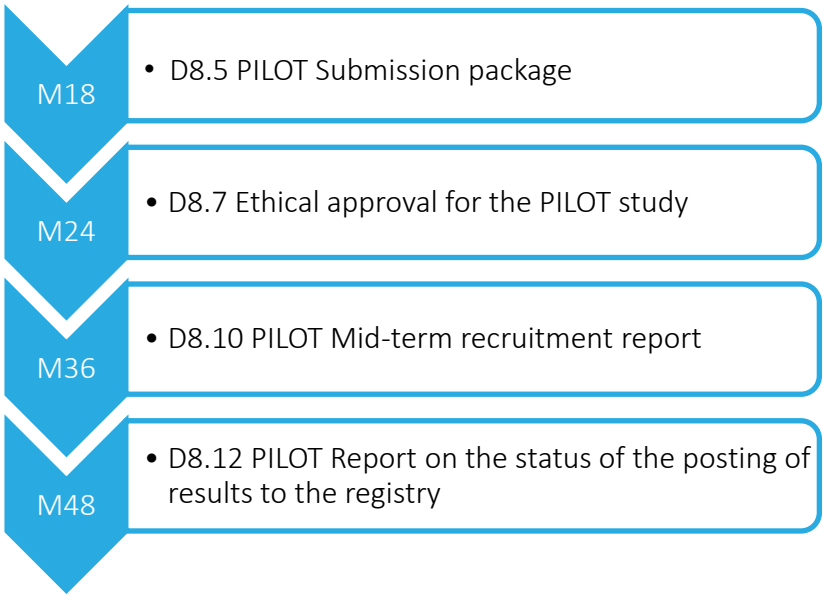


Figure 1. The progress towards competing the PILOT, documented in deliverables, from month 18 to 48.

# 2 SMASH-HCM PILOT study

PILOT is an open, retrospective, uncontrolled study designed to test the software developed in the SMASH-HCM project. Individuals with stable HCM during the 5-10 year follow-up period will be compared to those reaching the composite endpoint (as described above) during this time, to see whether the software can predict from the initial information the progress of the disease. Clinical data to be included in PILOT study will not be used to develop the SMASH-HCM algorithms and models, but will serve as validation.

## 2.1 Participants

The patients to be included are:

- 200 HCM adult patients with more than 20-year follow-up data from Azienda Ospedaliero-Universitaria Careggi, Florence
- 20 HCM patients from Finland, with at least 5-year follow-up data and preferentially carrying one of the founder mutations in Finland (MYBPC3-Gln1061X, TPM1-Asp175Asn or JPH2-Thr161Lys).
- 200 HCM consecutive patients From Rennes either comprising individuals with a known gene mutation and those without a known mutation but with a minimum of five years of follow-up data

Patients with phenocopies such as hypertensive heart disease, Fabry disease or amyloidosis will be excluded. A balanced sex representation is expected.

## 2.2 Data

The data to be included from these patients into the PILOT will consist of the following variables, recorded as many times as they are available in the patients' medical record. No new clinical data will be generated for the SMASH-HCM study; all required information will be obtained from existing patient records with patients' consent.

- ECG
- cardiac ultrasound
- Biomarkers – TnT and proBNP
- 24 Holter recordings
- Stress excersice tests
- Magnetic Resonance Imaging (MRI)
- Medication – Originally and the latest, and the time when medication affecting blood pressure or cardiac function is added
- Other diseases – especially the time when the following diseases are diagnosed: hypertension, valvular diseases, stroke or Transient Ischemic Attack (TIA), atrial fibrillation, heart failure, ventricular arrhythmias
- Type of gene mutation causing HCM – also Variant of Uncertain Significance (VUS) to be reported
- clinical data – New York Heart Association functional class (NYHA), palpitations, murmurs, blood pressure, swellings – originally and the latest, but also if and when something changed

- hospitalizations – when and the reason.

## 2.3 Ethical Considerations

Patients will be assigned unique codes, and their data will be provided in a pseudonymised format, ensuring that individuals cannot be directly identified. The ethical approval for this pilot study was obtained from the Wellbeing Services County of Pirkanmaa (PIRHA) Ethical committee (R24032L). All participants have signed the consent form.

All these clinical data will be stored in the manner, and according to same principles, as the other data used in SMASH-HCM. The data will be made accessible to the relevant researchers within the SMASH-HCM Consortium, who have the need for access to the data to carry out the research as set out in the Grant Agreement, as indicated by the Data Transfer Agreements.

# 3 Conclusions

In conclusion, the SMASH-HCM PILOT study serves as a critical first step in validating the digital decision support solution for improved stratification and management of HCM. By utilising real-world clinical data, the study will assess the clinical effectiveness laying the groundwork for broader implementation and future large-scale clinical evaluations.