DELIVERABLE

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

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

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Abstract (for dissemination)	This deliverable presents areas of clinical challenge, elicited through a series of engagement meetings to explore the aspects of diagnosis, stratification, care planning and monitoring of HCM patients that respond to clinical needs; challenges that clinicians face for which SMASH-HCM advanced digital solutions could help improve their decision-making accuracy. The heart of this deliverable presents the consensus areas of clinical challenge identified by HCM clinicians. These highlight diagnostic certainty dilemmas in athletes, the extent to which monitoring burdens should be imposed on asymptomatic patients, how non-HCM clinicians can determine when to refer a patient to an HCM specialist, the added complexity of making a diagnosis in patients with hypertension, risk stratification particularly for arrhythmias, which lifestyle changes can impact risk, the role of routine (digital) monitoring in early detection of deterioration and complications, and how quality of life including unmet needs may best be assessed. For each of these areas, the challenge is described followed by a list of functional

	requirements, and a high-level initial response from the software and decision support engineers.
Keywords	Decision support, machine learning, diagnostic certainty, risk stratification, monitoring

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This deliverable contains original unpublished work except where clearly indicated otherwise.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

HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter defibrillator
ECG	electrocardiogram
EHR	electronic health record
MRI	magnetic resonance imaging
AI	artificial intelligence
ML	machine learning
QoL	quality of life
PROM	patient reported outcome measure

Executive Summary

SMASH-HCM is conducting research and developing innovative technologies to improve the stratification and disease management of patients with hypertrophic cardiomyopathy. It will deliver digital-twin driven deep phenotyping and risk stratification tools to support clinical workflows and decision making, including new forms of guidance in the form of computer-based clinical decision support, enabling more personalised treatment and patient self-management.

SMASH-HCM needs to target decision support developments on aspects of diagnosis, stratification, care planning and monitoring that respond to clinical needs, i.e., challenges that clinicians face for which advanced digital solutions could help improve their decision-making accuracy and confidence.

This deliverable presents these areas of clinical challenge, elicited through a series of engagement meetings during the spring of 2024 with clinician experts in hypertrophic cardiomyopathy (HCM) from three different countries. The scope of this work is introduced in Section 1. The methodology for engaging with the clinicians is explained in Section 2. Section 3 outlines the care pathway points that were discussed with the clinicians, as the possible areas in which they may experience challenges.

Section 4 presents the consensus areas of clinical challenge they identified. These highlight diagnostic certainty dilemmas in athletes, the extent to which monitoring burdens should be imposed on asymptomatic patients, how non-HCM clinicians can determine when to refer a patient to an HCM specialist, the added complexity of making a diagnosis in patients with hypertension, risk stratification particularly for arrhythmias, which lifestyle changes can have an impact on risk, the role of routine (digital) monitoring in early detection of deterioration and complications, and how quality of life and unmet needs may best be assessed. For each of these areas, the challenge is described followed by a list of functional requirements.

This deliverable is a companion to SMASH-HCM Deliverable 7.2, which presents functional requirements obtained from patient organisations for a patient platform in HCM.

The software engineers in the project will utilise both deliverables to design digital tools for clinician and patient use, through iterative cycles of consultation with end user representatives, which may therefore evolve the requirements presented here. Their initial response to these requirements is presented in Section 5, and next steps are reported in Section 6.

1 Introduction

SMASH-HCM (https://smash-hcm.eu/) will 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 and substantial societal and psychological needs. It will deliver human digital twin driven deep phenotyping and risk stratification tools to support clinical workflows and decision making with a cost-effective solution, enabling the development of effective personalised treatment and patient self-management.

In addition to conducting new research, the project aims to provide new forms of guidance to clinicians, to pilot and test in the project, in the form of computer-based clinical decision support. It also aims to provide patients with personalised guidance on topics such as lifestyle and exercise, and to provide the option to collect monitoring data from them, e.g. via a platform that could be implemented as an online portal, an app, and/or wearable technologies.

This document summarises a series of engagement meetings during the spring of 2024 with clinician experts in hypertrophic cardiomyopathy (HCM) from three different countries. These meetings have sought to identify from HCM specialists the areas of diagnosis, stratification, personalisation and prediction that are challenging today even for experts, as possible areas that the modelling approaches and data analytics might help address – a clinical "wish list" for the more technical teams to focus on. These might be considered as decision-making dilemmas, situations where the published evidence or guidelines plus the patient-specific information in the hands of the clinician do not enable a precise enough or confident enough decision to be made. The clinician needs to balance an imprecise prediction of risks with the disruption a diagnosis or intensive/invasive treatment might cause, and arrive at a joint decision with the patient about the optimal decision to take if there is some uncertainty. The initial goal is to identify and prioritise the care pathway points (clinical use cases) where existing knowledge could be better leveraged through advanced advisory systems.

This clinical wish list is formalised in this deliverable as functional requirements.

In reality, the development of the decision support solution will be iterative and interactive, with further clinical input and pilot testing during the four-year project. The tool may be limited to areas in which new insights are possible to obtain based on the available data. The research team do not yet know the extent to which they will be able to discover precise-enough combinations of biomarkers to achieve sufficiently accurate stratifications and predictions for each of the wish list areas, as this is part of the research. Additionally, current guidelines focus more on arrhythmias and sudden cardiac death associated with HCM, but the risk of heart failure is also present. This deliverable will therefore serve as the starting point for this iterative process.

A parallel engagement with patient organisations is helping to identify a patient "wish list" for a patient facing platform that HCM patients would find useful. Some of this will be about information patients wish to have about their health and about HCM, and some functions will enable the collection of data that clinicians will also find useful. This is being published as the same time as Deliverable 7.2: Requirements for disease patients self-management.

1.1 Scoping the clinical problem

It should be recognised that the clinical management of HCM at present does not significantly alter the clinical history of the disease, as nothing is sufficiently validated for this. Studies have shown that many commonly employed drugs, for example ACE inhibitors, may be able to reduce the early progression of disease from presymptomatic to symptomatic or pre-hypertrophic to the hypertrophic phenotype, which might selectively be used for patients with particular risk profiles. This is an active area of research where many current or forthcoming drugs have been shown to have a possible effect in a non-obstructive patient to reduce, for example, circulating cardiac troponin I (TNI), indicating that it might be possible in the future to reduce disease progression.

Clinicians are currently lacking a tool that predicts a general score and helps them to stage the disease, rather than predicting the risk of arrythmias, i.e. a tool that can assess certain patient features to tell clinicians where the patient is and whether they are in the initial or an advanced stage of the disease. This tool needs to go beyond a clinical assessment during the intermediate steps, to advise if a patient has certain features to suggest an adverse clinical course in terms of disease progression, not solely in terms of arrythmia risk. They need to be able to have a comprehensive, synoptic view of the stage of the patient's disease which would otherwise only be obtained through biomarker analysis, MRI scans or other symptomatic analysis.

In general cardiology practice, the stage of disease is often unappreciated and neglected, which can lead to late referrals for transplants. Many patients with cardiomyopathies are referred late because their systolic function is preserved, and clinicians are more accustomed to the classic model of heart failure. It would therefore be useful to be able to reassess the patient stage, especially if a physician lacks experience. Such a tool could be multi-purpose or disease specific, allowing for periodic reassessment. Such solutions already exist for other diseases which involve staging over time. HCM is a slowly evolving disease where decision making is slow and staging can be helpful, unlike myocardial infarctions where everything happens much quicker.

A multi-parametric assessment of the patient would be valuable, in terms of quality of life, sleep, exercise, performance, and side effects of drugs. This might include measurements like pulmonary pressure or systolic parameters.

2 Methodology

The first part of the methodology to develop the functional requirements was through interviews with clinicians who are experts in HCM and members of the three project pilot sites. A total of five clinicians were interviewed, clustered on a site level:

- 08.04.2024 Florence, Italy
- 24.04.2024 Tampere, Finland
- 14.05.2024 Rennes, France

Three separate rounds of interviews were held to ensure that interviewees would start from a green field and not influence each other in the first discussion rounds. The interviews were structured using the following outline:

- Presentation of the SMASH-HCM project overview
- Description of the method for the session
- Presentation of a checklist of possible care pathway steps to trigger the discussion
- Open discussion

Typically, a session lasted approximately 75 minutes. Technical partners and the project coordinator were attending the call in an observing role.

Having understood the purpose and scope of the project, the clinicians were presented with a list of the possible steps in a patient's care pathway for which new decision support tools could potentially be useful, and that could serve as the Wish List from the clinical side, for the biomedical engineers, data scientists, and software developers to consider. This list of care pathway steps is given in the next section.

Each meeting was recorded and detailed meeting minutes were transcribed, with the most important outputs informing this deliverable and its functional requirements being the decision-making challenges that HCM clinicians face. The reasons for why each decision is difficult were explored during the discussions, and the possible contributions of a decision support tool to improve accuracy and confidence in those decisions were further detailed.

The consolidated meeting notes from the three sessions were shared back with all participants to correct misunderstandings and ambiguities and to incorporate any additional afterthoughts.

This deliverable summarises those discussions and clinical challenges under themes, relating to, but not precisely mapping to the steps in the care pathway that framed those discussions. For each theme, the functional requirements for a decision support tool, including its user interaction behaviour and connection to the electronic health record, system are enumerated. Each table of functional requirements lists them in clinical workflow order. There is substantial overlap of the functional requirements across the different themes. To support their adoption by the technical research and development teams, the requirements have been repeated where appropriate so that each table of functional requirements is complete. Repeated requirement statements re-use the same statement numbers.

In some cases, the evidence base is considered insufficient, even when allowing for the possible contribution of advanced modelling and machine learning, to provide a trustworthy decision support tool for clinical use. In those cases, a research objective is instead proposed for SMASH-HCM to consider investigating. The outcomes of that research would need further validation before being considered reliable enough for clinical decision support.

The final step in the methodology was to present these clinical challenges and proposed functional requirements to the decision support implementation team, for their initial response as to feasibility.

Their responses are included as a separate section in this deliverable, so as not to interfere with the clinician driven requirements.

The final section of this deliverable explains how the content will subsequently be used by the technical research and development partners who will work on the decision support system, after which an updated version of these functional requirements reflecting what has proved realistic to implement will be created.

3 Steps in the care pathway for which decision support may be useful

Patient journey care points and goals that might be in scope for a SMASH-HCM decision support tool, and were the subject of the clinical engagement discussions:

- Improved diagnostic accuracy
- Improved initial risk stratification
    - -> more personalised care plans
    - -> more personalised lifestyle guidance
    - -> identifying patients' needs and priorities: agree unmet needs and goals, how would a patient weigh up risks, capability to perform activities, side effects, longevity
    - -> need for counselling including familial counselling
- Targeted (personalised) therapies
- Prognostic options (assessing the risks of adverse outcomes)
- Better predicting the patients who will benefit from an implantable cardioverter-defibrillator
- Monitoring disease progression in a formalised way, including PROMs and side effects of drugs, enabling more effective disease management

During the discussions, additional areas were added to this list:

- Distinguishing between HCM and athlete's heart, as athletes often have physiological hypertrophy that can complicate diagnosis.
- Challenges in interpreting ECG - changes in athletes' ECG can be variable and may not always indicate pathological hypertrophy.
- The importance of considering differential diagnoses, such as inherited metabolic disorders, when evaluating patients with left ventricular hypertrophy.
- Another important diagnostic challenge in every day practice is to distinguishes HCM from Hypertensive Heart Disease which is sometimes particularly complicated as HCM patients often also suffer from hypertension (prevalence 35 to 50%), which could be an external factor in the development of the disease in addition to a genetic risk background.

4 Thematic organisation of the functional requirements

This section presents the clinical challenges prioritised by the interviewed clinicians as being the most important areas for which they would appreciate better (more specific) clinical guidance in diagnosis, risk stratification, the decision about whether to treat, how and how invasively, and which risks to proactively manage. For each sub-section, which highlights a specific challenge, the clinical difficulty is first described followed by a list of functional requirements for a decision support tool, should its development prove possible. A few areas highlighted by the clinicians need further research first, so requirements functional requirements for these are not provided.

4.1 Diagnosis in athletes

Discussion of the clinical challenge

Athletes present a diagnostic challenge, as normal heart wall thickening can sometimes be hard to differentiate from HCM. These are normally young and otherwise healthily people who want to continue with sports (e.g., they might be competitive athlete, perhaps intending a sporting career). If the diagnosis is not HCM, the hypertrophy might be reversible if they reduce sporting activities to some extent. Clinicians have to be careful not to make the wrong diagnosis. They need the best evidence they can obtain evidence of the benefit/harm ratio for lifestyle change (e.g. when should they give the advice to "stop competitive sports").

ECG changes are difficult to disentangle between (a small number of) vigorous athletes and HCM. It is therefore not easy to make a definitive diagnosis, or to determine if those who manifest ECG changes belong in a different risk group for the future. Additional value is therefore possible from ECG analysis to inform prognosis, via AI support. This might provide new models and AI based tools to provide a better insight on top of the standard evaluation of 12- or 24-hours ECG that patients will undergo.

There is a dilemma in advising asymptomatic HCM patients on lifestyle, as restricting physical activity may lead to circulatory problems, while excessive exercise may worsen hypertrophy and disease progression. Clinicians find it hard to give the "right" advice to such patients. There is an important risk that less experienced cardiologists will wrongly advise a patient to stop sports. A decision support tool could help to quantify the risk that a person who is an athlete with cardiac muscle hypertrophy does in fact have HCM.

Clinicians also have concerns about arrhythmia risk – this is hard to predict, so patients are hard to risk stratify. Clinicians find it difficult to accurately determine if and when to insert an ICD, even though there are algorithms in clinical guidelines, but the grey zone is broad. This difficulty to choose the right patient for ICD is not specific for athletes with HCM but this population is often young and the psychosocial consequences of the implantation of this device are probably worst especially since they can (rarely but it happens) experience inappropriate shocks by the device. A decision support tool could possibly help to reassure in cases where an ICD is not needed.

Clinical requirements for a decision support module
Utilise the history, examination findings and the results of investigations in order to quantify (ideally as a statistical probability) • that the patient has a diagnosis, or is at high risk of developing, HCM • that the patient will develop an arrhythmia in the future

Functional requirements for a DS module that can support diagnostic certainty in athletes	
1	The SMASH-HCM clinical application shall require the clinician to identify the patient to focus on.

2	The decision support module shall run utilising EHR data specific to that patient.
3	It shall extract an agreed list of patient specific electronic health record data element values, including (as far as available): • genotypic sex • date of birth or age • recent height and weight • the presence of a family history of HCM • the presence or absence of an agreed list of symptoms with particular emphasis on symptoms suggesting an impaired cardiac output or occurrences of an arrhythmia • a formalised indication of the extent of sporting activity and its duration • the presence or absence of an agreed list of lifestyle risk factors such as smoking • the latest values from an agreed list of structured and coded physical examination findings • the genotype of the patient • structured and coded findings from recent investigations including ECG, echocardiogram, MRI and other imaging studies • whether the patient is currently taking any treatments • if the patient already has an implanted cardiac device.
4	If it is able to run successfully it shall present: • the likelihood of a diagnosis of HCM • the likelihood that the patient will develop an arrhythmia in the future without any new clinical intervention or risk factor changes.
5	This information shall be presented as numeric values or percentages, and as a graphical chart in which the individual risks can be seen against the background of the risk for a similar patient population (recognising that a limited number of background population risks will be available early in the project). Where AI has generated the risk information, the clinician should be able to determine which variables have contributed to the AI execution and find an explanation of how the findings were reached (explainable AI). The risk of each future adverse event could be represented in an integrated way that is easy on the eye, yet accurate, like with “Kiviat diagram” or radar plot.
6	If it is not able to run successfully because of an insufficient set of input data from the patient’s EHR, it shall offer a form to be completed by the clinician to provide the data item values that are necessary for algorithm execution, or a warning of a possible wide range of confidence in the advice, or for the clinician to cancel the execution.
7	If it is unable to provide any risk stratification relating to diagnosis or arrhythmia because the data values for this patient fall outside the parameters for which the DSS can calculate, an appropriate explanatory message shall be displayed to the clinician.
8	The clinician shall be able to annotate the presented risk stratification information with a personal free text comment which could be reasons to have limited confidence in the calculation or to indicate an interpretation of it.
9	The displayed information shall be capable of export from the DSS component so that it can be saved in the EHR system as computable data.
10	If that system is not capable of importing such data, possibly including its graphical presentation if this is offered, then it shall be possible for the clinician to generate a PDF report that could be saved in a correspondence section of the EHR.
11	The clinician shall be able to export a visualisation of the risk scores to the patient’s SMASH-HCM portal or app.
12	In the event that the patient acquires access to the SMASH-HCM portal or app at a later stage, clinician shall have the capability to export one or more historic risk calculation reports to the patients SMASH-HCM portal or app.
Notes:	

The precise details (data structures, code lists, value ranges) for the health data listed in statement 3 still need to be worked out between the clinical and decisions for teams in the project. It is not proposed, within this project, to respond to the clinician wish for decision support to provide guidance on whether an ICD should be fitted or is unlikely to be needed. This would take the solution towards being a medical device, which at this stage would be beyond the resources and expertise of the project.

4.2 Diagnosis and management of asymptomatic patients

Discussion of the clinical challenge

A referred patient or a family member might be carrying a mutation that is often associated with HCM but might not manifest any clinical features of HCM. They will need clinical review every 1-3 years in order to screen for the early presence of HCM. There is not usually any pharmaceutical treatment indicated, as a preventive drug hasn't been developed. Such patients might never manifest HCM, but it may still be appropriate to recommend some prevention-related lifestyle advice including guidance on exercise, whilst recognising that there is limited confidence that these lifestyle changes will prove necessary. Clinicians would like guidance on what lifestyle/exercise advice should be given to these asymptomatic patients.

It will be useful to explore the potential of wearable devices in stratifying risk and monitoring asymptomatic HCM patients for arrhythmias over extended periods. It would be valuable to have a better way to predict the likelihood and speed of a manifestation trajectory.

Newer early-stage drugs have side effects. Clinicians also need more evidence of the benefit/harm ratio for novel drug treatments.

It is also important to consider the impact of specific genetic mutations on the classification and management of asymptomatic HCM patients, as some mutations may be associated with higher risks of arrhythmias or sudden cardiac death.

Clinical requirements for a decision support module
Utilise the history, examination findings and the results of investigations in order to quantify (ideally as a quantitative probability) the occurrence of HCM within the next 1-3 years, and to highlight any modifiable risk factors in the patient that could be improved through the use of lifestyle advice and behavioural guidance.

Functional requirements for a DS module that can highlight the risk factors for a patient to develop HCM within the next 1-3 years	
1	The SMASH-HCM clinical application shall require the clinician to identify the patient to focus on.
2	The decision support module shall run utilising EHR data specific to that patient.
3	It shall extract an agreed list of patient specific electronic health record data element values, including (as far as available): • genotypic sex • date of birth or age • recent height and weight • the presence of a family history of HCM • the presence or absence of an agreed list of symptoms with particular emphasis on symptoms suggesting an impaired cardiac output or occurrences of an arrhythmia • a formalised indication of the extent of sporting activity and its duration

	• the presence or absence of an agreed list of lifestyle risk factors such as smoking • the latest values from an agreed list of structured and coded physical examination findings • the genotype of the patient • structured and coded findings from recent investigations including ECG, echocardiogram, MRI and other imaging studies • whether the patient is currently taking any treatments • if the patient already has an implanted cardiac device.
13	If it is able to run successfully it shall present: • the likelihood of a diagnosis of HCM within the next 1-3 years • the modifiable risk factors that contribute to this risk predication • a list of risk factor related health education advice topics that the clinician can select from.
5	This information shall be presented as numeric values or percentages, and as a graphical chart in which the individual risks can be seen against the background of the risk for a similar patient population (recognising that a limited number of background population risks will be available early in the project). Where AI has generated the risk information, the clinician should be able to determine which variables have contributed to the AI execution and find an explanation of how the findings were reached (explainable AI). The risk of each future adverse event could be represented in an integrated way that is easy on the eye, yet accurate, like with “Kiviat diagram” or radar plot.
14	The list of lifestyle educational advice topics shall be pre-presented as a checklist that the clinician can select from.
6	If it is not able to run successfully because of an insufficient set of input data from the patient’s EHR, it shall offer a form to be completed by the clinician to provide the data item values that are necessary for algorithm execution, or a warning of a possible wide range of confidence in the advice, or for the clinician to cancel the execution.
15	If it is unable to provide any risk prediction relating to diagnosis or arrhythmia because the data values for this patient fall outside the parameters for which the DS can calculate, an appropriate explanatory message shall be displayed to the clinician.
16	The clinician shall be able to annotate the presented risk prediction information with a personal free text comment which could be reasons to have limited confidence in the calculation or to indicate an interpretation of it.
17	The clinician’s choice of which educational topics to offer the patient shall be retained as part of the record of this DS interaction
9	The displayed information shall be capable of export from the DSS component so that it can be saved in the EHR system as computable data.
10	If that system is not capable of importing such data, possibly including its graphical presentation if this is offered, then it shall be possible for the clinician to generate a PDF report that could be saved in a correspondence section of the EHR.
18	The clinician shall be able to export a visualisation of the risk prediction to the patient’s SMASH-HCM portal or app.
19	The clinician shall be able to export the selected list of education topics, or a list of links to them, to the patient’s SMASH-HCM app or portal, and additionally have the option of printing the education topics in case the patient prefers a non-digital approach.
20	In the event that the patient acquires the SMASH-HCM portal or app at a later stage, clinician shall have the capability to export the complete set of education topics selected to date for that patient, to the patients SMASH-HCM portal or app.
Notes:	

It is recommended that education topics are exported as links to an online library of education resources for the patient, so that these resources can be maintained, and up to date versions be accessed, most easily. It is not proposed, within this project, to respond to the clinician wish for decision support to provide guidance on when to consider novel therapy treatments.

4.3 Referral guidance for non-HCM specialists

Discussion of the clinical challenge

ECG changes are often the trigger for referral from a GP or from a less experienced cardiologist to an HCM specialist. An echo or MRI will then be performed by the HCM specialist to rule in or rule out HCM, based on the extent of hypertrophy.

There is a need for guidance such as a referral algorithm for less experienced clinicians, in order to ensure that patients with early diagnosis or who are at risk are referred early, but without generating patient anxiety by referring patients who seem not to be at risk.

Clinical requirements for a decision support tool
Provide a referral screening tool that may be used by non-specialist clinicians to determine if a patient should be referred to an HCM specialist. It is not required that the execution of this tool requires connection to the EHR system of any primary care or non-specialist clinical user. It is not required that the outputs of this tool are included electronically within the content of a referral or directly saved within the EHR system of the user.

Functional requirements for a DS module that can highlight the risk factors for a patient to develop HCM within the next 1-3 years	
21	Any clinician with access to a web browser and Internet connection shall be able to launch a decision support tool that can provide guidance on whether a given patient should be referred or not to an HCM specialist.
22	The clinician shall be able to launch the tool and have access to a data entry form without requiring any identification, credentials or authentication.
23	After reading any initial guidance information, a clinician shall be able to easily navigate to a data entry screen in which patient specific information can be added.
24	The clinician shall be prompted to complete as much information as is available to them for the following areas of health information, in a structured format, all of which shall be optional fields: • patient's name • genotypic sex • date of birth or age • recent height and weight • the presence of a family history of HCM • the presence or absence of an agreed list of symptoms with particular emphasis on symptoms suggesting an impaired cardiac output or occurrences of an arrhythmia • a formalised indication of the extent of sporting activity and its duration • the presence or absence of an agreed list of lifestyle risk factors such as smoking • the latest values from an agreed list of structured and coded physical examination findings • the genotype of the patient

	• structured and coded findings from a recent ECG • structured and coded findings from a recent echocardiogram
25	The DSS shall present the predicted risk of a diagnosis or future risk of HCM as a simple recommendation to refer or not.
26	The clinician shall be able to execute the advisory algorithm, review the outputs, modify the health data information and re-execute the algorithm multiple times.
27	The clinician shall be able to print or save as a PDF a screen that shows the data entered and the recommendation, for their records or to share with the patient or to accompany.
28	The DSS shall retain no permanent record of the data entered after the user session has completed.
Notes: This tool is proposed as a stand-alone online tool that does not connect to the local EHR system of the user, does not require complete patient identification or retain a permanent copy of the information entered. This is for practical and data protection reasons.	

4.4 Family screening

Discussion of the clinical challenge

It is important for clinicians to check the cardiac status of family members: i.e., to check both the genotype and phenotype (because there can be variable gene expression).

Business requirements for a decision support module
There are no business or functional requirements for decision support related to this topic because there is no decision-making challenge to address.

4.5 Risk prediction for disease progression

Discussion of the clinical challenge

When patients have been diagnosed with HCM, either asymptomatic or with minimal symptoms, they are at risk of sudden complications that are difficult to predict, i.e. whether they will occur and when they might occur:

- arrhythmia
- sudden (cardiac) death
- obstructive hypertrophy leading to heart failure
- disease progression in non-obstructive patients leading to mechanical dysfunction and terminal heart failure

The risk of arrhythmia and cardiac death is in fact sudden and can occur in asymptomatic patients. The risk of heart failure is something more progressive with a progressive increase of symptoms until heart failure. This risk is increased in case of obstructive hypertrophy but can also occur in HCM without obstruction.

The anatomical distribution of the hypertrophy, assessed using a stress echocardiography, is an important predictor of obstruction. Patients with obstructive HCM will exhibit more symptoms: e.g. pain, shortness of breath, and generally experience a lower quality of life.

Current risk scores focus a lot on the risk of arrhythmia. However, the current evidence is not yet strong enough to show that a specific anatomical distribution of the hypertrophy is clearly associated with significant more risk of arrythmias, an aspect which requires further investigation. Better risk assessment methods are vitally needed for ventricular arrhythmia and (especially) sudden cardiac

death. This is challenging because sudden death is a rare event. The project might discover whether there is a proxy that can be used in clinical studies, such as non-sustained ventricular tachycardia. This proxy is already used in clinical studies but is not as strong as a sustained ventricular arrythmias or a sudden cardiac death event. It could be used if there is not enough of these last to run algorithms

There is a need for risk scores to position the patient more accurately on their disease progression trajectory, based on symptoms, laboratory biomarkers (level of NTproBNP), imaging biomarkers (left atrial disease, presence of pulmonary hypertension, extent of myocardial fibrosis etc.).

European guidelines estimate disease progression risk at 5 years while US guidelines profile risk factors. However, neither are very accurate, so many patients are in a "grey" zone of clinical guideline uncertainty, e.g., having a partial match to the criteria to have an ICD fitted may prove unnecessary for implanting an ICD in a young person, which can lead to complications, inappropriate shocking. More research is needed to formally assess the risk of arrhythmia and sudden death, so that ICDs are only fitted when they are needed. It might be possible to characterise this grey zone of patients via computable phenotypes (digital twins), potentially also as a method to use in future research.

Patients may spend some years relatively well – it is important for these patients to minimise iatrogenicity, to avoid unnecessary treatment side effects and excessive healthcare interventions. It can sometimes be possible to give patients reassurance that they are not in a high-risk situation and that their trajectory is slow, e.g., that they are able to do sports and do not need to take any special precautions. Could a decision support tool advise in which scenarios a patient is at highest risk of developing e.g. sudden death, arrhythmia, HF – plus an approximate timing in years?

Modifying the clinical history of the disease is currently very difficult. Endocannabinoids (eCB) might delay the onset or worsening of the disease, but need to be given to the appropriate patients. If the disease trajectory is not easily predictable, the outcomes impact of novel (e.g. gene) therapies might be difficult to measure.

Clinical requirements for a decision support module
To utilise a combination of HCM risk factors and the findings of clinical investigations such as ECG, stress echocardiogram and MRI to predict: • the risk of developing and arrhythmia • the risk of sudden cardiac death caused by an arrhythmia • the risk of progressive hypertrophy causing obstructive symptoms and potentially leading to heart failure • The risk of disease progression in non-obstructive patients leading to mechanical dysfunction and terminal heart failure

Functional requirements for a DS module that can highlight the risk factors for a patient to develop HCM within the next 1-3 years	
1	The decision support module shall be capable of execution from the clinician desktop, only when he or she is logged into the EHR of a specific patient.
2	It shall run utilising EHR data specific to that patient.
3	It shall extract an agreed list of patient specific electronic health record data element values, including (as far as available): • genotypic sex • date of birth or age • recent height and weight • the presence of a family history of HCM • the presence or absence of an agreed list of symptoms with particular emphasis on symptoms suggesting an impaired cardiac output or occurrences of an arrhythmia • a formalised indication of the extent of sporting activity and its duration

	• the presence or absence of an agreed list of lifestyle risk factors such as smoking • the latest values from an agreed list of structured and coded physical examination findings • structured and coded findings from recent investigations including ECG, echocardiogram, MRI and other imaging studies • the genotype of the patient • whether the patient is currently taking any treatments • if the patient already has an implanted cardiac device.
29	If it is able to run successfully it shall present risks (probabilities) of the patient experiencing one of these events in the next 12, 24 and 36 months: • the risk of developing and arrhythmia • the risk of sudden cardiac death caused by an arrhythmia • the risk of progressive hypertrophy and of developing obstruction • the risk of progression towards terminal heart failure (end-stage disease)
5	This information shall be presented as numeric values or percentages, and as a graphical chart in which the individual risks can be seen against the background of the risk for a similar patient population (recognising that a limited number of background population risks will be available early in the project). Where AI has generated the risk information, the clinician should be able to determine which variables have contributed to the AI execution and find an explanation of how the findings were reached (explainable AI). The risk of each future adverse event could be represented in an integrated way that is easy on the eye, yet accurate, like with "Kiviat diagram" or radar plot.
6	If it is not able to run successfully because of an insufficient set of input data from the patient's EHR, it shall offer a form to be completed by the clinician to provide the data item values that are necessary for algorithm execution, or a warning of a possible wide range of confidence in the advice, or for the clinician to cancel the execution.
7	If it is unable to provide any risk stratification relating to diagnosis or arrhythmia because the data values for this patient fall outside the parameters for which the DS can calculate, an appropriate explanatory message shall be displayed to the clinician.
16	The clinician shall be able to annotate the presented risk prediction information with a personal free text comment which could be reasons to have limited confidence in the calculation or to indicate an interpretation of it.
9	The displayed information shall be capable of export from the DSS component so that it can be saved in the EHR system as computable data.
10	If that system is not capable of importing such data, possibly including its graphical presentation if this is offered, then it shall be possible for the clinician to generate a PDF report that could be saved in a correspondence section of the EHR.
Notes: Because this set of predictions is likely to require careful clinical interpretation and decision-making, it is not proposed that this set of calculations is designed to be exported to the patient's platform.	

Given the limited extent of evidence yet available to accurately risk assess and predict disease progression and complications, the clinicians identified some areas of research that SMASH-HCM might be able to explore by applying AI to the datasets that it accumulates.

Research objectives for SMASH-HCM
1. Predicting the risk of developing heart failure, especially the risk of developing ventricular dysfunction 2. Defining phenotypes (digital twins) that could be used to risk stratify patients as being appropriate for the fitting of an ICD

3. Measuring the impact of lifestyle and environmental factors (sport, smoking, diet…) on trajectory and outcomes
4. Phenotype/genotype correlations that point to a more malignant disease trajectory
5. Genetic mutation (carriers) in children and young adults, to determine if the different mutations indicate different risk profiles e.g. risk of arrhythmia
6. Whether the diagnosis of HCM should alter other care pathways, especially for (unrelated) comorbidity

4.6 Diagnostic and treatment complexity in the case of hypertension

Discussion of the clinical challenge

Hypertension can be a complication of HCM, but it can also cause hypertrophy. Additionally, hypertension due to HCM is sometimes treatment resistant. Patients referred to a cardiologist for the treatment of hypertension might therefore have (as yet undiagnosed) HCM.

The challenge to consider then is to confirm the diagnosis of HCM. Left ventricular hypertrophy alone is usually not an indicator of HCM, as it is too common in hypertension. Many other conditions can also cause left ventricular hypertrophy.

There is a need for further research into phenotypic biomarkers that could alert a cardiologist treating a patient with hypertension to consider HCM.

Research is also needed to identify if the treatment of hypertension should be different depending on the presence or absence of HCM, and if there a drug that should be avoided in HCM.

Clinical requirements for a decision support module
There are no business or functional requirements for decision support related to this topic because there is insufficient research evidence as yet to inform the design of an accurate enough algorithm.

Research objectives for -SMASH-HCM
1. To determine if there is a profile of phenotypic biomarkers that could predict the risk of a patient having HCM if they already have hypertension. 2. To determine the safety and efficacy profile of anti-hypertensive drugs used in patients with HCM.

In the event that robust research findings are obtained for either of these research questions, the possibility of developing a decision support tool will be reconsidered, and new functional requirements will be developed.

4.7 Prediction for advanced heart failure with need of cardiac transplantation

Discussion of the clinical challenge

It would be useful to have early prediction of who is most suitable and/or urgently in need of transplantation. This is an area in which there is presently insufficient robust evidence, although ESC

2023 guidelines provide high level criteria: “Orthotopic cardiac transplantation is recommended for eligible cardiomyopathy patients with advanced heart failure (NYHA class III–IV) or intractable ventricular arrhythmia refractory to medical/invasive/device therapy, and who do not have absolute contraindications”.

More research is needed on large patient numbers to match characteristics of those who had a transplant with a corresponding cohort of patients who did not, in order to compare outcomes. If a robust message to characterise patients against outcomes can be developed, then a risk stratification decision support tool might be developed, for which functional requirements could be specified.

Clinical requirements for a decision support module
There are no business or functional requirements for decision support related to this topic because there is insufficient research evidence as yet to inform the design of an accurate enough algorithm.

Research objectives for SMASH-HCM
1. To determine a set of clinical characteristics that could be used to risk stratified patients as having the potential to benefit from transplantation.

4.8 Patient monitoring

Discussion of the clinical challenge

The detection of transient or silent arrhythmias can be difficult. Monitoring is triggered by symptoms or level of risk of the patient. However, a 24-hour ECG is disturbing for the patient and only captures heart rhythm within a limited time window when a transient arrhythmia might not manifest.

Smart watch monitoring of heart rate and rhythm is becoming more accurate, ubiquitously available and affordable, and might be useful. Apple, Samsung, Withings and other watch solutions can detect and record arrhythmias and could be used as a screening tool over long periods of time to help to identify patients in whom a more sophisticated measurement such as a 24-hour ECG is indicated.

In addition to detecting arrhythmia, information about heart rate variability which reflect the autonomous nervous system balance might be useful to predict adverse events in HCM.

When considering arrythmias it is important to distinguish between

- Atrial arrythmias which are important prognosis factor for cardioembolic event such as stroke and the development of heart failure; and
- Ventricular arrythmias, typically non-sustained VT which are risk markers of the sudden cardiac death risk.

Both can be silent, and both can be better detected by more intensive monitoring to improve prediction.

Additionally, when considering device monitoring, clinicians also should consider potential information that could be extracted from patients who are already wearing an ICD who are permanently monitored by their implanted device.

It is therefore desirable to conduct research on which patients might be suitable to monitor heart rate and rhythm on a continuous basis, and to utilise large population volumes of continuous monitoring data to risk stratify patients for intervention.

SMASH-HCM does not presently plan to conduct studies of patient monitoring using wearables, so this area of research is presently out of scope of the project.

4.9 Risk reduction (lifestyle) advice

Discussion of the clinical challenge

It is generally accepted that mild to moderate levels of physical activity can be beneficial for health (e.g. cardiovascular disease and diabetes prevention) without increasing the progression of cardiomyopathy nor accelerating its complications. According to ESC 2023 guidelines for HCM, HCM patients with mild LV hypertrophy, normal-sized or enlarged LV, normal diastolic function, and no evidence of impaired cardiac output can also usually continue with moderate exercise. The evidence on which patients might continue with vigorous exercise or moderate-to-high-intensity competitive sport is based on small patient numbers. More evidence is therefore needed to classify risks, particularly for arrhythmia and sudden cardiac death amongst patients undertaking moderate or greater levels of exercise.

There is a need for more research on the role of physical activity in prevention and improving symptoms and quality of life (as opposed to activity only being regarded as a risk). A combination of exercise history data from health records and continuous exercise monitoring data via technology (e.g. smart watches) may help to find the right patient-specific balance between the positive and negative aspects of exercise.

This is an area needing research which is probably beyond the scope of SMASH-HCM: offering tailored lifestyle advice and education that has been personalised by the clinician (not by the software)

- for improved quality of life
- for improved knowledge of the disease and factors with potentially devastating effects
- for improved understanding of various arrhythmias and their effect on the disease progression, e.g. atrial fibrillation and for early prevention of those
- to reduce risks of sudden cardiac death

4.10 Assessing patient outcomes and quality of life

Discussion of the clinical challenge

Patients with HCM might be asymptomatic, some might be active sports persons, or might have very mild symptoms. The possibility of having to curtail sporting activities, the threat of a potential deterioration in cardiac function, the risk of sudden death from arrhythmia and the possibility of having medicinal or operative interventions whose necessity cannot be assured, all potentially contribute to psychological distress. Lifestyle changes recommended for prevention or risk reduction purposes may also reduce quality of life.

If the HCM actually causes arrhythmia or obstruction, then physical limitations will arise that also impair quality of life. To date, few quality-of-life studies have been undertaken in HCM patients. The opportunity to analyse large volumes of data on cohorts of HCM patients across multiple countries offers the opportunity to capture the historic values of health outcomes and quality of life metrics if they have been documented precisely. This is unfortunately not common. Patient Reported Outcome (PRO) studies show that patient driven endpoints must be focused on, collected and used, to a greater extent than currently. Clinical priorities are not necessarily patient priorities: topics such the anxiety of transmitting the disease to children are unlikely to be routinely documented.

Combining longitudinal (multi-parametric) HCM clinical data with the prospective and formalised collection of standardised PRO and quality of life metrics would allow for better quality insights into the human impact of an HCM diagnosis or an HCM risk. Measurable outcomes and quality of life are also important for establishing a data baseline that is needed for new clinical trials and regulatory submissions.

If such evidence is prospectively collected to a high quality, this would enable clinicians to take the negative quality of life impact into account of interventions when there is some uncertainty about their necessity.

This is an area needing further research ideally including prospective data collection. It is probably beyond the scope of this project to perform such a prospective observational study. However, the intended SMASH-HCM patient platform (portal or app) may allow for the collection of some quality-of-life indicators on a small number of patients enrolled in the pilots.

4.11 Patient unmet health, lifestyle and social care needs

Discussion of the clinical challenge

The clinicians interviewed indicated the importance, and their lack of high-quality insights, into the unmet needs in health, lifestyle and care terms, of HCM patients in general, even though they do ask their patients such questions individually. There is a need for greater engagement with patient representatives and groups of patients to better understand how such unmet needs may best be identified, addressed individually and the learning shared more broadly. Some patient needs' assessment scores and scales, that might be useful to consult, have been published by Cardiomyopathies Matter and the Global Heart Hub. This topic will be useful to explore within SMASH-HCM with its patient representatives, in case some suitable questions or templates can be added to the patient platform, such as a list of frequently occurring unmet needs and patient priorities. It is not an area for which clinician or patient decision support could be implemented.

Patient reported outcomes like pain, discomfort, quality of life, psychological impacts of disease and general well-being, as well as valuing the difference between patients' priorities and doctors' priorities, are important. Clinicians need to move away from the classical approach of them leading the conversation regarding diagnosis and treatment, and towards a more patient centric approach where patients' experiences with pain and disease management form an integral part of the treatment plan. A tool designed with patient feedback will cater to, and incorporate, several unmet patient needs that clinicians often don't usually prioritise.

4.12 Generic user requirements for the SMASH-HCM decision support tool and application

In addition to the specific functional requirements listed earlier in this deliverable, some cross-cutting high-level requirements also arose during discussions and are included here for reference and uptake by the decision support and clinical application developers.

Generic user requirements	
30	The implemented solutions must be quick and easy to use, not requiring a lot of data entry.
31	Given that many health and lifestyle data points will be processed, the clinicians would benefit from visualisations that assist their human sense making of a patient's risk factors and risk projections.
32	A patient may have multiple risk scenarios (for different complications and outcomes) and therefore there may often be multiple risk scores per patient, which need a way to be visualised.
33	The decision support solutions must provide transparency behind any computations: what data points were considered, how was the calculation made, and if there is a level confidence in that recommendation.

34	Care must be taken to minimise false positives and false negatives. On the one hand, clinicians must not be falsely guided away from intervening unless the evidence for no intervention is strong, but on the other hand they must also not be guided towards intervening in asymptomatic patients such as athletes when intervention may unnecessarily be damaging to their future sporting career prospects.

5 Initial response from the SMASH-HCM decision support developers

Despite American (2020) and European (2023) guidelines on HCM, there remain gaps in the available guidelines in particular relating to formalising unmet need and the role of wearables and apps in measuring them. Knowing how unmet needs have changed over the past 3 years would allow the clinicians and developers to extrapolate and predict how they might also change in the future and in what direction they might go for clinicians and patients.

There are gaps in how to undertake risk stratification, for example in the management of arrythmias and patient facing aspects, self-management (especially in the light of new ICT developments). It could be valuable to explore how a better diagnosis of HCM could potentially change care pathways for related conditions.

The implementation should be iterative in the sense that the developers should first try to implement the simplest decision support algorithm that has clinical value, for example to take an existing risk score and try to improve it with modern machine learning methods and custom data we are able to collect. Focusing on the more complex scenarios may result in implementation that is never ready.

It will be important to focus the system architecture and "actual program" on algorithms and decision support methods that are known to work and can be implemented, i.e. quick proof-of-concepts before wasting lot of resources in implementing something that is a long shot. Increasing complexity and pushing the boundaries of scientific knowledge in machine learning is sometimes better suited to publications than actual implementation in the software system.

User stories are needed for the developers and should be clear, e.g. a clinician selects a patient from UI, system fetches -omics data from database and simulates what are the best drug candidates for this patient. Without concrete user stories that are understandable for both developers and clinicians there is high risk that the demonstrator is not usable.

Endpoints are the most important item in the data. Supervised learning cannot be done without clinically relevant endpoints.

More insights will be needed from clinicians regarding the backend and research aspects, i.e. mechanisms, models, metrics and areas that will assist more in understanding the disease itself. Considerations here include if going deeper into the scientific exploration of the disease will be useful to incorporate in the tool.

Notable feedback from the solution developers was that the clinicians were often talking in subjective, generic terms and focusing much on the patient experience, whereas for the solution developers it would also be useful to have insights from a scientific research and mechanism of disease perspective.

6 Conclusion and next steps

This deliverable has focused on capturing the challenges HCM clinicians face in making the HCM diagnosis, particularly in some patient subgroups like athletes, their challenges in imposing a necessary and sufficient burden on monitoring (especially for asymptomatic patients), in risk stratification and in giving patients relevant and suitably predictive lifestyle guidance.

SMASH-HCM intends both to utilise large volumes of HCM patient data and AI to obtain new insights that could assist with these areas of clinical decision making. In order to do this, it needs as much clarity as possible about the clinical needs, a process which has been started with this deliverable and its lists of functional requirements. Detailing through user stories might assist the developers further. However, in the end they will be limited to the inferences that can be made with reasonable rigour, from the available data using machine learning.

Through this deliverable, the solution developers have been provided with high-value areas on which to focus on, to begin identifying the relevant data to which machine learning can be applied. As predictive signals become more apparent, the developers will be able to embody that knowledge as decision support guidance for validation by the clinicians.

The next steps in this work will be to define with greater precision the datasets on which AI should be trained and the questions the AI should attempt to answer.

This deliverable will therefore be revised in the future, with additional feedback from the clinician to developer iterative cycle, as an update to these functional requirements.