SILICOFCM

Project Title: *In Silico* trials for drug tracing the effects of sarcomeric protein mutations leading to familial cardiomyopathy

Project acronym: SILICOFCM

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Disclaimer

Executive summary

Deliverable report D9.9 is the third iteration of the Roadmap on Business Model for the SILICOFCM project key exploitable results (KERs), with the first and second reports submitted in M12 and M24, respectively. The report analyses the business road map for the KERs as of until M36, including the (i) 3D image segmentation tool, (ii) Bioinformatics tool, (iii) MUSICO tool, (iv) Finite element tool, (v) Decision support (Risk stratification) tool, (vi) Virtual population tool for animal experiments and human trials, (vii) Multi-criteria decision making (MCDM) tool and ultimately, the (viii) SILICOFCM platform.

The report presents a market assessment related to products and technologies similar to the one developed in SILICOFCM, in order to differentiate the unique value proposed by SILICOFCM KERs. The technology watch and market analysis uses several tools and methods such as the SRD-I semantic analysis tool, Google Trend analysis, AnswerThePublic analytics among others for a global and project specific overview of the recent trends in the in silico platforms for cardiomyopathy, including familial cardiomyopathy (FCM). Chapter 3 uses the business model canvas previously mentioned in D9.8 has been explored for the KERs complimenting the D9.5 Exploitation plan. Three potential service options suited to exploit the SILICOFCM KERs beyond the project duration are presented in Chapter 4. The section on exploring the regulatory challenges and landscape for the SILICOFCM platform (and the associated tools) are explored in Chapter 5, with an update to the EU regulation 2017/745 on medical devices (MDR). Lastly, the intellectual property related strategy has been expanded from D9.5 and would be further extended with inputs from the partners at the last year of the project.

The key updates from the D9.8 include:

Updates from Roadmap to Business Model v2 (D9.8)	Section
Competing project analysis using network graphs generated from semantic similarity analysis using the SRD-I analysis.	2.1
Patent search analysis for identifying relevant patents using Google Patent search tool.	2.2
Global trends associated with cardiomyopathy and in silico platforms using Google Trend Analytics tool.	2.3
Business model canvas for each KER based on inputs from D9.5	3
Evaluation of service options including the ERRA initiative which aims to provide European research innovations and level-based service options.	4
Updates related to the EU MDR in the Regulatory Landscape	5.2

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List of Abbreviations

Abbreviation	Explanation
BIOIRC	BioIRC doo Kragujevac, Serbia
BSC	Barcelona Supercomputing Center
CEG	Core Exploitation Group
FCM	Familial cardiomyopathies
HCM	hypertrophic cardiomyopathy
DCM	Dilated cardiomyopathy
CORDIS	Community Research and Development Information Service
EPO	European Patent Office
USPTO	United States Patent and Trademark Office
ICVDV	Institute of Cardiovascular Diseases Vojvodina, Clinic of cardiovascular surgery, Sremska Kamenica
IIT	Illinois Institute of Technology
ISO	International Organization for Standardization
KER	Key exploitable results
R-Tech	Steinbeis Advanced Risk Technologies
SBG	Seven Bridges Genomics SME
SME	Small and medium enterprise
TRL	Technology readiness level
UHREG	University Hospital Regensburg
UL	University of Ljubljana
UNEW	Newcastle University, Faculty of Medical Sciences
UNIFI	University of Florence
UNIKENT	University of Kent
UOI	University of Ioannina
WP	Work package
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
TRL	Technology readiness level
MDD	Medical Device Directive
ERRA	European Risk & Resilience Assessment initiatives

1. Introduction

The SILICOFCM project will deliver a computational cloud platform for conducting *in silico* trials of Familial cardiomyopathies (FCMs), considering a range of patient specific features including genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects. The platform leverages the integrated multidisciplinary and multiscale methods for analysis of patient-specific data and development of patient-specific models for monitoring and assessment of patient condition from current status through the progression of disease. The goal of the platform is to maximize positive therapeutic outcome, avoid adverse effects and drug interactions, prevent sudden cardiac death and shorten the time required from commencing drug treatment to attaining the desired result. Besides, it reduces animal and clinical studies for new drug development.

The SILICOFCM cloud-based platform provides a suite of integrated solutions supporting simulation of various computational workflows, including those related to virtual population generation, FE analysis, bioinformatics, MUSICO and image segmentation among others with the aim of shedding light on the underlying clinical pathways of the HCM.

The Deliverable D9.9 – Road map on Business Model v3, is the 3rd iteration of the Roadmap on Business Model reports on the updates related to the WP9 - Exploitation and Dissemination, specifically related to technology watch market analysis, which is a precursor to developing a business model. The report includes information on competing research projects and patents using data analytics tools in addition to analysis of general trends in the market related to in silico methods or computational platforms related to cardiovascular cardiomyopathy. These will be used to identify potential risks and opportunities before the end of the project and the consequent launch of the SILICOFCM cloud platform.

This deliverable bridges the objectives of Task 9.2 and 9.3 with Task 9.4 and is expected to facilitate creation and developing a connection with the industry and other external representations. This will promote interaction and collaboration with different stakeholder groups and will allow consortium members to be acquainted with up-to-date knowledge, to benchmark best-practice solutions, especially with the end user requirements.

The report proposes 3 different service options for the SILICOFCM KERs which can be exploited individually or combined as SILICOFCM platform depending on the respective beneficiaries. Based on the inputs from 2nd review (online) meeting, and the updates to D9.5, this deliverable also includes an updated analysis of the regulatory landscape emphasising the recent changes in the MDR in EU, which is related to tasks in WP8: Report to EMA.

The deliverable will be updated in its final form in M45 taking into account the project progress and the subsequent changes in the market. At the end of the project, the deliverable will serve as a Roadmap on Business Model for the SILICOFCM consortium members with clear avenues of exploiting the SILICOFCM platform as a product.

With prospective events planned with interested stakeholders from pharmaceutical industry and policymakers, an additional section will be added to the next version on the business model roadmap v4, highlighting the results obtained from the feedback from the end-user perspective. The interaction with various stakeholders and most importantly with the end users can bring other added value to the project such as:

- Provide feedback on SILICOFCM activities and results
- Help identify priorities and tailor project activities to the needs of the end users
- Help implement and develop services that will bring the project benefits to the end users

- Enhance project's visibility through promotion using the contact network
- Maximize the impact and cost-effectiveness of project activities

2. Technology watch and Market analysis

Technology watch monitors external developments that may influence the outcome of the project and/or the use of the project results. This will include developments of new technologies, competitors, patents, regulations and market trends to help assess the exploitation opportunities and to identify, understand and mitigate barriers to market entry. This includes desk-based research (e.g. published market, business and technical reports), text-based data analysis using advanced tools, and informal ad-hoc interviews with stakeholders and insights gathered by partners during dissemination activities.

Market analysis is done based on the interaction chain between various end users and other stakeholders. Depending upon their role, competencies and other costs/benefits, a road map to business model has to be developed to demonstrate full market potential and viability of the project outcome. To achieve this, it is important to identify various stakeholders involved in different sectors, such as medical, IT, research and education.

2.1 Competing EU research projects

For analysing the competing or similar EU research projects, a search on Community Research and Development Information Service (CORDIS) website with a search string related to “computational platform for in silico clinical trials” and “heart related conditions, such as cardiomyopathies” is shown in Table 1. In addition to this desk-based research results, an in-house text analytics tool called “SRD-I” was used for performing semantic similarity analysis, i.e., calculation of similarity in meaning between the text in a document.

Firstly, the project-related data such as name, short description, etc. were obtained from the CORDIS website. Keywords used for the analysis included: Insilico platform to obtain 16 results with unique projects and related data.

This is followed by creating “wordbags” for each project, i.e. extracting and decomposing individual words from the project description. Pre-processing of data is performed by removing stop words (the words in any language which does not add much meaning to a sentence) and stemming (strip endings like "-s", "-ed", etc. if the result is a valid word). This provides a vector of keywords for each item, the “wordbag” w(i), i.e., the projects obtained from CORDIS.

The second step includes the calculation of the similarity score is obtained between the values of 0 and 1, where the similarity score is mathematically defined as:

$$S(i,j) = \frac{no.of\ words\ occuring\ in\ w(i)\ and\ w(j)}{Max\ (no.of\ words\ in\ w(i), no.of\ words\ in\ w(j)}$$

Step 3 involves extracting the structure and cluster of related items. The result from Step 2 is an n-by-n matrix representing a fully connected network which cannot be readily visualized. To extract structure from this data, we apply a couple of rules, i.e., firstly only those links between items should be displayed which have the highest similarity scores and secondly, the network should be connected, that is there should be no isolated nodes or disconnected clusters.

Step 4 is related to the layout and creating the network graph (Figure 1). The similarity score calculated by the overlap of semantic similarity of project descriptions in the previous steps is imported to Gephi,

an open-source network analysis and visualization software package. The nodes in the figure are based on eigenvector centrality is generally considered to be a measure of the "influence" of a node in a graph: the more central a node is, the more central its neighbours are and so forth similar to page ranking of web search engines.

Table 1: Other EU H2020 funded projects from CORDIS that have similar ambition as SILICOFCM.

Project	Brief summary	Relevant Keywords	Start and End Dates
C3-Cloud[1]	C3-Cloud aims to develop personalized care plans for complex multimorbid patients, supported by ICT tools and managed by a coordinated multidisciplinary team that promotes integrated care and the involvement of the patient and/or caregiver.	✓ Cloud platform ✓ ICT tools ✓ Multi-morbidity ✓ Personalized care	01/05/2016 - 31/08/2020
HEARTEN[2]	HEARTEN aims to design, develop and validate an ICT co-operative environment that will enable the heart failure (HF) patients to achieve sustainable behavior change regarding their adherence and compliance, and the ecosystem actors to be engaged and improve the patients HF management.	✓ Mobile health Platform ✓ Ecosystem ✓ Sensor integration ✓ Data analytics	01/01/2015 - 31/03/2018
ATMOSPHERE[3]	The project aims to design and implement a framework and platform relying on lightweight virtualization, hybrid resources and Europe and Brazil federated infrastructures to develop, build, deploy, measure and evolve trustworthy, cloud-enabled applications.	✓ Rheumatic heart disease ✓ Medical Imaging Processing ✓ Cloud & Post-processing pipelines	01/11/2017 - 31/10/2019
EurValve[4]	EurValve implements, tests and validates a modelling based decision support system (DSS) for aortic and mitral valve diseases that allows simulating, comparing and understanding the effects (outcomes) and risks of different treatment strategies.	✓ Valvular Heart Disease ✓ Decision support system ✓ Clinically compliant ✓ Predict disease progression	01/02/2016 - 31/01/2019

[1] https://c3-cloud.eu/
[2] http://www.hearten.eu/
[3] https://www.atmosphere-eubrazil.eu/
[4] https://www.atmosphere-eubrazil.eu/

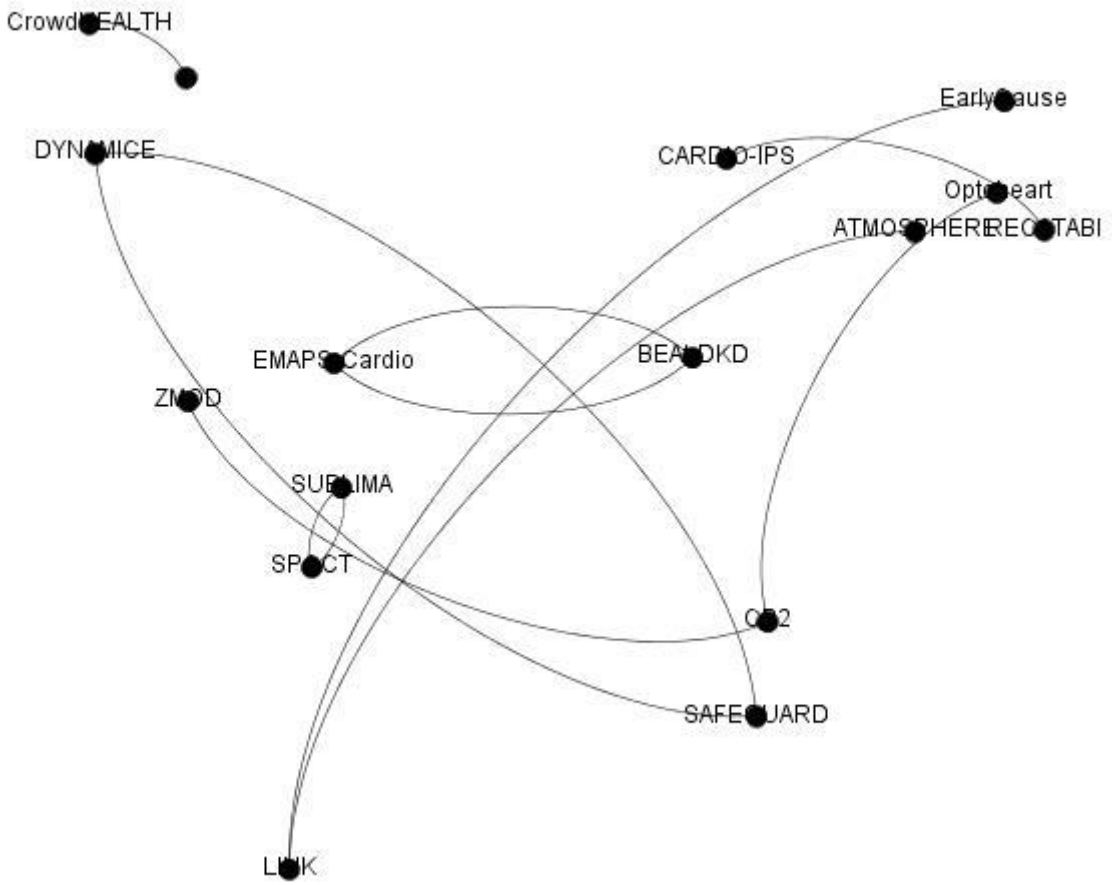

Figure 1: SRD-I analysis for competing projects. The network graph is computed from a similarity score calculated by overlap of semantic similarity of project descriptions (obtained from CORDIS)

2.2 Competing Patents

For the patent search analysis, Google Patents (www.google.com/patents) was used. Google patents is one of the largest repositories for patents and includes over 120 million patent publications from 100+ patent offices around the world, as well as many technical documents and books indexed in Google Scholar and Google Books. Google Patents is the global patent search engine that lets users search through patents from the USPTO (United States Patent and Trademark Office), EPO (European Patent Office), etc.

Based on our search keywords “in silico”, “platform” “clinical trial” “heart” Google Patent provided more than 2.380 results out of which the 5 most relevant patents were selected and shown in Table 2.

Table 2 Patent search analysis for SILICOFCM

Patent number	Title	Abstract	Year of publication	Status
WO2017172825A2	Methods and systems of predicting agent induced effects *in silico*	The disclosure presents a new computer based model framework to predict drug effects over multiple time and spatial scales from the drug chemistry to the cardiac rhythm. The disclosure presents a new computer based model framework to predict drug effects from the level of the receptor interaction to the cardiac rhythm.	2017	US/pending
US20110144967A1	System and method for dynamic cardiac analysis, detection, prediction, and response using cardio-physiological mathematical modeling	A system and a method for evaluating the cardiac status of a heart by evaluating a plurality of cardio-physiological parameters, and in particular, to such a system and method in which a plurality of cardio-physiological mathematical models are evaluated to produce a user specific cardiac model.	2009	WO/application filing
US20120022843A1	Method and System for Comprehensive Patient-Specific Modeling of the Heart	A method and system for patient-specific modeling of the whole heart anatomy, dynamics, hemodynamics, and fluid structure interaction from 4D medical image data is disclosed. The anatomy and dynamics of the heart are determined by estimating patient-specific parameters of a physiological model of the heart from the 4D medical image data for a patient. The patient-specific anatomy and dynamics are used as input to a 3D Navier-Stokes solver that derives realistic hemodynamics, constrained by the local anatomy, along the entire heart cycle.	2011	US/active
EP2672889A2	System and method for planning a patient-specific cardiac procedure	A method of planning a patient-specific cardiac procedure according to an embodiment of the current invention includes receiving three-dimensional imaging data of a patient's heart, simulating at least one of electrophysiological or electromechanical activity of at least a portion of the patient's heart using the three-dimensional imaging data, and planning the patient-specific cardiac procedure based on the simulating.	2020	US/pending
US20110086348A1	Method for assessing heart disease	A method for assessing heart disease in a subject includes generating an expression profile of at least two or more miRNAs in a sample from the subject. The miRNAs can be selected from the group consisting of hsa-miRNA-1, hsa-miRNA-7, hsa-miRNA-29b, has-miRNA-125b, hsa-miRNA145, hsa-miRNA-181b, hsa-miRNA-214, hsa-miRNA-342, hsa-miRNA-378 and combinations thereof.	2010	US/abandoned

2.3 Trend Analysis

2.3.1 Google Trend Analysis

Google Trend is a keyword research analysis tool and is used for tracking trends to see how frequently a given search term is entered into Google's search engine relative to the site's total search volume over a given period of time. The tool is used here for:

- Discover event-triggered spikes in keyword search volume, e.g. *in silico* (platform) as depicted in Figure 2.
- Comparing keyword-related data including search volume index and geographical information about search engine users for keywords including cardiomyopathy, hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) as analysed in Figure 3, Figure 4,
- Figure 5 and Figure 6.

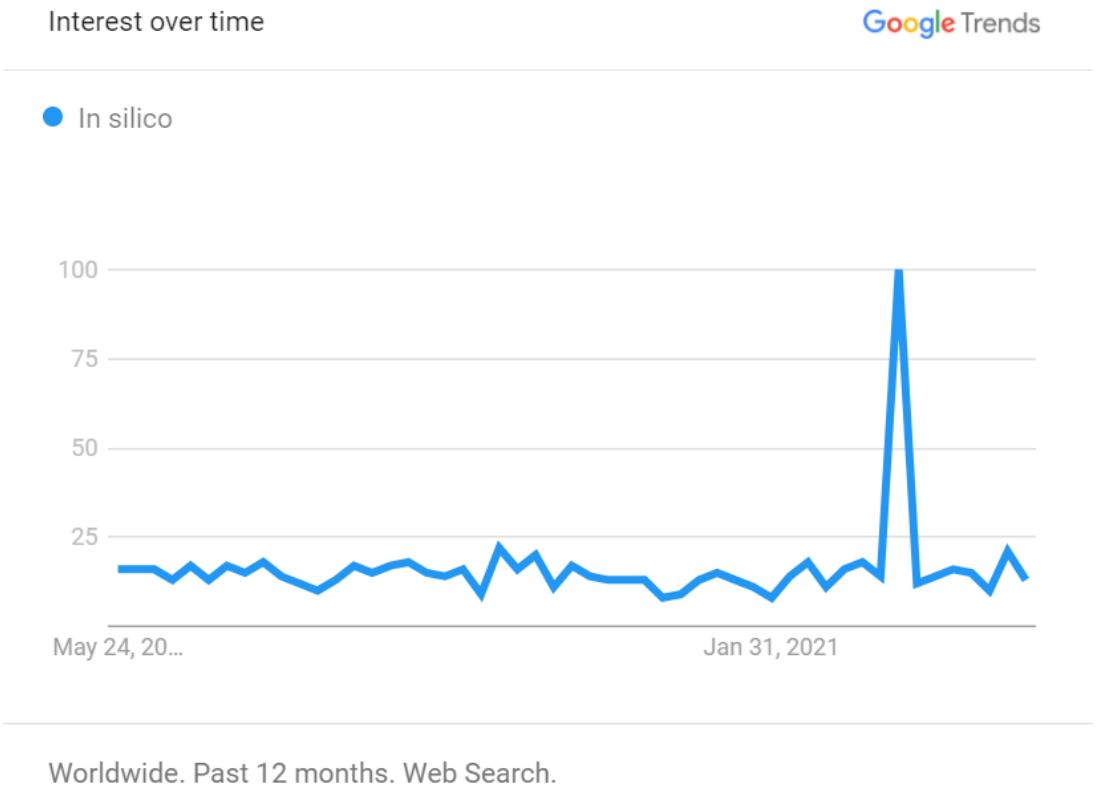

Figure 2: Google Trend Analysis for the keyword *in silico*

The Google trend anaylsis of the keyword "*in silico*" for the last 12 months from May 2021 (Figure 2) shows an increasing interest in "in silico" as a topic and a search keyword with an unusual spike at the beginning of 2021. This period coinciding with clinical trials of COVID-19 vaccines may be the reason for the increase in interest. As *In silico* trials allow pharmaceutical companies to test their drug candidates in "virtual patients" using computational modelling and simulation techniques are based on computer simulations, they have not been affected by the ongoing COVID-19-related travel and social distancing restrictions, which have impacted many conventional trials.

Figure 3 shows the trends associated with cardiomyopathy, in relation to hypertrophic and dilated cardiomyopathy searched among Google search users. A moving average is calculated from the average values for a specified period (48 weeks) for eliminating any fluctuations in the trend series as

shown in Figure 4. An increasing trend is observed for all 3 keywords indicating their growing popularity and interest among the Google search users.

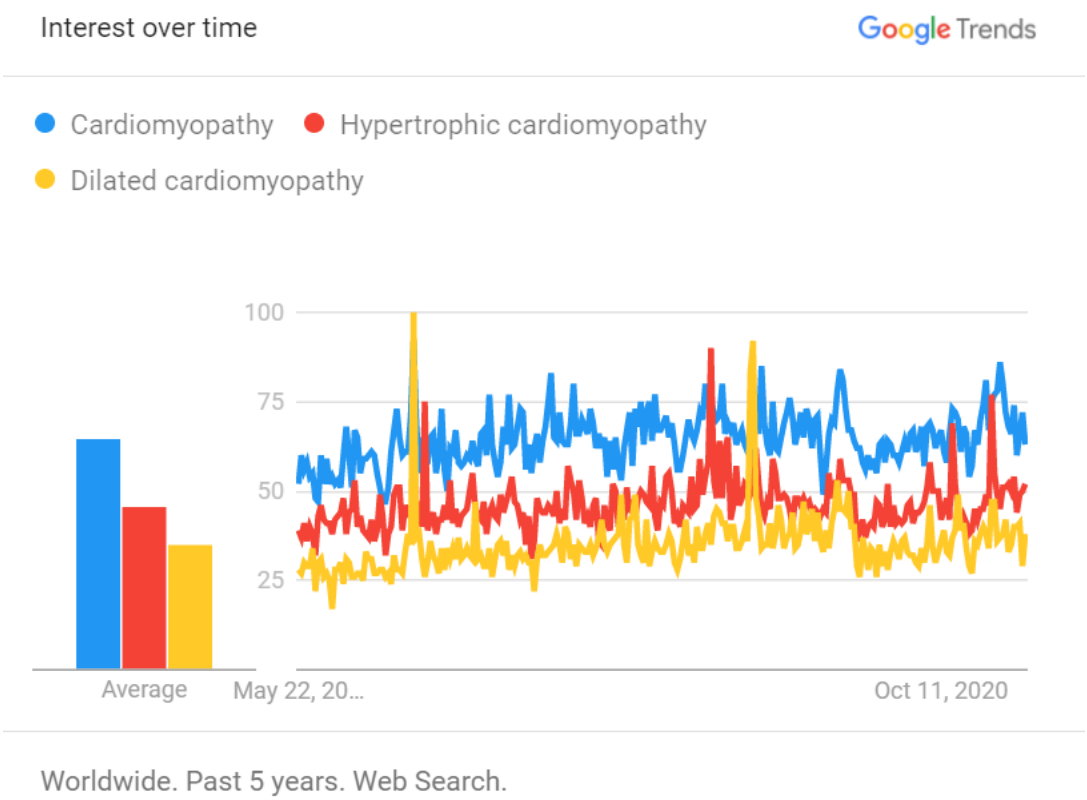

Figure 3: Google Trend Analysis for the related key words over a 5 years period

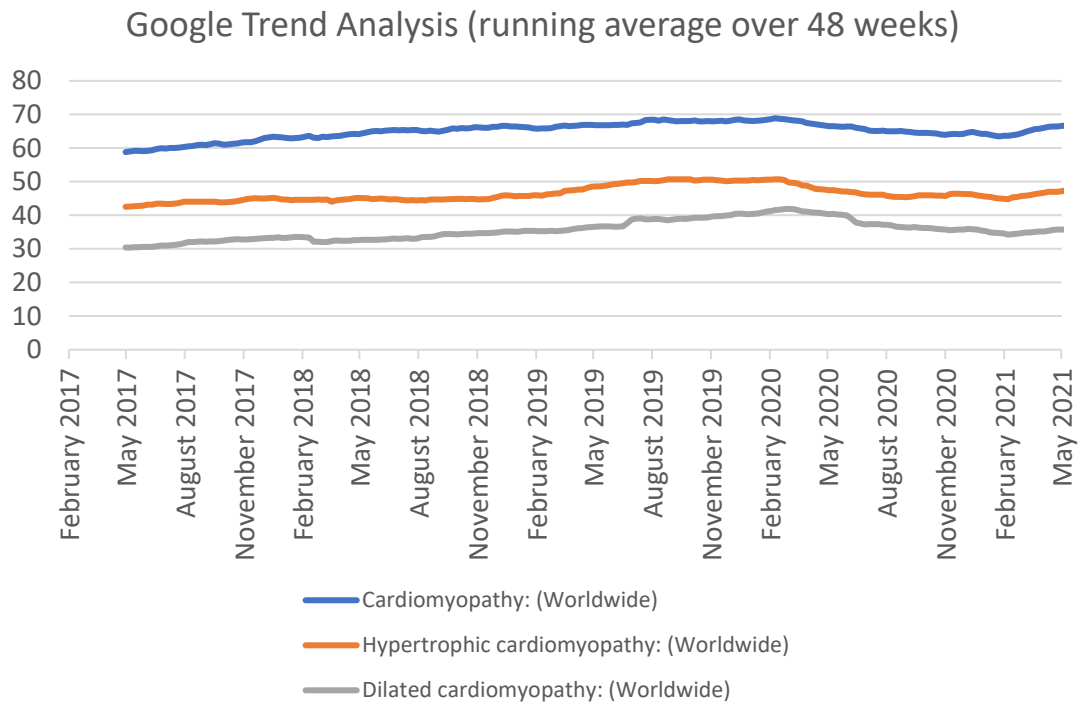

Figure 4: Google Trend Analysis for the related keywords (Feb. 2017- May. 2021)

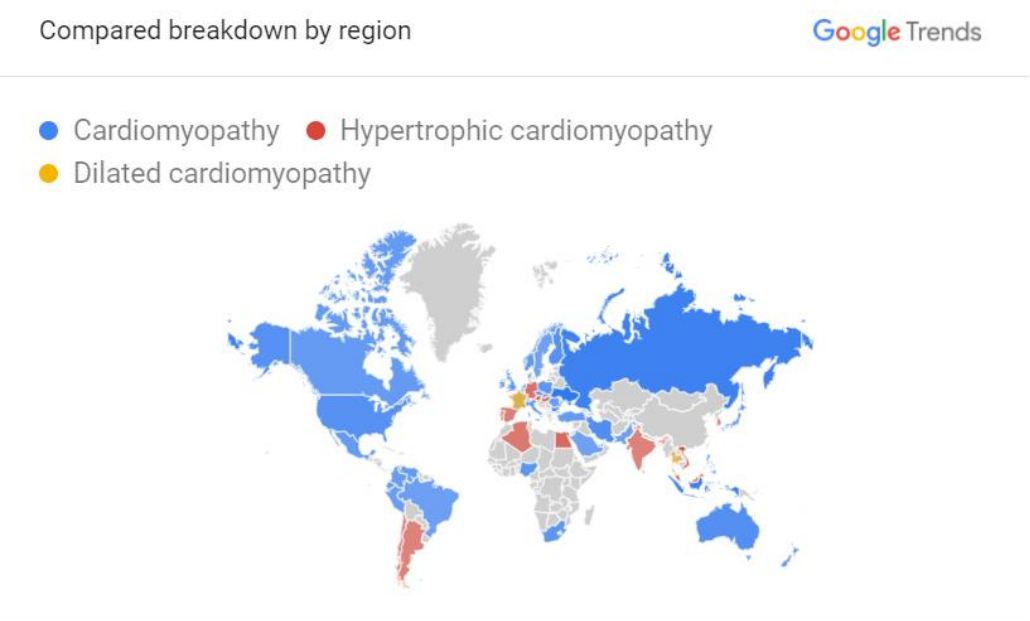

Figure 5: Google Trend regional analysis for the related keywords

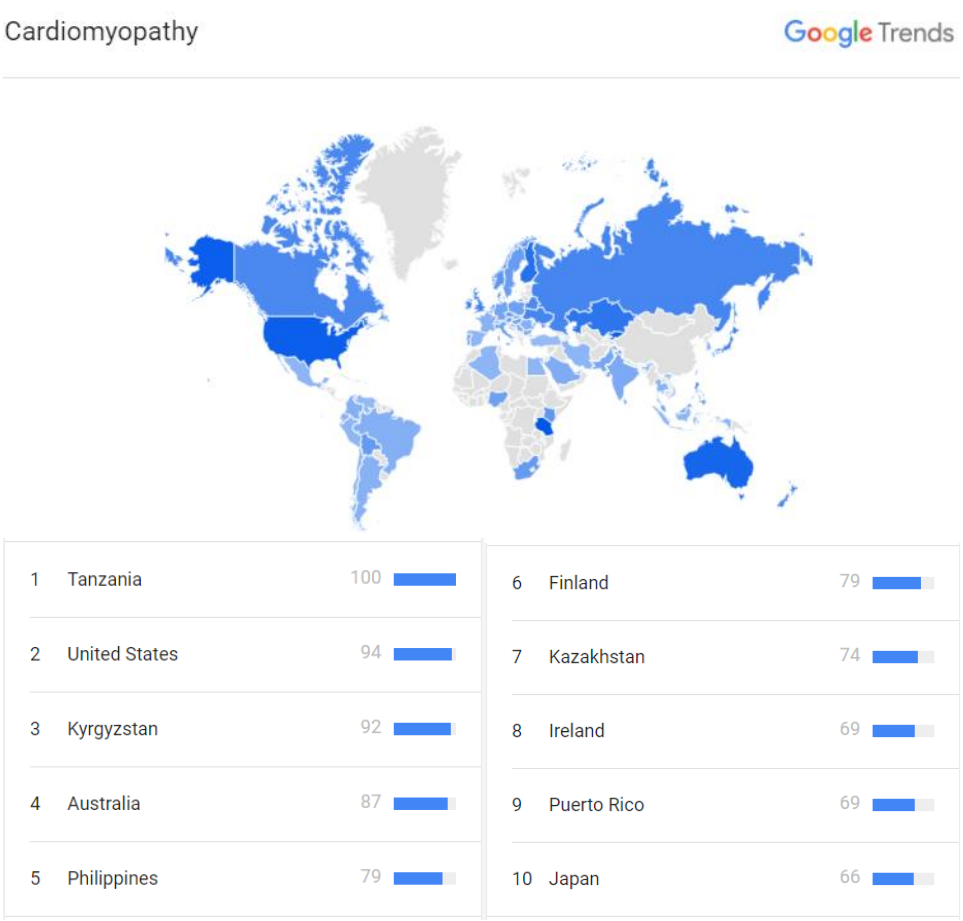

Figure 6: Google Trend regional analysis for the keyword *Cardiomyopathy*

Related topics to "cardiomyopathy" with increasing user interest (shown as % of increase in traffic volume over 1 year) include:

1. Transthyretin – Protein (+1750%)

2. ICD-10 (800%)
3. Hypertensive heart disease (300%)
4. Ventricular natriuretic peptide (180%)
5. Restrictive cardiomyopathy and premature ventricular contraction (both at 130%)

2.3.2 AnswerThePublic Analytics

With the advent of voice searches and increasing ability of search engines to better understand natural language (Google voice, Alexa, Siri, Cortana etc.), searchers have started phrasing their queries as questions rather than separate words. AnswerThePublic is a keyword tool that combines your main keywords with various question words (like who, what, why, etc.).

For SILICOFCM, we analysed the most common search queries performed as questions with the results shown in Figure 7. Furthermore, the tool also analyses "preposition" keywords (where the keyword cardiomyopathy is combined with another keyword via a preposition), shown in Figure 8 and "comparisons" where the keyword is compared with another keyword as shown in Figure 9.

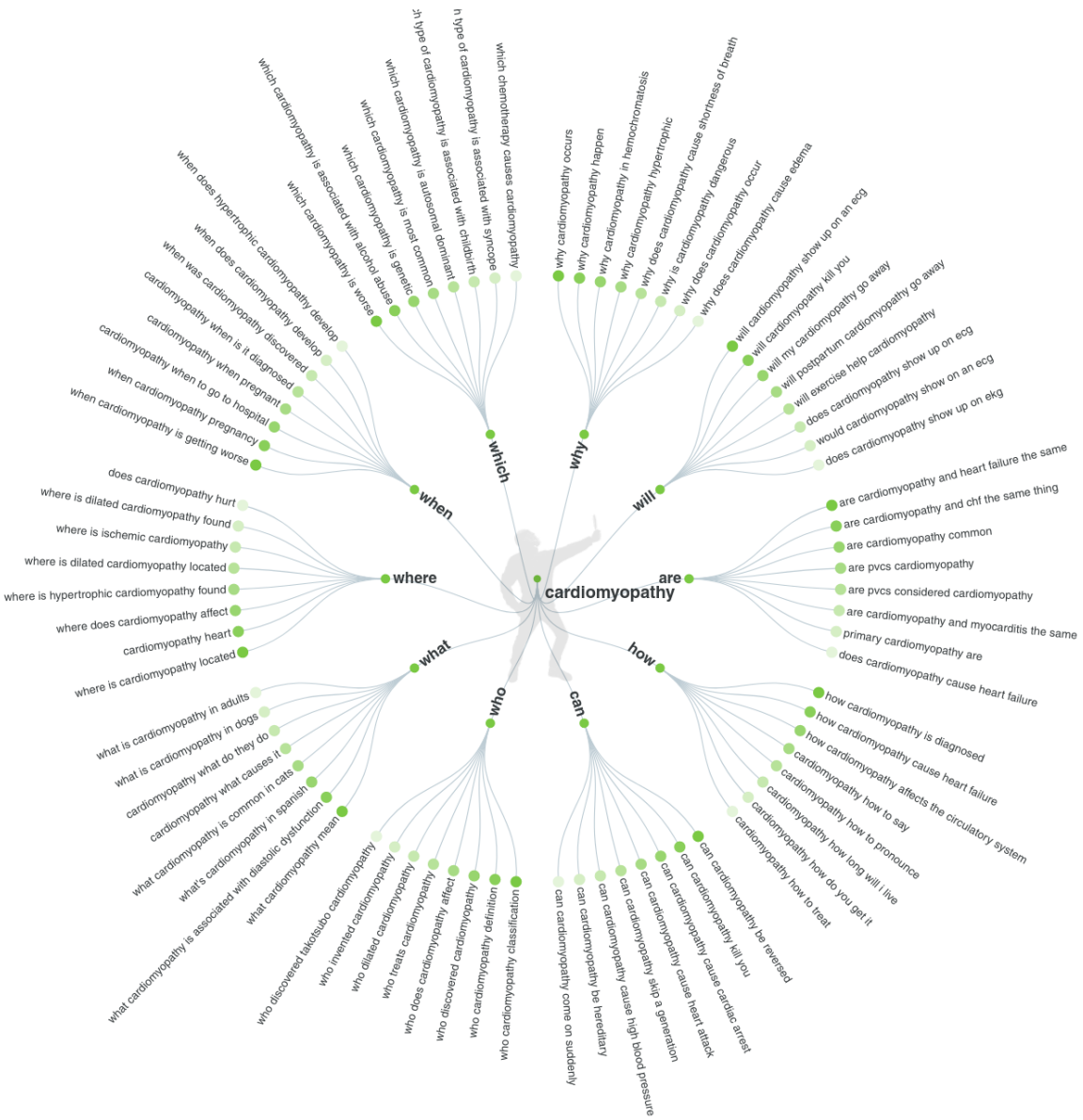

Figure 7: Search insights for the keyword *Cardiomyopathy*

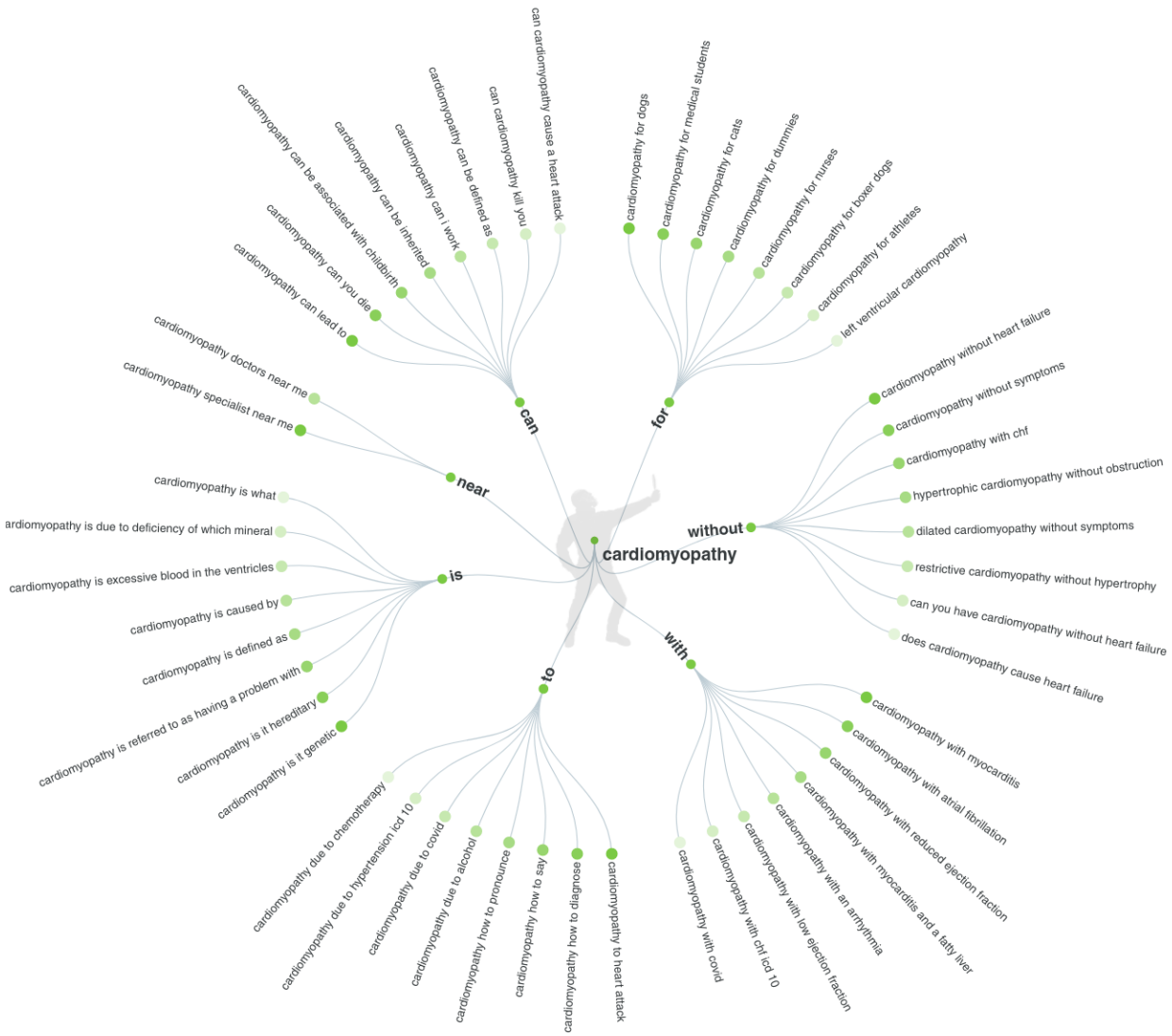

Figure 8: Search insights for the keyword *Cardiomyopathy* combined via propositions

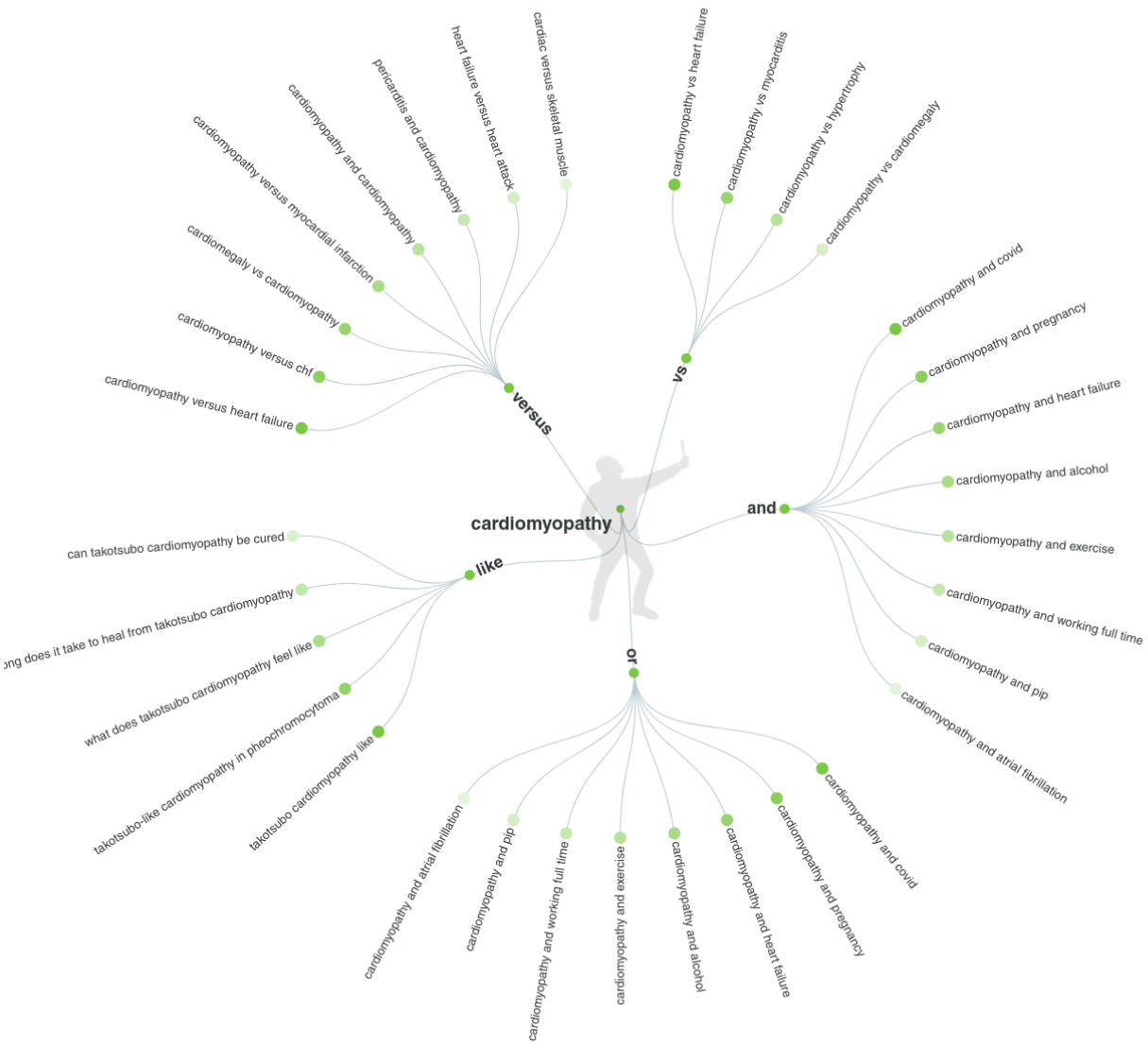

Figure 9: Search insights for the keyword *Cardiomyopathy* compared with other keywords

2.4 SILICOFCM KERs and targeted end users and competitors

At the end of the project, under WP8, a report will be developed for all the *In silico* drug testing and different anatomical geometry and boundary conditions which will be sent for EMA/FDA approval. A new drug Entresto (sacubitril/valsartan) will be given to the *In silico* patients with familial cardiomyopathies and the outcome of *In silico* study will be transformed in the standard report for EMA/FDA approval. The estimated market size, market maturity, key players are listed in Table 3.

Table 3: The estimated market size, market maturity, market by application, key players and expected release for commercialization.

Key exploitable result	Target market size	Market maturity	Market by application	Market competitor		Expected release
				Companies	Key Features	
KER1: 3D image segmentation tool	Expected to reach USD $21,341 million by 2022[5] and USD $41,260.8 million in 2025[6]	Competitive	✓ Government and defense ✓ Aerospace ✓ Manufacturing ✓ Architecture ✓ Health care	Materialize[7]	✓ Uses bidirectional electro-mechanical models that can solve excitation-contraction-coupling problem of the heart ✓ Simulation of effect of genes mutation on the heart behavior	2022
				Medviso Segment (Sweden)[8]	✓ MR Scar analysis ✓ MR Flow analysis ✓ MR LV and RV analysis	2022
KER2: Bioinformatics tool	Expected to reach $18,233 million by 2025[9]	Competitive	✓ Medical ✓ Academics ✓ Agriculture	GenScript[10]	✓ Bioinformatics tools focused in Molecular Biology, Peptide and Protein	2022
KER3: MUscle SImulation COde (MUSICO) tool	Development		✓ Medical ✓ Academics	Synopsys Simple[11]	✓ Anatomy-specific automated segmentation for hearts ✓ Segments blood pool cavities and selected muscle tissue ✓ Heart segmentation from CT scans includes: left and right Atriums and Ventricles, Aorta, Pulmonary Artery.	2022
KER4: Finite Element tool	Expected to reach $ 8.35 billion by 2022[12]	Competitive	✓ Aerospace ✓ Automotive ✓ Electronics	Dassault Systems- SIMULIA[13]	✓ Predict the fit of a new device ✓ Efficiently create a high-quality patient-specific FEA mesh from medical image data.	2022
KER5: Decision support tool (Risk stratification tool)	Expected to reach $17.1 billion by 2021	Competitive	✓ Aerospace ✓ Hospital ✓ Electronics	Emis Health[14]	✓ Proactively identify patients at risk of unplanned hospital admission. ✓ Clinically validated and peer-reviewed algorithm, developed for use in England.	2022

[5] https://www.alliedmarketresearch.com/3D-imaging-market
[6] https://www.globenewswire.com/news-release/2018/09/24/1574970/0/en/3D-Imaging-Market-is-expected-to-reach-USD-41-260-8-million-in-2025-CAGR-24-54.html
[7] https://www.materialise.com/en/medical/mimics-innovation-suite/finite-element-meshing
[8] http://medviso.com/segment/
[9] https://www.alliedmarketresearch.com/bioinformatics-market
[10] https://www.genscript.com/tools.html
[11] https://www.synopsys.com/simpleware/software/auto-segmenter-modules.html
[12] https://www.techsciresearch.com/report/global-simulation-analysis-software-market-by-product-type-finite-element-analysis-computational-fluid-dynamics-etc-by-end-use-industry-automotive-aerospace-defense-etc-by-region-competition-forecast-and-opportunities/970.html
[13] https://www.3ds.com/
[14] https://www.emishealth.com/

KER6: Virtual population tool (animal experiments and human trials)	Expected to reach $13,029.2 Million by 2025[15]	Competitive	✓ Hospitals ✓ Pharmaceutical companies	3D4Medical[16] IQVIA[17] Oxford Virtual Assay[18]	✓ Carry out ✓ measurements according to the recommendations of the European Society of Cardiology ✓ Can define mesh density, boundary condition for both fluid and solid domains ✓ Optimization of clinical trials ✓ Speedy and efficient access to the market ✓ Maximization of data	2022
KER7: Multi-criteria decision method (MCDM) tool	In 2017 estimated at $150 Million[19]	Competitive	✓ Biomedical and biotechnology companies ✓ Hospitals ✓ Insurance industry ✓ Clinical decision makers ✓ Policy makers and funding agencies	Cohesic Inc[20] TAPA Healthcare[21] The Medical Algorithms Company Ltd.[22]	✓ appraise multiple beneficial or non-beneficial clinical endpoints to help tailor decision making based on the user needs ✓ enables each decision maker to prioritize the criteria of evaluation (using weights) ✓ Allows to address the difficulty and complexity involved with conflicting priorities set by different stakeholders ✓ Quantitative evaluation and prioritization of treatment/drug combination alternatives based on a defined set of criteria defined by experts or users	2022
KER8: SILICOFCM platform	Development		✓ Hospitals ✓ Pharmaceutical companies ✓ Regulators	AWS health[23] IBM Health[24]	✓ Optimization of clinical trials ✓ Maximization of data	2022

[15] https://www.medgadget.com/2019/10/virtual-healthcare-market-2019-industry-analysis-size-share-growth-trends-and-forecast-to-2025-cagr-of-26-79.html
[16] https://3d4medical.com/apps/complete-heart
[17] https://www.iqvia.com/our-customers/medical-technology/clinical/cardio
[18] https://www.cs.ox.ac.uk/ccs/virtual-assay
[19] Customer Experience Management Market Report, 2021-2028 (grandviewresearch.com)
[20] https://cohesic.com/products/cardio-di
[21] https://www.tapahealthcare.com/
[22] https://www.medicalalgorithms.com/top-algorithms
[23] https://status.aws.amazon.com/
[24] https://www.ibm.com/watson-health

2.5 Network oriented bibliography analysis

Product networks as a result of a bibliography analysis can be an important tool in identifying the key players and collaborative network related to the specific product or service. The bibliometric analysis is a statistical analysis of books, articles, or other publications. It is frequently used for analysing science, technology and innovation. The analysis uses text based semantic analysis to identify and map relevant publishers of research using meta-data (such as university, country of publication, etc.) related to a product or service.

An example of such analysis is done using research data obtained from the web of science. Figure 10 shows the collaborative network of organisations who published research articles on 'risk stratification tool'. The network map is created using the co-authors and organizations they are working at. This provides access to the most reliable, integrated, multidisciplinary research connected through linked co-authors and organizations from multiple sources within a single interface. The data for this study were retrieved in May 2019 from the Web of Science using the keyword 'risk stratification tool' 449 documents were retrieved for this search for the period of 1991-2019. For statistical analysis and visualization, the results VOSviewer is used. VOSviewer is a software tool for constructing and visualizing bibliometric networks. The coloured nodes show different collaborative networks. In Figure 10, it can be seen that the University of Washington has a great collaboration with the University of Cambridge, Harvard Medical University, University of Toronto, McMaster University and many more. A similar analysis will be done for various products that are identified in SILICOFCM project to understand their collaborative network.

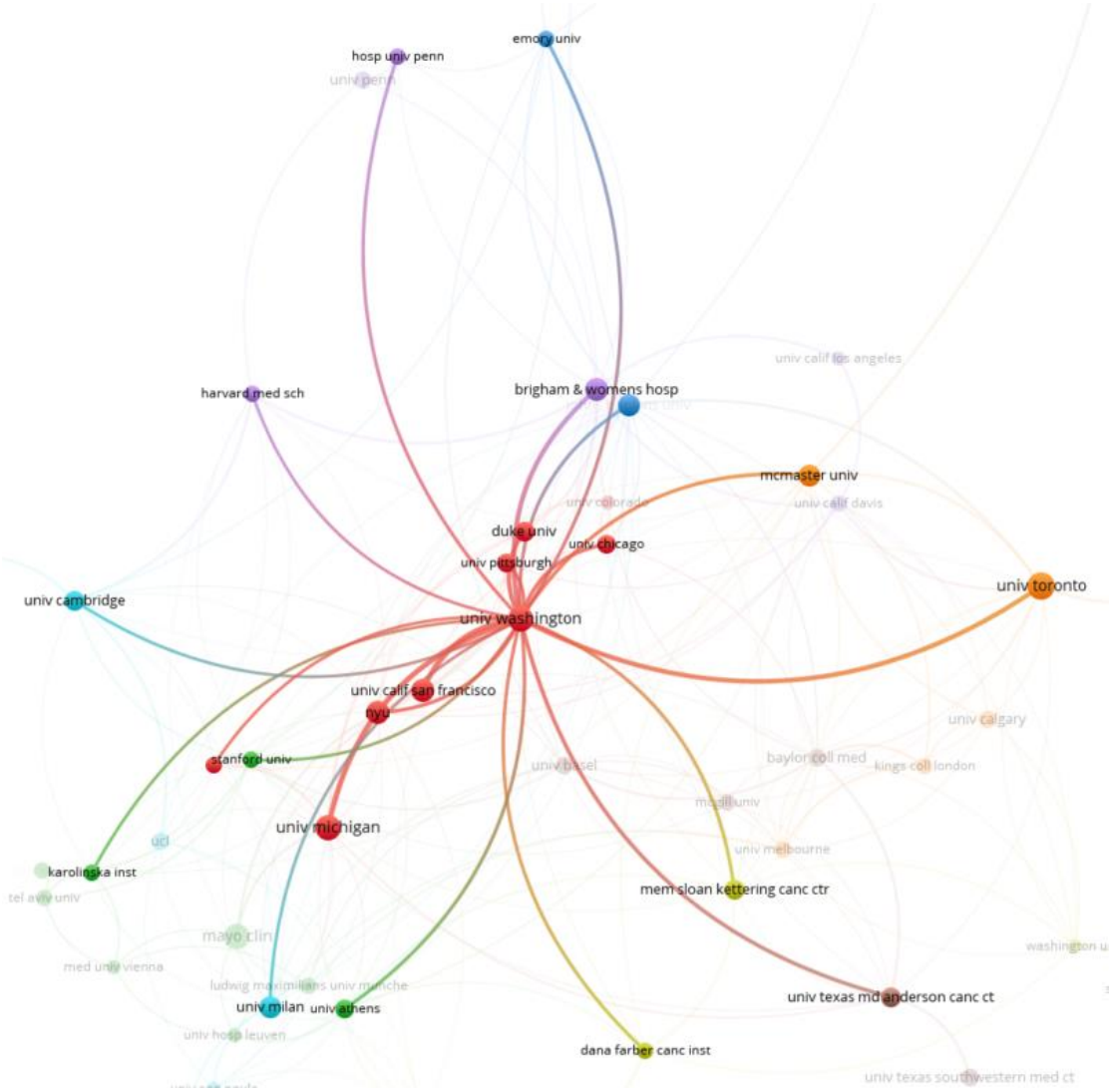

Figure 10: Bibliographic couplings of institutions publishing articles on risk stratification tool

3. Business model canvases for the KERs

The business model canvas is the structure of a business plan in one page. As mentioned before, SILICOFCM platform consists of 7 different tools, each developed by specific partners within the project. Based on the inputs from D9.5, the graphical representation of the business canvases provide a general overview of each tool and the companies which contributed to develop the tool besides the marketing and financial strategies for that tool. In this section a business model canvas is introduced for each of the KERs in SILICOFCM project as well as a canvas for the SILICOFCM platform in an overall perspective (Figure 11, Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, Figure 17, Figure 18).

In the business model canvas several parameters have been identified for each KER:

- Key partners: Relationships that companies have with each other to help the business model work
- Key activities: The core activities that a company must do to execute its Value Propositions
- Key resources: The most important assets required to make a business model work
- Value propositions: How the company wants to get to the moment in which its products and services create value for a specific Customer Segment
- Channels: How a company communicates with his Customer Segments and how it reaches them to deliver its Value Proposition
- Customer segments (Target/End users): Groups of people or organizations that a company aims to reach or serve with its products and services
- Cost structure: The expenses of a company to operate its business model
- Revenue streams: The strategies that enable a company to generate an income
- Customer relationships: The connections a company establishes with each specific Customer Segments. Following term have been used to such specify these relationships:
  - Transactional (there is no real relationship, the company interacts with the customer on a transactional basis)
  - Long-Term (a deep relationship is established; the company interacts with the customer on a recurring basis)
  - Personal Assistance (based on human interaction, the customer can communicate with a real customer representative to get help during the sales process or after the purchase is complete and it may happen onsite at the point of sale, through call centers, by e-mail, or through other means)
  - Dedicated Personal Assistance (it involves dedicating a customer representative specifically to an individual client, it represents the deepest and most intimate type of relationship and normally develops over a long period of time)
  - Self-Service (a company maintains no direct relationship with customers and it provides all the necessary means for customers to help themselves)
  - Automated Services (they mix a more sophisticated form of customer self-service with automated processes that can recognize individual customers and their characteristics, and offer information related to orders or transactions)
  - Communities (utilized to become more involved with customers/prospects and to facilitate connections between community members, online communities allow users to exchange knowledge/solve each other's problems and help companies better understand their customers)

- Co-Creation (this approach goes beyond the traditional customer-vendor relationship to co-create value with customers and it is about engaging customers to assist with the design of new and innovative products)

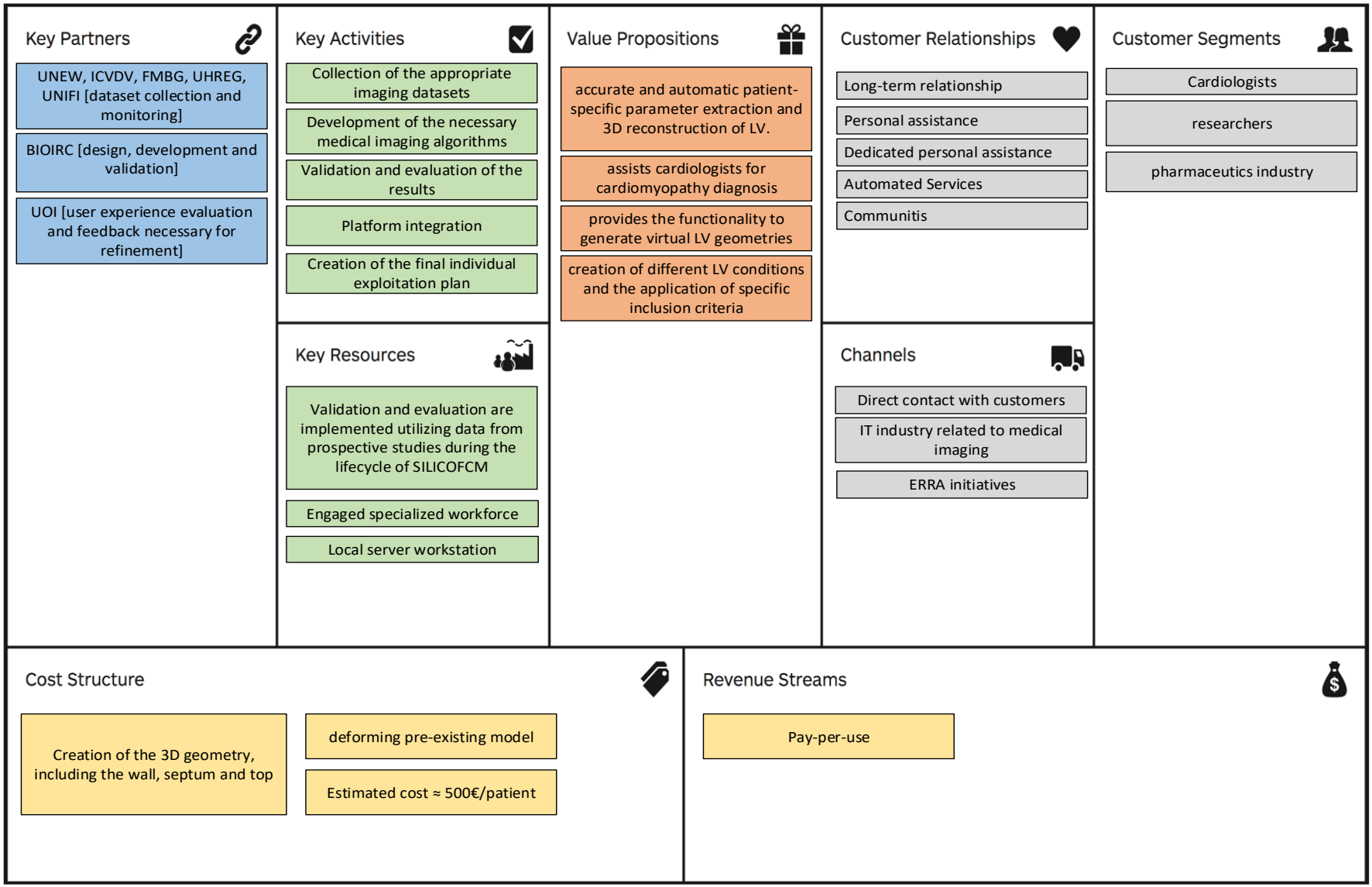

Figure 11: Business model canvas proposed for the 3D Image Segmentation tool

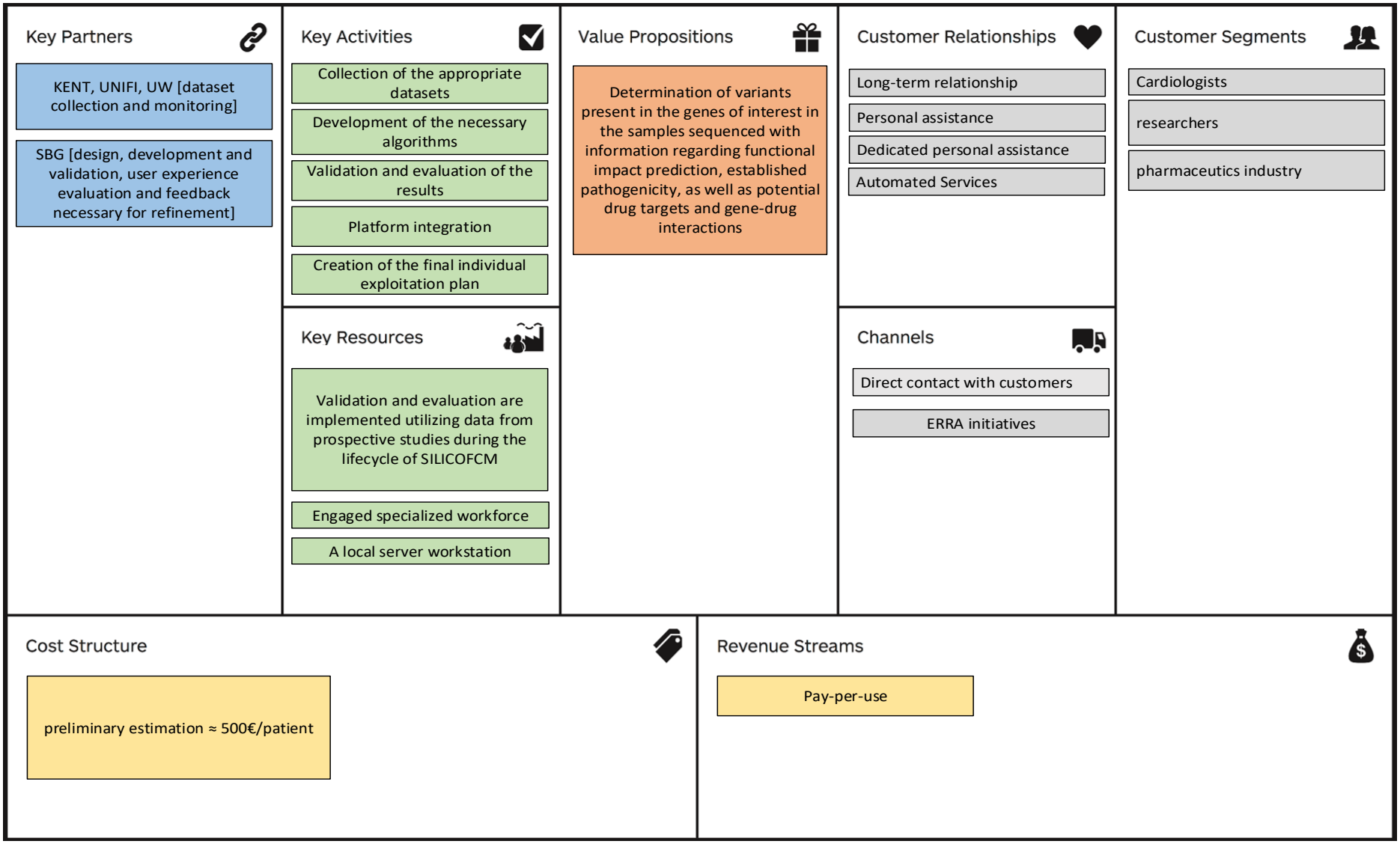

Figure 12: Business model canvas proposed for the Bioinformatics tool

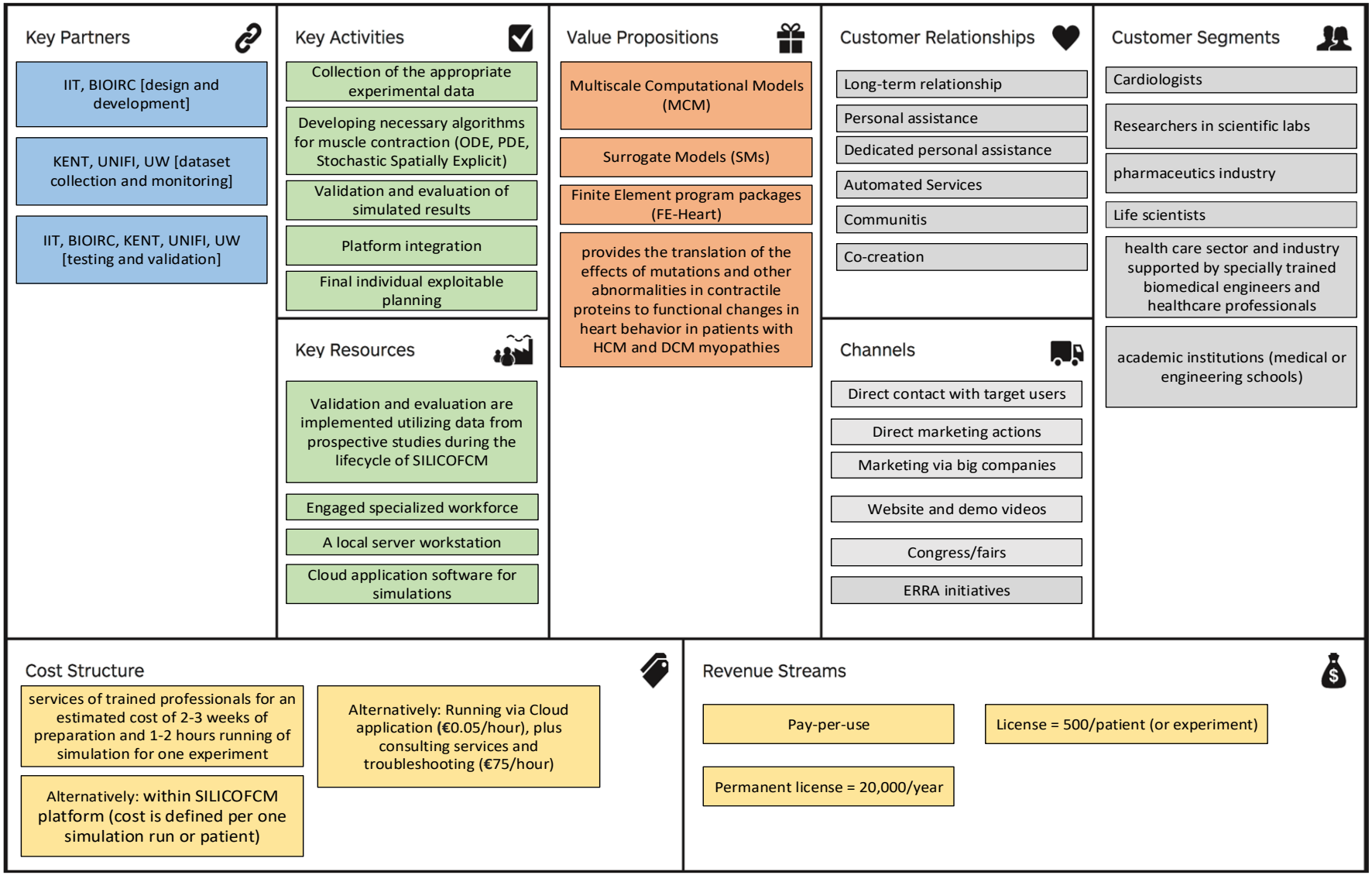

Figure 13: Business model canvas proposed for the MUSICO tool

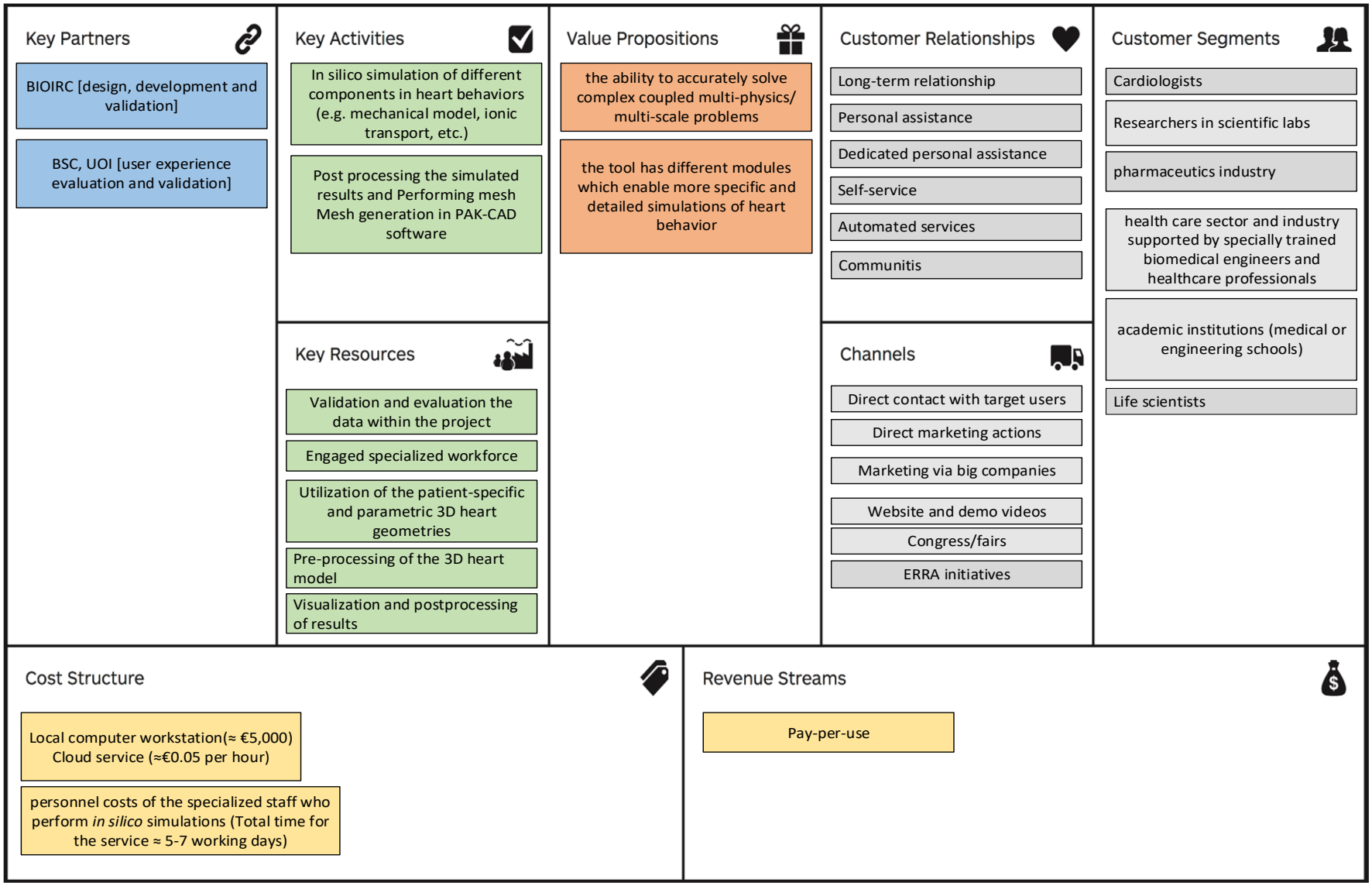

Figure 14: Business model canvas proposed for the Finite Element tool

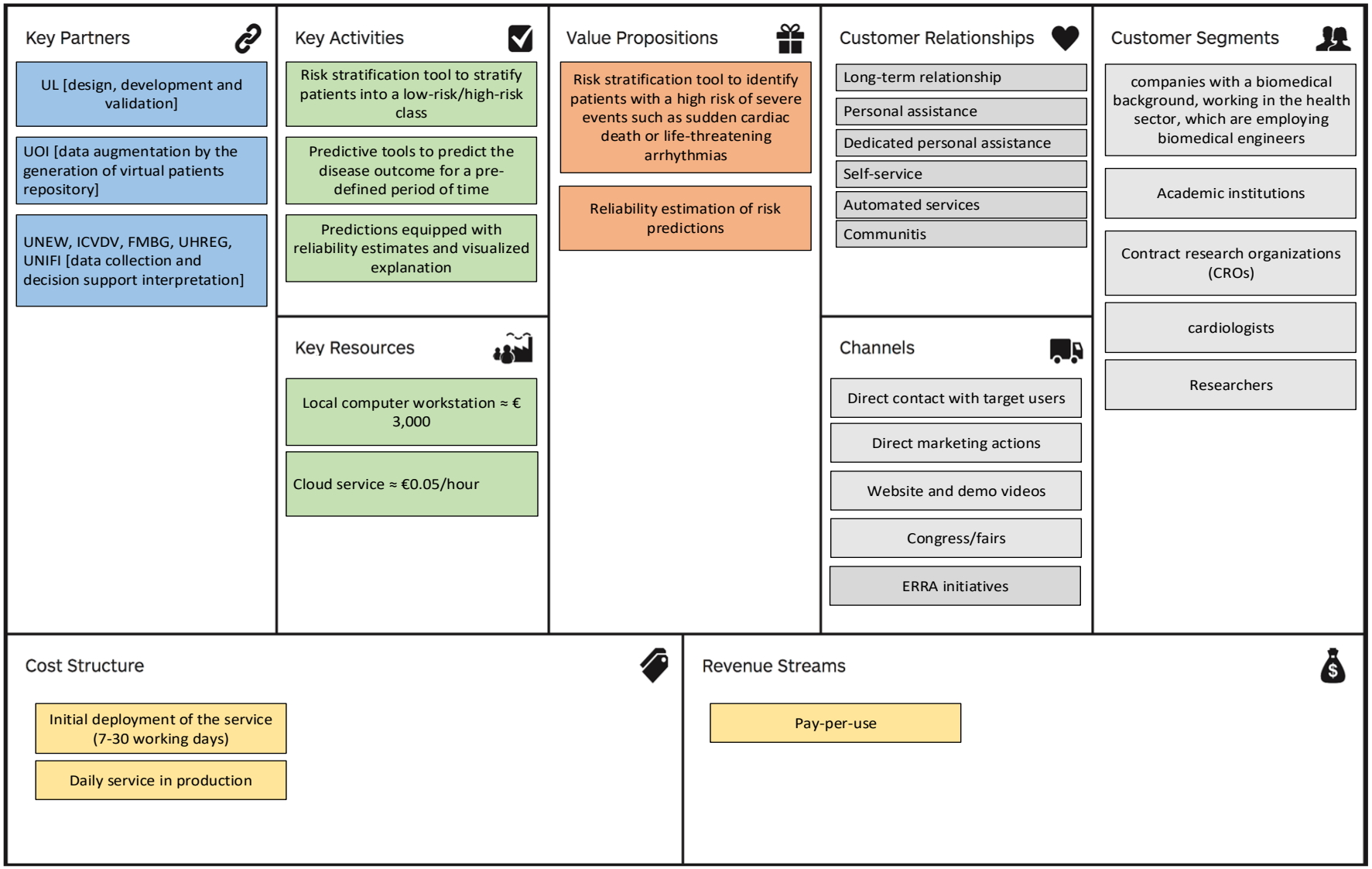

Figure 15: Business model canvas proposed for the Decision Support tool

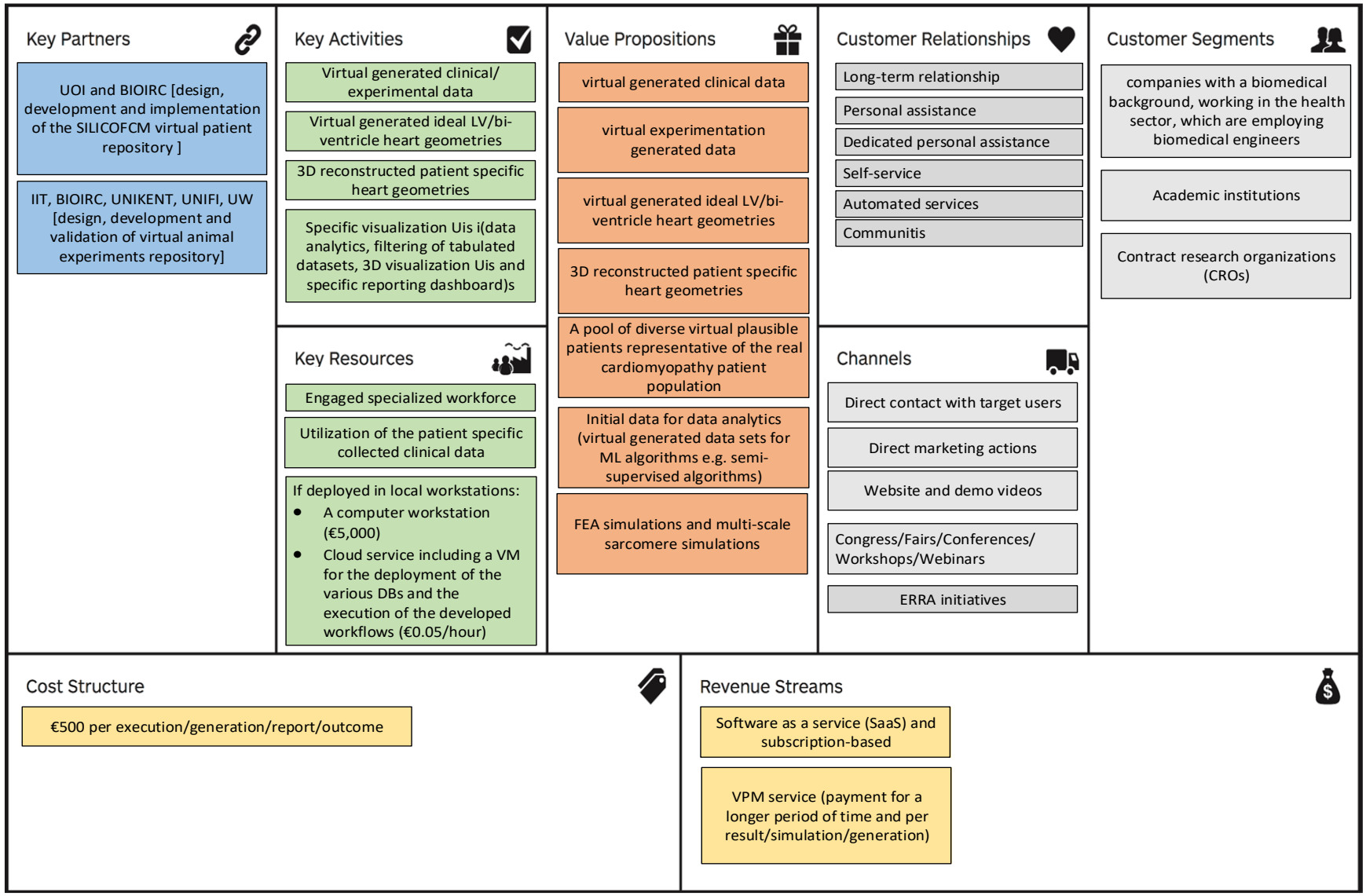

Figure 16: Business model canvas proposed for the Virtual Population tool

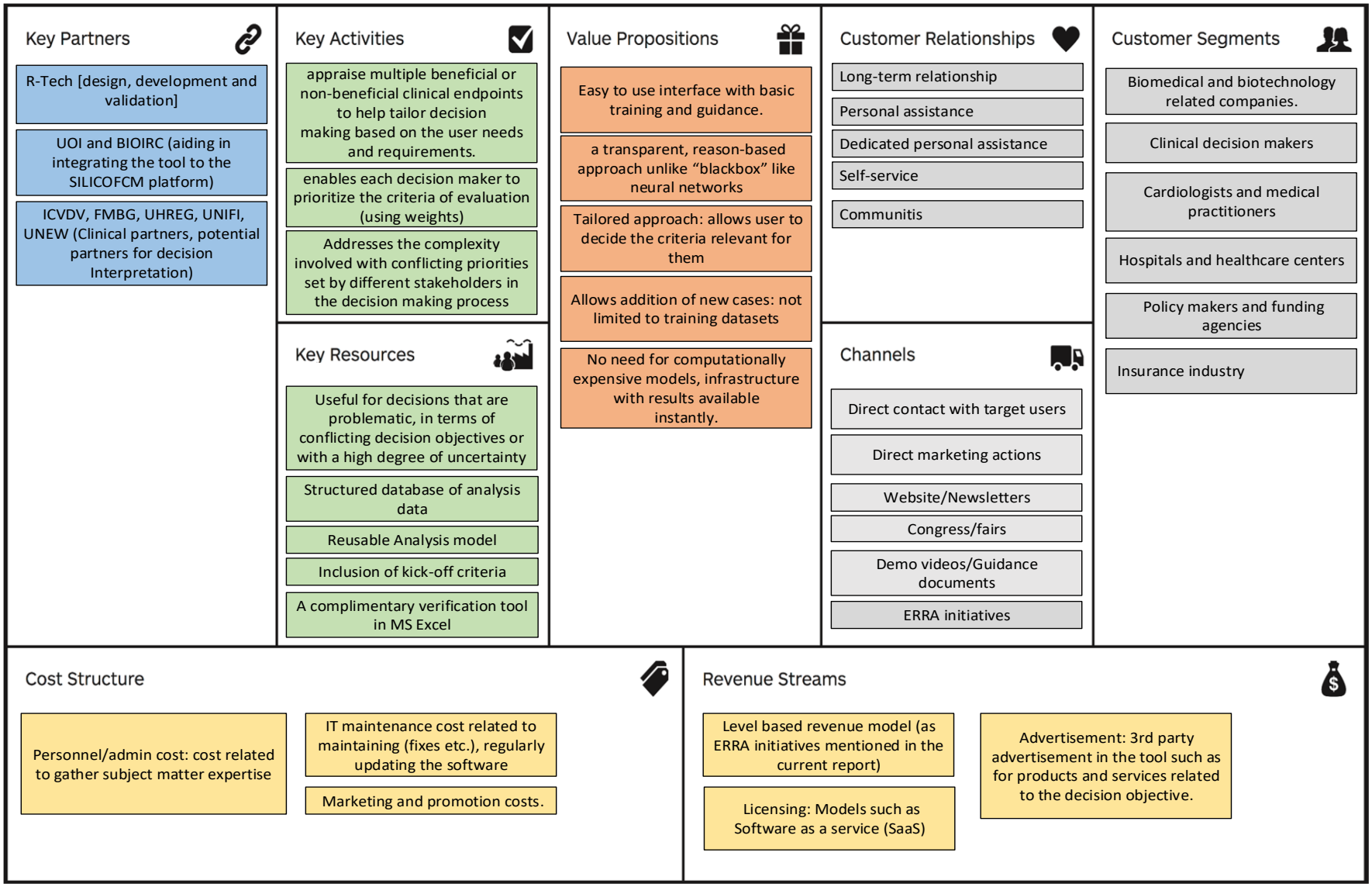

Figure 17: Business model canvas proposed for the MCDM tool

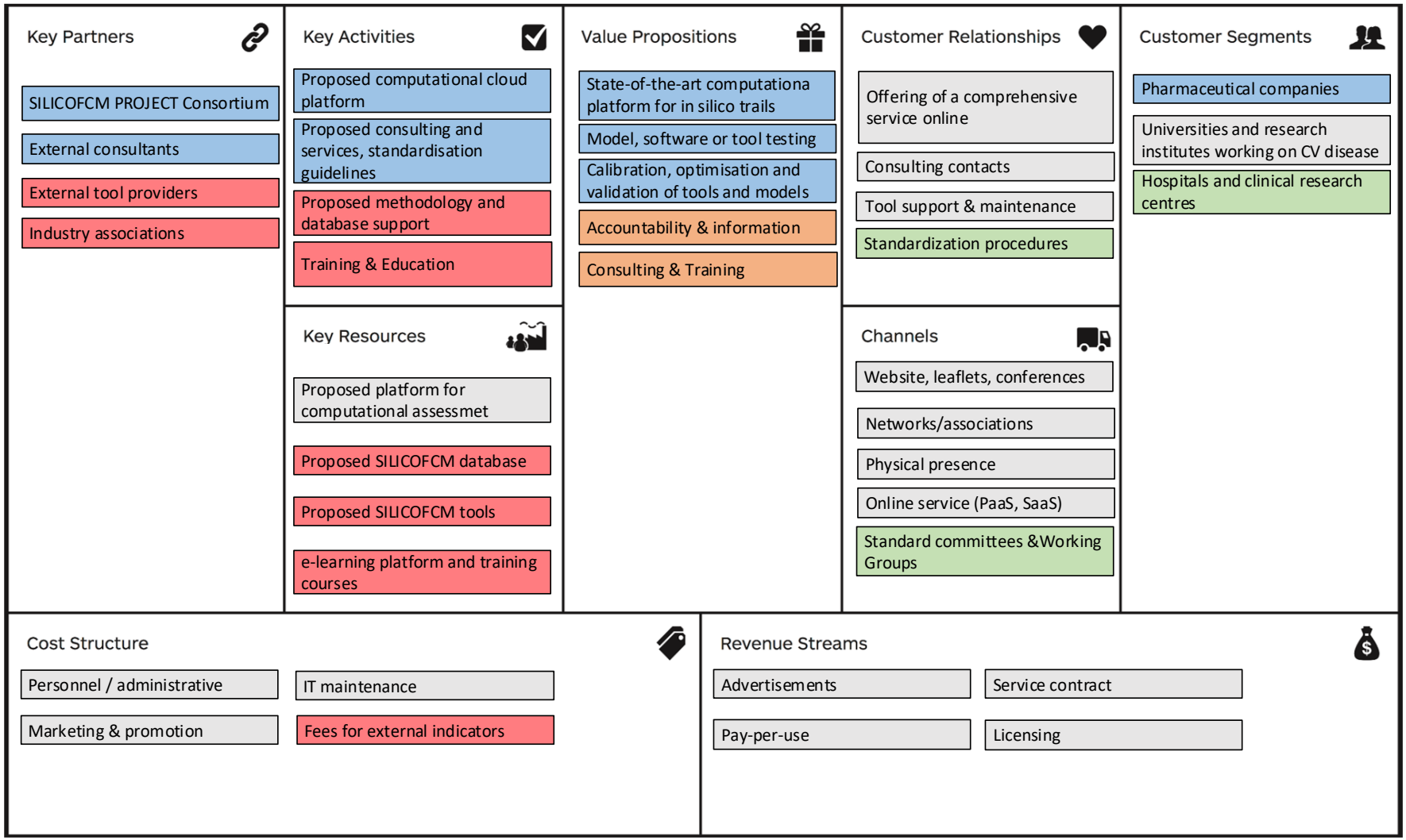

Figure 18: Business model canvas proposed for the FCM Services as a basis. Different colors are used to indicate the relationships between the elements at different sections

4. Service Options

The core idea of SILICOFCM project is to make the cloud computational platform connect:

- basic experimental research
- clinical study
- bioinformatics, data mining and image processing tools
- drug and patient database
- Regulatory engagement and framework

The goal of the SILICOFCM project is to promote the computational platform for *In silico* clinical trials, developed within the project duration. The approach uses very advanced computer models of FCM with the benefit of potentially reducing expensive and time-consuming animal and clinical studies.

At the end of the project, SILICOFCM project will provide an integrated platform for CAD patient management, classified as a TRL 6 (technology demonstrated in a relevant environment). Considering the output (software tools, databases, computational cloud platform etc. as described in D9.5) and its competitiveness in reaching the market, the SILICOFCM KERs can either be exploited individually or combined to be used as a user-friendly and easy to use software as research tool to offer an efficient and economical methodology for in silico drug trials. Detailed description of how the service is provided to different target users has been gathered in the previous versions of this deliverable (D9.6, D9.8).

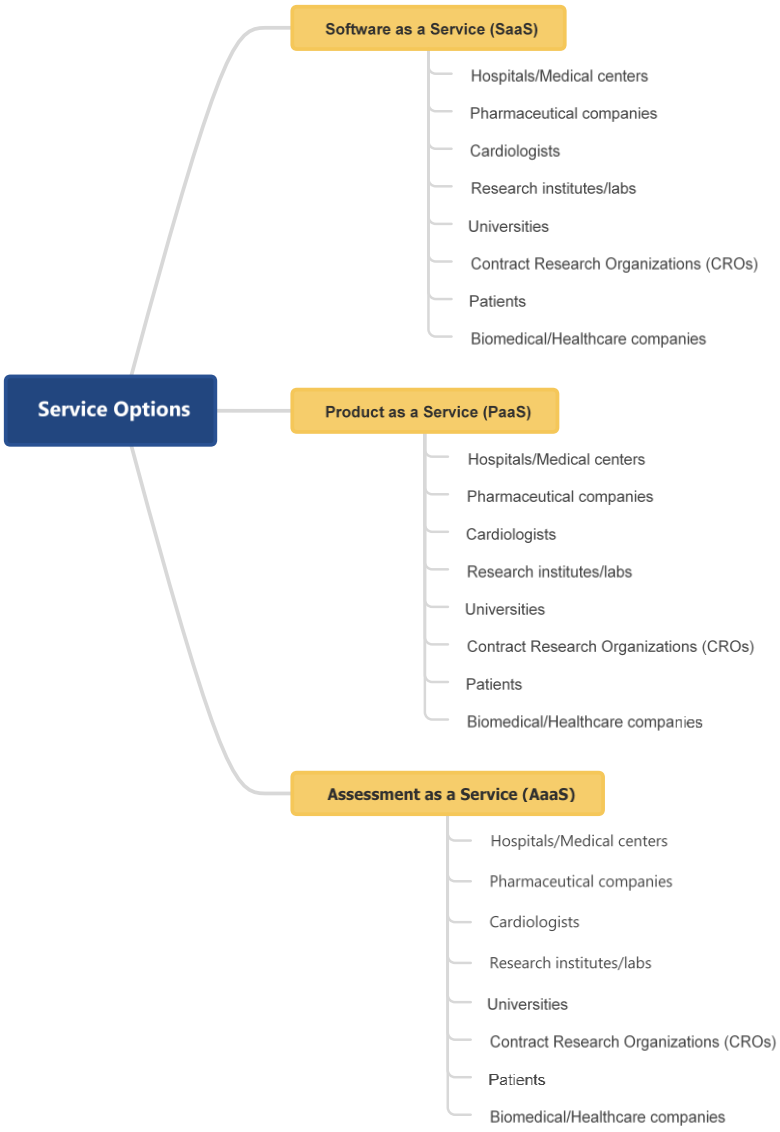

Figure 19: Service options for different target users in SILICOFCM project

In general, three common service options for exploiting the platform as shown in Figure 19 include:

4.1 Software as a product (SaaP):

It involves delivering a copy of the software product to the customer and the customer gets usage rights, usually in the form of a license, for using the software for a specified purpose. The customer does not get ownership of a product, but rights to use the software for a compensation back to the software company, in this case the legal entity. Cost of support and of providing maintenance releases is carried by the IP Lessor. The cost of operations of the solution and the license fees are carried by the customer.

4.2 Software as a service (SaaS):

Includes customer given access to the software as well as usage rights for a specified time and a specified purpose. The software runs at a hosting provider or in the cloud and is not delivered physically to the customer. The Inventor business pattern creates the software product that is underlying the service. The software is operated leveraging the business patterns physical lessor (hardware usage), IP Lessor (usage rights) and Contractor (operating, maintaining and supporting). The software company carries the sunk cost of development, the cost of support and maintenance as well as the cost of operations of the software. For most SaaS offerings in the market, the customer pays for the usage of the SaaS offering, but not for each of the business patterns contained in SaaS. Business canvas is shown in Section 3.

Before evaluating the specific service pathways, the KERs must be evaluated based on:

- **Value creation**: How does the platform create value for the targeted consumer? Does it lead to a dramatic lowering of the price and the time to generate usable results, or develop further solutions of value? Can the new researchers/scientists/medical personnel/developers can build, programme and share modules?
- **Value capture mechanisms**: Can the SILICOFCM platform be as a two-sided digital platform wedged between two sides of the market. On one side, it can provide the developers' community (external innovators developing their items using the free platform features) with additional paid services, such as professional technical support, training, form filling. On the other side, it maintains an online store allowing customers/consumers to create their own projects and build communities.
- **Scaling up**: to increase its market impact, SILICOFCM platform can also developing its business through API integration with other platforms, facilitating the connection with the tools on which other platforms are built. The entity responsible for the platform can engage the developers' community to scale up and prove itself in the market.
- **Strategies to build an ecosystem:** Can the platform engage the developers' community to leverage on indirect network effects?

4.3 Assessment as a Service (AaaS), ERRA initiatives:

This approach takes advantage from the European Risk & Resilience Assessment (ERRA) initiatives[25]. It can be performed together by the Initiative and the Initiative members (hospitals/institutes/individuals) bundling different competencies needed to meet the specific needs of specific application cases. In particular, the service will be performed by ERRA together with and subcontracting by its member organizations (organizational members and individuals) which have the different competencies needed to meet the specific needs of specific applications within the platform. In the most general terms, experts among ERRA members process the contract with customer and guarantee the quality of assessment. The user of ERRA services can first decide to make the self-assessment, then to audit it, and in the final step do the full-scale 3rd party audit. Main services provided by ERRA can be categorized into 3 levels as described in Figure 20.

[25] ERRA > Home ERRA NEW (eu-vri.eu)

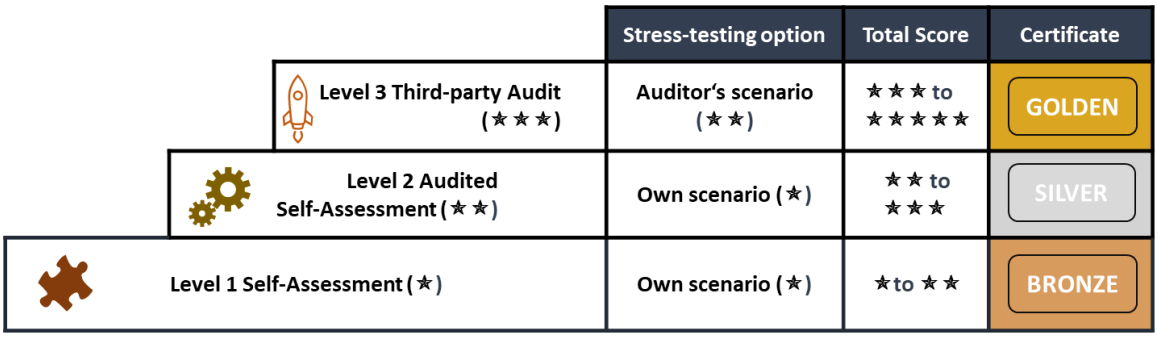

Figure 20: ERRA assessment level and score

- **Level 1: Free Service (no fee applied): Self-assessment (★):** The customer (end-user) registers at the platform and submits a request for using the tools. Once the request is approved, access right to the tool and supporting documents is granted.
  At Level 1, the end-user freely uses available tools & guidelines for self-assessment and has the option of perform the assessments by his own scenario (counted as an additional 1 star). In total, the end-user will get maximum 2 stars (★★), respective to a "BRONZE" Certificate issued by ERRA.

- **Level 2: Charged Service (audit fee applied): Audited self-assessment (★★):** At this level, the end-user's self-assessment is audited by ERRA appointed assessor/auditor. The customer has the option to either perform the modelling by his own scenario (counted as an additional 1 star), Assess the improvement of resilience in the case of investment scenarios with the consultation and support of involved experts or Choose consultation of other related services. In total, the end-user will get maximum 3 stars (★★★) with testing option or 2 stars without one, respective to a "SILVER" Certificate issued by ERRA.

- **Level 3: Charged Service (audit fee applied): 3rd Party Audit service (★★★):** At Level 3, ERRA provides 3rd party full-scale audit service performed by appointed assessor/auditor. The end-user will have all the options mentioned in Level 1 and 2 with additional. In addition, they will have the option to Perform the assessments by auditor's scenario (counted as an additional 2 star, which is different from other two levels or Choose the supporting services of the Initiative. I n total, the end-user will get maximum 5 stars (★★★★★) with audit option or 3 stars without one, respective to a "GOLDEN" Certificate issued by ERRA.

5. Regulatory landscape

The market reach of medical devices is regulated by clear legislation across the world. Manufacturers and producers need to comply with specified requirements, guidelines, testing methods and acceptance criteria for the specific country of registration. Time taken to introduce an innovative new medical device also varies depending upon the country and its regulatory policies. For example, EU's Medical Device Directive (MDD) provided quicker routes to the implementation of new devices than its equivalent in the USA, the Food and Drug Administration (FDA). FDA approval process in the U.S. demands not only product safety but the effectiveness.

5.1 The United States of America (USA)

In the United States, governmental risk assessment of medical devices is mainly based on recommendations from members of 16 medical speciality panels[26], and devices are categorized into three classes.

FDA approval process in the U.S. demands not only product safety but effectiveness. The medical devices are classified into a three-tiered classification system (I, II and III) in the U.S. This is based on the perceived risks associated with using a product. Class III devices are defined as those used for supporting or sustaining human life or are critical for preventing the potentially unreasonable risk of illness or injury. Class I and Class II devices are lower-risk devices.

5.2 The European Union (EU)

5.2.1 CE Mark

CE Mark is the requirement for health, safety, and environmental protection standards for selling and distributing products as a single market within the European Union. Without the CE Mark, the product produced in the EU or outside the EU cannot be sold or distributed within the European Union. The CE Mark represents compliance with a specific device regulation, which can be achieved either through a Competent Authority (Class I) or a Notified Body (Class Is, Im, IIa, IIb & III). For medical & in vitro diagnostic devices, the European Union requires compliance with two special regulations (MDR 745/2017 & IVDR 746/2017) in order to affix the CE Mark on a device. The normal procedure for CE Mark goes as follows[27]:

1. Identify the applicable directive for the product to understand if the product can be CE marked or not.
2. List out the requirements for the respective directive. Here, the classification of the product and its intended use by meeting the requirements of applicable harmonized European Norms.
3. Identify the appropriate route to conformity.
4. Assessment of the product to make sure that the essential requirement of the directive is met.
5. Compile the technical documents that consists of technical description, specification, details of any design, bills, manual, copy of declaration, etc.
6. Get a CE Mark

[26] https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device
[27] https://www.cemarkingassociation.co.uk/process/

5.2.2 EMA

In the EU, the classification scheme for medical devices are rule-based that categorize medical devices according to their perceived potential hazards. The European Union assigns three classes with class II being sub-divided into IIa and IIb (effectively, four classes)[28].

The EU is moving to replace the 40-year-old model, Medical Devices Directive (MDD), with the Medical Devices Regulation (MDR). MDR is considered as a more extensive regulatory document, introducing significant revisions to quality and safety standards and the range of regulated devices. This is because the Medical Device Regulation (2017/745)[29] repeals the following existing directives on medical devices:

- Medical Devices Directive [93/42/EEC]
- Active Implantable Medical Device Directive [90/385/EEC]

The regulation was published on 5 May 2017 and comes into force on 25 May 2020. Currently approved medical devices will have a transition time until 26 May 2020 to meet the requirements of new MDR. Once the classification of the medical device is done based on the regulation 2017/745, same regulation can be used to define the approval assessments as shown in Table 4.

Table 4: Conformity assessment procedure for MDR (Source: MD101 Consulting blog, https://blog.cm-dm.com)

Class #	QMS assessment	Technical file assessment	Clinical investigation	Post-market followings
I	Article 10	Self-declarations of conformity of Annex II and Annex III Technical Documentation	Not mandatory	Updated as appropriate
IIa	Annex IX QMS Chapters I, III	Annex IX Chapter II Technical Documentation per device category	Not mandatory, but difficult to avoid with innovative functions	Updated every two years
	Annex XI – Part A Production Quality Assurance	Annex II and Annex III Technical Documentation Assessed per device category		
IIb	Annex IX QMS Chapters I, III	Annex IX Chapter II Technical Documentation per generic device group	Not mandatory, but difficult to avoid with innovative functions	Updated every year
	Annex XI – Part A Production Quality Assurance	Annex X Type Examination		
III	Annex IX QMS Chapters I, III	Annex IX Chapter II Technical Documentation for every device	Mandatory	Updated every year and sent to Notified Body
	Annex XI – Part A Production Quality Assurance	Annex X Type Examination		

[28] http://ec.europa.eu/DocsRoom/documents/10337/attachments/1/translations/en/renditions/native
[29] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745

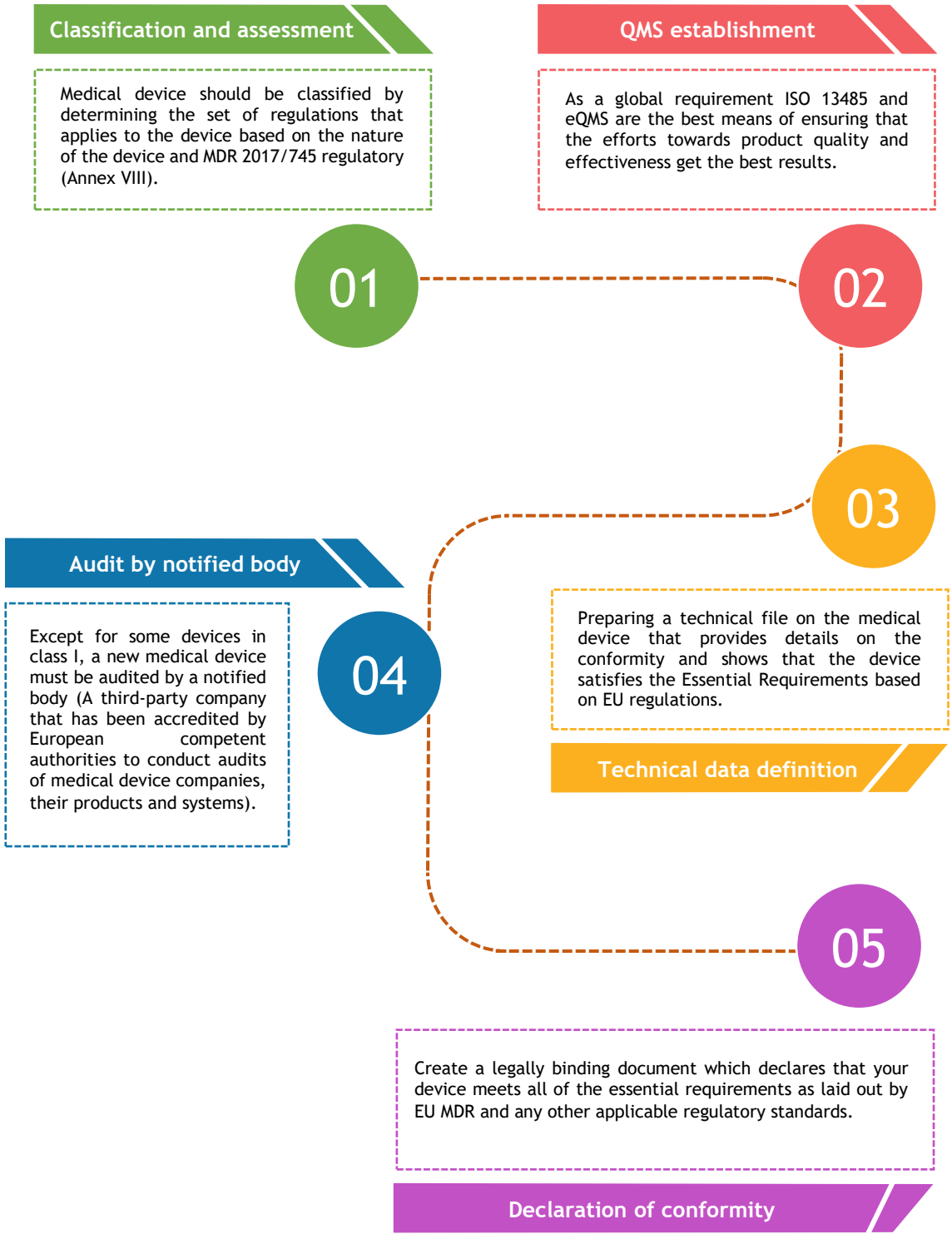

Figure 21: MDR admission process based on EMA regulations

Figure 21 depicts the 5-steps process to get the CE mark for medical devices based on European regulations. Implementation of the new European Medical Device Regulation (MDR) is expected to impact different stakeholders, such as the economic impact on manufacturers, due to the cost of implementation of new regulations for new devices and can also strongly affect distributors and importers. The MDR covers clinical evaluations and clinical investigations with medicinal devices in the EU, depending on the type of sponsor (industry, non-commercial, and academia). The new regulation will also have a significant impact on the introduction of new devices in short-term before its proper establishment and development of familiarity with it by the stakeholders.

Some of the crucial changes introduced in the MDR include (please refer to D9.1 for the full list):

- Notified bodies (NB), manufacturers and importers will be required to register (MDR certificate)
- Technical documentation (Annex II) must be updated continuously
- Labelling requirements have been massively increased
- Creation of a European database on medical devices (Eudamed) open to National Competent Authorities, Notified Bodies, Manufacturers, Importers, etc. will for the first time allow all the stakeholders to research devices so they will be able to make informed decisions before proceeding with procedures. For example, doctors and other medical professionals will be better informed of any device related issues and the public will have access to the same data[30].
- Harmonized Evaluation of high-risk devices

Therefore, the new MDR demands tremendous changes in this field, which have to be implemented by various stakeholders involved in manufacturing and distribution of medical device products in Europe and most importantly this has to be done in the above-specified timeframe.

5.3 China

The National Medical Products Administration (NMPA), previously the China Food and Drug Administration (CFDA), is the institution responsible for pharmaceuticals and medical devices regulations in China. Similarly, to the FDA in the United States, the NMPA classifies medical devices into three classes (from I to III) depending on their potential risk. Class I devices are associated with the lowest risk, while Class III devices are associated with the highest risk[31].

Class I–includes all devices, which safety and effectiveness can be ensured through routine administration.

Class II – includes all devices that require further control to ensure their safety and effectiveness.

Class III – includes devices that are used for life support or sustenance, pose a potential threat to patients' health, and are implanted into the body.

If a medical device company wants to register a device that is not manufactured in China, it is required that the company provide device samples to the NMPA for testing. In the case of registering Class II and Class III devices, manufacturers are obligated to send the appropriate documents showing that the device has been approved in its country of origin (i.e. CE Mark, 510(k) letter, ISO 13485 certification, approved Premarket Approval Application). It may also be required to provide supportive

[30] https://eudamed.eu/index.php/2018/09/19/mdr/
[31] https://www.emergobyul.com/sites/default/files/china-order-no-4-provisions-for-medical-device-registration.pdf

clinical data along with the application. All product information on packaging and labelling must be translated to Simplified Chinese.

Medical device registration in China is valid for 5 years. If a manufacturer wants to renew a device's registration, a renewal application should be submitted 6 months prior to the expiration date to the same department that received the original registration submission. Foreign manufacturers must also hire China-based agents that will represent their interests in China. The responsibilities of the designated agents include providing technical service and maintenance support for the device, assisting with device recall (if recall is required), overseeing the registration process, and providing support for the manufacturer in case adverse events occur due to device malfunction. Manufacturers should also provide the personal information of their designated agents (i.e. name, address, and contact information) in the registration application.

6. Conclusion

SILICOFCM aims to develop a computational platform for *in silico* clinical trials of Familial cardiomyopathies (FCMs) and will integrate a suite of software tools, back-end engines, back-end services, visual analytics dashboards and functionalities and databases to a “one-stop shop” cloud-based SILICOFCM platform. With an ageing population, changing lifestyle, increased chronic disease, as a background SILICOFCM through its comprehensive list of tools and solutions (KERs) are uniquely positioned to be exploited as services in a growing market for in silico products related to cardiomyopathy and other heart diseases.

Deliverable D9.9 presents an update to the Roadmap on Business Model based on the existing key exploitable results (KERs) developed during the SILICOFCM project. The report analyses seven KERs as individual services with one integrated service for the SILICOFCM platform. The KERs include the: (i) 3D image segmentation tool, (ii) Bioinformatics tool, (iii) MUSICO tool, (iv) Finite element tool, (v) Decision support (Risk stratification) tool, (vi) Virtual population tool for animal experiments and human trials, (vii) multi-criteria decision making (MCDM) tool and ultimately, the (viii) SILICOFCM platform.

The technology watch and market analysis in this report focusses on the global and industry-specific trends to monitor the dynamic scientific, technological, regulatory landscape especially following the COVID-19 pandemic. With biotechnology and healthcare industries expected to grow at an increasing rate in the next decade, SILICOFCM with its suite of value-added tools and solutions is well placed to benefit from this trend. Three potential service options including Software as a product (SaaP), Software as a Service (SaaS) and more recently, Assessment as a Service (AaaS) are explored for the SILICOFCM platform. . The next version of the business model will include modelling of different service option scenarios related to the uptake of the platform, with a detailed revenue stream for each of the KERs projected in the future. It is expected to act as a foundation for the next version of the roadmap on business model including the feedback and suggestions expected from the planned stakeholder and end-user meetings expected to be held during the latter half of the year 2021.

The section on exploring the regulatory challenges and landscape for the SILICOFCM platform (and the associated tools) are explored in Chapter 5, with an update to the EU regulation 2017/745 on medical devices (MDR). This information would also be used for developing a reporting tool in WP 8: Report to FDA or EMA.