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Project acronym: SILICOFCM

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Disclaimer

Executive summary

Deliverable report D9.10 is the final iteration and version of the Roadmap on Business Model for the SILICOFCM project key exploitable results (KERs), with the first, second and third versions of the report submitted in M12, M24 and M36, respectively. The report analyses the business road map for the KERs as of until M45, 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 in the field of in silico platforms for clinical trials, in order to differentiate the unique value proposed by SILICOFCM KERs (Chapter 2). The technology watch and market analysis use several tools 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 consists of the business model canvases including the key elements of the SILICOFCM KERs by setting their value proposition, the key players, services, infrastructure and core components needed for launching. Three potential service options suited to exploit the SILICOFCM KERs beyond the project duration are presented in Chapter 4. An example financial analysis of launching SILICOFCM Platform-as-a-service is provided as an application case based on best and worst-case scenarios with different service options (Section 5). Chapter 6 explores the regulatory landscape for the medical device software, with potential business impacts of the EU regulation 2017/745 (MDR) on SMEs. Following the SILICOFCM (online) review meeting in July 2021, key updates are highlighted based on the reviewers' comments in addition to the updates from the last report D9.8 (M36) including:

Comments from the Review meeting	Updates
C1. The list of competing EU research projects is outdated as no related project that has started after 2017 has not been identified	The list of the competing EU research projects is updated and presented in Table 1. Additionally, text-based analysis of related projects has been performed and analysed using a text analytics tool called "SRD-I". The resultant network graph based on the similarity of keywords in their project description obtained from the CORDIS website is shown in Figure 1.
C2. The target number of patent applications should be included in D9.10	The most relevant patent applications which can impact the exploitation of the SILICOFCM platform are compiled in Table 2. The textual description of the patents is then analysed using the text analytics tool, the "SRD-I".
C3. It is not clear how the obtained trend analysis findings contribute to the formulation of a business model and a link is missing between these findings and the various business model elements.	The link between the trend analysis indicating the popularity and market interest and business model is included as an introduction to Section 2.3.
C4. The AaaS (Assessment as a Service) option included in the deliverable is valuable, but the justification on its applicability across the SILICIFCM tools is not sufficiently detailed in D9.9	An example of a financial analysis of launching SILICOFCM Platform-as-a-service combining the individual tools and models is provided as an application case based on best and worst case business scenarios with different service options (Section 5).
C5. Even though the details on the regulatory landscape are valuable, clear links to their impact on the SILICOFCM business plan and model need to be identified in D9.10	The possible impacts of the new Regulation (EU) 2017/745 for medical devices (MDRs) can have on medical technologies including medical device software is described in Section 6.

Table of Contents

1 Introduction 7
2 Innovative technology watch and updated market analysis 9
2.1 SILICOFCM's Competing EU research projects 9
2.2 Competing Patents 12
2.3 Trend Analysis 14
2.3.1 Google Trend Analysis 15
2.3.2 AnswerThePublic Analytics 19
2.4 SILICOFCM KERs and targeted end users and competitors 21
2.5 Network oriented bibliography analysis 22
3 Business model canvases for the KERs 24
4 Service Options 34
4.1 Software as a product (SaaP): 35
4.2 Software as a service (SaaS): 36
4.3 Assessment as a Service (AaaS), ERRA initiatives: 36
5 Revenue Model and Financial Analysis 38
6 Regulatory landscape and its impact 40
6.1 The United States of America (USA) regulatory landscape 40
6.2 The European Union (EU) regulatory landscape 40
6.2.1 CE Mark 40
6.2.2 EMA Medical Device Regulation (MDR 2017/745) 41
6.3 China regulatory landscape 44
7 Conclusion 46
8 References 47

List of Figures

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) 11
Figure 2: SRD-I analysis of current patents related to SILICOFCM *in silico* platform. The network graph is computed from a similarity score calculated by overlap of semantic similarity of patent descriptions (obtained from Google Patents, see Table 2 for the selected patents) 12
Figure 3: Google Trend Analysis for the keyword *in silico* 16
Figure 5: Google Trend Analysis for the related key words over a 5 years period 17
Figure 6: Google Trend Analysis for the related keywords (Feb. 2017- May. 2021) 17
Figure 7: Google Trend regional analysis for the related keywords 18
Figure 8: Google Trend regional analysis for the keyword *Cardiomyopathy* 18
Figure 9: Search insights for the keyword *Cardiomyopathy* 19
Figure 9: Search insights for the keyword Cardiomyopathy combined via propositions 20
Figure 11: Bibliographic couplings of institutions publishing articles on risk stratification tool 23
Figure 12: Business model canvas proposed for the 3D Image Segmentation tool 26
Figure 13: Business model canvas proposed for the Bioinformatics tool 27
Figure 14: Business model canvas proposed for the MUSICO tool 28
Figure 15: Business model canvas proposed for the Finite Element tool 29
Figure 16: Business model canvas proposed for the Decision Support tool 30
Figure 17: Business model canvas proposed for the Virtual Population tool 31
Figure 18: Business model canvas proposed for the MCDM tool 32
Figure 19: 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 33
Figure 20: Service options for different target users in SILICOFCM project 35
Figure 21: ERRA assessment level and score 37
Figure 22: MDR admission process based on EMA regulations 43

List of Tables

Table 1: Other EU H2020 funded projects from CORDIS that have similar ambition as SILICOFCM. ... 10
Table 2 Patent search analysis for SILICOFCM 12
Table 3: The estimated market size, market maturity, market by application, key players and expected release for commercialization. 20
Table 4 An example of financial analysis of launching SILICOFCM Platform-as-a-servicee in one country: Serbia 39
Table 5: Conformity assessment procedure for MDR 41

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

It is estimated that about 1 to 3 billion dollars is spent on developing a new drug. With only one out 5000 drugs developed reaching the market, it can be assumed that the development of drugs is highly competitive with most of the drug candidates with several years of study often not resulting in a marketable product. COVID-19 pandemic showed that this overly-long and expensive needs to be accelerated. And as evident from the contributions from in silico studies drugs including cobicistat, ritonavir, lopinavir, and darunavir on their potential effectiveness as CoV-2 protease inhibitors (Pant et al. 2020; Shah, Modi, and Sagar 2020), simulation is the best way to speed up development of new drugs.

The main barriers in this transition from physical to in silico clinical trials are mainly three including (i) the very high costs to develop new computational models; (ii) the costs for the IT infrastructure and software that go into making them work; (iii) the high expertise required for their use. Presently, only large pharmaceutical companies can afford to use simulation[1].

The global bio-simulation market was estimated to be around $ 1.65 billion in 2018 and is expected to hit 4.58 billion by 2025, with a CAGR of 15.7% between 2019 and 2025. One of the goals of SILICOFCM is to facilitate access to a computational cloud platform for conducting in silico trials of Familial cardiomyopathies (FCMs), developed within the SILICOFCM project. It is expected that based on the simulation results, it would be possible to test and optimize the new and existing drug molecules ensuring they meet as all the safety requirements to be authorized and be accessible to patients.

The SILICOFCM project delivers 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 D9.10 – Road map on Business Model v3, is the 4^{rth} and final 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 relevant 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. The data-driven results from the analysis can be used to identify potential risks and opportunities before the end of the project and the consequent launch of the SILICOFCM cloud platform.

[1] https://thehealthcareinsights.com/insilico-trials-launches-a-simulation-model-that-accelerates-the-development-of-new-medicine-with-cloud/

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 is 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, this deliverable report will serve as a Roadmap on Business Model for the SILICOFCM consortium members with clear avenues of exploiting the SILICOFCM platform as a product.

2 Innovative technology watch and updated market analysis

The innovative 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.

The updated market analysis is done based on the interaction chain between various end users and other stakeholders and further researches. 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 SILICOFCM's 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.

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

Project	Brief summary	Relevant Keywords	Start and End Dates
INSPIRE[2]	INSPIRE aims to advance and "inspire" Safety Pharmacology by exploring new technological capabilities to address emerging cardiovascular safety concerns.	✓ prediction of adverse effects ✓ cardiovascular events	01/01/2020 - 31/5/2024
SimCardioTest[3]	SimCardioTest project aims to implement computer modelling, simulation and artificial intelligence to design and test cardiac drugs and medical devices. Scientists will establish a platform for running in silico trials and obtaining scientific evidence based on controlled investigations.	✓ In silico trials ✓ Cardiac drugs ✓ Computer Modelling	01/01/2021 – 31/12/2024
MDOT[4]	MDOT project develops a series of coordinated procedures to support SMEs to bring testbeds and device innovations to the level of clinical evaluation. The project will enable conformity assessment using a database procedure and access to medical device testing data through a secure and transparent platform	✓ Clinical evaluation ✓ Medical Device	01/01/2019 - 31/12/2023
C3-Cloud[5]	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
MYOCURE[6]	MYOCURE project aims to develop an innovative gene therapy platform to cure rare hereditary muscle disorders, specifically focusing on myotubular myopathy (MTM) and glycogen storage disorder (GSD) type II.	✓ Medical Device ✓ Platform	01/01/2016 - 31/12/2019
ATMOSPHERE[7]	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 pipelines	01/11/2017 - 31/10/2019
EurValve[8]	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	01/02/2016 - 31/01/2019
HEARTEN[9]	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

[2] https://cordis.europa.eu/project/id/858070
[3] https://www.simcardiotest.eu/
[4] https://mdot.eu/
[5] https://c3-cloud.eu/
[6] https://cordis.europa.eu/project/id/667751
[7] https://www.atmosphere-eubrazil.eu/
[8] https://www.eurvalve.eu/
[9] http://www.hearten.eu/

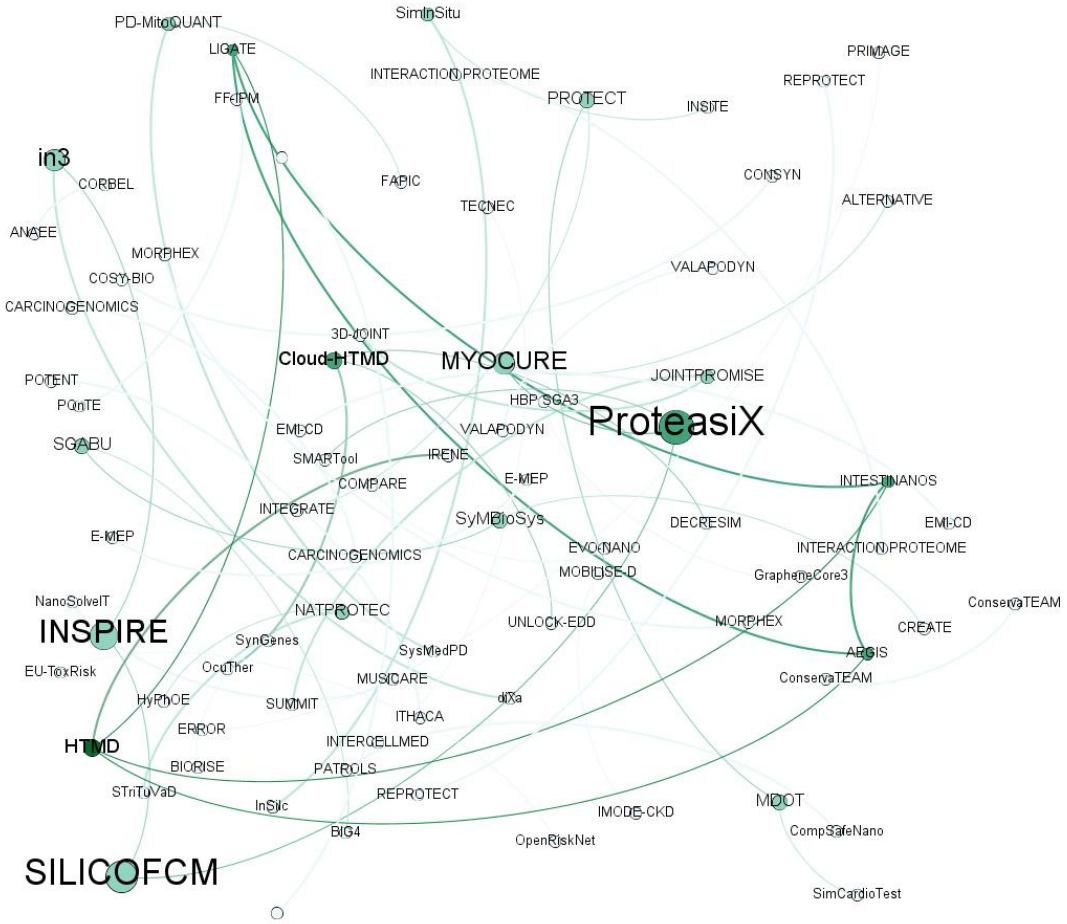

Figure 1: SRD-I analysis for competing projects. The network graph is computed from a similarity score calculated by overlap of semantic similarity of project descriptions (obtained from CORDIS)

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 node (circle) size is proportional to its document centrality or eigenvector centrality. The 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. The colour indicates the node's degree (the deeper the green, the higher the degree). The thickness of the links indicate projects' similarities.

The network graph (in Figure 1) shows that SILICOFCM has a relatively high "influence" or centrality score (0.64) in the field with project centrality scores ranging from 0.17 (Primage) to 0.80 (ProtesiX). SILCOFCM as seen in the graph has a unique position within in its domain and linked to only couple of projects in the field. The links it shares among other EU project includes the one from INSPIRE and ProteasiX based on the analysis.

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.

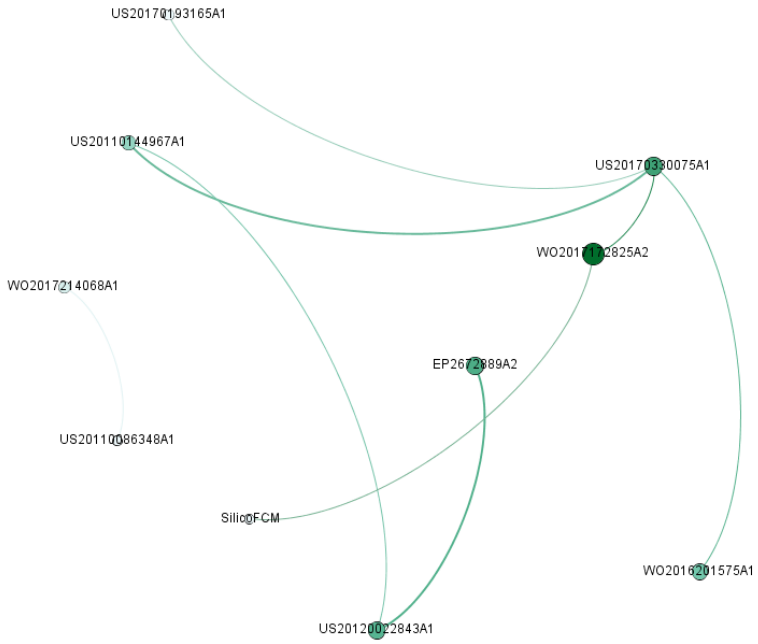

Figure 2: SRD-I analysis of current patents related to SILICOFCM *in silico* platform. The network graph is computed from a similarity score calculated by overlap of semantic similarity of patent descriptions (obtained from Google Patents, see Table 2 for the selected patents)

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 https://patents.google.com/patent/WO2017172825A2/en	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

Patent number	Title	Abstract	Year of publication	Status
US20110144967A1 https://patents.google.com/patent/US20110144967A1/en	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 https://patents.google.com/patent/US20120022843A1/en	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 https://patents.google.com/patent/EP2672889A4	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 https://patents.google.com/patent/US20110086348A1/en	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
WO2017214068A1 https://patents.google.com/patent/WO2017214068A1/en	Systems and methods for patient stratification and identification of potential biomarkers	The method includes processing molecular profile data for a plurality of subjects where the molecular profile data includes data obtained before, during and/or after administration of an agent to the plurality of subjects	2017	US/Pending
WO2016201575A1 https://patents.google.com/patent/WO2016201575A1/en	Systems and methods for predicting cardiotoxicity of molecular parameters of a compound based on machine learning algorithms	Systems and methods are provided for predicting cardiotoxicity of molecular parameters of a compound. A computer can provide as input to a machine learning algorithm the molecular parameters of the compound. The	2016	US/Pending

Patent number	Title	Abstract	Year of publication	Status
		molecular parameters can include at least structural information about the compound. The machine learning algorithm can have been trained using respective molecular parameters of compounds known to have cardiotoxicity and of compounds known not to have cardiotoxicity.		
US20170330075A1 https://patents.google.com/patent/US20170330075	System and method for deep learning based cardiac electrophysiology model personalization	A method and system for deep learning based cardiac electrophysiological model personalization is disclosed. Electrophysiological measurements of a patient, such as an ECG trace, are received. A computational cardiac electrophysiology model is personalized by calculating patient-specific values for a parameter of the computational cardiac electrophysiology model based at least on the electrophysiological measurements of the patient using a trained deep neural network (DNN). The parameter of the computational cardiac electrophysiology model corresponds to a spatially varying electrical cardiac tissue property.	2017	US/Pending
US20170193165A1 https://patents.google.com/patent/US20170193165	Method and system for managing patient healthcare prognosis	The disclosed system consists of web and mobile applications, engaging healthcare all stakeholders in healthcare to continuously collect the data, monitor, intervene and learn to predict and prevent the incidents which is avoidable and can make the care quality superior and available to all sorts of patients; young or old and near or remote. Current application platform focuses on Cardiac and other related comorbid chronic diseases.	2016	US/Abandoned
WO2017106196A1 https://patents.google.com/patent/WO2017106196A1/en	Compositions and methods for treating cardiac dysfunction	The invention provides compositions and methods for treating cardiac dysfunction, particularly cachexia-associated or RAGE-associated cardiac dysfunction, using an anti-RAGE agent. The invention also provides compositions and methods for identifying therapeutic agents useful for disrupting (slowing, reducing, reversing, or preventing)	2016	WO/Application Filing

2.3 Trend Analysis

A trend can be defined as an assumed future development or as an overall direction of the market. And a trend analysis is the process of comparing macro data over time to identify any consistent results or trends. This can facilitate developing a strategy to respond to these trends in line with the business goals.

There are different kinds of trends such as macro trends, historical trends, geographical trends, consumer trends etc. We limit ourselves discussing the macro trends and the historical trends for this report.

Macro trends are the trends which develop over a long period of time and affect the majority of the industries. They are often caused by major shifts in society and the global economy. For example, the collapse of major banks in the U.S. in the financial crisis of 2009 had a striking impact on consumer demand and spending habits as the stock market plummeted. Analysing these trends provides an overview of the global market and developments with long-lasting consequences. It's crucial to keep these in mind for your overall business strategy.

Historical trends provide insights on how a product or service is developing or has developed in the past. The time frame can range anywhere from the past 24 hours, the previous week, and even three months to several years ago. An example is shown for such a trend in Section 2.3.1.

Identifying macro and historical trends in the market can allow new business ventures such as the SILICOFCM Platform can:

- identify areas or markets where the in silico platform for clinical trials be well-received grow
- identify areas or markets where the business can underperform based on the macro-level trends used as indicators
- develop an understanding and insight of consumer behaviour, especially related to their search result for services required which can be used to tailor the product and business, accordingly.

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 3.
- 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 4, Figure 5, Figure 6 and Figure 7.

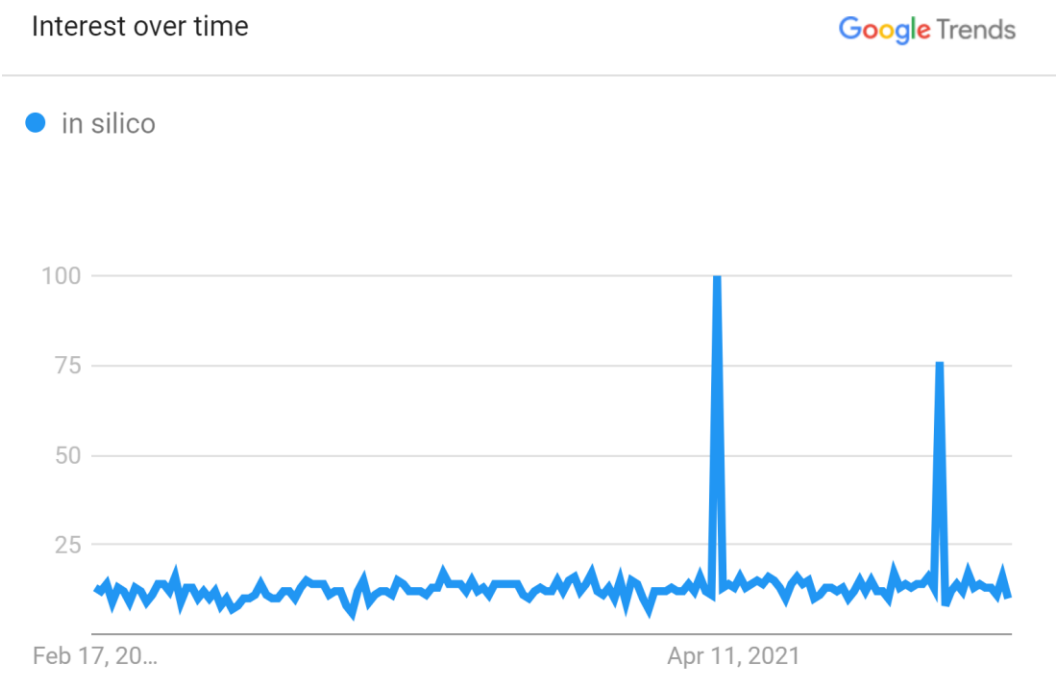

Figure 3: Google Trend Analysis for the keyword *in silico*

The Google trend analysis of the keyword "*in silico*" for the last 36 months from March 2019 to 2022 (Figure 3) shows an increasing interest in "in silico" as a topic (a positive slope of 0.5% on linear trend line) and a search keyword with an unusual spike at the beginning and end of year 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 4 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.

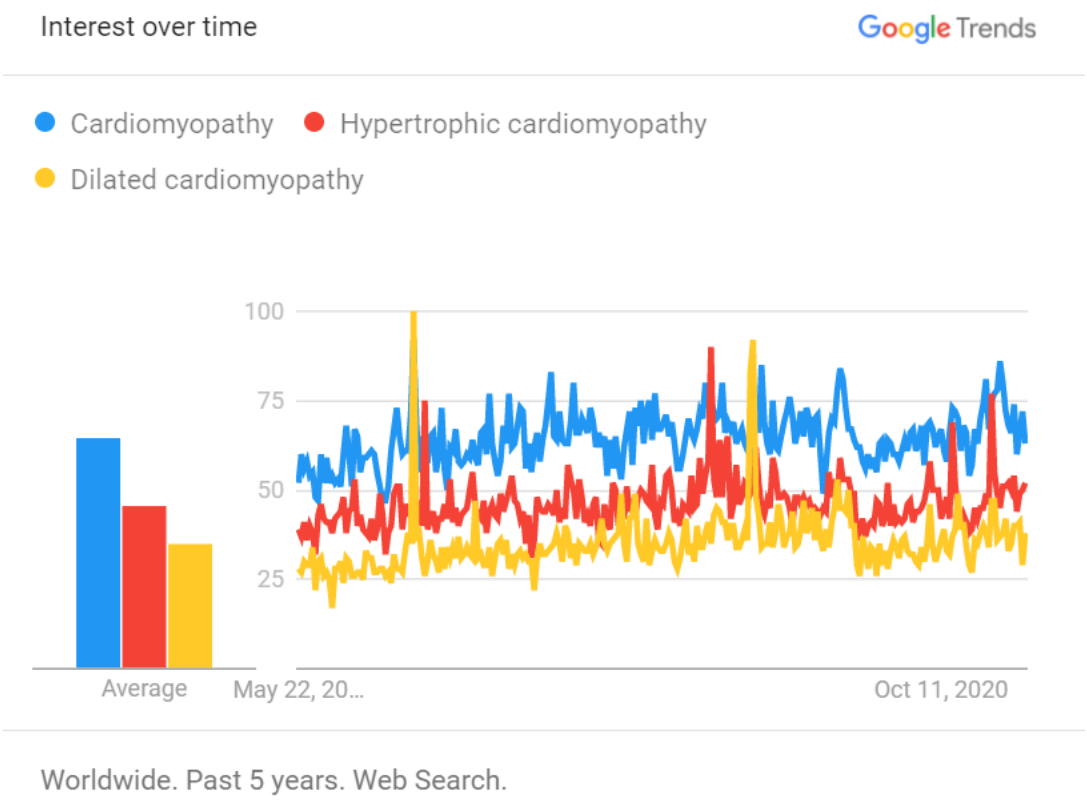

Figure 4: Google Trend Analysis for the related key words over a 5 years period

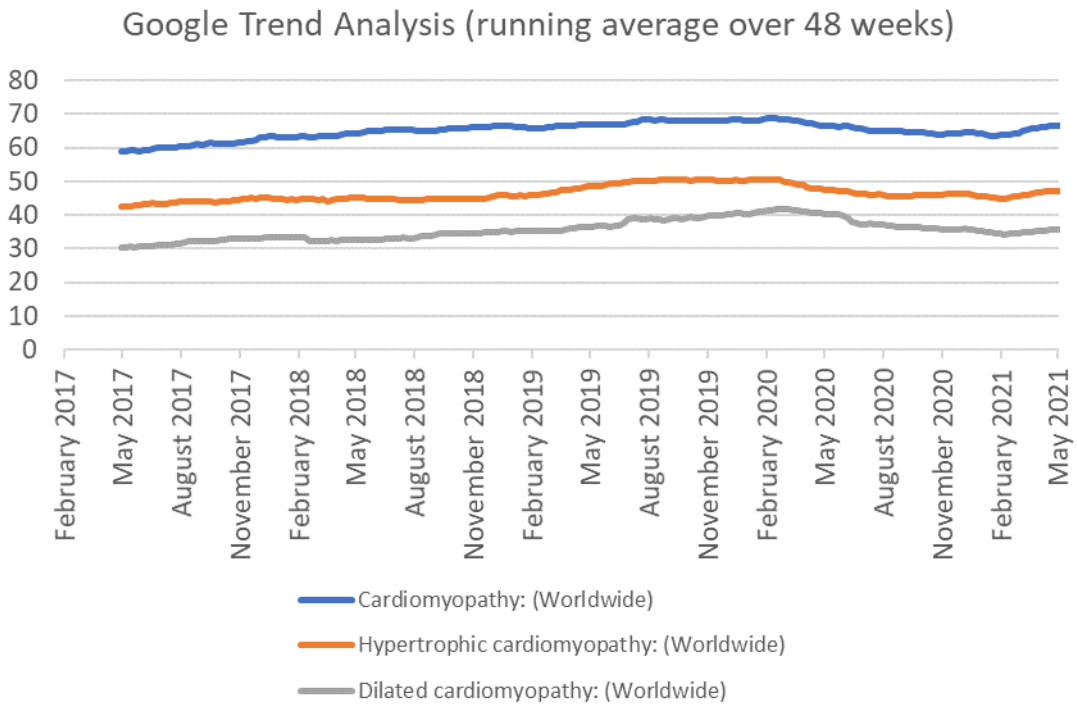

Figure 5: Google Trend Analysis for the related keywords (Feb. 2017- May. 2021)

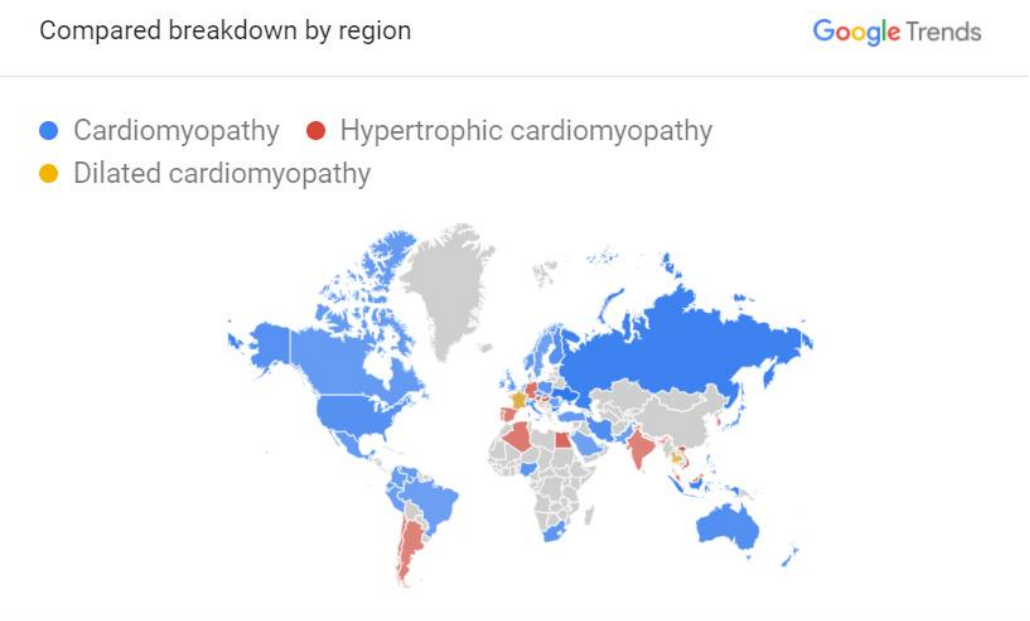

Figure 6: Google Trend regional analysis for the related keywords

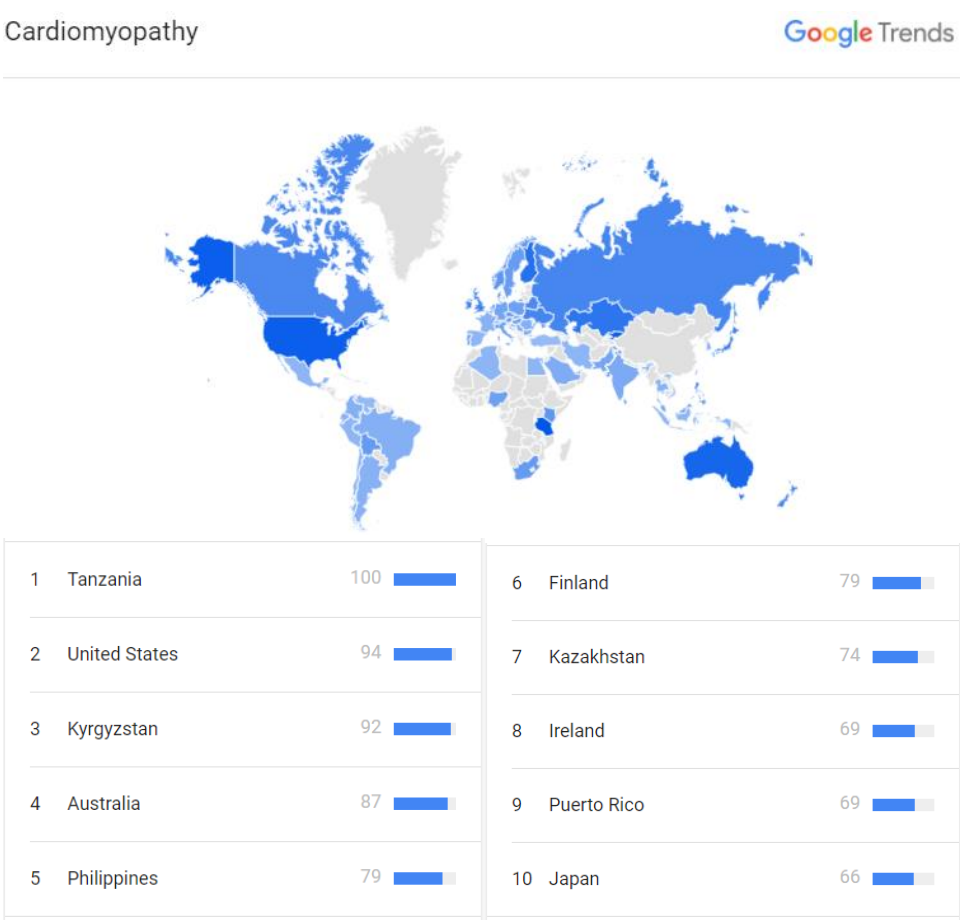

Figure 7: Google Trend regional analysis for the keyword *Cardiomyopathy*

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 8. Furthermore, the tool also analyses "preposition" keywords (where the keyword cardiomyopathy is combined with another keyword via a preposition), shown in Figure 9 and "comparisons" where the keyword is compared with another keyword as shown in Figure 10.

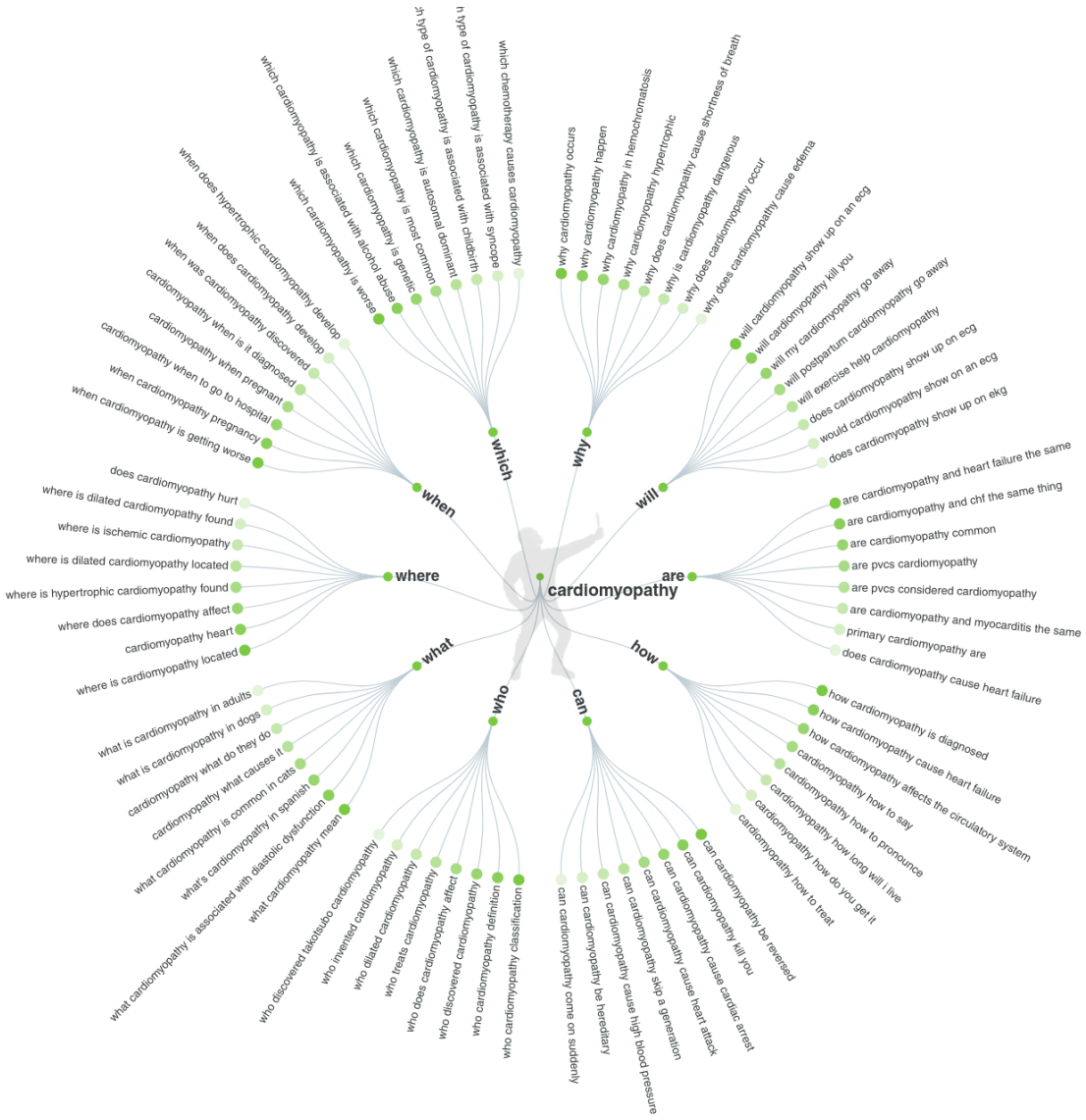

Figure 8: Search insights for the keyword *Cardiomyopathy*

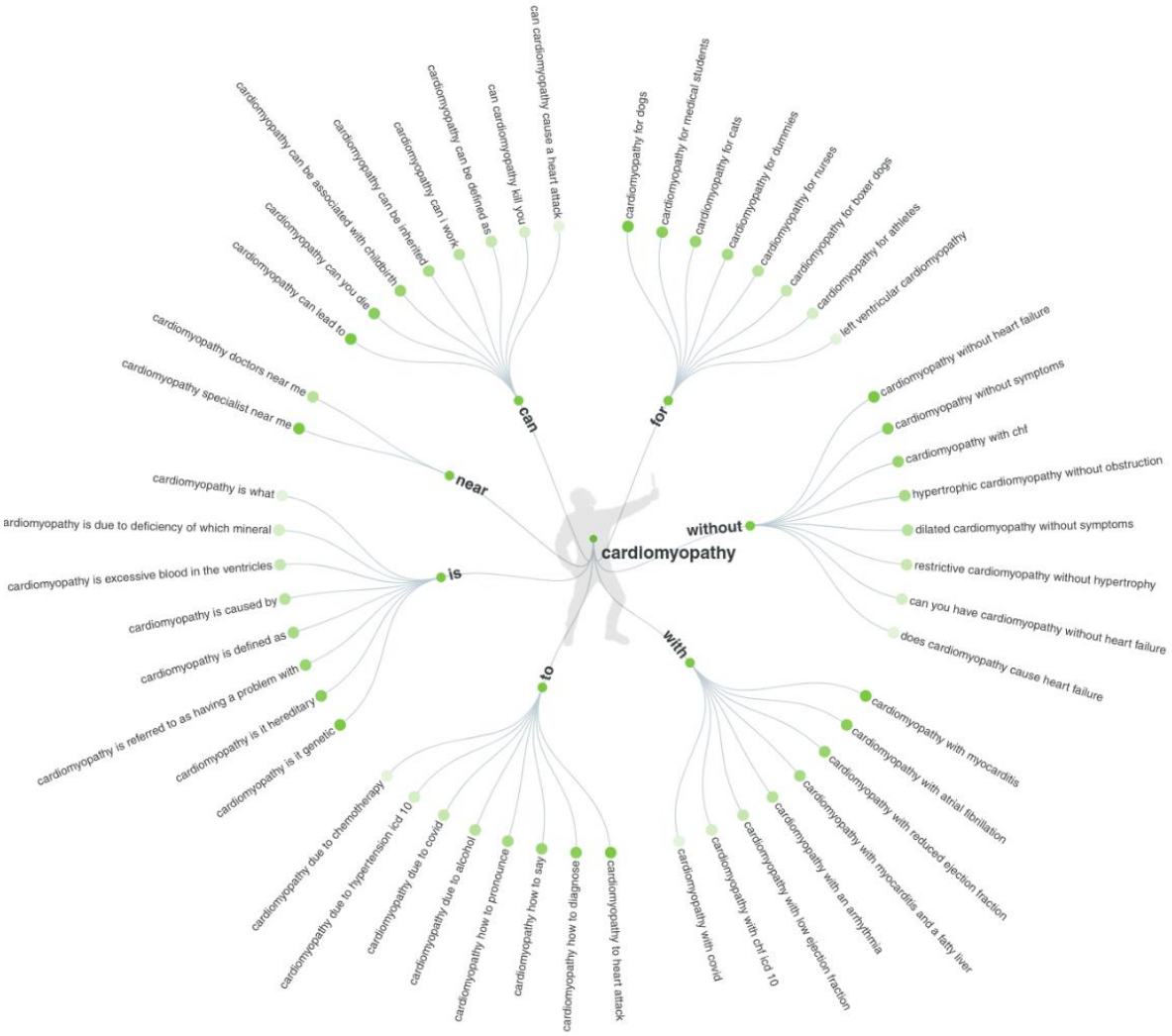

Figure 9: Search insights for the keyword Cardiomyopathy combined via propositions

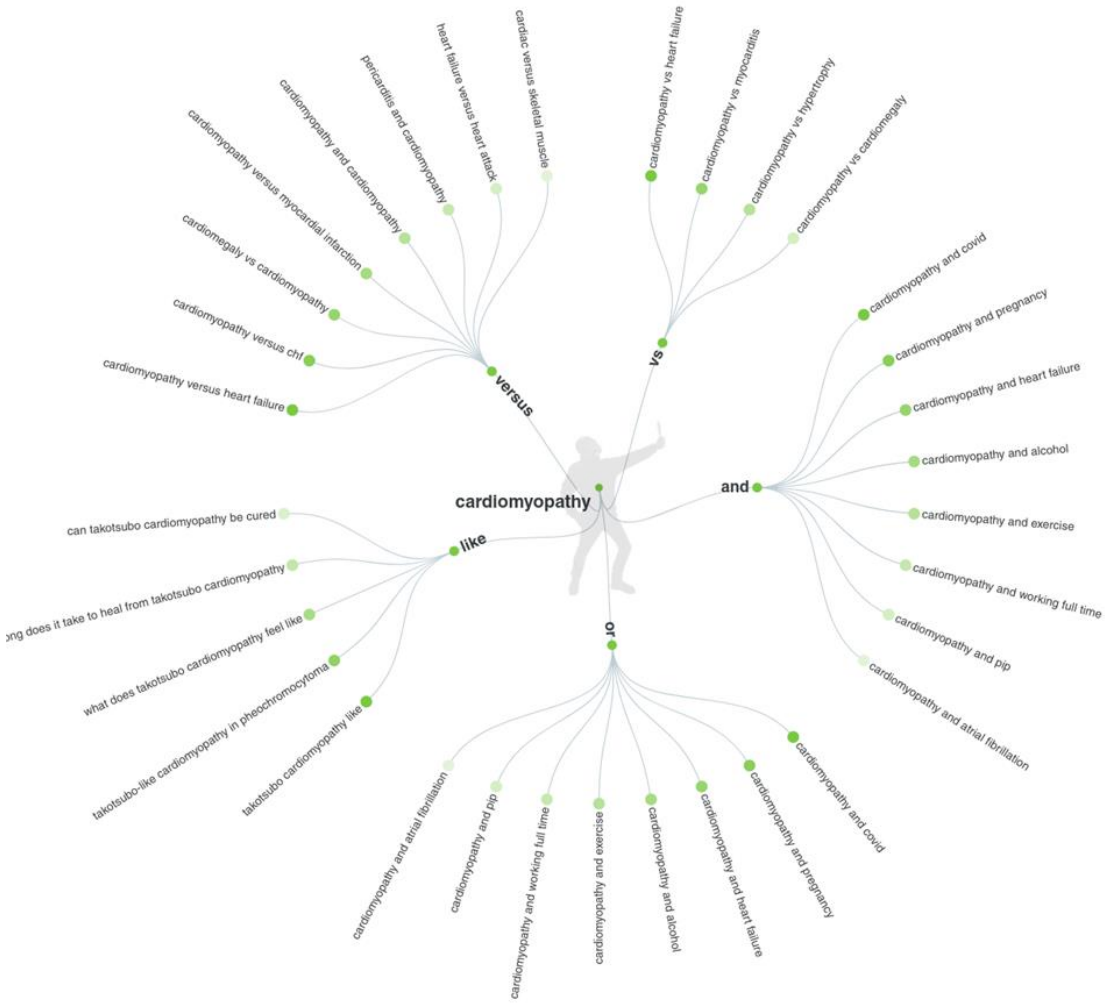

Figure 10: Search insights for the keyword Cardiomyopathy comapred with other keywords

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[10] and USD $41,260.8 million in 2025[11]	Competitive	✓ Government and defense ✓ Aerospace ✓ Manufacturing ✓ Architecture ✓ Health care	Materialize[12]	✓ 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)[13]	✓ MR Scar analysis ✓ MR Flow analysis ✓ MR LV and RV analysis	2022
KER2: Bioinformatics tool	Expected to reach $18,233 million by 2025[14]	Competitive	✓ Medical ✓ Academics ✓ Agriculture	GenScript[15]	✓ Bioinformatics tools focused in Molecular Biology, Peptide and Protein	2022
KER3: MUscle SImulation COde (MUSICO) tool	Development		✓ Medical ✓ Academics	Synopsys Simple[16]	✓ 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[17]	Competitive	✓ Aerospace ✓ Automotive ✓ Electronics	Dassault Systems- SIMULIA[18]	✓ 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[19]	✓ Proactively identify patients at risk of unplanned hospital admission. ✓ Clinically validated and peer-reviewed algorithm, developed for use in England.	2022

[10] https://www.alliedmarketresearch.com/3D-imaging-market
[11] 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
[12] https://www.materialise.com/en/medical/mimics-innovation-suite/finite-element-meshing
[13] http://medviso.com/segment/
[14] https://www.alliedmarketresearch.com/bioinformatics-market
[15] https://www.genscript.com/tools.html
[16] https://www.synopsys.com/simpleware/software/auto-segmenter-modules.html
[17] 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
[18] https://www.3ds.com/
[19] https://www.emishealth.com/

Key exploitable result	Target market size	Market maturity	Market by application	Market competitor		Expected release
				Companies	Key Features	
KER6: Virtual population tool (animal experiments and human trials)	Expected to reach $13,029.2 Million by 2025[20]	Competitive	✓ Hospitals ✓ Pharmaceutical companies	3D4Medical[21] IQVIA[22] Oxford Virtual Assay[23]	✓ 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[24]	Competitive	✓ Biomedical and biotechnology companies ✓ Hospitals ✓ Insurance industry ✓ Clinical decision makers ✓ Policy makers and funding agencies	Cohesic Inc[25] TAPA Healthcare[26] The Medical Algorithms Company Ltd.[27]	✓ 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[28] IBM Health[29]	✓ Optimization of clinical trials ✓ Maximization of data	2022

[20] 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
[21] https://3d4medical.com/apps/complete-heart
[22] https://www.iqvia.com/our-customers/medical-technology/clinical/cardio
[23] https://www.cs.ox.ac.uk/ccs/virtual-assay
[24] Customer Experience Management Market Report, 2021-2028 (grandviewresearch.com)
[25] https://cohesic.com/products/cardio-di
[26] https://www.tapahealthcare.com/
[27] https://www.medicalalgorithms.com/top-algorithms
[28] https://status.aws.amazon.com/
[29] 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 11 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 11, 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.

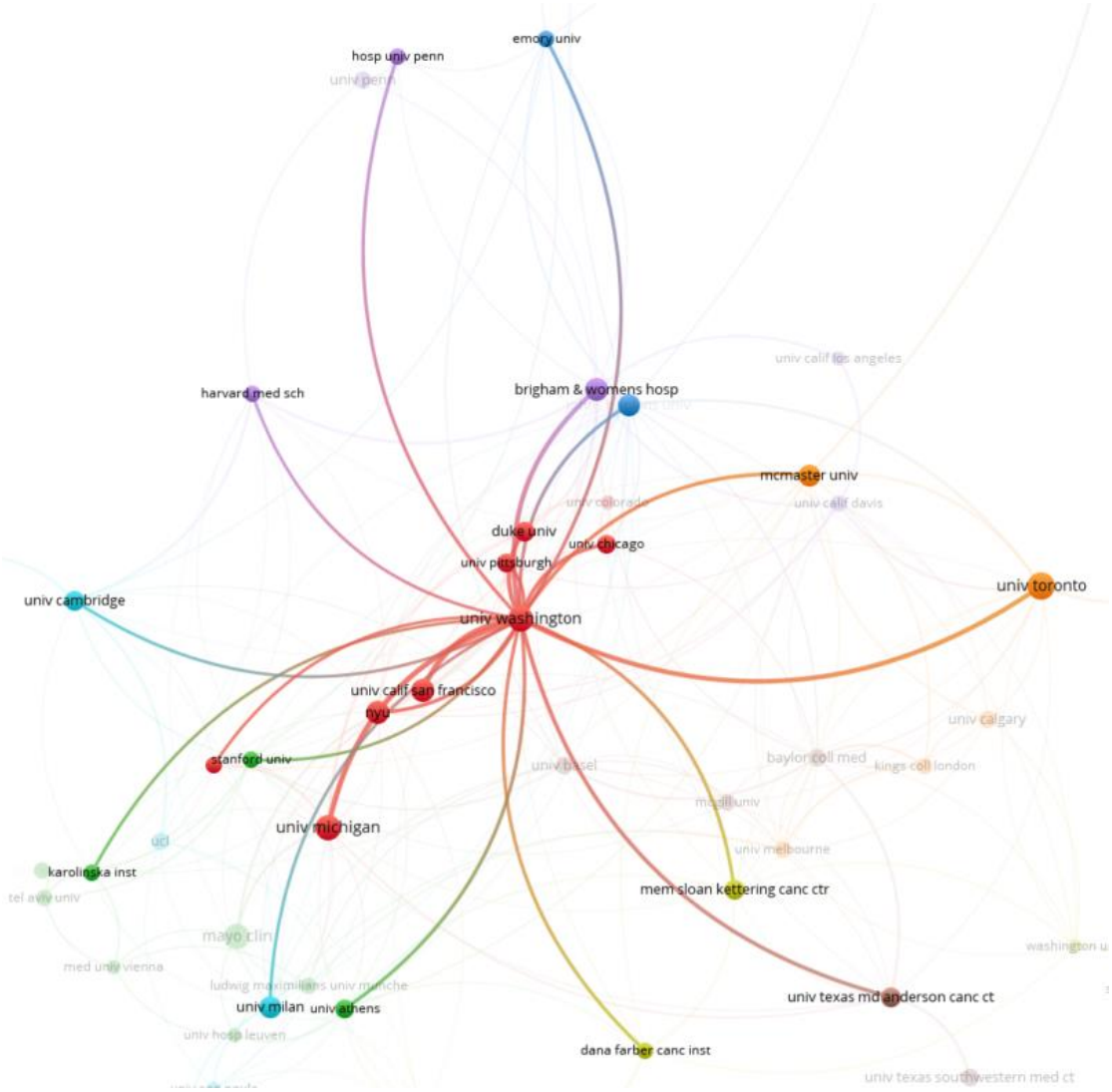

Figure 11: Bibliographic couplings of institutions publishing articles on risk stratification tool

3 Business model canvases for the KERs

The business model canvas is the structure of a business plan in one page. A Business Model describes how an organization creates, delivers, and captures value. The Business Model Canvas is a strategic management template for developing new or documenting existing business models. The process of identifying one or more possible business models may become laborious. The canvas, quite simple and intuitive to use, facilitates discussion and work and supports in remaining focused on the main elements of a Business Model.

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 12, Figure 13, Figure 14, Figure 15, Figure 16, Figure 17, Figure 18, Figure 19).

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)

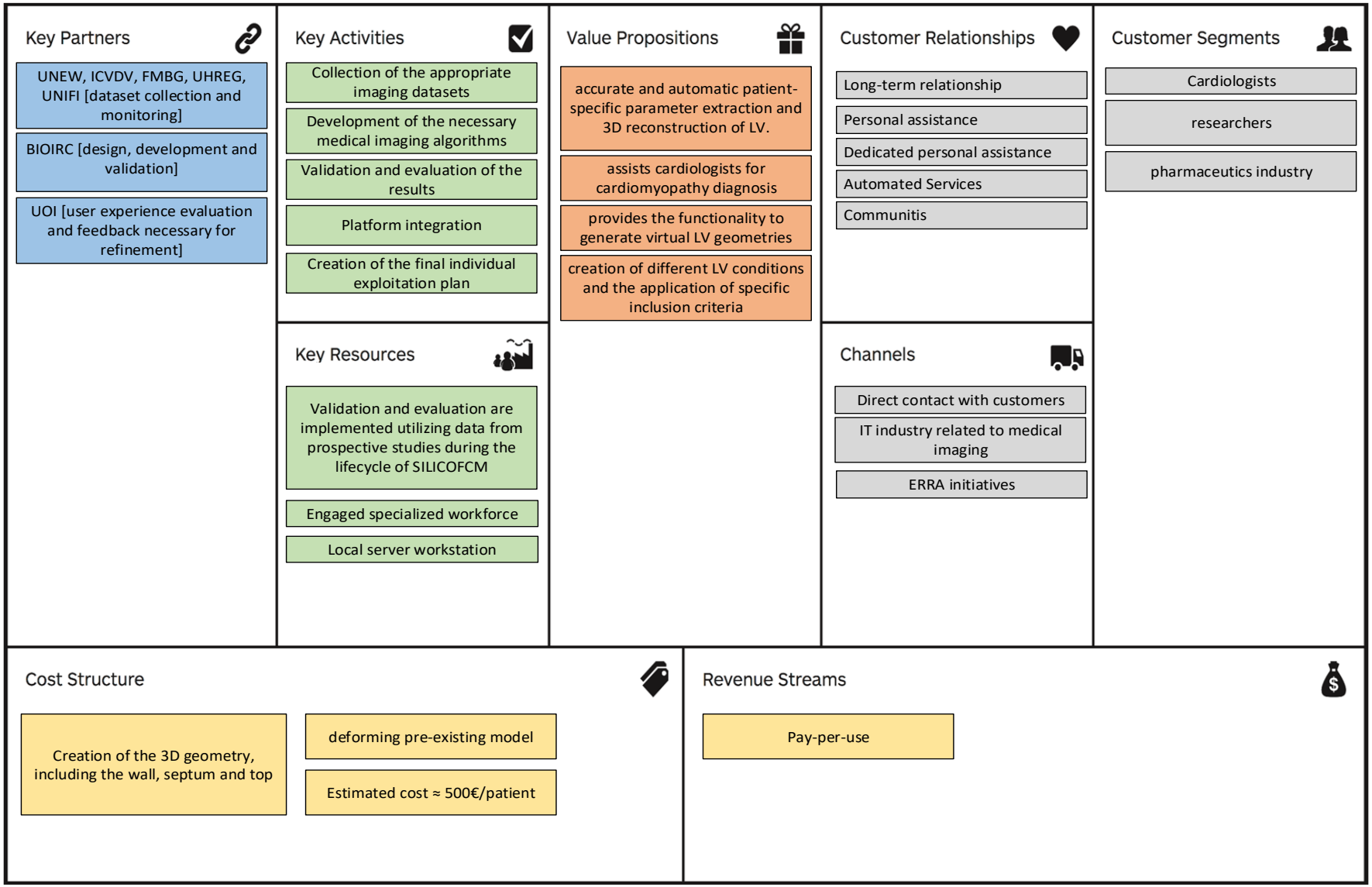

Figure 12: Business model canvas proposed for the 3D Image Segmentation tool

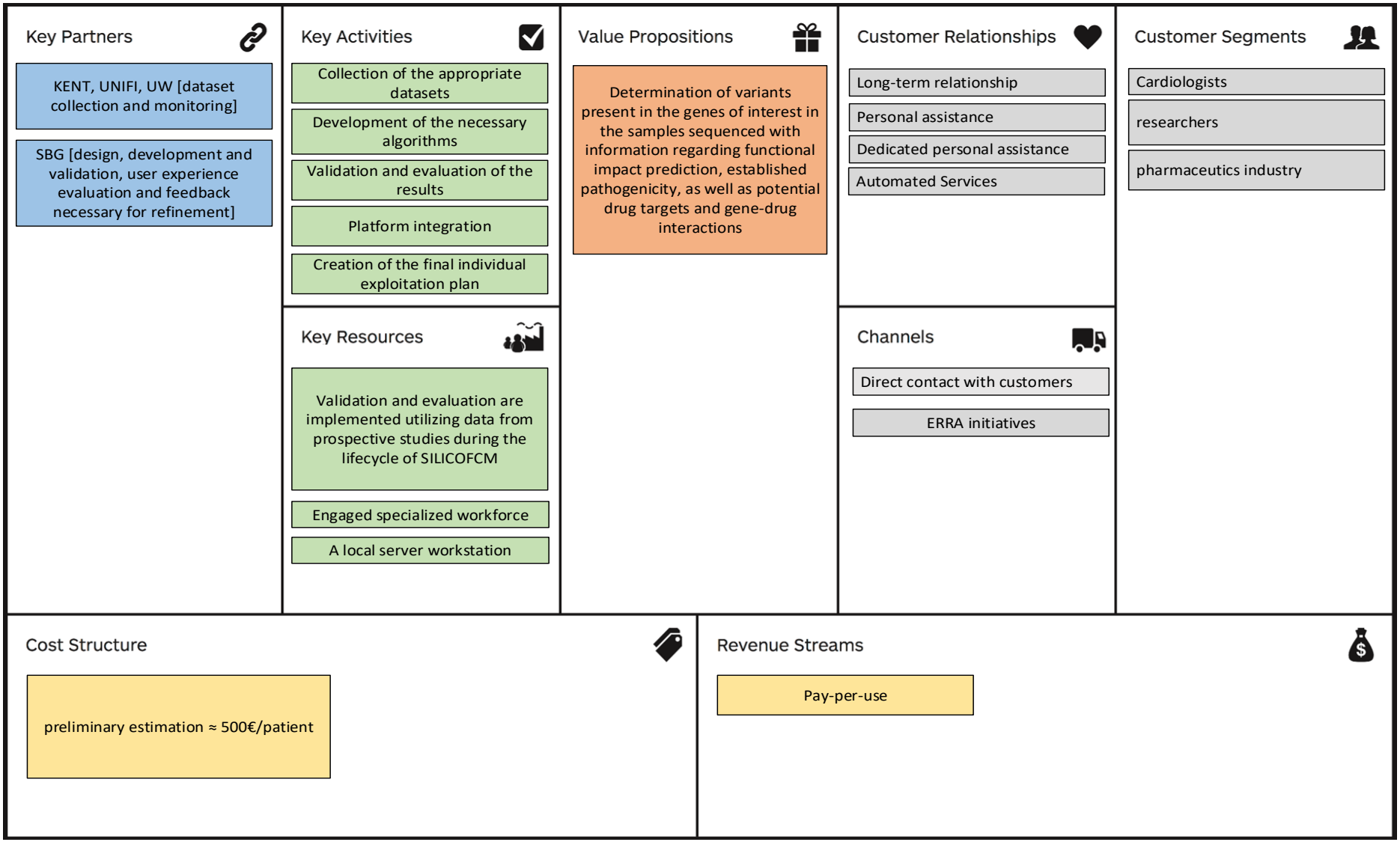

Figure 13: Business model canvas proposed for the Bioinformatics tool

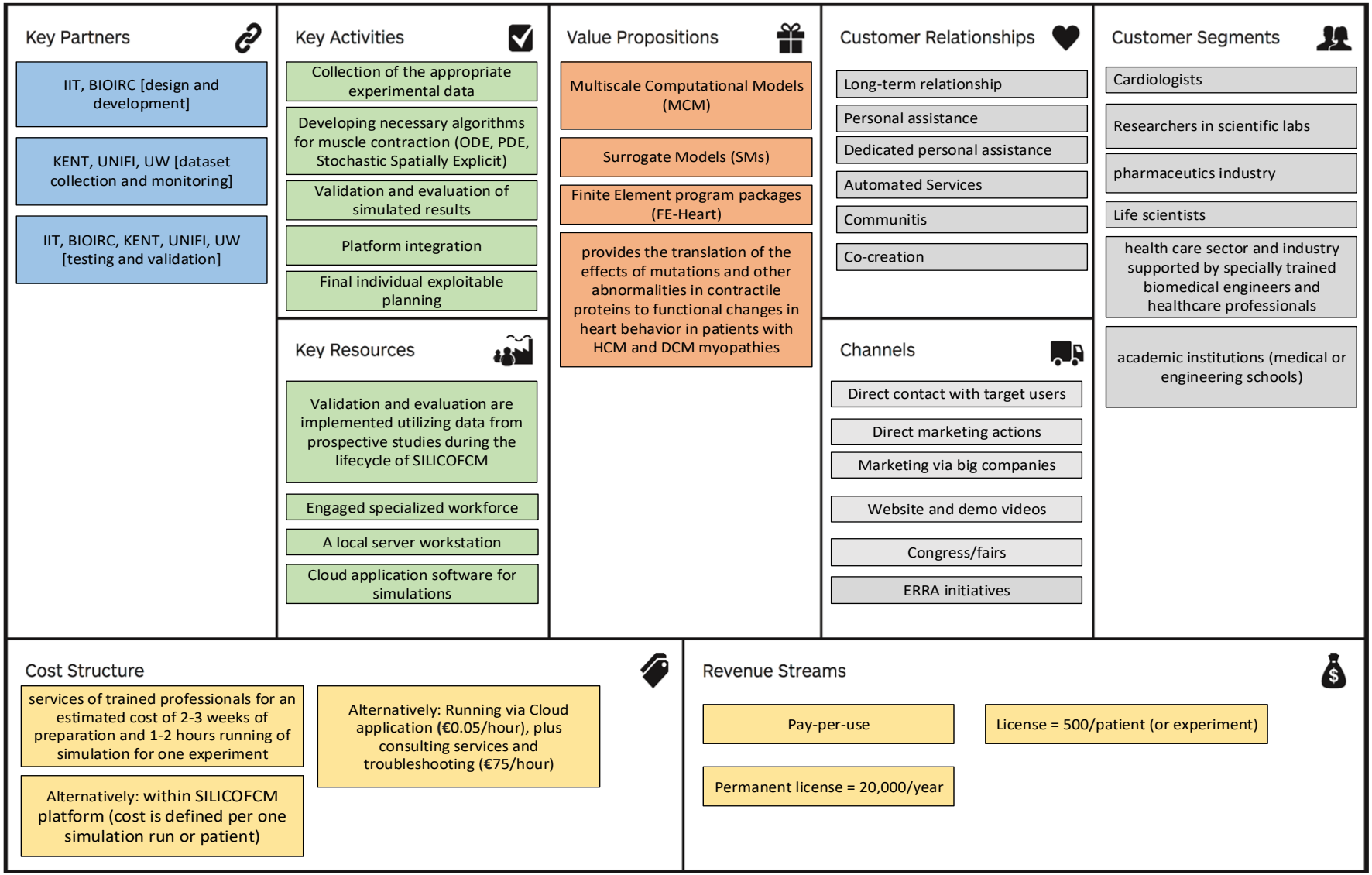

Figure 14: Business model canvas proposed for the MUSICO tool

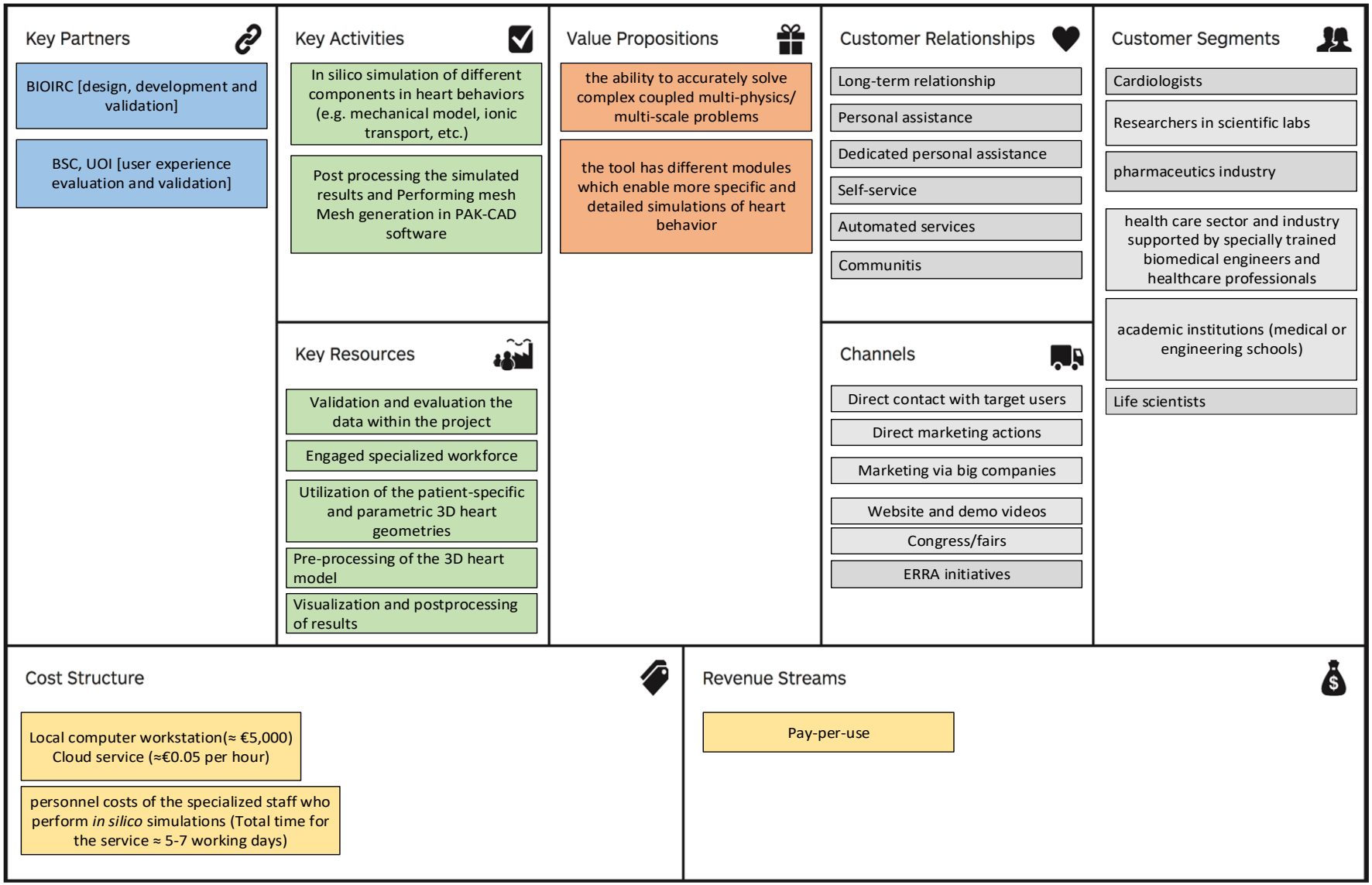

Figure 15: Business model canvas proposed for the Finite Element tool

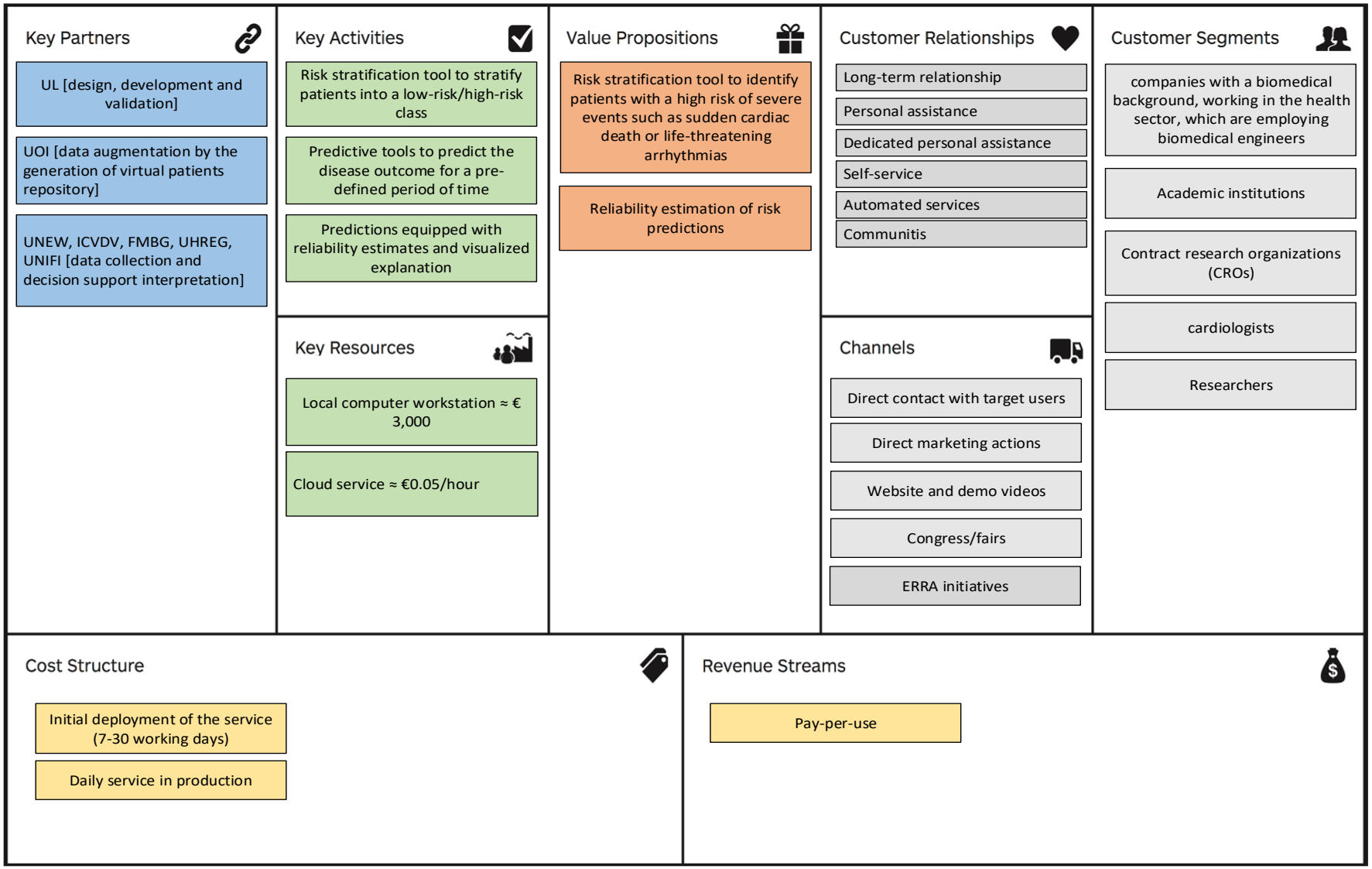

Figure 16: Business model canvas proposed for the Decision Support tool

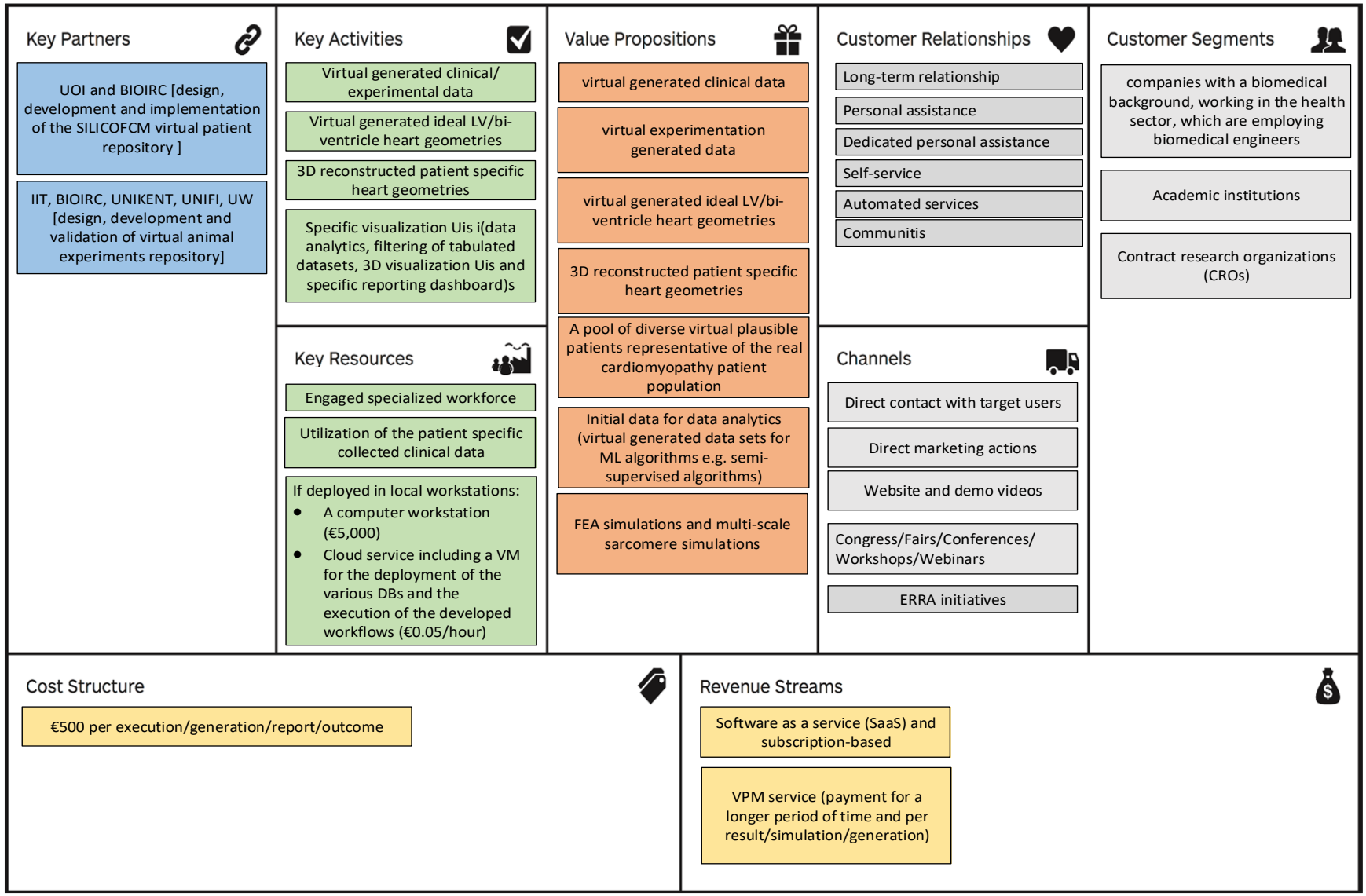

Figure 17: Business model canvas proposed for the Virtual Population tool

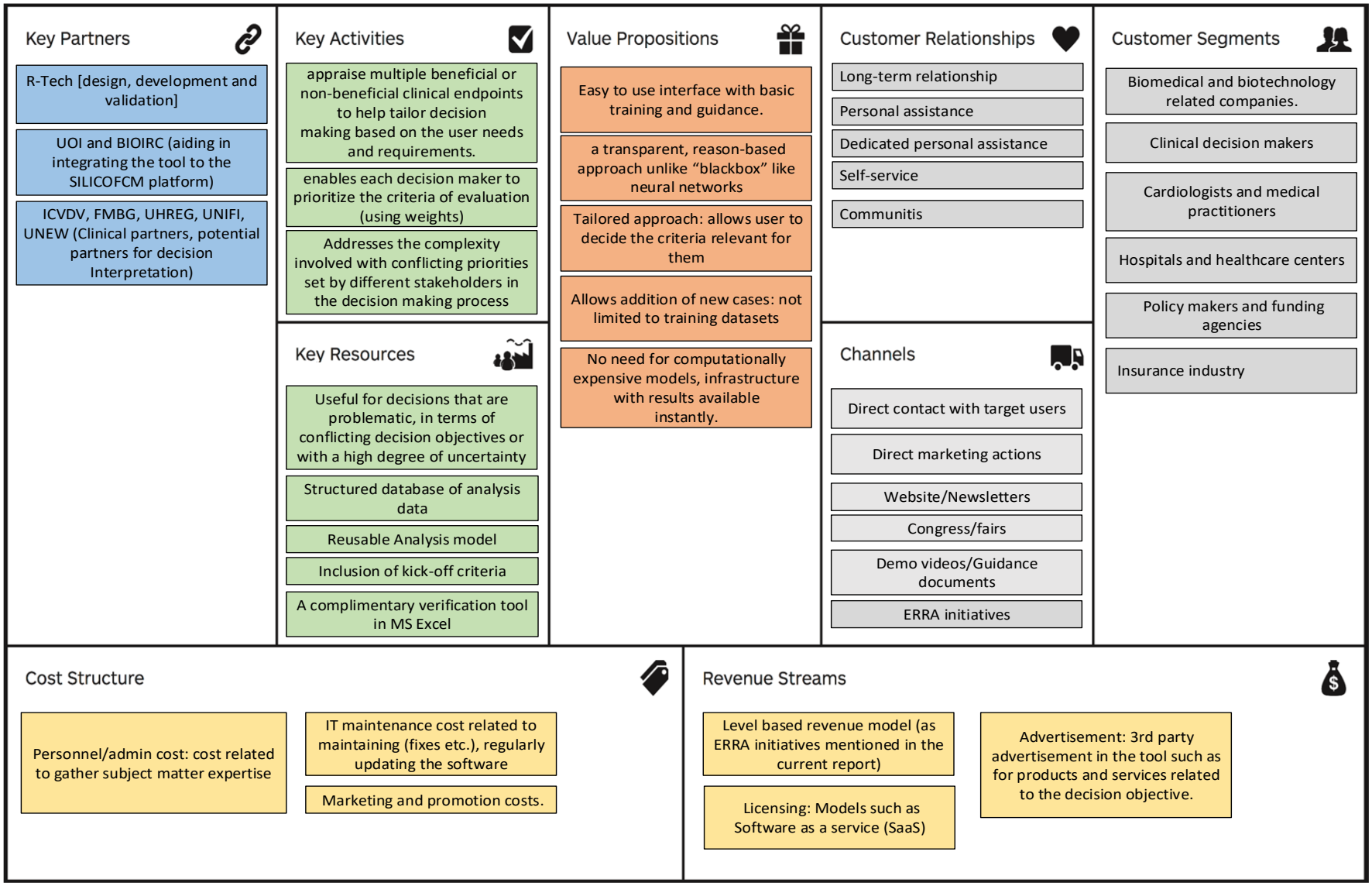

Figure 18: Business model canvas proposed for the MCDM tool

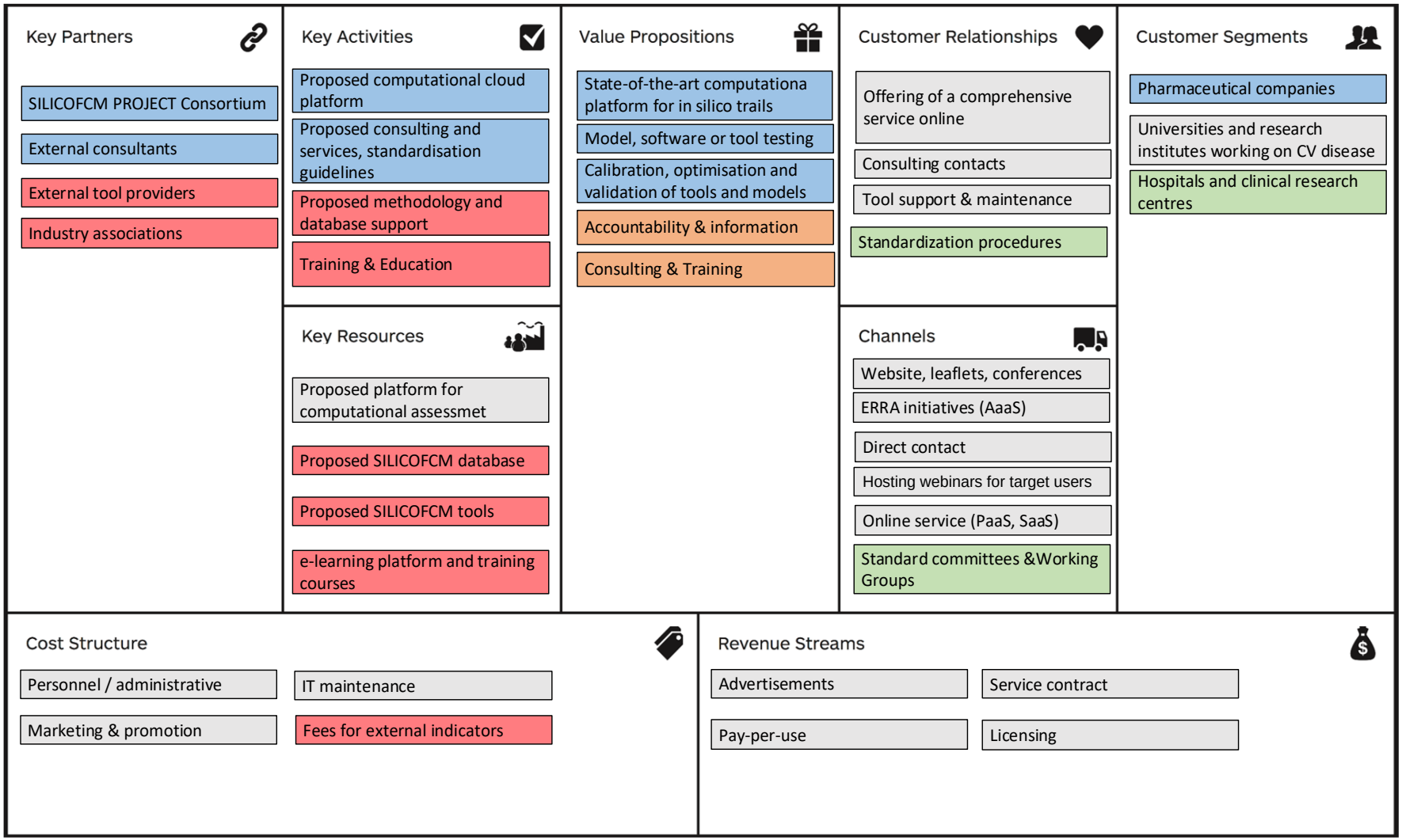

Figure 19: Business model canvas proposed for the FCM Services as a basis. Different colors are used to indicate the relationships between the elements at different sections

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. A 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).

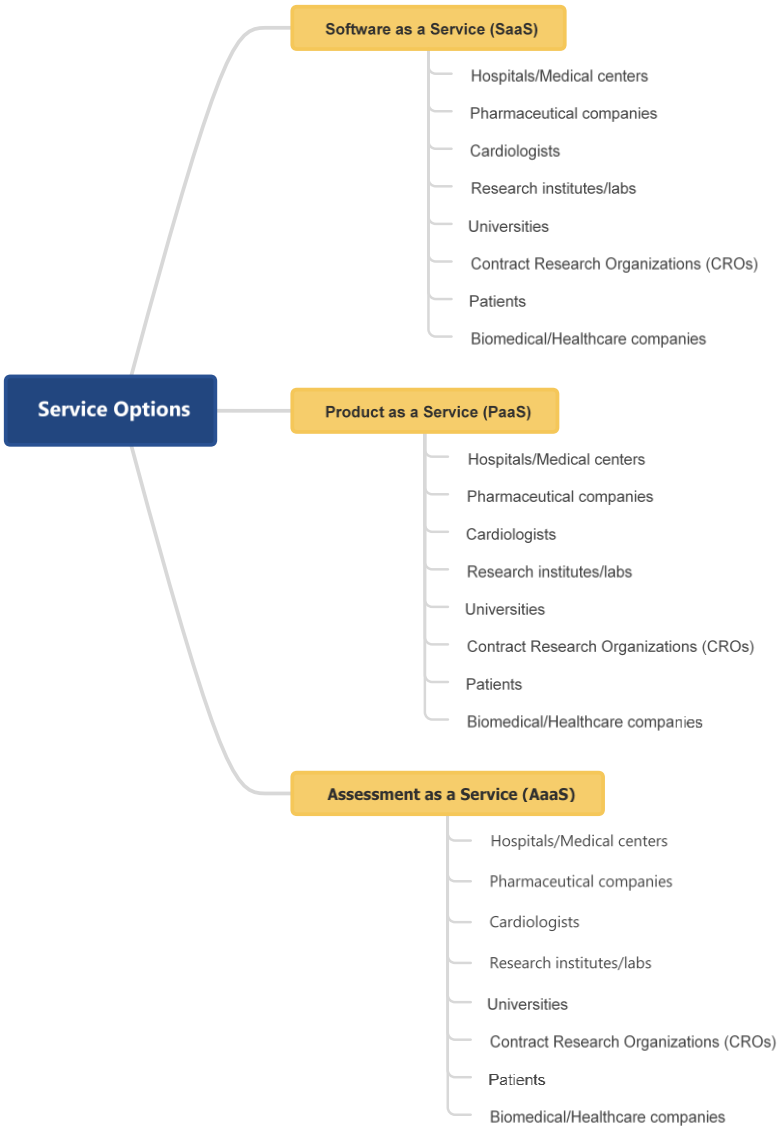

Figure 20: Service options for different target users in SILICOFCM project

In general, three common service options for exploiting the platform as shown in Figure 20 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.

The projected cash flow for this option can be modelled as:

4.2 Software as a service (SaaS):

This involves a subscription-based business model that charges customers a recurring fee — typically monthly or yearly — to access a product or service. Based on this model, customers are 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 Chapter 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 of the European Risk & Resilience Assessment (ERRA) initiatives[30]. 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 21.

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

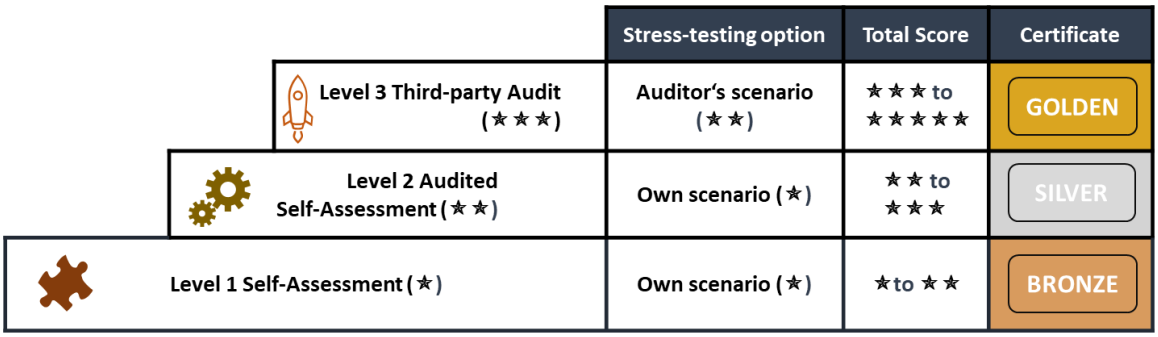

Figure 21: ERRA assessment level and score

- **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 Revenue Model and Financial Analysis

In this scenario, the SILICOFCM platform is a value-in-use based platform, this means that value is generated while interaction and transaction occurs within the cloud-based platform. Hence, the platform is a relational and interactive platform. Dynamics between peer firms all along the *in silico* study and drug development chain will create opportunities for market development and business growth. Dynamics are based on the following point:

- Generating results for *in silico* trials of drug or medical device within the FCM domain.
- Finding specialized modellers and tool developers for expanding the current capacity of the platform services.
- Exchanging information (i.e. certifications, prices, etc.).
- Negotiating.
- Doing business through sales, collaborations, etc.

As for the switching costs, these will be related to the technical costs and time assumed by a firm for entering the SILICOFCM Platform at the beginning. These costs are mainly the elaboration of electronic catalogues and loading the requested information on the platform. Also, the Platform will require personnel for keeping updated the information on the tools, scientific know-how and the changing operational and regulatory processes. The time required for feeding the Platform with electronic information (catalogues with instructions and how to procedures, certifications, etc.) is saved as this information has already been created and uploaded to the Platform by the project partners during the SILICOFCM project duration. Additionally, demo videos have been created and published in the project website which can migrated to the SILICOFCM platform.

The revenue model for this service option is based on a pay-per-use fee that participant firms (end-users) must defray. At the beginning, it is expected a single fee which is estimated to be 30-50€/month for a complete access to the platform and all its functionalities (from January 2023). From April 2022 till January 2023 only new companies, not the Early Adopters (EAs) during SILICOFCM project duration will pay. This fee will be earned starting at April 2022. With the SILICOFCM Platform live and deployed, the estimation fees are:

- **Basic fee** (30€/month): accessing to platform for searches on already existing results (no editing options)
- **Regular fee** (50€/month): downloading and editing existing analysis and the ability to use existing models and database (in addition to automated help and guidance within the Platform).
- **Premium fee** (100€/month): advance service packs (include ability to run user-specific simulations within the platform, data analytics, support for integrating SILICOFCM tool workflows within their existing workflows etc.).

On the costs part, there are some fixed costs for running operatively the SILICOFCM Platform, while other costs are related to personnel in order to make the Platform grow in functionalities and number of members:

- Hosting: hosting the FMP in the cloud (servers, domains, etc.).
- Personnel costs: people for helpdesk tasks (attending members of the platforms with technical support) and salesforce for recruiting more members and attending their service needs (type of fees, positioning the firm in the FMP, etc.).
- Technical costs: for developing and improving the FMP according to market necessities.

- Marketing costs: promotion of the FMP in other websites, industrial associations´ media, social networks, etc.
- Other related costs: licenses for running the FMP (i.e. Apache, Keycloack…).

There are also some variable costs, which will depend on the number of members and the incidences related to the SILICOFCM Platform deployment:

- Maintenance costs: improvements and bugs revision in the Platform
- Unforeseen circumstances: should be around 15% of the budget, just in case unexpected issues arise (i.e. legal issues, communication costs, etc.).

In Table 4, we report 2 possible scenarios (the best and the worst one) taking into account the number of customers and different fees associated based on the level of access and utilization of the SILICOFCM Platform. It is worth highlighting that:

- the reported figures are based on internal analysis and brainstorming and the values can be updated based on evidence, insights and suggestions from early adopters at a later stage.
- the financial analysis is based on the scenario where the Platform is hosted in Serbia. It is needed a more complex sheet exploiting the platform in multiple countries with the involvement of commercial partners.

Table 4 An example of financial analysis of launching SILICOFCM Platform-as-a-servicee in one country: Serbia

SILICOFCM (SFCM) Platform tentative financial analys				**Scenario 1 (best)**		
Scenario description				One country (RS)		
				Participation goals achieved		
				Target 100 SFCM EAs by Dec 2022 (free)		
				2023: Wide market launch		
Years	**2022**	**2023**	**2024**	**2022**	**2023**	**2024**
Target number of end-users	**35**	**200**	**300**	**50**	**100**	**200**
Basic users (% of total registrations)	60%	50%	40%	90%	70%	50%
Regular users (% of total registrations)	40%	45%	50%	10%	25%	40%
Premium users (% of total registrations)	0%	5%	10%	0%	5%	10%
New EAs fee (10€/month) [Until December 2022]	3,500.00 €	- €	- €	- €	- €	- €
Basic fee (30€/month) [Since January 2023]	- €	54,000.00 €	57,600.00 €	5,400.00 €	50,400.00 €	54,000.00 €
Regular fee (50€/month) [Since January 2023]	- €	81,000.00 €	120,000.00 €	1,000.00 €	30,000.00 €	72,000.00 €
Premium fee (100€/month) [Since January 2023]	- €	18,000.00 €	48,000.00 €	- €	12,000.00 €	36,000.00 €
TOTAL REVENUE	**3,500.00 €**	**153,000.00 €**	**225,600.00 €**	**6,400.00 €**	**92,400.00 €**	**162,000.00 €**
Legal incorporation	500.00 €	500.00 €	500.00 €	500.00 €	500.00 €	500.00 €
Technical training	- €	- €	- €	1,600.00 €	- €	- €
Hosting cloud (AWS)	2,000.00 €	3,200.00 €	4,000.00 €	2,000.00 €	3,200.00 €	4,000.00 €
Licenses (Apache, Keycloack, Kibana etc.)	- €	- €	- €	2,000.00 €	2,000.00 €	96,000.00 €
Technical programming (BioIRC/UoI or external firm)	26,280.00 €	35,000.00 €	35,000.00 €	72,000.00 €	96,000.00 €	2,000.00 €
Personnel: Researcher	25,000.00 €	35,000.00 €	35,000.00 €	30,000.00 €	45,000.00 €	45,000.00 €
Personnel: Platform Technician	18,765.00 €	25,000.00 €	25,000.00 €	18,765.00 €	25,000.00 €	25,000.00 €
Personnel: User's Helpdesk (1/2)	9,000.00 €	12,000.00 €	12,000.00 €	9,000.00 €	12,000.00 €	12,000.00 €
Personnel: Sales	18,765.00 €	25,000.00 €	25,000.00 €	18,765.00 €	25,000.00 €	25,000.00 €
EU MDR compliance (CE certificate)	15,000.00 €	- €	- €	20,000.00 €	- €	- €
TOTAL FIXED COSTS	**115,310.00 €**	**135,700.00 €**	**136,500.00 €**	**174,630.00 €**	**208,700.00 €**	**209,500.00 €**
Unforeseen circumstances (+15% i.e. legal services…)	17,296.50 €	20,355.00 €	20,475.00 €	26,194.50 €	31,305.00 €	31,425.00 €
Marketing actions	4,000.00 €	15,000.00 €	12,000.00 €	4,000.00 €	24,000.00 €	24,000.00 €
TOTAL VARIABLE COSTS	**21,296.50 €**	**35,355.00 €**	**32,475.00 €**	**30,194.50 €**	**55,305.00 €**	**55,425.00 €**
TOTAL COSTS	**136,606.50 €**	**171,055.00 €**	**168,975.00 €**	**204,824.50 €**	**264,005.00 €**	**264,925.00 €**
EXPECTED RESULT	**- 133,106.50 €**	**- 18,055.00 €**	**56,625.00 €**	**- 198,424.50 €**	**- 171,605.00 €**	**- 102,925.00 €**
MARGIN (ROI)	**-97.44%**	**-10.56%**	**33.51%**	**-96.88%**	**-65.00%**	**-38.85%**

In the best scenario, in the third-year SILICOFCM Platform starts with annual benefits and generating profits from somewhere between the fourth and the fifth year. In the worst scenario, better not to continue after the second year.

6 Regulatory landscape and its impact

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.

Since 2021, European manufacturers face the new Regulation (EU) 2017/745 for medical devices (MDRs). The new regulation is a major update to the regulatory framework in the European Union (EU). Although the regulation varies from product to product, the primary additions are related to documentation, with additional product information and traceability requirements. Medical technology companies or medical device manufacturers must adopt more stringent quality assurance measures so that individual devices can be speedily tracked and retrieved in emergencies. Among the new requirements introduced by the MDR is creating a unique position to be filled by a candidate with proof of experience in medical device regulations. This person is to be entrusted with managing all matters related to regulatory requirements (Zippel and Bohnet-Joschko 2017).

It is estimated that are about 25,000 Medical technology enterprises in Europe, with 95% of them being SMEs[31] such as the one which can be expected from SILICOFCM. These SMEs will be impacted the most as the regulatory compliance will significantly affect their administrative costs and effort. Thus, a business model within the medical technology sector should consider the regulatory landscape and the cost estimation for regulatory compliance and approval within their business plan.

6.1 The United States of America (USA) regulatory landscape

In the United States, governmental risk assessment of medical devices is mainly based on recommendations from members of 16 medical speciality panels[32], 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.

6.2 The European Union (EU) regulatory landscape

6.2.1 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

[31] https://www.theparliamentmagazine.eu/news/article/thought-leader-medtech-europe-innovative-smes
[32] https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device

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[33]:

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

6.2.2 EMA Medical Device Regulation (MDR 2017/745)

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)[34].

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)[35] 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 5.

Table 5: Conformity assessment procedure for MDR[36]

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		

[33] https://www.cemarkingassociation.co.uk/process/
[34] http://ec.europa.eu/DocsRoom/documents/10337/attachments/1/translations/en/renditions/native
[35] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
[36] MD101 Consulting blog, https://blog.cm-dm.com

Class #	QMS assessment	Technical file assessment	Clinical investigation	Post-market followings
		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		

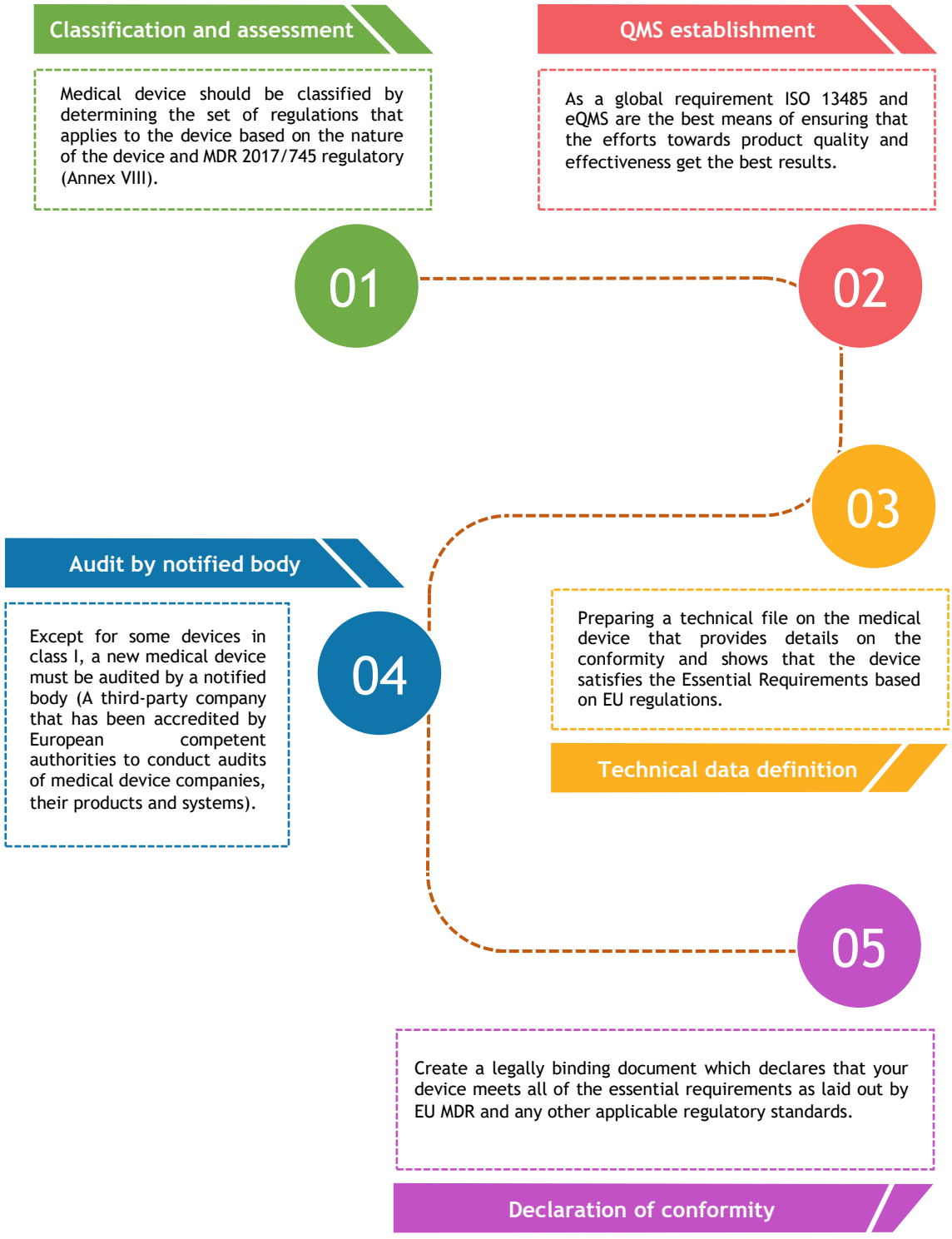

Figure 22: MDR admission process based on EMA regulations

Figure 22 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[37].
- 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.

6.3 China regulatory landscape

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[38].

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

[37] https://eudamed.eu/index.php/2018/09/19/mdr/
[38] 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.

7 Conclusion

SILICOFCM developed 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. Chapter 5 on revenue model and financial analysis is added which presents 2 potential best and worst-case scenarios with different service options related to the uptake of the platform: it shows an estimated revenue stream for all the KERs combined in the SILICOFCM Platform with projections till the year 2024.

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). It is expected that the new regulations will increase the administrative cost and effort, especially for the SMEs like the one we envisage for SILICOFCM Platform and a fixed cost is currently estimated for applying and passing a conformity assessment for their medical device software.

8 References

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