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

Project acronym: SILICOFCM

Grant Agreement number: 777204

Coordinating Institution:
Bioengineering Research and Development Center BioIRC doo Kragujevac, BIOIRC

Start date: 1st June 2018

Duration: 42 months

WP number, Deliverable number and Title	**WP9** Exploitation and Dissemination **D9.8** Roadmap to business model v2
Related Task	**Task 9.4** - Business Plan & Business Model
Lead Beneficiary	R-Tech
Deliverable Type	Report
Distribution Level	Public
Document version	v1.0
Contractual Date of Delivery	31/05/2020
Actual Date of Delivery	15/06/2020

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

Version history

Version	Description	Date of completion
0.1	Prepared table of contents	18/05/2020
0.2	Initial draft prepared	20/05/2020
0.3	Comments received from (BioIRC)	08/06/2020
0.4	Final draft sent on the internal review	10/06/2020
0.5	Integrated comments received from internal reviewers	14/06/2020
1.0	Final version	15/06/2020

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Executive summary

This report presents the second version of the deliverable D9.6: Roadmap on Business Model and demonstrates the updated work since the first version was published at M12. The model identifies the business road map for the key exploitable results as identified until M24, such as the (i) 3D image segmentation tool, (ii) Bioinformatics tool, (iii) MUSICO tool, (iv) Finite element tool, (v) Decision support tool, (vi) Virtual population tool for animal experiments and human trials (vii) SILICOFCM platform.

Chapter 1 (Introduction) of the Roadmap on Business Model highlights the scope of the SILICOFCM project, task description and the objectives of the deliverable. In Chapter 2, the market analysis that includes market channel and competitors including the broad list of various stakeholders involved in the sector and specific list of end users are discussed. Chapter 3 describes different Service Options, such as ownership, start-up summary, key partners, customer relationships, resources and potential offerings and finally, Chapter 4 analyses the regulatory landscape. Next, the business model will be further developed in the coming months and the updated deliverable will be published at M36 and M42 together with the consortium members to trigger the economically viable commercialization of the project outcome and its potential competitiveness in the market (Chapter 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
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

1. Introduction

The SILICOFCM project is developing an *In silico* computational cloud platform, which will integrate from stopped-flow molecular kinetic assays to magnetic resonance imaging of the whole heart, bioinformatics and image processing tools with state of the art computer models with the aim to reduce animal and clinical studies for new drug development and optimized clinical therapy of FCM.

The developed system will be distributed on the cloud platforms in order to achieve efficient data storage and high performance computing that can offer end users results in a reasonably short time. Technical partners IIT, UOI, UL and BSC are developing and integrating the *In silico* cloud computational platform with multi-scale cardiac muscle modelling which include experiments on protein mutation in vitro from UNIKENT, UNIFI and UW. The American company, SBG is in charge of integrating Bioinformatics tools. Clinical partners UNEW, ICVDV, UPMC and UHREG carry out the retrospective and prospective studies. SME partner R-Tech is in charge of regulatory issues and preparing the reports to FDA and EMA, and BIOIRC is currently exploring the exploitation of the project (described more in D9.5).

The main objective of task 9.2 is to create a connection to the industry and other external representation. 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 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 projects' visibility through promotion using the contact network
- Maximize the impact and cost-effectiveness of project activities

The Deliverable D9.8 – Road map on Business Model v2, reports on the work performed in WP9 - Exploitation and Dissemination, which accounts for the projects' exploitable results and regulatory aspects, conditions for the commercialisation, such as market analysis, SWOT analysis, proposals for exploitation, funding estimates and other financial projections. The deliverable will assess the viability and commercialisation of project results, the pathway for commercialisation and the potential competition in the market. The deliverable will be updated yearly by R-Tech (M36, M42) taking into an account of 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.

2. Market analysis summary

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 Identifying stakeholders and end users

The stakeholder groups can be generally classified into following categories, based on their roles:

- ***Providers*** (Involved in product development and assessment such as clinical research organisations, academics, universities, hospitals, consultants, data banks, hardware & software companies, other service providers)
- ***Producers*** (Large and small companies, pharmaceutical companies and industries who test drugs, industries who provide artificial heart devices, medical devices, health technologies, hybrid products, third sector producers driven by non-profit organisations)
- ***Payers*** (insurance companies, health providers, assessment agencies that advise the payers on the cost-benefit ratio)
- ***Regulators*** (Food and Drug Administration (FDA) in the USA, the European Medicines Agency (EMA) in Europe, China Food and Drug Administration (CFDA) in China, National agencies, International Organization for Standardization (ISO), and research ethical committees that monitor clinical trials)
- ***Consumers*** (patients', clinics, universities and charities organisations)

In the above classification, SILICOFCM audience is divided into few segments; the first being the personnel or entities who would be directly using or utilizing the software tools, methodologies, cloud platform etc. and secondly, the indirect users such as other researchers or institutes which will build on the SILICOFCM approaches and methodology.

However, the **end user** refers to the stakeholders who will use the proposed SILICOFCM software tools, cloud platform and other exploitable project results. Some of the most relevant end users of SILICOFCM can be listed below:

- Medical doctors and Hospitals
- Pharmaceutical companies (Bayer, Sanofi, BMS, J&J etc. who produces products in the cardiovascular market.)
- Researchers
- Clinical research organisations
- Universities (Maastricht University, Newcastle University etc.)
- Biotech companies
- Bioinformatics companies
- Animal Testing Organisations
- Companies producing medical equipment for cardiovascular diseases (Endonovo Therapeutics, Inc. (OTCQB: ENDV), 22nd Century Group, Inc. (XXII), Corbus Pharmaceuticals Holdings, Inc. (NASDAQ: CRBP), Emerald Health Therapeutics, Inc. (CVE: EMH) (OTCQX: EMHTF), and Lexington Biosciences, Inc)

2.2 Market Channel

2.2.1 Website

The website of SILICOFCM (https://silicofcm.eu/) aims to get the general public acquainted with the project objectives and tasks, to present the project outputs, and to keep consortium members and the general public informed about project related news and forthcoming events regarding exploitable results. The project website serves the main two needs of the project: internal communication within the consortium and external communication and dissemination of the project objectives and results.

The exploitable results/services could build and maintain its home website on a landing page of the SILICOFCM platform, which can be connected to the project website itself. Hence, the project website can act as an effective preliminary channel to direct to the offered services through news articles and other awareness creation activities.

2.2.2 Key Activities

- The SILICOFCM **social networks profiles** on Facebook, Twitter and LinkedIn have been created to reflect the general project branding in an engaging, interactive way. Each account is aimed at a different group of users reflecting the specificities of the network itself. These social network profiles can be updated regularly and be kept alive after the project duration to increase project visibility and to promote the project related news and results.
- All project members are being encouraged to post information that is likely to be of interest for the public and the consortium. This could include article alerts, forthcoming meetings, and other information relevant to the SILICOFCM activities and exploitable results.
- Consortium partners can regularly organise a **webinar series** dedicated to their exploitable results to attract public attention.

2.2.3 Direct Emails and Selling

Consortium partners can send emails to different stakeholders within their network to promote the competences of their software and database in different business units. Consortium can use different physical events, such as seminars, conferences and exhibition to promote the exploitable results.

2.3 Competitors

SILICOFCM aims to reduce animal and clinical studies and aims to provide cost and time-effective optimized therapy for FCM. SILICOFCM project also develops huge amount of physiological experiment database. Once introduced in market, it is expected to remain unique in the field where it remains as sole developer of the computational cloud platform for FCM. By doing this, SILICOFCM can be the market leader and the primary developer of the product leveraging its position as the early adopter with a high market segment than its possible competitors. It is still very difficult to predict who will be the key players/competition during the introduction of the product to market. Once the methodology and tools are accepted by the authorities and auditing becomes more common as a product, competition from minor consultancies/independent contractors is expected to develop, mainly in niche and high risk industries.

2.3.1 Competing EU research projects

For analysing the competing or similar EU H2020 projects, a search on CORDIS website with a search string related to "computational platform for in silico clinical trials" and "heart related conditions, such as cardiomyopathies" shows a total of four projects, as shown in Table 1. Out of the four identified projects, only one project is still running along with SILICOFCM project. While the running projects might have competing KERs with SILICOFCM, it can also be an opportunity to collaborate, in a complimentary manner, which can further strengthen the portfolio of KERs which can be exploited in combination.

Table 1: The 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 personalised 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/

2.3.2 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 2.

Table 2: 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	Mijailovich Lab[11]	Development of computational models and quantitative analytical tools for muscle research	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

[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.mijailovichlab.org/musico
[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/

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
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 domain ✓ Optimization of clinical trials ✓ Speedy and efficient access to the market ✓ Maximization of data	2022
KER7: SILICOFCM platform	Development		✓ Hospitals ✓ Pharmaceutical companies ✓ Regulators	AWS health[19] IBM Health[20]	✓ Optimization of clinical trials ✓ Maximization of data	2022

The mapped the estimated market size, market maturity, market by application, key players and expected release for commercialized KERS.

[14] https://www.emishealth.com/
[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] https://status.aws.amazon.com/
[20] https://www.ibm.com/watson-health

2.4 Product oriented market analysis

For the next update of the deliverable, a product oriented market analysis will be done using the Market-Radar developed by R-Tech. This is a technique/tool used to collect the information (usually web-based) relevant for a given topic-e.g. 'FCM' or '*in-silico* trial for heart disease'. The tools offer an easy-to-access interface where topics can be set up for monitoring. After setting up the topic, the tools collect information available from the web-based online sources relevant to the concerned issues. Then, the tools use this information to perform data analytics to rank the relevance or importance of the keywords that are based on user-defined search queries. Relevance or importance of the keywords defined by a measure called Document Centrality, which is a proposed Natural Language Processing technique to rank documents and their content by their frequency and the source of the information. The technical process is explained in detail in a publication: Klimek, Jovanovic, Egloff, Schneider. Scientometrics 107.3 (2016): 1265-1282.

The three-step approach of Market-Radar could be;

Step 1: Identify and monitor novel online content for a certain topic

Based on a simple user-defined search query that defines the topic of interest (for example "FCM"), the tools search their respective field of sources for relevant content. The field of sources covers different websites for the Radar such as Google News, BBC News, CNN, Blogs etc. Every month, the tools retrieve and store relevant contents based on the user's query, which can be narrowed or broadened using Boolean combinations of search queries (eg. "FCM AND (products OR technology OR innovation)").

Step 2: Identify potential high impact trends - evaluating the retrieved online content to identify those texts and documents that have the highest potential for impact for the insurance industry with using an unsupervised, quantitative big data analysis

The tools automatically perform the processes of collating and analysing data. Once the topic is assigned, the system automatically searches using crawler software in the defined online content, and internally stores the information in the database. The relevant articles are collected in .html file format, which then goes to the next stage of a segmentation process. Here, an algorithm identifies the articles that contain large number of relevant terms and/or contains terms that are also relevant for a large number of other documents, that have the highest relevance, frequently repeated in sources, and that are most likely to have a substantial impact in the future. The filtered articles are identified according to their criticality, based on two aspects; (i) how active the topic is currently, and (ii) how fast the trend in the topic is growing.

Step 3: Visualize recommendations - providing recommendations for new innovations to be included in the market analysis catalogue by identifying those topics within the high-impact documents that have the highest novelty value

The third step of the methodology provides recommendations for innovations based on the documents identified in the second step. To this end, the topics of the potential high-impact documents are extracted and ranked according to their novelty values. This can be done by comparing the frequency of a given term in the current month with its frequency in the past months. A strong increase between these two frequencies indicates substantial novelty value within the high-impact documents. We could equally assign a high novelty value to a term if not its frequency itself, but the words that co-occur in the texts together with the given term change. To extract topics from these terms we can again consider co-occurrences of terms in the sense that a topic can be described by a "bag of words" that are often used in texts about the given topic. The output of the recommendation

system of the tools consists of topics that have, both, (i) potential for high future impact in particular market and (ii) are new issues in the sense that they have not been discussed in the given contexts before.

2.5 Network oriented market analysis

Product network is very important in identifying the key players and collaborative network among them. A semantic analysis identifies the product network using web semantic tools.

An example of such analysis is done using research data obtained from the web of science. Figure 1 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 1, 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.

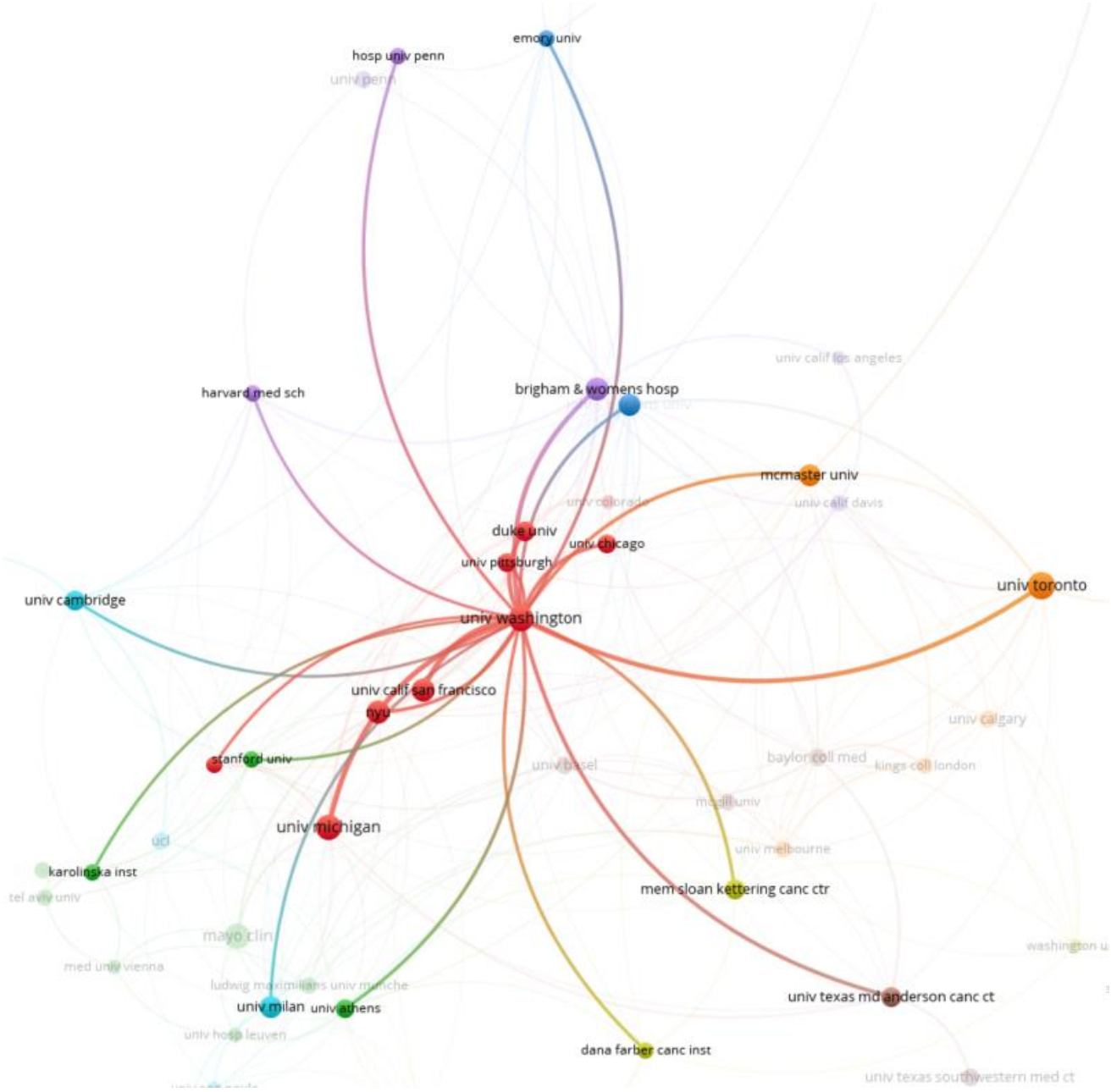

Figure 1. Bibliographic couplings of institutions publishing articles on risk stratification tool

3. 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. The two common options for exploiting the platform include:

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.

Software as a service (SaaS): involves 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 Figure 2.

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?

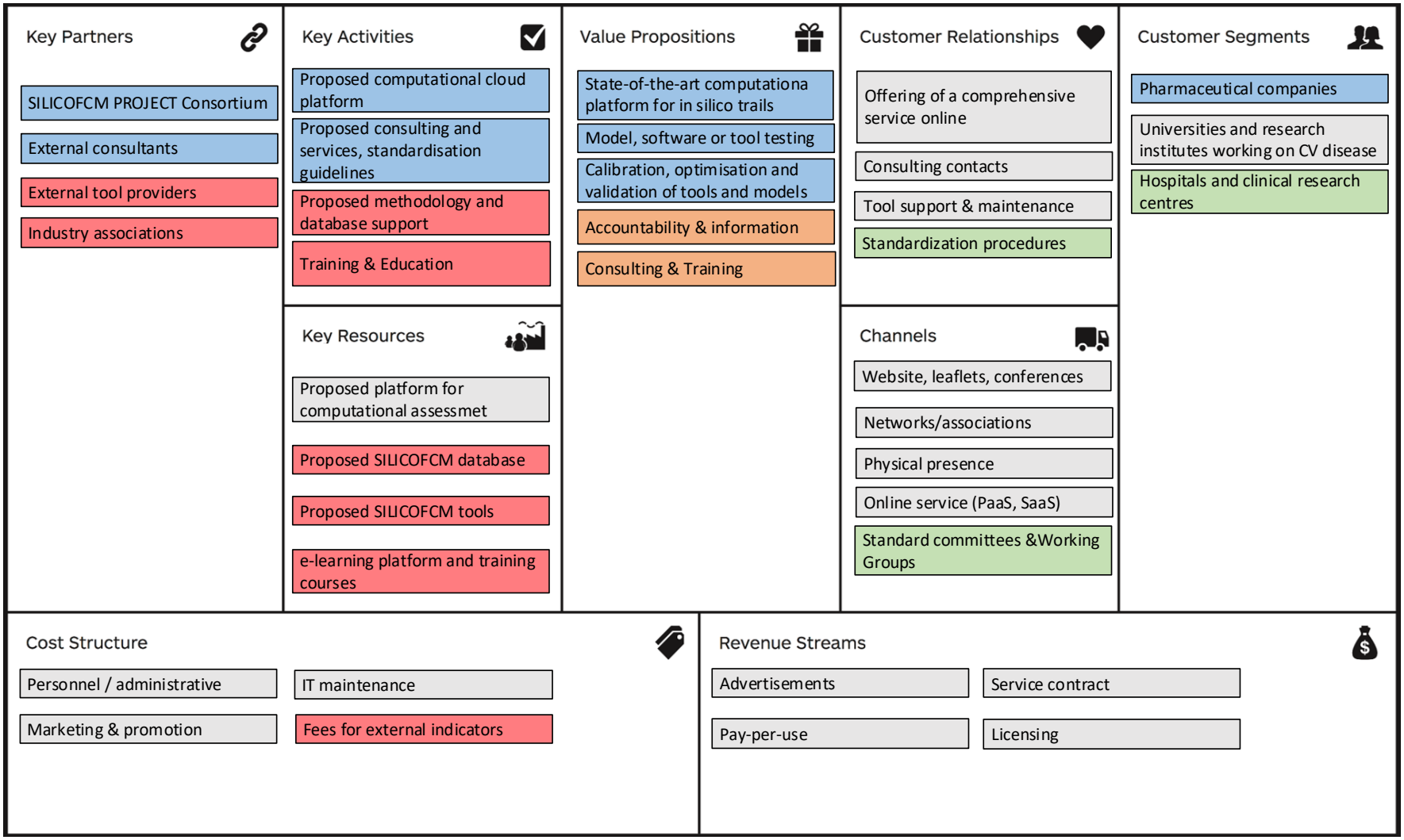

Figure 2: shows a business model canvas proposed for the FCM Services as a basis. Different colours are used to indicate the relationships between the elements at different sections of the Business Model Canvas.

The potential business model and related options for exploitation of the results from the SILICOFCM project can include providing SILICOFCM KER in the form of:

- Education and Research Platform
- Collaborative partner
- Spin-off company (independent legal entity)

3.1 Education and Research Platform for Medical school or Hospitals

Based on the involvement of key partners in the development of the Platform, a legal entity can be formed and this entity would act as an inventor and as an IP Lessor at the same time. Providing the platform for research will allow the platform to be used for research in the field of insilico drug trials, with the potential of replacing in vitro animal experiments in the pre-clinical phase of drug development. This option can be adopted without the need for going through regulatory registration (FDA, EMA etc.) as required for medical devices, even low-risk Class I.

The Platform can makes relevant methods, standard practices and tools in silico drug trials in populations of human models accessible to non-experts in modelling and simulations, providing a user-friendly interface and a potentially efficient simulation engine. Furthermore, the platform can be a useful tool for designing and aiding surgical procedures. Similar support can be provided for the patients who undergo ablation. With patients who are in recommended medication, the platform can simulate concentration of biomarker/genetic profile or social behaviour etc.

Revenue can be generated by offering consultancy services. Consultancy can generate revenue by having their individual consultants charge for Platform use and training potentially employing IP licensing, multi-year contracts, master service agreements, etc. This would ensure the scalability, recurring and repeatability of the Platform related services.

3.2 Collaboration or Integration with major pharmaceutical companies

Different KERs within the SILICOFCM project will be explored further in the next version of this deliverable as a possibility to collaborate or integrate with major pharmaceutical companies, such as Bayer, Roche, and J&J etc to bring the project results to the wider audience with higher impact. Web-based delivery mode segment of clinical trial management system market was valued at $ 668 million in 2018 and is expected to show considerable growth in future[21]. Ability of web-based clinical solutions to offer wide range of applications and provide centralized database for secured sharing of clinical trial information will increase its adoption over the analysis timeline. Pharmaceutical companies conduct large numbers of studies in-house and require an efficient CTMS to support study execution. Fully integrated online systems offered by cloud services provide solutions to small scale and medium-scale companies with limited IT resources to set up and manage a complex system.

Big pharmaceutical giants have developed specific innovation related programs, which allow collaboration in some form to explore, discover, test and co-create leading customer-centric solutions in health and nutrition. Such options are open to academia, start-ups and even industry– to prototype,

[21]https://www.globenewswire.com/news-release/2019/03/07/1749531/0/en/Clinical-Trial-Management-System-Market-to-hit-2-5bn-by-2025-Global-Market-Insights-Inc.html

incubate and scale up solutions, which can demonstrate potential long-term value. They typically offer: Start-up acceleration, Funding of novel ideas, tailored collaborating programs, Co-working / lab space.

3.3 Independent legal entity providing the SILICOFCM Platform as a Medical device

3.3.1 Proposed Objectives of the Entity

While this deliverable focusses on proposing the road for the business model, which will be implemented for SILICOFCM, this report proposes a prospective legal entity (consultancy) consisting of CEG within the project.

Some of the major objectives will be following:

- To train users on how to use the SILICOFCM computational cloud platform
- To sell the software tools developed to end users:
    - Pharmaceutical companies (Bayer, Sanofi, BMS, J&J etc. who are among the top companies who dominates the cardiovascular market.),
    - Hospitals and clinical research centers as mentioned in the European Society of Cardiology which are in Europe,
    - Companies producing medical equipment for cardiovascular diseases (Endonovo Therapeutics, Inc. (OTCQB: ENDV), 22nd Century Group, Inc. (XXII), Corbus Pharmaceuticals Holdings, Inc. (NASDAQ: CRBP), Emerald Health Therapeutics, Inc. (CVE: EMH) (OTCQX: EMHTF), and Lexington Biosciences, Inc)
    - Universities (Maastricht University, Newcastle University etc.
- Provide training for the software tools
- Provide online training courses

In order to materialize this opportunity, the main objectives will include:

- To generate demand and highlight the novelty of the anticipated computational platform with *In silico* trials for hypertrophic cardiomyopathy to the end users. This will be achieved by disseminating the SILICOFCM exploitation results and promoting them to the end users. A major effort for this activity will be already done during the project period through dissemination and communication activities.
- To improve the base platform and tools offered (as consultants) by expanding the knowledge base through partner and sponsored case studies. The number of completed cases or assessments can measure the impact.

The start-up expenses of FCM Services could range from 1€ to 25000€ will depend upon the following:

- Where? – which country
- What? - which type of company; GmbH, Ltd., EEIC
- How? – whether established as an independent company or under one of the already existing consortium member

Initial funding, outside of initial investment, can also be supported from initiatives such as BIC (Business Incubation Center) call for Germany, which can be supported by the German partner R-Tech.

3.3.2 Commercialization

The Road map on Business Model would revolve around the cloud based computational platform and the various software tools and databases as identified as the KERs, which the consortium members will develop for exploitation that can be accessed by the end users. The offered services will utilise the developing interest in using multi-scale computational modelling in heart mechanics to create a multi-scale framework to understand the heart physiology, from genes to the whole cardiovascular function which will be of high demand for the end users working on cardiovascular diseases.

Services will provide the following:

- Leverage the tested and validated tools and services developed by SILICOFCM partners,
- Offer expert consulting service to enable prospective end users to learn methodologies, best practices, tips, and techniques from experienced SILICOFCM CEG.

3.3.3 Ownership

The consultancy/start-up could be an independent privately held company owned by the ***Core Exploitation Group (CEG)*** of the project or can be established under one of the already existing consortium member. This could be decided at a later stage of the project (M36) through a voting process.

3.3.4 Key partners

To optimize operations and reduce business risks, external organizations may cultivate the customer-supplier relationships so that the Services can focus on the core activities that will assist us to reach the objectives.

- **External consultants:** External consultant may perform key activities to deliver the value of the SILICOFCM Services, implementing the to-be-developed methodologies and tools to perform Insilco trials.
- **External tool providers:** Different organizations may provide new tools complementing the SILICOFCM catalogue of tools and services.
- **Industry associations:** Industry associations may provide new tools and methodologies, and furthermore, suggest improvements for the overall functionality of the platform.

3.3.5 Customer relationships

The offered services with the SILICOFCM platform will aim to fulfil the relationship models proposed by the SILICOFCM project:

- **Offering a comprehensive service for Insilco trials:** The customer can use a variety of online tools and services online to-be-developed during the SILICOFCM project.
- **Consulting contacts:** Value may be delivered to the customers in a one-to-one approach to address each customer's needs.
- **Tool support & maintenance:** FCM Services may provide support to the customers as to how to use the tool, resolve issues etc.
- **Standardization procedures:** To adopt the SILICOFCM approaches as a standard, a proposal submission is required.

3.3.6 Key resources

The platform services will have direct access to the available resources and be utilized during the SILICOFCM project and its past activities:

- **Proposed SILICOFCM Software Tools:** including 3D image segmentation tool, Bioinformatics tool, MUSICO tool, Finite Element tool and Risk stratification tool.
- **Proposed SILICOFCM database:** Virtual patient population database and physiological and clinical experiments databases.
- **e-Learning platform & courses:** e-Learning platform and online courses for training in the state-of-the-art approach to be introduced during the SILICOFCM project.
- **The big data analytics**: It will allow users to do an analysis of big data to derive valuable insights and results for various applications.

4. 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.

4.1 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[22], 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.

4.2 The European Union (EU)

4.2.1 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[23]:

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

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

4.2.2 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)[24].

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) 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 (see the timeline in Figure 3).

[24] http://ec.europa.eu/DocsRoom/documents/10337/attachments/1/translations/en/renditions/native

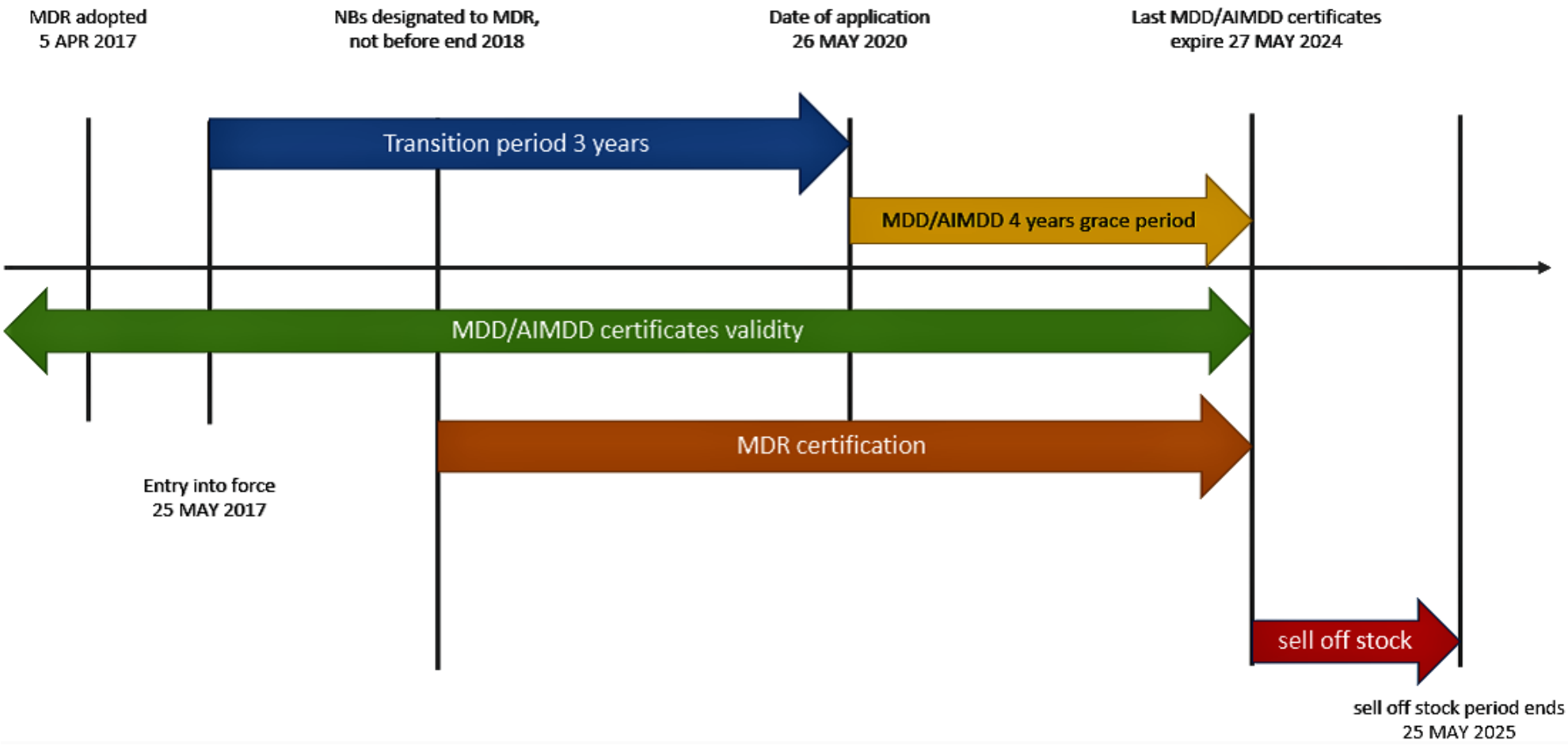

Figure 3: ***Timelines of MDR 2017/745 (Source: Brown, Handbook of Early Childhood Care and Education)***

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[25].
- 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.

4.3 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[26].

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

[25] https://eudamed.eu/index.php/2018/09/19/mdr/
[26] 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.

5. Deviation from the work plan

No deviation from the work plan.

6. Conclusion

The deliverable reports consist of the Road map on Business Model for the SILICOFCM project. While many of the key results for exploitation (see D9.5 for more) are still under development, the road map proposed at the initial stage of the project is based on the assumption that the plan will cover and possibly enhance the research work towards the exploitable results. A detailed analysis of stakeholders and end users is identified and presented in the document with target market size, market maturity, market by application, potential competitors and expected release of the KERs for exploitation and commercialization. The cost-effective and time-saving solutions produced in the project will be highly efficient when compared to already available solutions for Familial Cardiomyopathy (FCM).

Throughout the next stage of the project, the exploitable results will be evaluated more in detail and the consortium members will be able to refer to the current document and modify/implement changes in a way that best supports the objectives of the project and meets the requirements of the EC and end users. The ultimate aim would be to adapt the project towards commercialization as planned such that the product and services generated from the project activities are economically viable and has a potential to be competitive in the market.

Proposals on services options is given with details on objectives, services and tools offered, ownership suggestions, start-up expenses etc. which will be decided and finalized among the consortium. The Core Exploitation Group will serve as the partners who might be interested in starting FCM services. The deliverable will be updated at M36 and M42, involving all consortium members with the updated findings.