Result Report

Development process - pilot projects

German-Danish network for innovation and cooperation in healthcare

ACCESS & ACCELERATION   Interreg
Deutschland - Danmark   EUROPEAN UNION

Imprint

This result report presents a compilation on the key findings provided by the partners working in the work package:

Work Package 1 — Project management

Work Package 4 — Ideation process

Work Package 2 — Project communication & PR

Work Package 5 — Development process

Work Package 3 — German-Danish platform for innovations in the health sector

Work Package 6 — Market access

Table of content

The Access & Acceleration project

The aim of the Access & Acceleration project is to provide an overview of the relevant players within the medical innovation sector in the German-Danish border region (*access*), and to signpost ways to speed up the cycle of medical innovation (*acceleration*). In the last three years, the Access & Acceleration project has examined both the fundamental barriers to market entry and the innovation process in the healthcare sector. The results were integrated into a digital platform where users from the clinical, academic and industrial sectors can find the skills to develop new ideas and create new products for the healthcare markets in Denmark and Germany. The partners participated in pilot projects, pursuing the innovation process from the ideation stage to testing and evaluation, right through to the prototype phase. All of the stages were also documented on the platform. The platform also contains examples of good cooperation between research institutions, hospitals and companies. A database linking regional stakeholders offers the opportunity for future cooperation and the further use of the platform even after the end of the project.

Project facts

March 2019 – March 2022

2.9 million Euros budget, thereof 1.7 million Euros funds

7 partner organisations from Denmark and Germany

Project aims

✓ strengthen cooperation between medical providers, companies and universities in the German-Danish region

✓ promoting the involvement of patients and healthcare professionals in the user-centred development of innovative services and technologies in the health sector

✓ increasing the innovative capacity of companies and supporting them in accessing cross-border markets

Project partners

Introduction to the challenges addressed

The aim of the Access & Acceleration innovation platform is to cover the entire range of innovation processes and also to promote projects that are already further advanced. This work package therefore develops pilot projects that have a higher technology readiness level (TLR), either because they are linked to previous products and the first stages of the innovation process have already been initiated and carried out or because they are the first ones to be developed.

The advantage of including such projects into the health innovation platform also include the difficulties that can develop at the various levels, and which must also be taken into account. However, these advanced projects can have a pilot character for all other projects starting in an earlier stage of the innovation process. Here, the projects can learn from each other by having a lively exchange between the respective work packages and by identifying critical core issues.

In principle, the closer the pilot projects are thematically to each other, the greater the expected synergy effects, since certain techniques and environmental parameters are more similar and therefore occur more frequently and thus the problems that arise are more comparable. However, the exchange of information between projects that are thematically more distant from each other can also lead to synergy effects, especially in regard to administrative functions as well as innovation management. Another advantage of including advanced projects is the expected completion of a product at a pre-commercial level or a launch system within the project funding period. This has a stimulating effect on further projects in earlier stages that should not be underestimated.

Pilot 1 "Treatment of geriatric fractures"

Introduction – „Gamma4 with ADAPT"

"Gamma4 with ADAPT" unites partners from universities, clinical practices and the medical technology industry in the German-Danish border region, with the aim of improving the care and clinical practice around geriatric hip fractures.

Stryker Trauma GmbH specialises in the development and production of trauma surgical implants and instruments, for example for treatments using cepha/intramedullary nailing. Medullary nails stabilise broken bones very effectively using a comparatively simple and gentle surgical technique.

The gamma nail has been developed to provide rapid, stable treatment of geriatric hip fractures. Now in its fourth generation, the focus is on innovations that will simplify operational challenges for users. The process uses the ADAPT digital assistance system, which supports the operation and makes it safer, with automated X-ray image analysis and increased position accuracy.

Figure 1: Gamma nail © Stryker

Medical device development at Stryker

Product safety and quality are paramount in the development of medical devices. All legal and regulatory requirements of the global target markets must be met. This includes a large number of safety and quality-specific verifications that are part of the development process: During the design and phase reviews of the development process, defined in quality management procedures, the evidence is developed, documented and regularly reviewed and approved at each step.

The development of every product is supported by the findings from a continuous innovation process rooted in knowledge. Regular exchange with users, employees and cooperation partners is not aimed at receiving suggestions for new products or approaches for problem solving, but at looking for unsolved problems or potential for improvement. The focus is on how to measure the success of a problem solution. With

the help of creativity techniques, problem solving approaches are developed, compared and evaluated according to measurable success criteria. This ensures that optimal approaches and new technologies are taken into account. In addition, cross-departmental analyses accompany the innovation process. The data collected is documented and fed into ongoing development projects as part of regular reviews. The company's internal priorities are set according to economic and strategic aspects and resources and budget are allocated according to the priorities.

Elements of the innovation process

Interaction	Analysis	Strategy
• Users • Partners • Employees	• Publications • Patents • Market development and trends • Product performance • Evaluation of proposals and ideas • Research and feasibility study	• Product pipeline • Business models • Project strategies • Development plans

The product development process follows defined phases, each with several design reviews assigned by topic. A new phase only begins after a phase review has been completed and approved. The project phases ensure that the required framework is completed for optimum product specification, quality control, production, testing (verification and validation), clinical evaluation and regulatory approval procedures.

Elements of the development process

Research phase	Planning	Development	Verification and validation	Launch
• Feasibility studies • Project and development plan • Customer and product requirements • Regulatory plan • Resource plan and schedule • Financial plan, including order-volume plan	• Design input and performance requirements • Risk management plan • Design concepts • Risk assessment • Investment plan for process design • Labelling plan • Update of documentation from the previous phases	• Product specifications • Product master records • Packaging checklist • Functional interface analysis • Finality analysis and design transfer plan • Verification and validation reports • Product and process freeze • Update of documentation from the previous phases	• Marketing materials • Evidence of usability • Evidence of verification and validation for product and process • Labelling and instructions for use • Clinical evaluation • Technical records • Regulatory approval process • Update of documentation from the previous phases	• Training modules • Product approvals • Logistics approvals • Early Product Surveillance

Prototype development for Gamma4 and ADAPT 2.1

Cooperation partners from universities and clinical practices were involved in both the innovation and development processes of the project. Two students from the University of Southern Denmark (SDU) contributed to the foundational knowledge for the innovation process with their Master's theses, with a focus on simulation. In total, more than 50 trauma surgeons participated in design reviews and prototype testing in the form of operation simulations on human specimens, and contributed to optimising the designs.

Voice of Customer (VOC)-Concept

Integration of the customer is an integral part during the design process as it secures the clinical need to be sufficiently take into consideration. For this reason, a detailed system requirement specification sheet was developed in the beginning of the project based on the previous Gamma generation development phase and subsequent continuous improvement process. Within the project we therefore had three cadaveric laboratories with surgeons involved, evaluating the design its usability. At the same time EU and international design panels in the US and Japan secured novel the geriatric osteosynthesis device to be in line with the clinical need observed in the various hospitals worldwide. As treatment patterns differ between countries and regions, we also include special feedback from our partners at the Odense University Hospital to match the specific local needs in the German-Danish border region. In this feedback rounds key aspects of improvements were communicated via interview, tangible design results or by practical work with the demonstrators, resulting in a world-class next generation medical device arising in the programme region.

Conclusion and outlook

A main objective of the project was to find medical solutions for an aging population in the program region suffering from demographic change with reduced bone quality and limited regenerative capacity on the one hand, and exploding healthcare costs for society on the other. This main issue was successfully addressed by a new osteosynthesis device that allows fracture treatment of fractures with low bone quality and the often-associated complication of cutting out. On the one hand, this represents an improvement for the future medical care of the program region, while at the same time making the medical device industry at this location more resilient, securing local jobs and enabling the generation of revenue and added value. The new developments in this high-value manufacturing sector thus have an impulse effect on other economic and social sectors that goes beyond the effect within the industry. Furthermore, the intended lighthouse character of the project could be successfully integrated into the Access & Acceleration platform, as it is located in the higher range of the technology readiness levels. Thus, more basal projects within the platform can learn, for example

how to deal with approval regulations at an early stage. Within the project, the design review process was considered from a static model of sequential point processing to a dynamic method with overlapping process stages, thus enabling faster development and introduction of innovations into the healthcare market with a streamlined system. Speed is an important criterion here in this highly regulated but competitive area to allow for later market penetration. This is of crucial importance for the German-Danish healthcare border region to succeed in the competitive global market that the industry faces. Furthermore, the collaborative character of the innovation platform should be emphasized, which not least allows the important cooperation of local research, clinics together with industry in the first place, which will also play an important role in the formation of clusters in the future.

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Pilot 2 "Clinical decision support based on electronic health records"

Introduction to the challenges addressed

Most individuals suffering from Alcohol Use Disorder (AUD) never undergo specialist treatment during their addiction due to the poor performance of conventional AUD identification methods, the lack of systematic screening for alcohol problems, and the stigmatisation associated with harmful drinking. Qualitative studies have shown that hospital staff wishes to be rather sure that alcohol use plays a key role for the patients' health issues before starting a conversation about alcohol and the benefits of reducing its intake. The recent availability of Electronic Health Records (EHR) and the advancement of Machine Learning (ML) algorithms have made it easier to offer clinical reasoning when advising patients. Therefore, this pilot project aimed to use patients' EHRs and ML algorithms to develop predictive models which can be used to allow an identification and early detection of patients with AUD.

This project was a multidisciplinary research project that was developed in close collaboration with computer scientists from University of Southern Denmark and clinical alcohol researchers from Odense University Hospital. In this research project, clinical researchers have been involved through all the phases of the methodology. For example, as the dataset owner, they have stored data in a secure database and declared the main idea of labelling patients based on the Relay study. Moreover, medical reasoning about the set of the selected feature was discussed in detail with them.

Methodology

The partners proposed an iterative and exploratory research methodology based on the Agile Scrum framework in this project. It consists of three phases: Planning and Design, Development, and Testing and Documentation.

The planning and design phase started with the setting of the initial problem statements, formation of research questions, aims, and objectives of this project.

In the development phase, the partners started with data handling which consisted of data collection and data pre-processing. The data for this study was collected from two sources, including the Relay Study and EHRs. After that, the collated data were pre-processed to overcome challenges such as imbalanced classes distribution as well as data scaling. Through the social network analysis, feature selection, and the ML methods, novel insights were extracted from the pre-processed data. The main elements being considered in this research encompassed the imbalanced class distribution, high dimensionality, the selection of an appropriate ML model, and the complexity of models for the identification and early detection of patients with AUD. For each step in this research, several evaluation metrics were considered to describe the predictive performance and validation. The outcomes of all analyses and development have then been compiled into several documents such as a Ph.D. thesis, scientific articles, and internal reports which also served as contributions to this research.

Conclusion and outlook

In the context of a multidisciplinary research project, which used the Agile Scrum framework as a methodology, and through the close collaborations of computer scientists and clinical alcohol researchers, this project contributed to the body of knowledge involving the identification and early detection of patients with AUD, based on EHRs using ML techniques. The partners' efforts pinpointed several contributions which have implications for the development of accurate predictive models for AUD related studies. This project had designed and developed a novel comorbidity network which can be used to identify the most exclusive comorbidities for the Hazardous and Harmful drinkers. This can aid clinical staff in understanding the high-risk comorbidities of AUD, hence their ability to consider suitable interventions. Moreover, this project had investigated the different sampling approaches, to overcome the imbalanced class in the datasets, and to boost the performance of the ML models, thereby achieving better predictive accuracy.

This project had also promoted the development of a novel multilayer feature selection framework which was useful for condensing the number of features to a manageable number, for improving the predictive accuracy of ML model to identify AUD-Positive and AUD-Negative, and for identifying the clinical factors that were strongly correlated with AUD. This, therefore, proved that gender disparity should be considered when building predictive models to identify patients with AUD. And finally, this project had established several predictive models that can identify Normal, Hazardous, and Harmful drinkers. It had utilized ML algorithms to develop a novel approach that aids in the early detection of patients with AUD. Three retrospective time periods were used to accurately detect Hazardous drinkers, thus initiating interventions in the advice level.

The complexity of a multidisciplinary project may result in the loss of central control, thereby leading to a breakdown. To overcome the possible challenges of a multidisciplinary project, we proposed an iterative and exploratory methodology in which medical researchers played vital roles.

There were a lot of factors related to data collection which could cause delays in projects, or the poor quality of the final product. Having access to a multidimensional dataset would be the most ideal situation. However, due to the sensitivity of EHRs, collecting such datasets was restrictive and time-consuming.

An important factor in ML based studies is to train a variety of ML and deep learning models based on well pre-processed data, well-defined features, and the best possible hyperparameters. The generality of our approach, in terms of methodologies and techniques, was to examine as many scenarios, techniques, and algorithms as possible in order to achieve the best possible solution as noted in the intended objectives.

In future work, the partners would like to set up a procedure in order to validate the results in the hospitals of the regions of Southern Denmark. This will be done by collaboration with Cambio, which is well on track, and an agreement with Odense

University Hospital (OUH) which has been settled to implement the developed model. Up to now, the model has been developed based on Danish EHRs only and will be tested at the OUH site. Together with Cambio and OUH, the adjoining partners are looking for additional funding options. The idea is to spread the model first to different departments of OUH and then to further hospitals and regions in Denmark.

Integrating German data could be the ultimate goal, but it takes that time and focus are laid on the above-mentioned steps first. In order to have the predictive model tested in other hospital settings, a CE marking is required. With regard to German data, data structure and protection are relevant issues that are not taken up easily.

The project partners have tried to publish most of their findings in scientific journals to make sure that clinicians can use them, and it can be followed up by others in practice and science.

Scientific Publications

Analysis of Comorbidities of Alcohol Use Disorder – by Ali Ebrahimi, Uffe Kock Wiil, Marjan Mansourvar, Amin Naemi, Kjeld Andersen, Anette Søgaard Nielsen. Submitted to the in 2021 IEEE Symposium on Computers and Communications (ISCC).

Deep Neural Network to Identify Patients with Alcohol Use Disorder – by Ali Ebrahimi, Uffe Kock Wiil, Marjan Mansourvar, Amin Naemi, Kjeld Andersen, Anette Søgaard Nielsen. Accepted in 31st Medical Informatics Europe Conference (MIE 2021).

A Predictive Machine Learning Model to Determine Alcohol Use Disorder – by Ali Ebrahimi, Uffe Kock Wiil, Marjan Mansourvar, Anette Søgaard Nielsen. Published in 2020 IEEE Symposium on Computers and Communications (ISCC), Rennes, France.

Prediction of Alcohol Use Disorder: A Scoping Review – by Ali Ebrahimi, Uffe Kock Wiil, Marjan Mansourvar, Anette Søgaard Nielsen. Published in 2019 IEEE Symposium on Computers and Communications (ISCC), Barcelona, Spain.

Predicting Risk of Alcohol Use Disorder Using Machine Learning: A Systematic Literature Review – by Ali Ebrahimi, Uffe Kock Wiil, Thomas Schmidt, Amin Naemi, Anette Søgaard Nielsen, Ghulam Mujtaba Shaikh, Marjan Mansourvar. Published by the IEEE ACCESS.

Clinical Factor Identification for Alcohol Use Disorder from Electronic Health Records using Feature Selection Methods – by Ali Ebrahimi, Uffe Kock Wiil, Marjan Mansourvar, Kjeld Andersen, Anette Søgaard Nielsen. Under review in the BMC Medical Informatics and Decision Making.

Early detection of Patients with Alcohol Use Disorder from their Historical Electronic Health Records: A temporal and Machine Learning comparative study – by Ali Ebrahimi, Uffe Kock Wiil, Marjan Mansourvar, Kjeld Andersen, Anette Søgaard Nielsen. Submitted to PlosOne.

AUD-DSS: A Decision Support System for Early Detection of Patients with Alcohol Use Disorder – by Ali Ebrahimi, Uffe Kock Wiil, Marjan Mansourvar, Kjeld Andersen, Anette Søgaard Nielsen. On process of writing.

Other Publications

- Video on pilot 5.2 at project website: *Clinical decision support based on health records*

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