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Innovative approach for self-management and social welfare of children with cystic fibrosis in Europe: development, validation and implementation of an mHealth tool (MyCyFAPP)

Joaquim Calvo-Lerma,[1,2] Celia P Martinez-Jimenez,[3,4] Juan-Pablo Lázaro-Ramos,[5] Ana Andrés,[2] Paula Crespo-Escobar,[1] Erlend Stav,[6] Cornelia Schauber,[7] Lucia Pannese,[8] Jessie M Hulst,[9] Lucrecia Suárez,[10] Carla Colombo,[11] Celeste Barreto,[12] Kris de Boeck,[13] Carmen Ribes-Koninckx,[1] on behalf of MyCyFAPP

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For numbered affiliations see end of article.

Correspondence to
Professor Carmen Ribes-Koninckx; ribes_car@gva.es

ABSTRACT

Introduction: For the optimal management of children with cystic fibrosis, there are currently no efficient tools for the precise adjustment of pancreatic enzyme replacement therapy, either for advice on appropriate dietary intake or for achieving an optimal nutrition status. Therefore, we aim to develop a mobile application that ensures a successful nutritional therapy in children with cystic fibrosis.

Methods and analysis: A multidisciplinary team of 12 partners coordinate their efforts in 9 work packages that cover the entire so-called 'from laboratory to market' approach by means of an original and innovative co-design process. A cohort of 200 patients with cystic fibrosis aged 1–17 years are enrolled. We will develop an innovative, clinically tested mobile health application for patients and health professionals involved in cystic fibrosis management. The mobile application integrates the research knowledge and innovative tools for maximising self-management with the aim of leading to a better nutritional status, quality of life and disease prognosis. Bringing together different and complementary areas of knowledge is fundamental for tackling complex challenges in disease treatment, such as optimal nutrition and pancreatic enzyme replacement therapy in cystic fibrosis. Patients are expected to benefit the most from the outcomes of this innovative project.

Ethics and dissemination: The project is approved by the Ethics Committee of the coordinating organisation, Hospital Universitari La Fe (Ref: 2014/0484). Scientific findings will be disseminated via journals and conferences addressed to clinicians, food scientists, information and communications technology experts and patients. The specific dissemination working group within the project will address the wide audience communication through the website (http://www.mycyfapp.eu), the social networks and the newsletter.

Strengths and limitations of this study

- Innovative evidence-based method for pancreatic enzyme replacement therapy adjustment and self-management by means of a mobile application.
- Multidisciplinary team of experts for an integrative and co-designed patients-directed approach.
- Envisaged medium-term to long-term market uptake of the resulting mobile health application.
- Limited but statistically significant number of patients from five European countries will be included in the clinical validation.

INTRODUCTION

Cystic fibrosis (CF) is the most common life-threatening autosomal inherited disease in Europe, with over 38 000 cases of CF currently registered in Europe.[1] Along with pulmonary dysfunction and recurrent lung infections, the majority of patients (85%) suffer from life-long pancreatic insufficiency (PI), which leads to maldigestion of foods and malabsorption of nutrients, especially lipids. In fact, pancreatic enzyme deficiency is occurring in ~50% of infants by the age of 2 with a further 28% of the cases developing PI in early childhood.[2] These malfunctions secondarily cause malnutrition, fat-soluble vitamin deficiencies and gastrointestinal symptoms.

There is high-grade evidence that maintaining normal growth and nutrition adds 10 years more to the median survival since a close relationship between pulmonary function and nutritional status has been repeatedly ascertained.[2–4]

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Malnutrition and growth stunting can only be avoided by accurate pancreatic enzyme replacement therapy (PERT) and close nutritional follow-up, as well as by early nutritional support and intervention. Nowadays, PERT consists of oral supplements containing a mixture of pancreatic enzymes—amylases, proteases and especially lipases—that have to be taken with every meal, while nutritional therapy relies on a high-energy and high-fat diet.[5–9] However, at present, there is a lack of evidence-based methods to adjust PERT dosing and there are few handy tools or resources adequately available to promote a balanced and adapted diet (figure 1).[5 10 11]

Current recommendations for PERT dose adjustment rely on low level of evidence[12] and counsel a number of units of lipase per gram of lipids. This means that in every meal, fat content should be known by the patient to estimate the corresponding PERT dose. The only way to achieve this would be by roughly estimating fat content from nutritional information databases and those should be easily available for patients. This approach is challenging for the patients and imprecise to maintain satisfactory levels of fat absorption. In this regard, clinical trials aimed at elucidating maldigestion in CF have led to inconsistent conclusions.[5] Therefore, the demand for an evidence-based criterion for PERT adjustment has been highlighted,[5 10 13] and the corresponding development of new innovative tools is imperative.

Dietary lipids need to be accessible to digestive enzymes so that digestion and absorption can occur. The food matrix is dissociated through the digestion process, thus allowing the release of the embedded lipids and the access of the enzymes (lipases) to their substrates (lipids).[5 14] Recent advances in food science research revealed that the different food structures modulate fatty acids release during digestion and their final metabolic fate.[15–17] In addition, pancreatic lipase exhibits different hydrolytic activity depending on the intramolecular structure of the lipids.[14 18 19] Therefore, lipolysis may cause different kinetics of release of absorbable fatty acids. This can be translated into different enzymatic dosage depending on the inherent-to-food characteristics, so nutrition and dietary habits play a key role in PERT effectiveness.[20 21]

Moreover, the lack of appropriate tools and resources for nutritional management can impair quality of life and lead to a lack of treatment adherence. For instance, if an incorrect nutritional behaviour or an inadequate PERT dosage occurs, the most likely scenario is that it will occur repeatedly and, in the majority of the cases, it will not be detected and corrected until the next contact at the CF unit. This could lead to long periods of omissions and/or wrong decisions. Consequently, the small daily actions related to nutrition that contribute to the overall disease prognosis would not be optimally used to improve the health status.

Hence, nutritional treatment in CF can be considered as one of the ideal targets of mobile health (mHealth) and patients' self-management. In fact, CF is one of the most representative examples in which patients' monitoring and self-management can lead to a great improvement in the evolution and prognosis of the disease. Among other priorities in health, the current European Union's Research and Innovation Programme, Horizon 2020, strongly supports that current and future lines of research and technological development should be focused on this area (http://www.ec.europa.eu). In this framework, the MyCyFAPP Project (http://www.mycyfapp.eu) has been granted to develop an innovative approach focused on paediatric children with CF, self-management of nutrition and PERT by means of a mobile application (APP) linked to a web-based professional management tool.

Figure 1 Overview of current nutritional therapies in cystic fibrosis and the tools needed for successfully achieving a good nutritional status, quality of life and disease prognosis.
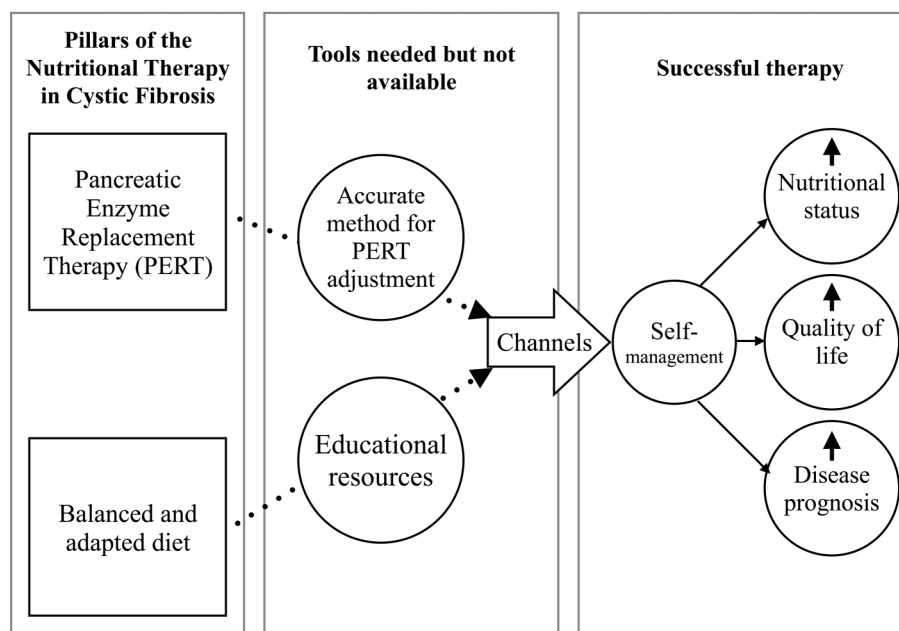
The objective of the present work is to describe the overall approach and study design of the MyCyFAPP Project as an example of multidisciplinary research and innovation project in mHealth.

METHODS
The consortium
The Consortium was established in 2015 with the signature of the grant agreement with the European Commission. The multidisciplinary research team comprises nutritionists–dieticians, paediatric gastroenterologists and pulmonologists, food engineers, IT experts, game developers, software developers, psychologists, sociologists, biologists and patients' representatives. We have brought together our expertise to ensure the successful development of the project through a holistic and integrative approach of the different and complementary areas of knowledge and experts included.

There are 12 organisations involved: 6 clinical partners linked to their corresponding research institutes or foundations, 3 small–medium enterprises (SMEs) related to mHealth, 1 Information and Communications Technology (ICT) Research Institute, 1 Food Technology Research Institute and the European Federation of Patients with CF (table 1).

Funding
The MyCyFAPP Project is funded by the European Union through the Horizon 2020 Research and Innovation Programme (PHC-26-2014: self-management of health and disease: citizen engagement and mHealth) under grant agreement number 643806.

Study design
The 4-year long project (1 January 2015 to 31 December 2018) is constructed on nine inter-related work packages (WP; figure 2). Four multidisciplinary WP (1, 2, 3, 4) set the ground and generate the necessary knowledge and resources to develop the APP. A central technical WP (5) integrates the information in the development of the different software tools. These tools are thereafter tested for impact through a European multicentre clinical trial (WP6) and once the ICT tool is validated, another WP (8) takes care to bring the tool to the market by following different business models. Along the whole project, a specific WP (7) ensures the dissemination of the project to the very wide spectrum of audiences and another is devoted to the coordination of the consortium and the management of the implementation.

WP underpinning the project
European study on dietary habits in children with CF (WP1)
One of the first actions of the project aims at obtaining information related to nutritional habits and dietary assessment of children with CF in the participating countries. It is used to establish the current nutritional habits of children with CF, PERT dosage, nutritional status and dietary assessment as a ground setting. The final milestone is then the generation of educational tools and resources for a customised nutritional self-management of the disease and patients' empowerment.

In vitro assessment of enzyme requirements for foods and dishes (WP2)
In parallel to the development of the European survey, we have set up a methodology to simulate in vitro digestion of a wide range of foods and meals under standardised CF gastrointestinal conditions. It allows for characterising inherent-to-food factors (chemical composition, molecular structure of lipids, food matrix) and gastrointestinal conditions (composition of digestive fluids and pH of the digestive environment), which affect fatty acids release and enzyme activity. The ultimate goal is to apply these results for determining the optimal PERT doses for foods and meals. They conform a key database supporting the mathematical algorithm.

Development of the PERT dose predictive model (WP3)
We conduct a pilot study with the enrolled children with CF. They follow a fixed menu consisting of a selection of foods and fixed enzyme doses according to the in vitro studies (theoretical optimal dose, TOD). Analyses of fat in stools reveal the degree of effectiveness of the predicted dose in each individual.

Biostatistical modelling of the results determines an individual correction factor (ICF) calculation that will be able to correct the in vitro dose, for any other meal (even one not tested in the pilot study). Thus, from WP2, the TOD estimates the requirements of PERT considering food characteristics. Then, from WP3, the ICF will adjust the TOD according to patients' individual characteristics. These two key elements conform the predictive model, which calculates for each patient an individual optimal dose.

User requirements specification for CF self-management (WP4)
User requirements describe how software solutions work in a certain context of use; how the end users will benefit from it; how the application is managed and maintained; and how it is technically and organisationally deployed. As already mentioned, MyCyFAPP is an ecosystem of APPs, as well as a number of tools and components devoted to support the execution of those APPs.

It is critical to gather a multidisciplinary team (developers, clinical partners, psychologists, experts in user experience and acceptance, paediatric and adult end users and patients' associations) to define in detail what the mobile applications will do, and how the clinical processes implemented through the web professional tool will be perceived by the users, both children and caregivers. MyCyFAPP has selected a methodology for the

Table 1 List of participating organisations in the MyCyFAPP Project

Country	Organisation	Type of activities
Spain	Instituto de Investigación Sanitaria La Fe	Non-profit organisation pursuing the fostering and promotion of excellent research, scientific and technological knowledge and the translation to the productive sector. It manages research activities of Hospital La Fe, where the regional CF unit is the reference.
Spain	Soluciones TSB	R&D and innovation SME focused on knowledge-intensive solutions for healthcare and well-being.
Germany	YOUSE GmbH	Interdisciplinary SME working on increasing the usability and user experience of products and services
Italy	Imaginary SRL	Experienced SME in creativity and innovation backed by solid technical competence and an understanding of the commercial potential of serious games and gamification
Norway	STIFTELSEN SINTEF	Research organisation with expertise within user-centred design, software architecture, software development methods, mobile and social computing and evaluation of technology
Spain	Universitat Politècnica de València—Instituto de Ingeniería de Alimentos para el Desarrollo	University Research Institute focused on food engineering. It applies its strong experience in industrial food processing to the area of the digestive food processing, involved in numerous collaborative projects between the industry and academia.
Belgium	University of Leuven	The CF reference centre is based at the University Hospital of Leuven and has a strong research focus since many years.
Portugal	Associação Portuguesa para a Investigação e Desenvolvimento da Faculdade de Medicina	It is the funding body that supports medical research in the Hospital de Santa Maria. The CF team conforms the reference unit in the country.
Italy	Università degli studi di Milano	Research group linked to the Ospedale Maggiore Policlinico with a wide experience in CF multicentre projects, which is the largest CF reference unit in the region.
The Netherlands	Erasmus Medical Center, Sophia Children's Hospital Rotterdam	The hospital embraces the reference CF unit for children in the region. The medical team has a commitment to science and research integrity and therefore is actively involved in research projects.
Spain	Servicio Madrileño de Salud. Hospital Universitario Ramón y Cajal	The hospital is one of the reference CF units for children in the region. The medical team has a broad experience in clinical trials and research in the field of CF
Belgium	Cystic Fibrosis Europe	It is the representation of the Patients Organisations in Europe, which is actively involved in dissemination of CF activities and has been playing a key role in EU research projects.

CF, cystic fibrosis; EU, European Union; R&D, research and development; SME, small–medium enterprise; TSB, Tecnológicas para la Salud y el Bienestar.

identification of user requirements, called 'co-creation', with the goal of maximising the opportunities for further adoption.

A series of activities including interviews, focus groups and hands-on workshops to establish the needs and preferences regarding the APP usage will be conducted. We establish five focus groups (three patients and two parents): patients aged >16 years, patients aged 12–16 years, patients <12 years, parents of patients aged 12–16 years and parents of patients younger than 12 years. The APP will have different functions according to the role and responsibility of the target group in the self-management.

The results will be translated into tailored interfaces and will be easily accessible and user-friendly for the different target populations.

Software development of APP and health professional management tool (WP5)

The results from WP4 are translated into technical specifications, and finally to software mobile and web applications. To this purpose, the system architecture, technical specifications, integration plan and software testing strategy are defined. Finally, after software development for full CF self-management, the implementation and integration of the algorithm developed in WP3 and the
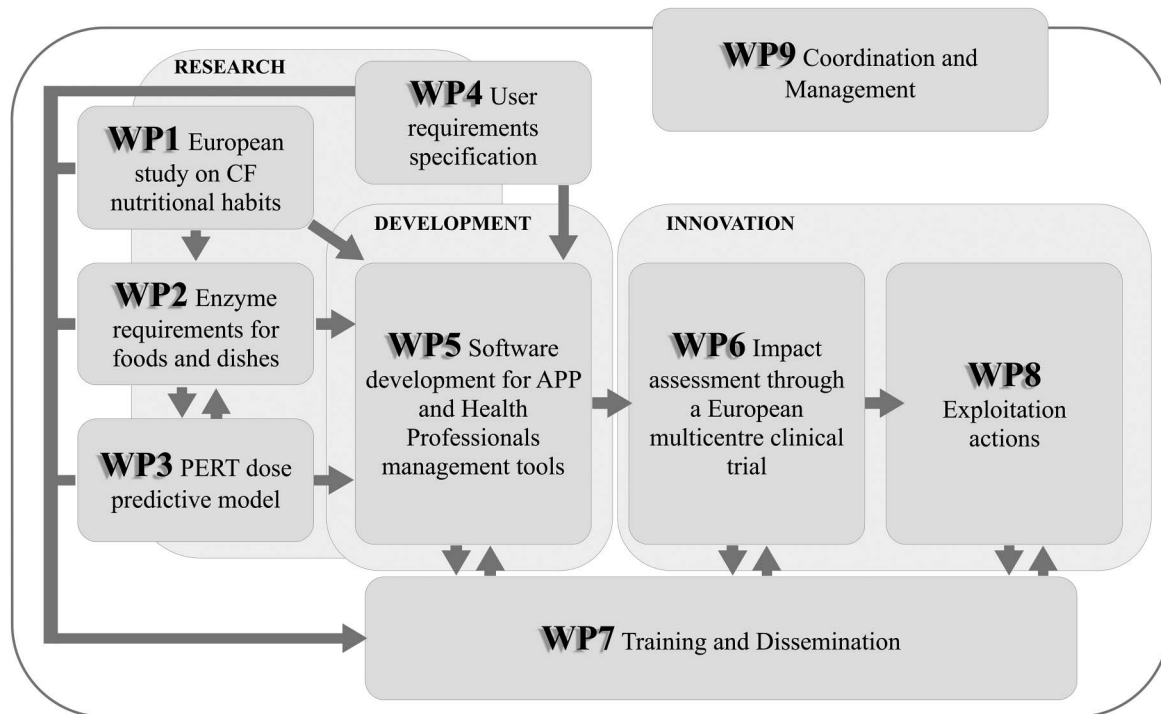
Figure 2 General overview and inter-relation of WP. CF, cystic fibrosis; PERT, pancreatic enzyme replacement therapy; WP, work packages.

other resources developed in WP1 are conducted. At that point, the overall system will be delivered for the clinical trial in WP6.

Impact assessment through a European multicentre clinical trial (WP6)

We will carry out a European multicentre clinical trial to assess the impact derived from the usage of the APP on children's quality of life (especially related to nutrition and gastrointestinal symptoms), nutritional status and healthcare usage. A cohort of 200 patients will be recruited. The sample size was estimated using Monte Carlo simulations assuming normally distributed variables, and aiming for a precision of ±10% for each variable. A validation step is crucial for implementing MyCyFAPP in the usual clinical practice and transferring the self-management utility to patients with CF.

Training and dissemination (WP7)

This WP embraces a double scope. Training activities are aimed at achieving patient's engagement in self-management of their own disease so that specific workshops and webinars are scheduled prior to the start of the clinical trial addressing both patients and health professionals.

Dissemination pursues the project's awareness, through all media channels, among the key stakeholders: patients and their families, patients' associations, health authorities, professionals from the different disciplines involved in the project, the industry and the

general public. Overall, it targets the successful implementation of MyCyFAPP.

Exploitation actions (WP8)

This WP takes care of the exploitation of the final product and the Intellectual Property Rights (IPR) protection plans envisaged in the project. Specific actions include the identification of business models for the exploitation of the project's outcomes, the definition and execution of the strategy for exploitation and the coordination of the exploitation activities with disseminations to maximise the impact and awareness of the project.

Coordination and management (WP9)

It is aimed at orchestrating all the activities and partners of the project towards the successful implementation of the action and the reach of the goals and milestones.

EXPECTED RESULTS

The MyCyFAPP Project pursues a final scenario where children with CF and their families and the health professionals can jointly and barriers-free manage the treatment of the disease. On the one side, patients and families count on the APP to self-manage nutrition and PERT and, on the other, health professionals use the professional tool to supervise and monitor patients' progress, ensuring feedback between the two parts when needed. This process is possible thanks to the specifically developed procedures and tools (features) that are

addressed in the framework of the project from a rigorous scientific approach, responding to the current gaps on the resources needed but not available for a successful nutritional therapy (figure 3).

Tools and resources for MyCyFAPP

Throughout the first WPs of the project, we conduct research that results in the generation of the needed tools and resources for the APP (figure 3A). The 'mathematical predictive model' of the optimal dose of enzymes is the main feature, tackling the currently existing gap to successfully adjust PERT. It is fed by the 'theoretical PERT doses database' including the optimal dose to digest a particular food or meal plus the ICF of each patient. It becomes functional when the users indicate the foods consumed and the amounts. A full and 'interactive nutritional recommendations handbook' is also available in the APP supporting children's dietary habits towards avoiding and correcting nutritional imbalances and reaching the recommendations. A 'food and symptoms record' is automatically generated and stored from the data introduced by the patients into the APP. This feature works thanks to the calculation algorithms and the 'foods databases', which include specific foods and meals/recipes according to the survey on nutritional habits and the complete nutritional profile information. The record allows for consulting at any time

patients' progress in terms of nutritional composition of their diets, their symptoms and the actions they have performed in the system. 'Educational games' are developed in order to convey educational content of the recommendations handbook to the youngest children who cannot consult it. Games also have versions for older patients, these being aimed at consolidating the knowledge learnt by the other features. Finally, 'alerts and messages' systems smooth the usability of the APP between the two sides of MyCyFAPP—the patients and the clinical teams—making the experience profitable and appealing.

Other specific features will be incorporated in the management system to enable health professionals to play their role: the professional tool. This module contains several features, such as a patients' dashboard displaying a summary of each patient—energy intake, percentage of nutrients, symptoms, number of depositions, etc—from where patients' profiles (especially focused on nutrition) can be accessed. Then 'adjustment of parameters' allows for making a more focused follow-up and to set up goals, and the 'care plan management module' is to define the overall strategy for patient. Complementarily, an education content management module and a report module are in charge of creating a report to be sent to the patients describing how they fit to their personalised plan. Through an iterative process with partners and final
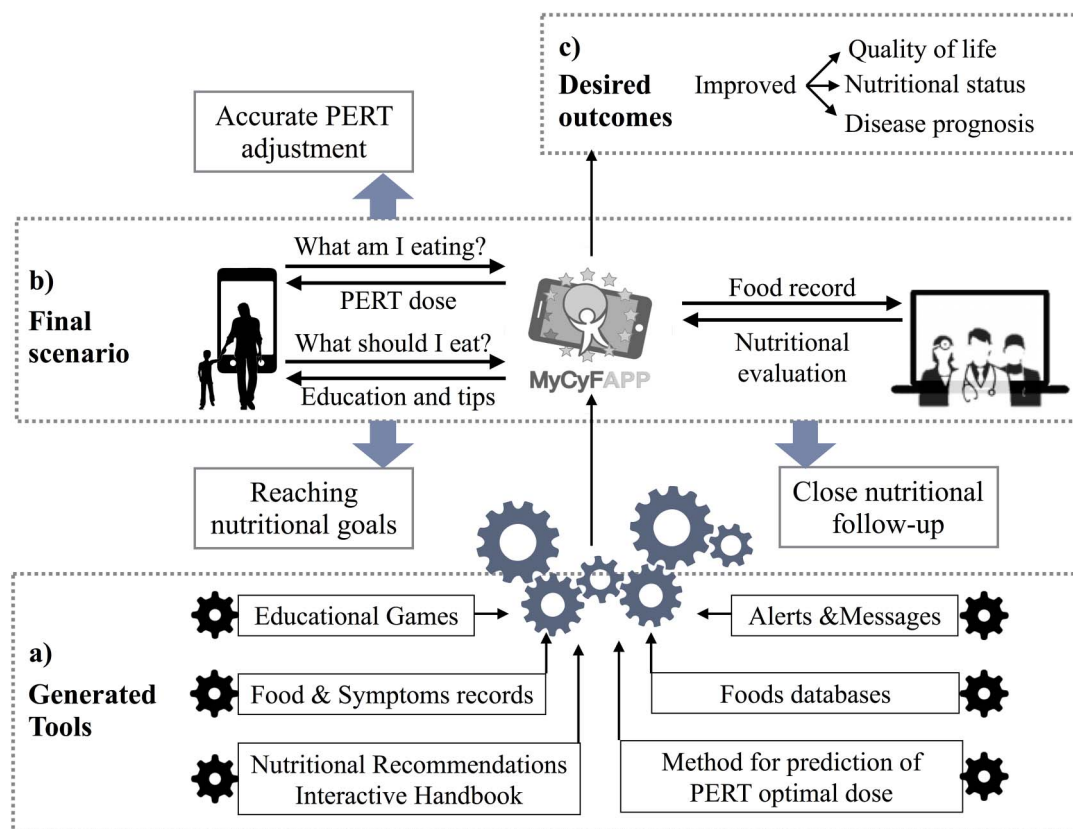

Figure 3 Summary of the project: generated tools (A), expected final scenario at the end of the project (B) and desired outcomes (C). PERT, pancreatic enzyme replacement therapy.

users, updates and corrections are periodically applied. Thus, the final set of features and tools will be decided along the project.

The ultimate goal is to motivate the users to adhere to the plan with positive messages when needed, and proposing new challenges.

Final scenario

When the APP is ready to use (figure 3B), patients introduce the food products or dishes and the APP indicates in real time the optimal PERT dose for the particular meal and considering the ICF of the patient. This, at the same time, generates in real time a food record and its automatic nutritional report. Complementary patients are already taught and skilled to build up their menus according to the dietary recommendations and, when needed, they are offered to consult for suggestions or practical tips.

Some of the functions enabled by the interaction between the patients and the clinical teams include the periodic check of the daily results of the nutritional profile of the diet. The software is programmed to alert patients and medical teams in case of a deviation from general or personalised recommendations (eg, percentage of lipids does not reach the threshold this week). If a deviation is identified as relevant—according to the definition of a risk and the plan for the patient—the health professionals can be notified, through the professional web tool, and are then responsible to decide which correction procedure has to apply (eg, consult educational resource number 1.3). For some situations, however, the software is programmed to automatically pop up reaction messages. Thus, the overall aim is to provide feedback and assistance to the patients outside the scheduled face-to-face visits.

Of note, the aforedescribed situation is thoroughly assessed through a multicentre clinical trial that will allow for the identification of errors and the features and procedures showing room for improvement. Therefore, updates and modifications can be applied before upgrading the system to the final and fully functional version. If success in the clinical validation occurs, MyCyFAPP can be able to reach the market by following the defined exploitation plan.

Desired outcomes

Overall, we expect that the mHealth solution contributes to reach the project's goals: an evidence-based method for PERT adjustment, reaching nutritional goals and close nutritional follow-up. The desired outcomes derived from its long-term usage are a triple improvement: quality of life specifically related to gastrointestinal symptoms, nutritional status and disease prognosis (figure 3C).

CONCLUSION

Through MyCyFAPP, we have brought together highly experienced professionals from various European countries with different areas of knowledge to jointly address the challenges faced by adequate nutrition and PERT in the management of CF. We mainly tackle two gaps within the project: first, we develop from scratch the required tools for effective PERT and nutritional therapy; second, we make the tools available to patients, enabling effective adherence to the disease treatment through self-management but still, when needed, maintaining a close and dynamic interaction with the medical teams throughout the mHealth tool.

The beneficiaries of the projects' results comprise patients, caregivers, families and healthcare professionals. MyCyFAPP is designed in a tailored way and clinically tested for CF self-management and monitoring. Additionally, MyCyFAPP has a pivotal role as a decision support system and provides a solution to the current gaps in the treatment. The participating SMEs and business models will ensure the commercial exploitation of the results, the market uptake and the MyCyFAPP distribution for the benefit of the patients. We envisage a prominent impact on nutritional status, quality of life and overall disease prognosis in the near future.

> When people ask me to provide an example of how patients, caregivers, researchers, a Foundation, NIH and industry can all work together to find cures, I point to cystic fibrosis. It's the very best example. Francis S Collins, MD, PhD, Director of the National Institutes of Health and a member of the international team that discovered the CF gene

Author affiliations
[1]Instituto de Investigación Sanitaria La Fe. Avenida Fernando Abril Martorell, Valencia, Spain
[2]Instituto de Ingeniería de Alimentos para el Desarrollo, Universitat Politècnica de València, Valencia, Spain
[3]University of Cambridge, Cancer Research UK Cambridge Institute, Cambridge, UK
[4]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK
[5]Soluciones Tecnológicas para la Salud y el Bienestar, Paterna, Spain
[6]STIFTELSEN SINTEF, Trondheim, Norway
[7]YOUSE GmbH. Kyreinstraße, München, Germany
[8]Imaginary SRL. Piazza Caiazzo, Milano, Italy
[9]Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
[10]Servicio Madrileño de Salud—Hospital Universitario Ramón y Cajal, Colmenar Viejo, Spain
[11]Università degli Studi di Milano. Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy
[12]Associação Portuguesa para a Investigação e Desenvolvimento da Faculdade de Medicina, Lisbon, Portugal
[13]Department of Paediatrics, University Hospital of Leuven, University of Leuven, Leuven, Belgium

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Victoria Fornes Ferrer, David Hervas Marin, Vanessa Garzón Rams, Sandra Martinez Barona and Etna Masip.

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