POWER2DM

"Predictive model-based decision support for diabetes patient empowerment"

Research and Innovation Project
PHC 28 – 2015: Self-management of health and disease and decision support systems based on predictive computer modelling used by the patient him or herself

Deliverable 7.13

D7.4.1b Report on Industry Liaison and Exploitation Activities II

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Dissemination Level		
PU	Public	
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	X

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EXECUTIVE SUMMARY

This deliverable reports on the second development stage of Task 7.4 outcomes: Utilization of partner TNO's Small Business Innovation Research (SBIR) programme named "Technology seeks Entrepreneur" forming liaisons with the European SMEs to bring the innovations produced in POWER2DM in the European market. Specifically, the Deliverable reports on:

1. The application of the TNO Technology Transfer Procedure to assess the best route of exploitation of TNO's Foreground related to Predictive Modelling resulting from POWER2DM, in a joint effort with selected Dutch SME's.
2. The forming of liaisons with additional research partners and SME's for joint projects at regional, national and international levels aiming to advance evaluation and acceptance of e-health/ m-health propositions that include POWER2DM Results.

To avoid duplication, this Deliverable does not repeat the content of D7.12: "D7.4.1a Report on Industry Liaison and Exploitation Activities I", which should be considered in unison with the present Deliverable.

POWER2DM Consortium Partners

Abbv	Participant Organization Name	Country
TNO	Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Netherlands
IDK	Institute of Diabetes “Gerhardt Katsch” Karlsburg	Germany
SRDC	SRDC Yazilim Arastirma ve Gelistirme ve Danismanlik Ticaret Limited Sirketi	Turkey
LUMC	Leiden University Medical Center	Netherlands
SAS	SAS Servicio Andaluz de Salud	Spain
SRFG	Salzburg Research Forschungs Gesellschaft	Austria
PD	PrimeData	Netherlands
iHealth	iHealthLabs Europe	France

OPEN ISSUES

No:	Date	Issue	Resolved
1			

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1 INTRODUCTION

1.1 Purpose and Scope

This document describes the 2nd development stage of the outcomes of Task 7.4: Utilization of partner TNO's Small Business Innovation Research (SBIR) programme named "Technology seeks Entrepreneur" forming liaisons with the European SMEs to bring the innovations produced in POWER2DM in the European market. It is a follow-up on Deliverable D7.12: "D7.4.1a Report on Industry Liaison and Exploitation Activities I", which should be considered in unison with the present Deliverable. The present deliverable reports on progress made in forming an Industry liaison of TNO with Dutch SME's ExpertDoc and PEXLife, under the name of MiGuide, and on new liaisons with these and other companies to attract funding for further innovation based on or closely related to POWER2DM.

After positive evaluation of the MiGuide Business case, the MiGuide team developed and deployed an implementation strategy, based on acquiring resources to integrate the respective technologies and to reach field-trial implementation so as to establish clinical value and cost efficacy (see D7.12).

The overall strategy is based on two pillars:

1. Establish and independent entity (Joint Venture (JV)) that allows to absorb and accumulate external investments
2. Establish a clinical field trial environment to assess clinical efficacy and cost-efficacy in order to allow acquisition of health insurance reimbursement status of MiGuide, and formulation of a further implementation strategy.

Chapter 2 reports on work done in relation to the first bullet point; Chapter 3 reports on work done in relation with the second bullet point.

1.2 References to POWER2DM Documents

- POWER2DM Description of Work (Proposal)
- POWER2DM D7.8: "D7.3.1a Exploitation Plan I "
- POWER2DM D7.5: "D7.2.2 Intellectual Property Rights Agreement "
- POWER2DM D7.6: "D7.2.3a Report on Intellectual property management I "
- POWER2DM D7.12: "D7.4.1a Report on Industry Liaison and Exploitation Activities I"
- POWER2DM D7.13: "D7.3.1b Exploitation Plan II "

1.3 Definitions, Abbreviations and Acronyms

Table 1 List of Abbreviations and Acronyms

Abbreviation/ Acronym	DEFINITION
GP	General Practitioner
HIS	Huisarts Informatie Systeem (Information System used by Dutch GP's)
JV	Joint Venture
n.a.	Not Applicable
PoC	Proof of Concept
SMSS	Self Management Support System
T1D	Type-1 diabetes
T2D	Type-2 diabetes
TRL	Technology Readiness Level

2 EVALUATION OF MIGUIDE FOR INCLUSION IN TNO'S TECHNOLOGY TRANSFER PROGRAM

2.1 Introduction

To prepare for the establishment of independent 3-party entity (joint venture, JV) that allows to absorb and accumulate external investments, companies ExpertDoc and PEXLife together created a mutual JV called MiGuide BV (http://www.miguide.nl/). In order to proceed to include TNO in this JV, the project idea had to be evaluated in TNO's internal Technology Transfer Program. This program is described in Section 2.2, and the outcome of the evaluation in Section 2.3.

2.2 TNO's Technology Transfer Program

2.2.1 Overview

The different stages of the TNO Tech transfer program are schematically shown in Figure 2.1.

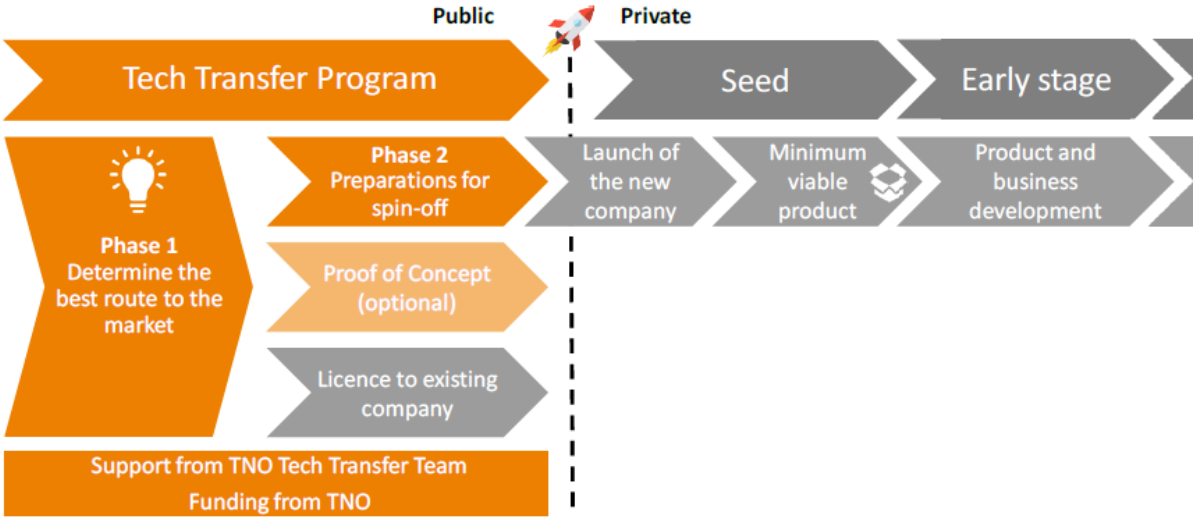


Figure 2.1. Scheme of TNO's Technology Transfer program.

The goal of the Tech Transfer Program is to introduce more TNO technology faster to the market via spin-offs or licences with existing organisations. TNO being a not-for-profit organization, it cannot as such act as a company e.g. in a JV such as initially proposed for MiGuide. Instead, market-ready technology can be spun out in a spinoff company and that company can then form a JV. An alternative is, to license technology to other companies (in the present case: MiGuide BV which is the JV of ExpertDoc and PEXLife. The spin-off would be a new company established to further develop and commercialize specific TNO technology resulting from POWER2DM and possibly other projects as well. For TNO, this approach is a way to ensure that innovative products and services are introduced to the market, which in turn contributes to high-quality job opportunities.

The Tech Transfer program focuses on the 'pre-seed' phase: the phase prior to the actual launch of the new company. During the pre-seed phase, preparatory activities are conducted, such as carrying out market research, formulating a business plan and making agreements between the spin-off, TNO, and

any other stakeholders. In order to improve the deal flow from TNO, a Tech Transfer Team and Tech Transfer Board have been set up. The team is available to provide advice and support with regard to IP assessment, licensing, new business development, venturing, business law, labour affairs, funding, and real estate. In addition, a budget is made available by TNO to fund the program.

Propositions admitted to the programme must have a Technology Readiness Level (TRL) of at least 4. Supplementary funding can be requested if R&D activities are necessary for a Proof of Concept (PoC), e.g. to strengthen the IP position, making it a more attractive proposition for investors. A 'launching customer' and additional external funding for the PoC are two conditions for this supplementary funding.

2.2.2 Phase 1: Determine the best route to market

The objective during phase 1 is to determine the best route to market for the technology in question. The process followed in Phase 1 is schematically shown in Figure 2.2.

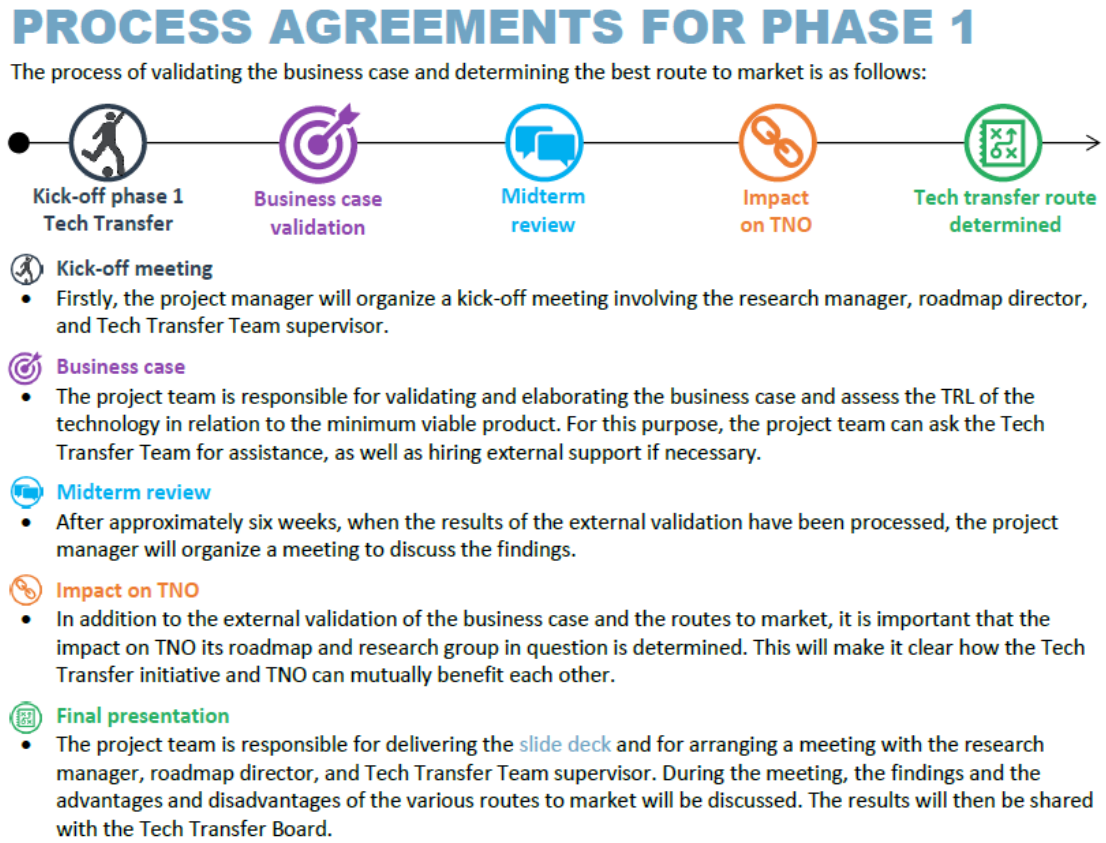


Figure 2.2. Process description of Phase 1 of TNO's Technology Transfer program.

The activities conducted in this phase result in a validated business case and an overview of the advantages and disadvantages of the various routes to market. The applicant will put together a project team to carry out the work. The project team will be supervised and supported by the Tech Transfer Team. In addition, the project team can decide to seek external support, e.g. by hiring a market-research agency, an external entrepreneur or by participating in YES!Delft's Validation Lab (https://www.yesdelft.com/all-programs/validation-lab/). Upon approval of the application for admission to phase 1, a maximum budget of EUR 30,000 will be allocated for the activities to be

executed over a period of three months. The activities will result in the creation of a slide deck, for which a template is available containing instructions, tips, and guidelines. If the conclusion of Phase 1 results in an advice that a TNO spin-off is the recommend route to market, then the project team can submit an application for phase 2. The MiGuide proposition was successfully entered for Phase 1 evaluation and received 30,000 funding from TNO to carry out the pertinent activities.

2.2.3 Phase 2: Preparations for spin-off

The objective of phase 2 is to prepare the actual establishment of the spin-off. The essentials of Phase 2 are schematically shown in Figure 2.3.

Figure 2.3. Essential activities and results of Phase 2 of TNO's Technology Transfer program.

The phase 2 processes are initiated once the Tech Transfer Board approves the results of phase 1 and the application for phase 2. During phase 2, the project team will work on a business plan, including a financial plan. In addition, the spin-off team will be formed and agreements will be made between the spin-off, TNO, and any other stakeholders. Upon approval of the application, a maximum budget of EUR 50,000 will be allocated to fund the phase 2 activities, which are to be conducted over a period of six months. A template for the slide deck is available for formulating the business plan.

As will be described in the next section 2.3, the outcome of Phase 1 evaluation of the MiGuide proposition was that entering Stage 2 currently is premature and has to be delayed notably until Evaluation & Acceptance by HIS-systems & early adopters within GPs, and T2D clients is fully realized. Therefore, no further details of the processes pertaining to Phase 2 are described here.

2.3 Outcome of TNO's Technology Transfer Program Phase 1 evaluation of Miguide

2.3.1 Description

In the following, a set of slides documenting important aspects of the Phase 1 evaluation process are included. These slides are considered self-explaining.

TNO HEALTH SIMULATOR
MODULE TYPE 2 DIABETES

TECH TRANSFER ANALYSIS PHASE 1

May 2018 – Heleen.Wortelboer@tno.nl

EXECUTIVE SUMMARY

Market need & size

Product: high potential; both need and size

Currently no:
- "combined integrated health advice" for sustainable prevention & cure of Type 2 Diabetes.
- "policy advice by simulation" to support prevention programs prior to real (expensive) health programs

Target clients/markets

General Practitioners (GP)/Health Insurances: Gain most and Fast

Employers/Municipalities : important stakeholders
E/M-health suppliers : essential launching customers for product-development
Health Data /ICT Orgs : essential Service providers

Value proposition

Software: Simulation of prognosis of personal health-markers of Type 2 Diabetes
Product : Integrated E/M-health tooling with TNO software inside to support both Patiënt & GPs for effective behavioural change

What's unique

A blended E/M-health prognose-simulation tooling
- based upon integration of health knowledge, Dynamic Bayesian's Network Analyses, GPs acceptance, E/M-Health communication and real time interaction with personal data
- to speed up Medical Training of GPs on Lifestyle as Medicine

Route to market (license / open source / spin-off / spin-out / joint venture)

1. Perform Pilot study & Evaluate Acceptance Patients & GPs (MIT-2); Based upon acceptance of the tool version 1.0 decide to
2. License TNO Software via "One Portal" (a Health Data Management/ICT provider: either ExpertDoc, or in new "MiGuide-BV") who connects to 1. various e/m-Health suppliers, 2. supports NL Human Cohort health data storage, essential for iterative improvement of the tooling and personal health advices.

MARKET NEED & SIZE (1)

Market need is huge:

- Type 2 Diabetes (T2D) is a global pandemic
  WHO : in 2014 : 422 Million; in 2040 ; 620 Million
- in NL *> 1.0 Million T2D Patients ; 8700 General Practioners*

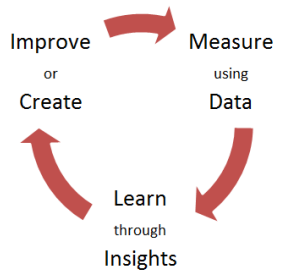
T2D develops slowly over time, ca 10 years ahead of symptoms,
other symptoms co-develop (eg CVD, Retinopathy, Nephropathy)
Recent studies indicate that T2D can be reversed:
- T2D is curable with Personalized Integrated Lifestyle Intervention
- T2D is preventable with Lifestyle Coaching & System Change

Need for: Evidence-based Lifestyle Interventions
Integration of biopsychosocial aspects in care
Sustainable Behavioral & Healthcare System change

MARKET NEED & SIZE (2)

- Currently :
  - no "combined integrated E/M-health advice" available for GPs & Patients
    for sustainable (> yrs) cure and prevention of Type 2 Diabetes
  - examples of Simulation-Software exists; none, however, for T2D integrated in existing primary care
  - an "app" alone, i.e. a non-integrated health advice, has shown to be not sustainable effective

Therefore Market is NEW, and for TNO Technology difficult to quantify :
For sustainable (societal) behavioral change,
only a blended approach based upon
integrated knowledge, real time (personal)
health data, and mutual agreed interventions have been
shown to be effective (climate, energy, economics)



- If successful, the IMPACT is Huge & beyond T2D !

VALUE PROPOSITION

Current focus:
Single E-health products aiming at
Symptom Treatment & Advice
based upon Random Clinical Trial-data
& NHG-Guidelines Advice

Our focus:
Blended E/M-health product ("MiGuide") aiming at
Combined Lifestyle Intervention Advice
via Simulation of Personalized Health Prognose
based upon Individual (cohort) data leading towards
new NHG-approved Personal Lifestyle Advice

MARKET MATURITY

- High Need: Reduction of HealthCare Costs,
  via focus on Efficient Cure & Prevention of Lifestyle Diseases
- Doctors, Insurances, Clients, Employers, Government, "*all need to take responsibility*"
- **Currently no Evidence-based Simulation of Personal Integrated Health Prognose (> yrs) on market**
- **Currently no blended E/M-health accepted by GPs approach for T2D available**
- **No competitors ; but – without enough GP & patiënt acceptance - risk of collapse**

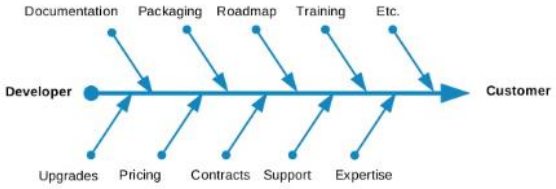
- **Huge market need** focussing on Cure and Prevention via Lifestyle & System Change
  - Government "170 MEUR voor preventie/gezondheidsbevordering; 40 MEUR voor E-health"
    → "Combined Personal Lifestyle Intervention Advice" in 2019 in basis-pakket"
    → "Gezondste stad" van NL: Groningen, Rotterdam, Haarlem , Roermond, Almere, Zwolle etc ..
  - Health Insurances: Zilveren Kruis: "Gezond Ondernemen" ; VGZ: "Gezond Leven" ; CZ :"ZorgInnovatie" etc ..
  - Medical Education needs improvement towards Prevention by Lifestyle
- **Minimum Winning Game:** via Partnership towards Acceptance of Health Simulation Software by GPs
  for Health Prognoses integrated in primary care for mutual awareness and personalized lifestyle advices
  open for iteratively improvement, via a blended E/M-health approach

IP RIGHTS & TECHNOLOGY READINESS LEVEL

- **Simulation Software alone is not a product !**
- IP Software fully owned by TNO (algorithm developed within H2020 Power2DM,
  based upon unique integration of detailed Physiology knowledge & human Whitehall cohort data (UK-data)
- TRL Software 4 (NL) – 5 (UK) ; TRL Product 3

- Minimal Viable Product : A TNO simulation software tool integrated within a blended tooling, focussing on
  Personalized Type 2 Diabetes Prognosing & Lifestyle Advices
  fully accepted by GPs and Clients, supporting effective & sustainable Behavioural Change

- Product Roadmap:

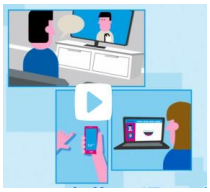


General Practioners
T2D patiënts
Expert Doc – Digital Guidelines
E/M-health – Suppliers

BUSINESS MODEL

Software
Provided by TNO

Market value



Product
with Software-Inside &
Personal Health Advices

Algorythms
Evaluation
Simulation
Demonstarors
Use Case 2DM

Research & Development

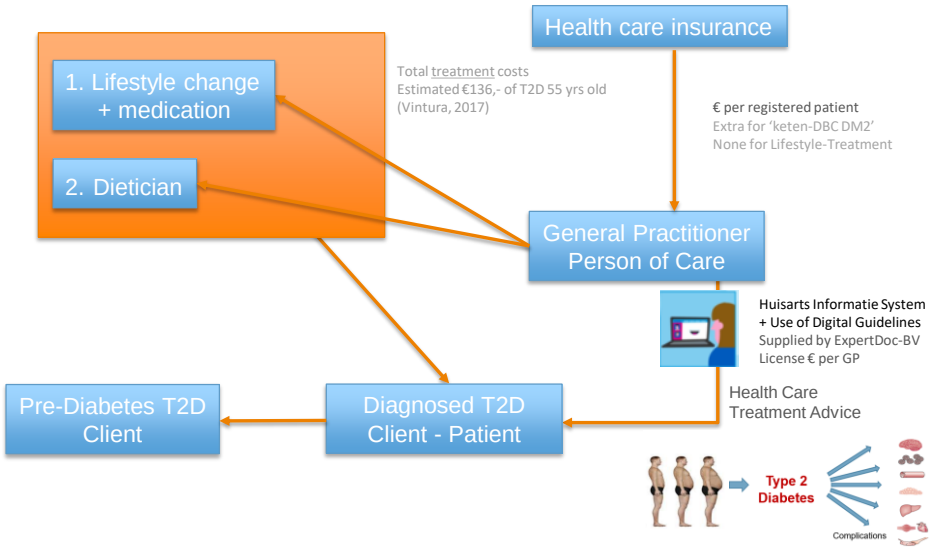
Data communication
User Requirements
Documentation
Implementation
Upgrades
Bug fixing
Case studies
Training
Support
Pricing
Contracts
Early adopters
Other users
Etc

Predictability
Efficiency
Quality
Trust

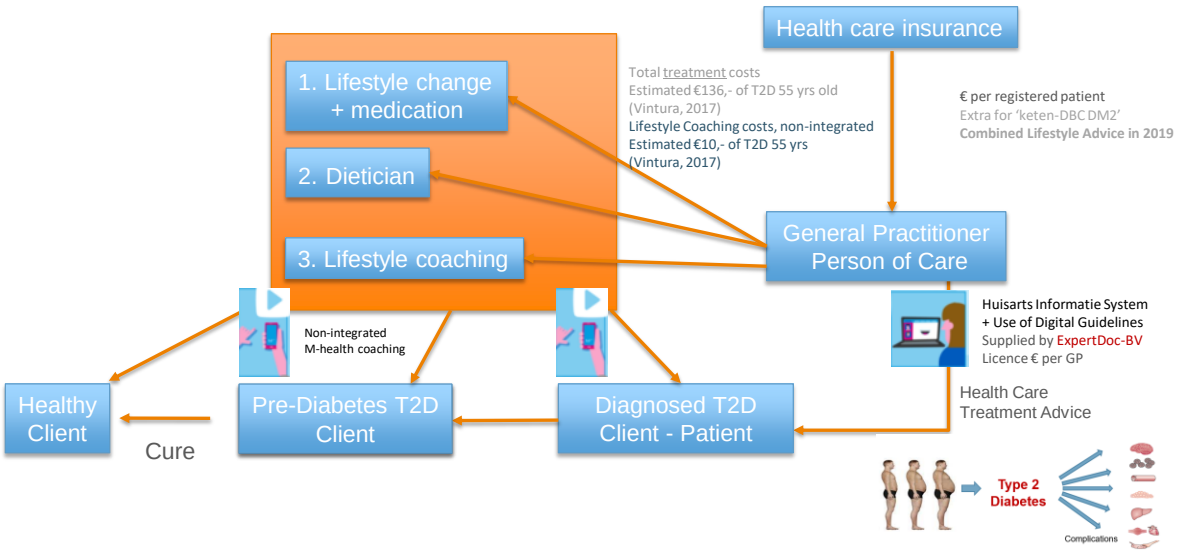
Delivery Challenge

Value Creators = a network of Contributors, Health Data Management Orgs , E/M-Health Suppliers,
System Integrators, Open Source Organisations, Distributor Vendors, Users

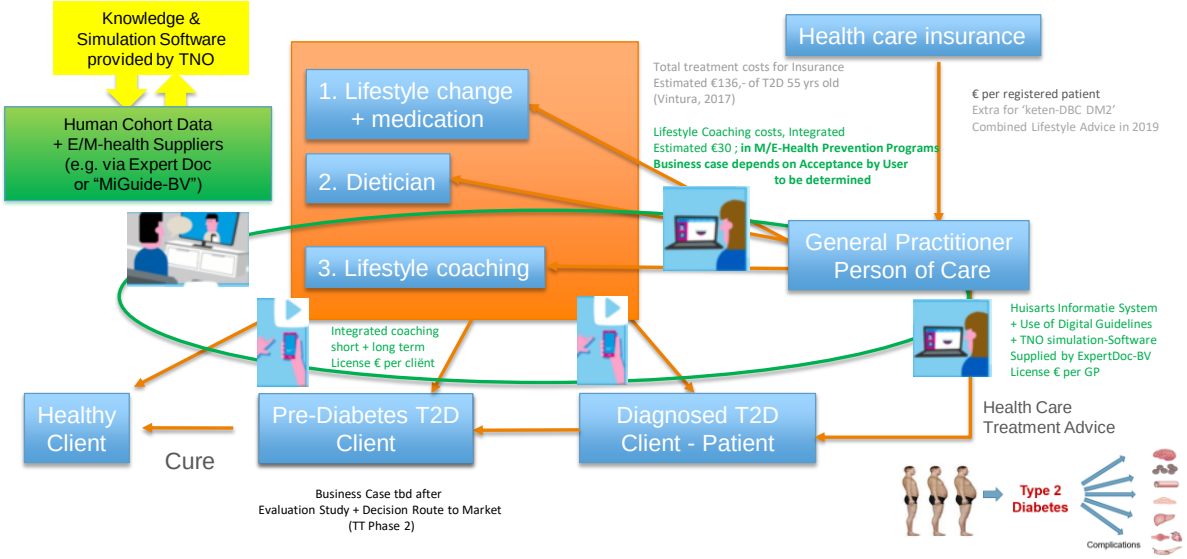
CURRENT SYMPTOM TREATMENT OF T2D



INCLUDING LIFESTYLE COACHING TO CURE T2D



BLENDED E-HEALTH COACHING



ROUTE TO ENTER THE MARKET (ANALYSIS)

Route to Market	Advantage	Dis-Advantage	Advice
Co-development & further differentiation with public/private partners/MKB	Low risk Innovation with experts & Users	Less IP : Chance of IP "dilution" Slow : Discussions/Agreements Funding needed (acquisition time)	+++ A clear vision on strategy, agreements (user groups & differentiation), other projects *prior to* proposal-submission. Support of YESDelft in Acquisition Trajectory
Spin off	n.a.	Software tool alone is not a product	---
License - Static	Fast & Simple One single agreement	Limited contact → High Risk of failure No interaction with Users & individual human data for iterative improvement	---
License – "One Portal" Dynamic Upgrading	Regular Upgrading Higher chance of acceptance by GPs & Client Interaction real time human data	Commitment may disappear TNO-connection needs to be arranged for at least 2 years for optimal evaluation & implementation. Storage of human NL cohort data needs to be arranged	++ (decide after evaluation phase) Choose "One_portal" : Health Data-manager Orgs + 24/7 software service provider, e.g. Expert Doc; Arrange TNO-er involvement for at least 2 years
Joint Venture eg "MIGuide-BV"	Clear commitment & exposure - direct communication for fast iterative improvement & business planning - easier to get Investors aboard - easier to get Health Cohort Data - easier to get Revolving Business	Partner-choice: PEXLife the right one ? - other M-health providers are available Some aspects needs further research - Who is responsible for 24/7 software service & health data-interactions? - Who is responsible for Human Data Storage	+++ (in case evaluation-phase is successful) Choose "One_portal" : e.g. "Mi-Guide-BV" with TNO as shareholder and TNO -er involved. BV is responsible for service, not TNO
Open Source of older versions (common licence-agreement)	*Faster acceptance of tooling by Medical Students & GPs*	*Education using simulation software tools not core business of TNO (yet)*	*+++* *Choose co-development with E-learning developer*

ADVICE ROUTE TO ENTER THE MARKET

- Focus on Evaluation & Acceptance by HIS-systems & early adopters within GPs, and T2D clients
- Licence product to GPs/clients via "One Portal"
  = a Health-Data-management /ICT Org who delivers to E/M-health Suppliers, eg Expert-Doc (TNO-er is involved)
  = a "Mi-Guide BV" entity, in which TNO is shareholder + TNO-er is involved (tbd, after evaluation–study)
- Time to market  : 1-2 years (first need is a fully acceptance by early adopters)
- Customer of TNO = Preferably One Portal (Health Data Management /ICT Orgs)
- Health Insurance Companies as support for launching beachhead market
- Governmental support for Investment on (inter)national health market
- Employers support for investment on Prevention Programs@Work, facilitating behavioural change

- **Founders dream**: TNO wants to translate our unique integrated health knowledge into *personalized policy support* by communication using *real time* human data, algorithms, and *simulation of health prognoses* to improve GPs personal lifestyle advices & effective behavioural change, reducing healthcare and societal costs.

STEPS AHEAD + FINANCE

- The financial page will be defined in detail in the second stage of the tech transfer program

- Steps ahead:
  - Evaluation of Implementation within HIS-systems and GP-usage
    + valuation Simulation Software Tooling using NL Patiënt Data
    for **fully acceptance** by 10 GP-Centra & 400 Patients before going to Market
    (MIT-2 (340 kE), Zilveren Kruis (12 kE), TNO (kE)
  - Discuss with Dutch Government to support "Open Availability"
    of E/M-Health Simulation Modules & Personal Health Advices
    provided by TNO to create **IMPACT!**

- Future steps:
  - Go Worldwide (US, Singapore etc, and
  - Start Human Health Data Cohorts (like UK Whitehall)

2.3.2 Continuation of MiGuide industry liaison

The Stage 1 evaluation concluded that a JV with MiGuide BV potentially is the preferred route to market, provided however that evaluation and acceptance prove successful, and the 24/7 availability of the services is guaranteed and fully adequate personal data protection is implemented. Therefore, TNO wishes to strengthen industry liaisons with MiGuide BV, notably as a vehicle towards broad acceptance of TNO technologies, to be obtained from further joint research projects. For this purpose, TNO is currently preparing IP agreements with MiGuide on licensing of relevant TNO technology developed in projects FP7 Mission-T2D, H2020 POWER2DM, and other proprietary, EU and national projects. Relevant further research studies notably, include the ZonMw project "E-manager chronic diseases" and H2020 "P4M2DM". Such projects will significantly contribute to the evaluation and broad acceptance of the MiGuide proposition, including POWER2DM Results, preparing the ground for entering Phase 2 of the Technology Transfer Program and further valorization.

3 INDUSTRY LIAISONS WITH MIGUIDE AND ADDITIONAL PARTNERS IN NEW PROJECTS

3.1 Introduction

To establish a clinical field trial environment to assess clinical efficacy and cost-efficacy in order to allow acquisition of health insurance reimbursement status of MiGuide, and formulation of a further implementation strategy, partners ExpertDoc, PEX Life with support of TNO successfully applied for a second stage of funding for the Top Sector Life Sciences and Health, with the Dutch Regional SME innovation stimulation program called MIT, in the province of Zuid-Holland (Dutch: https://www.zuid-holland.nl/loket/subsidies/subsidies/subsidies/mkb-innovatie/, English: http://www.zuid-holland.eu/europe/economic-potential/economic-cluster-0/). The funded project (referred to as MIT-2 in one of the preceding slides documenting the Phase 1 evaluation) includes a pilot study in the regional primary care setting which is co-sponsored by Dutch health insurance company Zilveren Kruis Achmea. In that pilot study, which is due to start Q1 2019, the TNO risk prediction models developed in POWER2DM will be included. No further description of this project is given in the present Deliverable.

Further to this, TNO, ExpertDoc, PEXLife together with other Dutch academic and SME partners successfully applied for funding for a joint project "E-manager Chronic diseases" by Dutch organization ZonMw. Specific TNO-contributed content to POWER2DM Behavioural Change Interventions (WP3) will be used as Background in this project. A brief description is given in Section 3.1.

Whereas the "E-manager Chronic diseases" is a Dutch national initiative which has limited contributions related to POWER2DM, the team of TNO, ExpertDoc and PEXLife liaised once again, now with the POWER2DM Consortium as a whole and additional European academic and SME partners, to apply for a true POWER2DM follow-up project called P4M2DM: PERSONALIZED, PREDICTIVE, PREVENTIVE, AND PARTICIPATORY MEDICINE-BASED HEALTHCARE FOR DIABETES MELLITUS PATIENTS. This is an Innovation Action under H2020 call topic SC1-BHC-25-2019 "Demonstration pilots for implementation of personalised medicine in healthcare" (2-stage). The proposal, which recently successfully passed stage 1, is described in Section 3.2.

3.2 Project "E-manager Chronic Diseases"

3.2.1 Project data

Project title:	E-manager Chronic Diseases
Funding organisation	ZonMw - The Netherlands Organisation for Health research and Development (https://www.zonmw.nl/en/)
Research partners	University Maastricht, TNO, NIVEL, University Twente (together forming the Centre of Care Technology Rerearch (CCTR)
Co-funding partners:	Boehringer Ingelheim, Lung Alliance Netherlands, ZIO (Care In Development), FEA (Almelo Primary Health Care Federation), Roessingh Research and Development, Nictiz (centre for standardisation and eHealth), PEXLife, ExpertDoc, Sananet (e-coaches), MicroHIS (GP Information System)
Programme:	Innovative Medical Devices Initiative (IMDI)
Call topic:	Technology for Sustainable Healthcare
Project type:	Applied research
Duration:	48 months
Start date:	01-07-2018
Total budget	2.5 million Eur
Status	In progress

3.2.2 Project Summary

People's health and healthcare in Western societies are currently facing a number of serious challenges. There is a growing number of older people and an increasing incidence and prevalence of chronic diseases. Over 5.3 million people in the Netherlands have a chronic condition and 36% of these people have more than one chronic disease. With an ageing population, this number is expected to increase. There is a high pressure on the quality of healthcare as well as on associated healthcare costs. Personalised self-management could be a key solution to overcome these challenges in long-term care. However, for many patients, it is difficult to adequately self-manage their disease. Formulating specific treatment goals for lifestyle behaviour, searching for tailor-made interventions and being supported therein is a challenge, especially as these elements are not often discussed with a healthcare professional. In recent years, many apps have been developed that aim to help self-manage a disease. However, as these apps usually do not take into account patients' behaviour, coaching cannot be fully tailored to the patient. An integrated device would be the solution to the aforementioned challenges, but an appropriate tool is lacking. The Centre for Care Technology Research (CCTR, http://caretechnologyresearch.nl/) therefore proposes the development, evaluation and implementation of an E-manager Chronic Diseases, which aims to improve the quality of life and perceived quality of

care in patients with chronic conditions. The e-manager is used for patients with COPD, asthma and/or diabetes mellitus type 2 (DM2). The e-manager has two main components.

The first component is the Assessment of Burden of Chronic Conditions (ABCC) tool. This tool measures and visualises the experienced burden of disease and facilitates shared decision-making, as healthcare professionals and patients are supported to set goals and decide on a personal treatment plan together. The ABCC tool is a follow-up to the Assessment of Burden of COPD (ABC) tool (see Figure 3.2.1), which has been developed in recent years by Maastricht University and has shown to be very effective in improving the quality of life and quality of care perceived by patients with COPD. In this project, we propose to develop the tool further by adding disease-specific modules for asthma and DM2.

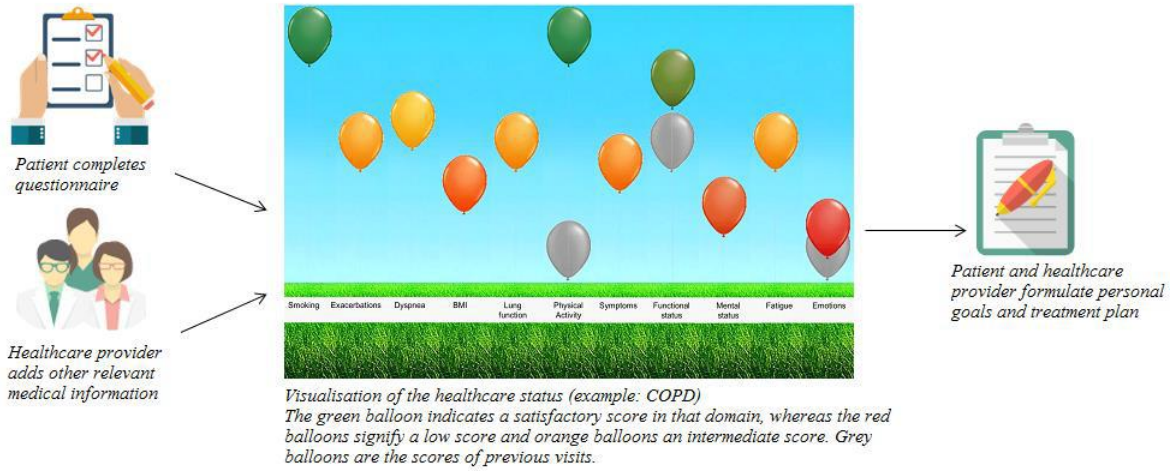


Figure 3.2.1. The existing ABC tool: Assessment of Burden of COPD [Slok A.H.M., et al. BMJ Open, 2016;6(7):e011519.]. The five domains for the experienced burden of COPD, as measured on the ABC scale, are represented by the final five balloons: symptoms, functional status, mental status, fatigue and emotions. Dyspnoea and the level of physical activity are also reported by the patients. Smoking status, exacerbations, body mass index (BMI) and lung function are reported by the healthcare providers.

The second component is the e-supporter, which promotes pursuing a personalised treatment plan in daily life. This e-supporter integrates various e-coaching apps already developed by MUMC+, TNO, University of Twente and commercial parties, supporting various aspects of a healthy lifestyle. It will be further enriched with an intelligent interface that uses information from the ABCC tool, the various coaching tools and daily behaviour, thoughts and moods to provide tailor-made information on health-related behaviour to the patient in order to improve self-management behaviour. The coaching content will be developed according to the I-Change model and coaching will be provided to the patient via an app using text, graphics and videos.

This research proposal consists of five work packages (Figure 3.2.2). The aim of Work package 1 is to extend the existing ABC tool for COPD by building disease-specific modules for asthma and DM2, and to validate the ABCC tool. Work package 2 focuses on the development and validation of the e-supporter. Work package 3 involves the implementation and process evaluation of the E-manager Chronic Diseases. Work package 4 focuses on the effect evaluation of the E-manager Chronic Diseases by means of a cluster randomised controlled trial (RCT).

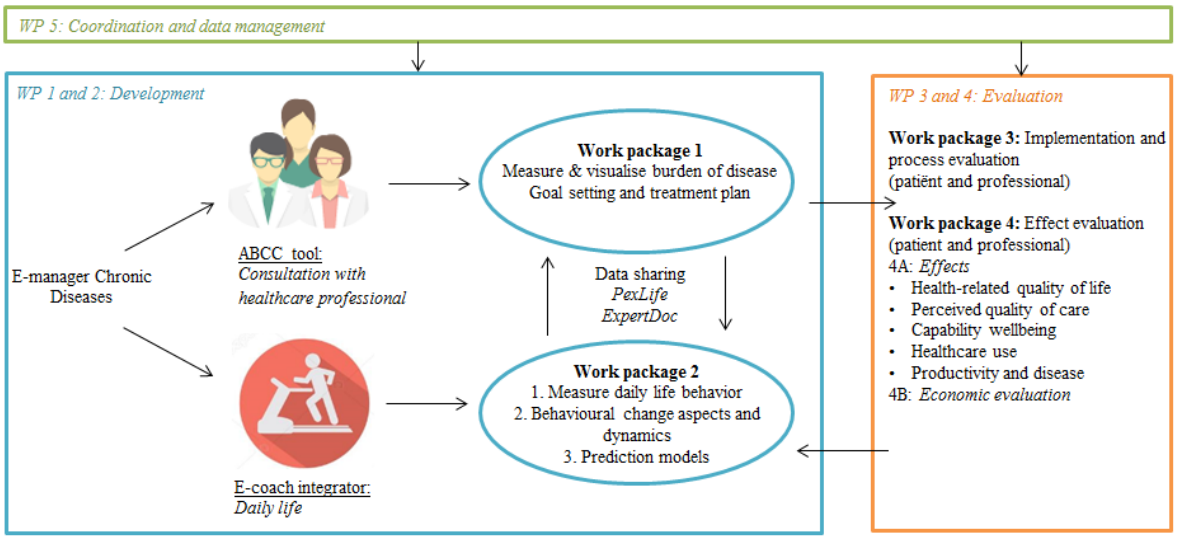


Figure 3.2.2. E-manager Chronic Diseases work plan structure

Health Technology Assessment (HTA) will be used to evaluate the impact on health, well-being and costs, and to provide an estimate of the value for money. As the project will be iterative, data collected in WP3 will be used to improve the ABCC tool and the e-supporter further. Work package 5 involves the coordination and data management of the project. The innovation in this project can only be a success when it is properly implemented in daily practice. The ABCC tool and the e-supporter are two separate but connected tools. The ABCC tool will be implemented in electronic medical systems and the e-supporter will be implemented in the patients' personal digital environment such as their computers and mobile phones. The ABCC tool and the e-supporter will be connected to one another by the collaboration of several public and private partners. We believe that this e-manager will realise important steps towards care that is effective, sustainable and of high quality, as patients become better able to self-manage their disease in everyday life. In addition, the healthcare professional is better informed about the patient and better able to deliver personalised care. In future, the e-manager can be expanded to create a generic e-manager for the most prevalent chronic diseases in primary and secondary care.

3.3 Project P4M2DM

3.3.1 Project data

Project title:	P4M2DM: PERSONALIZED, PREDICTIVE, PREVENTIVE, AND PARTICIPATORY MEDICINE-BASED HEALTHCARE FOR DIABETES MELLITUS PATIENTS
Funding organisation	EU
Research partners	TNO (NL), MiGuide BV (NL), Univ. Medical Center Groningen (NL), Tervise Arengu Instituut (EE), LUMC - Leiden Univ. Medical Center (NL), SAS - Servicio Andaluz de Salud (ES), IDK - Institut für Diabetes Gerhardt Katsch Karlsburg e.V. (DE), iHealthlabs Europe (FR), SRFG - Salzburg Research Forschungsgesellschaft m.b.H (AT), SRDC (TR),

	Fondazione Bruno Kessler (IT), Vrije Universiteit Medical Center (NL), INESC TEC (PT), Instituto de Saude Publica da Univ. do Porto (PT)
Co-funding partners:	n.a.
Programme:	H2020 pillar Societal Challenge 1: Health, demographic change and wellbeing
Call topic:	SC1-BHC-25-2019 "Demonstration pilots for implementation of personalised medicine in healthcare" (2-stage)
Project type:	Innovation Action
Duration:	72 months
Intended start date:	01-02-2020
Total budget	20 million Eur
Status	Invited for second stage 23/01/2019

As can be appreciated from the table, the complete POWER2DM Consortium with exception of PrimeData participates in P4M2DM. The role of PrimeData will be taken over by Portuguese partner INESC TEC.

3.3.2 Project summary

3.3.2.1 1. Excellence

P4M2DM addresses the topic "Demonstration pilots for implementation of personalized medicine in healthcare" in the work programme "Health, demographic change and wellbeing". P4M2DM focuses on diabetes, a disease with very high burden to society primarily due to its associated comorbidities. During the last decade, a variety of tools for Precision, or Personalised Medicine (PM), has been developed and the added value in the prevention, prediction and/or treatment of diabetes and its comorbidities has been demonstrated. Today, validated PM tools based on e.g. genetic background, or refined patient stratification for risks of co-morbidities, life expectancy, etc. are used in diabetes care. However, these are predominantly local initiatives limited to one, or a subset of PM tools that has been tailored to, and integrated into the local/national health care system. Contrastingly, EU-wide adoption of a PM- model for integrated diabetes care will require, on the one hand, the integration of validated PM tools addressing both prevention, prediction and treatment and, on the other hand, a detailed assessment of the health economic, ethical, legal and societal aspects in a diverse series of setting across Europe. Both requirements are lacking fulfillment as of today.

P4M2DM will therefore introduce, demonstrate on a large scale, and evaluate a PM-based diabetes care model for which air traffic control systems can be considered a useful metaphor: based on "personomic" stratification, each diabetes patient is assigned a personal corridor within which his or her trajectory should remain confined (and dynamically adjusted in case of significant variations in her condition) to reach specific care targets. The patient receives continuous behavioral support by the P4M2DM system in daily life to remain on track in between caregiver visits following a stepped-care approach. Online e-health support can be invoked when desired. Based on duly authorised remote monitoring of patient data, fully controlled by the patient, the system will signal to the patient and the clinical professional when he/she appears to go off track, suggesting to schedule a personal contact or a screening visit. This signaling can be made anticipatory to an adjustable degree, i.e. on the base of predictive algorithms,

and the sensitivity of detection can be adjusted depending on the severity of complications risks involved. Regarding lifestyle, a strong predictor of all-cause and cause-specific mortality in patients with diabetes and therefore the cornerstone of self-management in diabetes, P4M2DM will exhibit one of its major strengths, offering individual, personalized tailoring to get the most effective intervention for any specific patient.

3.3.2.2 Objectives

The chief objective of P4M2DM is to demonstrate the benefit for patients, as well as the implementability and economic viability of personalized diabetes healthcare in different real-life healthcare settings across Europe. The specific technical objectives (TO) of P4M2DM are:

- **TO1** - Deliver a design for the demonstration pilots in real life healthcare settings that includes a state-of-the art fully interconnected toolset for diabetes PM, together integrated in the P4M2DM system and building on POWER2DM as the core system; and well connected to existing healthcare ICT systems to provide the basis for personalized, predictive, preventive and participatory type-1 and type-2 diabetes treatment based on detailed and dynamic holistic patient stratification ("personomics"), as well as privacy/security-by-design of personal data processing and -sharing;
- **TO2** - Deliver a Personalized Diabetes Management Support System (PDMSS) with web- and mobile user interfaces for use in the demonstration pilots that shows high accessibility and acceptance for patients and healthcare professionals. The PDMSS will be connected to local healthcare systems including EHR, will pay special attention to privacy, and will offer dynamically adjusted action (care) plans and coaching in terms of changes in lifestyle, nutrition, physical activity and therapy adjustment, based on predictive models for short term optimal metabolic control, medium term prevention of deterioration and long-term avoidance of diabetes complications;
- **TO3** – Perform Demonstration Pilot studies (~1000 patients per country) in existing regional healthcare settings in The Netherlands, Spain, Estonia, Italy, and Portugal, using P4M2DM functionalities connected with local healthcare systems in compliance with the regional guidelines for diabetes care and prevention. Define study objectives and design for assessing individual health benefits as well as economic viability, tailoring to the different national contexts. Prepare locally required Medical Device dossiers and Medical Ethical study approvals. Training of clinical staff & patients in use of the P4M2DM predictive model-based decision support system
- **TO4** - Deliver evidence of benefits of the integrated P4M2DM system in terms of health outcomes, cost effectiveness, adherence to care programmes, promotors and barriers in using the new organizational and treatment delivery process including the ICT components by patients, care providers and other stakeholders, also bringing evidence for its feasibility, implementability and economic viability, and scalability.

3.3.2.3 Concept

P4M2DM will establish a personalized diabetes care system for both T1DM and T2DM in which a broad toolset of diabetes PM approaches from different origins (See Table 3.3.1) will be combined and integrated for the first time, and made available for large-scale implementation studies.

Table 3.3.1. Existing PM toolsets combined in P4M2DM with tools from POWER2DM for deployment in P4M2DM Demonstration pilots.

Existing Toolsets	P4M2DM Prediction, Prevention and Treatment Solutions	TRL
Personalized Prediction and Risk Stratification (gender-specific)		
VUMC retinopathy model	Automated retinopathy screening; Prediction of the risk of sight threatening retinopathy and calculation of a risk-based screening frequency (van der Heijden AA, et al. Validation of automated screening for referable diabetic retinopathy with the IDx-DR device in the Hoorn Diabetes Care System. Acta Ophthalmol 2018;96:63-8)	8
Ahlqvist et al. 2018 diabetes stratification	New classification of diabetes which also predicts the risk of serious complications and provides treatment suggestions (Ahlqvist E, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018;6:361-9)	5
Genetic testing	Genetic screening for monogenic diabetes (e.g.the MODY test panels available from Quest Diagnostics)	9
TNO/VUMC/FBK dynamic forecasting tools	Dynamic updating of patient stratification and personalized prediction by supervised self-learning of predictive Big Data/AI algorithms on health data accumulating in the project, cohort studies and EHR databases	6
Personalized Care Planning and Shared Decision Making		
Netherlands Innovation Centre for Lifestyle Medicine (TNO and LUMC)	Innovative Lifestyle-as-Medicine approaches to support healthy lifestyle choices that can lead to reversal (cure) of type-2 diabetes (https://nilg.eu/)	3-4
C3CLOUD Coordinated Care and Cure Delivery Platform (C3DP)	Collaborative (multi-disciplinary care team members including specialists, GPs, and nurses) creation and monitoring of personalised care plans (goals, action plans, etc) for patients suffering from diabetes and its related complications (http://c3-cloud.eu/c3/project-summary) Personalized Clinical Decision Support providing suggestions for treatment goal and activities (e.g. medications, follow-up appointments, diet, exercise, lab tests) via clinical guideline automation	7
Dutch Diabetes Federation interview toolkit	Evaluation interview toolkit to help identify patient needs from an holistic perspective (NDF Personalized Diabetes Care project (https://diabetesfederatie.nl/ndf-personalizeddiabetescare)	7
Personalized Self-Management Support and eCoaching		
MiGuide	A "blended behavior change coach", prescribed by the GP, to coach the diabetes patient towards a healthier lifestyle based on clinical decision support, sensor data, actual behavior and clinical patient data. Insights and gamification. Community support.	8-9
FBK PERKAPP Virtual Coach	An AI-based motivational virtual coaching platform interconnected with EHRs and patient generated data incorporating ontologies for virtuous nutrition (i.e. Mediterranean diet), advice on physical activity and other lifestyle and clinical parameters for managing diabetic condition (Maimone R, et al. PerKApp: a General Purpose Persuasion Architecture For Healthy Lifestyles. J Biomed Inform 2018;82:70-87)	8
Data Collection and Integrations		
Established secure health	FAIR and GDPR compliant data exchange services connected by local partners to existing EHR applications in the different pilot countries	6-7

data exchange procedures	Integration of privacy by design technologies and methodologies related to access management and processing of sensitive data, thereby enhancing trust and transparency.	
MiGuide	Data exchange with Dutch EHR and Primary Care Information systems. Integration of data from 180 devices via Selfcare platform (www.selfcare4me.com/en/)	7-9
TreC, Diraya	Trentino TreC Personal Health Record incorporating EHRs and patient generated data; Diraya is an EHR used by 9.000.000 patients in Spain.	9
Remote Care		
MiGuide	Blended care. Digital CX Chatbot platform. Secure chat with caregivers. Online consults.	8-9

The key enabling component of the P4M2DM approach is the Predictive Model-based Decision Support system that was recently established in H2020 project POWER2DM that is currently at TRL7-9 and being evaluated in pilot studies with 140 T1DM and 140 T2DM patients in The Netherlands and Spain. This system, and the P4M2DM system that builds upon it, is schematically shown in Figure 3.3.1.

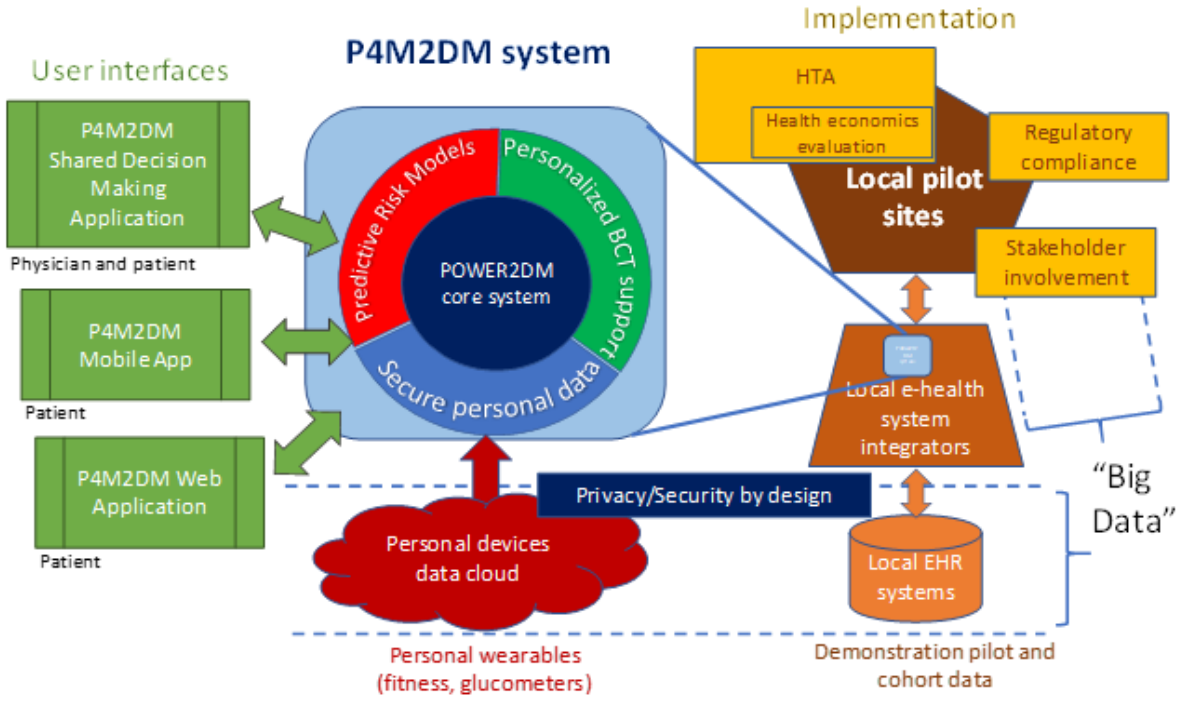


Figure 3.3.1. Concept of the P4M2DM project. The core of P4M2DM is formed by the existing POWER2DM (www.power2dm.eu) system and user interfaces described in the text. The project will first add a set of available state-of-the-art PM tools to this core. Demonstration pilots with ~1000 patients per country, designed in close interaction with local/regional/national stakeholders, will be carried out in 5 European countries. Personal health data from EHR, glucometers and personal wearables will be integrated in P4M2DM in a privacy&security-by-design manner, such that all PM tools can operate on the P4M2DM secure data platform in one single application. The Consortium is strategically positioned to include partners in each country that are able to integrate the P4M2DM system in locally/regionally used healthcare ICT applications. The P4M2DM e-health system will be deployed in the secure Microsoft Azure cloud to make it fully scalable also beyond the large-scale pilots.

Because it builds on the POWER2DM system, P4M2DM offers for the first time the possibility to link different initiatives for diabetes PM together, and integrate these in a single e-health system so that they can be applied in unison. The challenging problem however is that the EU-wide scaling up of the

resulting P4M2DM system with all the linked tools is highly complex because it involves a whole new organisation of diabetes care, which is moreover different in each country, because of the different systems of reimbursement, the necessary embedding in different existing care models, the integration in different ICT systems used in healthcare, the current different practices of diabetes care, cultural differences, etc. Therefore, P4M2DM will work closely together with local healthcare actors in the design and execution of large-scale (~1000 patients per country; equal numbers of males and females) demonstration pilots that will be carried out in 5 different EU countries. Moreover, the P4M2DM consortium is strategically positioned to include partners in each country that are able to integrate the P4M2DM system in locally/regionally used healthcare ICT applications. Demonstration pilots will be subjected to full Health Economic (HE) evaluation as part of a complete Health Technology Assessment (HTA) involving a wide range of stakeholders.

3.3.2.4 Methodology

P4M2DM's methodology comprises the following main elements and associated activities:

1. Design of P4M2DM demonstration pilots:
   - Define how the toolset for personalized support in prediction, prevention and treatment, as detailed in Table 1, will be combined and integrated into e-health/m-health functionalities of the P4M2DM system for tailored use by patients and caregivers in the demonstration pilots
   - Define the corresponding technical requirements of the P4M2DM integrated system architecture
2. Establish the integrated P4M2DM system:
   - Establish the P4M2DM system according to the design: user interfaces, system components, secure data exchange, component interlinkage, performing software management, integration, component testing and chain testing; and country-specific integration with local EHR and healthcare ICT applications
3. Perform Demonstration Pilot studies:
   - Define study objectives, inclusion criteria, and design for assessing individual health benefits, process evaluation to assess determinants of implementation as well as economic viability, tailoring to the different national contexts;
   - Prepare locally required Medical Device dossiers and Medical Ethical study approvals
   - Recruit patients
   - Training of clinical staff & patients in use of the P4M2DM predictive model-based decision support system
   - Perform Feasibility studies (stepped introduction-1st stage)
   - Deploy and operate large scale pilots (stepped introduction-2nd stage), and collect data
4. Assess impact and sustainability of P4M2DM
   - Define precise evaluation criteria and cost-effectiveness model
   - Perform data management, -processing and -analysis
   - Assess benefit for individuals (taking into account gender differences in outcomes), feasibility of implementation, and economic viability of P4M2DM personalized diabetes care
   - Assessment of legal as well as ethical aspects and stakeholder concerns (wider HTA)

5. Dissemination of key information on the project, associated activities and outcomes
    - Perform dissemination and communication activities, regular stakeholder liaison activities to discuss progress and get feedback; provide reports to stakeholders to provide guidance on EU-wide implementation of P4M2DM
    - Management of innovation and intellectual property rights
    - Identification of business and market opportunities, and providing exploitation plans

3.3.2.5 Ambition

The main ambition of P4M2DM is to advance the care and cure of diabetes in a personalized way in Europe, thereby reducing severity of the disease, the risk of complications, and related costs. To this end P4M2DMs key advance beyond state-of-the-art lies first, in establishing a system as described above and secondly, demonstrating its implementability and economic viability on a large scale in real life healthcare settings in 5 European countries that differ considerably in established healthcare practice, both from a technical, organisational and economic point of view.

P4M2DM is therefore highly ambitious and will advance beyond state-of-the art specifically by:

- Establishing a "personomics" approach to replace the current standard one-size-fits-all medical care based on highly protocolled procedures developed for the average patient;
- Anticipating on dynamic changes in the patient profile to replace standard reactive care;
- Implementing predictive model-based decision support to help decide on treatment, replacing time-consuming trial-and-error approaches;
- Performing risk prediction considering multiple comorbidities in an integrated fashion, replacing standard monodisciplinary approaches;
- Empowering patients in their self-management capabilities, replacing over-reliance on treatment by medical professionals;
- Bringing advanced e-health/m-health functionalities to diabetes patients on a large scale, avoiding patients lack of support between regular healthcare visits;
- Duly addressing by-design the risk of improper data use/privacy violation;
- Overcoming the technical complexity involved in establishment of PM systems that adopt a "personomics" view, fully connected with existing healthcare ICT systems, and providing adequate training thereby empowering the healthcare professional to use PM in practice;
- Making the e-health/m-health system fully scalable by deployment in the secure Microsoft Azure cloud, thus avoiding the limitation to low-capacity locally deployed ICT systems;
- Providing evidence that diabetes PM can be integrated in a variety of different national healthcare systems for the first time;
- Providing evidence that PM diabetes can be integrated in a variety of ICT systems used in healthcare including EHR for the first time;
- Providing for the very first time insight in country-specific barriers and promotional factors for implementing PM diabetes care;
- Providing data on economic viability of PM diabetes healthcare in different national settings across Europe for the first time.

P4M2DM is ground-breaking in delivering the technical, practical and economical proof for long-term sustainability of large-scale deployment of its new PM-based diabetes care model across Europe. As a consequence, EU diabetes healthcare will be reformed, and organised in new, more efficient ways that

fully exploit the possibilities of the P4M2DM system. New healthcare reimbursement schemes need to be created in the different national or regional contexts. As a consequence, new revenue models will arise, and corresponding new products and services will be created, starting around the P4M2DM components (i.e. POWER2DM Results (see Deliverable 7.6) combined with the additional toolsets from Table 3.3.1.

3.3.2.6 Expected Impacts

The expected impacts of P4M2DM can be itemized as follows:

- Evidence for a PM-based model of care that can be used as a basis for the delivery of new ways of care organization
- Demonstration of the viability and feasibility of PM approaches in real-life settings and at a large scale, exemplifying potential for savings in overall healthcare costs.
- Widening of PM approaches to include diseases other than cancer and rare diseases.
- Linking of different actors for healthcare, economy, lifestyle, healthy living and regulation (see Table 3.3.2), making use of the multitude of data available.

Table 3.3.2. Healthcare actors from different countries with established links to the P4M2DM Consortium

Domain	Actor
Healthcare	
Secondary Care	Leiden University Medical Center (LUMC) - The Netherlands VU University Medical Center (VUMC) - The Netherlands Andalusian Health System (SAS) – Spain Tervise Arengu Instituut (TAI) – Estonia Provincial Company for Health Services (APSS) – Trento, Italy Institute of Public Health University of Porto (ISPUP)
Primary Care	LUMC, VUMC, APSS, ISPUP, SAS
Lifestyle and Healthy Living	
Research	Salzburg Research Forschungs Ggesellschaft (SRFG) – Austria Netherlands Innovation Centre for Lifestyle Medicine (TNO and LUMC) University Medical Center Groningen – The Netherlands FBK – Italy Maimonides Institute for Biomedical Research at Cordoba (IMIBIC, SAS) - SPAIN
App. Providers	MiGuide (Blended Care Platform) -The Netherlands
Healthcare Economy	
Health Insurance	Estonian Health Insurance Fund – Estonia
Personal Health Application Vendors	iHealthLabs Europe, MiGuide (integrating Selfcare (https://www.selfcare4me.com/en/))
Software Providers	SRDC, INESCTEC
Non-profit Organizations, Initiatives	
Professional Organizations	International Diabetes Federation (IDF) NDF (Dutch Diabetes Federation) APSS (Trento Health Trust) Estonian Endocrine Society

	Portuguese Society for Obesity Study
Patient Organizations	DVN, ADICOR, FEDE, Estonian Diabetes Association
Regulation Bodies	
	Province of Trento (PAT) – Italy Andalusian Health System (SAS) – Spain NHG - Dutch Practitioners Association North Health Regional Administration (ARS Norte) - Portugal

3.3.3 Outcome of 1st stage evaluation

For the Topic SC1-BHC-25-2019 (2-stage), 42 proposals were submitted, 9 passed the threshold (8.0 points). P4M2DM was one of these, and was invited to submit a full proposal for stage 2 of

the evaluation. It is expected that 3 proposals will finally receive funding.

4 CONCLUSION

The previously established industry liaison with Dutch SMEs ExpertDoc and PEXLife was favourably evaluated for inclusion in TNO's Tech Transfer Program. This evaluation, which received 30 kEur proprietary funding from TNO, concluded that indeed a JV with these SMEs is the preferred route to market, provided that the proposition is duly evaluated and accepted by healthcare professionals and patients, 24/7 service is guaranteed and personal data privacy and security standards are fully met. Preparing for such a scenario, ExpertDoc and PEXLife already created their JV MiGuide BV.

TNO, ExpertDoc and PEXLife have teamed up in several additional regional, national and international projects (MIT-2 (in progress), E-manager chronic diseases (in progress), and P4M2DM (proposal)) to work towards proper evaluation and full acceptance by healthcare professionals and patients of the MiGuide proposition. These projects include Results from POWER2DM to different extents, with H2020 P4M2DM including the POWER2DM SMSS in its entirety.