C3-Cloud personalised care plan development platform for addressing the needs of multi-morbidity and managing poly-pharmacy: Protocol for a pilot technology trial

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Abstract

Background: There is an increasing need to organise the care around the patient and not the disease, as well as taking into account the complex realities of multiple physical, psycho-social conditions and polypharmacy. Integrated patient-centred care delivery platforms have been developed for both patients and clinicians. These platforms could provide a promising way to achieve a collaborative environment that improves the provision of integrated care for patients via enhanced ICT solutions.

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Trial registration https://www.clinicaltrials.gov/ct2/show/NCT03834207

Keywords: multimorbidity, polypharmacy, guidelines reconciliation, clinical decision support, personalised care plans, diabetes mellitus type 2, heart failure, depression, renal failure, acceptability, usability, evaluation, user-centred design

Introduction

Older age is associated with an increased accumulation of multiple chronic conditions called multi-morbidity and includes functional and cognitive impairments. More than half of all older people have at least three chronic conditions and a significant proportion have five or more [CITATION Lup08 \l 1031]. Chronic diseases take many forms such as hypertension, depression, diabetes renal failure. They are the main reason for poor health and a restricted activity. They affect over one third of the European population and represent 70% of the healthcare expenditure in Europe [CITATION Ret12 \l 1031].
The management of care for patients with multi-morbidity is more complex and time consuming than those with a single disease [CITATION Aus07 \l 1031]. Managing multiple diseases concurrently creates an added challenge for health service delivery and provision. Therefore, many individuals with chronic and long-term care needs experience shortcomings in the care they receive. One reason for this is the inconsistency across single-disease clinical guidelines when they cover situations with more than one disease. Current European medical models are often dictated by national clinical guidelines, which focus primarily on managing a single disease. Evidently, this can cause inconsistencies and contradictory information when providers are following more than one guideline for their patient. Furthermore, it can result in avoidable inefficiency for patients and health systems, for example incompatible treatment regimens and duplicate clinical visits and tests [CITATION Gut12 \l 1031].

Polypharmacy, induced by multi-morbidity, is itself an important factor that leads to an increased risk of further complications in the provision of safe and effective care for patients, as well as the increased potential for adverse drug interactions and events [CITATION NHS13 \l 1031]. Because of polypharmacy redundancy and duplication of medication is common: it not rare for elderly patients to be taking nine or more medications concurrently [CITATION Haq09 \l 1031]. This current approach of managing multi-morbidity also fails to integrate care across providers and the interactions of chronic diseases and their treatments is overlooked [CITATION Pav12 \l 1031]. As the number and complexity of health conditions increase with age, the type and number of care providers also increase. This often leads to fragmented care: it becomes significantly more difficult for providers to align and coordinate care teams and settings. This is exacerbated by poor inter-professional communication and lack of appropriate information sharing infrastructure that exist in many health systems and even at local level. Without secure information exchange among the actors involved in health, social and informal care services, it becomes almost impossible to reconcile potentially conflicting treatment plans or avoid potentially harmful interventions. An insufficient information exchange complicates the application of data processing techniques developed under paradigms such as data science, machine learning and artificial intelligence that could support medical decision making with information analysis and predictive models.

Moreover, patients and their informal caregivers often do not have a voice in the

management of their own care. This can lead to patients feeling disempowered, less well informed and therefore less likely to follow the treatment regime "imposed" on them. Among elderly people, non-compliance has a prevalence of 25-75% and the likelihood rises in proportion to the number of drugs and daily doses prescribed [CITATION Gel11 \l 1031]. There is an increasing need to focus care organisation around a patient with multiple diseases, rather than targeting each disease separately. This requires a patient-centred approach: considering each patient's multiple physical conditions, psycho-social conditions and the realities of multi-morbidity and polypharmacy. An interactive collaborative environment is needed to address these issues in the current care of patients with multi-morbidities.

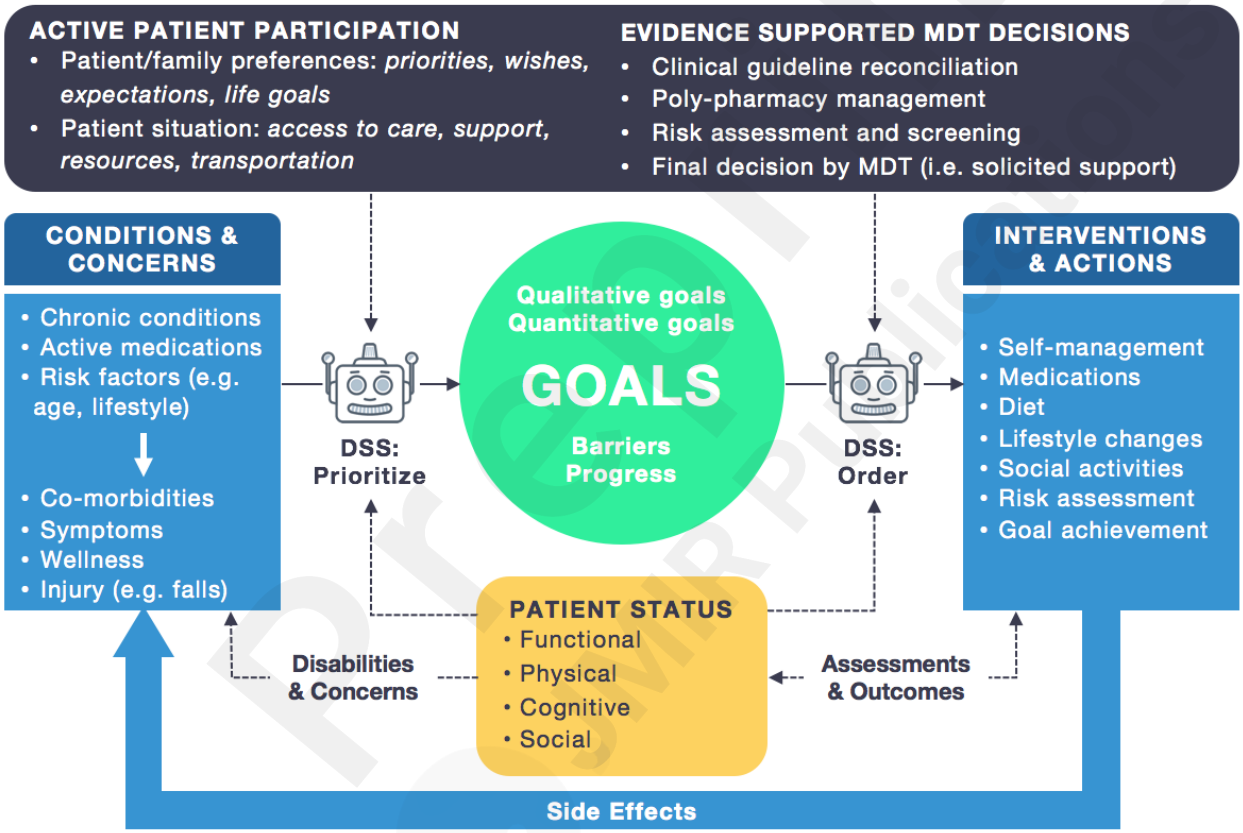

Figure 1: C3-Cloud platform aims

In response, C3-Cloud a European Commission supported Horizon 2020 innovation project was created to pilot test collaborative computer platforms for patients and for members of the Multi Disciplinary Team (MDTs) in three different European settings. The platform's aims are to improve the provision of integrated care for patients with multi-morbidity, resolve guideline conflicts (by reconciliation of varying, and potentially conflicting, recommendations from single disease clinical guidelines), support clinical decision making through clinical decision support services and facilitate communication among MDT

members and with the patients through an interoperable platform (see Figure 1). Traditional, “paper based” health records have strong limitations for the integration of care or collaborative decision making and electronic health records (EHRs) attempt to widen the scope of health records[CITATION Eva16 \l 1031]. As the healthcare landscape is ever changing, EHRs have the potential to replace paper records and add many more capabilities, beyond mere replication of data in an electronic format. New tools such as C3-Cloud can enhance the interaction among MDTs, patients and their informal caregivers. The objective of the study is to determine the impact the platform will have on patients, MDT members and health systems with the guiding research question being: “Is the use of a personalised ICT tool that facilitates coordinated care planning, treatment optimisation and patient self-management acceptable to patients with multiple long-term conditions and their team of health professionals?”. The overall C3-Cloud system architecture is shown in Figure 2 and Table 1 describes the main components of the C3-Cloud system.

The purpose of this paper is to present the research protocol of the C3-Cloud technology trial, as a sustainable protocol guiding the development, testing and evaluation of other interactive healthcare platforms targeting patients and MDT members.

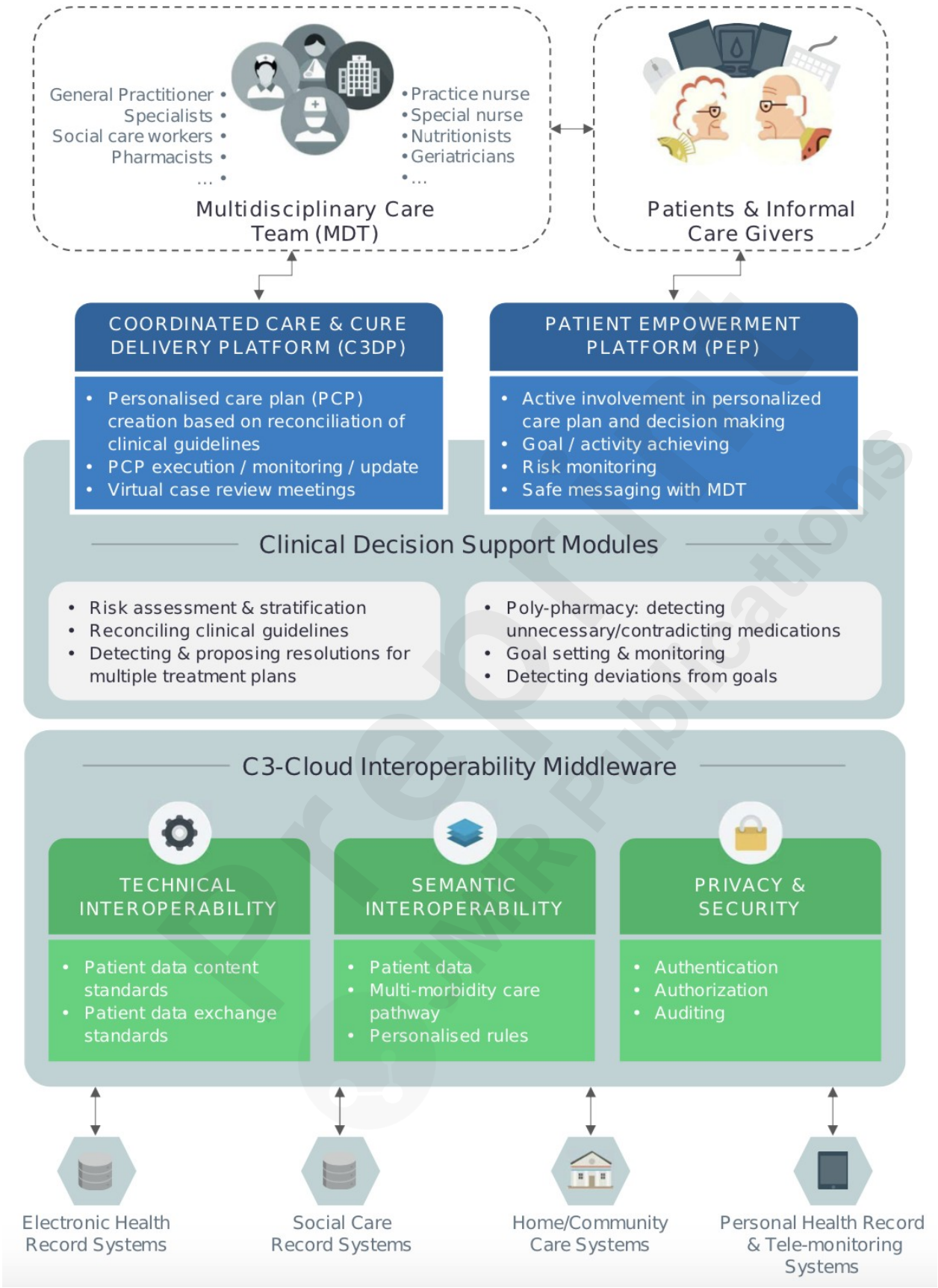

Figure 2: Overall C3-Cloud Architecture

The C3-Cloud system aims to facilitate the realization of two main components: the Coordinated Care & Cure Delivery Platform (C3DP) and the Patient Empowerment Platform (PEP). It also involves a variety of other components: The clinical decision support modules (CDSM), the interoperability middleware which includes modules of technical and semantic interoperability, as well as privacy and security. All these components constitute the solution that will be used for the technological trial of the C3-Cloud application.

The Coordinated Care and Cure Delivery Platform (C3DP) is an innovative online means for Multi-Disciplinary Team (MDT) members to collaboratively manage (execute, monitor, update) the integrated personalized care plans for patients with multi-morbid conditions. The health professional will have a personal log-in account. MDT members and patients have the ability to send messages via the messaging portal to each other. The aim of the C3DP is the creation and execution of personalised care plans for multi-morbid patients, with the help of Clinical Decision Support Modules (CDSM) for recommendation reconciliation, poly-pharmacy management and goal setting.

The Patient Empowerment Platform (PEP) is for patients and their informal caregivers to access their care plans online and support them in self-managing their care. It aims to improve the interaction between patients and health professionals and to collect relevant information (home-based self-measurement data on blood pressure and weight) to enable the monitoring of care plan related activity status and progress. Clinicians can send medication or lifestyle change reminders as well as answer questions patients might have about their care.

The Technical Interoperability Suite (TIS) enables health data sharing between C3-Cloud high-level components, including information systems of local care providers and tele-monitoring devices, in order to support integrated care plan development, care plan progress monitoring and evaluation, as well as patient engagement across multiple care settings.

The Semantic Interoperability Suite (SIS) handles structural mappings among different information models and resolves semantic mismatches due to use of different terminology systems and different compositional aggregations to represent the same clinical concept.

The Security and Privacy Suite (SPS) guarantees authentication and authorisation of members of the MDT while they are managing personalised care plans of patients and accessing sensitive personal data. The SPS ensures that data exchange within and across C3-Cloud software components is encrypted and audited properly.

Clinical Decision Support Module (CDSM) provides guideline-based alerts, reminders or suggestions to support clinical pathways, and implements widely accepted polypharmacy criteria and risk assessment algorithms to support care plan reconciliation and patient risk stratification.

Table 1: C3-Cloud terminology (accompanying Figure 1)

Methods

Overview

The C3-cloud study uses a mixed method research design to gain insights into the usability, acceptability and usefulness of the C3-Cloud system. The project has developed the innovative care planning system called ‘C3-Cloud’ which is being tested with patients, their informal caregivers and healthcare professionals in the United Kingdom (South Warwickshire), Sweden (Region Jämtland Härjedalen) and Spain (Basque Country). The tests and evaluation activities generate data to assess the usability and usefulness of the C3-Cloud system as well as its acceptance and satisfaction among user groups. The study is designed to go through four evaluation phases. The adoption of phases corresponds to the study’s aims to develop the C3-Cloud system together with its users in an iterative approach of testing, feedback and subsequent improvements which corresponds to the UK’s Medical Research Council (MRC) recommendations for carrying out complex interventions. The MRC suggests employing modelling and exploratory trials before aiming to carry out randomised controlled trials [CITATION Cra08 \l 1031]. Following this advice, the project has been designed to evaluate through four phases (Figure 3).

Study development and timeline

Phase 1 and phase 2 of the evaluation have been completed iteratively during C3-Cloud development with a restricted number of selected participants. They were carried out before the technology trial over the course of two and a half years (2016-2018).

Subsequently, the C3-Cloud system has been deployed at the pilot sites, which is followed by the pilot phase 3 with a larger number of users. The project aims for a 7-months exploratory technology trial (phase 3) and the final phase 4 will be the remaining time for system acceptance analysis and impact assessment of C3-Cloud (Figure 3). All test participants' data, patient and clinician data are retrieved anonymously or anonymized and aggregated in the pilot sites before sharing the datasets for analysis. Control group data for the period of phase 4 will be extracted from care centres in the pilot sites in February 2020. Information retrieved will be on health care resource consumption and it will be anonymized. To ensure that data cannot be traced, the data extracts will not include demographic descriptors and identifiers. Data entry of resource utilization dates will be manipulated automatically and randomly within a range of +/- 30 days for each entry.

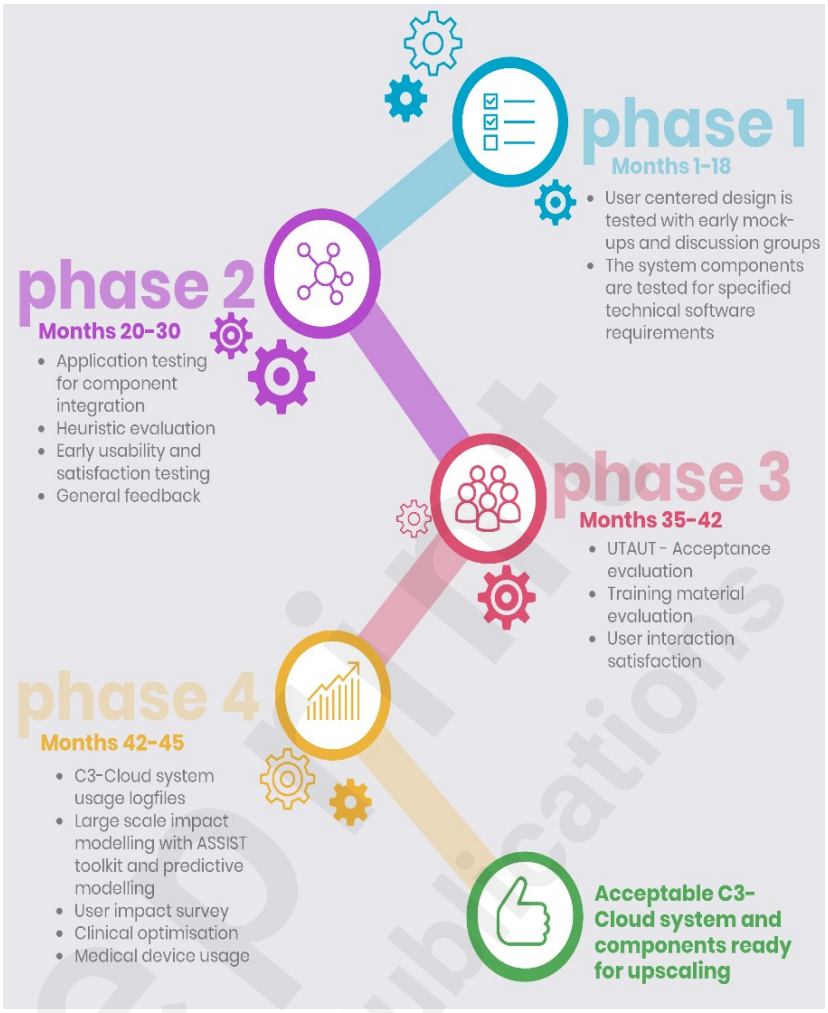

Figure 3: C3-Cloud system evaluation phases

Phase 1

User-centred design

C3-Cloud system mock-ups (screenshots of the early platforms) were shown to experts and potential platform users in the three pilot sites to evaluate the user-centred design from the very beginning of the project. A mock-up is a prototype if it provides at least part of the functionality of a system and enables the testing of a design. The most common use of mock-up in software development is to create user interfaces that show the end user what the software will look

like without having to build the software or the underlying functionality. Mock-ups are intuitive to users, give a realistic perspective and allow for early testing and revision of the development plans.

In order to increase the feedback received from the end users, the evaluation of the PEP was performed in the three pilot sites on different dates, using the most recent available versions of the platform as mock-ups. The target size for the test participant groups was defined as ~4 patients and 13 MDT members at each pilot site based on convenience sampling and availability (Error: Reference source not found). In all settings, high-level system information was provided to testers with the aim to give them a general understanding of the project and the C3-Cloud system. The main platforms (C3DP and PEP) with the main foreseen functionalities were explained in detail. Finally, a discussion took place on the basis of the testers' comments and inputs. Screenshots were reviewed and comments on the presented information was then sent in writing to the software developers.

The discussions were moderated by a set of 7 questions [CITATION Bar19 \l 1031]:

1. To what degree do you think the use of the C3-Cloud services can contribute to improving your understanding of health information that you receive from health professionals, as well as information received in a written form such as test results, medical reports, etc.?
2. To what degree do you think the use of the C3-Cloud services will help you better understand your health/disease, its possible developments, and treatment options available?
3. Do you think the use of the C3-Cloud services will contribute to making you become more involved in monitoring your health status and treatment progress, and if so to what degree?
4. To what extent do you think the use of the C3-Cloud services will help you better adhere to treatment plans and lifestyle adjustments?
5. Do you think the use of the C3-Cloud services will help you become more actively involved during a consultation with healthcare professionals, and if so to what extent?
6. How will the use of the C3-Cloud service impact on your relationship with healthcare professionals?
7. Other issues emerged in respect of empowerment

In addition, the system design was discussed along the topics "functionality; content; language used; the level of data detail and user-friendliness".

Component testing

The C3-Cloud system components include the C3DP, PEP, the clinical decision support module (CDSM), the technical interoperability suite (TIS), the semantic interoperability suite (SIS) and the security and privacy suite (SPS). For all six software components, templates based on the IEEE 829 standard [CITATION IEE08 \l 1031] were used, which defines a set of documents to use in software and system test documentation. Rather than developing the full set of distinct IEEE 829 standard's template for all components, a pragmatic approach was followed after considering the workload implications among the technical team. Thus, technical partners agreed on component test plans and test design topics focusing on relevant features to test in the scope of C3-Cloud. The test plan

objectives were to i) define the scope of what will be tested; ii) specify the approach taken to testing and iii) specify how the testing results will be evaluated. Then each component owner conducted the testing independently. In addition, a form [CITATION Tra18 \l 1031] for the test results, which gathers the test execution description, test data and results, as well as incident reports and a conclusion, were developed for each component by its owner. The pragmatic approach permitted to obtain component testing results by focusing on key features to be tested within the C3-Cloud project. Test cases for the components were defined along specified technical software requirements for the C3-Cloud system.

Phase 2

Application testing

For phase 2, the target size for the test participants was defined as a total of 52 MDT members and 40 patients: 16 MDTs and 20 patients in the Basque Country; 20 MDTs and 10 patients in Region Jämtland and 16 MDTs and 10 patients in South Warwickshire, based on convenience sampling and availability in the pilot sites (Error: Reference source not found). It was planned to apply convenience sampling among people with sufficient English language proficiency and proximity to the local project managers or clinicians as to allow for swift recruitment of participants. All participants received login credentials for the online demonstrators of the C3DP and the PEP and training material including a walkthrough that guides them through certain activities on the demonstrators. A language facilitator from the pilot sites moderated each session and was available for any question that was raised from the participants. The application testing included a questionnaire on the integration of the system components (Delphi method) [CITATION Dal631 \l 1031], a questionnaire on user interaction satisfaction (QUIS7), the collection of ‘unstructured, oral feedback’ during the test session and ‘product reaction cards’ (PRCs) [CITATION Bar10 \l 1031] [CITATION Ben02 \l 1031]. The methods are explained below.

	Phase 1 – User Centred Design		Phase 2 – Usability / Usefulness		
Pilot Region	**Patients**	**membersMDT**	**Health ICT Experts**	**Patients**	**membersMDT**
South Warwickshire	5	8	4	10	16
Basque Country	5	8	-	20	16
Jämtland Härjedalen	5	14	-	10	20
Total	15	30		40	52

Table 2: Number of trial participants in phase 1 and 2

The *Delphi method* [CITATION Dal631 \l 1031] was used for the creation of questionnaire items to evaluate how people interact with the software and tests the integration of all C3-Cloud components. Pilot application scenario requirements (PARs) were specified and matched with C3-Cloud specific use cases for four user profiles: patients, informal caregivers, members of the MDT and healthcare professionals. Questionnaire items were developed for each use case and tested with a clinician and an ICT developer in line with the Delphi method step “brainstorming”. In the steps “refining and prioritization” these questionnaires were merged into two questionnaires: one for MDTs and healthcare professionals and one for patients and their informal caregivers, while dropping irrelevant items, following the maxim “as little as possible, as much as required”. Finally, the questionnaires were built on an online platform for test participants to complete them at the end of the test session.

Usability testing

An early *usability testing* was performed with the Questionnaire on User Interaction Satisfaction (QUIS7)[CITATION Nor19 \l 1031]. It measures users’ attitudes towards the following interface factors: screen factors, terminology and system feedback, learning factors, system capabilities, technical manuals, on-line tutorials, multimedia, voice recognition, virtual environments, internet access and software installation. After the participants finalized the test session, they answered the QUIS7 online.

Product reaction cards

The *product reaction cards method* [CITATION Bar10 \l 1031].was used as a fast and simple method used for an overall evaluation of the users’ perception of the software design. The principle of this method is that it does not rely on a questionnaire or rating scales. The participants were presented a predefined list of 118 words (see Figure 4 [CITATION Ben02 \l 1031]) and asked to pick five words that best describe the product or how using the product made them feel. The descriptive analysis was used to report testers’ perception of the C3-Cloud system design.

Accessible	Creative	Fast	Meaningful	Slow
Advanced	Customizable	Flexible	Motivating	Sophisticated
Annoying	Cutting edge	Fragile	Not Secure	Stable
Appealing	Dated	Fresh	Not Valuable	Sterile
Approachable	Desirable	Friendly	Novel	Stimulating
Attractive	Difficult	Frustrating	Old	Straight Forward
Boring	Disconnected	Fun	Optimistic	Stressful
Business-like	Disruptive	Gets in the way	Ordinary	Time-consuming
Busy	Distracting	Hard to Use	Organized	Time-Saving
Calm	Dull	Helpful	Overbearing	Too Technical
Clean	Easy to use	High quality	Overwhelming	Trustworthy
Clear	Effective	Impersonal	Patronizing	Unapproachable
Collaborative	Efficient	Impressive	Personal	Unattractive
Comfortable	Effortless	Incomprehensible	Poor quality	Uncontrollable
Compatible	Empowering	Inconsistent	Powerful	Unconventional
Compelling	Energetic	Ineffective	Predictable	Understandable
Complex	Engaging	Innovative	Professional	Undesirable
Comprehensive	Entertaining	Inspiring	Relevant	Unpredictable
Confident	Enthusiastic	Integrated	Reliable	Unrefined
Confusing	Essential	Intimidating	Responsive	Usable
Connected	Exceptional	Intuitive	Rigid	Useful
Consistent	Exciting	Inviting	Satisfying	Valuable
Controllable	Expected	Irrelevant	Secure	
Convenient	Familiar	Low Maintenance	Simplistic	

Figure 4: complete set of 118 Product Reaction Cards

Unstructured feedback

Any *unstructured user feedback* given during the test sessions was recorded in writing by the session moderators both for the C3DP and the PEP. Feedback from the different pilot sites complemented each other. There is general feedback on the platform and specific feedback on system functionalities or flaws that were experienced during the testing. Where it was needed, the feedback was supported with screenshots. The unstructured feedback was used for a report to the software development team.

Heuristic evaluation

A *heuristic evaluation*[CITATION Nie951 \l 1031] of the C3-Cloud system was performed to systematically identify any usability problems in the user interface design. Issues are classified in a number of recognized usability principles – the 'heuristic categories'.

Five usability evaluation reviewers from the Institute of Digital Healthcare, University of Warwick, UK, conducted the Heuristic Evaluation in June 2018. The spread of expertise of the reviewers ranged from systems and software engineers, to clinical scientist, with experience in using, as well as developing health IT systems. The heuristic evaluation was performed via following steps:

1) Reviewers attended a thirty minutes presentation that explained the purpose of the evaluation, the process that would be followed and its documentation, as well as the definition of the heuristics that would be reviewed.
2) Reviewers reviewed C3-Cloud system manuals, which describe the functionality and an example walkthrough, designed by the system developers, to ensure coverage of the entirety of functionality and menus

that can be accessed through the interfaces.

3) The reviewers made a first structure-free evaluation of the interfaces, keeping unstructured text notes.
4) A second structured pass was done by following the workflows described in the manuals; comments were classified under each heuristic.
5) Based on the comments collected, reviewers filled out a spreadsheet with common issues for each heuristic category, further structuring the process, ensuring that all interfaces had been considered for all issues of interest. The spreadsheet also requested a subjective evaluation of frequency of each issue, along with a reviewer-based assessment of criticality for each issue. Frequency and severity were combined to create an overall risk metric that will prioritize the modifications by the technical teams.

The technology trial in phase 3 and phase 4

Study setting

A technology trial will be used to test the C3-Cloud system with MDT members, patients and their informal caregivers (when available). The technology trial runs approximately 7 months and take place in three European pilot site regions: Basque Country, Spain; Jämtland Härjedalen, Sweden; and South Warwickshire, UK. Study settings will include various locations that are relevant for the provision of health care, e.g. healthcare centres, general practitioner (GP) offices, hospitals and patients' homes. The technology trial registration is under https://www.clinicaltrials.gov/ct2/show/NCT03834207.

Sampling and recruitment

The recruitment period for patients starts 3 months before the launch of the pilot test to allow sufficient time for the identification of eligible participants and obtaining informed consents, while also keeping the time-period between recruitment and piloting start as short as possible.

MDT members will be contacted individually by pilot site managers using convenience sampling, taking into account their individual profiles, willingness to participate and a few general inclusion criteria (Table 4). This non-probabilistic sampling involves the sampling of MDT members that are nearby, aiming for a total sample size of 62 across the three pilot sites.

For the iterative evaluation phase 3 and phase 4 we defined the patient number that we need to observe based on power calculations as the "observation goal", which is 420 patients. An unknown number of patients may withdraw from their participation during the technology trial. Thus we added a 25% dropout margin to the observation goal, summing up to 526 patients to be recruited for the piloting trial participation (the "recruitment goal"). It is anticipated that a number of patients that will be approached for participation, will decline from the outset. Accordingly, the number of patients that will be approached for participation (the "approaching goal") will be 16% larger than the recruitment

goal, summing up to 610 intervention patients across the three pilot sites. The number of comparator patients whose resource consumption data will be monitored anonymously will match the intervention patient numbers at each pilot site.

Potential candidates will be selected through each pilot site screening their databases for eligible patients who meet the inclusion and exclusion criteria (Table 4). No inclusion criteria for informal caregivers have been defined, however, exclusion criteria will be applied (Table 4). Once the pilot sites have provided a list of eligible patients, they will be randomised as study candidates to avoid selection bias. A first randomization round generates lists with a number of candidates that is 16% larger than the actual recruitment target (including a 25% dropout rate) of patients per pilot site and to adjust for patients that are approached but deny their participation.

Table 3 details the number of involved participants per pilot site and evaluation phase. The number of trial participants in each pilot site for evaluation layer 4 reads as follows: “minimum number of trial participants as calculated for the observation goal + 25% dropout rate (“recruitment goal”) + 16% denial rate (“approaching goal”)” and sums the total number of trial participants that will be approached for participation.

	Phase 3 - Exploratory trial for application evaluation		Phase 4 – Monitoring to model large scale impact		
Pilot Region	Patients	MDT members	Patients	Comparator patients	MDT members
South Warwickshire	50	16	70+18+14	102	16
Basque Country	50	16	175+44+35	254	16
Jämtland Härjedalen	50	30	175+44+35	254	30
Total	150	62	610	610	62

Table 3 Number of trial participants to approach

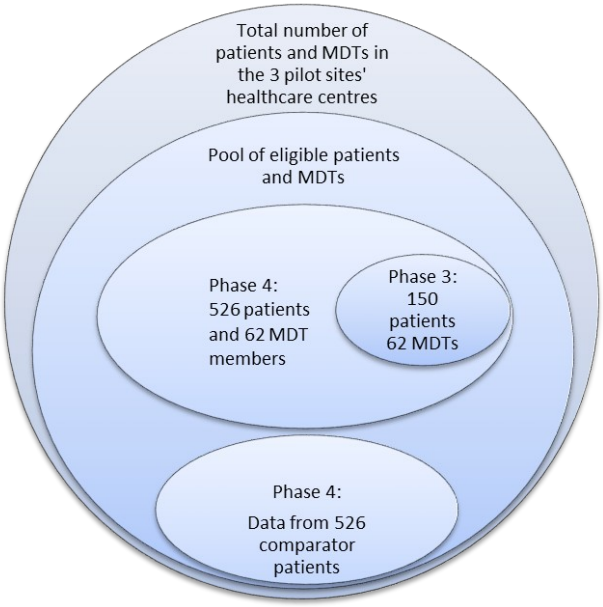

Figure 5: Trial participant cohorts

Research assistants at each site will contact (email, mail, phone or face-to-face meetings) the selected study candidates and provide them with material and information about the study and its objectives. Supportive activities such as videos and presentations may be used in a supplementary role to clarify any questions. Candidates who agree to participate in the study must sign an informed consent form for documentation to confirm they have read and understood the information and want to participate in the technology trial.

Inclusion criteria	Exclusion criteria	Inclusion criteria for MDT members	Exclusion criteria for informal caregivers
Patients must be aged 55 or older	Patients are aged 54 or below	The MDT member would normally be involved in the selected patients care.	They are aged 17 or below
They are multimorbid patients that suffer from two or more of the following four conditions in various disease combinations: • Type II Diabetes • Renal Failure with estimated or measured glomerular filtration rate (GFR/eGFR) of 30 – 59 • Heart Failure in compliance with NYHA I-II (New York Heart Association classification of heart failure) • Mild or moderate Depression	They suffer from any of the following conditions: • Severe Renal Failure with GFR/eGFR <30 • Severe Heart Failure in compliance with NYHA III-IV • Severe Depression	The MDT member should be open to new ways of working, specifically as part of a MDT (including GPs; consultant nurses or specialist nurses; district nurses; social workers; consultants; physiotherapists or pharmacists).	They are not available most of the time in person or via telephone, email, SMS or other means to respond to calls for help.
They still live and generally plan on living in their home (or in the community) for the trial duration.	They live in a care institution, for instance in a residential home or nursing home.	The MDT member should be open to the use of new technology: MDT members do not	

Inclusion criteria	Exclusion criteria	Inclusion criteria for MDT members	Exclusion criteria for informal caregivers
		have to be technologically knowledgeable but they should be willing to learn how to use technology to support their work.	
They or their informal caregiver pass an ICT Handling Self-Check	They or their informal caregivers do not pass the ICT Handling Self-Check (i.e. they do not have access to suitable IT devices and do not have some familiarity with the use of ICT).		They do not have some familiarity with the use of ICT or do not have the capability to help the patient out with ICT usage if necessary.
They are able to provide informed consent.	They are unable to provide informed consent for trial participation.	They are able to provide informed consent.	They are unable to provide informed consent for trial participation.
They, or their informal caregiver, have stable access to the internet and at least one of the following devices readily available to use the C3-Cloud components: Computer; Notebook; Smartphone; Tablet. This includes the use of Internet	They have disabilities or other health conditions that would prevent their active involvement in the study project or which prevent them from carrying out essential functions of the trial.		They do not have stable access to the internet and at least one of the following devices readily available to use the C3-Cloud components: Computer; Notebook;

Inclusion criteria	Exclusion criteria	Inclusion criteria for MDT members	Exclusion criteria for informal caregivers
Browsers to open the C3-Cloud patient dashboards online.			Smartphone; Tablet. This includes the use of Internet Browsers to open the C3-Cloud patient dashboards online.
	They have other debilitating conditions that impair their decision making capability or their life expectancy (e.g. end-of-life patients or cancer patients). Patients with further chronic diseases and other co-morbidities or symptoms, for example, frailty, sleeping problems, malnourishment or anxiety, will not be excluded from recruitment. Informal caregivers who pass the ICT Handling Self-Check can substitute for the patient if the patient does not pass the ICT Handling Self-Check – the patient-informal caregiver pair can still be recruited		They have debilitating conditions that impair their decision-making capability.

Inclusion criteria	Exclusion criteria	Inclusion criteria for MDT members	Exclusion criteria for informal caregivers
	They do not speak the regional language: English for SWFT; Spanish for the Basque country; Swedish for RJH		They do not speak the local language: English for SWFT; Spanish for the Basque country; Swedish for RJH
	Their health care expenses are covered by a private insurance: in the C3-Cloud pilot sites, private insurances have no data exchange with EHRs.		

Table 4: Inclusion and exclusion criteria for patients and informal caregivers

Study procedure

Early in the pilot technology trial, there is training for all participants in how to use the platforms. The pilot technology trial is used to evaluate the user experience, satisfaction and acceptability of the C3-Cloud application as well as the patient training material (phase 3). It also serves to obtain anonymous patient data on resource usage for the impact modelling and sustainability planning for up scaling C3-Cloud in phase 4. At the start of the trial the patients have a care plan created on the C3-Cloud system that they develop and manage with their healthcare professionals during the study. Once the patient's care plan is prepared, they are given access to the C3-Cloud system and can view and update their care plan whenever they wish. Moreover, patients are able to send messages to their care team members via the system. The patients care plan in the C3-Cloud system is reviewed and adapted each time they visit a healthcare professional that is also taking part in the study.

In the final phase of the project a comparison will be made on the care and treatment received by patients that have used the system and those that have not (comparator patient group). The comparator group data will be taken from similar patients and retrieved anonymously from the local healthcare systems. This data will contribute to determining the full impact of C3-Cloud by assessing the use of resources and medication across both groups of patients (phase 4).

Phase 3

This phase will evaluate the user experience, satisfaction and acceptability of the C3-Cloud application and patient training material by collecting evaluation data. Data will be collected from a subset of participants - 150 patients and 52 MDT members from questionnaires they have completed. In phase 3 data on user experience and satisfaction will be collected from training material questionnaire and QUIS questionnaire. The data collected on acceptability of the technology will be taken from a refined version of the UTAUT questionnaire. The questionnaires will be administered as one online survey a few weeks after the trial start and another survey at the trial end. Trial participants will be able to access them through the messaging service of the platforms.

The training material questionnaire

The training material will be assessed from the results of a survey that will be given to patients after the training period to determine whether the patients and their informal caregivers found the training materials useful and informative. Data will be gathered on user experience and whether users feel more knowledgeable about their conditions and if they feel enabled to use C3-Cloud to take care of their conditions after the training. It will also consider whether the materials are a contributing factor to improve care coordination.

The questionnaire for user interaction satisfaction (QUIS)

Similar to the early usability testing with a limited number of test users, the QUIS7 questionnaire[CITATION Nor19 \l 1031] will be used for both MDT members and patients when the technology trial is in full scope and will be conducted partly after the initial user-training at the beginning of the trial and partly at the end of the trial. The results from both questionnaires compared and used, in an iterative fashion, for shaping the design and redesign of the C3-Cloud platform and for providing potential recommendations for areas of improvement.

The Unified Theory of Acceptance and Use of Technology questionnaire (UTAUT)

A C3-Cloud-adapted version of the UTAUT questionnaire [CITATION Ven03 \l 1031] will be used, covering some of the original UTAUT modules. The UTAUT is developed to predict individual adoption and use of new ITs. It posits that individuals' behavioural intention to use an IT is determined by two beliefs: perceived usefulness, defined as the extent to which a person believes that using an IT will enhance his or her job performance and perceived ease of use, defined as the degree to which a person believes that using an IT will be free of effort. A limited UTAUT version will be conducted at the beginning of the pilot trial, just after participants) have had training sessions on how to use the C3-Cloud components. This version includes the following UTAUT modules: performance expectancy, effort expectancy, social influence, technology anxiety, adoption timeline and behavioural intention. The questionnaire will be repeated in a more comprehensive version shortly before the end of the trial. This second version includes the additional modules: cultural trends and language factors. The results from the initial UTAUT will be compared to the closure UTAUT questionnaire in order to evaluate the differences in acceptance and use of C3-Cloud technology over the trial duration.

Phase 4

Phase 4 will carry out the modelling for large scale impact of C3-cloud implementation after the technology trial. The health and economic benefits of the intervention at population level will be evaluated to generate insights on savings that C3-Cloud could generate systemically in the long term. The digitalisation of clinical patient histories and the coding of all contacts between patients and their MDTs into the EHR, allows to better understand the health demand of a population and to quantify the health and social burden of the disease. Because of that, healthcare resource usage data of all patients will be used and compared using modelling techniques with anonymous comparator patient data. The modelling tool used for this analysis has been developed by merging discrete event simulation modelling methods with a cost-benefit assessment tool [CITATION Ham14 \l 1031]. The merger tool (Table 5) will help predict the return on investment and time to break even for integrated care implementation at large-scale. It will be used to inform decision making in the management of integrated care in general and on the expected impact of scaling up the use of C3-Cloud. The aim is to develop a combined tool taking advantage of two existing approaches (ASSIST[CITATION Ham14 \l 1031] and predictive modelling [CITATION Lar18 \l 1031],[CITATION Sot17 \l 1031]) that have been previously applied in other European projects like CareWell [CITATION emp19 \l 1031] and smartcare[CITATION emp191 \l 1031] . Merging them aims to improve reliability and validity of the tool by incorporating the comprehensive perspective applied by ASSIST and the flexible engine developed in predictive modelling to represent mathematically

the natural history of the disease. The conceptual model includes not only the health system but also the complete set of stakeholders. Model parameterization is a challenge as data required for all stakeholders cannot probably be obtained from evidence-based sources. The data will focus on healthcare resource utilization, frequency of use of C3-Cloud components and service satisfaction. The data needed for this type of modelling will be taken from administering additional questionnaires to participants: the eCare client impact survey (eCCIS) for patients, the eCare user impact survey (eCUIS) for MDT members and a few additional questionnaire items for patients, MDT members and informal care givers.

In addition, C3-Cloud logfiles and EHR exports will be taken from electronic health records of the intervention and also from comparator patients in order to evaluate the differences in healthcare resource utilization during the trial. This includes for example: changes to drug use; re-admissions; number of adverse drug events; number of virtual sessions; or resource redistribution. The comparator group will be taken from another practice and statistically adjusted for the differences based on historic data.

Assist cost-benefit analysis tool	Predictive modelling
ASSIST is an assessment and evaluation tool originally developed for use in the context of telemedicine and telehealth services, specifically to assess the economic viability of telemedicine pilot projects [CITATION Ham14 \l 1031]. During the validation phase, ASSIST was successfully applied by five telemedicine projects. A core aim of ASSIST is to facilitate the transposition of a pilot project into routine service operation and to support service providers in achieving a sustainable economic model where service benefits are higher than service costs. It also facilitates the transposition of a pilot project into routine service operation and supports service providers in achieving a sustainable economic model. The assessment process of the tool includes three steps: 1) Service assessment model setup: the service change is analysed to identify the key components like applicable governance and the reimbursement model, stakeholders and the financial impacts (costs and benefits on the stakeholders); 2) Data collection and monetization and 3) Calculation of performance measure: the main outcome measure is based on the ratio of total costs to total benefits, i.e. including financial costs and benefits, resource costs and benefits and intangible costs and benefits.	Modelling serves to calculate the Budget Impact Analysis (BIA) by reproducing the natural history of multi-morbid patients in both the standard scenario and the new scenario related to the new intervention which results in implementation, effectiveness (i.e. how does new intervention affect the number of contacts to health professionals) and costs. A BIA projects the burden of the target population within the conventional or baseline scenario and analyses how this burden would change if the intervention achieved the organizationally defined goal.

Table 5: Predictive modelling

The eCare Client Impact Survey (eCCIS) and the eCare User Impact Survey (eCUIS)

The eCCIS and eCUIS will be used to evaluate the utility that the C3-Cloud application brings to the patients and MDT members. It measures how patients and informal carers perceive the utility of C3-Cloud. To this can be added scales addressing time use, willingness-to-pay and perception of care integration. In addition, the overall satisfaction with the C3-Cloud system as a service, whether the service is worth the effort involved in using it and whether the respondent would want to continue using the service or to use it again is evaluated.

Additional questionnaire items

A few questionnaire items have been added to the surveys to evaluate the impact of C3-Cloud implementation on patients, their informal caregivers, MDT members and the wider service system. This will be administered early in the trial and again at the end. The evaluation uses open and closed questionnaires, targeting patients and MDT members. It will evaluate the impact of the different software components and focuses on the following evaluation topics: usefulness; ease of use/usability; safety; process quality and changes and the respondents' perspective on clinical optimization.

Medical devices

In addition, medical sensor device usage and connected device usage will be evaluated with a sub-set of patients at RJH pilot site only. Patients will be individually selected from the group of intervention patients at the discretion of local clinicians. The testing serves to evaluate the technical possibility of including sensor and connected devices as part of the patient care planning.

Results

The evaluation phases 1 and 2 were completed in winter 2018. It included feedback regarding the system components, the application and the usability of the platform.

Results of phase 1:

System components testing: Each component owner checked and verified that the implemented component functionalities meet the specified requirements. The testing was documented in accordance to the IEEE 829 [CITATION IEE08 \l 1031] including a component test plan, the test design and execution procedure as well as test results presenting the test data, incident reports and a conclusion. The test team comprised experts from the component developers as well as owners of the other components.

Usability testing: C3DP mock-ups were presented first as a series of screenshots to four health ICT experts in September 2016. Between October 2016 and December 2016, clinicians and patients from the pilot sites in the Basque Country (11 MDTs and 9 patients) and Jämtland Härjedalen (4 MDTs and 12 patients) performed the tests. The pilot site in South Warwickshire performed the test in autumn 2017 (7 MDTs and 5 patients). This later version consisted of a real online demonstrator, during which testers gave direct feedback on the screen.

Results of phase 2:

For phase 2 test sessions a total of 20 MDT members and 27 patients were recruited across the three pilot sites: 6 MDTs and 2 patients in the Basque Country; 2 MDTs and 12 patients in Region Jämtland and 12 MDTs and 13 patients in South Warwickshire. Convenience sampling was applied among people with sufficient English language proficiency.

Convenience sampling was used as it has shown that specifically phase 2 was difficult to perform due to language barriers. It implies a massive increase in efforts if the system demonstrator as well as training was translated to all three languages already at an early stage. Thus it was decided to recruit test users with sufficient English language proficiency in the three pilot sites. The early usability test results obtained with the QUIS7 survey were aggregated and a descriptive analysis was provided to the software developers for subsequent improvement. The Delphi method was used to formulate overall 57 questions; 33 for MDTs and 24 for patients and informal caregivers. The results of evaluation phases 1 and 2 were published at MedInfo 2019 [CITATION Tra19 \l 1031].

The pilot testing (phase 3) was launched in July 2019. Data collection is underway and results are forthcoming. Difficulties were experiences in recruiting the envisaged trial participants, specifically with the intervention patients (Table 6).

Pilot Region	**Intervention patients**					**MDT members**	
South Warwickshire	**Approached**	**recruited**	**Consented in Nov 2019**	**Additionally expected**	**Gender distribution**	**Consented**	**Comments**
planned	70+18 +14 = 102	88	70	0	50/50	16	
actual	241	25	21	0	tbd	16	3 GPs, 2 practice nurses, 4 dieticians, 2 diabetes specialists, 5 district nurses, 1 heart failure nurse
Basque Country	**Approached**	**recruited**	**Consented in**	**Additionally**	**Gender**	**Consented**	**Comments**

			Nov 2019	expected	distribution		
planned	175+44 +35 = 254	**219**	**175**	0	50/50	16	
actual	**250**	**45**	**45**	230	tbd	12 2	67 GPs, 55 primary care nurses
Region Jämtland Härjedalen	**Approached**	**recruited**	**Consented in Nov 2019**	**Additionally expected**	**Gender distribution**	**Consented**	**Comments**
Planned	175+44 +35 = 254	**219**	**175**	0	50/50	30	
Actual	**692**	**223**	**210**	0	tbd	30	3 patients deceased during study trial delay. Another 10 patients withdrew their consent before trial start. MDTs include 20 doctors, 10 nurses
Total	610		276	230		168	-

Table 6: Number of trial participants (summary)

The technology trial protocol was submitted in several revisions to the three regional ethics committees in reflection of updates regarding project information that would be communicated to trial participants; the way of involvement of

control group patient data the recruitment procedure of for patients; trial participants training or adaptations to some questionnaires.

Evaluation results of the pilot technology trial are anticipated to become available by mid-2020.

Strengths of the approach taken are that it allows for an early feedback to the software developers for further improvement of the software before starting the technology trial with an increased number of patients and MDT members in real settings. The combination of structured and unstructured feedback from the test sessions complemented each other. However, the validity of test results may be reduced based on the dependency on test participant's fluency in the English language and the unequal distribution of test users across the pilot sites.

Discussion

Many older people suffer with more than one illness. Managing these illnesses can be very challenging for patients and healthcare service providers. In response to these challenges, the C3-Cloud project evaluation activities in phases 1-4, including a technology trial will determine whether the C3-Cloud computer system can improve the care of patients aged 55 & over who have more than one long term condition. The C3-Cloud system is designed so that patients can work more closely with their healthcare professionals to create, develop and manage their personal care plans. The platforms enable care plans to be personalised for multi-morbid conditions through systematic and semiautomatic reconciliation of digitally represented clinical guidelines. This paper has presented the research protocol of the C3-Cloud technology trial as well as the development of the C3-Cloud platforms. C3-Cloud has developed a modified impact modelling tool in phase 4 (a merged tool of the ASSIST tool and the predictive modelling), for informing integrated care management on a large scale deployment potential of systems such as C3-Cloud. Results will be published in forthcoming project publications. The number of patients and MDT members varies across the three pilot sites based on convenience sampling as participation depends fully on the commitment of the pilot site organizations. Their commitment was and is crucial to conduct the technology trial throughout the different phases.

The research design leans on the MRC guidance for complex interventions[CITATION Cra08 \l 1031]. The usefulness of complex interventions is determined also by the way they are implemented [CITATION Sot19 \l 1031]. C3-Cloud is in an early development and implementation phase and solutions need thorough testing along various dimensions to better understand the benefits of ICT in health care and to respond to the challenge of implementing complex interventions.

Much of the results will be available as open published results and to some extent as open source software for other parties to make use of. It is likely but dependent on the evaluation of the project that the present technical solutions will be offered for routine expanded use in the three pilot regions and of course also in a wider scale throughout these countries. The strong inclusion and commitment by the public health care organisations in the three regions implies that there is a strong probability of the results to be taken further after the study period transformed into routine improved health care services for this important group of patients. Trial evaluation results will become available and be published at project end (summer 2020) and report further on difficulties experiences when following the presented research protocol. Future research will include the possible reorganization of multi-professional care services for elderly patients using collaboration tool such as C3-Clouds. Also the establishment of more decision support based on clinical guidelines for other conditions than the four diseases tested in the project.

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Conflict of Interest

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Abbreviations

BC	Basque Country
BIA	Budget Impact Analysis
C3DP	Coordinated Care and Cure Delivery Platform
eCCIS	eCare client impact assessment
eCUIS	eCare user impact survey
EHR	Electronic Health Record

MDT	Multi Disciplinary Team
MRC	Medical Research Council
PEP	Patient Empowerment Platform
QUIS7	Questionnaire on User Interaction Satisfaction (7th version)
RCT	Randomised Control Trial
RJH	Region Jämtland Härjedalen
SWFT	South Warwickshire NHR Foundation Trust
UTAUT	Unified Theory of Acceptance and Use of Technology

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Inclusion diagnosis codes for patient screening

The exact diagnosis codes used in the pilot sites to screen for eligible patients are listed in the following table.

Condition	READ Codes: South Warwickshire	ICD-10 / ICD-9 Basque Country and Jämtland Härjedalen
Type II Diabetes	Type 2 Diabetes: C10F** (including all codes below in the code tree)	Diabetes = E11 Diabetes with CF= E11.2 or I13.0 Diabetes with complications = E11.8P ATC = N06A
Renal Failure with eGFR/ GFR 30 – 59 (measured or estimated glomerular fi ltration rate)	K05* (Chronic renal failure) and all codes below in the tree. 1Z1* (chronic renal impairment) (including all codes below in the code tree)	RF = N18.9 or I12.0 or I13.1 or N19 .9 or N19.-P or N18.2 to N18.5 Hypertension +RF+ CF = I13.2
Heart Failure in compliance with NYHA I-II (New York Heart Association classification of heart failure)	C58* (including all codes below in the code tree) 420300004 (NYHA Class I) and 421704003 (NYHA Class II) classification will be an individual check by a GP	CF= I50 or I11.0 Diabetes with CF= E11.2 or I13.0 Hypertension +RF+ CF = I13.2
Mild or moderate depression in adults	Anxiety with depression – include all. (Read Code: E2003) Depression NOS – include all.	Depression = F32.9 or F32.1 or F33.1

	(Read Code: Eu32z-1) Depressive episode, unspecified – include all. (Read Code: Eu32z) Endogenous depression – include all. (Read Code: E112-4) Reactive depression NOS include all. (Read Code: Eu32z-4) Chronic depression – include all. (Read Code: E2B1) Recurrent depression – include all. (Read Code: E1137) Endogenous depression – recurrent – include all. (Read Code: E113-1) Low Mood – include all. (Read Code: 1BT-1)	or F32.0 or F32- or F33-

Table : Diagnosis codes used for patient screening

Multimedia-appendix

Description	Website
C3-Cloud project website	http://c3-cloud.eu/
Project video	https://youtu.be/2lvff9kjUxo
Project short video	https://youtu.be/Y3K_lUQkupg
Surveys used in the evaluation phases	https://c3-cloud.eu/c3-cloud_surveys_09_oct_2019/