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Deliverable Type		
R	Document, report	[X]
DEM	Demonstrator, pilot, prototype	
DEC	Websites, patent fillings, videos etc.	
OTHER		
Dissemination Level		
PU	Public	[X]
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CI	Classified Information (Commission Decision 2015/444/EC)	

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1 Executive Summary

The aim of this deliverable is to introduce the CAPABLE evaluation plan, including the activities carried out both during the development of the system and those to be performed once the system is complete. Special attention is devoted to the clinical pilot study that will take place during the last year of the project. For this study, we provide a draft of the study protocols that will have to be presented to the Ethical Committees (EC) of the two hospitals where the studies will be performed.

Section 2 provides a general introduction to the CAPABLE evaluation plan, including a timeline of all the activities that will be carried out.

Section 3 presents the user experience evaluation that, following a user-centred design paradigm, will be performed during the development of the system.

Section 4 presents an overview of the technical evaluation strategy, considering all the project phases, and including also some details on the technical support that will be provided during the clinical pilot study.

Section 5 presents a description of the pilot study. First of all, a draft of the study protocol is provided, which includes the rationale for the study, the study design, inclusion and exclusion criteria, and study endpoints. In addition, we present an overview of the activities that will be performed during all the pilot phases (enrolment, follow-up, end of the study). As a third point, the draft of the protocols for the user experience (UX) study protocol is presented. Finally, the structure of the informed consent that will be delivered to the study participants at the two clinical centres is provided.

This document has been an important starting point for discussing the evaluation activities and the pilot study design. Although a consensus has already been reached among all the partners on the main points related to the clinical study, further refinements will be allowed in project years 2 and 3 to prepare the final version to be submitted to the ECs. The final protocols will be reported on deliverable D7.6 on M36. The results of the UX evaluation are the focus of task T7.2, and will be reported in deliverables D7.3-D7.5. Finally, the activities related to the technical and functional evaluation will be the main focus of task T7.4, which will start on M18.

2 Introduction to the CAPABLE evaluation plan

WP7 is devoted to the definition of the evaluation plan for the CAPABLE system and to the definition and implementation of the final clinical study. Figure 2.1 shows a timeline of the foreseen evaluation activities, which include technical, UX and clinical evaluation. Thanks to the user-centred design approach chosen by the project consortium, the evaluation activities start at the beginning of the second year, and go on until the end of the project.

The evaluation activities will be divided into two phases:

- Phase1: carried out while the system is under development (M12-M36)
- Phase 2: carried out when the system is complete (M36-M48)

During Phase 1, the focus of the validation activities will be on testing and UX evaluation. Testing is aimed at fixing possible bugs and improving the system from the technical and functional point of view. UX evaluation will be guided by the development of different functional prototypes. This phase will involve users such as patients, clinicians, experts on the development of decision support systems, and the developers of CAPABLE. The last part of Phase 1 will be referred to as *Pre-Pilot* and will be conducted using a beta version of the final system, which will be used by healthy volunteers in order to make the final adjustments before the real clinical study.
Phase 2 will be referred to as *Pilot*, and it is the evaluation of the final version of the system deployed at the clinical centres that take part in the project. During this phase, we will perform a clinical study on patients and a study on the functional and technical performance of the system.
The aim of this deliverable is to introduce the overall evaluation plan, and propose a draft of the study protocols that will be submitted to the hospitals Ethical Committees in year 3 for the clinical study and the UX evaluation study.

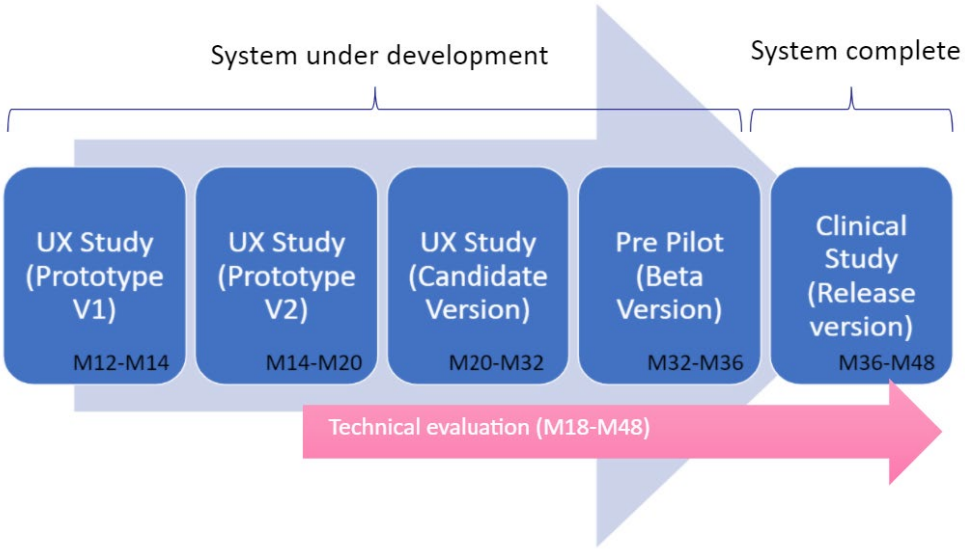

Figure 2.1 CAPABLE evaluation activities timeline

3 User experience evaluation during the development of the system

This chapter details the user experience evaluation that will be conducted during the design and development of the system (Phase 1). This type of evaluation is a broad concept that aims to assess the overall interaction as “consequence of the presentation, functionality, system performance, interactive behaviour, and assistive capabilities of the interactive system” [1]. User experience is a complex construct that encompasses more classical approaches based on the

Technology Acceptance Model (TAM) [2] in which utility and usability are key components that are basic enablers for the adoption of a technology extended with the desirability of the product and the overall experience using the product. The following figure shows the relationship among these concepts.

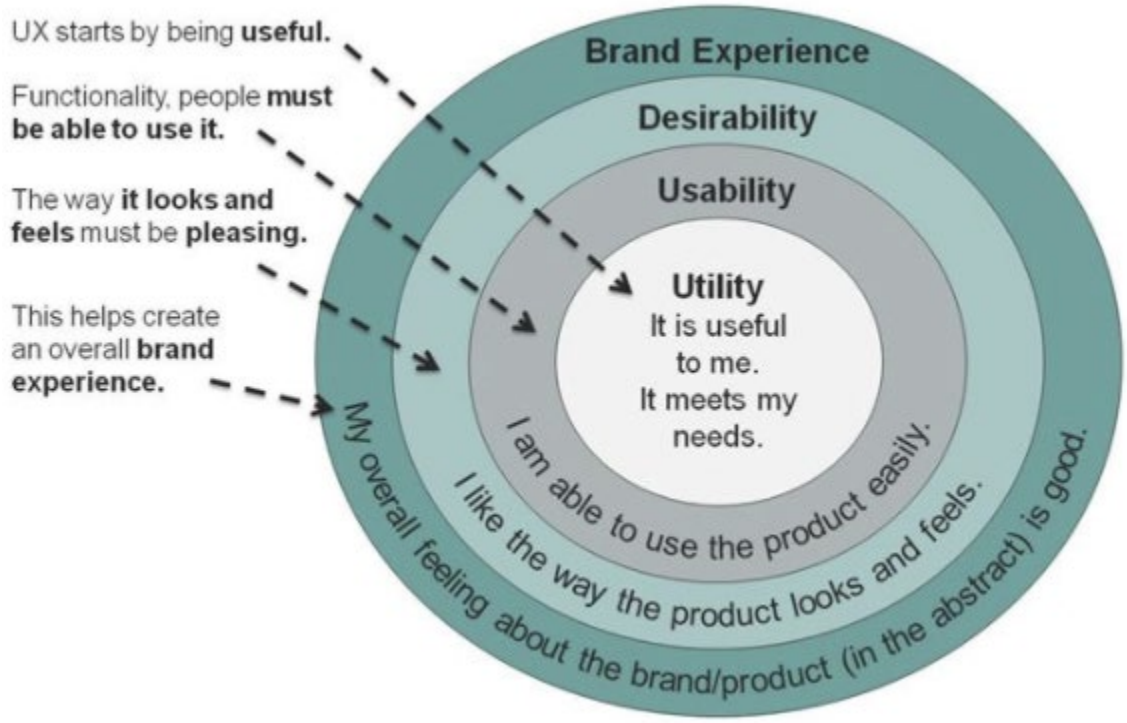

Figure 3.0. The UX and its relationship to the concepts of the TAM model (*http://www.neospot.se/usability-vs-user-experience/*)

The project adopted a user-centred design approach [3] and according to this, it is crucial to periodically assess the overall solution to check if the solution meets the user requirements and if it is easy and understandable for the users. The following subsections detail the process of validation that has been defined for this project.

3.1 Flowchart of the UX evaluation process

The Consortium plans to perform, during Phase 1, three periodic validations that incrementally assess the proposed solution to health professionals and patients. The overall process will include three types of participants and it will be performed three times in accordance with the three versions of the prototype that will be developed (V1, V2 and Candidate Version, namely CV).

- User interaction experts and professionals (researchers, engineers, designers) working in the domain of digital technologies: this group is the first one that will assess the system using specific domain methods. They will assess the solution for patients and health professionals.
- Health professionals: they will participate in this activity to assess if the overall solution covers the clinical needs; they will also inspect the health professional solution and the patient one.
- Cancer patients in treatment and post treatment will assess the overall CAPABLE concept and they will provide feedback on the functionalities proposed for the Patient App.

The following figure sketches the proposed process of iterative validation.

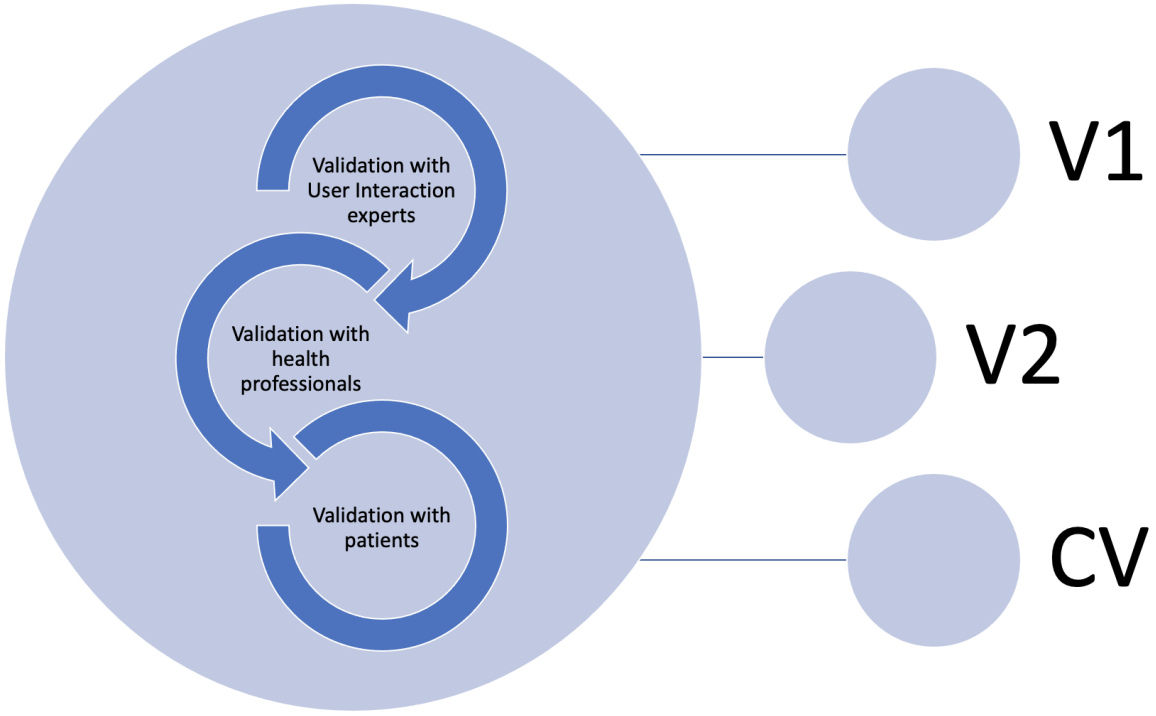

Figure 3.1 The iterative UX validation process, followed in Phase 1.

The next section details the protocols and the instruments that will be used to perform the overall validation of the user experience.

3.2 Draft of Protocols for user experience evaluation

In order to perform the validation with the three proposed groups (experts, health professionals and patients) the following approaches are proposed.

Three methods can be applied:
Heuristic validation of the user experience and usability performed by user Interaction experts. Three partners (UPM, UNIPV and UoH) will inspect the developed prototypes and will report the violations of the heuristic principles. A total of 10 participants will provide feedback on the CAPABLE solutions. The work will be done leveraging the collaborative functionalities of invisionapp (https://www.invisionapp.com/) (participants can put some notes on the Graphical User Interface).

Interviews with healthcare professionals (HCPs) and experts in digital health. This interview aims to collect overall feedback of the overall solution, understand if the clinical and patients needs are covered. Table 3.2.1 details the types of information that will be gathered.

Table 3.2.1 Information regarding the HCP and Patient UXs that will be gathered in HCPs interviews

Type of data	Description
Profile of the HCP participant/expert in digital health	Age, profession, educational background and experience in health domain, knowledge of health technology
Overall concept	Qualitative feedback on the overall CAPABLE concept and of the high level functionalities
Feedback on specific CAPABLE functionalities (Web portal)	Qualitative observation of the participant while using the prototype, performing a specific set of tasks. Techniques: Unobtrusive observation of performed tasks, Think aloud. Quantitative information: score of easiness and usefulness, time to complete the task.
Feedback on specific CAPABLE functionalities (App)	Qualitative observation of the participant while using the prototype, performing a specific set of tasks. Techniques: Unobtrusive observation of performed tasks, Loud thinking. Quantitative information: score of easiness and usefulness, time to complete the task.
Perceived usefulness and acceptance	Quantitative scale (Likert scale) on perceived utility and acceptance of the solutions to be used in the clinical practice
Missing features	Qualitative information on missing features
Usability	System Usability Scale
Barriers	Qualitative feedback on possible barriers for successful deployment and for the execution of a clinical study

Interviews with patients. This interview aims to collect feedback from the end users of the Patient App: Melanoma and Kidney cancer patients during the treatment phase. For this validation, other types of cancer patients may be included, cancer survivors (treatment finished since no more than 2 years) or experts in patients needs, such as a cancer patient association (AIMAC). Table 3.2.2 describes the information that will be collected during the interview with patients.

Table 3.2.2 Information regarding the Patient UXs that will be gathered in interviews with cancer patients or with experts in patient needs

Type of data	**Description**
Patient participant profile	Type of cancer, stage of disease, age, gender, use of Smartphone, Internet technology, lifestyle profile
Overall concept	Qualitative feedback on the overall CAPABLE concept and on the high level functionalities
Feedback on specific CAPABLE functionalities (App)	Qualitative observation of the participant while using the prototype, performing a specific set of tasks. Techniques: Unobtrusive observation of performed tasks, Think aloud. Quantitative information: score of easiness and usefulness, time to complete the task.
Perceived usefulness and acceptance	Quantitative scale (Likert scale) on perceived utility and acceptance of the solutions to be used daily. Compatibility with user's expectations and daily routine.
Missing features	Qualitative information on missing features
Perceived care improvement	Perceived possible improvements of the level of care
Usability	System Usability Scale

Adaptation to social distancing for the COVID-19 pandemic

The best way to perform these types of validation activities is via face-to-face interviews. Due to the current pandemic, WP7 designed a contingency plan to be able to perform these interviews online, to grant social distancing and ensure the participants' safety. To do so, the following digital tools will be used:

- Email: as an official channel of communication in which users will receive invitations, informed consent. This tool will also be used to gather consent for the participation in the study
- Online Video Conference system (using anonymous link, not personal accounts. Zoom, Webex). The study will use the video conference, the recording and the sharing screen functionalities.
- Online prototype viewer, namely INVISIONAPP (https://www.invisionapp.com/) service provided by BITSENS to access the prototype. This will be used for the early stages of the prototype (V1 and partially V2)
- Screen sharing tools for mobile, in order to be able to share the patient APP via the teleconference system. (e.g. screen mirror app)
- Tools to manually insert collected data (Excel, Limesurvey)

Prerequisite: The participant will receive an official invitation message and they will provide a digital confirmation (via mail) to accept the interview. The user will receive back a scheduled appointment.

Inclusion criteria:
Apart from the types of participants (user interaction experts, domain experts, patients, health professionals) there is a technical requisite to be able to participate in the online interviews using a laptop or a PC and being able to join a teleconference meeting and share the screen. This is crucial in order to inspect the usability of the system and being able to observe how the users will use the system.

Type of interview: scheduled teleconference with shared screen, at the beginning of the interview the presenter will share a presentation of the Capable concept, then the participant will share the screen to show to the presenter the usage of the prototype.

Other possible approaches
In case that there are difficulties with the use of the shared screen and with arranging appointments with the participants, it will be possible to create an online survey that contains a simplification of the described protocol. This is a less effective method most oriented to get more quantitative information.
Furthermore, as soon as the pandemic will fade out and it will be possible to arrange a face-to-face meeting, the validation could optionally be carried out non-remotely.

3.3 Data management policy

WP7 will prepare a specific informed consent for the studies. The informed consent will state that personal data (Name, Surname and email) will be managed by the interviewer that will be responsible to securely store this data and forbid unauthorized accesses. The data controller of

this data will be the Universidad Politécnica de Madrid (UPM). For the case of the patients, since patients will be selected by the health professionals, they also will have access to this information. This data will be gathered only for the scope of the interview. The other data collection sheets (that will leverage on online survey platforms or Excel tools) will be completely anonymous. Furthermore the online interview will be also recorded. Once the data from the interview has been compiled and anonymized the personal data will be deleted permanently.

4 Technical Evaluation

Technical evaluation includes testing that the different components of the CAPABLE system as well as the system as a whole, are functioning correctly. This will be done by the components' developers and by volunteers, who would use the system in the *Pre-pilot* phase to screen it for errors so that it could be improved and ready for the pilot phase.

4.1 During development

Two specific task forces (TF), involving mainly WP3, WP4, WP5 and WP6, guide the technical development process of the CAPABLE system. TF1, which started on Month 1, is dedicated to defining the overall CAPABLE system architecture, the general principles to be followed when designing and implementing its components, and system iterations to deliver a pilot-ready system at M36, when the pilot studies are planned to start. On the other hand, the activities of TF2, which started on Month 6, are dedicated to a shorter time horizon. TF2 coordinates, in close collaboration with TF1, all the technical efforts directed to delivering system proofs of concept (PoCs), and connected demonstrations/presentation according to the project plan.

In this high-level framework, coordination and planning of the development efforts is provided by TF1 and TF2, while single component development is handled by the relevant consortium partner. TF1 and TF2, considering the inputs of the requirements elicited in WP2, define detailed use-cases and scenarios to drive implementation at each development iteration. TF2 and TF1 meetings have been scheduled periodically every 2 weeks, since the inception of the task forces. In the first year of the project, since July 1, 2020, TF2 meetings have focused on delivering a functional and robust M12 demonstrator, as per project planning. TF2 meetings have been the main venue for presenting updates on components development, support for use-cases and the agreed demonstration scenario (see D4.1) and integration testing among different components.
Single components developers have successfully been coordinated and achieved a successful first demonstration of the 1st CAPABLE PoC at M12, during the 3rd consortium meeting taking place on 2nd Dec 2020.
Technical issues resolution, unit testing, integration testing and debugging, has been carried out in a TF2 internal iterative development process according to the roadmap described in D4.1. Feedback from the consortium potential users, including oncologists and patient representatives,

as well as the project Scientific Advisory Board (SAB) has been collected during the 3rd CM, and will drive system development beyond M12.

4.2 During *Pre-pilot*

Once the development of the system will be complete, specific evaluation activities are planned for ensuring the correct functioning of pivotal parts of the system. Following the functional test, evaluation with users and stakeholders will also be employed as user-acceptance questionnaires, conducted in collaboration with relevant users of CAPABLE partner organizations (e.g. patient representatives from AIMAC, physicians and nurses from ICSM and NKI) (see Section 3).
Details on specific activities to be performed in this phase will be provided in subsequent deliverables of WP7, as we approach the *Pre-pilot*. For the sake of clarity and appropriate planning, here in D7.1, we provide below some high-level examples.

- PROforma Clinical Guideline Engine/GoCom/Virtual Coach will be tested on the basis of testing scenarios agreed upon at project level (e.g. in TF1/TF2)
- Data Platform and Case manager will also be (indirectly) tested through the same scenarios.
- UX with the user-interfacing components will also undergo extensive evaluation, according to the details provided in Section 6.
- Export of data from the hospital electronic health record (EHR) into the CAPABLE system will be tested using fabricated patients, so that no personal and/or sensitive data would be exposed at this stage, but in the same way that would later be used for production-level testing at NKI and ICSM.

To coordinate the evaluation activities by volunteers during the *Pre-pilot*, a set of iterative steps are planned:

1. Each volunteer uses the system
2. Every time an error, an unexpected behaviour or a perceived missing functionality is detected, this issue must be reported (see next paragraph)
3. The technical partner(s) in charge of addressing the issue takes care of it, performing restricted meetings if necessary
4. A new release of the involved component(s) is prepared and harmonized in a new version of the system
5. New versions are installed on the smartphones or deployed in the deployment environments. All volunteers are notified that an update has been performed together with the details of the changes that were made in the new release.
6. During periodical WP7/TF1 telcos, all the points are revised and open issues are discussed

To manage Step 2), we will define a template to allow efficient bug reporting and communication. Alternatively, a more structured bug-tracking/service ticketing solution will be evaluated, and

eventually adopted if the analysis shows that it can substantially improve the way the consortium can address technical issues in a timely and efficient manner. All the partners will have access to the shared list of reported issues, that will be checked and updated on a daily basis during the *Pre-pilot* phase. In particular, each technical partner is responsible for identifying the issues related to its specific component(s), and providing a solution or mitigate them.
The minimal structure of the bug-reporting template should include the following:

- Date: the date when the issue was found
- Domain: Renal Cell Cancer or Melanoma
- User: the volunteer who detected the issue
- App: interface app where the issue was detected (physician app or patient app)
- Issue: description of the behaviour that generated the issue
- Context: all the contextual information that might help in reproducing/debugging the issue. E.g. action that was being performed, immediately previous action, selected test patient, etc.
- Blocking issue (yes/no): if the issue prevents continuing the normal usage of the system
- Comment: comment or possible solution of the technical partner who is in charge of fixing the issue

Since CAPABLE is a complex system, the management of a single issue may require working on more than one component. As a consequence, step 3) requires the coordination of different partners.

4.3 During the clinical study

Detailed logging of component- and system-level activities will be enforced during the clinical study. To achieve this, the following log records will be maintained by each component and shared at the consortium level:

To analyse user interactions

- Physician web-app
- Patient smartphone app

To analyse technical performance (internal processes, interaction among components, technical error analysis)

- Physician web-app
- Patient smartphone app
- Case Manager
- Data Platform
- Virtual Coach
- PROforma Guideline Engine
- KDOM
- GoCom

The log track record has been agreed upon at project-wide level as an integral part of WP7 activities. The following minimal set of information will be included in each instance of a logged event:

1. Date of the action
2. Logged in user/owner component
3. Type of action
4. CAPABLE ID of the target patient/recipient component
5. Feedback on the performed action

This commonly agreed log-structure will enable log analysis at a system-wise (as opposed to a component-level) scale, allowing to draw conclusions that may be relevant for WP7 too.

An example log record, In the case of user interactions through the Physician app, is provided here:

1. *06/11/2020 16:45:20*
2. *physician1*
3. *newpatient_enrolled*
4. *CAPABLE001*
5. *OK*

Furthermore, an example log for the interaction among components (technical performance log) is presented here:

1. *06/11/2020 16:45:21*
2. *Case_Manager*
3. *newpatient_enrolled*
4. *Virtual_Coach*
5. *Fail: component not available*

4.4 Technical support during the clinical study

During the pilot study, a bug-tracking/issue reporting solution similar to the one employed in the *Pre-pilot* will be implemented.
In addition, in order to provide support to patients and physicians participating in the study, a two-level technical support chain has been defined. The general structure of this chain is shown in Figure 4.4.1.

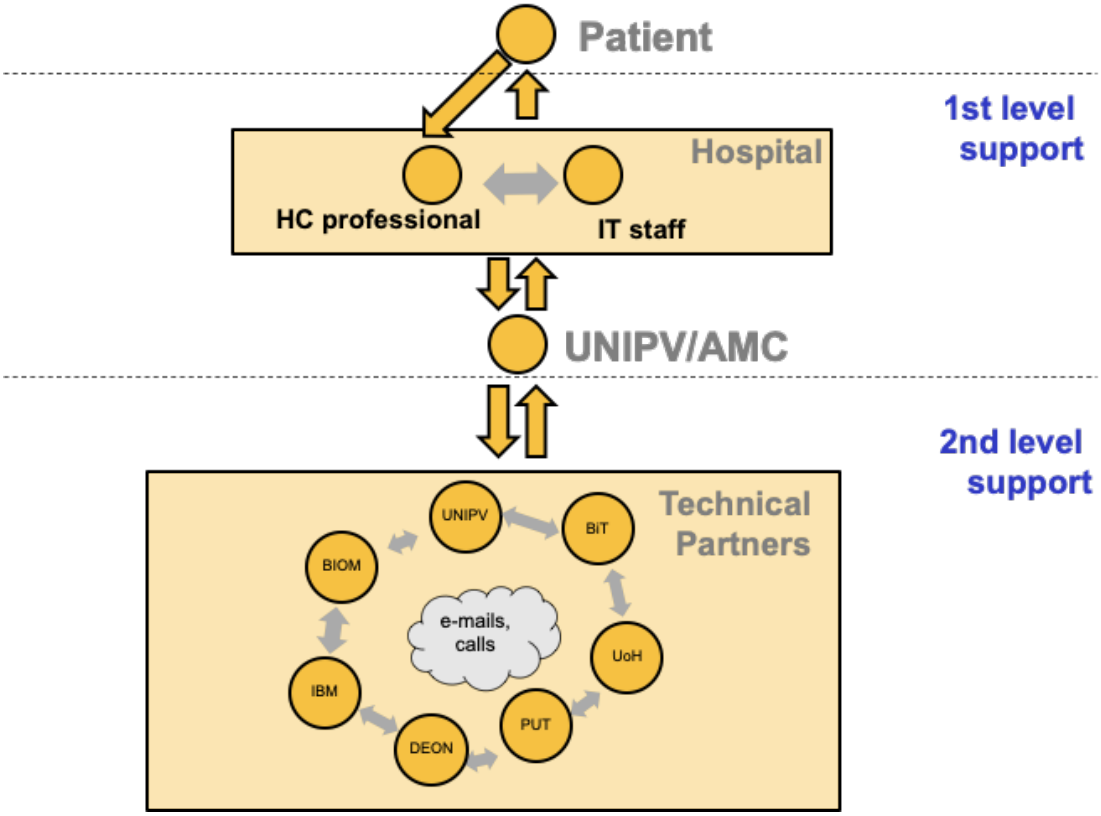

Figure 4.4.1. Technical support chain for the clinical study. UNIPV will manage escalation of issues to 2nd level support for the ICSM site, while AMC will do the same for the NKI site.

The main idea is to provide the patient with a single point of contact in case he/she is experiencing technical difficulties or issues. The simplest solution is that the patient contacts the physicians and nurses at the hospital. In case the problem of the patient is of technical nature, and not manageable at the 1st support level, physicians and nurses with the help of the Information Technology (IT) staff at the hospital contact the CAPABLE technical partner that works in closest contact with the hospital (i.e. UNIPV for ICSM and AMC for NKI). It is a UNIPV/AMC task to understand the issue and to bring it to the attention of the appropriate technical partner(s). This represents the first level of support. At the second level of support, all the technical partners are involved in an iterative process, coordinated by WP7 and implementation WPs, similar to the one described for the *Pre-pilot* phase. In particular:

1. First level support reports the issue
2. The technical partner(s) in charge of the issue manages/solves it
3. A new release of the component(s) is prepared and harmonized in a new version of the system. This is done in the effort of bundling several fixes in a single update and minimizing the need for too frequent updates.
4. The patient app is updated on the *Pre-pilot* smartphones and backend components are deployed in the *Pre-pilot* test environment
5. The issue is addressed/mitigated/solved

6. All the technical partners, clinicians and IT staff are notified
7. The new version is propagated from the test environment to the production environment of the pilot studies.

The main difference with respect to the *Pre-pilot* phase process is that in the pilot phase, before installing on patient smartphones and deploying a new version of the backend components, several tests are performed using fabricated patients in the *Pre-pilot* dedicated environment and smartphones. This is to ensure, with proper confidence, soundness and robustness of the new version before rolling it out to real patients and clinician users.

5 Pilot Study

5.1 Rationale and Motivation

Melanoma and immunotherapy

The European incidence of malignant melanoma varies from 3–5/100000 in Mediterranean countries to 12–35/100000 in Nordic countries. The incidence of melanoma has been rising steadily over the last 40 years [4, 5]. In recent years, the introduction of immunotherapy with immune checkpoint-inhibitors (ICIs) have significantly improved the outcome of melanoma patients and have become standard of care [6, 7]. However, immunotherapy treatment is associated with specific immune-related adverse events (irAEs). irAEs possibly result in a diminished health-related quality of life (HRQoL) [7]. With immunotherapy becoming standard care in advanced melanoma patients, an increasing number of patients experience symptoms of irAEs, most commonly occurring in skin, liver, gastrointestinal, pulmonary and endocrine organs [6, 7]. Inadequate symptom monitoring and reporting might lead to worsening of the adverse events and also more frequent emergency department visits and hospital admissions [8, 9].

Renal Cell Carcinoma treatments

Kidney cancer accounts for 5% and 3% of all adult malignancies in males and females, respectively, representing the seventh most common cancer in men, and the tenth in women [10], corresponding to about 400000 patients globally each year, and 115000 patients in Europe. Renal Cell Carcinoma (RCC) accounts for about 80% of all kidney cancers.

Tyrosine kinase inhibitors targeting vascular endothelial growth factor receptors (VEGFRs) have been the first-line standard of care for the last decade [11]; however, almost all patients acquire resistance over time. The recent introduction of immune checkpoint inhibitors has further improved the outcome of those patients. Presently, the monoclonal antibody Nivolumab, and its immune combination with the Ipilimumab have been registered for use in patients refractory to VEGFR-targeting agents as well as in the first line treatment of patients with poor or intermediate risk features. Furthermore, combination of immune checkpoint inhibitors with anti-VEGFR agents [12, 13] are emerging as novel treatment options. Immune checkpoint inhibitors have a specific toxicity profile which is challenging the historical oncologists' practices. Indeed, the clinical management of these often ill-defined irAEs is new to many oncologists. Moreover, despite most

of them remaining mild in intensity, around 10% of patients treated with these agents will develop severe, sometimes life-threatening, dysimmune toxicities [14].

Electronic symptom monitoring during cancer treatment

The referral of patients developing immunotherapy-related toxicities, together with their prompt and aggressive treatment is thus mandatory to maximize the likelihood of both resolving these adverse events, as well as safely continuing the anticancer treatment. The collaboration of patients, who must be informed of the need of referring any unusual sign or symptom to their oncologist, is thus crucial, as it is an instrument which could help the patients in this matter.

An approach to improve symptom control can be the collection of symptom information through patient-reported outcome measures (PROMs) [15, 16]. Furthermore, symptom self-reporting and monitoring is associated with improved clinical outcomes [17]. Moreover, several web-based monitoring systems have also been shown to intensify symptom management, improve symptom control [18, 19] and improve overall survival [20]. Besides, web-based tools have other advantages, such as showing insight in the course of symptoms, availability of information about follow-up appointments, personalized advice and tailored supportive care [21].

In more detail, Basch et al. [17] were one of the first to provide evidence for the impact on clinical outcomes using symptom monitoring during routine cancer care using PROs. This study, carried out in New York, randomly assigned patients receiving routine outpatient chemotherapy for advanced solid tumours to report 12 common symptoms via tablet computers in one arm, compared to receiving usual care consisting of symptom monitoring by clinicians in the other arm. Among 766 patients allocated, HRQoL improved among more participants in the intervention group than usual care (34% v 18%) and worsened among fewer (38% v 53%; P=0.001). Overall, mean HRQoL declined by less in the intervention group than usual care (1.4- v 7.1-point drop; P=0.001). Patients receiving intervention were less frequently admitted to the Emergency Room (ER) (34% v 41%; P = 0.02) or hospitalized (45% v 49%; P = 0.08) and remained on chemotherapy longer (mean, 8.2 v 6.3 months; P = 0.002). Benefits were greater for participants lacking prior computer experience. Most patients receiving intervention (63%) reported severe symptoms during the study [17].

Moreover, a study following the previously documented results, performed by Denis et al. gave evidence for improved overall survival (OS) when using a web-mediated follow-up algorithm based on self-reported symptoms, due to early relapse detection and better performance status at relapse. This study was carried out within French advanced-stage lung cancer patients without evidence of disease progression after or during initial treatment. Patients were randomly assigned to compare a web-mediated follow-up algorithm in one arm, based on weekly self-scored patient symptoms, with routine follow-up with CT scans scheduled every three to six months according to the disease stage in the other arm. In total, 121 patients analysed by intention -to-treat analysis. The median OS was 19.0 months in the experimental and 12.0 months in the control arm. The performance status at first detected relapse was 0 to 1 for 75.9% of the patients in the experimental arm and for 32.5% of those in the control arm (two-sided P < 0.001). Optimal treatment was initiated in 72.4% of the patients in the experimental arm and in 32.5% of those in the control arm (two-sided P < 0.001) [17].

In short, the most convincing data for web-based applications monitoring cancer patients, exist on patients receiving chemotherapy or undergoing follow-up for lung cancer [17, 20]. Less is known about monitoring symptoms related to immunotherapy treatment, and very little research

has been done into monitoring subsets of patients receiving immunotherapy, for example advanced melanoma or RCC patients. Furthermore, there is a lack of reporting well-being and HRQoL of cancer patients in web-based applications [22].

Iivanainen et al. (Kaiku Health) carried out the first investigating study about ePROs in the follow-up of cancer patients receiving immune checkpoint inhibitor therapies [23]. Kaiku Health ePRO tool is a web-based solution scaled to be used fluently in smartphones and home computers. Kaiku Health IO module developed by Kaiku Health consists of 18 questions. The symptoms selected for the Kaiku Health symptom-tracking tool for cancer immunotherapy are based on the most common adverse events that have occurred during clinical trials of anti-PD-1 (anti - Programmed death 1), anti-PD-L1 (anti - Programmed death ligand 1), and anti-CTLA4 (anti - Cytotoxic T-lymphocyte associated antigen 4) monotherapies. The symptom selection is based on the reported publications of clinical trials and Food and Drug Administration (FDA) labels for Nivolumab, Pembrolizumab, and Atezolizumab. The questions for each symptom in the instrument were developed based on National Cancer Institute-CTCAE (NCI-CTCAE) v.4.03 register by converting the description of gradings into a patient-friendly language. QoL was captured with electronic QLQ-C30-questionnaire included in the Kaiku ePRO module. Adherence to symptom monitoring was high, while the answering rate to QoL questionnaires was much lower compared to symptom reporting rate. Results of this study show that ePRO follow-up of cancer patients treated with immune checkpoint inhibitors is feasible. The symptom variety, incidence, and grading collected with ePRO questionnaire from real-world patients mimics what has been reported in anti-PD-(L)1- trials making the results clinically convincing. This study did however not compare to standard care and therefore did not elaborate on clinical outcomes such as hospitalization, overall survival, differences in symptom severity or others mentioned in the trials of Basch et al. [17] and Denis et al. [20].

Regardless of study outcomes described above, a recently published study of Tolstrup et al. did not show reduction of irAEs by actively involving Danish advanced melanoma patients in the reporting of symptoms using an electronic PRO tool compared to standard care. However, they could not exclude the positive impact of this tool on other endpoints such as HRQoL. Their study examined if the number of severe irAEs for Danish melanoma patients receiving immunotherapy could be reduced by involving the patients in the reporting of symptoms. The results do not justify the expansion of the pilot study into a regular phase III study with this particular set-up. However, a significant difference in the number of phone contacts was found as patients in the intervention group called more frequently, indicating that their attention to AEs was increased [24].

Contradictory evidence is found in the studies described [17, 20, 23, 24]. First, this can be due to the fact that the healthcare system in Europe is different from the healthcare system in the United States. Herewith, Tolstrop et al. might reflect better on the healthcare provided in The Netherlands and Italy (health monitoring is performed during treatment) and this has to be kept in mind while doing the CAPABLE trial. Second, consistency in reporting immunotherapy related toxicities has not been found yet and no validated questionnaires are present regarding this matter. Studies so far have only focused on reporting chemotherapy-related adverse events. Third, little to no research into electronic symptom monitoring in advanced melanoma patients has been done before and differences between countries may arise in future studies. We therefore still believe more research into electronic follow up of (melanoma and RCC) patients receiving immunotherapy is necessary.

In the panorama of the eHealth tools for the care of patients affected by cancer [25, 26, 27], the ones who suffer from metastatic renal cell carcinoma or kidney cancer in general are quite neglected.

There are of course apps that are built for the general cancer population [25], but very few specific eHealth tools are available.
In the literature there is only a very preliminary study that targets this population [28] with tools developed with the collaboration of an hospital team. The study was conducted on only two patients and concludes that more research is needed following the promising results. The research is instead still focused on the best treatment options for the patients [29, 30, 31]. There are few commercial tools available online [32, 33], but they all lack peer review studies that show their effectiveness in the care of the kidney cancer population. They lack the most in the involvement of the caregiver. The caregiver is a very important role for our patients, in general and in particular for our project, since our population is quite old and may need some help with eHealth tools [34].

The most rated app for our needs according to [33] is “Kidney cancer management” app, available in the Google play store [35]. The app has a Mobile Application Rating Scale (MARS) score of 4.6 out of 5, and it is well rated in the store too.

“Kidney cancer management” app is developed by Point of care [36], an US based company that wants to take care of the health of patients affected by different diseases with a series of specific tools and apps. Their tools share some similarities with our project.

In the app for the patient, he can register his adherence to the treatment, symptoms, adverse events, mood, vital signs, medications, and appointments; it also presents a big educational section. A community section for talking with other patients is included too.

In the clinician’s interface he can see what was reported by the patient and there is a collection of the most updated guidelines and literature resources.

Both tools have a user-friendly interface that includes data analysis and graphics to monitor the wellbeing of the patient in a simple way. Their apps are targeted for the US market.

Online it is available another app developed by Pfizer, specifically addressed to patients who are treated with their Sutent® (Sunitinib) in the United States. It tackles adherence to the treatment, symptoms, medical appointments, reminders and it creates reports that can be emailed to the clinicians.

The app we want to develop combines the best of the eHealth tools already available while also tackling the aspects not considered before, like a role for the caregiver and active methods to improve the wellbeing, also from the psychological point of view. The results will be also available to the scientific community.

Preliminary study results of information needs and user requirements for CAPABLE

As a result of the literature review presented in the previous paragraphs, in WP2 we initiated a study in our patient population at NKI-AVL and ICSM about their intended needs and usage of an eHealth tool (CAPABLE). Preliminary results are detailed in deliverable D2.1, and show four main findings. First, patients tend to feel more secure when having such app due to distant monitoring.

Patients therefore have the feeling a doctor is always watching them. Second, and supporting the first finding, patients feel the app is more low-key. Patients usually feel very insecure to call the hospital while having a complaint. They do not want to disturb the doctor if the complaint is not severe enough, and therefore patients tend to make the decision not to call while in fact having an adverse event of immunotherapy. Third, patients feel they are more empowered by being autonomous and self-manage their disease when using such an app. Patients feel the need of being able "to do something" themselves, outside of being just a patient. They want to be in control about what they can do themselves to improve their quality of life and treatment progress. Lastly, patients experience insecurity in what to expect during their treatment and after. They feel a lot of information is missing there and questions cannot be answered properly. Need for experiences from fellow patients is necessary.

These study results might suggest that with the implementation of an eHealth tool symptoms can be discovered in an early stage and could prevent hospitalization resulting from calling a doctor too late. Furthermore, when providing an app that covers unmet needs and requirements, slight changes in HRQoL might be expected. Patients' self-management, secureness, empowerment and functioning domains might increase, whereas declines in HRQoL symptom scales might be expected. This study provided evidence that advanced cancer patients treated with ICIs have unmet and continuing needs for a self-management system. A web-based system like CAPABLE is needed to meet their information needs and to be able to be autonomous apart from their disease. When developing this app we might be able to learn from an already existing app that patients use as support nowadays at NKI-AVL, called UnTire. Results of a clinical trial in which this app is studied have not yet been published, but this app is believed to reduce cancer-related fatigue by supporting the patient in domains like worrying, relaxation and nutrition.

5.2 Draft of the clinical pilot study protocols

Objectives

By carrying out this study, we want to generate evidence on the effect of 'a systematic web-based collection of patient-reported symptoms and mobile coaching system (CAPABLE)' on health-related quality of life outcomes, and the number and severity of therapy-related toxicity in melanoma and metastatic renal cell carcinoma (mRCC) patients treated with systemic therapy. Moreover, we will measure the effect of CAPABLE on the number of emergency visits and hospitalizations, referrals to additional care (*e.g.,* psychosocial support) and fulfilment of information needs/self-management. We will do so by carrying out a clinical pilot trial. This will be a prospective experimental cohort study with patients receiving the CAPABLE app throughout their systemic treatment, and one prospective cohort study with patients receiving standard care (without CAPABLE app).

Study design

This is a prospectively enrolling, multicentre quasi-experimental cohort study in melanoma and mRCC patients, eligible for undergoing systemic treatment in The Netherlands and Italy. The quasi-experimental cohort receives the CAPABLE smartphone application and a multi-sensorial smartwatch throughout their treatment. Outcomes of this study will be compared with two historical cohorts consisting of melanoma (The Netherlands) and mRCC patients (Italy) with the same features, but receiving standard care. Study outcomes will be obtained via questionnaires

and clinical data will be extracted from the EHR and compared to the same variables in the historical cohort, to identify the impact of the CAPABLE app on patient reported outcomes and on health service outcomes. Questionnaires will be administered to the patients through the CAPABLE application on baseline and every three months. The minimum follow-up of included patients will be 6 months.

Inclusion/Exclusion Criteria

General inclusion and exclusion criteria

Inclusion criteria:

- Adults ≥ 18 years of age
- Sufficient understanding of the language spoken at the clinical centre where the pilot is carried out (Italian/Dutch/English)
- Participants or their caregiver can use a smartphone (upon patient's consent)

Exclusion criteria:

- Recruitment and consent denial
- Capable of understanding and complying with the protocol requirements (including basic technological abilities) and must have signed the informed consent document.

The patients have the right to withdraw from the study at any time, without giving an explanation and without prejudice to their subsequent care.

Renal cell carcinoma

Inclusion criteria

Patients that suffer from kidney cancer must meet the criteria listed below to be eligible for the project :

- Histologically or cytologically confirmed advanced RCC (at least one measurable neoplastic lesion as defined by Response Evaluation Criteria In Solid Tumors-RECIST-version 1.1) indicated to be treated with systemic treatment (targeted agents, immune checkpoint inhibitors, or a combination of the two)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 at the start of the treatment.

Exclusion criteria

In the following, we list the criteria that cause the exclusion of patients from the treatment, and consequently from the CAPABLE clinical pilot study.

- Has a history of substance abuse or medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.

Melanoma

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria (in addition to the criteria he met to be included in the treatment protocol):

- Histologically confirmed melanoma (high-risk (resectable stage III) and advanced (stage IV and unresectable stage III)) patients indicated to receive treatment with immune checkpoint-inhibitors, according to the clinical guidelines.

Exclusion criteria

A potential subject who meets the following criteria will be excluded from participation in this study:

- Inclusion in experimental clinical trials.

Sample size

Historical cohorts:

Around 100 new patients will be eligible for this study per year in the NKI. With a 1.5-year inclusion period, an expected response rate of 70% and possible inclusion in other experimental clinical trials, which would exclude the participation in the CAPABLE study, we expect a total of 100 patients to participate in this study. As this is an explorative study, no sample size calculation was performed. Inclusion starts in Q1, 2021.

Experimental cohort:

In the experimental cohort we want to start inclusion in Q1, 2023. Follow-up needs to be at least 6 months and end-of-study is expected at the end of 2023. The inclusion period will therefore take up to Month 6, 2023. An expected 100 patients will be eligible for participation and with an expected response rate of 70% and not fulfilling the inclusion criteria, we want to include 30-40 patients in the experimental cohort per centre. As this is an explorative pilot study, no sample size calculation was performed.

Methods

Study parameters/endpoints

Primary and secondary study outcomes will be collected through questionnaires. Description of the questionnaires is further elucidated below. All questionnaires will be administered every 3 months. Adverse event monitoring will be done weekly.

Main study parameter/endpoint

The main study parameter is the difference in mean outcome over time of The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core 30 (EORTC QLQ-C30) between this experimental cohort and the historical cohort, after adjustment for the baseline values. The EORTC QLQ-C30 is a self-reported questionnaire, specifically developed for patients with cancer who are receiving cancer treatment. The EORTC-QLQ- C30 is widely accepted and validated in clinical studies and is the most common quality of life

instrument used in melanoma studies. [37, 38]

Secondary study parameters/endpoints

Secondary study parameters include outcomes of other questionnaires regarding the number and grading of adverse events, anxiety and depression, fear of cancer recurrence, melanoma-specific HRQoL, symptoms of immunotherapy; and work ability in high risk and advanced melanoma patients treated with immune checkpoint-inhibitors.

- Adverse events from immunotherapy (toxicity) will be monitored using an immunotherapy-specific (Patient-Reported Outcomes -) Common Terminology Criteria for Adverse Events ((PRO-)CTCAE) questionnaire. Patients self-report their toxicity, after a scoring algorithm calculates the PRO-CTCAE grade to a CTC-AE grade.
- The EuroQoL-5D (EQ-5D-5L). The EQ-5D is a standardized 5-level, 5-dimensional multi-attribute utility questionnaire that measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression, using a 5 dimension scale. [39] This questionnaire can be used for cost-effectiveness analysis since Quality-Adjusted Life Years (QALY's) can be calculated.
- In the NKI, a melanoma-specific questionnaire will be used, namely the Functional Assessment of Cancer Therapy – Melanoma (FACT-M). Of the FACT-M, we use the Melanoma Subscale and the Melanoma Surgery Subscale. High scores show a high quality of life. Testing has shown that the FACT-M is a reliable and valid instrument to assess quality of life in patients with melanoma. [40,41]
- The Cancer Worry Scale (CWS) is a questionnaire that assesses the fear of cancer recurrence. [42, 43] The life-threatening problems in melanoma patients are expected to be psychologically burdensome. The CWS will be used to assess the prevalence of cancer-specific distress in the melanoma patients.
- Psychological distress will be assessed with the Hospital Anxiety and Depression Scale (HADS). The HADS, a 14-item questionnaire, assesses symptoms of mood disturbance, yielding separate scale scores for anxiety and depression, as well as a total score. Numerous studies have applied the HADS to assess distress among cancer survivors and the questionnaire has been validated for use in the Dutch and Italian population. [44, 45].
- As patients may no longer be able to work or work to a lesser extent, insight will be gained in the work performance of the patients at baseline and over time, using the Work Ability Index (WAI). The questionnaire assesses changes in a patients' working situation over time, regarding the patients' position, capacity, activities and number of working hours, and reasons for possible changes, both physically and mentally.
- Impact of diagnosis and treatment on sexual health will be assessed using four items from the EORTC Sexual Health Core Questionnaire (SHQ-C22). [46]
- Immunotherapy-specific questionnaire. In assessing quality of life in cancer patients, it is recommended to use a general and cancer-specific measure of quality of life plus a treatment-specific questionnaire. However, to date the available validated measurements do not include the problems and symptoms of novel treatments such as immunotherapy [47]. Therefore, we identified, based on literature and expert opinion 19 symptoms and created a symptom list based on items of the EORTC item Library [EORTC Item Library, qol.eortc.org/item-library].

Other secondary study outcomes comprise information needs fulfilment and self-management and clinical endpoints such as the number of emergency visits, hospitalizations and referrals to additional care.

- Fulfilment of information needs will be measured by the EORTC QLQ-INFO25 questionnaire. This validated 25-item questionnaire incorporates four information provision subscales: perceived receipt of information about the disease, medical tests, treatment and other care services [48].
- Number of emergency visits, hospitalizations and referrals to our Centre for Quality of Life (CKvL) or other additional care will be extracted from the EHR and compared between the experimental and historical cohort.

Other study parameters

Clinical data will be extracted from the EHR. Cancer-related characteristics, data on disease status (progression/recurrence/response) and additional treatments can be obtained from the EHR. Sociodemographic details will be asked in the questionnaire; patients' education and marital status will be obtained by 5 questions. Furthermore, comorbidity will be assessed on baseline using part of the Self-Administered Comorbidity Questionnaire (SCQ). This questionnaire is an efficient method to assess comorbid conditions and consists of 17 items [49].

Study procedures

All potential eligible patients for this study will be informed by their treating medical specialist (e.g., medical oncologist, surgeon, nurse practitioner) about this study and the study procedures before the start of systemic treatment. Furthermore, the medical specialist will provide patients an information letter, which outlines the study objectives, study procedures, and includes an informed consent. Moreover, the medical specialist will provide contact details of the eligible patient to the coordinating researcher (after the patient agrees on that), and consequently the coordinating researcher will contact the eligible patient to provide more information and if available to answer questions. Written informed consent will be asked and obtained if the patient wants to participate in this study. The research team will keep track on this procedure.

We plan to dedicate the entire last year of the project to the clinical study, starting the enrolment procedures of first patients at the end of the 3rd year (M36), and having the last patients enrolled observed for at least six months (M42). The study protocols will be prepared in advance (by month M28) and submitted to the Medical Ethics Review Committee (MERC) of the two hospitals, to have time to manage possible additional requests from MERC themselves.

Historical cohort

Nothing will change to the treatment of the patient. Patients will only be asked to complete PRO questionnaires. After patient enrolment in this study, questionnaires will be sent to the patient through a link via the hospitals' digital platform, post on set times throughout follow-up, or filled in

on paper during follow-up visits. Completed questionnaires can be submitted through the local digital platform or sent back by post, or personally. The minimum follow-up of a patient will be 6 months, and the PRO questionnaires will be delivered every three months. Patients will be followed-up for up to 5 years. This historical cohort, at NKI, will be involved also in another study that will last 5 years. Within CAPABLE, every patient will be followed-up for a minimum of 6-months and a maximum of 3 years.

Experimental cohort

After obtaining informed consent, the patient will be invited by the research team prior to a consultation with the medical oncologist to install the app and smartwatch and to go through the app together. During the consultation with the doctor, the CAPABLE enrolment process will be performed and goals will be set. When setup is complete, the patient will use CAPABLE in addition to his/her standard treatment. CAPABLE will be used for a minimum follow-up of 6 months. Endpoints of this study will be collected through questionnaires and clinical data will be extracted from the EHR or CAPABLE system. Questionnaires used for outcomes of this study will be administered every three months. Data collection will be combined with existing PRO data collection in daily clinical routine.

Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki, version 9, October 2013 and in accordance with the Medical Research Involving Human Subjects Act.

Recruitment and consent

Potentially eligible patients will receive an invitation to participate in the study by their treating medical specialist, including a patient information letter, a response letter and an informed consent form. Patient contact information will be retrieved so patients can be contacted by the coordinating researcher to retrieve further explanation. Patients willing to participate will be asked to send back the signed and dated informed consent form to the study team within two weeks. Furthermore, patients' contact information will be used to call potential participants if they have not responded after two weeks. Written informed consent will be obtained before any study procedure will be performed. In the historical cohort, questionnaires will be sent (digitally) by the study team of the NKI. For the experimental cohort, after obtaining informed consent, the research team will install CAPABLE together with the patient and enrolment will be done together with the treating physicians.

Statistical analysis

The study involves both patient-reported/QoL data collection (PRO questionnaires) as well as clinical data collection (data collected in the EHR). Therefore, data will consist of socio-demographic-, patient-, tumour-, and treatment details, information on immune-related adverse events, PRO's and information on hospitalization, emergency visits, referrals to additional care,

and fulfilment of patient information needs. Descriptive statistics will be performed to provide information about the patient population. A recently published study of Coens et al. on the international recommended statistical analyses and handling of missing data in PRO data will be followed for making choices regarding statistical analyses in this study [50]. Statistical analyses will be done using Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and R (https://www.R-project.org/). Interim analyses will be performed on preliminary data.

Primary study parameter(s)

Mean scores of the PRO questionnaires will be calculated using algorithms in existing literature and these scores will be used as endpoints for analyses. Summarizing and visualising methods will be used to make the data better interpretable. Effect sizes will be calculated using standard statistical procedures. Differences between mean scores of the questionnaires of each time point will be calculated. A comparison in mean difference in QoL (over time) between the experimental cohort and historical cohort will be done. Therefore, between-group differences in mean scores will be tested using multilevel analysis. Difference in outcome (improvement or worsening) over time (baseline and follow up moments) within the two groups will be analysed using either a linear mixed model or generalized estimating equation (GEE) analysis. A p-value of <0.05 will be seen as statistically significant, however, according to Cocks et al, a mean difference in change scores (per subdomain) can be seen as clinically relevant even if this is not statistically significant. Therefore, statistical differences and clinically meaningful differences will be analysed [51]. We will adjust for baseline PRO scores and other covariates such as sociodemographic variables, disease and treatment characteristics and other relevant variables.

Missing items from the EORTC QLQ-C30 will be imputed according to EORTC guidelines. The scale score will be set to missing if fewer than half of the items on a given scale is answered. Where at least 50% of the relevant scale scores will be present, the missing values can be replaced by the mean of the present values. Missing items from all used questionnaires will be imputed according to the guidelines. Of all questionnaires mentioned above, the scale score will be set to missing, if fewer than half of the items on a given scale were answered.

Secondary study parameter(s)

Statistical procedures as described above will be done on all questionnaire data and clinical relevance and/or cut-off values will be used complying to questionnaire reference manuals/guidelines. Cost-effectiveness analyses can be performed using the EQ-5D-5L questionnaire. Comparisons will be made between the number of hospitalizations, emergency visits and referrals to additional care between the experimental cohort and the historical cohort.

Benefits and risks assessment, group relatedness

Historical cohort

Patient burden for filling in the questionnaires is low. All the questionnaires will be combined into one questionnaire set. Different persons have filled in the questionnaire, resulting in a burden of

around 30 minutes per questionnaire set. Patient burden of this questionnaire is comparable to a recently completed study [52]. This study has fewer questionnaires and the response rate to the questionnaires was around 85% in this study. If we consider a follow up of 3 years, questionnaires will be administered 7 times over 36 months. The total burden for the patient over 3 years is 210 minutes (3.5 hours). There are no risks associated with participation, nor are there any additional benefits.

Experimental cohort

Patient burden for the use of CAPABLE will be depending on the intended use of the patient. Patient burden for filling in the questionnaires for study endpoints assessment is moderate. All the questionnaires will be combined into one questionnaire set. Patient burden will be around 30 minutes per questionnaire set and this will be administered on baseline, at 3 months and 6 months.

A possible risk associated with using CAPABLE is the greater insight a patient may achieve in his own health. This can possibly cause more stress to the patient. However, this can also be a benefit to the patient. Another benefit of using CAPABLE is the additional services from which we expect to have a positive impact on quality of life and adverse event management.

Handling and storage of data and documents

Storage of data will be at both hospitals (NKI/ICSM). Consortium agreement between both hospitals and the consortium members is needed.

5.3 Activities to perform during the pilot studies

In the final part of the project, the system will be first tested on healthy volunteers (*Pre-pilot*) and then evaluated by real users during the pilot study.

5.3.1 Activities performed during *Pre-pilot*

During the Pre-pilot, three professionals selected from the clinical staff (e.g. physicians, psychologists, nurses) and five volunteers selected from the technical and research team in each site will test CAPABLE. They will use an almost final version of the system to interact with all the CAPABLE functionalities. This will allow collecting initial and useful feedback from a population of experts who are familiar with the characteristics and needs of patients, and possibly identifying remaining bugs. As well, usability issues could be highlighted during this phase, even if final users probably will detect additional ones.
The tests will be performed in the real software environments at ICSM and NKI, where the clinical study will take place. A set of demo patients will be created, and smartphones and sensors will be prepared for all the volunteers, who will simulate all the phases of the process from enrolment. Key performance indicators for Phase I will be measures of usability and acceptability. Specific questionnaires that measure the level of acceptance of CAPABLE will be administered to both

patients and HCPs (See Section 3 for details).

5.3.2 Activities performed during the pilot study

In this section, we will detail the activities that patients and physicians will carry out during the pilot study, starting at M36. In particular, we will describe the enrolment phase, the home management and the follow-up visits, and the conclusion of the study.
CAPABLE will foster the multidisciplinary management of cancer patients. Thus, besides oncologists, the project will involve other professionals (psychologists, social workers and nutritionists) and provide them with a collaborative platform. For this reason, in this section we will also present the flowcharts of the psychological and nutritional assessment. These flowcharts are a result of a close interaction process among a multidisciplinary team, made up of oncologists, psychologists and nutritionists at both the clinical centres and AIMAC. These HCPs have been working together, coordinated by the research teams at UNIPV and NKI, to reach a consensus on these clinical workflows, which are new with respect to standard care for both centres. Psychological and nutritional support are currently available for cancer patients both at NKI and ICSM, but such services are not fully integrated in the cancer-related workflow. In particular, cancer patients are informed that supportive care is available but then it is up to them to refer to such service if they want. In this way, it sometimes happens that patients refer to the psychologist/nutritionist when his/her condition is already advanced. The solution envisioned in the CAPABLE project allows an early detection of possible problems, so patients are taken in charge of the specialists as soon as possible.

5.3.2.1 Enrolment

In this paragraph we list the activities that will be carried out during enrolment.
For the cohort of patients using the CAPABLE system, the actors involved in this phase are: patient, oncologist, engineer, psychologist (ICSM), CAPABLE research team (NKI).

The activities performed will be (not necessarily in this order):

- Sign consent form
- Enrolment through the physician app (import from EHR)
- Patient profile definition (from physician app)
    - Patient habits
    - Clinical history
    - Treatment plan
    - Capsules selection
- Activation of the patient app
- Setup of the sensors
- Training
- Questionnaires at baseline (through the patient app, explained by the oncologist / psychologist/ researcher):

    - EORTC QLQ-C30
    - Nutritional assessment questionnaire (MST, see section 5.3.2.4)
    - Psychological assessment questionnaires (see Section 5.3.2.5)
    - Insomnia Severity Index
    - Fatigue Rating Scale
- UX evaluation questionnaires

5.3.2.2 Home management and follow-up visits

During the clinical study involving the cohort with the CAPABLE system, both the patients and the HCP will have to perform a set of activities.

The patients will perform the following activities through the CAPABLE app:

- Symptoms reporting
- Sensors and vital signs reporting
- Periodic questionnaires
- Capsules
- Recommendations
- Reminders

In addition, patients will undergo regular follow-up visits. Besides standard clinical evaluation, during follow-up visits patients will complete questionnaires for UX evaluation, as described in Section 5.4.

The activities that HCPs will have to perform in addition to normal clinical practice are the following:

- Oncologist:
    - Periodically check the physician CAPABLE app to monitor the evolution of the patients
    - Manage alerts for severe ADE or questionnaires exceeding thresholds
- Clinical psychologist:
    - Periodically check the CAPABLE physician app to monitor the evolution of the patients (e.g. emotional thermometers)
    - Manage alerts for psychological questionnaires exceeding thresholds
    - Administer questionnaires during visits for patients in charge
- Nutritionist:
    - Periodically check the physician app to monitor the evolution of the patients (Malnutrition Screening Tool questionnaire)
    - Administer questionnaires during visits for patients in charge

In addition, HCPs will complete questionnaires for UX evaluation, as described in Section 5.4.

5.3.2.3 End of the study / Dropout

At the end of the study the patient will fill in the final questionnaires (same as baseline). In addition, he/she will perform the final UX evaluation (see Section 5.4 for detailed description).
The app will be uninstalled and the devices returned if needed.

Dropout
If a patient wants to withdraw from the study, he/she will be able to signal this intention through the app. The process will then be in the hands of the oncologist. The patient will be removed from the physician app and his data managed according to General Data Protection Regulation (GDPR) regulations. If the app was installed on the patient's personal smartphone, it will be uninstalled. If the smartphone was provided to the patient by the project, it will be returned and reset. The patient will be asked to return the sensors.

5.3.2.4 Nutritional assessment

For the cohort of patients using the CAPABLE system, a novel process related to the nutritional assessment has been defined (see Figure 5.3.2.4.1).
At enrolment, the oncologist performs the patient's first nutritional assessment, submitting the Malnutrition Screening Tool (MST) questionnaire through the patient's application. If the score obtained during this first evaluation of MST is <2, the patient can go home and start the home monitoring. Otherwise, if the score obtained during the execution of MST >=2, the oncologist sends the patient to the nutritionist for further tests. During the visit, if needed, the nutritionist prescribes some blood tests (Vitamin D, Vitamin B12, folate, zinc, prealbumin, protein, electrophoresis, homocysteine and, if not already done in routine blood tests, lipids, carbohydrates and electrolytes). The prescription is not performed using the CAPABLE application, but through the order entering system of the hospital. During the visit the nutritionist, together with the patient and through the CAPABLE physician app, fills in the NRS2002 (Nutritional Risk Screening) questionnaire. The nutritionist, considering results of blood tests and the answers provided in the questionnaire, decides whether to take in charge the patient for nutritional treatment or not. If the patient is taken in charge for treatment, the nutritionist schedules the date for the next visit. Alternatively, the patient can go home and start home monitoring.
During the home monitoring, the system waits for three months from the last compilation of MST and then makes the patient fill in the questionnaire. If the score obtained by the patient is less than two, the system waits for another three months for another compilation. However, if the score is >=2, the nutritionist receives an alert through the physician app that suggests contacting the patient for a possible take in charge.

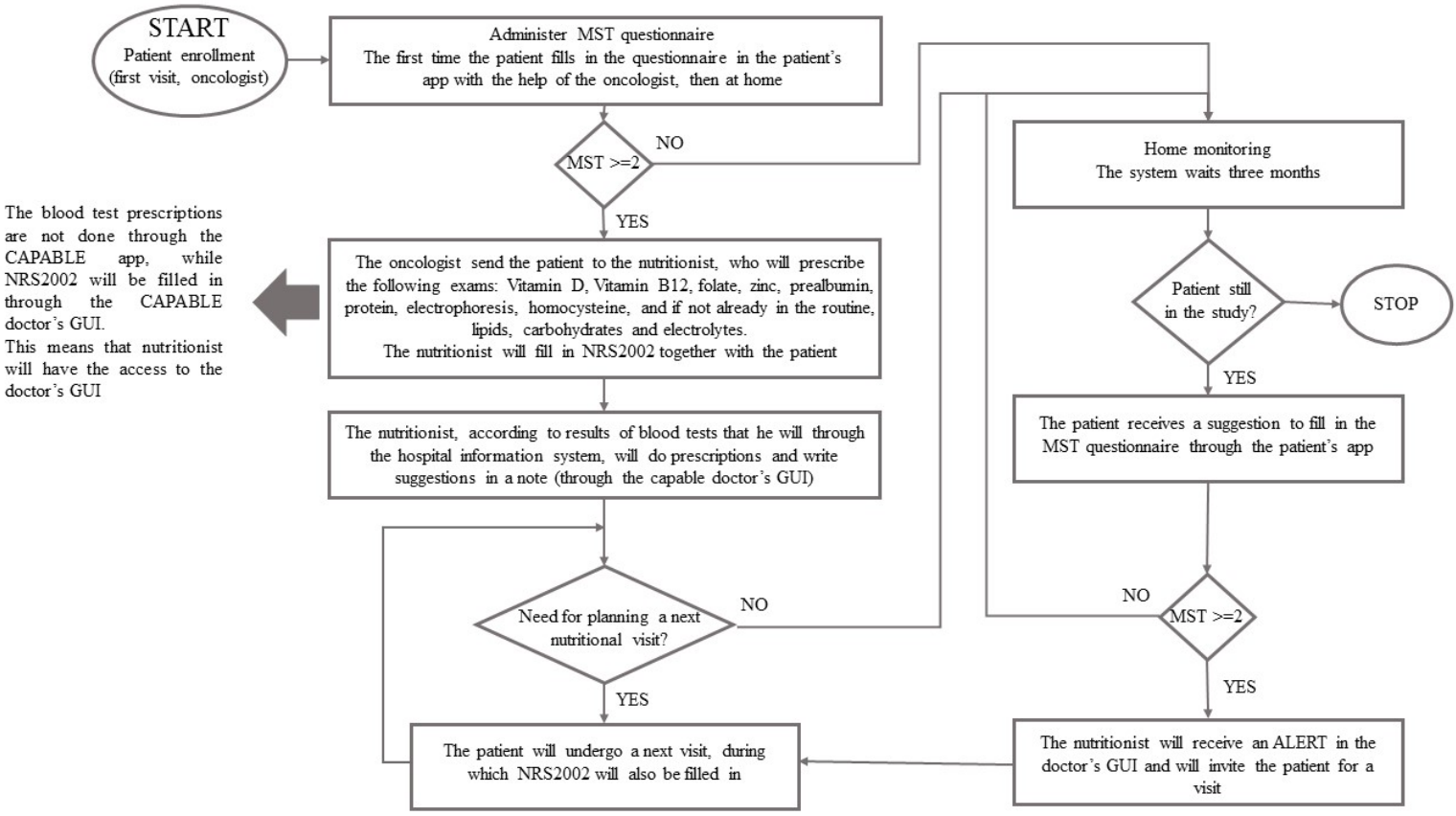

Figure 5.3.2.4.1 Nutritional flowchart

5.3.2.5 Psychological assessment

This section describes how the collaboration with psychologists is envisaged for the cohort of patients who will use the CAPABLE system. This process is illustrated in Figure 5.3.2.5.1.

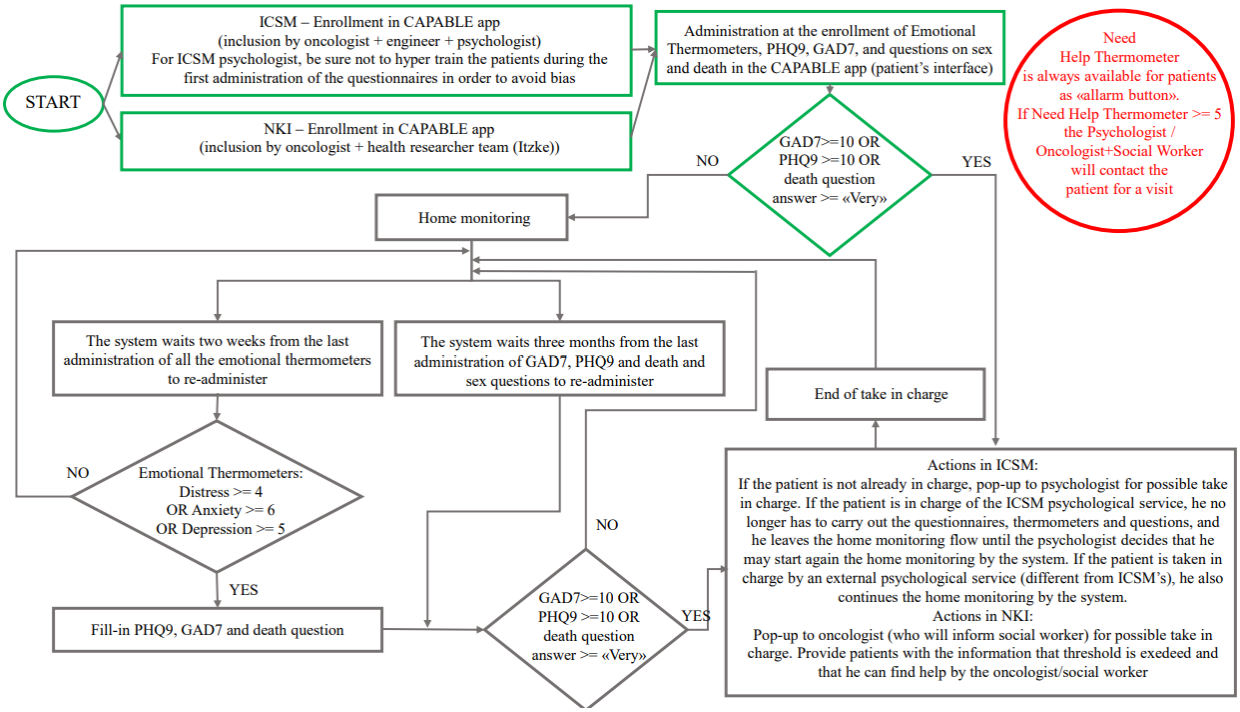

Figure 5.3.2.5.1 Psychological flowchart

At enrolment, the patient meets several HCPs. In particular, at the ICSM of Pavia, Italian patients enrolment is made by an oncologist, an engineer and a psychologist, and it is the psychologist who carries out the first psychological assessment during the visit. At the NKI the enrolment of Dutch patients is carried out by an oncologist and a health researcher member of the CAPABLE team. In this case, the first psychological assessment is made by the health researcher.
During enrolment, the following questionnaires are administered for psychological assessment:

- PHQ-9 questionnaire for depression (see Annex 7.7)
- GAD-7 (General Anxiety Disorder - 7)questionnaire for anxiety (see Annex 7.8)
- emotional thermometers [53] (see Annex 7.9)
- Two additional questions that psychologists think to be very important to assess mental wellbeing:
    - question about sexual life: How have you perceived your sexual life in the last month? (possible answers: Not satisfactory / Little satisfactory / Satisfactory / Inconstant / It is a sphere in which I am no longer interested)
    - question about thoughts of death: In the last month, how much has your mind been focused on thoughts regarding the fear of illness and death? (Possible answers: Not at all / A little / Sometimes / Frequently / Very frequently).

The clinical psychologist / health researcher, considering the answers provided in the questionnaires, decides whether to take in charge the patient for psychological treatment. If the patient is taken in charge for treatment, the date for the next psychological visit is scheduled. Otherwise, the patient will start the home monitoring.

At home, the system waits for two weeks from the last administration of the emotional thermometers and then asks the patient to fill-in the thermometers again. The PHQ9 and GAD-7 questionnaires, and the questions about sex and death are instead administered every three months.
If the patient, during one of the periodic administration of the emotional thermometers, enters one of the values of emotional thermometers above the thresholds (DISTRESS >= 4 or DEPRESSION >= 5 or ANXIETY >= 6), the patient's application generates a reminder for the immediate administration of PHQ-9, GAD-7, and question about death. If one of the two questionnaires reaches a score >=10, or if the patient answers “Frequently” or “Very frequently” to the question about death, then she/he can be taken in charge for a more in-depth psychological evaluation. In particular, as regards ICSM, an alert for the psychologist appears on the physician application for possible patient take in charge. When the patient is taken in charge by a clinical psychologist at ICSM, she/he temporarily suspends the psychological home monitoring via the CAPABLE app and is followed with periodical encounters at the hospital. At the end of the psychological follow-up treatment, the patient will start again to fill in the questionnaires through the app. If, on the other hand, the patient is taken in charge by a different psychological service (outside ICSM), the patient continues to fill in the questionnaires periodically with the CAPABLE app. As for NKI, in case the oncologist gets an alert that one of the questionnaires exceeds the threshold, he/she will have to contact the social worker, who carries out the triage for possible contact between the patient and the psychologist.
The "Need help" thermometer is available at any time and has an alarm function. If the patient enters a need help thermometer value >=5, the HCP (psychologist at ICSM and oncologist at NKI) is notified for a possible psychological visit.
For patients using the system, if the patient refuses to be taken in charge by the psychologist, the system will record this as a “non compliance”. The patient will keep receiving the reminder to fill in the thermometers and the questionnaires.

5.4 Draft of the UX study protocol

The participants of the clinical studies will also join a sub-study designed to assess the User Experience and the overall satisfaction of the proposed CAPABLE technology. This protocol is tailored for the three main actors involved in the study: patients, caregivers and health professionals.

5.4.1 Patient protocol

The main goals of this study are:

- Assess the acceptance and usability of the CAPABLE solution
- Identify barriers and problem during the use
- Measure the perceived benefit from the user

During the clinical follow-ups in the hospitals the patients will fill an online or paper questionnaire. In case of elderly patients it will be also possible that the interview will be guided

by the health professional (and the survey will keep track). Patient will participate to this study at three different timepoints:

1. **After the enrolment**. At this stage the goal is to measure the user's expectations in terms of ability to use the system and benefits. The metrics to be used are: TAM and privacy concerns.
2. **After one month of system usage**, during a hospital follow-up. The goal of this assessment is to evaluate the first approach to the technology, barriers, and perceived usefulness of the system. The following metrics will be used: SUS Scale (System Usability Scale- see Section 5.4.4 for description of this scale and the other standard instruments mentioned in Section 5.4), easiness of core App tasks, technical errors, missing functionalities (see table 5.4.5).
3. **At the end of the study**. When the users finalize the study the participants will assess overall experience with CAPABLE, through the following metrics: SUS Scale, uMARS (Mobile Application User Scale, user version), AttrakDiff and PATAT (The PAtient Trust Assessment Tool), overall system easiness, exploitation questionnaire (will you recommend to others, will you pay for the service?), errors, missing functionalities, privacy concerns.

Quick periodic assessment
Aside from this structured protocol of follow-up, WP7 also proposes a lightweight periodic assessment to be used in the rest of the follow-up and patient's encounters. Two simple questions will be asked to the user:

- Are you satisfied with the app? How much (please rank from 1 to 5)?
- Do you have to report some issues or suggestions?

5.4.2 Caregiver

The main goal of this study is to assess the following:

- The type of support provided to the patients. Explorative questions will investigate the type of support that the caregiver provided to the patient.
- The level of burden of the caregiver. Caregiver Burden Inventory (CBI) will be used. The instrument can be found at Annex 7.10.
- The level use of the Capable system If users used the system we can give the final questionnaire of the patient
- Perceived benefits from the use of CAPABLE system (of patient and caregivers)

The caregiver will receive a questionnaire to be filled at the end of the study.

5.4.3 Health Professional

Main goals:

- Assess the health professionals user's experience during the study. Discuss barriers, limitations, opportunities for a further use of the technology in clinical settings.

- Explore with health professionals best strategies for clinical applicability,
- Acceptance and barriers of the CAPABLE solution (a questionnaire adapted from the Technology Acceptance Model)
- User satisfaction, willingness to pay

5.4.4 Overall Description of Standard Metrics

System Usability Scale
(Available: https://www.usability.gov/how-to-and-tools/methods/system-usability-scale.html)

The System Usability Scale (SUS) is a tool to measure the usability of an application, consisting of a 10-item questionnaire with five response options from “Strongly agree” to “Strongly disagree” possibilities. The SUS questionnaire orders the questions in such a way that the odd-numbered questions have “positive approaches”, while the even-numbered questions have “negative approaches”. The overall SUS score is calculated adding up the contribution of each item and multiplying by 2.5, resulting in a score range from 0 to 100. Before performing the sum, the results of the questions should be normalized as follows: the odd-numbered questions are calculated as their value minus 1 and the even-numbered questions are calculated as 5 minus their values in the scale. The purpose of this evaluation is to compare the usability of a tool with the study done over 5000 users across 500 different tools evaluations. The questionnaire can be found in the Annex (7.2).

Technology Acceptance Model (TAM) [54] has been one of the most influential models of technology acceptance, with two primary factors influencing an individual’s intention to use new technology: perceived ease-of-use and perceived usefulness.
To evaluate the tools developed in the project this questionnaire will be adapted and customized to assess the user acceptance of the tools and identify how and when the users will use them; and for this reason, two variables will be added: intention to use and facilitating conditions.
The questionnaire is a 5-point Likert scale ranging from “Totally disagree” to “Totally agree”, where scores are calculated considering the mean of all the items included in each theoretical dimension. An example of the TAM questionnaire that will be executed in the CAPABLE project is included in subsection 7.6.

AttrakDiff
(Available: http://www.attrakdiff.de/index-en.html)
AttrakDiff measure is a questionnaire that helps to understand how users are satisfied or not with the product or tool evaluated, based on four different categories: Pragmatic Quality, Hedonic Quality Identity, Hedonic Quality Stimulation and Attractiveness. AttrakDiff questionnaire are composed by 28 pairs of words whose are opposite adjectives (e.g. "confusing-clear", "unusual-ordinary", "good-bad"), and the user must select in a 7-point scale which adjective best suits their perception of the tool. The AttrakDiff tool is developed to support various usage scenarios: i)

single evaluation: to evaluate the product by the users only once time, ii) comparison between product A and B: to compare two products in terms of usability and design and iii) comparison before-after: to perform the evaluation at several stages of product development. The tools developed in CAPABLE project will be evaluated through the scenario comparison before-after, in this way it can be identified if the optimization carried out during the development of the tools has also improved the user satisfaction of the tools.
Subsection 7.3 includes the AttrakDiff questionnaire that will be executed during the tool assessment.

uMARS

Moreover, to assess the quality of the mobile app developed in the CAPABLE project, we propose to use the **uMARS** tool [55] which is an end-user version of the MARS, rating scale tool. The MARS scale is a well-known standardized tool developed by the Queensland University of Technology by which health apps can be compared.
Both tools provide a multidimensional, reliable, and flexible app-quality rating scale for researchers, developers, and health-professionals. The uMARS quality rating tool describes the overall quality of an app through the following criteria: engagement, functionality, aesthetics, and information quality, as well as app subjective quality. To evaluate the mobile app the end-users (patients) will be the evaluators, and they will follow 3 steps before answering the questionnaire to rate the mobile app: i) the end-users should first use the app and trial it thoroughly for at least 10 minutes, ii) determine how easy it is to use, how well it functions and does it do what it purports to do, and finally iii) review app settings, developer information, external links, security features. The responses are rated on a 5-point scale from “1.Inadequate” to “5.Excellent” and the evaluators must select the number that most accurately represents the quality of the app component they are rating. Each response category or criteria is provided by descriptors to help the evaluators during the assessment task. The uMARS scale is attached in Subsection 7.4.

PATAT

The PATAT [56] (The PAtient Trust Assessment Tool) questionnaire is designed to assess specifically the trust of a patient in a telemedicine tool focusing on the perceptions of factors that make up trust in a telemedicine service. PATAT assesses the following trust factors that CAPABLE will take in account:

- Trust in the care organization. An individual’s belief that a healthcare organization acts for the individual with the individual’s best interests in mind.
- Trust in the care professional. An individual’s belief that a care professional (or a team of care professionals) acts for the individual with the individual’s best interests in mind.
- Trust in the technology. An individual’s belief that using a specific technology is safe and secure
- Trust in telemedicine service. An individual's perception of the system.

The PATAT questionnaire is attached as Annex 7.5.

5.4.5 Other non-standard metrics

The protocol of the UX study will also include non-standard questions that are necessary to better explore users though and experience. These types of questions are summarized in the next table.

Table 5.4.5 Non-standard evaluation questions

Outcome	**Example of question**
Overall feedback	What is your overall opinion of the CAPABLE concept? What do you like the most and what you dislike? (open questions)
Easiness / usefulness	Please score the level of easiness / usefulness from 1 (very easy) to 5 (very difficult) the following tasks …. (e.g. report symptoms, execute capsule etc)
Willingness to pay	Would you pay for CAPABLE? How much? (open questions)
Errors	Did you experience some technical errors while using CAPABLE? What was the frequency? Were the problems solved? (open questions)
Missing functionalities	Do you think that CAPABLE has any missing functionalities? (open questions)
Recommend to others	Will you recommend CAPABLE to a friend or relative? (open questions)

5.5 Informed consent drafts

5.5.1 Study procedures

The informed consent procedure will conform to the International Council for Harmonization guidelines on Good Clinical Practice (https://www.ich.org/). Investigators must ensure that patients are clearly and fully informed about the purpose of the study, potential risks, the patient's rights and responsibilities when participating in this study. All patients will be informed about the aims of the study and the study procedures. A patient information sheet giving details of the study will be provided for the patient to read and retain. After the patients have had time to consider the information and have been encouraged to ask questions, they will be asked to give informed consent by signing and dating an informed consent form. All informed consent forms will be countersigned and dated by the medically qualified investigator, co-investigator or nurse

practitioner. Written informed consent will be obtained before performing any study procedures, including study-specific screening procedures. Procedures that are part of standard care may occur before informed consent is obtained. The original of the informed consent form will be filed in the patient's file. A copy will be given to the patient. The Project Coordinator will also receive a copy of the signed informed consent forms for archiving following the required procedures.

5.5.2 Patient information and informed consent ICSM

In ICSM, the patients that participate to clinical studies are provided with two documents:

- information sheet, including data regulation and privacy policy
- Informed consent, to be signed by the patient

These two documents are written in Italian.

5.5.2.1 Patient information

The information sheet includes the following sections:

- Data Controller
- Data Protection Officer: name and contacts of the Data Protection Officer
- Categories of Personal data involved in the study: categories of data that will be collected during the study
- Data Source: source of the data collected during the study
- Aim and description of the study: brief description of the project and the clinical study is explained to the patient
- Legal basis and purpose of data processing: among the purposes of the data processing there are the participation to the study, the communication of possible incidental findings, and the communication of the results of the project to the General Practitioner (GP) of the patient. Each of the purposes is related to the specific legal details referring to the appropriate GDPR articles.
- Data retention period: the period of data retention and the rules concerning the retention of the data, also in case of withdrawal from the study
- Mandatory nature of the provision
- Methods of processing data: description of the anonymization or pseudonymization procedures (explained to the patient)
- Recipients of the data
- Subjects authorized for the processing
- Rights of the data subject, according to the GDPR

5.5.2.1 Informed consent

The informed consent of ICSM contains the following and mandatory parts:

Title as described in the patient information document.

- I have read the patient information sheet and I have received exhaustive explanations. I was given the possibility to ask questions and discuss the provided explanations. My questions have been answered sufficiently and I have had enough time to discuss with a person of trust.
- I know that participation is voluntary and I fully understand the risks and benefits implied in my participation. I also know that I can decide anytime to quit.
- I give permission to inform my [*general practitioner*] that I participate in this trial.
- I have free access to the documentation of this trial and to the assessment of the Ethical Committee
- I give permission to collect and use my [*data*] for answering the research questions and aims of this trial according to the GDPR.
- I want to participate in this trial.

Signatures of patient and coordinating researcher:

Name patient:

Signature: Date : __ / __ / __

Name coordinating researcher (or his/her representative):

Signature: Date: __ / __ / __

The subject receives a full information letter, together with a signed version of the informed consent.

5.5.3 Patient information and informed consent NKI

Patients will be informed and asked by their treating medical specialist to participate in the study and they will be asked whether the medical specialist may share patients' contact information (name, address, email and/or telephone number) with the study team at the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL).

In NKI, the patients that are eligible for participation in a clinical trial will be given a document of detailed information and an informed consent document. The detailed information and informed consent has to contain specific information for which NKI has a writing manual constructed by the institute's medical ethical committee (METC).

5.5.3.1 Patient information

The patient information document contains the following parts:

1. General introduction, including the invitation to participate in the trial
2. Aim
3. Background (relevance of the trial)
4. What does participation entail (description of study procedures)
5. What is expected from the patient (what the patient has to do and/or fill in during the trial)
6. Possible side effects/complications/negative affects to the patient as a result of participation
7. Possible pros and cons of participation for the patient
8. What to do when the patient does not want to participate or wants to quit participation
9. What happens after stop of the trial
10. Use and storage of (personal) data (data processing, privacy, etc.)
11. Insurance for patient and/or subject
12. Informing other specialists involved in treatment (for example GP)
13. Compensation for participation (yes or no)
14. Contact information in case questions arise

5.5.3.1 Informed consent

The informed consent of NKI contains the following and mandatory parts:

Title as described in the patient information document.

- I have read the patient information folder. Also I could ask questions. My questions have been answered sufficiently. I have had enough time to decide if I want to participate.
- I know that participating is voluntary. I also know that I can decide anytime to not participate or quit participation. I do not need to give a reason for that.
- I give permission to inform my [*health care specialist*] that I participate in this trial [*and if necessary to inform about:...*].
- [*If necessary*] I give permission to request information from my [*health care specialist*].
- I give permission to collect and use my [*data*] for answering the research question and aim of this trial.
- I know that for monitoring this research project some people will have access to all my personal data. These people are mentioned in this patient information letter. I give permission to these people for insight in my personal data.
- I want to participate in this trial.

Optional to add:

- I give (**yes/no**) permission to use and store my personal data longer for future research in the area of [*disease/intervention/etc.*].
- I give (**yes/no**) permission to reach out to me after this trial for future research projects.

Signatures of patient and coordinating researcher:

Name patient:

Signature: Date : __ / __ / __

I declare that I have fully informed this subject/patient about the described study.

If critical information shows up during this study that could influence the consent of the subject/patient, I will inform him/her in time.

Naam coordinating researcher (or his/her representative):

Signature: Date: __ / __ / __

The subject receives a full information letter, together with a signed version of the informed consent.

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7 Annexes

7.1 Glossary

(PRO-)CTCAE	(Patient-Reported Outcomes -) Common Terminology Criteria for Adverse Events
CBI	Caregiver Burden Inventory
CKvL	Centre for Quality of Life
CTLA4	Cytotoxic T-lymphocyte associated antigen 4
CWS	Cancer Worry Scale
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic Health Record
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core 30
ER	Emergency Room
FACT-M	Functional Assessment of Cancer Therapy – Melanoma
FDA	Food and Drug Administration
GAD-7	General Anxiety Disorder-7
GDPR	General Data Protection Regulation
GEE	Generalized estimating equation
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare Professional
HRQoL	Health-related quality of life
ICI	Immune checkpoint-inhibitor
irAE	Immune-related adverse event
IT	Information Technology
MARS	Mobile Application Rating Scale
MERC	Medical Ethics Review Committee
mRCC	Metastatic renal cell carcinoma
MST	Malnutrition Screening Tool
NCI	National Cancer Institute
NRS2002	Nutritional Risk Screening

OS	Overall survival
PATAT	PAtient Trust Assessment Tool
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
Phase 1	Phase 1 of the evaluation process: activities carried out while the system is under development
Phase 2	Phase 2 of the evaluation process: activities carried out when the system is complete
PHQ-9	Patient Health Questionnaire-9
PoC	Proof of Concept
Pre-pilot	Evaluation study on healthy volunteers taking place during the last 6 months of Phase 1
PROM	Patient-reported outcome measure
QALY's	Quality-Adjusted Life Years
RCC	Renal Cell Carcinoma
SAB	Scientific Advisory Board
SCQ	Self-Administered Comorbidity Questionnaire
SHQ-C22	Sexual Health Core Questionnaire
SUS	System Usability Scale
TAM	Technology Acceptance Model
uMARS	Mobile Application User Scale , user version
UX	User Experience
VEGFR	Vascular Endothelial Growth Factor Receptor
WAI	Work Ability Index

Partners:

AIMAC	Associazione Italiana Malati di Cancro
AMC	Academish Medish Centrum BiJ de Universiteit Van Amsterdam
ICSM	Istituti Clinici Scientifici Maugeri
NKI AVL	Nederlands Kanker Instituut - Antoni van Leeuwenhoek
UNIPV	Università degli Studi di Pavia

UoH University of Haifa

UPM Universidad Politécnica de Madrid

7.2 System Usability Scale

System Usability Scale

	Strongly disagree				Strongly agree
1. I think that I would like to use this system frequently	1	2	3	4	5
2. I found the system unnecessarily complex	1	2	3	4	5
3. I thought the system was easy to use	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use this system	1	2	3	4	5
5. I found the various functions in this system were well integrated	1	2	3	4	5
6. I thought there was too much inconsistency in this system	1	2	3	4	5
7. I would imagine that most people would learn to use this system very quickly	1	2	3	4	5
8. I found the system very cumbersome to use	1	2	3	4	5
9. I felt very confident using the system	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with this system	1	2	3	4	5

TAM questionnaire

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
The use of the *[system]* could help me to execute my *[mention activities]* activities more rapidly					
The use of the *[system]* could help me to *[description of activities]*					
I think that I could easily learn how to use the *[system]*					
I think it is a good idea to use the *[system]* to *[description of system goal]*					
The use of the *[system]* may imply major changes in my *[description of activities]*					
I think that my work center has the necessary infrastructure to support my use of the *[system]*					
I feel comfortable with information and communication technologies					

I have the intention to use the *[system]* when it becomes available in my work center					

7.3 AttrakDiff

Please provide your impressions of the product you have tested by check marking your impression on the scale between the terms offered in each line.

	1	2	3	4	5	6	7	
human	☐	☐	☐	☐	☐	☐	☐	technical
isolating	☐	☐	☐	☐	☐	☐	☐	connective
pleasant	☐	☐	☐	☐	☐	☐	☐	unpleasant
inventive	☐	☐	☐	☐	☐	☐	☐	conventional
simple	☐	☐	☐	☐	☐	☐	☐	complicated
professional	☐	☐	☐	☐	☐	☐	☐	unprofessional
ugly	☐	☐	☐	☐	☐	☐	☐	attractive
practical	☐	☐	☐	☐	☐	☐	☐	impractical
likeable	☐	☐	☐	☐	☐	☐	☐	disagreeable
cumbersome	☐	☐	☐	☐	☐	☐	☐	straightforward
stylish	☐	☐	☐	☐	☐	☐	☐	tacky
predictable	☐	☐	☐	☐	☐	☐	☐	unpredictable
cheap	☐	☐	☐	☐	☐	☐	☐	premium
alienating	☐	☐	☐	☐	☐	☐	☐	integrating
brings me closer to people	☐	☐	☐	☐	☐	☐	☐	separates me from people
unpresentable	☐	☐	☐	☐	☐	☐	☐	presentable
rejecting	☐	☐	☐	☐	☐	☐	☐	inviting
unimaginative	☐	☐	☐	☐	☐	☐	☐	creative
good	☐	☐	☐	☐	☐	☐	☐	bad
confusing	☐	☐	☐	☐	☐	☐	☐	clearly structured
repelling	☐	☐	☐	☐	☐	☐	☐	appealing
bold	☐	☐	☐	☐	☐	☐	☐	cautious
innovative	☐	☐	☐	☐	☐	☐	☐	conservative
dull	☐	☐	☐	☐	☐	☐	☐	captivating
undemanding	☐	☐	☐	☐	☐	☐	☐	challenging
motivating	☐	☐	☐	☐	☐	☐	☐	discouraging
novel	☐	☐	☐	☐	☐	☐	☐	ordinary
unruly	☐	☐	☐	☐	☐	☐	☐	manageable

7.4 Mobile Application User Scale , user version (uMARS)

Mobile Application Rating Scale: user version (uMARS)

App Name: _____

Circle the number that most accurately represents the quality of the app you are rating. All items are rated on a 5-point scale from "1.Inadequate" to "5.Excellent". Select N/A if the app component is irrelevant.

App Quality Ratings

SECTION A

Engagement – fun, interesting, customisable, interactive, has prompts (e.g. sends alerts, messages, reminders, feedback, enables sharing)

1. **Entertainment: Is the app fun/entertaining to use? Does it have components that make it more fun than other similar apps?**
   1 Dull, not fun or entertaining at all
   2 Mostly boring
   3 OK, fun enough to entertain user for a brief time (< 5 minutes)
   4 Moderately fun and entertaining, would entertain user for some time (5-10 minutes total)
   5 Highly entertaining and fun, would stimulate repeat use

2. **Interest: Is the app interesting to use? Does it present its information in an interesting way compared to other similar apps?**
   1 Not interesting at all
   2 Mostly uninteresting
   3 OK, neither interesting nor uninteresting; would engage user for a brief time (< 5 minutes)
   4 Moderately interesting; would engage user for some time (5-10 minutes total)
   5 Very interesting, would engage user in repeat use

3. **Customisation: Does it allow you to customise the settings and preferences that you would like to (e.g. sound, content and notifications)?**
   1 Does not allow any customisation or requires setting to be input every time
   2 Allows little customisation and that limits app's functions
   3 Basic customisation to function adequately
   4 Allows numerous options for customisation
   5 Allows complete tailoring the user's characteristics/preferences, remembers all settings

4. **Interactivity: Does it allow user input, provide feedback, contain prompts (reminders, sharing options, notifications, etc.)?**
   1 No interactive features and/or no response to user input
   2 Some, but not enough interactive features which limits app's functions
   3 Basic interactive features to function adequately
   4 Offers a variety of interactive features, feedback and user input options
   5 Very high level of responsiveness through interactive features, feedback and user input options

5. **Target group: Is the app content (visuals, language, design) appropriate for the target audience?**

   1 Completely inappropriate, unclear or confusing
   2 Mostly inappropriate, unclear or confusing
   3 Acceptable but not specifically designed for the target audience. May be inappropriate/ unclear/confusing at times
   4 Designed for the target audience, with minor issues
   5 Designed specifically for the target audience, no issues found

SECTION B

Functionality – app functioning, easy to learn, navigation, flow logic, and gestural design of app

6. **Performance: How accurately/fast do the app features (functions) and components (buttons/menus) work?**

   1 App is broken; no/insufficient/inaccurate response (e.g. crashes/bugs/broken features, etc.)
   2 Some functions work, but lagging or contains major technical problems
   3 App works overall. Some technical problems need fixing, or is slow at times
   4 Mostly functional with minor/negligible problems
   5 Perfect/timely response; no technical bugs found, or contains a 'loading time left' indicator (if relevant)

7. **Ease of use: How easy is it to learn how to use the app; how clear are the menu labels, icons and instructions?**

   1 No/limited instructions; menu labels, icons are confusing; complicated
   2 Takes a lot of time or effort
   3 Takes some time or effort
   4 Easy to learn (or has clear instructions)
   5 Able to use app immediately; intuitive; simple (no instructions needed)

8. **Navigation: Does moving between screens make sense; Does app have all necessary links between screens?**

   1 No logical connection between screens at all /navigation is difficult
   2 Understandable after a lot of time/effort
   3 Understandable after some time/effort
   4 Easy to understand/navigate
   5 Perfectly logical, easy, clear and intuitive screen flow throughout, and/or has shortcuts

9. **Gestural design: Do taps/swipes/pinches/scrolls make sense? Are they consistent across all components/screens?**

   1 Completely inconsistent/confusing
   2 Often inconsistent/confusing
   3 OK with some inconsistencies/confusing elements
   4 Mostly consistent/intuitive with negligible problems
   5 Perfectly consistent and intuitive

SECTION C

Aesthetics – graphic design, overall visual appeal, colour scheme, and stylistic consistency

10. **Layout: Is arrangement and size of buttons, icons, menus and content on the screen appropriate?**

    1 Very bad design, cluttered, some options impossible to select, locate, see or read
    2 Bad design, random, unclear, some options difficult to select/locate/see/read
    3 Satisfactory, few problems with selecting/locating/seeing/reading items
    4 Mostly clear, able to select/locate/see/read items
    5 Professional, simple, clear, orderly, logically organised

11. **Graphics: How high is the quality/resolution of graphics used for buttons, icons, menus and content?**

    1 Graphics appear amateur, very poor visual design - disproportionate, stylistically inconsistent
    2 Low quality/low resolution graphics; low quality visual design – disproportionate
    3 Moderate quality graphics and visual design (generally consistent in style)
    4 High quality/resolution graphics and visual design – mostly proportionate, consistent in style
    5 Very high quality/resolution graphics and visual design - proportionate, consistent in style throughout

12. **Visual appeal: How good does the app look?**

    1 Ugly, unpleasant to look at, poorly designed, clashing, mismatched colours
    2 Bad – poorly designed, bad use of colour, visually boring
    3 OK – average, neither pleasant, nor unpleasant
    4 Pleasant – seamless graphics – consistent and professionally designed
    5 Beautiful – very attractive, memorable, stands out; use of colour enhances app features/menus

SECTION D

Information – Contains high quality information (e.g. text, feedback, measures, references) from a credible source

13. **Quality of information: Is app content correct, well written, and relevant to the goal/topic of the app?**

    N/A There is no information within the app
    1 Irrelevant/inappropriate/incoherent/incorrect
    2 Poor. Barely relevant/appropriate/coherent/may be incorrect
    3 Moderately relevant/appropriate/coherent/and appears correct
    4 Relevant/appropriate/coherent/correct
    5 Highly relevant, appropriate, coherent, and correct

14. **Quantity of information: Is the information within the app comprehensive but concise?**

    N/A There is no information within the app
    1 Minimal or overwhelming
    2 Insufficient or possibly overwhelming
    3 OK but not comprehensive or concise
    4 Offers a broad range of information, has some gaps or unnecessary detail; or has no links to more information and resources
    5 Comprehensive and concise; contains links to more information and resources

15. **Visual information: Is visual explanation of concepts – through charts/graphs/images/videos, etc. – clear, logical, correct?**

N/A There is no visual information within the app (e.g. it only contains audio, or text)
1 Completely unclear/confusing/wrong or necessary but missing
2 Mostly unclear/confusing/wrong
3 OK but often unclear/confusing/wrong
4 Mostly clear/logical/correct with negligible issues
5 Perfectly clear/logical/correct

16. **Credibility of source: does the information within the app seem to come from a credible source?**

N/A There is no information within the app
1 Suspicious source
2 Lacks credibility
3 Not suspicious but legitimacy of source is unclear
4 Possibly comes from a legitimate source
5 Definitely comes from a legitimate/specialised source

App subjective quality

SECTION E

17. **Would you recommend this app to people who might benefit from it?**

1	Not at all	I would not recommend this app to anyone
2		There are very few people I would recommend this app to
3	Maybe	There are several people I would recommend this app to
4		There are many people I would recommend this app to
5	Definitely	I would recommend this app to everyone

18. **How many times do you think you would use this app in the next 12 months if it was relevant to you?**

1 None
2 1-2
3 3-10
4 10-50
5 >50

19. **Would you pay for this app?**

1 Definitely not
2
3
4
5 Definitely yes

20. **What is your overall (star) rating of the app?**

1	★	One of the worst apps I've used
2	★★	
3	★★★	Average
4	★★★★	
5	★★★★★	One of the best apps I've used

Perceived impact

SECTION F

1. **Awareness – This app has increased my awareness of the importance of addressing the health behaviour**

Strongly disagree Strongly Agree
1 2 3 4 5

2. **Knowledge – This app has increased my knowledge/understanding of the health behaviour**

Strongly disagree Strongly Agree
1 2 3 4 5

3. **Attitudes – The app has changed my attitudes toward improving this health behaviour**

Strongly disagree Strongly Agree
1 2 3 4 5

4. **Intention to change – The app has increased my intentions/motivation to address this health behaviour**

Strongly disagree Strongly Agree
1 2 3 4 5

5. **Help seeking – This app would encourage me to seek further help to address the health behaviour (if I needed it)**

Strongly disagree Strongly Agree
1 2 3 4 5

6. **Behaviour change – Use of this app will increase/decrease the health behaviour**

Strongly disagree Strongly Agree
1 2 3 4 5

Further comments about the app?

THANK YOU!

7.5 PATAT Questionnaire

The PAtient Trust Assessment Tool (PATAT).

Trust in the care organization	
1	[Care organization] has a good reputation
2	At [Care organization] they handle my personal information carefully
3	At [Care organization] they take action when something goes wrong
4	At [Care organization], I feel at ease
5	At [Care organization], they take my specific needs into account
Trust in care professional	
6	I trust my [doctor's] judgment about my medical care
7	My [doctor] provides me with all the information on all potential medical options
8	My [doctor] keeps all my medical information private
9	I always follow my [doctor's] advice
10	My [doctor] does not do everything [he or she] should about my medical care
Trust in technology	
16	When I use [the website], I am in control
17	Everything that I do on [the website] remains private
18	The personal information that is stored at [the website] will not get lost
19	[the website] is easy to use
20	Legal policy and technological safeguards make [the website] a safe environment
Trust in telemedicine service	
21	I can trust [this website]
22	I can trust that possible problems with [this website] will be solved properly
23	I can trust this service less than other online services, such as Bol.com and the website of my municipality
24	I feel at ease when working with [this website]
25	I do not like to enter my personal data on [this website]

Note: the terms 'doctor' and 'website' should be adapted to the application context (e.g., doctor may be replaced by physical therapist, or website with smartphone app).

7.6 Technology Acceptance Model questionnaire (Health professional)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
The use of the *[system]* could help me to execute my *[mention activities]* activities more rapidly					
The use of the *[system]* could help me to *[description of activities]*					
I think that I could easily learn how to use the *[system]*					
I think it is a good idea to use the *[system]* to *[description of system goal]*					
The use of the *[system]* may imply major changes in my *[description of activities]*					
I think that my work center has the necessary infrastructure to support my use of the *[system]*					

I feel comfortable with information and communication technologies					
I have the intention to use the *[system]* when it becomes available in my work center					

7.7 Depression questionnaires - PHQ-9

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "√" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite —being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns	+	+	

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

7.8 Anxiety questionnaires - GAD-7

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

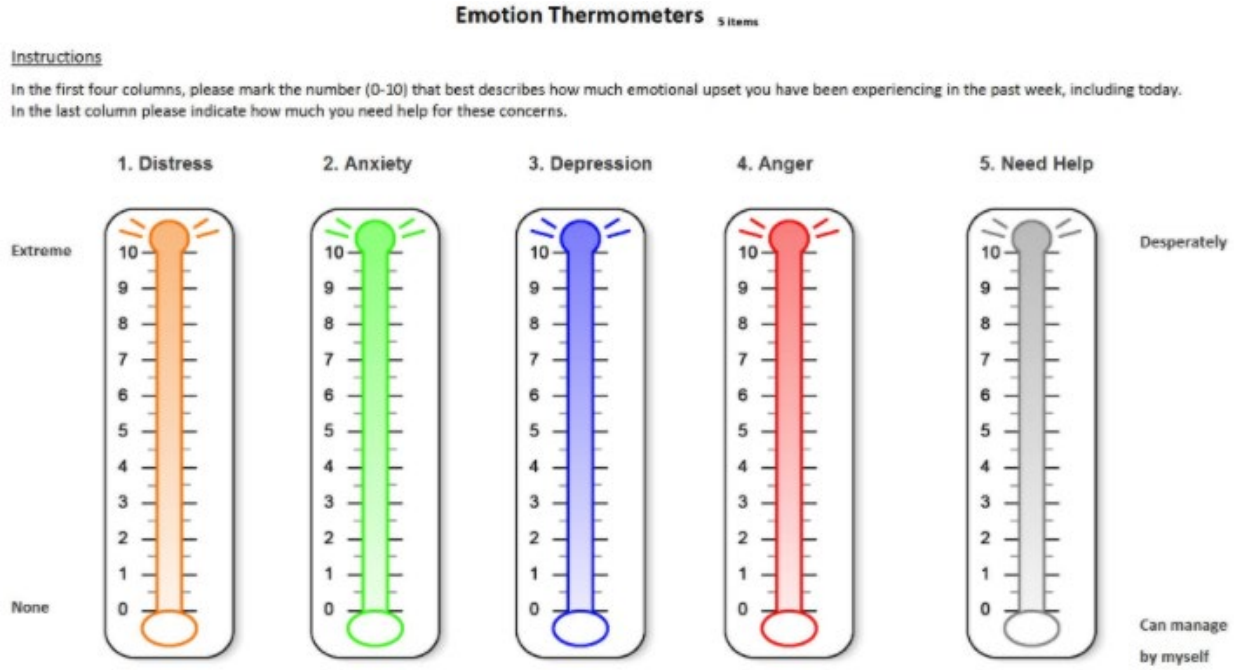
Scoring

Scores of 5, 10, and 15 are taken as the cut-off points for mild, moderate and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.

Using the threshold score of 10, the GAD-7 has a sensitivity of 89% and a specificity of 82% for GAD. It is moderately good at screening three other common anxiety disorders - panic disorder (sensitivity 74%, specificity 81%), social anxiety disorder (sensitivity 72%, specificity 80%) and post-traumatic stress disorder (sensitivity 66%, specificity 81%).

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Inern Med.* 2006;166:1092-1097.

7.9 The emotion thermometers



7.10 Caregiver Burden Inventory

Caregiver Burden Inventory
(Novak and Guest, 1989)

The Case Manager will administer the inventory by reading the statement and marking the responses.
Choose the number that best represents how often the statement describes your feelings.
0 - Never
1 - Rarely
2 - Sometimes
3 - Quite Frequently
4 - Nearly Always

Client Name_____ **Caregiver Name** _____**Date**_____

Time Dependency Items	
He/she needs my help to perform many daily tasks	⓪①②③④
He/she is dependent on me	⓪①②③④
I have to watch him/her constantly	⓪①②③④
I have to help him/her with many basic functions	⓪①②③④
I don't have a minute's break from his/her chores	⓪①②③④

Development Items	
I feel that I am missing out on life	⓪①②③④
I wish I could escape from this situation	⓪①②③④
My social life has suffered	⓪①②③④
I feel emotionally drained due to caring for him/her	⓪①②③④
I expected that things would be different at this point in my life	⓪①②③④

Physical Health Items	
I'm not getting enough sleep	⓪①②③④
My health has suffered	⓪①②③④
Care giving has made me physically sick	⓪①②③④
I'm physically tired	⓪①②③④

Emotional Health Items	
I feel embarrassed over his/her behavior	⓪①②③④
I feel ashamed of him/her	⓪①②③④
I resent him/her	⓪①②③④
I feel uncomfortable when I have friends over	⓪①②③④
I feel angry about my interactions with him/her	⓪①②③④

Social Relationships Items	
I don't get along with other family members as well as I used to	⓪①②③④
My care giving efforts aren't appreciated by others in my family	⓪①②③④
I've had problems with my marriage (or other significant relationship)	⓪①②③④
I don't get along as well as I used to with others	⓪①②③④
I feel resentful of other relatives who could but do not help	⓪①②③④

Total Score:

Scores near or above 36 indicates a greater need for respite and other services.

It is important to seriously look at any item on the burden scale where the answer was scored as a 3 or 4 ('quite frequently' or 'nearly always'). If you have a 3 or 4 as an answer, give careful thought about why the caregiver scored so high on the question and see if you can find away to reduce the stress.