International Journal of Medical Informatics 131 (2019) 103972

Contents lists available at ScienceDirect

International Journal of Medical Informatics

journal homepage: www.elsevier.com/locate/ijmedinf

Design and evaluation of a mobile application for monitoring patients with Alzheimer's disease: A day center case study

Alma Chávez[a], Gilberto Borrego[a], J. Octavio Gutierrez-Garcia[b], Luis-Felipe Rodríguez[a,*]

[a] Instituto Tecnológico de Sonora, Cd. Obregón, Sonora 85000, Mexico
[b] ITAM, Río Hondo 1, Ciudad de México 01080, Mexico

ARTICLE INFO

Keywords:
Monitoring mobile application
Alzheimer's disease
Participatory design software methodology
Alzheimer's day center
Design recommendations

ABSTRACT

Background and objective: This paper presents Alzheed, a mobile application for monitoring patients with Alzheimer's disease at day centers as well as a set of design recommendations for the development of healthcare mobile applications. The Alzheed project was conducted at Day Center "Dorita de Ojeda" that is focused on the care of patients with Alzheimer's disease.
Materials and methods: A software design methodology based on participatory design was employed for the design of Alzheed. This methodology is both iterative and incremental and consists of two main iterative stages: evaluation of low-fidelity prototypes and evaluation of high-fidelity prototypes. Low-fidelity prototypes were evaluated by 11 day center's healthcare professionals (involved in the design of Alzheed), whereas high-fidelity prototypes were evaluated using a questionnaire based on the technology acceptance model (TAM) by the same healthcare professionals plus 30 senior psychology undergraduate students uninvolved in the design of Alzheed.
Results: Healthcare professional participants perceived Alzheed as extremely likely to be useful and extremely likely to be usable, whereas senior psychology undergraduate students perceived Alzheed as quite likely to be useful and quite likely to be usable. Particularly, the median and mode of the TAM questionnaire were 7 (extremely likely) for healthcare professionals and 6 (quite likely) for psychology students (for both constructs: *perceived usefulness* and *perceived ease of use*). One-sample Wilcoxon signed-rank tests were performed to confirm the significance of the median for each construct.
Conclusions: From the experience of designing Alzheed, it can be concluded that co-designing with healthcare professionals leads to (i) fostering group endorsement, which prevents resistance to change and (ii) helps to meet the needs of both healthcare professionals and patients, guaranteeing the usefulness of the application. In addition, evaluation of mobile healthcare applications by users involved and uninvolved in the application's design process helps to improve the ease of use of the application.

1. Introduction

The world's population pyramid has changed through the years due to increasing life expectancy. Whereas a long life expectancy is associated with a healthy population, it is also associated with age-related diseases, e.g., Alzheimer's disease [1]. According to Winblad et al. [2], Alzheimer's disease is the most common type of dementia with 50–70% of dementia cases. In fact, the World Alzheimer Report 2018 [3] indicates that in 2018 the number of people affected by dementia worldwide was 50 million, representing an estimated cost of US$1 trillion and about 82 billion hours spent by informal caregivers. In this regard, Brookmeyer et al. [4] estimate that by 2050 approximately 1.18% of the world's population will suffer from Alzheimer's disease. Particularly, the number of people with Alzheimer's is projected to double every 20 years [2,3]. This becomes a global issue because, among other aspects, there will be an even higher need for senior care, and in particular, for specialized care for patients with Alzheimer's disease [3].

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive deterioration of vital brain functions [5]. According to the Alzheimer's Association [6], patients with AD pass through several stages including early stage, middle stage, and late stage. In the early stage, patients may be independent and may have memory lapses, lose objects, and/or have difficulties in planning. In the middle stage, patients may be confused about time and space, may have bladder control problems, may show mood swings, and may forget

* Corresponding author.
E-mail addresses: alma.chavezq@gmail.com (A. Chávez), gilberto.borrego@itson.edu.mx (G. Borrego), octavio.gutierrez@itam.mx (J.O. Gutierrez-Garcia), luis.rodriguez@itson.edu.mx (L.-F. Rodríguez).

https://doi.org/10.1016/j.ijmedinf.2019.103972
Received 12 June 2019; Received in revised form 8 August 2019; Accepted 15 September 2019

events of their personal history. In the late stage, patients' abilities to communicate, walk, and even swallow are likely to be deteriorated dramatically and may even become vulnerable to infections [6].

Alzheimer's day centers are organizations that help with the daily care of patients with AD. A day center provides patients with cognitive and physical therapies, social activities, educational programs, nutrition programs, among other programs [7]. Alzheimer's day centers commonly enroll patients on these programs depending on the progression of their disease. This is the case of Day Center "Dorita de Ojeda" located in Ciudad Obregón, Sonora, Mexico, where the case study of this present work was carried out.

The different stages of AD emphasize the need for continuous monitoring of patients by caregivers at day centers. Data on their behavior and/or physical abilities may help to determine the type of medical care patients with AD should be receiving according to the progression of their disease. However, this continuous monitoring is, in some cases, carried out by caregivers using physical notepads at the end of their journey or at the same time they provide patients with medical care. In this regard, caregivers at day centers must focus their attention mainly on patients as the behaviors of people with dementia may lead to critical situations such as self-harm [8]. Moreover, data collection sometimes is regarded as an informal process with no standard workflows. As a result, this monitoring process is both time consuming and error-prone.

To facilitate this continuous monitoring of patients with AD, this work proposes Alzheed, a mobile application for monitoring patients with AD at day centers.

The purpose of this work is to provide insights gained from designing Alzheed at Day Center "Dorita de Ojeda" into how mobile applications in the context of Alzheimer's day centers should be designed and evaluated. It should be noted that Alzheed was implemented as a mobile application because, as indicated in [9], (i) mobility is fundamental to support healthcare workflows and (ii) many healthcare professionals already recognize the benefits of mobile computing, which eases the adoption of mobile applications. In addition, a mobile application allows healthcare professionals to reduce the time that patients with AD (whose behaviors may lead to self-harm [8]) are left unattended.

Alzheed is a type of *mobile health monitoring system* according to the classification proposed by Baig and Gholamhosseini [10], as Alzheed relies on mobile devices for the monitoring of patients with AD by caregivers at day centers. The classification by Baig and Gholamhosseini organizes this type of systems as (i) remote, (ii) mobile, and (iii) wearable *health monitoring systems*. In particular, the type of monitoring implemented in Alzheed is characterized by the type of data collected and the data collection strategy. The types of data collected by means of Alzheed are (i) behavioral data such as aggression, wandering, apathy, and drowsiness; (ii) clinical and health related data; (iii) activities carried out; (iv) performance in cognitive and physical therapies; (v) attitudes and crises such as anger, delusions, mood swings, and anxiety; (vi) hygiene habits; (vii) eating performance; and (viii) administrative data such as arrival time to the day center. The data collection strategy of Alzheed is characterized by manual data registration, continuous monitoring, unobtrusive patient monitoring, and contextual data input.

Importantly, the healthcare context of Alzheimer's day centers pose several challenges to mobile software design, including (i) the incorporation of highly specialized knowledge of healthcare professionals, (ii) matching the peculiarities of AD with software requirements, (iii) dealing with potentially subjective perception of AD's symptoms, and (iv) handling frequent monitoring of a number of patients.

Due to the above challenges and monitoring requirements, this work adopted a software design methodology based on participatory design where target users and developers co-design applications [11]. This type of software design methodology leads to a user-centered design that captures the needs of both healthcare professionals and patients [12]. Furthermore, participatory design has proved its value in the context of healthcare, see [13–15] for successful examples.

To design Alzheed, both low-fidelity and high-fidelity prototypes were developed. A low-fidelity prototype is a tangible sketch of an application design with the aim of (i) verifying whether an application meets previously identified requirements and (ii) checking usability. A high-fidelity prototype is a realistic representation of the application in terms of visual design, content, and functionality. The objective of a high-fidelity prototype is to provide users (e.g., caregivers) with an application as similar as possible to the final version of the application. By creating low-fidelity and high-fidelity prototypes, working software was prioritized and prompt feedback from users was received. Target user collaboration was promoted by (i) conducting interviews as part of the requirement analysis and (ii) evaluating the design progress by giving a presentation on low-fidelity and high-fidelity prototypes to final users.

To formally evaluate Alzheed's design, a technology acceptance model (TAM) questionnaire [16] was used. The TAM was selected because it measures both *perceived usefulness* and *perceived ease of use* using a short 12-item questionnaire. In addition, it is a universal questionnaire [17] that can be adapted to the domain of the application. Moreover, the TAM questionnaire is widely accepted in the literature [18]. The TAM questionnaire was completed by both (i) target users involved in the initial phases of Alzheed's design and (ii) potential target users uninvolved in the design. This is because previous participation of the users in the design may compromise their opinions, hence, users uninvolved in the design may be better judges for the usability and usefulness of Alzheed.

The novelty of this work rests on (i) the introduction of a phase for matching software requirements with the peculiarities of a given condition (e.g., Alzheimer's condition) to a participatory software design methodology for healthcare mobile applications, and (ii) the introduction of a formal evaluation methodology for healthcare mobile applications where the feedback from users involved and uninvolved in the design of the mobile applications is taken into account. The relevance of this work rests on its contributions towards further understanding how mobile applications in the context of Alzheimer's day centers should be designed and evaluated, which are as follows:

- An iterative and incremental participatory software design methodology for healthcare mobile applications, which includes a phase for matching software requirements with the peculiarities of a given condition to help to assure that the requirements elicited take into account relevant aspects associated with the condition (see Section 3).
- An evaluation methodology for healthcare mobile applications where both users involved and users uninvolved in the design of the applications formally evaluate high-fidelity prototypes (see Section 3.2).
- A mobile application for monitoring patients with AD that is currently used at an Alzheimer's day center in Mexico (see Section 4.2.1).
- A set of design recommendations for the development of healthcare mobile applications in the context of Alzheimer's day centers (see Section 5).
- A participatory design experience that can be used as a reference for future mobile application developments in the context of Alzheimer's day centers.

The rest of the paper is structured as follows. Section 2 presents a brief literature review on design experiences and design recommendations of mobile application developments for AD and/or dementia care. Section 3 describes the materials and methods used to design and evaluate Alzheed. Section 4 presents results regarding the design and evaluation of Alzheed's low-fidelity and high-fidelity prototypes.

Table 1
Related work comparison.

	Authors' present research	Slegers et al. [13]	Maiden et al. [23]	Zachos et al. [24]	Edmeads and Metatla [25]	Muriana and Hornung [15]
Application domain	Monitoring patients	Mealtime monitoring	Caregivers support	Caregivers support	Reminiscence engagement	General
Target user	Psychologists, physiotherapists, nurses, and social workers	Caregivers	Caregivers	Caregivers	Senior citizens	Senior citizens
Participatory design	Yes	Yes	Yes	Yes	Yes	Yes
Low-fidelity prototype	Yes	Yes	No	No	Yes	Yes
High-fidelity prototype	Yes	Yes	No	No	Yes	No
Design evaluation technique	Formal TAM questionnaire	NA	NA	Pilot case study in residential home	Observation of participant exploration of prototypes	Open conversations of participants
Design evaluation by target users where at least some users were involved in the design process	Yes	NA	NA	Yes	Yes	Yes
Design evaluation by target users uninvolved in the design process	Yes	NA	NA	No	No	No
Number of participants involved in the evaluation	41	NA	NA	7	26	12
Application implemented	Yes	No	Yes	Yes	Yes	No

Section 5 presents design recommendations for the development of healthcare applications in the context of Alzheimer's day centers. Section 6 provides some concluding remarks and future research directions.

2. Related work

It is acknowledged that there is a myriad of research efforts implementing ad-hoc (mobile) applications focused on AD and/or dementia-related diseases, see [19–21]. However, frequently the focus of those efforts is on technical challenges, e.g., Helmy and Helmy's work [19] focuses on activity recognition algorithms for dementia, autism, and AD. Moreover, specialized surveys on computer-assisted technology for AD have been published, see, for instance, the survey by Ienca et al. [22]. Nevertheless, literature on design experiences and design recommendations for mobile applications for AD and dementia-related conditions is scarce. Table 1 presents a comparative overview of healthcare applications for patients with dementia. These selected works were identified from the results of a Google Scholar search using the following keywords: *dementia*, *Alzheimer's disease*, *software/application design*, and/or *mobile applications*.

As observed in Table 1, in the domain of healthcare applications for patients with dementia, participatory design is commonly performed (see [13,23–25,15]), however, the design of the applications is either not evaluated (as in [23]) or evaluated informally (as in [15] via open conversations). Moreover, some research efforts [23,24] skip the design evaluation phase and request target users to evaluate a pilot application, which may result in applications that may not meet the needs of target users entirely. In this regard, this present work's participatory design methodology includes both low-fidelity and high-fidelity prototypes to help to assure that user requirements are met. Unlike previous research on the design of healthcare applications focused on AD (see [13,23–25,15]), to evaluate the design of Alzheed, a formal design evaluation technique, namely the TAM questionnaire, was used. Furthermore, in contrast to other research efforts [24,25,15], in addition to evaluating prototypes using target users involved in the initial phases of the design, Alzheed's design was also evaluated by target users uninvolved in the design, which may be better judges for the usability and usefulness of Alzheed. Also, as shown in Table 1, the number of participants involved in the evaluation of healthcare applications for patients with dementia is relatively small, ranging from 7 (as in [24]) to 26 (as in [25]). This may be due to the complexity of recruiting participants to some degree connected with or familiar with dementia-related diseases. In this regard, the results presented in this work were obtained from the evaluation of Alzheed by 41 participants.

3. Materials and method

The software design methodology (Fig. 1) employed is both iterative and incremental and consists of two main iterative stages: evaluation of low-fidelity prototypes and evaluation of high-fidelity prototypes.

3.1. First iteration: low-fidelity prototypes

The first iteration of the methodology focuses on the design and evaluation of low-fidelity prototypes that serve to (i) corroborate that all identified requirements are met and (ii) allow users to visualize how the mobile application would work so that they could provide feedback at this early design stage.

3.1.1. Objective

The main goal of this phase is to deeply understand (i) the daily activities and roles of people involved in the day center, (ii) the interactions between healthcare professionals/staff and patients, and (iii) the data to be collected about patients.

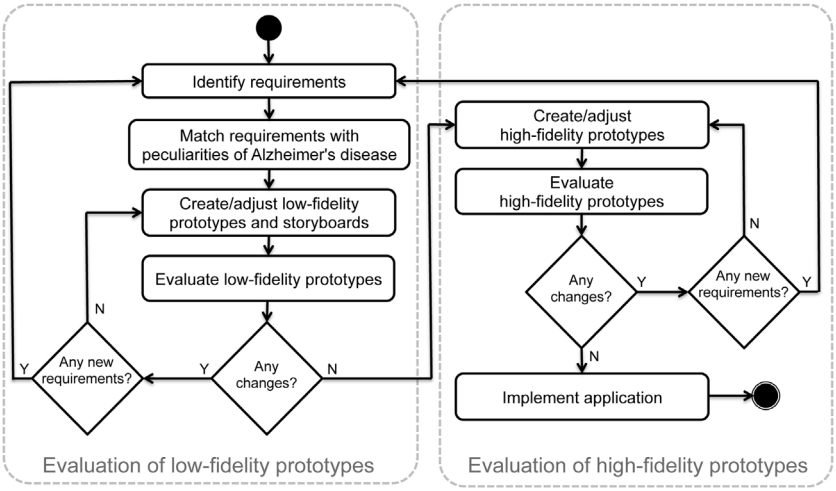

Fig. 1. Software design methodology employed for the development of Alzheed.

3.1.2. Instrumentation

In this phase, day center's healthcare professionals and staff were interviewed using an ad-hoc semi-structured interview. Table 2 includes the questions used as a reference to guide the interview.

3.1.3. Process

1. *Requirements elicitation.* The elicitation of requirements consisted of the following four activities:
   - *Interviews*: day center's healthcare professionals as well as staff were interviewed to obtain (i) a holistic view of the Alzheimer's condition and (ii) a global perspective of their daily activities.
   - *Observation*: an observation phase was carried out during one month visiting the day center three times a week from four to eight hours each day.
   - *Process modeling*: using information extracted from the interviews and the observation phase, a formal business process model was made, see Figs. 2 and 3 . This facilitated both understanding and formalizing the processes regarding the care of patients with AD carried out at the day center.
   - *User stories*: as a result of the requirement analysis, user stories were generated to clearly specify and represent the requirements identified.
2. *Matching software requirements with the peculiarities of Alzheimer's condition.* Based on the requirements elicited, a set of data elements to monitor patients with AD were identified. In this phase, the relationships between these data elements and either symptoms, causes, or risk factors of AD were verified. In doing so, it is expected to guarantee that the requirements elicited take into account relevant aspects associated with the Alzheimer's condition. In addition, during this phase, when the causes and/or symptoms are subject to the perception of either healthcare professionals or the patients in question, Likert scales were defined and proposed for each potentially subjective symptom/cause.
3. *Creation of low-fidelity prototypes and storyboards*. Once all the requirements were identified, a set of low-fidelity prototypes and storyboards were created. The storyboards consisted of sequences of low-fidelity prototypes of Alzheed's screens and their associated descriptions, which showed to each type of user the proposed procedure to record the data collected from monitoring patients with AD (see Fig. 4). These low-fidelity scenarios and storyboards allowed target users to understand and visualize how the mobile application would work with respect to data input items, graphical elements, navigation method, screen sequences, among other aspects.
4. *Validation of low-fidelity prototypes with healthcare professionals involved in the day center*. The low-fidelity prototypes were presented to the day center's healthcare professionals and staff. The objective was to promote their criticism under the assumption that observing a work-in-progress product may facilitate the expression of users' opinions. In this phase, users were able to propose modifications to both the form and content of the mobile application. Users were provided with materials such as sticky notes and markers so that they could point out the changes in each element of the proposed prototype. It is worth remarking that in this phase, new requirements could be found. In such a case, it is necessary to return to the requirements elicitation phase and match the new requirements with the peculiarities of Alzheimer's condition, followed by the creation of new low-fidelity prototypes and storyboards to be validated with the participants.

Table 2
Questions of the ad-hoc semi-structured interview used as a reference to guide the interview.

Q1	What do you know about AD (causes, symptoms, stages, treatment, etc.)?
Q2	What role do you play in the care of patients with AD?
Q3	Please describe your daily tasks
Q4	What data/information do you need to do your daily tasks?
Q5	What data do you register during the day in relation to your activities?
Q6	How do you currently register your data?
Q7	How often and how many times do you register data?
Q8	How much time do you spend registering data?
Q9	Who at the day center makes use of the information that you register?
Q10	What sort of data (that is not currently registered) do you think would be useful?
Q11	Is there any data that you monitor and keep in mind but you are not explicitly instructed to register?
Q12	How do you know which data is relevant to the evolution of the patient and which one is not?
Q13	What kind of decisions could be supported with this registered data?

3.2. Second iteration: high-fidelity prototypes

The second iteration of the methodology focuses on the design of a high-fidelity prototype to provide users with a realistic representation of the application so that aspects such as visual design, content, and functionality are formally evaluated before carrying out a computational implementation.

3.2.1. Objective

The main goal of this phase is to design a high-fidelity interactive prototype of the mobile application. This prototype allowed

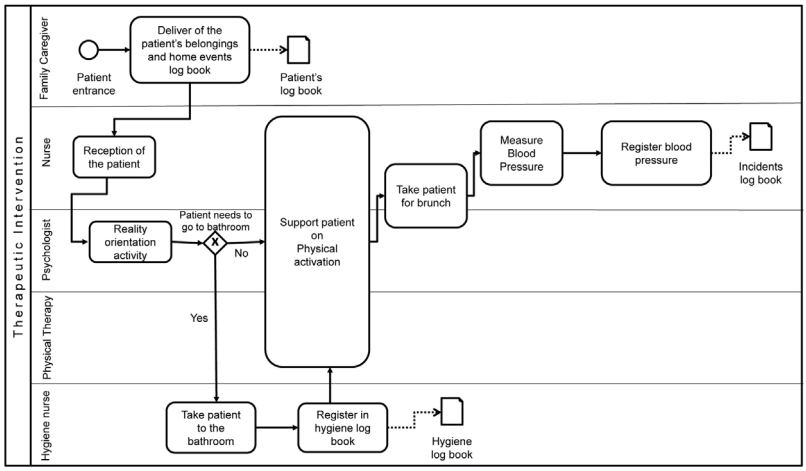

Fig. 2. Formal business process model of the day center (Part 1).

participants to evaluate its usability and usefulness from the perspective of the role each participant plays.

3.2.2. Instrumentation

A questionnaire based on TAM [16] (with a Likert-7 scale) was used to evaluate the user perception of usefulness and ease of use. According to Davis [16], perceived usefulness is defined as "*the degree to which a person believes that using a particular system would enhance his or her job performance*" and perceived ease of use is defined as "*the degree to which a person believes that using a particular system would be free of effort.*"

3.2.3. Process

1. *Creation of high-fidelity scenarios*. A high-fidelity prototype was designed based on the feedback from the day center's healthcare professionals and staff about the low-fidelity prototypes. It is worth highlighting that the high-fidelity prototype must allow final users to understand how the mobile application would work so that constructs such as *perceived ease of use* and *perceived usefulness* can be evaluated.
2. *Evaluation of the high-fidelity prototype by users involved and uninvolved in the design of Alzheed*. The high-fidelity prototype was evaluated through a focus group using a TAM questionnaire. The evaluation took place after a cognitive walk-through to show how users can interact with the mobile application and how this application assists in data collection. There were two evaluations: (i) one evaluation conducted by the day center's healthcare professionals and staff involved in the design of Alzheed, and (ii) one evaluation conducted by senior psychology students uninvolved in the design process of the low-fidelity and high-fidelity prototypes. The evaluation by participants uninvolved in the design of Alzheed may increase the probability that future healthcare professionals working at day centers for patients with AD will find the mobile application useful. If new requirements were identified in this evaluation phase, it is necessary to return to the requirements elicitation phase, match the new requirements with the Alzheimer's condition peculiarities, and create the corresponding low-fidelity prototypes to be re-evaluated. Otherwise, when participants proposed modifications that did not involve new requirements, the high-fidelity prototype was simply adjusted and re-evaluated by the participants.
3. *Implementation of Alzheed*. Once the high-fidelity prototype was fully approved, the implementation of the mobile application was carried out.

4. Results

This section presents the results of each iteration of the software design methodology described in Section 3.

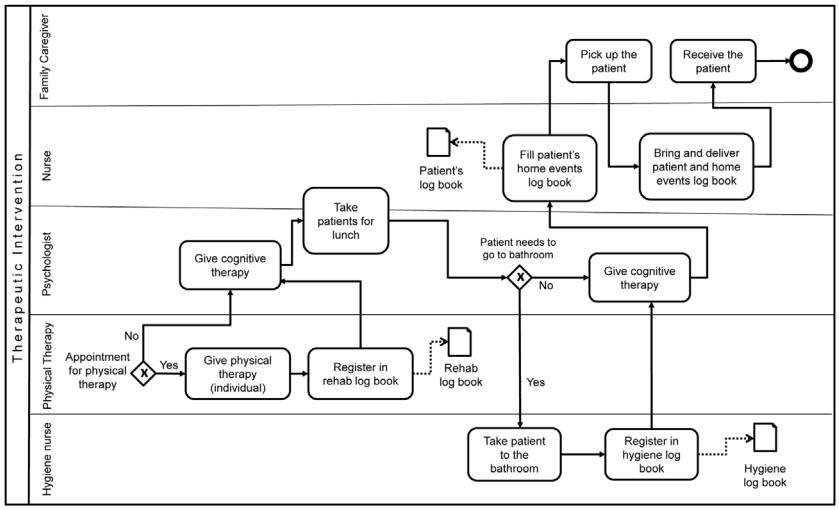

Fig. 3. Formal business process model of the day center (Part 2).

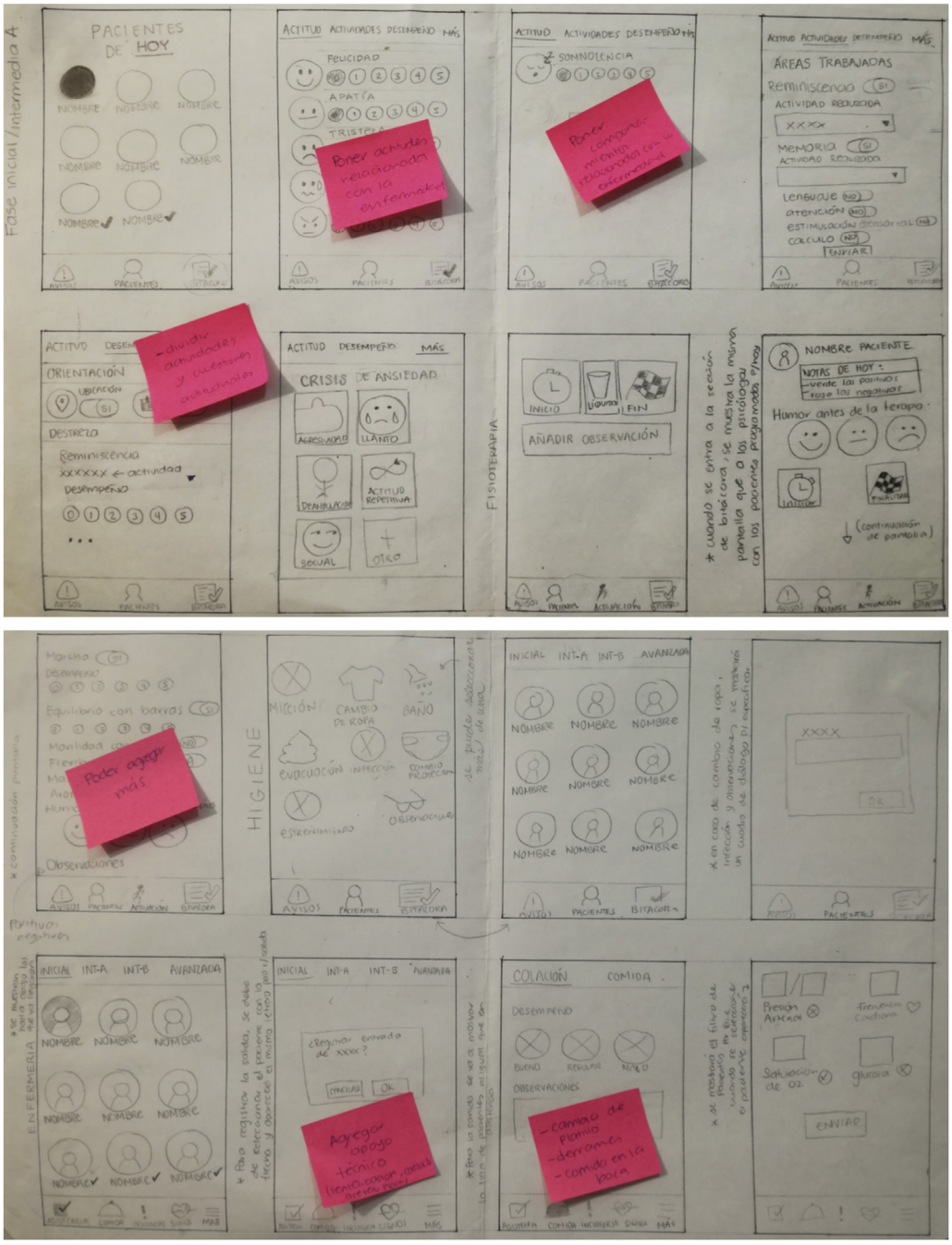

Fig. 4. An illustrative example of (i) storyboards composed of low-fidelity prototypes of Alzheed and (ii) corrections to low-fidelity prototypes by the day center's healthcare professionals.

Table 3
A representative user story.

	User story: Patient's log book
Number: 1	**User:** Psychologist
	Story name: Patient's log book
	Description:
As a psychologist I want to be able to record whether the patient is wandering, anxious, how many crises presents, the level of social disintegration, and level of drowsiness. Every item should be evaluated using values ranging from 0 to 5. This process must be simple and intuitive. When a patient's medication changes, the mobile application must notify the psychologists.	
Observations: Psychologists would like to have access to the information of all the patients of the day center.	

4.1. Low-fidelity prototypes

In this phase, the participants were the psychologists, nurses, social workers, and physiotherapists of Day Center "Dorita de Ojeda". Participants were interviewed individually about their daily routines. Each interview lasted between 20 and 40 minutes. After the interviews were completed, the observation phase took place.

From the observation phase and the interviews, a formal business process model was made (see Figs. 2 and 3), which helped to detect four main activity areas of the day center: cognitive therapy, physical therapy, nursery, and hygiene. So, tasks performed by healthcare professionals in these four activity areas were also analyzed. As expected, healthcare professionals at the day center perform tasks that take a great amount of time such as taking notes using physical notepads and

Table 4
Brief summary of user stories.

User story	User	Description
Patient's log book	Psychologist or social worker	The user will register crises, and different attitudes and behaviors of patients
Hygiene log book	Hygiene nurse	The application must register the time every patient urinates and defecates. The user must be able to add any other incidences regarding patient hygiene
Physical therapy summary	Physiotherapist	The user must be able to evaluate the activities done by patients during therapies, also, must be able to indicate whether any planned activity was not done by patients. Every activity will be evaluated in a 0 to 5 scale. Also, the user must be able to register the start and finish time of therapy as well as the initial and final mood of patients
Patient summary	Physiotherapist	The user must be able to see patient's summary, for instance, whether s/he has sleeping troubles or any trouble mood to deal with, and/or whether there was any recent injury
Physical activation	Physiotherapist	The user must be able to register the start and finish time of the physical activation
Incidences	Nurse	The user must be able to register different important notes about patients (for instance, incidences in and out of the day center such as injuries, sleep disorders, medication change, etc.)
Attendance	Nurse	The user must be able to register the entrance and exit of every patient
Patient's directory	Nurse	The user must be able to see a relative's contact details of patients
Meals performance	Nurse	The user must be able to evaluate eating performance of every patient during brunch and lunch
Vital signs	Nurse	The user must be able to manually register patients' vital signs (heart rate, blood pressure, oxygen saturation, and glucose)

sharing information with partners about diverse aspects of patients (e.g., their behaviors and attitudes).

User stories were developed based on the results of the interviews and observation. See Tables 3 and 4 for an example of a representative user story and a summary of the user stories created, respectively.

A low-fidelity prototype was designed based on the user stories and requirements identified. This low-fidelity prototype was made on paper and provided to the participants so that they could propose any modification (Fig. 4). The low-fidelity prototype was shown to the participants individually in a session conducted at the day center. Participants pointed out modifications using sticky notes that were pasted on the drawings. The modifications proposed ranged from including additional data fields to providing separate sections for registering patient's performance on cognitive therapies and physical activities. In general, the design and development of this low-fidelity prototype was carried out in a total of 7 weeks.

4.2. High-fidelity prototypes

A high-fidelity prototype was developed based on the feedback from the healthcare professionals of the day center about the low-fidelity prototypes. This high-fidelity prototype was designed and developed using the Adobe Experience Design Tool [26]. In the remainder of this section, key features of Alzheed and its evaluation are presented.

4.2.1. Alzheed's key features

Alzheed facilitates continuous monitoring of patients with AD at day centers. Alzheed allows healthcare professionals to manually register patients' (i) performance in cognitive therapies and (ii) observed behaviors related to the Alzheimer's condition such as aggression, wandering, apathy, and drowsiness. Also, healthcare professionals are able to manually input information on patients' attitudes and crises such as anger, delusions, mood swings, and anxiety. Alzheed also provides mechanisms for manually registering extraordinary events associated with patient behaviors. Using Alzheed, nurses and physiotherapists are able to manually register information about how many times patients go to the restroom, their eating performance, vital signs, medication changes, and their performance in physical therapies. It should be noted that Alzheed does not support automatic data collection, for instance, of vital signs, because the day center, for which Alzheed was developed for, was not provided with special devices and/or sensors to enable automatic data collection. Furthermore, Alzheed presents patient information grouped into five main categories: (i) nursery, (ii) hygiene, (iii) physiotherapy, (iv) cognitive behavior for early phases of AD, and (v) cognitive behavior for advanced phases of AD. It should be noted that these categories were determined based on the results of the requirement's elicitation and observation phases. See Table 5 for a list of other Alzheed's features and Fig. 5 for a set of selected Alzheed's screenshots depicting some functionalities.

4.2.2. Evaluation of Alzheed using the TAM

Alzheed was evaluated in terms of *perceived usefulness* and *perceived ease of use*. There were two participant groups: (i) a group of 11 healthcare professionals involved in the design of Alzheed, and (ii) a group of 30 senior undergraduate students pursuing a B.A. in psychology uninvolved in the design of Alzheed. Psychology students were selected because they are potential healthcare professionals that may be involved in the care of people with dementia, and at the same time, they are outsider evaluators (i.e., evaluators uninvolved in the design) of the high-fidelity interactive prototype.

Individuals of both participant groups were requested to answer a TAM questionnaire (Table 6) after observing a cognitive walk-through showing Alzheed's characteristics. It should be noted that the TAM is a customizable, standard questionnaire [17], which is interpreted by respondents according to their domain. For instance, in the context of healthcare professionals working at Alzheimer's day centers, the term *job performance* (in question 2 of Table 6) means how well healthcare professionals perform their job duties such as monitoring patients with AD. The results of the TAM questionnaire are presented in Tables 7 and 8 .

As for the evaluation by the healthcare professionals of the day center involved in the design of Alzheed, Table 8 shows that the median and mode are 7 (extremely likely) for both constructs: perceived usefulness and perceived ease of use. In addition, the minimum value is 4 (neither), and percentiles 75 are 7 for both constructs. Thus, in general, the healthcare professional participants perceived Alzheed as (extremely likely to be) useful and (extremely likely to be) usable.

As for the evaluation by the senior psychology undergraduate students uninvolved in the design of Alzheed, Table 8 shows that the median and mode are 6 (quite likely) for both constructs: perceived usefulness and perceived ease of use. It should be noted that the minimum value for both constructs is 1 (extremely unlikely). Nevertheless, as shown in Table 7, this minimum value was reported only by 3 (out of 30) participants. It is worth mentioning that none of the percentiles are lower than 5 (slightly likely). Furthermore, to verify whether these extreme values have a lower significance than a specified median, two one-sample Wilcoxon signed-rank tests were performed (one for each construct) on the evaluation results obtained from the senior psychology undergraduate students. The one-sample Wilcoxon signed-rank test was applied since the Likert scale is considered an ordinal scale and the obtained data of each construct was not adjusted to the normal curve based on the results of the Kolmogorov-Smirnov test of normality (p-value < 0.00001). In particular, for the usefulness construct with a specified median of 5, the one-sample Wilcoxon

Table 5
Key features of Alzheed for monitoring patients with AD by healthcare professionals.

Type of feature	User(s)	Name	Description
Administrative	Nurse	Attendance	Users are able to register patient arrivals to the day center and assistive devices (e.g., a walking stick) that bring with them. In addition, users are able to register patient departures from the day center
Health	Nurse	Vital signs	Users are able to manually register blood pressure, oxygen saturation, glucose, and heart rate of patients
Nutrition	Nurse	Meals	Users are able to register patients' performance during every meal either brunch or lunch
Administrative, discipline, and health	Nurse, psychologist, social worker and/or physiotherapist	Incidences and notifications	Users are able to register any incidence with patients. The incidence can be about physical conditions, sleep disorders, discipline issues or hygiene. In addition, users are able to indicate which individuals will receive a given notification regarding a given patient
Hygiene	Nurse	Hygiene log book	Users are able to register every time patients defecate and/or urinate in addition to registering whether patients have an infection and/or constipation, among other conditions
Cognitive	Psychologist and/or social worker	Activities	Users are able to register which therapy areas were stimulated (namely, reminiscence, calculus, language, sensory stimulation, attention and memory) and the activities done for each therapy
Cognitive	Psychologist and/or social worker	Performance	Based on the users' role, users are able to evaluate the performance shown by patients during a given activity from 0 to 5
Non-cognitive symptoms	Psychologist and/or social worker	Attitude log book	Users are able to evaluate attitudes (e.g., anxiety) shown by patients from 0 to 5
Non-cognitive symptoms	Psychologist and/or social worker	Behavior log book	Users are able to evaluate behaviors (such as wandering and apathy) shown by patients from 0 to 5
Non-cognitive symptoms	Psychologist and/or social worker	Crisis	Users are able to register patients' crises such as crying and repetitive attitudes, among others
Physical	Physiotherapist	Physical log book	Users are able to register activities done by patients in therapy sessions and evaluate patients' performance from 0 to 5. In addition, users are able to register patients' mood before and after therapies

signed-rank test ($W = 196.5$, p-value = 0.03732) shows that the median is significantly greater than 5 even with extreme values such as 1 and 2. For the ease of use construct also with a specified median of 5, the one-sample Wilcoxon signed-rank test ($W = 220.5$, p-value = 0.02138) shows that the median is significantly greater than 5, which means that extreme values do not affect the results. Thus, in general, the senior psychology undergraduate students perceived Alzheed as (quite likely to be) useful and (quite likely to be) usable.

It should be noted that the evaluation results obtained from each participant group are different. The answers of the day center's healthcare professionals involved in the design of Alzheed were more positive than the answers of the participants uninvolved in the design. These results were expected due to the unfamiliarity of the participants uninvolved in the design with both the project and the objective of Alzheed. This is because the psychology students had no previous experience with patients with AD or their care, so they were unable to fully understand the context of day centers and the corresponding workflows, and as a consequence, they were not entirely cognizant of how, when, and what information should be collected. Nevertheless, they were able to grasp (to some extent) how to use Alzheed and its purpose demonstrating the usability and usefulness of Alzheed. Moreover, in general, the evidence (see Table 8) shows that both participant groups perceived Alzheed as useful and easy to use. In fact, when taking into account the evaluation results obtained from both groups, the median for each construct is 6 (quite likely). In addition, for the *perceived usefulness* construct, the mode has a value of 6 (quite likely to be useful) and for the *perceived ease of use* construct, the mode has a value of 7 (extremely likely to be usable). In general, the design and development of this high-fidelity prototype was carried out in a total of 4 weeks.

5. Design recommendations

In this section, a series of design recommendations arisen from the experience of designing and developing Alzheed are presented.

5.1. Co-design with healthcare professionals to share ownership and foster group endorsement

Based on the experience of designing Alzheed, it is advisable that the design process of a healthcare application has the endorsement of at least one group of healthcare professionals to reduce resistance to change. Public support for the use of a healthcare application by a group of professionals and their public recognition about its usefulness and ease of use may lead other users to adopt the application more easily. Therefore, healthcare applications should be co-designed with healthcare professionals to achieve such endorsement, in addition to sharing ownership of the application. Furthermore, this helps to assure that the application meets the actual needs of healthcare professionals.

5.2. Validate peculiarities about the medical condition using related literature

It is a pertinent concern for designers and healthcare professionals the validity of the content managed by healthcare mobile applications. Therefore, the design process should include a literature review on the medical condition in question. This literature analysis should be focused on supporting and validating the concepts, measurements, scales, and requirements elicited.

5.3. Evaluation by users involved and uninvolved in the application's design process

In the healthcare domain, it is crucial for healthcare professionals to deeply understand the software systems they use as support for their daily tasks. Therefore, it is advisable that the mobile application (or its prototypes) are evaluated (i) by healthcare professionals involved in the whole design process, and (ii) by external users uninvolved in such design process. The evaluation by external users uninvolved in the design process and external to day centers may lead to a mobile application that remains useful and easy to use by future potential healthcare professionals (or any other person unfamiliar with the mobile application). Moreover, users uninvolved in the design process may evaluate the application with no preconceptions and help to improve

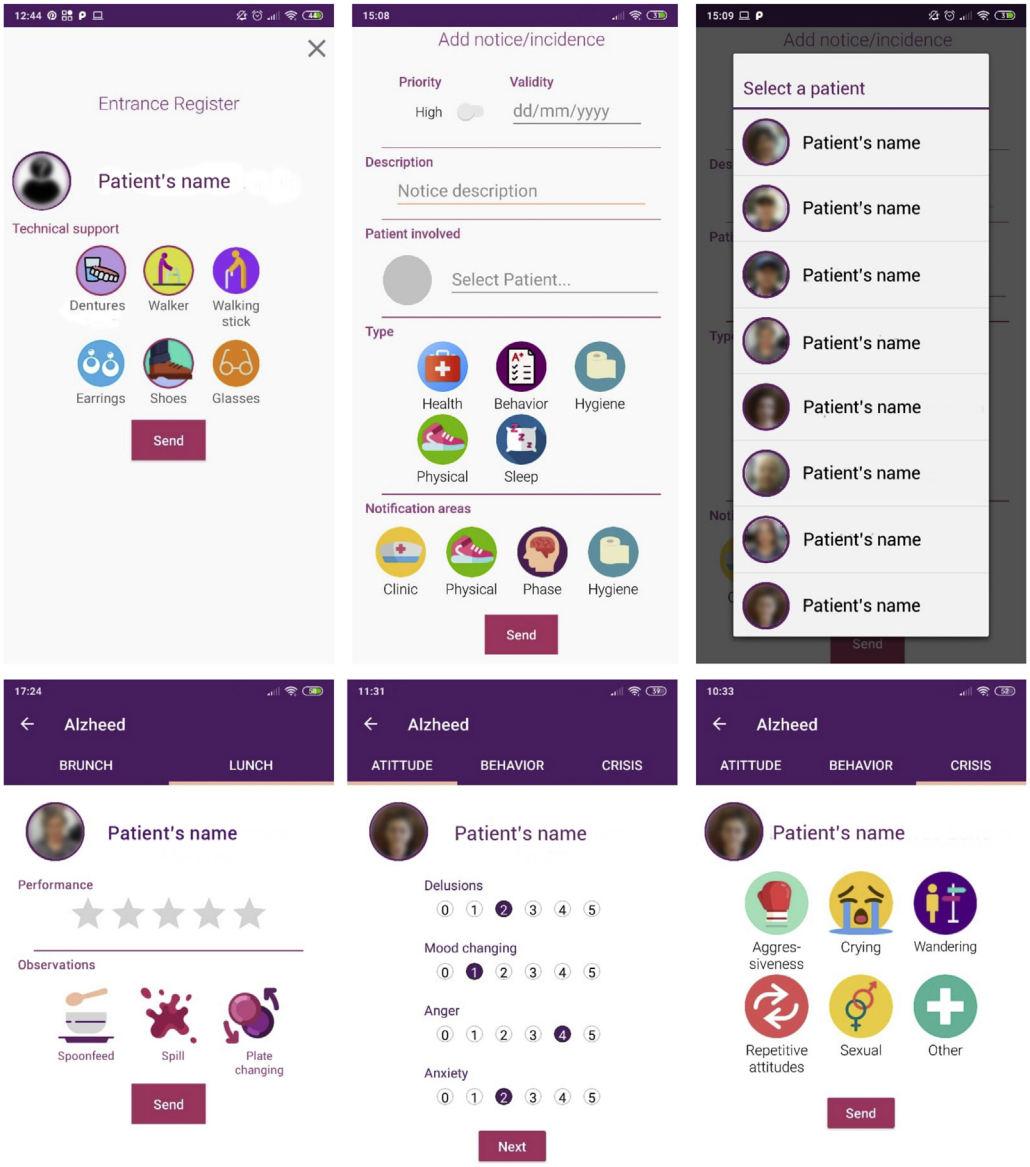

Fig. 5. A set of selected Alzheed's screenshots.

Table 6
TAM questionnaire for Alzheed evaluation.

	Perceived usefulness
Q1	Using Alzheed in my job would enable me to accomplish tasks more quickly
Q2	Using Alzheed would improve my job performance
Q3	Using Alzheed in my job could increase my productivity
Q4	Using Alzheed would enhance my effectiveness on the job
Q5	Using Alzheed would make it easier to do my job
Q6	I would find Alzheed useful in my job
	Perceived ease of use
Q7	Learning to operate Alzheed would be easy for me
Q8	I would find it easy to get Alzheed to do what I want it to do
Q9	My interaction with Alzheed would be clear and understandable
Q10	I would find Alzheed to be flexible to interact with
Q11	It would be easy for me to become skillful at using Alzheed
Q12	I would find Alzheed easy to use
Values and interpretation for possible answers are as follows: 7: extremely likely, 6: quite likely, 5: slightly likely, 4: neither, 3: slightly unlikely, 2: quite unlikely, and 1: extremely unlikely	

the ease of use of the application.

5.4. Create as many prototypes as needed

During a mobile application's development process, it is crucial for users to completely understand how such application will work and how users will interact with it. It can therefore be helpful to create at least one or more low-fidelity prototypes and one or more high-fidelity prototypes before the implementation of the mobile application takes place. This frequent and rapid prototyping based on user requirements allows designers to receive important feedback from users to avoid implementing functions that will not be used or that should be modified.

5.5. Prevent errors in data collection

Healthcare professionals at day centers are busy most of the time as they have to keep direct contact with various patients simultaneously. Therefore, a monitoring mobile application for patients with dementia should not be complex. In fact, the mobile application should be designed to prevent healthcare professionals from making errors when

Table 7
Detailed TAM results.

		Responses regarding usefulness (Q1-Q6) and ease of use (Q7-Q12)											
	Individual Id	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Group involved in the design	Individual 1	6	6	6	6	6	6	6	6	6	6	6	6
	Individual 2	6	6	6	6	7	7	6	7	7	6	7	6
	Individual 3	7	7	7	7	7	7	7	7	7	7	7	7
	Individual 4	7	7	7	6	7	7	7	4	7	7	7	7
	Individual 5	6	4	6	7	7	7	7	7	4	7	7	7
	Individual 6	7	6	7	6	6	7	7	6	6	6	7	7
	Individual 7	7	6	6	6	6	6	7	6	6	6	6	6
	Individual 8	7	5	5	5	7	7	7	7	7	7	7	7
	Individual 9	7	7	6	7	7	7	6	6	7	7	6	6
	Individual 10	6	7	6	6	6	6	4	6	6	6	6	6
	Individual 11	7	7	7	7	7	7	7	6	7	7	7	7
Group uninvolved in the design	Individual 12	6	5	6	5	5	6	5	5	5	5	6	5
	Individual 13	6	6	6	6	5	6	7	5	6	6	6	6
	Individual 14	6	6	6	6	6	6	7	5	7	6	7	7
	Individual 15	6	5	5	5	6	4	6	4	6	6	7	7
	Individual 16	2	2	2	2	2	2	1	2	2	2	1	1
	Individual 17	6	6	6	7	7	6	7	6	6	7	7	7
	Individual 18	6	5	5	6	5	6	7	6	6	6	6	6
	Individual 19	6	6	5	6	6	7	6	3	5	5	5	5
	Individual 20	7	6	6	7	7	7	5	5	6	6	3	5
	Individual 21	4	4	4	5	5	5	7	6	7	7	6	7
	Individual 22	5	5	6	5	5	5	6	5	5	5	4	5
	Individual 23	6	6	6	5	6	6	7	5	7	6	7	7
	Individual 24	6	5	5	5	5	7	6	6	5	4	6	6
	Individual 25	7	7	7	7	7	7	6	7	7	7	7	7
	Individual 26	7	7	7	7	6	6	5	5	6	6	6	6
	Individual 27	6	6	6	5	6	5	7	7	7	7	7	7
	Individual 28	7	6	7	7	7	7	7	6	7	7	6	7
	Individual 29	6	4	5	4	5	6	6	4	4	6	6	6
	Individual 30	1	2	2	2	1	1	1	2	3	2	1	1
	Individual 31	6	5	4	5	5	5	7	5	5	4	6	6
	Individual 32	7	7	7	7	7	7	7	7	7	7	7	7
	Individual 33	4	5	5	5	5	5	6	4	5	5	4	5
	Individual 34	7	7	7	7	7	7	7	7	7	7	7	7
	Individual 35	6	7	7	7	7	7	6	6	6	7	7	7
	Individual 36	5	5	5	4	6	6	7	6	6	6	6	6
	Individual 37	2	3	2	2	2	2	1	4	2	2	2	2
	Individual 38	5	4	3	3	5	6	4	3	5	5	6	6
	Individual 39	7	6	7	6	7	7	6	7	7	7	6	7
	Individual 40	4	4	5	4	4	4	3	4	4	3	3	4
	Individual 41	6	6	6	6	6	6	6	6	6	6	6	6

Values and interpretation for possible answers are as follows: 7: extremely likely, 6: quite likely, 5: slightly likely, 4: neither, 3: slightly unlikely, 2: quite unlikely, and 1: extremely unlikely

entering data. The mobile application should present clean graphical interfaces and avoid text input fields for unstructured data when possible, instead, predefined options should be provided to register data with a standard structure.

6. Conclusions and future work

This paper presents the design and evaluation of Alzheed, a mobile application for monitoring patients with Alzheimer's disease (AD). The design of Alzheed was based on a participatory design methodology, which involved creating low-fidelity and high-fidelity prototypes. This methodology also involved matching software requirements with peculiarities of the Alzheimer's condition, which helped to assure that the requirements elicited take into account relevant aspects associated with AD. The resultant Alzheed's high fidelity prototype was formally evaluated using a TAM questionnaire by participants involved and uninvolved in its design. Feedback from participants uninvolved in the design helped to improve the ease of use of the application. In addition, these participants may have been stricter judges for the usability and usefulness of Alzheed because their opinions may have not been

Table 8
Descriptive statistics of the TAM evaluation results.

Construct	Median	Mode	Min	Max	Percentile 25	Percentile 50	Percentile 75
Evaluation by healthcare professionals involved in the design of Alzheed							
Perceived usefulness	7	7	4	7	6	7	7
Perceived ease of use	7	7	4	7	6	7	7
Evaluation by senior psychology students uninvolved in the design of Alzheed							
Perceived usefulness	6	6	1	7	5	6	6
Perceived ease of use	6	6	1	7	5	6	7
TAM evaluation results taking into account both participant groups							
Perceived usefulness	6	6	1	7	5	6	7
Perceived ease of use	6	7	1	7	5	6	7

compromised as a consequence of previous involvement in the design. Evidence indicates that the target users perceived Alzheed as quite likely to be useful and quite likely to be usable.

This work contributes a mobile application for monitoring patients with AD. In this regard, at the time this paper was written, Alzheed has been already in use at Day Center "Dorita de Ojeda" for several months. Another contribution of this work is a set of design recommendations for the development of healthcare mobile applications. Additionally, from the experience of implementing Alzheed, it can be concluded that it is advisable to carefully conduct observation activities at the day center in order to avoid potential assumptions made by healthcare professionals and staff of the day center.

It is important to mention that Alzheed could be utilized to monitor and record data about patients with diseases related to AD, including Lewy Body dementia, Parkinson's disease, and Vascular Dementia. Patients with these types of diseases present similar symptoms and behaviors, such as memory loss, confusion, language impairment, personality changes, and depression [27,28].

The results of the present work may lead to further developments. For instance, the collected data using Alzheed at day centers may be used to carry out advanced data analysis supported by machine learning techniques to (i) find behavior patterns associated with the disease progression, (ii) predict patient crises so that healthcare professionals are prepared for action, and (iii) identify and understand the triggers of such patients' crises and behaviors as well as differences according to aspects such as age or gender, among other types of analyses. Particularly, collected data using Alzheed at day centers and the associated machine learning models may be utilized to feed clinical decision support systems, which are computer systems designed to improve the decision making in health organizations (e.g., in terms of defining cognitive and physical treatment for particular patients). In addition, further works could use Alzheed to extend the manual data collection strategy with automatic data collection supported by smart devices and sensors (e.g., wearables) to collect patients' data such as physiological signals (e.g., heart rate, body temperature, and galvanic skin response). Likewise, Alzheed may be extended to interoperate with remote healthcare monitoring systems deployed at patients' homes and hospitals. All these further developments may lead to (i) an increased capacity of day centers to better serve patients with AD, (ii) reduce costs associated with patient care and treatments, (iii) improve the integration and coordination of their different areas and, ultimately, (iv) have a positive impact on the well-being of patients, their primary caregivers, and healthcare professionals at day centers.

In particular, as a future research direction, it is planned to build machine learning models using the data collected at Day Center "Dorita de Ojeda" in order to assist healthcare professionals in determining whether patients with AD should be advanced to the next stage of treatment (e.g., from treatment for early stage to middle stage). In addition, it is planned to complement Alzheed with a web application where day center's staff can manage patients' clinical records and generate detailed patients' monitoring reports.

Summary Table

What was already known on the topic:

- The different stages of Alzheimer's Disease emphasize the need for continuous monitoring of patients by caregivers at day centers.
- Healthcare professionals recognize the benefits of mobile applications.
- Software design methodology based on participatory design leads to a user-centered design.

What this study added to our knowledge:

- Co-designing with healthcare professionals leads to (i) fostering group endorsement, which prevents resistance to change and (ii) helps to meet the needs of both healthcare professionals and patients, guaranteeing the usefulness of the application.
- Evaluation of mobile healthcare applications by users involved and uninvolved in the application's design process helps to improve the ease of use of the application.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AC, LR, JG, and GB developed the design methodology and designed the low-fidelity and high-fidelity prototypes. AC implemented the low-fidelity and high-fidelity prototypes. AC, LR, JG, and GB designed the experiments. AC performed the experiments. AC, LR, JG, and GB conducted the data analysis and interpretation. LR and AC conceived and designed the research project. All authors have contributed to the manuscript. All authors have read and approved the final manuscript.

Acknowledgments

The authors would like to thank (i) Day Center "Dorita de Ojeda" I.A.P for providing specifications about the application scenario and (ii) Luis Enrique Zepeda for his support during the application development. The first author would like to thank the Mexican Council for Science and Technology (Conacyt) for the financial support through scholarship 866354. J. O. Gutierrez-Garcia gratefully acknowledges the financial support from the Asociación Mexicana de Cultura, A.C. This work was supported by PFCE 2019.

References

[1] R. Mancino, A. Martucci, M. Cesareo, C. Giannini, M.T. Corasaniti, G. Bagetta, C. Nucci, Glaucoma and Alzheimer disease: one age-related neurodegenerative disease of the brain, Curr. Neuropharmacol. 16 (7) (2018) 971–977.
[2] B. Winblad, P. Amouyel, S. Andrieu, C. Ballard, C. Brayne, H. Brodaty, A. Cedazo-Minguez, B. Dubois, D. Edvardsson, H. Feldman, et al., Defeating alzheimer's disease and other dementias: a priority for European science and society, Lancet Neurol. 15 (5) (2016) 455–532.
[3] C. Patterson, World alzheimer report 2018: the state of the art of dementia research: new frontiers, Alzheimer's Disease International (ADI): London, UK.
[4] R. Brookmeyer, E. Johnson, K. Ziegler-Graham, H.M. Arrighi, Forecasting the global burden of Alzheimer's disease, Alzheimer's Dementia 3 (3) (2007) 186–191.
[5] C. Van Cauwenberghe, C. Van Broeckhoven, K. Sleegers, The genetic landscape of alzheimer disease: clinical implications and perspectives, Genet. Med. 18 (5) (2016) 421–430.
[6] Alzheimer'sAssociation, Basics of alzheimer's disease, (2019) URL https://www.alz.org/national/documents/brochure_basicsofalz_low.pdf.
[7] E.D. Jacobson, J. O'Hanlon, K. Perillo, The Role of Senior Centers in Mitigating Alzheimer's and Other Forms of Dementia, Institute for Public Administration, 2019 Tech. rep..
[8] R. Mitchell, Self-harm in older adults: room to improve clinical care, Lancet Psychiatry 5 (11) (2018) 859–860.
[9] N. Shah, G. Martin, S. Archer, S. Arora, D. King, A. Darzi, Exploring mobile working in healthcare: clinical perspectives on transitioning to a mobile first culture of work, Int. J. Med. Inform. 125 (2019) 96–101.
[10] M.M. Baig, H. Gholamhosseini, Smart health monitoring systems: an overview of design and modeling, J. Med. Syst. 37 (2) (2013) 9898.
[11] S. Bødker, M. Kyng, Participatory design that matters-facing the big issues, ACM Trans. Computer-Human Interact. (TOCHI) 25 (1) (2018) 4:1-4:31.
[12] J. Calvillo-Arbizu, L.M. Roa-Romero, M.A. Estudillo-Valderrama, M. Salgueira-Lazo, N. Aresté-Fosalba, N.L. del Castillo-Rodríguez, F. González-Cabrera, S. Marrero-Robayna, V. López-de-la Manzana, I. Román-Martínez, User-centred design for developing e-health system for renal patients at home (appnephro), Int. J. Med. Inform. 125 (2019) 47–54.
[13] K. Slegers, A. Wilkinson, N. Hendriks, Active collaboration in healthcare design: participatory design to develop a dementia care app, CHI'13 Extended Abstracts on Human Factors in Computing Systems, ACM, 2013, pp. 475–480.
[14] P. Escalada-Hernández, N.S. Ruiz, Design and evaluation of a prototype of augmented reality applied to medical devices, Int. J. Med. Inform. 128 (2019) 87–92.
[15] L.M. Muriana, H. Hornung, Towards participatory prototyping with older adults

with and without cognitive impairment: Challenges and lessons learned, IFIP Conference on Human-Computer Interaction, Springer, 2017, pp. 344–363.
[16] F.D. Davis, Perceived usefulness, perceived ease of use, and user acceptance of information technology, MIS Quarterly 13 (3) (1989) 319–340.
[17] A. Assila, H. Ezzedine, et al., Standardized usability questionnaires: Features and quality focus, Electronic J. Comput. Sci. Inform. Technol.: eJCIST 6 (1) (2016) 15–31.
[18] Y. Lee, K.A. Kozar, K.R. Larsen, The technology acceptance model: Past, present, and future, Commun. Assoc. Inform. Syst. 12 (1) (2003) 50.
[19] J. Helmy, A. Helmy, The alzimio app for dementia, autism & alzheimer's: Using novel activity recognition algorithms and geofencing, in: 2016 IEEE International Conference on Smart Computing (SMARTCOMP), IEEE, 2016, pp. 1–6.
[20] H.M. Fardoun, A.A. Mashat, J. Ramirez Castillo, Recognition of familiar people with a mobile cloud architecture for alzheimer patients, Disability Rehabilitation 39 (4) (2017) 398–402.
[21] S.S. Aljehani, R.A. Alhazmi, S.S. Aloufi, B.D. Aljehani, R. Abdulrahman, icare: Applying iot technology for monitoring alzheimer's patients, 2018 1st International Conference on Computer Applications & Information Security (ICCAIS), IEEE, 2018, pp. 1–6.
[22] M. Ienca, J. Fabrice, B. Elger, M. Caon, A.S. Pappagallo, R.W. Kressig, T. Wangmo, Intelligent assistive technology for Alzheimer's disease and other dementias: a systematic review, J. Alzheimer's Dis. 56 (4) (2017) 1301–1340.
[23] N. Maiden, S. D'Souza, S. Jones, L. Muller, L. Panesse, K. Pitts, M. Prilla, K. Pudney, M. Rose, I. Turner, et al., Computing technologies for reflective and creative care for people with dementia, Commun. ACM 56 (11) (2013) 60–67.
[24] K. Zachos, N. Maiden, K. Pitts, S. Jones, I. Turner, M. Rose, K. Pudney, J. MacManus, A software app to support creativity in dementia care, Proceedings of the 9th ACM Conference on Creativity & Cognition, ACM, 2013, pp. 124–133.
[25] J. Edmeads, O. Metatla, Designing for reminiscence with people with dementia, Extended Abstracts of the 2019 CHI Conference on Human Factors in Computing Systems, ACM, 2019 pp. LBW1721:1-LBW1721:6.
[26] Adobe, Adobe experience design tool, (2019) https://www.adobe.com/es/products/experience-design.experience-design-marquee.socialshare.html.
[27] S. Karantzoulis, J.E. Galvin, Salmon Braak, McKhann Mckhann, Sperling Jack, Butters Hodges, et al., Distinguishing alzheimer's disease from other major forms of dementia, Expert Rev. Neurotherapeut. 11 (11) (2011) 1579–1591.
[28] K.K. Gnanalingham, E.J. Byrne, A. Thornton, M.A. Sambrook, P. Bannister, Motor and cognitive function in lewy body dementia: comparison with Alzheimer's and Parkinson's diseases, J. Neurol. Neurosurg. Psychiatry 62 (3) (1997) 243–252.