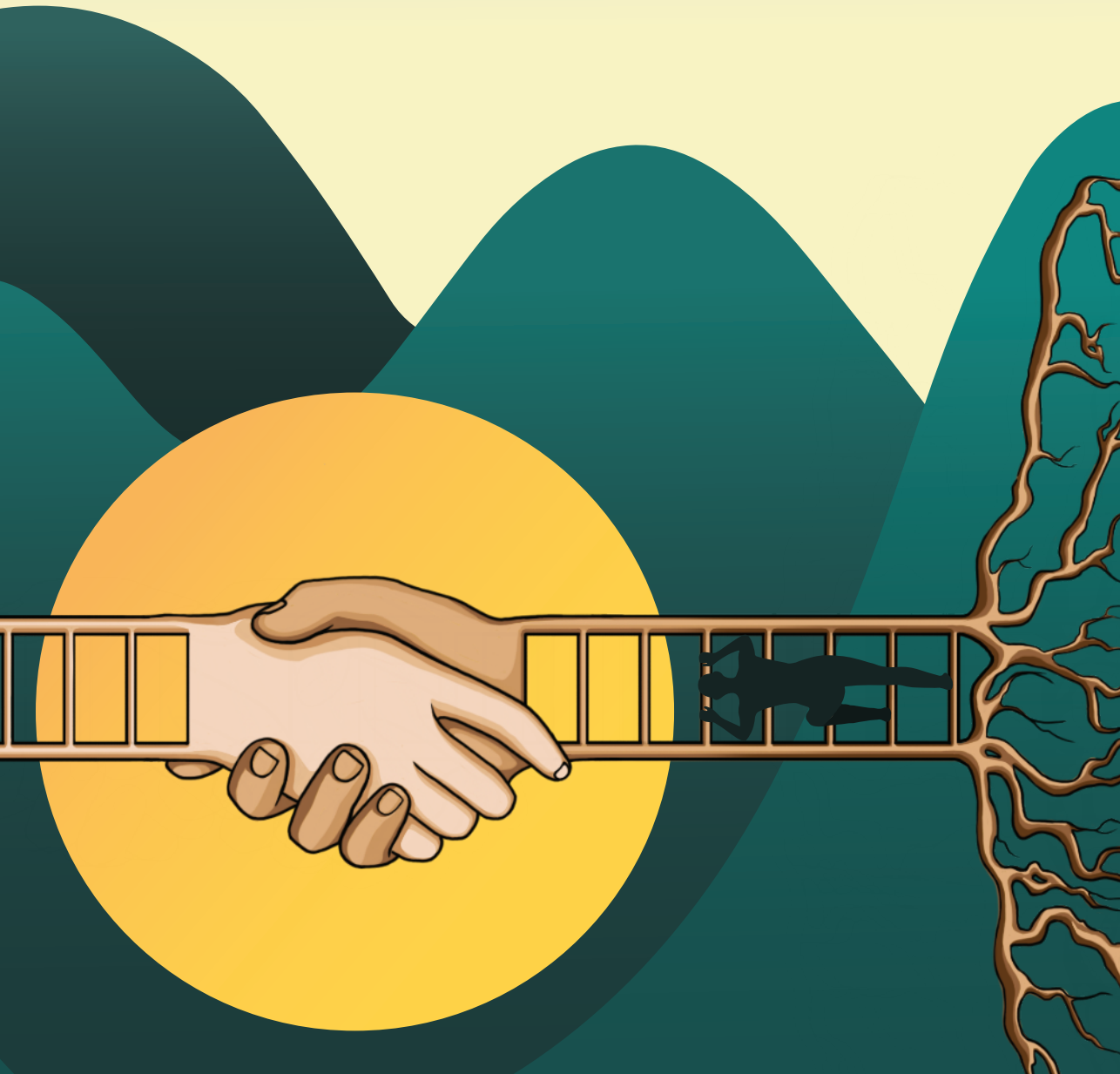
Building Bridges for Meaningful eHealth

Aligning people, technology and practice through collaboration and knowledge sharing

Charlotte Poot



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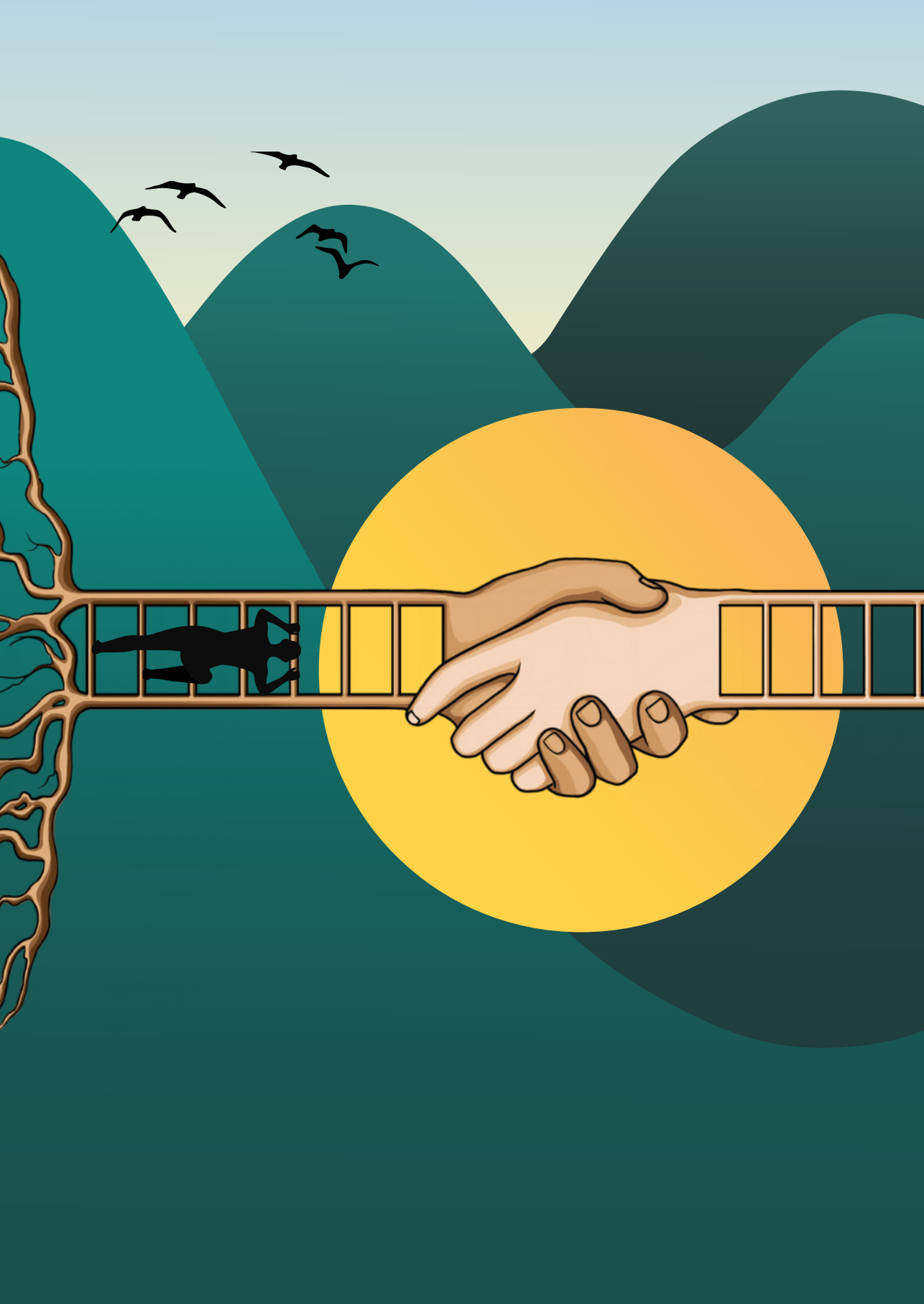

Chapter 1

General introduction

It is Wednesday morning, May 26th 2020. The country has been in lockdown already for two months due to the COVID-19 pandemic. Libraries are closed, and the social distancing measure is in effect everywhere. Vulnerable elderly individuals need to be extra protected, and it is advised not to visit grandparents. Social life has come to a standstill. This also holds true for 63-year-old Mrs. V from Leiden.

Her weekly bridge club is closed, and she has no family left. With only a landline, she feels disconnected from the outside world. As she looks at the local morning newspaper, an article catches her attention. It is about a local initiative called 'Blijf in Beeld' (ENG: 'Stay in Touch'). This initiative offers free smartphones to elderly villagers, donated by members from the community. Loneliness has been gnawing at her for weeks, growing stronger by the day. With the traumatic memory of a previous hacking incident still fresh in her mind, Mrs. V decides that it is time that she stops avoiding digital devices. She picks up the phone and dials the number listed at the bottom of the article.

***

This is the story of a 65-year-old woman who, after weeks of loneliness, feeling physically and digitally isolated from the rest of the world, decided to reach out to the founder of the 'Stay in Touch' initiative to obtain a smartphone. A volunteer, a digital buddy, listened to her fears and anxieties regarding all things digital. The buddy helped her become familiar with her new mobile phone and provided the necessary guidance.

Although, smartphones and digital tools seem commonplace, it turns out to be a completely different world for some people. A world that threatens to alienate them, if we are not careful.

Digital transformation

The current Dutch healthcare system is facing many challenges due to an aging population, increased prevalence of chronic diseases and advancements in medical treatment and technology placing a strain on the system in terms of finances and workforce shortages (1). To address the challenges, 'Het Integraal Zorgakkoord' (2023 -2026) (ENG: Integrated Care Agreement) was recently established in the Netherlands. This agreement, signed by the Ministry of Health, Welfare and Sport and a large number of parties in the Dutch healthcare sector aims to ensure the availability, affordability, accessibility, and appropriateness of healthcare both in the present and in the future. An important pilar within the agreement centres around the use and integration of eHealth within the digital transformation of healthcare. eHealth refers to the delivery or enhancement of health services and information through the internet and related technologies (2). As such, eHealth steers away from the traditional healthcare provision and offers alternative and innovative ways in providing healthcare, including remote and digital care. Originally introduced in 1999 as a term referring to internet-based medicine which provides information on symptoms and treatments, eHealth has since evolved with the introduction of

modern technologies. It now encompasses a wide range of digital health technologies, including electronic health records, clinical decision support systems, telemedicine, health apps, wearables, and sensors. Providing a myriad of opportunities, it is considered essential for addressing the existing healthcare challenges at both national and global levels.

Role and benefits of eHealth

The widespread uptake and use of mobile phones and internet access globally have made mobile phones a powerful platform for delivering personalized health in a for patient convenient way. This form of eHealth has particularly gained traction in the treatment and management of chronic lung conditions such as asthma, and Chronic Obstructive Pulmonary Disease (COPD) (3-5). Managing these chronic diseases is a multidisciplinary process, requiring close collaboration between healthcare professionals and active engagement of patients themselves. As such, technologies like remote monitoring devices and mobile apps can offer ongoing individual self-care support, facilitate regular monitoring for better health outcomes and stimulate patients in changing undesired behaviour into desired behaviour, such as adhering to a medication regimen (3).

Lack of widespread adoption and implementation

While the past decade is marked by an ongoing exponential growth of eHealth technologies, a substantial portion of these technologies pose health claims which are not supported by sufficient research to validate their effectiveness, safety, or impact on health outcomes. eHealth that is sufficiently evidence-based may still be challenged by poor uptake into practice. Hence, while there is an exponential growth in digital health technologies, only a small portion of them find their way into practice and benefit patients. This discrepancy between research and development efforts and practical application is characterized by low adoption rates, limited scalability, and inadequate integration into existing healthcare and reimbursement systems (6).

During the COVID-19 pandemic telemedicine and remote patient monitoring have proved instrumental in maintaining access to care, mitigating the spread of the virus, and optimizing resource utilization and as such has raised awareness on the usage and benefits of eHealth. However, while the COVID-19 pandemic has propelled the use of telemedicine, it has also exposed important gaps in effective integration of telehealth within the current health system (7). Hence, though initially marked as the turning point in the digitalization of healthcare, enabled by regulatory changes that enabling greater access and reimbursement and an increased user and provider willingness (8), its long term impact remains debatable and most importantly limited to the use of telemedicine (9-11).

Extensive literature before and after the COVID-19 pandemic has highlighted the reasons behind the failure of widespread eHealth adoption and implementation. As a result, research focus has shifted from primarily developing innovative digital health solutions to understanding the conditions necessary for successful implementation

(6,12). Considering this, this dissertation identified five challenges pertaining to the development, implementation and evaluation of eHealth solutions that require attention. These challenges can be metaphorically depicted as gaps that must be bridged to facilitate widespread implementation of eHealth in healthcare settings in order to be meaningful.

Challenges

Challenge one: misalignment with user needs

The limited adoption of eHealth solutions can be partly attributed to the lack of active involvement of end-users, such as patients, during the initial stages of design and development (6, 13). This can result in poor usability, poor user experience and, most importantly, misalignment with user needs (6, 14, 15). Recognizing the importance of end-user engagement in eHealth development, there has been a growing emphasis on co-creation and patient involvement in eHealth development (13, 16). However, in practice, patients are primarily involved during later stages when advanced prototypes or finished products already exist (17). During these stages, users are asked to test the prototypes or products, focusing mainly on usability, user-friendliness, and interaction with the user interface. Although this approach helps refine the eHealth technology and ensures certain aspects, such as understandable information and user-friendly navigation, it does not necessarily guarantee that the prototype effectively addresses users' problems or fulfils their unmet needs.

The initial design phase, often referred to as the "fuzzy front-end" research, aims to uncover the central challenges, understand the context, explore unmet needs in detail to then ideate potential solutions that align with those user needs (18, 19). The ideas generated during this phase are subsequently developed into concepts and prototypes, which are further refined based on user feedback (18) (see Figure 1).

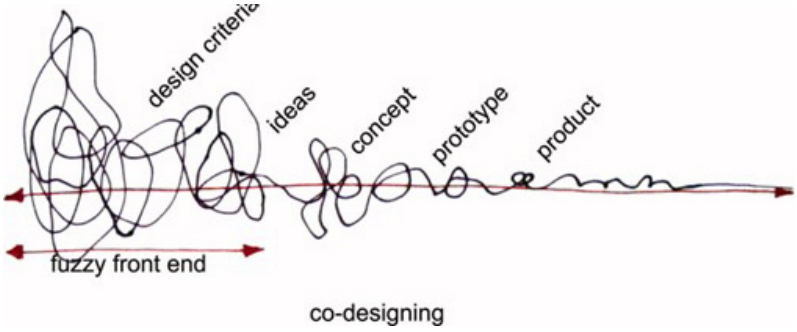

Figure 1. Design process adopted from co-design process by Sanders and Stappers (20)

One strategy to actively involve users in the design process is known as participatory design. This approach is based on the notion that users are regarded as "experts by experience" or experts of their "lifeworld" (21). It acknowledges that their

knowledge is equally valuable in a collaborative design process as the expertise of designers, developers, and researchers. Participatory design employs various tools and techniques to tap into users' knowledge and foster mutual understanding throughout the design process (22).

Within participatory design 'knowledge' is theoretically conceptualized into various levels of knowledge; explicit, observable, tacit and latent knowledge (see Figure 2). Explicit and observable knowledge – what people say and do – is the most accessible layer of knowledge and can be explored using conventional qualitative research techniques like interviews and observations. Deeper levels of knowledge such as tacit and latent knowledge respectively refer to knowledge that people can act upon but cannot readily express in words (like riding a bike or why something is funny) and knowledge people are not aware of yet (like knowing where to drive to, based on experience as a passenger) (23). Desires, needs, motivations and experiences are generally concealed in these deeper layers and require participatory design tools, such as creative and reflective exercises, to be elucidated (24). Consequently, employing participatory tools to effectively identify user needs and uncover deeper levels of knowledge is essential for developing eHealth interventions that address unmet user needs.

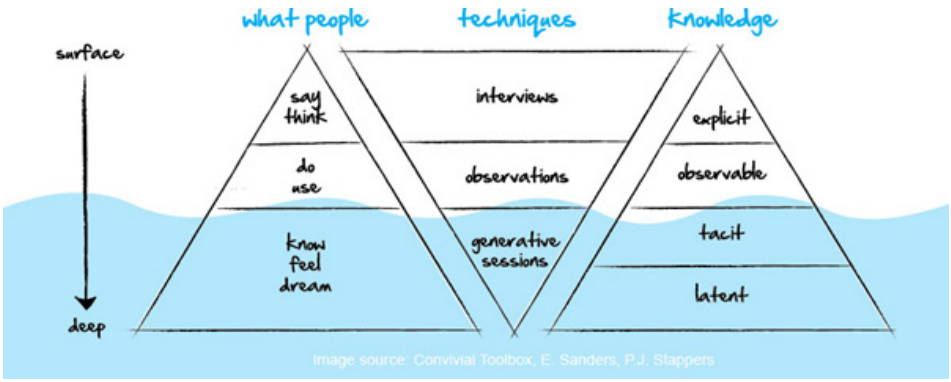

Figure 2. Different research techniques access various levels of knowledge (image adopted from Sleeswijk Visser et al., 2005)

While participatory design plays a pivotal role in the active involvement of end-users and stakeholders, the use of participatory design tools often remains limited to a single phase, is poorly substantiated or lacks methodological reasoning (17, 25). To support researchers in the use of participatory design it is imperative to substantiate and report on participatory design choices and establish a more comprehensive understanding of eHealth development methods (26). The creation of a knowledge base in this area requires more in-depth case studies that elucidate and reflect upon the specific applications of participatory design tools and methods.

Challenge two: user non-adherence and disengagement

A significant challenge encountered in the use and uptake of eHealth is non-adherence, referring to the extent that users use or keep using the intervention in the desired way (27, 28). One key factor contributing to non-adherence is the lack of user engagement with the technology or engagement for a brief time (29, 30). Engagement encompasses a broader set of psychological and behavioural factors related to individual's interaction and involvement with digital health technologies (31). As such, it reflects the level of interest, motivation, and connection users have with the technology (32).

To enhance user-engagement gamification principles are increasingly being integrated into the design of eHealth, aiming to make the digital health technology more appealing, motivating and engaging for users. These game design elements can be very specific, such as the inclusion of "badges" or "levels" in the interface, or they can be more comprehensive, such as incorporating a storyline to clarify personal behaviour change goals or stimulate enduring play (33). Persuasive game design has been applied in behaviour change-based eHealth interventions as means to encourage people to modify their behaviour (34), for instance by influencing people's attitudes to certain behaviour or by building new skills within the game world that can be applied in real-life situations (35).

While engagement plays a significant role in the adoption of and adherence to eHealth intervention, it is important to note that disengagement does not always imply non-adherence. The duration or frequency of use required to achieve the desired (behavioural) outcomes (e.g. increased medication adherence) may vary among different technologies and user groups (27). This is particularly true with digital health technologies that target behaviour change as the desired outcome. In such cases, disengagement from eHealth may be justified if the desired behaviour change has been accomplished, through for example the formation of a habit (36). Non-engagement is in these instances is not a consequence of, for example, losing interest.

Challenge three: missing those who benefit most

While the technology itself plays an essential role in engagement to and use of eHealth solutions specific user characteristics are equally important (29). Studies investigating demographic factors associated with lower eHealth usage have found that older adults, individuals with chronic diseases living alone, and those with lower income and/or education were less likely to use eHealth solutions (37). Another study showed that having a lower socio-economical position, indicated by lower levels of education and income, was associated with limited access to digital technologies and digital healthcare services (38). Consequently, individuals with lower socio-economic position are more likely to have lower levels of digital health literacy and health literacy compared to those with higher socio-economic position. Considering the association between limited health and digital literacy with lower eHealth usage and the recognized role of (digital) health literacy in reducing health inequality,

researchers and policymakers have focused on promoting (digital) health literacy as a means to address the digital divide.

The so-called 'digital divide' in which digital health systems and technologies are predominantly accessed and used by individuals with a higher education and higher health literacy, is of particular concern as people with lower education and fewer resources generally have an increased risk of developing chronic conditions and more often need ongoing medical care (39). Hence, while current healthcare is shifting and increasingly relies on remote healthcare and digital healthcare technologies and services, individuals with limited access to digital technologies may experience challenges in obtaining timely and reliable health information, seeking appropriate medical advice, or miss out on opportunities to adopt healthy behaviours. Consequently, this growing digital divide has the potential to widen health inequities and exclude digitally disadvantaged individuals (40, 41). This issue is not new. In fact, the WHO has recognized the digital divide, with risk of digital exclusion and unequal access, as one of the biggest challenges posed by the digital transformation of healthcare (42, 43).

While access within the digital transformation is often seen from the dimensions of material access, referring to the physical access to digital technologies such as computers, smartphones, and internet connectivity, access is considered a multifaceted phenomenon that encompasses various dimensions of access, including, material access, skills access and motivational access (44). This means that, even if access is available, disparities may still exist if people do not possess the proper competence to use the digital health technologies and services needed to effectively to use the technology (skills access). The emergence of diverse digital health technologies necessitates individuals to navigate through portals, actively engage with apps, remain motivated to use self-monitoring devices, interpret collected data, assess information reliability, and effectively communicate with digital health systems. This additional set of skills and abilities has been conceptualized into eHealth literacy. Shedding light on and addressing eHealth literacy needs of individuals is paramount to providing appropriate support and to develop eHealth that fit people's eHealth literacy needs (45, 46). The eHealth Literacy Questionnaire (eHLQ) is increasingly used globally as comprehensive person-centred instrument to measure eHealth literacy. However, despite the ongoing digital transition in the Netherlands a comprehensive Dutch person-centred instrument to measure eHealth literacy is lacking.

The third access dimension, motivational access, relates to the personal motivation, attitudes, and willingness to engage with digital technologies. People with lower social-economic positions or limited health literacy are seldomly actively involved in eHealth development, resulting in interventions that fail to meet their needs, motivation, attitude towards eHealth and eHealth literacy needs (47, 48). Involving individuals with low socio-economic positions or limited health literacy in participatory design seems logical to develop eHealth interventions that address their (unmet) needs. However, effective involvement of these groups in participatory design is often hindered by

barriers such as difficulties understanding study content, challenges with abstract thinking, language or literacy issues, anxiety towards research or the research team, feelings of stigmatization, and limited exposure to technology and the internet (49-51). Studies that do succeed in involving socio-economically disadvantaged groups often limit their involvement to later development stages, such as assessment of an app or patient portals on usability or readability of health information. To our knowledge there currently is no clear methodology for involving people with low socio-economic position or limited health literacy in the participatory design process of an eHealth intervention. Therefore, there is a need for best practice examples and guidance on how to effectively involve people with limited health literacy.

Hence, to ensure that eHealth benefits all people in need and is accessible in terms of skills and motivation, it is essential to involve socio-economically disadvantaged groups throughout all stages of development using participatory design. By doing so we can help bridge the gap between those who have access to digital health technologies and those that do not, rather than creating a range of interventions that are largely unused by those who could benefit the most.

Challenge four: limited evidence on the effectiveness of eHealth

The lack of evidence on the effectiveness of eHealth solutions presents a significant challenge to their widespread adoption and implementation of eHealth. Generally, practice and clinical decision making nowadays is based on evidence-based medicine. Therefore, demonstrating the effectiveness and clinical benefits of eHealth interventions has become a crucial aspect of the transition towards digital healthcare (52). It plays a vital role in distinguishing useful and beneficial eHealth interventions from potentially harmful ones, and even influences reimbursement decisions (53).

Randomized controlled trials (RCTs) based on the fundaments of creating two comparable groups to assess the true effect of an intervention, lie at the top of the scientific evidence pyramid. However, despite its robust evidence, there is growing uncertainty as whether the plethora of RCT evidence on eHealth actually translates into improvements in patient outcomes and care. One reason and challenge is formed by the fact that RTCs typically focus on well-defined, homogeneous populations, employ blinding techniques, follow specific protocols, and incorporate controlled clinical elements. These measures aim to ensure comparability between groups and attribute any differences in outcomes to the intervention itself. Paradoxically, these strict criteria limit the external generalizability of study findings, meaning that they may not readily apply to real-world practice or the broader population. They run the risk of overlooking the complexity of contextual factors that exist in everyday healthcare settings, creating a disconnect between research outcomes and practical application. Hence, there is an increasing need for real-world evaluation and generation of real-world evidence in terms of the effectiveness of eHealth technologies.

Challenge five: disconnection between evidence and application in practice

The generation and application of evidence is essential for the adoption of eHealth and its impact on healthcare and society. However, there is often a disconnection between the generation of evidence and its application in practice, leading to a 'knowledge-to-action' gap (54). This gap has been recognized as one of the significant challenges of our time and has prompted a global call for knowledge translation, which involves 'the synthesis, dissemination, exchange, and application of knowledge in an effort to improve health services and products and strengthen the healthcare system' (55).

The Knowledge-to-Action (KtA) framework offers a conceptual framework to aid in knowledge translation and the use of this evidence by healthcare professionals in their decision making regarding the adoption of health policies, practices, or programs (56). This framework consists of two interconnected components: the Action Cycle and the Knowledge Creation funnel. The Action Cycle encompasses the activities required to apply evidence-based knowledge into practice. It involves tailoring interventions to suit the local context, identifying and evaluating barriers and facilitators to implementation, and ensuring the effective application of evidence-based practices (57). On the other hand, the Knowledge Creation funnel represents the simultaneous process of generating tools and key messages that support the Action Cycle. It involves a funnel-like process translating scientific results into core messages that are actionable and easily understandable by stakeholders and decision-makers. Principles of science communication and data visualization play a valuable role in this knowledge creation process. However, there is currently a lack of guidance on how to practically implement the knowledge creation funnel (58).

Building bridges – why this dissertation

To conclude, while eHealth is promising in facing current healthcare challenges, measures should be undertaken to bridge the gaps that challenge the development, implementation, and evaluation. Addressing these gaps is crucial for the development of meaningful eHealth solutions that align with user needs, promote user engagement and adherence and ensure equal access to eHealth. In addition, to reach its full potential effort should be directed at generating evidence on effectiveness, and facilitating knowledge translation and dissemination, thereby bridging the gap between research and practice and strengthening the wide-spread adoption and implementation of eHealth.

Outline of this dissertation

This dissertation addresses the above-mentioned challenges in eHealth development, evaluation, and implementation. Through real-world examples and case studies it demonstrates how these challenges can be addressed and metaphorical gaps can be bridged.

1

The dissertation consists of three parts. Part 1 focuses on the challenges in eHealth development (**Challenge one, two and three**) and demonstrates, through three case studies, how these challenges can be tackled. The first case study showcases how participatory design can be utilized to involve end-users and other stakeholders in designing the innovative game 'Ademgenoot' to motivate people with asthma to adhere to their medication regimen (**chapter 2**). It shows how behaviour change and persuasive game design theory can be combined to create a fun and engaging game. In the second case study we focus our participatory design efforts on people with limited health literacy and provide an approach on how one can design with and for people with asthma and limited health literacy employing participatory design tools (**chapter 3**). **Chapter 4** presents the third case study, the Hospital Hero app, which demonstrates how participatory design can be employed to involve children and other stakeholders in the development of an app aimed at reducing preprocedural stress and anxiety among children visiting the hospital.

Part 2 continues with the evaluation of eHealth and addresses challenges related to generating evidence on effectiveness (**Challenge four**). We do so by presenting a protocol for a real-world pragmatic RCT to assess the effectiveness of a smart asthma inhaler, the ACCEPTANCE study (**chapter 5**). The protocol demonstrates how real-world evidence can be collected and provides an approach to identify which patients benefit most from the smart inhaler program. We continue our exploration on effectiveness studies by presenting a Cochrane systematic review and meta-analysis on integrated disease management for people with COPD, which are complex interventions that are pooled to generate an overall estimate of effect on multiple clinical and process outcomes (**chapter 6**). By doing so we touch upon the complexity of systematically pooling and evaluating real-world RCTs of complex interventions, the challenges of heterogeneity and the importance of contextual factors.

In **Part 3** we provide tools that can be helpful in working towards more equitable eHealth, addressing prerequisites in eHealth development such as understanding people's eHealth literacy needs (**Challenge three**) and supporting the translation of knowledge into practice (**Challenge five**). We present the Dutch version of the eHLQ and discuss its translation, cultural adaption, and validity assessment (**chapter 7**). In **chapter 8** we present a systematic, practical, and easy-to-implement tool for effective knowledge creation, and its use in a case study on chronic respiratory diseases in low- and middle-income countries. A detailed overview of the chapters, study aim and used design or research methods is provided in Table 1.

The closing chapter, **chapter 9**, reflects on the separate studies, places them into a larger context, identifies important lessons learned, and concludes with some final insights.

Chapter title	Research aim	Dissertation aim	Design or research method	Design or research phase	Deliverable	Stakeholders involved
Part 1 - Participatory Design						
2. Design of the persuasive game Ademgenoot.	To design a persuasive game to motivate people with mild asthma to adhere to their medication regimen.	To demonstrate how participatory design techniques, in combination with behaviour change and persuasive game theory, can be applied to develop an engaging game. To demonstrate how stakeholders can be involved in early stages of eHealth development.	Participatory design approach, generative techniques, semi structured interviews, persona creation, brainstorming, paper prototyping, WhatsApp prototyping, think-aloud exercise.	Define, create, prototype, user experience evaluation.	Prototype of a persuasive game based on automatic data logging using an electronic adherence monitoring device.	People with mild asthma, practice nurses, expert behaviour change, expert persuasive game design, patient advocates, smart inhaler developers, designers.
3. Designing with and for people with asthma and limited health literacy.	To demonstrate the application and tailoring of participatory design activities to fit the needs and skills of people with limited health literacy.	To explore how participatory design activities can be applied among people with limited health literacy.	Participatory design approach, brainstorming, co-creating stories, experience prototyping, think-aloud exercise.	Define, create, prototype, user experience evaluation.	Prototype of a medication adherence eHealth intervention.	People with asthma and limited health literacy, practice nurses, health literacy experts, smart inhaler developers, designers.
4. Design and pilot study of the Hospital Hero app	To design and evaluate an application to reduce preprocedural stress and anxiety among children visiting the hospital.	To demonstrate how participatory design can be combined with service design to develop and app based on the child's experience journey To illustrate how gamification and storytelling can be used to create an engaging serious game.	Participatory design, service design, experience journey mapping, paper prototyping, usability testing , pilot study, mixed method.	Define, create, prototype, evaluation on user experience in practice.	Hospital Hero smartphone application.	Children (between 4 and 12 years) visiting the outpatient clinic, healthcare professionals, educational content experts, app developers, designers.

Chapter title	Research aim	Dissertation aim	Design or research method	Design or research phase	Deliverable	stakeholders involved
Part 2 - Effectiveness Assessment						
5. Protocol for a cluster RCT on a smart asthma inhaler programme	To investigate the effectiveness of a smart inhaler asthma self-management programme on medication adherence and clinical outcomes in adults with uncontrolled asthma, to evaluate its acceptability, and to identify subgroups who would benefit most based on patient characteristics.	To illustrate collection of long-term real-world evidence of a complex eHealth intervention within a cluster RCT. To provide an approach on how to identify which patients benefit most, based on patient characteristics. To illustrate patient participation in the design and execution of a RCT.	Cluster RCT, pragmatic trial, patient involvement.	Protocol for an effectiveness evaluation.	Protocol for the evaluation of the effectiveness and cost-effectiveness of a smart asthma inhaler programme in primary care in the Netherlands.	Smart inhaler developers, patient advocates.
6. Cochrane review update	To compare the effectiveness of integrated disease management (IDM) programmes versus usual care for people with COPD on various clinical outcomes.	To shed light on the methodological challenges of complex health interventions, such as eHealth and the importance of contextual factors.	Systematic review, meta- analysis, Risk of Bias Grading, GRADE approach.	Synthesis and appraisal of all empirical evidence.	Various (eHealth and non-eHealth based) complex health interventions.	

Chapter title	Research aim	Dissertation aim	Design or research method	Design or research phase	Deliverable	stakeholders involved
Part 3 - Tools and Instruments						
7. Translation and validity assessment eHLQ	To translate and culturally adapt the original eHLQ into a Dutch version, and to examine validity of the translated instrument.	To provide an instrument to identify people's eHealth literacy needs and inform future digital health technology development and assessment.	Validity argument approach, cognitive interviewing, confirmatory factor analysis, invariance testing, multigroup comparison.	Instrument translation, cultural adaptation, and validity assessment.	Dutch version of the eHLQ.	People engaging with digital health technology or digital health services now or in the future, developer of the original instrument, translators, bilingual representatives, questionnaire administrator.
8. Systematic approach to knowledge creation	To provide researchers a systematic approach for putting knowledge creation into practice.	To provide a step-by-step-tool on how to create knowledge to inform evidence-based decision making . To demonstrate how to apply the tool into practice.	Framework design, case study demonstration.	Tool development.	Step-by-step instruction tool.	Science communication experts, UX designer.

RCT = randomized controlled trial; eHLQ = eHealth Literacy Questionnaire

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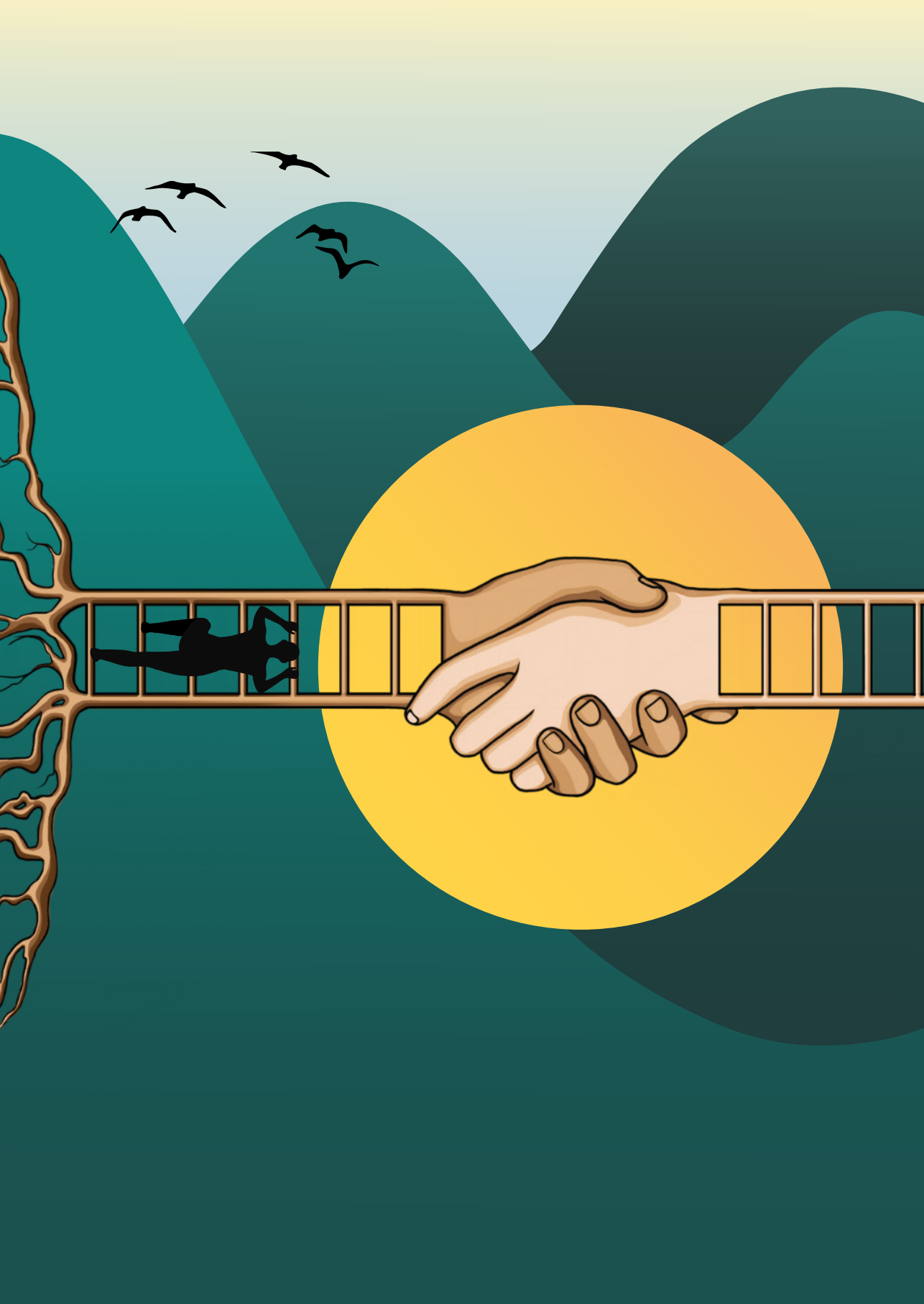
PART 1

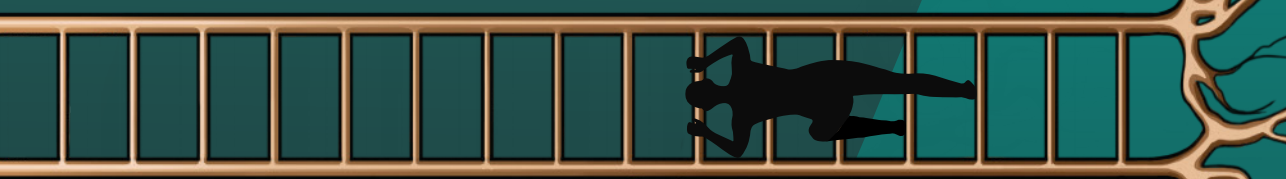
PARTICIPATORY DESIGN



Chapter 2

Design of the persuasive game ‘Ademgenoot’

The design of a persuasive game to motivate people with asthma in adherence to their maintenance medication



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Abstract

Objective

This study aimed to design a persuasive game, using objective adherence data, to motivate people with asthma to adhere to their medication regimen.

Methods

A participatory user-centered design approach was employed, involving end-users and other stakeholders throughout the study. The approach consisted of four phases. Semi-structured interviews and a survey were conducted to understand user needs and reasons for poor adherence (Phase 1: define). Key themes were identified, leading to the formulation of behaviour change strategies and design and game requirements. Several design directions were ideated, resulting in a concept for a serious game (Phase 2: ideate). Two rounds of user-tests were performed to evaluate a prototype of the serious game in terms of usability, perceived impact on medication adherence and motivation (Phase 3: prototype and Phase 4: evaluate).

Results

Findings from semi-structured interviews (n = 6) and the online survey (n = 20) revealed that people's non-adherence was often attributed to the perception of asthma as an episodic condition, the delayed experienced effect of maintenance inhalers, and lack of knowledge regarding difference of effect between maintenance and reliever inhalers. The study used behaviour change strategies to translate these insights into design requirements for the development of the narrative-based persuasive game 'Ademgenoot'. This six- week challenge-based game combines various behaviour change strategies, including personal goal setting and continuous visual feedback, as well as persuasive game design elements, such as a narrative and rewards, with the aim of enhancing motivation to adhere to their medication regimen. User-testing (n = 8; round 1 and 2) showed that Ademgenoot is feasible in clinical practice and has the potential to support people with mild asthma in adherence to their maintenance medication.

Discussion

Future efforts should be directed towards a larger evaluation to assess the impact on motivation and inhaler use behaviour.

Plain language summary

The goal of this study was to create a serious game that encourages people with asthma to take their medication regularly. During the study, we worked closely with individuals who have asthma and other stakeholders throughout the study. We conducted interviews and surveys to understand why people have difficulties using their maintenance inhaler as prescribed by their doctor. Based on the feedback we received, we developed a serious game called "Ademgenoot". The game uses information on inhaler use automatically collected with a device attached to the

inhaler. The game includes features like personal goals and visual feedback on inhaler use to motivate users to take their medication consistently. We tested a prototype of the game with users to see if it was easy to use and if it motivated them to use their maintenance inhaler. The results showed that Ademgenoot is a viable option for helping individuals with mild asthma stay on track with their medication.

Background

Despite the availability of effective inhaler medication, almost half of all asthma patients have poor asthma control (1,2). Poor adherence to maintenance inhalers is a major cause of inadequate asthma control and is associated with 2.5-fold increased risk of uncontrolled asthma. As such, non-adherence is associated with increased risk of severe asthma exacerbations, more asthma-related emergency department visits, hospitalization and decreased lung function and quality of life (3-5). Moreover, non-adherence has been shown to increase healthcare costs, as patients with uncontrolled asthma require more frequent medical visits, interventions and step-ups in medication regimen (6,7). In addition, medication non-adherence is often accompanied by over-reliance on short-acting B2 agonists (SABA) for symptom relief (8-11). This is of particular concern as high SABA use is associated with increased exacerbations and 2.2 times higher asthma-related healthcare costs than low SABA use (12). Hence, it is important to address poor medication adherence and promote appropriate SABA usage.

Numerous factors contribute to poor medication adherence, including forgetfulness, limited understanding of the importance of adherence (necessity), and concerns about medication side effects (13,14). Improving medication adherence may be especially challenging among people with mild asthma as they may have a lower feeling of necessity and underestimate the importance of adhering to the maintenance inhaler compared to people with severe asthma (15). Interventions, such as patient education, reminder systems, and simplified medication regimens, have been developed to target the problem of poor adherence (16). More recent technological developments targeting poor adherence include electronic monitoring devices (EMDs) to track and monitor inhaler usage, providing objective and accurate data on medication adherence. EMD data can be used by healthcare providers to identify patients who do not adhere to their medication regimens, intervene with appropriate education, and support or help in decisions on the step-up of treatment. EMDs that connect to patients' smartphones (also known as smart inhalers) can, in addition, provide patient self- management support by providing medication reminders, personalized feedback and motivational messages. Overall, EMDs have shown promise in improving medication adherence, however their impact on asthma control and the long-term sustainability in improving adherence and asthma control still require further investigation (17-21).

Studies on the effectiveness of smart inhalers have primarily focused on examining the overall effect on medication adherence, rather than identifying which patient groups benefit the most based on determinants of non-adherence. Nevertheless, it is generally believed that smart asthma inhalers, featuring electronic reminders, primarily benefit unintentional non-adherence due to forgetfulness (22). Furthermore, while people with severe or persistent asthma have shown interest in using an app to manage their condition (23). This interest may stem from their heightened necessity for effective asthma control (15,21-23). Moreover, it should be noted that self-management-based interventions are typically used by individuals who are

already motivated to self-manage their condition, feel more necessity in doing so and actively monitor their symptoms and behaviour. In addition, engagement with such self-monitoring programs can be challenged, as they often require people to enter their symptoms or asthma control manually (21,24-26).

Serious games are designed to motivate and engage users for non-entertainment goals, utilizing game elements and game mechanisms. Consequently, they are increasingly used as strategies within behaviour change interventions to overcome the challenges of disengagement. Although serious games are often applied to facilitate educational purposes, they have also proven effective in motivating users to adopt specific attitudes and health behaviours such as medication- and therapy adherence or adopting a healthy lifestyle (27). Notably, serious games have demonstrated effectiveness in improving medication adherence among cancer patients, promoting physical activity in people with diabetes and addressing several mental disorders (27-29).

To understand the underlying mechanisms through which serious games promote beneficial health outcomes, the Persuasive Game Design Model was developed (30,31). According to the model, the skills, attitudes, and beliefs developed within the game world can be transferred to the real world. The Persuasive Game Design Model offers, at the same time, a comprehensive step-by-step framework to standardize and guide the development of serious games. This framework entails (1) defining the transfer effect, including the type of effect and the type of change (e.g., reinforcing, altering or forming new behaviours or attitudes) (2) investigating the users' context, (3) identifying, developing and testing game components (e.g., challenges, game levels, and virtual rewards) and game mechanics (e.g., collaboration and competition), and (4) evaluating the effectiveness of the game in achieving the intended transfer effect (31). Given the potential of serious game to engage individuals and change behaviours, serious games could prove to be an effective way of motivating people to adhere to their maintenance inhaler.

When designing a persuasive game interconnected to an EDM, it is important to actively involve all stakeholders, to ensure alignment with stakeholder and end-user needs and preferences (22,32). In recent years, a participatory design methodology has emerged as a valuable approach to include end-users and other stakeholders in the development of eHealth. This approach emphasizes several key processes, including at least two iterative cycles of testing and feedback, involving end-users at all stages of the process, and incorporating input from other stakeholders such as clinicians and smart inhaler developers (33).

The objective of this study was to apply a participatory design approach to design a persuasive game aimed at improving medication adherence among people with asthma by leveraging the potential of smart inhalers and incorporating behaviour change and persuasive game design strategies. This paper describes the development cycle, design requirements and assessment of the final prototype on usability, usefulness, and perceived impact on improving medication adherence.

Method

Study design

This study employed a user-centred, participatory design approach, during which people with asthma, as the end-users, had an important role in the design process. The approach consisted of four phases: define, ideate, prototype, and evaluate. The define phase (phase 1) was used to gain a deep understanding of the users' needs, lived experiences and reasons for non-adherence and to identify design requirements. Design requirements were translated into several design directions in the ideation phase (phase 2). In two iterations, a prototype was developed (phase 3) and evaluated with end-users to gather user-feedback and improve the prototype (phase 4). Multiple stakeholder groups were included and consulted throughout the project. Healthcare professionals (i.e., general practitioner, practice nurse) provided input on medical content and feasibility for practice. Smart inhaler developers (i.e., representatives from pharmaceutical and medical device companies involved in the development and manufacturing of smart inhalers) provided input on technical and commercial feasibility. A visual representation of the study design and phases, including the core study activities and stakeholders involved, is presented in Figure 1.

Design context

The study was conducted between February 2019 and August 2019 in the area of Zuid-Holland, the Netherlands.

Participants and recruitment procedures

Participants

People with asthma were eligible for study participation if they reported the following: 18 years and older, self-reported diagnosis of asthma, use of an inhaled corticosteroids (ICS) inhaler, difficulties being medication adherent, adequate oral fluency in Dutch or English. Participants were sampled purposively to represent diversity in age, gender, frequency of inhaler use and educational level.

Recruitment procedure

Multifaceted strategies were utilized including advertising on social media and university websites, and posters placed in sporting clubs and on university noticeboards. The recruitment poster included an illustration of three people representing different reasons to be non-adherent, with the question "do you recognize yourself? Participate in our study". Upon expression of interest in participation a patient information sheet was sent by e-mail. The sheet contained information about the purpose of the study, the description of the study activity, that participation is voluntary, that audio is recorded, that data is treated confidentially and anonymously and that responses are reported pseudonymised. The information sheet was adapted per study activity (i.e., interview, survey, user test 1, user test 2, and online survey).

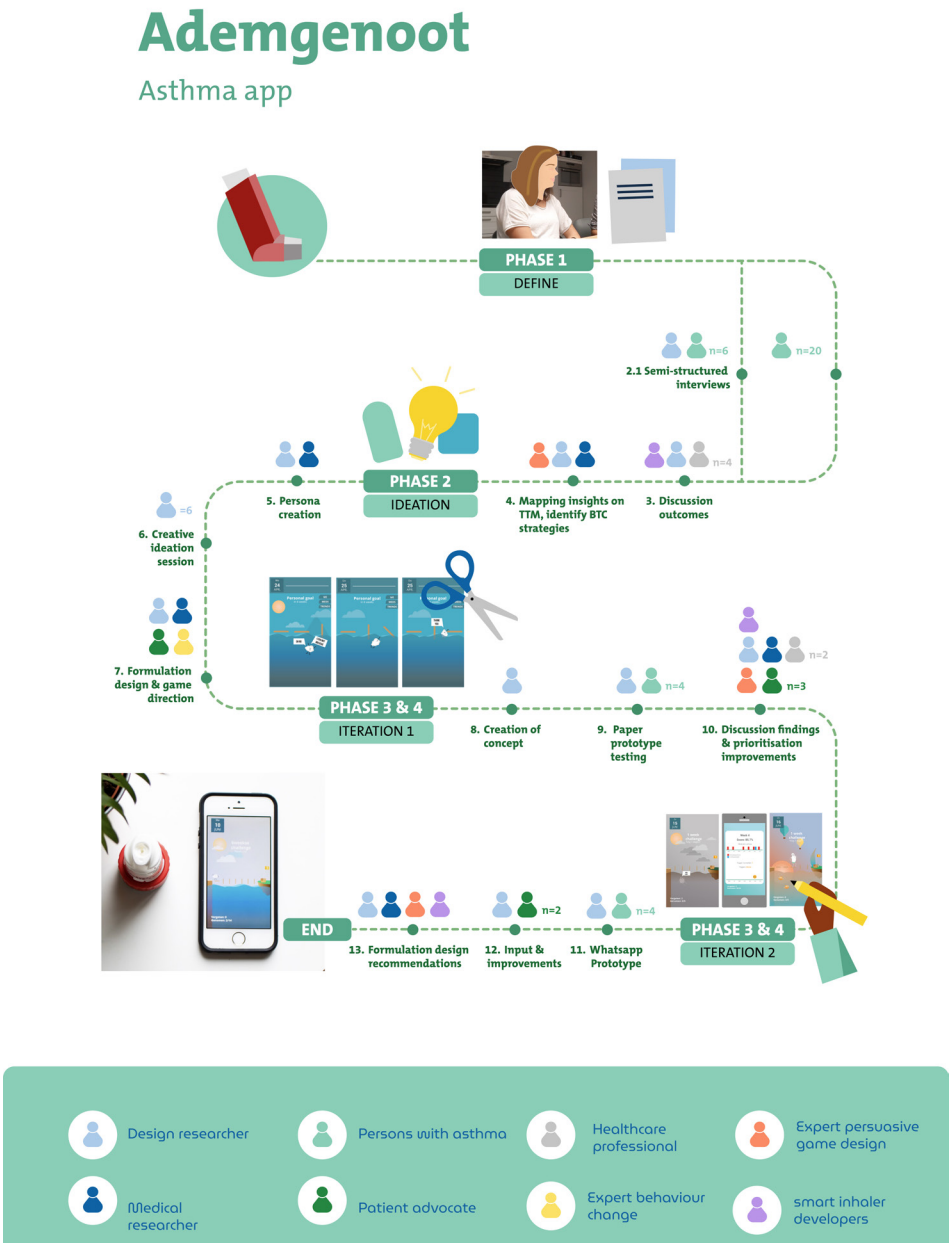

Figure 1. Schematic overview study design and design phases.

Ethical Considerations

The study was cleared for ethics by the Medical Ethical Review Committee of the Leiden University Medical Centre (No P18.158). The study was conducted in accordance with the Helsinki declaration. Written informed consent was obtained from all participants prior to all study activities.

Study procedures

The research was conducted in multiple phases using a mixed-methods approach. Throughout the phases, design methods such as personas, creative assignments, and prototyping were used to gain an in-depth understanding of user needs and preferences, identify opportunities for design and facilitate engagement of the participants with the research activities.

Phase 1: Define

To gain an in-depth understanding of people's inhaler use, reasons for non-adherence and their needs, semi-structured interviews (n = 6) were held. The number of participants were deemed sufficient in light of the specific study activity purpose (i.e., to identify design directions). Interviews were guided by a topic list including questions about inhaler usage, beliefs about medication and challenges in everyday life dealing with inhaler use and their asthma. Interviews were – in agreement with the participant – held at the participants' house or at another place which offered sufficient privacy (e.g., university). The duration of the interviews was approximately 30 to 60 minutes. Interviews were audio recorded and transcribed.

A 5-minute online survey was administered among people with asthma (n = 20), containing items on efficacy and attitude from the Knowledge Attitude Self Efficacy Questionnaire (KASE-Q)34 and Beliefs about Medication Questionnaire – Specific (BMQ-specific) used to measure beliefs about asthma medication (34,35). Both questionnaires were available in Dutch and used in previous studies (36-39). The online survey was distributed via social media. Descriptive statistics were obtained using SPSS.

Interview transcripts were analysed and triangulated with results from an online survey. Results were discussed with four primary care healthcare professionals to facilitate contextual understanding. Also, current strategies on how healthcare professionals motivate people to adhere to their maintenance medication were discussed to identify potentially useful behaviour change strategies. Themes were identified and mapped onto The Transtheoretical Model (TTM) for Behaviour Change to identify behaviour change strategies and place these within the five stages of behaviour change (i.e., pre-contemplation; contemplation; preparation; action and maintenance). The TTM helped to structure behavioural change strategies, without losing the complex interactions between individual and environmental factors that can impact behaviour out of sight.

Phase 2: Ideation

Insights from phase 1 were translated into personas. Personas are used to better understand the needs, goals and behaviours of different user groups and create solutions that tailor to those needs (40). Personas included background information (i.e., short biography to give each persona more depth), everyday challenges with asthma self-management, asthma medication beliefs and behaviours, personal goals regarding their asthma-related health and opportunities for design. Personas were used as illustrative scenarios in ideation sessions. Multiple ideation exercises were held with user-centred designers to spark creative thinking, envision a solution, and explore various design directions. Design directions were discussed with an expert on behaviour change strategies and a persuasive game design expert (author VV), which led to a number of design and game requirements (i.e. criteria, constraints, and specifications that a product, system, or service must meet in order to fullfill its intended purpose and meet the needs of its end-users). Design and game requirements were translated into the final design concept.

Phase 3 and 4: prototype and formative evaluation – iteration 1

The concept was translated to a paper-prototype (i.e., a physical representation of the design) to easily gather user feedback and make changes to the design as needed. This helped to improve the overall user experience and ensure that the final product or service is well aligned with user needs and preferences. The paper-prototype consisted of the different screens that the end-users would interact with. User feedback sessions were held with people with mild asthma. We estimated the number of participants based on guidelines for user testing. Five participants generally find 80% of all usability problems in prototype testing (41). During the user-feedback sessions, participants were introduced to the concept, and a step-by-step scenario was used to let the participant walk through all the elements of the concept. Participants were asked to verbalize their thoughts and reasoning. This "think aloud" method allowed the researchers to continuously capture feedback, with participants describing their actions and immediate thoughts for each step.

After the walk-through, participants were asked to rate their level of agreement with self-developed statements developed specifically for this study, regarding usability and usefulness on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree), for example, "I would find the app useful in managing my inhaler use". The feedback sessions were audio-recorded. Recordings were transcribed and analysed using content analysis to determine usability and user preferences and identify further improvements.

Insights from the feedback sessions were discussed with smart inhaler developers. Input was gathered on technical feasibility (i.e., does the concept require new technical functionalities to be developed) and commercial feasibility (i.e., does the concept add to the market value of existing smart inhalers). Healthcare professionals were asked to comment on accuracy, feasibility, and their overall opinion on the expected impact on medication adherence. Feedback was collected and used in combination with the

list of improvements to identify necessary features and improvements.

Phase 3 and 4: prototype and evaluation – iteration 2

Improvements were made to the paper prototype, which was then translated to a WhatsApp prototype. The prototype mimicked the use of the new concept in practice. Using WhatsApp as a communication tool between the investigator and the participant, the participants received the screens they would interact with if they were using the real app. This approach allowed participants to interact with the concept for a longer period of time, within their own setting (e.g., at home) and at the same time did not require the costly development of a functional app in this early phase. Participants were asked every day at a fixed time (12 pm) "Did you use your maintenance medication this morning (yes/no)"? and "Did you use your reliever medication yesterday (yes/no)"? Based on their answers, participants received the corresponding screen via WhatsApp. The participants did not receive any instructions on inhaler use. After the five-day testing period, participants were invited for a semi-structured interview. The participants were asked to reflect on the screens they had received in terms of motivation to use their maintenance inhaler, usefulness, inhaler use and usability. During the interview, the other screens (e.g., those that were sent with a different combination of answers) were also presented and asked to provide feedback on. In total, the interviews lasted approximately 1.5 hours. The interviews were audio recorded and transcribed. Transcripts were analysed and used to formulate design recommendations.

Results

Phase 1: define

All participants of the questionnaire (n = 20) expressed that they found it difficult to use their maintenance inhaler on a daily basis. While the initial answer of all participants was that they did not adhere to their inhaler, because they simply forgot, further questioning revealed additional reasons and motives. Based on the interview data and data from the online survey, five key themes were identified regarding reasons for non-adherence to maintenance medication. Each theme is described below. Demographics of the participants of the interviews and the online survey are depicted in Appendix 1. Although not a specific inclusion criteria, participants in the interviews (and subsequent study activities, as chosen design focus) included participants with mild asthma only.

Theme 1: Asthma feels episodic and no need for medication when feeling well

Participants found it difficult to use their inhaler daily because their asthma felt episodic rather than chronic, marked by periods where they hardly experienced any symptoms. During these periods, they did not use their maintenance inhaler until their symptoms increased. Participants initially indicated that they believed

there was no necessity to use the maintenance inhaler in the period they hardly felt any symptoms. Not experiencing symptoms or feeling "well enough" were reasons to not use their maintenance medication on a regular basis for the majority of the participants. Comparable results were seen in the online survey. Half of the participants agreed, or completely agreed with the statement "Asthma feels episodic to me".

Theme 2: Not wanting to feel like a patient

Participants mentioned that using the inhaler made them feel like "a patient". Two out of six participants mentioned that even filling in a symptom and asthma control questionnaires reminded them of "being a patient" and made them more conscious of their asthma, which they preferred to not be aware of. They explained that they rather "live in the moment" and not be reminded of having asthma. In line with these qualitative findings, 33.3% of the online survey participants strongly agreed with the statement "using my maintenance inhaler is not necessary when I feel well". When asked how to deal with flare-up of symptoms, one interviewee answered that he would use the reliever inhaler more often, up to six times a day.

Theme 3: Health and symptom burden as an important motivator to use a maintenance inhaler

All participants experienced moments of worsening of their asthma. During these moments, all except one participant used their maintenance inhaler daily or occasionally. The increased burden of disease on everyday life activities was a reason to start using the maintenance inhaler after a period of non-adherence. For two participants, important sport performances, requiring optimal physical condition, were reasons to be medication adherent. During these periods of performance (e.g., an important hockey tournament) they were more consciously self-managing their asthma which meant using their maintenance inhaler daily (temporarily), stopping smoking and avoiding other triggers.

Theme 4: (delayed) experienced effect of medication

When discussing reasons why participants rather used the reliever medication, the fact that people did not feel an effect of maintenance medication but did feel the effect (i.e., being able to breath and feeling of relieve) of their reliever medication were the main reasons, as one participant explained:

> *"I find it hard to feel the effect of the medication. I do notice it when I feel bad, but I don't notice it when it goes well."*

Another participant indicated that she found it difficult to distinguish between breathlessness as the result of asthma or 'bad' condition.

Theme 5: Need for knowledge on inhaler differences

Other reasons for not using the maintenance inhaler included participants' limited

knowledge regarding the distinction between the maintenance and reliever inhaler, as well as fear of potential side effects (e.g., sore throat), they associated with the use of inhaled corticosteroids (ICS). Three participants expressed a desire for more information about the difference in effect between the different inhalers. This need for more information was reinforced by the results of the online survey in which 50% of all respondents agreed or completely agreed with the statement "I would like to have more knowledge about the effect of my medication".

None of the participants were familiar with EDMs. However, when asked if insight into their inhaler use and symptoms would help them gain a better understanding of how inhaler use can help in controlling their asthma, the majority of the participants affirmed the potential benefits. They clarified that seeing trends between medication use and asthma control would help them understand how proper inhaler use can facilitate asthma control. Two participants also indicated that they also would like to have more insight in their triggers.

Based on the aforementioned findings, eight behavioural change techniques were identified which were mapped onto the TTM to identify the stage in which the technique should intervene. Behaviour change techniques were: i) motivational interviewing, ii) patient education, iii) personal goal setting, and iv) commitment to support contemplation, v) feedback on inhaler usage behaviour, vi) self-monitoring of behaviour, and vii) self-monitoring of asthma control to support action; and viii) evaluation moments to support maintenance.

Phase 2: ideation

Five personas were created (see Appendix 2 for an example) and used to identify three design directions each focusing on a separate stage within the TTM (see Appendix 3 for the three design directions and the different ideas). A discussion meeting of the three design directions with an expert on persuasive game design and behaviour change led to the formulation of design requirements (see Table 1). Game requirements were deducted from persuasive game design theory to ensure that the persuasive game is fun, engaging and effective in promoting adherence to maintenance inhalers. These included that the game must be rewarding if the desired behaviour is carried out, visualize the effects of medication use, create an overview of medication use over time and be entertaining to engage with (see Table 1).

Final concept – Ademgenoot

The desired design and game requirements were translated into a serious game concept 'Ademgenoot'. The name of the concept was based on a wordplay of the Dutch words "Ademnood" (Breathlessness) and "genoot" (Buddy). Using automatic data logging with an EDM to detect inhaler use and narrative game-elements, Ademgenoot aims to motivate people with mild asthma to adhere to their prescribed maintenance medication treatment. Ademgenoot does so by focusing on the positive effects of taking the daily maintenance medication. Moreover, the application gives the patients the opportunity to try-out the daily intake of their medication as prescribed,

by offering them a six-week challenge linked to an asthma-related personal goal (e.g., join friends on a skiing weekend). During this six-week period Ademgenoot visualizes inhaler use (maintenance and reliever inhaler) in a playful way to make the effect of the medication visible and to stimulate engagement with the game and thus use of their inhaler. Six weeks was chosen as this is generally the period in which individuals respond to ICS with an improvement in pulmonary function (42). At the end of the challenge, users should have gained insights into the effect of the daily use of their Figure 2 for a visual representation of the game). As such, Ademgenoot supports the intention, action, and evaluation of behaviour change.

Table 1 Behavior change strategies and design and serious game requirements

	Behaviour change strategies	**Design requirements**	**Serious game requirements**
Support intention	Motivational interviewing	Support self-efficacy.	
	Patient education	Education on differences between maintenance and reliever inhaler.	
	Personal goal setting	Set personal goal as driver for internal motivation.	
	Commitment	Commit to a try out period to experience effect and benefits and form a habit.	
Support action	Feedback on behaviour	Direct, real-time feedback to user on maintenance and reliever inhaler use.	Visualize effect of inhaler use. Provide reward if desired behaviour is conducted. Be entertaining to engage with.
	Self-monitoring of behaviour	Possibility to track and monitor maintenance and rescue inhaler use in a (semi)automatic way.	Visualize medication use over time. Create overview of medication use over time.
	Self-monitoring of disease progression	Tracking and monitoring asthma control.	Be effortless.
Sustain maintenance	Evaluation moments	Evaluation on behaviour and impact on daily asthma control.	Link reliever usage to trigger moments.

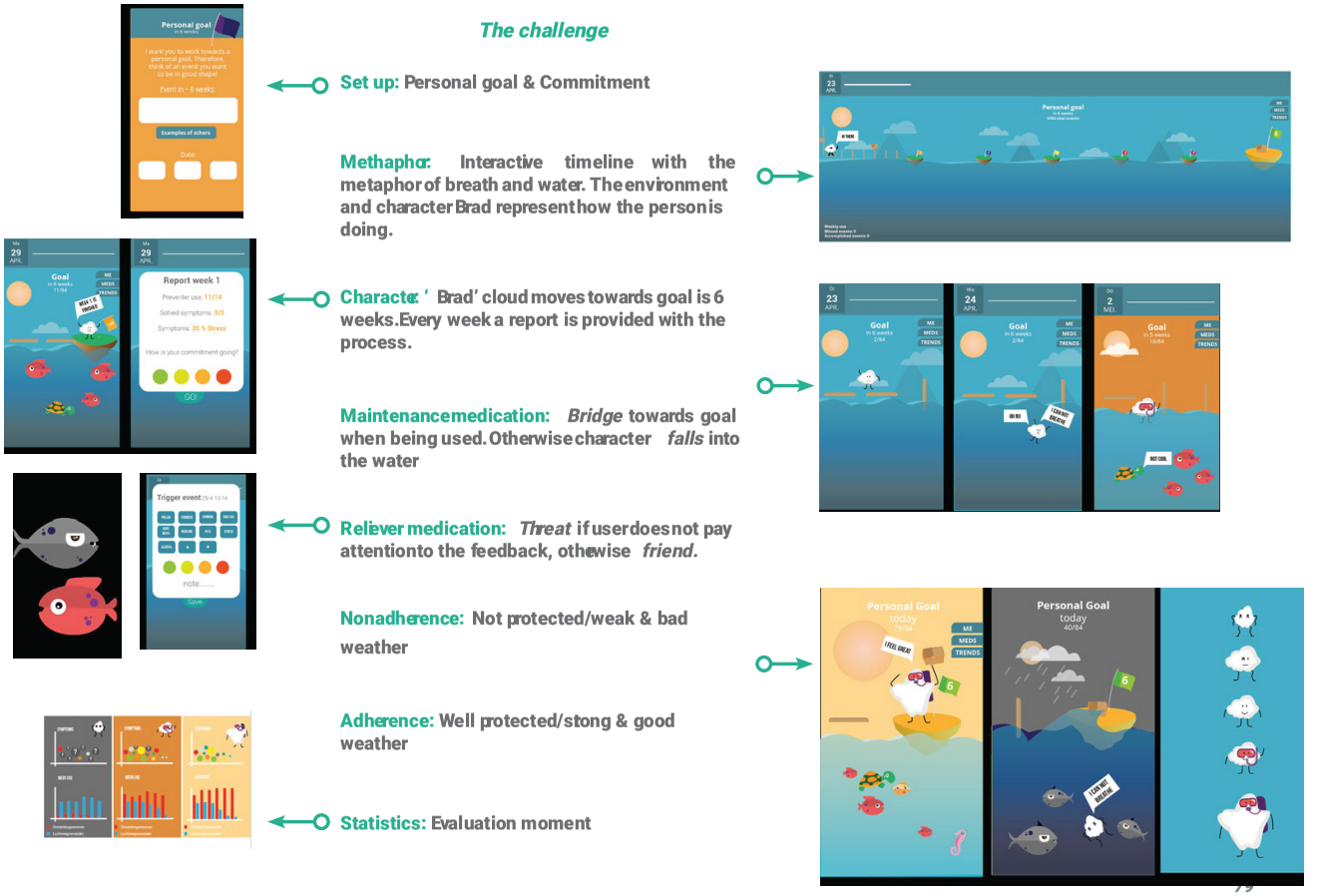

Figure 2. Visual representation of the core elements of the persuasive game 'Ademgenoot'.

Intention

Upon onboarding the app, Ademgenoot offers a brief instruction on inhaler technique and the difference between maintenance and reliever inhaler and its effect on the lungs. Motivational Interviewing techniques are included through the use of personal goal setting and creating a commitment. After the onboarding screens, users are offered a six-week challenge, linked to a personal goal. Upon accepting the challenge, users enter the game world.

Action

Use of narrative and game elements

Ademgenoot employs the use of a narrative and metaphors to motivate users to adhere to their maintenance inhaler. The narrative involves a cloud-like character named Brad, whose mission is to reach a treasure island, which represents the user's personal adherence goal. To do so, Brad must cross over water. Connected to the EDM, Brad is able to "safely" cross the water when inhaler use is detected. However, when inhaler use is not detected he falls into the water. Therefore, it is the patient's responsibility to create bridges for Brad to safely cross the water by adhering to the inhaler regimen. The user is also confronted with the possibility of Brad falling into the water and drowning when not adhering to the regimen. In the scenario of one missed dose, Brad can hang on to the bridge.

Visualization effect of maintenance inhaler use

The protective effect of maintenance medication on the lungs is visualized through the environment and Brad's physical appearance. Whereas one missed dose is not detrimental (i.e., Brad is able to hang on to the bridge), the negative impact of multiple non-adherence days is represented through a gradual shift towards a greyer and gloomier environment, with Brad sinking deeper. On the other hand, longer streaks of adherent days, result in a stronger Brad, equipped with a diving goggle to be able to endure longer under water (i.e., metaphor for protection of the lungs). The environment also becomes brighter, and users are rewarded with an enriched environment, which for example includes a turtle underwater. Users are provided with a report on the medication usage every three days, represented as intermediate treasure chests.

Visualization effect of relieve inhaler use

Use of the reliever inhaler is logged through a reliever EMD. When reliever inhaler use is detected, a push-notification is sent to the user, who is then prompted to indicate the reason for use by selecting triggers from a pre-specified list of triggers. Additionally, the user is asked to indicate their level of asthma control using a colour scale. To improve engagement with the app and improve the input of self-monitoring data, which can be a challenging aspect of self- monitoring interventions, the to be filled in form is depicted as a piranha, which transforms upon completion of the form into a friendly-looking fish.

Evaluation

Overview Medication Use and Asthma Control

After six weeks, users are provided a report that displays their maintenance inhaler usage, reliever inhaler usage, triggers, and level of asthma control. The report serves as a tool to identify trends and assess the impact of increased adherence to their maintenance inhaler on asthma control.

Phase 3 and 4: prototype and evaluation – iteration 1

Feedback on the paper prototype (see Figure 3) was obtained from four people with mild asthma who had not participated in previous activities. This number was deemed sufficient to identify major issues on usability (43,44). Overall, the participants enjoyed the games and the six-week challenge. They appreciated the ability to set a personal goal. However, two participants mentioned finding it difficult to think of one. The commitment to the challenge itself was motivating enough for them to start using Ademgenoot. One participant suggested to incorporate more daily goals, such as cycling to work without feeling out of breath, rather than linking the goal to a specific event (e.g., entering a sporting competition). Some participants preferred a weekly overview instead of updates every three days. While two participants considered the cloud character Brad to be childish, the other two felt affection for the character and found him not too childish.

The paper prototype was also reviewed by two general practice nurses who commented on the clinical feasibility and provided additional clinical feedback. They expressed their enthusiasm and found the game to be feasible in practice. However, they pointed out that inhaler use may not always result in better asthma control. Therefore, it is important for healthcare professions and the serious game to manage expectations to maintain user's motivation to continue with the challenge. Instead of "promising" improvement it is important to reflect on the effect of behaviour and asthma control together. The data collected with the app can be useful for health care professionals to evaluate inhaler usage behaviour and asthma symptoms. In addition, three patient advocates provided feedback and expressed that the game, despite its playful appearance, could appeal to a broad range of patients, including children and those over the age of 45. They appreciated the breathlessness metaphor but emphasized the importance of providing a proper explanation for the piranha/fish aspect to avoid being perceived as punishment for reliever use. A review and discussion of the prototype with smart inhaler developers showed that the Ademgenoot concept was technically feasible as EDM can be used for several reliever and maintenance inhalers. However, as some patients receive Symbicort as Symbicort Maintenance and Reliever Therapy (SMART), the commercial feasibility (i.e., complementing business strategies) may be less clearly defined.

Figure 3. Paper prototype testing of the persuasive game 'Ademgenoot' with a participant.

Based on the first prototype evaluation, several improvements were made to the prototype: a weekly report instead of every three days, icons instead of text in the trigger self-monitoring form, a more human-like character, a different colour pallet and design style to appear less child-like.

Phase 3 and 4: prototype and evaluation – iteration 2

Four novel individuals with mild asthma participated in the WhatsApp prototyping and provided feedback during a semi- structured interview afterwards. Two participants indicated that they never until rarely used their maintenance inhaler, two participants occasionally used their maintenance inhaler. During the test period, one participant had multiple non- adherent days (i.e., received the grey and gloomy screens), while the other three were fully adherent during the test period.

Usability and user-friendliness

All participants understood the purpose of the game and found the game user-friendly and engaging. Participants appreciated the ease of registering trigger moments with the push-notification and the use of icons.

"If I get such a pop-up in my screen, I open it and tap it [the trigger icon]. Easy".

Use of metaphors and narrative

All participants enjoyed the narrative of Brad and indicated that it motivated them to use the app more often. Two out of the four participants mentioned that the character motivated them to use their maintenance inhaler daily. They emphasized with the character and felt responsible for his "wellbeing", becoming concerned if Brad would fall into the water or drown. This was reinforced when they were presented with the grey and gloomy screens (i.e., the result of longer streaks of non-adherence) during

the interview. The gloomy screens would motivate them to "get Brad back on track" and use their maintenance inhaler again. The other two participants did not require Brad as a motivator and stated that the challenge in itself was sufficient. The end report was helpful, but they predicted that it without the narrative the reports would only become monotonous over time, and they would lose interest in the game.

Usefulness

All participants indicated that the game helped them to be more aware of their asthma and their inhaler use. Importantly, they also mentioned that due to playful and non-medical appearance it did not make them feel like a patient.

Effect on adherence behaviour

Three of the four participants indicated that Ademgenoot had a positive effect on their inhaler use during the test period. One participant, who had practically never used her maintenance inhaler before the challenge, reported improvement but still encountered difficulties in using her inhaler in the morning. Nonetheless, the gloomy screens served as motivating factor to exert her best effort:

> *"The confrontation with the screen worked for me. I am very sensitive to color. I like that, the grey sky with the character. I start with sunshine and a beautiful sky. I'm doing a bad job and really have to do something"*

Furthermore, participants expressed curiosity to continue using Ademgenoot for the following six weeks and stated that this first week was a good first motivator. Various reasons to continue after the first week were mentioned. For instance, one participant was curious to see if taking their medication would have a positive effect on their symptoms:

> *I now have more symptoms, and I want to try to see if it [using maintenance inhaler daily] helps. I have not used it for such a long period now and I am learning to live with that. I am however short of breath. If I use it for a longer period, do I notice it? I am very curious about that.*

Another participant mentioned that especially getting insight into her trigger moments would be a reason to continue with Ademgenoot.

Effect on sense of control over the asthma

Three participants expressed their expectation that, if Ademgenoot helped them to adhere to their maintenance inhaler and experience fewer symptoms, they would gain a greater sense of control over their asthma. They mentioned that continuing to track symptom triggers over time would help them get better insight into their triggers, recognize trigger events, and respond better to the triggers. In addition, the weekly overviews provided them with a sense of control. Participants trusted that the Ademgenoot could also help in controlling their asthma symptoms. However,

two participants mentioned that relying on reliever use as a benchmark was not appropriate, as they rarely used their reliever medication despite feeling breathless and experiencing symptom flare-ups. They suggested the possibility of reporting on their level of asthma control regardless of reliever use, and the user could be rewarded with a fish in the water for doing so.

Evaluation of the concept with two patient advocates showed similar findings. The patient advocates found Ademgenoot easy to use and particularly valuable for individuals recently diagnosed with asthma and children, owing to its playful and fun approach. The combination of game elements and medication usage statistics was especially appreciated, as they expected that this would motivate people to be adherent. However, the patient advocates emphasized the importance of evaluating the inhaler behaviour and asthma control with a healthcare professional during regular consultations as improvement may be less when medication is not properly adjusted. They considered the weekly reports to be helpful in reflecting together on medication use, asthma control and trigger events. Furthermore, they emphasized that the report on symptoms or control should reflect how one feels, as one might be medication adherent yet still experience significant discomfort. Finally, both patient advocates suggested that Ademgenoot could also be beneficial for individuals with limited health literacy due to its prominent visual component.

Discussion

This paper demonstrates that a participatory user-centred design approach, combined with involvement from healthcare professionals, behaviour change experts and persuasive game design experts, can result in an engaging, fun persuasive game that has the potential to motivate people with mild asthma to be adherent to their maintenance medication. We identified reasons for non-adherence and user needs, identified behaviour change strategies (phase 1) and translated these into design and serious game requirements (phase 2). Several iterations were performed in which prototypes were evaluated with end-users, which led to the final persuasive game Ademgenoot (phase 3 and 4). Final evaluation showed that Ademgenoot has the potential to motivate people to adhere to their maintenance inhaler, promote long-term behaviour change and is feasible in clinical practice.

A key finding during the define phase (phase 1) was that people's non-adherence was often due to their perception of asthma as an episodic rather than chronic condition. This perception stems from the intermittent periods of symptom worsening and has been previously reported in qualitative research studies on reasons for non-adherence (45). Furthermore, non-adherence was influenced by the delayed perceived effect of maintenance medication, and a lack of comprehension regarding the distinction between maintenance and reliever inhaler. Consistent with our findings, multiple studies have reported perceived lack of efficacy and suboptimal knowledge of reliever and maintenance medications as drivers for non-adherence (45–48).

Our study is unique as it targets multiple drivers for non-adherence, serving as a foundation for the design of Ademgenoot, a six-week challenge-based game designed to increase medication adherence. Ademgenoot aims to motivate users, employ goal-oriented strategies, and provide visual feedback on adherence behaviour to raise awareness of the effect of adherence on asthma control. Ademgenoot incorporates various behavioural change strategies, such as personal goal setting and continuous direct feedback, along with persuasive game design elements, including a narrative and rewards. These combined elements are intended to increase patients' motivation to adhere to their maintenance inhaler regimen.

Self-determination theory and motivation

Increasing motivation to adhere to the maintenance inhaler and sustain the behaviour is an important design strategy and in accordance with the Self-Determination Theory's motivational underpinnings. According to this theory, there are three essential psychological needs – autonomy, relatedness, and competence – that are critical in forming motivation (49, 50). In the context of asthma medication adherence, Self-Determination Theory suggests that patients are more likely to adhere to their medication regimen when they have a sense of autonomy in decision-making, feel competent in managing their asthma, and have a supportive relationship with their healthcare provider.

To promote autonomy, the six-week challenge of Ademgenoot, along with personal goal setting, contributes to patients' sense of control. Competence is targeted through patient education on inhaler differences and fostering a sense of accomplishment through being adherent. Generally, patients experience better well-being and a greater sense of being in control over their asthma when they comply with their medication regimen. Relatedness, another vital aspect, can be achieved by integrating Ademgenoot into a blended-care setting, as suggested by the patient advocates, and by incorporating evaluation moments that focus on successes, thereby providing support for competence. Ademgenoot could facilitate conversations between patients and healthcare providers on adherence behaviour, asthma control and decisions regarding therapy step-up.

Ademgenoot employs a combination of internal motivation (e.g., personal goal setting), external motivation (such as motivating screens featuring Brad's progression), additional rewards (e.g., the environment becoming richer) and intrinsic motivation by fostering engagement and enjoyment with the app itself (instead of using the inhaler itself having to be enjoyable). While short-term motivation is achieved through these fun and rewarding elements, long-term adherence requires the internalization of extrinsic motivation according to the Self-Determination Theory (51). The six-week challenge stimulates long-term engagement, allowing users to experience the benefits of using a maintenance inhaler and facilitating the process of internalizing extrinsic motivation, thereby increasing the chances of maintaining desired behaviour in the long run.

Use of narrative to complement behaviour change

The internalization of motivation is further facilitated by a narrative with the protagonist (Brad). Narratives have been successfully employed in serious games to complement behaviour change theories and have shown to effectively support behaviour change (52). Through immersion and the creation of affection for the narrative protagonist, people can mentally envision the health benefits related to the desired behaviour and apply them in the real life. Furthermore, narratives can provide intriguing incentives for people who, having affection for the protagonist, feel obliged to finish the story and act on feeling of relatedness to the protagonist (53). As such, our protagonist Brad may foster internalization of external motivation to complete the game and adopt the behaviour promoted in the game. Furthermore, a narrative can serve as an analogy of a real-world setting, enhancing a possibly boring and unstimulating context, and inspiring players by adding a narrative overlay (54).

Ongoing feedback on behaviour to change behaviour

Ademgenoot utilizes EDM logging to offer direct and continuous feedback on inhaler usage. Feedback delivered through digital technologies, in order to facilitate behaviour change', has been promising to disrupt and change undesired habits or automatic behaviour (55). Effective feedback depends on factors such as timing, delivery, modality, and content (55). Generally, continuous, real-time feedback delivered visually, enabling reflection-in-action (i.e., in the moment), is the most effective.

Ademgenoot offers continuous real-time visual feedback on inhaler usage and perceived asthma control, which is an improvement over the current reflection-on-action-based (i.e., afterwards) practice during regular consultations. Future developments should explore how best to provide feedback on perceived asthma control, for example, by incorporating asthma questionnaires such as the Asthma Control Questionnaire (ACQ). Moreover, integration of automatic monitoring of environmental triggers (e.g., pollen data) or peak flow data could provide a more comprehensive self-management tool (56).

Strengths and limitations

Our paper takes a distinctive approach by utilizing participatory user-centered design with service design techniques, behaviour change principles, and persuasive game theory. This approach involves creating personas and multiple prototype iterations. By actively involving end-users, key design requirements were identified, increasing the chances of the intervention being accepted and adopted. Furthermore, by integrating theoretical frameworks, we promote understanding of mechanisms explaining motivational effects (57). As such, our study contributes to the knowledge base of persuasive game design as an effective method for changing health-related behaviour. Another strength of our study is that besides the end-users, multiple other stakeholders were involved, including healthcare professionals, patient advocates and developers of smart inhalers. Their involvement ensured the accuracy, feasibility,

and commercial and technical viability of Ademgenoot, making it a strong candidate for future implementation.

Our study is subject to several limitations. First, the relatively young participants could have limited the representativeness of our findings and the applicability of the Ademgenoot concept. However, by involving various stakeholders, we were able to achieve a wider perspective. Second, the small number of participants per design phase may have an influence on the study findings. Nonetheless, considering that we were able to involve participants throughout all phases of design and development, involving individuals that had not been involved during the previous phase and iterate on the previous feedback, we believe we were able to capture their needs in a valid way. Third, the formative evaluation of Ademgenoot may also present some limitations as not all components of the Ademgenoot game were tested. In addition, interference by the researcher may have led to changes in behaviour (i.e., improved medication adherence) due to the individual being observed. Finally, the limited duration of the testing period (i.e., five days) calls for caution in drawing conclusions regarding long-term usage. Furthermore, the focus of our study on individuals with mild asthma may limit the generalizability of our findings to other patient groups.

Implications for practice

Our paper demonstrated how data logging through EDMs can be utilized to provide a fun persuasive game to motivate, in the first place, adults with mild asthma to adhere to their medication regimen. Despite its potential, EMDs have not yet been implemented on a large scale in practice due to, amongst others, the need for evidence on long-term effectiveness and disengagement challenges with existing apps (56). Adoption of EDMs may be facilitated by offering different types of adherence support programs that cater to the needs, reasons for non-adherence, capabilities and preferences of individual patients, in a shared-decision making way (22,58). This requires EMD programs to be compatible with existing inhalers preferably integrated within existing electronic health records. Inquiring into reasons for poor-adherence should be standard practice to provide appropriate adherence support. We observed, in our study, behind the initial answer of "simply forgetting" were several underlying reasons for non-adherence, which should be addressed to support medication adherence effectively. Moreover, to reach its full potential, developments with EMD should focus on providing feedback on inhalation techniques to ensure proper usage. Ademgenoot offers an engaging way to incorporate inhalation techniques into self-management interventions for asthma. Finally, the concept of providing feedback on medication use via automatic logging, such as through electronic pill bottles, may also be applicable to other chronic diseases with medication non-adherence as a common challenge and where there is no direct tangible benefit of being adherent.

Implications for research and future directions

The evaluation of Ademgenoot through WhatsApp prototype testing provided a low-cost and efficient way to assess people's perceived impact on medication adherence and motivation. However, further research should focus on a real-world evaluation of

Ademgenoot as a fully functional prototype to assess its long-term usage, impact on inhaler usage, and the expected shift from external to internal motivation, and include people with limited (health)literacy (59). Long-term evaluation should in addition provide more understanding of the degree of adherence to the app to acquire the desired behaviour (60). Eventually, effectiveness on clinical outcomes (e.g., asthma control) and medication adherence should be evaluated by including considering study design appropriate for summative evaluation of eHealth interventions (e.g., step-wedged-design). While the involvement of healthcare professionals within this study ensured that Ademgenoot fits with care processes, feasibility in practice should also be assessed through pilot studies, taking into account the perspectives of patients, healthcare professionals in both first (i.e., general practitioners and practice nurses) and secondary care (i.e., respiratory physicians), and decision makers. Finally, considering that smart inhalers are a relatively new field of research, further research is needed to determine which patients would benefit the most from these programs (39). Hence, we encourage that studies into the effectiveness of smart asthma inhalers include patient characteristics (e.g., beliefs about medication and eHealth literacy) to gain insight into which smart inhaler programs benefit which patients based on these characteristics and reasons for non-adherence (57).

Conclusion

Combining a participatory user-centred design with behaviour change principles and persuasive game theory, we developed an innovative six-week challenge-based persuasive game that was evaluated as user-friendly and useful and has the potential to increase motivation to be medication adherent. Active involvement of all stakeholders throughout the design process ensured that our solution does not only meet the end-users needs but is also technically, commercially, and practically feasible and has the potential to improve medication adherence among people with mild asthma and other chronic conditions in which non-adherence is a common challenge.

Data sharing statement

Individual de-identified participant data supporting the findings are available from the corresponding author on reasonable request.

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Author contributions

JdB and CCP conceptualized and designed the study. JdB was responsible for data collection, data analysis and interpretation. CCP, LG, VTV and EM made substantial contributions to the design and collection of data. CCP, EM, SJvH and NHC made substantial contributions to interpretation of data. CCP wrote the manuscript and EM provided feedback at each version of the manuscript. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no competing interests in this work.

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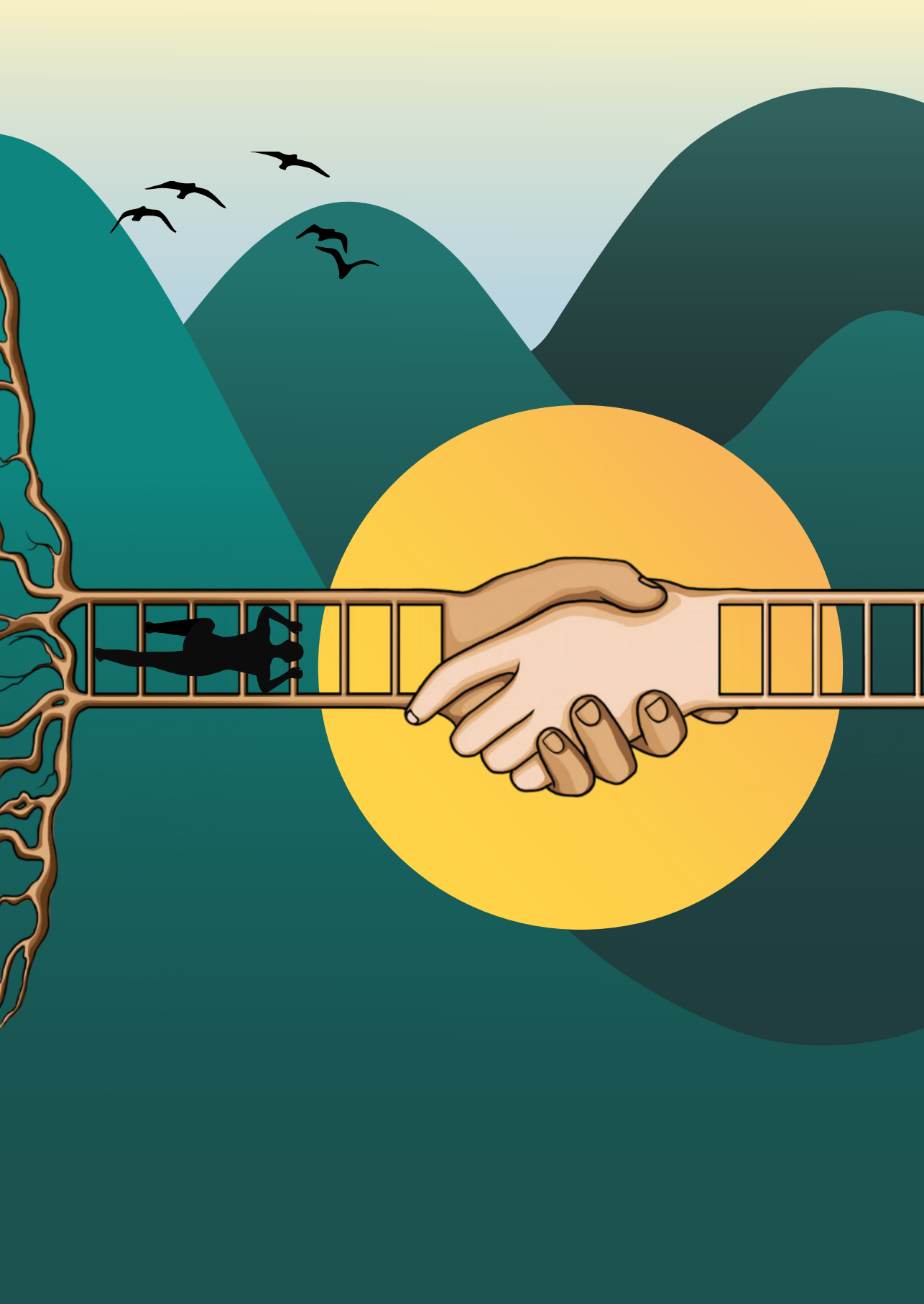
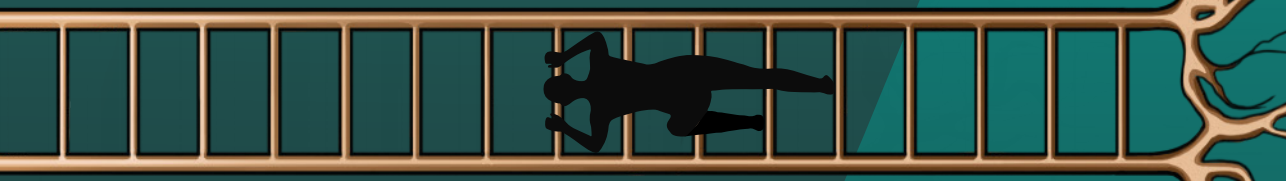


Chapter 3

Designing with and for people with limited health literacy

Developing a digital medication adherence intervention for and with patients with asthma and low health literacy: protocol for a participatory design approach



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Abstract

Background

Current eHealth interventions are poorly adopted by people with low health literacy (LHL) as they often fail to meet their needs, skills, and preferences. A major reason for this poor adoption is the generic, one-size-fits-all approach taken by designers of these interventions, without addressing the needs, skills, and preferences of disadvantaged groups. Participatory design approaches are effective for developing interventions that fit the needs of specific target groups; yet, very little is known about the practical implications of executing a participatory design project for and with people with LHL.

Objective

This study aimed to demonstrate the application of participatory design activities specifically selected to fit the needs and skills of people with LHL and how these were manifested within an overarching eHealth design process. In addition, the study aims to present reflections and implications of these activities that could support future designers to engage people with LHL in their design processes.

Methods

We used the design process of a smart asthma inhaler for people with asthma and LHL to demonstrate participatory design activities. The study was framed under five stages of design thinking: empathize, define, ideate, prototype, and test within two major iteration cycles. We integrated three participatory design activities deemed specifically appropriate for people with LHL: co-constructing stories, experience prototype exhibition, and video prototype evaluation.

Results

Co-constructing stories was found to deepen the understanding of the participant's motivation to use or not to use maintenance medication. This understanding informed and facilitated the subsequent development of diverse preliminary prototypes of possible interventions. Discussing these prototypes in the experience prototype exhibition helped provoke reactions, thoughts, and feelings about the interventions, and potential scenarios of use. Through the video prototype evaluation, we were able to clearly communicate the goal and functionality of the final version of our intervention and gather appropriate responses from our participants.

Conclusion

This study demonstrates a participatory design approach for and with patients with asthma and LHL. We demonstrated that careful consideration and selection of activities can result in participants that are engaged and feel understood. This paper provides insight into the practical implications of participatory activities with people with LHL and supports and inspires future designers to engage with this disadvantaged target group.

Introduction

Over the past decades, digital health (eHealth) interventions have been developed to support self-management. Such interventions can combine patient monitoring and education and include multiple behaviour change strategies (1-5). Examples of such applications are SMS text messaging systems to reinforce self-management skills, pill boxes generating alert messages when medication is missed, and interactive voice responses (6).

One specific group of people that would benefit from such interventions are people with low health literacy (LHL). A large-scale survey showed that, in Europe, nearly half of all adults reported having problems with health literacy (7). People with LHL have problems obtaining, processing, and understanding basic health information and communicating their needs to healthcare professionals (HCPs) (8). Furthermore, LHL is associated with lower patient activation. Patient activation refers to the "knowledge, skills, and confidence" of a person in managing their health and has also been called the "mindset" needed to change behaviour (9-11). This is amplified by the fact that people with LHL have differentiating illness perceptions and beliefs about their medication (12-15). As a result, they experience difficulties in following treatment recommendations, for example taking medication as prescribed (16-18).

Approximately 50% of the people taking medication for chronic illnesses such as chronic obstructive pulmonary disease, diabetes, or cardiovascular disease are considered non-adherent (19). Medication non-adherence has a significant impact on patients' quality of life and has been shown to lead to poor health outcomes and increased use of healthcare services (20). Medication adherence in patients with asthma is consistently low, which results in unfavourable health outcomes such as an increase in experiencing symptoms and hospitalization (21). Previous reviews have shown promising results on the effectiveness of eHealth interventions to enhance patients' adherence to asthma medication (6,22-24). Yet, these interventions are mostly designed for patients with sufficient motivation, health literacy, and self-management skills and fail to address the needs, skills, and preferences of patients with LHL.

Within the design domain, it is acknowledged that involving users in the design of eHealth interventions facilitates alignment with their needs and preferences. Besides action- and community-based approaches (25), participatory design and its methods are increasingly receiving attention. These approaches are based on the notion that when users are involved in the design and development of interventions, they are more likely to be successfully adopted (26-28). Participatory design could uncover potential reasons for non-use and allow designers to discover, through their participants, how technologies could be acceptable and engaging (29).

Participatory design is human centred and especially useful in the context of LHL. First, participatory methods are visual, interactive, and concrete. This benefits people who have difficulties thinking in abstract terms or who have language barriers to understand and engage with the process (26,30). The flexibility of a participatory

approach also allows to adapt and align research methods if judged inappropriate. Second, participatory methods can also bridge the gap between researchers and participants by creating a more equal and collaborative environment. This can help reduce distrust, friction, and misunderstanding that can arise due to differences in social, cultural, and economic backgrounds. Finally, a participatory design approach is iterative, which allows multiple engagements with the end user. This benefits the development of rapport and mutual trust between researcher and participant, which is known to be a strong facilitator for participant retention (31).

Nevertheless, participatory design is still seldom applied in intervention design among people with LHL. Only a few examples exist of participatory design studies on people with LHL (32,33). The time, resource, and skill intensity of such a process, in combination with its results being difficult to generalize, decrease the attractiveness of the approach (34), and evidence regarding why and how to conduct such an approach in intervention design is falling short (35). In addition, effectively involving disadvantaged groups, such as people with LHL, in research efforts is challenging. It has been marked by several barriers, such as participants having difficulties understanding the content of the study (36), finding it difficult to think in abstract terms (37), language or literacy problems (36), anxiety toward research or the research team (38), feelings of stigmatization (39,40), and limited exposure to technology and internet (41). While participatory design methods have the potential to overcome these barriers, the scientific literature is unclear about which forms of participatory design can be used to develop eHealth (35). Consequently, there is also no clear methodology on how to involve people with LHL in the participatory design process of an eHealth intervention.

Hence, the aim of this paper was to demonstrate how participatory design can be used to design an eHealth intervention that fits the needs and preferences of people with LHL. We present the development of an asthma medication adherence intervention for people with LHL to illustrate our approach.

Methods

The study was conducted between February and September 2019. The study was framed under the five stages of design thinking by Hasso Plattner Institute of Design (42) and consisted of the following stages: (1) empathize to understand the user, (2) define to analyse and interpret the data, (3) ideate to explore and identify innovative solutions, (4) prototype to explore feasibility and develop a research instrument, and (5) test to evaluate usability and acceptance of the prototypes. While defined as distinct modes, in practice, the stages are iterative. This allows the researcher to reflect on previous activities and incorporate knowledge from the different stages.

Figure 1 displays an overview of the overall design process. It shows how the five design thinking stages were structured across two major design iterations, including design activities used and outcomes generated. Throughout this paper, we distinguish between the three participatory design activities and the other generic

design activities, with a specific focus on the former to illustrate how people with LHL can be involved in a participatory design process of an eHealth intervention. We specifically chose to embed the participatory activities at the beginning (to develop an understanding) and end (to evaluate this understanding) of the design iterations.

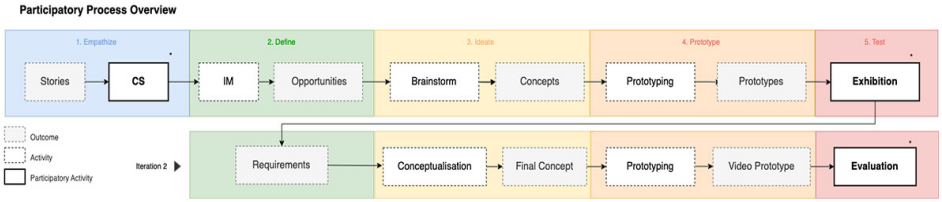

Figure 1. Schematic overview of the process, illustrating the different design thinking stages and its iterative character. * Defines a participatory design activity; CS, Co-constructing stories; IM, Intervention Mapping

Participatory design methods

Overview

Within this framework, we integrated three participatory activities deemed specifically effective for people with LHL. These were (1) "co-constructing stories" (43), (2) "experience prototype exhibition" (44), and (3) "video prototype evaluation" (45). These activities were specifically selected as they would allow to effectively engage with the target group and understand their perspective.

Co-constructing stories

The creation of stories helps to discover users' thoughts and beliefs regarding a particular phenomenon. In a previous study, for example, co-constructing stories was used to gather insights regarding an interactive system to support collaboration in a meeting room (43). Stories can be presented visually, which decreases the interview's abstractness and verbality. As such, the use of visuals has been successfully applied in other LHL-related intervention design processes as conversation starters or design tokens (46-48). Apart from the benefits of visuals, using a fictional but relatable character in stories helps to shift the conversational focus from the individual, thereby decreasing possible anxiety-related barriers.

Experience prototype exhibition

Experience prototypes extend beyond the usability of a product and focus on understanding a person's attitude toward a product by envisioning what it might be like to engage with it (44). People with LHL have little prior experience regarding the use of technologies for health (41). Using these technologies in an experience prototype evaluation session could, therefore, provoke responses and reveal attitudes toward new technological solutions that would otherwise remain undiscovered. Moreover, the physical and interactive nature of the experience prototypes allows the researcher to describe the concepts non-verbally, thereby increasing the engagement of participants with communication difficulties.

Video prototype evaluation

Paper-based prototypes are a common tool to evaluate design concepts of eHealth interventions (35). Nevertheless, these prototypes often fail to adequately represent the concept's core functions and interaction scenarios. A combination of paper and video prototypes would be more effective in communicating the concept toward people with LHL than paper-based prototypes alone. (45,49). Videos have proven to be an effective tool in other intervention research and design efforts for asthma patients with LHL (50,51).

Participants and recruitment

The participants involved in the study included patients with asthma who have LHL and stakeholders. Patients with asthma and with LHL (n = 5) were recruited by the first author and an HCP working in a disadvantaged neighbourhood in The Hague, Netherlands. Qualitative and explorative approaches that aim to develop a pragmatic and in-depth understanding of a small number of participants have been argued to be effective in research approaches where not the generalizability, but the values, beliefs, and attitudes of individuals are central. This benefits the study by allowing for more flexibility and in-depth investigation of the included participants (52,53). The patients were purposively sampled based on a self-reported diagnosis of asthma, being prescribed medication, and a subjective health literacy assessment based on the person's characteristics (e.g., migration background, occupation, educational level, and cognitive disorder) by the involved HCP. We decided to not objectively assess participants' health literacy as this was likely to be perceived as stigmatizing and imped building a trustful relationship. The first and second authors also recruited other stakeholders, consisting of respiratory nurses (n = 5), health literacy experts (n = 2), design experts (n = 3, TD, NRH, VTV), and eHealth researchers (n = 4, NHC). These stakeholders were selected because they had long-standing experience with treating asthma, people with LHL, or participatory design methodology. We recruited five "language ambassadors" through an expertise centre in health disparities to evaluate the final concept.

Ethics approval

The study protocol was cleared by the Ethical Committee of the Leiden University Medical Centre (approval number: P18.158). Informed consent was obtained prior to study participation. If written informed consent could not be given, participants provided verbal informed consent, which was recorded.

Results

Stage 1: empathize

The empathize stage served to understand the thoughts, beliefs, and perceived barriers of patients with asthma and with LHL regarding medication adherence. In this stage, we wanted to validate and discuss literature-based personas (Multimedia

Appendix 1) with patients with asthma and with LHL. Personas often consist of a detailed written description (54), which was deemed suboptimal as a research tool for people with LHL as understanding and processing this type of information is often cognitively demanding for people with LHL (37). Therefore, we converted the written persona descriptions into visual storyboards (Figure 2) using the "storyboard that tool" (55).

Figure 2. An example storyboard used during the co-constructing stories sessions (translated into English).

Two participants with asthma and LHL participated in the co-constructing stories sessions. The sessions took place at the facilities where the participants worked, lasted approximately 1 hour, and were audio recorded. Observations and impressions about reasons for non-adherence and the co-constructed stories were collected in the form of a written report after the sessions. Using the storyboards, we asked non-directive questions such as: "How does this character experience the instructions given by the caregiver?" "How do you experience these instructions?" and "can you relate with the character and why or why not?"

The sessions helped to deepen our understanding of the preliminary insights from the initial literature review. For instance, we learned from the literature that an important reason for medication non-adherence in LHL groups is that the patients have misconceptions about the medication (14,15,56). However, through our sessions, we gained a more nuanced view of these beliefs. The participants reported trusting their doctor's expertise blindly, as they had difficulties understanding the purpose of the maintenance medication. Despite trusting the advice, they used their reliever inhaler instead when they experienced symptoms. When asked, participants indicated not knowing or remembering the explanations given by their HCP:

> *"According to the doctor, I just have to use it (the medication). That is what I know". (Male)*

Stage 2: define

We used the intervention mapping approach (57) to translate the user insights, through change objectives, toward practical design opportunities. We discussed the 22 identified change objectives (Multimedia Appendix 2) with the stakeholders and developed three overarching design opportunities (Table 1). In a consensus meeting with design experts, we agreed on the most feasible and important design opportunity—creating awareness about the effects of medication on symptoms through patient engagement in logging and monitoring.

Table 1. Design opportunities

Design opportunity	Determinant	Description
Improve capabilities of patients to understand and organize their medication intake behaviour.	Capabilities	Empower the patient to gain authority and confidence in self-managing their asthma.
Create patient awareness about the importance and effect of the medication.	Awareness	Let the patient see the effect of the medication on the body and the relation between usage and experience of symptoms.
Change patients' attitudes to sustain motivation over a longer period.	Attitude	Help the patient acknowledge that long term benefits of maintenance inhaler are as important as directly noticeable effects of the reliever inhaler.

Stages 3 and 4: ideation and prototyping

The ideation and prototyping stages were directed at developing ideas and concepts that could be used to reach the design objective that resulted from the first two phases. To achieve this, the first author executed a brainstorming session with industrial design students to explore engagement strategies for the monitoring process (i.e., monitor asthma symptoms and monitor inhaler use) and how the data can be presented to patients with LHL to promote awareness.

Four overarching design concepts resulted from these sessions, each combining multiple solution possibilities. The concepts included were (1) a smart wheeze-detecting sensor to objectively monitor asthma state, (2) an immersive experience using augmented reality to engage the user in the monitoring process, (3) a playful spirometer, and (4) a wake-up experience, displaying the result of nocturnal asthma symptoms. We translated the concepts into low-fidelity prototypes to explore their feasibility and facilitate the upcoming feedback session with the participants. The prototypes consisted of cardboard mock-ups, physical artifacts, and off-the-shelf products, such as an augmented reality T-shirt with a projection of the lungs (Figure 3).

Figure 3. Low-fidelity prototypes and visual explainers positioned in an exhibition-style setup during a evaluation session.

Stage 5: test

Three patients with asthma and with LHL participated in the experience prototype evaluation sessions. The evaluations took place at the health facility in their neighbourhood, were audio recorded, and took approximately 1 hour. Participant responses (e.g., experiences, attitudes, thoughts, and needs) for each (part of the) prototype were captured with corresponding quotations. Two days before the session, the participants received a link to a short introduction video. In the video, the researcher introduced himself and explained in lay terms the research setup. This helped set a familiar face, manage expectations, and build initial rapport. This was deemed essential to facilitate the participants' engagement, as anxiety toward research and the research team is a common barrier in socially disadvantaged groups (36).

The session started with a brief individual interview about the demographics, living conditions, and how the participant experienced their asthma. Thereafter, the first author presented the prototypes and invited the participant to interact freely with

them. Verbal and non-verbal responses were carefully observed and documented. Following initial responses, probing questions were asked, such as: "What aspects do you like about this product?" and "How do you envision yourself using this product daily?" The prototypes were discussed in random order. At the end of the session, the first author asked the participant to name the prototype or combination of prototypes they liked or did not like the most and why.

The experience prototypes were successful in provoking reactions, thoughts, and feelings about the product concepts and potential scenarios of use. Through the monitoring aspects of the concepts, we learned that participants were positive about the possibility of tracking symptoms over time, as they expected symptom tracking to give them a better understanding of their respiratory health. Through the sensor-patch included in the wake-up experience, we learned that tracking should occur almost automatically, as the participants wanted the monitoring process to be as effortless as possible.

> *"It is just like sticking a bandage on your wound. You feel nothing, and after a while, you just remove it". (Male)*

Through the augmented reality experience (projecting life-like lungs on the body using augmented reality technology on a T-shirt), we learned that the participants were particularly enthusiastic about novel and innovative technologies, as they improved the perception of the product's usefulness. The augmented reality visualization of the respiratory tract provided a realistic presentation of the lungs as "their own." It allowed them to explore the respiratory system entirely by zooming into its various aspects, such as airways and alveoli. As one of the participants expressed:

> *"Sometimes, I think the medication is not that important. (...) Only when you really experience complaints you look for your medication. However, when you use something like this (augmented reality T-shirt), and you see it is not going well over there, you directly are going to use it. Yes, I have the feeling that now I want to use my maintenance medication". (Male, 44)*

Based on the gathered insights regarding the target group's attitudes toward the prototypes, three design requirements were formulated: 1) the design should be able to objectively monitor the user's respiratory health semi-automatically over time. 2) the design should engage the user in this monitoring process by providing a feeling that the product is innovative and useful. 3) the design should create awareness about respiratory health through feedback that is realistic and displays the respiratory system in its entirety.

Second Iteration—the final concept

Following the formulated design requirements, we conducted a second iteration consisting of another ideate, prototype, and test stage to arrive at a final concept. This process consisted of concept detailing and technical design, with descriptions extending beyond this paper's scope. The final concept aims to provide awareness

through a smartphone app demonstrating data on inhaler use and asthma control. The system allows the user to zoom in on the lungs and explore relations between respiratory concepts. Simplistic icons and illustrations are used to visualize the more complicated underlying physiological processes. For example, a blue arrow that depicts a person's asthma state is presented as the amount of air that can flow through the bronchi. Inhaler data, a proxy for underlying respiratory inflammations, are visualized as respiratory cilia being "in- or out-of-balance," depending on the frequency of maintenance inhaler use. Hence, the maintenance medication is framed as a "helper" to bring back balance to the disturbed respiratory system.

An animation video describing the concept, its functionality, and scenarios of use was developed by the first author with Adobe Premiere Pro (Adobe) (58). The video communicated the concept in a concise and engaging way to the participants. In addition, the first author developed paper-based visual prototypes of the key interface screens that would facilitate the discussion afterward.

For the evaluation sessions, Pharos, an expertise centre familiar with developing and evaluating education material for people with LHL invited five people with LHL to participate in 1.5-hour interview sessions during which the prototype was discussed. A trained and experienced employee of the expertise centre conducted the interviews. Each interview started with displaying the video-prototype, after which the participants were asked about their opinion and if they had any questions. Subsequently, the interface screens were presented and discussed following an interview topic guide. Interview questions included "what do you think they mean with this?" or "what do you think is presented here?" Whenever an element was unclear, we asked the participant to provide suggestions for improvement. The representative of Pharos provided a summary with recommendations for improvement after the last session. In addition, observations and participant responses by the investigator were collected in a written report.

Overall, the participants were positive about the concept as they felt that it would help them gain awareness of being non-adherent to their maintenance medication and the consequences for their lungs. The visual presentation style was understood, and the overall system was perceived as useful and innovative. However, some interface details were unclear, confusing some of the participants. For example, colours were deemed confusing when they were unrealistic (i.e., a blue lung). In addition, a colour-coded performance bar was suggested to visualize the improvement of the cilia.

Discussion

Principal findings

This paper demonstrates a participatory design approach of a medication adherence intervention for patients with asthma and LHL. We explored the potential of applying several participatory design techniques in health intervention design for a LHL population. These consisted of co-constructing stories, an experience prototype exhibition, and a video prototype evaluation. The demonstrated activities provide novel insight in the practical use and implications of participatory design activities with people with LHL and have positive indicative value for supporting their participation in the design process.

There is a need for more insight into new and adapted methods to effectively reach and engage disadvantaged groups. Current approaches are insufficient in reaching and retaining undeserved populations (36,59). While participatory design is increasingly receiving more attention, it is still seldom applied by designers with people with LHL. Models, approaches, and guidelines for participatory design do exist; yet, they do not provide concrete steps that fit specific contexts and people. A previous study suggests there is a need for a broad range of methods that facilitate the practical application of these models (30). The demonstration of these methods in specific contexts and target groups (i.e., patients with psychiatric illness (30) and LHL could severely improve the alignment of interventions with disadvantaged populations.

Indeed, we believe that some of the reasoning behind the activities will also apply to other disadvantaged groups. First, our activities are aimed at facilitating our participants to "tell" their stories using probes of visual scenarios and story elements (60). Several sources on this topic state that groups experiencing communication barriers, such as people with low (health) literacy, learning difficulties, and cultural differences have difficulties understanding the purpose and contents of participatory research activities and vocalizing their thoughts and experiences (36,37). Using scenarios and story elements as a "probe" has helped our participants in telling their stories without relying merely on verbal communication skills. In addition, the probes helped to shift the focus from the individual. This has helped our participants to become more at ease with the research setting, which could be observed based on the extensiveness of their responses. This is deemed especially helpful for groups at risk of stigmatization (i.e., LHL, obesity, and mental illness) (38-40). We propose that the non-verbal and low-threshold nature of such probes positively impacts collaboration with disadvantaged groups. Besides storyboarding and scenarios, other non-verbal participatory probing tools, such as cards, artifacts of discussion, taking pictures, and using emoticons could be equally useful (35,61,62).

Second, another facet of participatory design we applied in this project was allowing our participants to "enact" future scenarios by physically trying out new concepts (60). Age and education are associated with having limited knowledge of and experience with health technologies (41). Therefore, we expect that societal groups, such as people with low socio-economic status or the elderly, could experience barriers in

imagining technologies and usage scenarios. "Priming" is a participatory facet that allows participants to immerse themselves in a domain (63). Our use of experience and video prototypes has helped the participants to get a feeling of possible technologies and imagine scenarios of future use. This could be observed, for example, through the responses the augmented reality T-shirt provoked in our participants. Therefore, we propose participatory tools that facilitate interaction and immersion, such as prototypes, mock-ups, and role-play to facilitate priming for technologies.

Some aspects of the approach demonstrated in this paper could also be used in practice settings. For example, a practice nurse can use co-constructing stories to discuss multiple aspects of medication use in an easy-to-understand, non-obtrusive, and more concrete way with the patient by presenting and discussing recognizable but fictional situations. Hence, it would be interesting to explore co-constructing stories as a low-cost tool during consultations.

Limitations

Through the participatory activities, we were able to gather important insights into the needs, skills, and preferences of people with LHL that would otherwise remain unarticulated. However, the findings of this study should be interpreted in the context of its limitations. Like most studies that address LHL, recruitment was challenging. Having practice nurses identify and invite patients for participation was effective. However, it could also have led to selection bias, resulting in, for example, people who were above average engaged with their health.

Moreover, recruitment was intensive as it required efforts to build rapport and trust and resulted in a relatively small number of participants. The small sample size should be considered regarding the representativeness of the acquired insights for the adherence intervention for patients with asthma and with LHL. In addition, researchers should be mindful in adapting the practical implications mentioned in this paper to fit their context and target group.

While the study provides insight into the practical implications of using participatory methods with people with LHL, we did not thoroughly assess the impact of this approach. Previous research has shown that participatory design can improve the process on many levels. It improves participant advocacy, trust, and sense of purpose; leads to better usability and desirability of the intervention; and achieves better health outcomes, equity, and access (64). Therefore, future researchers could set the next step by studying if a participatory process leads to more desirable and effective health interventions for people with LHL.

An important facet of participatory design that was not integrated into our approach is allowing the participants to "make" and embody thoughts in physical artifacts (60). In this study, the "making" stages (i.e., ideating and prototyping) were done without the active involvement of people with LHL. Engaging participants in co-creating prototypes helps to generate ideas for the physical manifestation of the intervention and has been done to align interventions to the needs of disadvantaged groups

(62,65). Considering the non-verbal and tangible nature of such activities, these could have yielded fruitful interactions.

Conclusion

In this study, we demonstrated a participatory design approach for and with people with LHL. We showed how the participatory activities could result in engagement and mutual understanding within the research process. The eHealth intervention concept resulting from this design process was perceived as an acceptable solution that creates awareness about medication adherence through understandable feedback on medication use and asthma symptoms. The participatory methods applied in this study provide a first step and inspiration for succeeding efforts to help overcome common challenges in the involvement of people with LHL in the design of eHealth interventions.

Acknowledgments

The authors thank all participants and healthcare professionals who participated in the study for their time and for sharing their experiences and thoughts. The authors thank the healthcare centres and their professionals for their expertise and for facilitating the recruitment of patients. We thank Pharos for their expertise and guidance on low health literacy. This work was supported by AstraZeneca with an unrestricted grant.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. All data provided will be anonymised.

Conflicts of Interest

The authors declare that they have no competing interests

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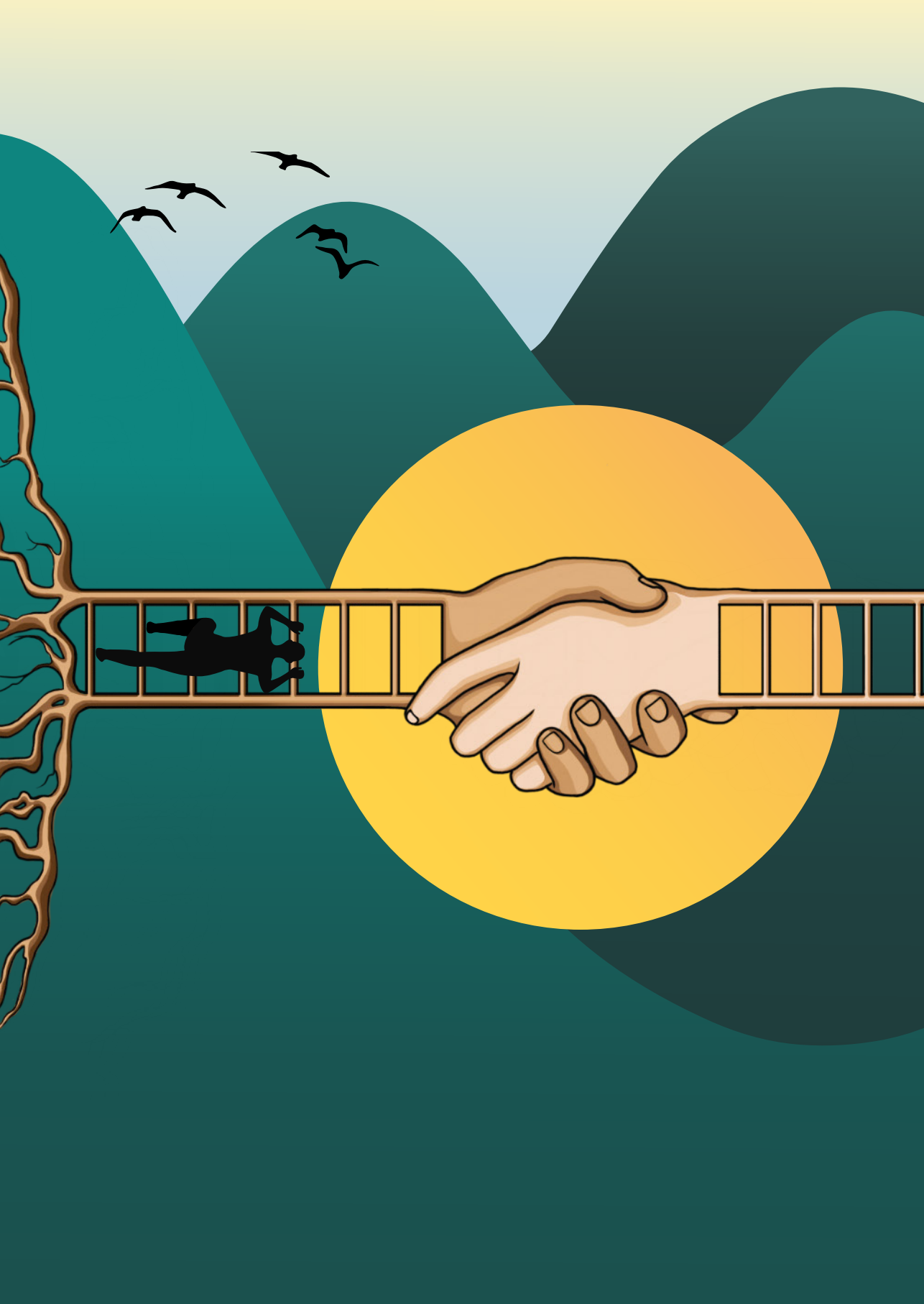
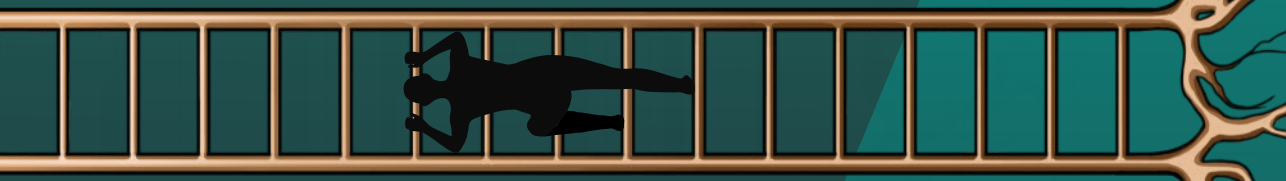


Chapter 4

Development and evaluation of the Hospital Hero app

How to use participatory design to develop an eHealth intervention to reduce preprocedural stress and anxiety among children visiting the hospital: The Hospital Hero app multi-study and pilot report



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Abstract

Background

Medical procedures can cause considerable stress and anxiety among children. Current interventions mainly diminish stress and anxiety during procedures, while stress and anxiety often build up at home. Moreover, interventions often focus on either distraction or preparation. eHealth can combine multiple strategies and provide a low-cost solution that can be used outside the hospital.

Objective

To develop an eHealth solution to diminish pre-procedural stress and anxiety, and to evaluate the app on use, usability and user experience in practice. We also aimed to gain in-depth insights in children's and caregivers' opinions and experiences to inform future improvements.

Methods

This is a multi-study report on the development (Study 1) and evaluation (Study 2) of a first version of the developed app. In study 1 we adopted a participatory design approach in which children's experiences were central to the design process. We performed an experience journey session with stakeholders (n = 13) to map the child's outpatient journey, identify pains and gains, and formulate the desired experience journey. Iterative development and testing with children (n = 8) and caregivers (n = 6) resulted in a working prototype. The prototype was tested with children, resulting in a first version of the Hospital Hero app. The app was evaluated on use, user-experience and usability during an eight-week pilot study in practice (Study 2). We triangulated data from online interviews with children and caregivers (n = 21) and online questionnaires (n = 46).

Results

Multiple stress and anxiety experience touchpoints were identified. The Hospital Hero app supports children in their hospital journey by facilitating preparation at home and providing distraction at the hospital. The pilot study showed that the app was evaluated positively on usability and user-experience and is considered feasible. Qualitative data showed five themes: (1) user-friendliness, (2) coherence and power of storytelling, (3) motivation and reward, (4) fit with real hospital journey and (5) procedural comfort.

Discussion

Using participatory design, we developed a child-centred solution that supports children in the entire hospital journey and may diminish pre-procedural stress and anxiety. Future efforts should create a more tailored journey, define an optimal engagement window and formulate implementation strategies.

Background

(Pre)procedural anxiety and its negative (health)consequence in children – short and long term

Medical procedures in children such as blood drawing performed at the outpatient department are often accompanied by stress and anxiety before and during the procedure (1). Feelings of stress and anxiety during procedures may elicit strong behavioural responses such as crying, withdrawal or showing uncooperative behaviour. Subsequently, procedural distress, especially experienced in early life, can result in numerous disadvantageous psychological health outcomes (2) and pose a substantial burden on children, their caregivers and healthcare providers involved. Generally, children are able to remember their experiences and exaggerate these negative memories when considerable distress is experienced, which in turn can lead to more distress in subsequent hospital visits (3). In the long term, procedural distress can have severe implications for the individual experiencing distress and the society as a whole.

A growing body of evidence shows that early childhood hospital-related trauma is associated with hospital-induced anxiety and needle trauma later in life (4-6). Also negative experiences with healthcare may negatively influence a child's attitude towards healthcare and healthcare providers in general and influence appropriate coping skills in adulthood (6). In addition, distress may increase pain sensation and decrease analgesic efficacy, resulting in a higher titration need and decreased compliance with future procedures and treatments (7).

Coping strategies

While invasive procedures such as blood drawing or injections are a common source of pre-procedural distress, non-invasive procedures or the hospital environment in general can also cause stress and anxiety (6). As such, procedural comfort, directed at minimizing distress throughout a hospital visit, is considered an essential part of paediatric care and has been included in medical guidelines as a necessary adjuvant to procedural sedation. In fact, more recently, academics have opted for procedural comfort as the starting point and sedation as the adjuvant. Procedural comfort aims to provide children with appropriate coping skills. As such, these non-pharmacological interventions can roughly be categorized into (1) distraction (i.e., diverting the attention from the procedure to something more positive; e.g., focus on an object, watching a funny movie), (2) emotional control (e.g. use of comfort talk, relaxation), (3) psychological preparation (i.e. information about procedures and sensations to expect, normalization of anxiety) and giving the child a feeling of autonomy and control. Providing children with coping skills is especially important for younger children, as they are not yet able to verbally express their feelings and understand the rationale for a specific procedure as a way to cope with a stressful event (8). Additionally, the child's understanding of the degree of discomfort expected is not well developed.

Limitations of current interventions

While studies show that the above-mentioned coping strategies help to alleviate the pain, stress and anxiety, this relief is often only effective at the moment and thus temporary. Moreover, no single intervention is equally effective on its own. Hence optimal procedural comfort asks for a combination of strategies. However, these multi-strategy interventions also require skilled and trained staff and a favourable family-centred environment. Unfortunately, this is far from reality within daily procedural care with departments facing fast patient turnover, high workload, limited time to explain procedures and limited budget for the training of all the staff (11).

Another limitation is the fact that current efforts mainly focus on reducing stress and anxiety experienced within the consultation or treatment room or relatively shortly beforehand (e.g. explain what is going to happen). However, stress and anxiety often build up already at home in anticipation of the visit and the pain induced by the procedure, and can peak during the procedure, causing the child to be distressed and upset. Hence, minimizing this so called pre-hospital and pre-procedural stress and anxiety is important to alleviate feelings of stress and anxiety during the visit. Psychological and educational preparation is an important way to achieve this and happens in an out-patient setting through information leaflets or online information. However, most information and research on the impact of proper preparation is focused on children undergoing surgery (9, 10).

Moreover, the available information resources often lack child-centred information, are not easily accessible, are dispersed and vary in quality (11). In addition, there seems to be a mismatch between the current provision of procedural information and children's and caregivers' expectations that information will be provided directly to them by healthcare professionals (12). This mismatch is strengthened by the fact that caregivers may, in their gatekeeping role, limit access to preparation materials and thereby unwillingly disempower their child (11, 13). Hence, interventions aimed at reducing pre-procedural stress and anxiety should be child-centred, combining multiple effective strategies and directed at diminishing stress and anxiety already at home.

Leveraging potentials of eHealth

Digital health technologies such as (health) apps offer the potential to provide a low-cost solution outside of the hospital setting. In addition, multiple procedural comfort strategies can be combined and offered in a way that does not require additional training or disruptions of daily workflows of hospital staff. As such, apps can create engaging, interactive child-appropriate content, including elements of play that can be delivered and accessed in a time-appropriate manner and within the comfort of the child's own home. Innovations that leverage the potentials of digital health technologies such as "Xploro" (i.e., a platform that provides child-centred healthcare using gameplay and artificial intelligence) demonstrated that procedural knowledge is improved and levels of self-reported anxiety are reduced (14). Also, virtual reality has been shown to be promising in reducing distress during painful procedures (15,

16). Nonetheless, these interventions either have a single purpose (either preparation or distraction), are situated within the hospital, or require training of staff.

Design and implementation of eHealth

Despite its potential, digital health technologies are abundant in number but only sparsely implemented as standard care. Reasons for lack of uptake include issues in usability (i.e. ease of use, task performance using the app), poor integration within current healthcare workflows and habits, and issues regarding the value it brings to the user (e.g. making a task more efficient, or more pleasant) (17). To stimulate uptake and usage, apps need to fit the user's needs and daily lives, be considered useful and user friendly. Involving children and caregivers early in the design and development is paramount in ensuring that the app is child-centred and fits children's daily life and experience world. In addition, stakeholders need to be involved in the design process to ensure optimal uptake in practice and fit with everyday healthcare practices.

Participatory service design

One way to accomplish this is by applying a Participatory Design approach (PD) in combination with a service design approach. PD is a methodology that promotes the participation of users and other stakeholders in the design of technology, such as apps, by involving them in several phases during the design process (18). Service design adds by taking the experience journey as a starting point, including varying processes, experiences and people who contribute herein (19). PD can be divided into four phases: the identification of users' needs (phase 1, discover); the generation of ideas and development of prototypes and testing (phase 2, prototype); realization (phase 3) and evaluation (phase 4). PD can be seen as an iterative process where each phase is planned by reflecting on the results of the previous phase with respect to the participants' contributions. The iterations ultimately result in a first version of a digital health technology or service (minimum viable product; MVP) that can be evaluated in practice. Evaluation in practice is important to gain in-depth insight into actual use of the product or service, its usability, and how the productor service is used (user-experience), and to identify improvements and inform further implementation and scale-up.

Study objectives

The objective of this study was two-fold. First, following a PD approach, we aimed to develop an eHealth solution to reduce pre-procedural stress and anxiety among children visiting the hospital's outpatient clinic. The second objective was to evaluate the app on use, user experience and usability in practice and to gain in-depth insight into the opinions and experiences of children and their caregivers to inform future improvements.

Method

Study design

In this paper, we report on two studies performed to develop and evaluate the eHealth solution. The first study describes the development process that led to a first version of an application. The process can be roughly divided into three phases, corresponding with the first three PD phases. In phase 1, users-needs were identified. Phase 2 consisted of two iterations during which prototypes were developed, refined and tested together with children. In phase 3, results from the final prototype testing were used to realize a first version of the app. The second study describes the evaluation study in the form of a pilot study at the outpatient clinic. The study corresponds with the fourth and final PD phase and closes with recommendations for improvement and future implementation. See Figure 1 for a schematic representation of the study design.

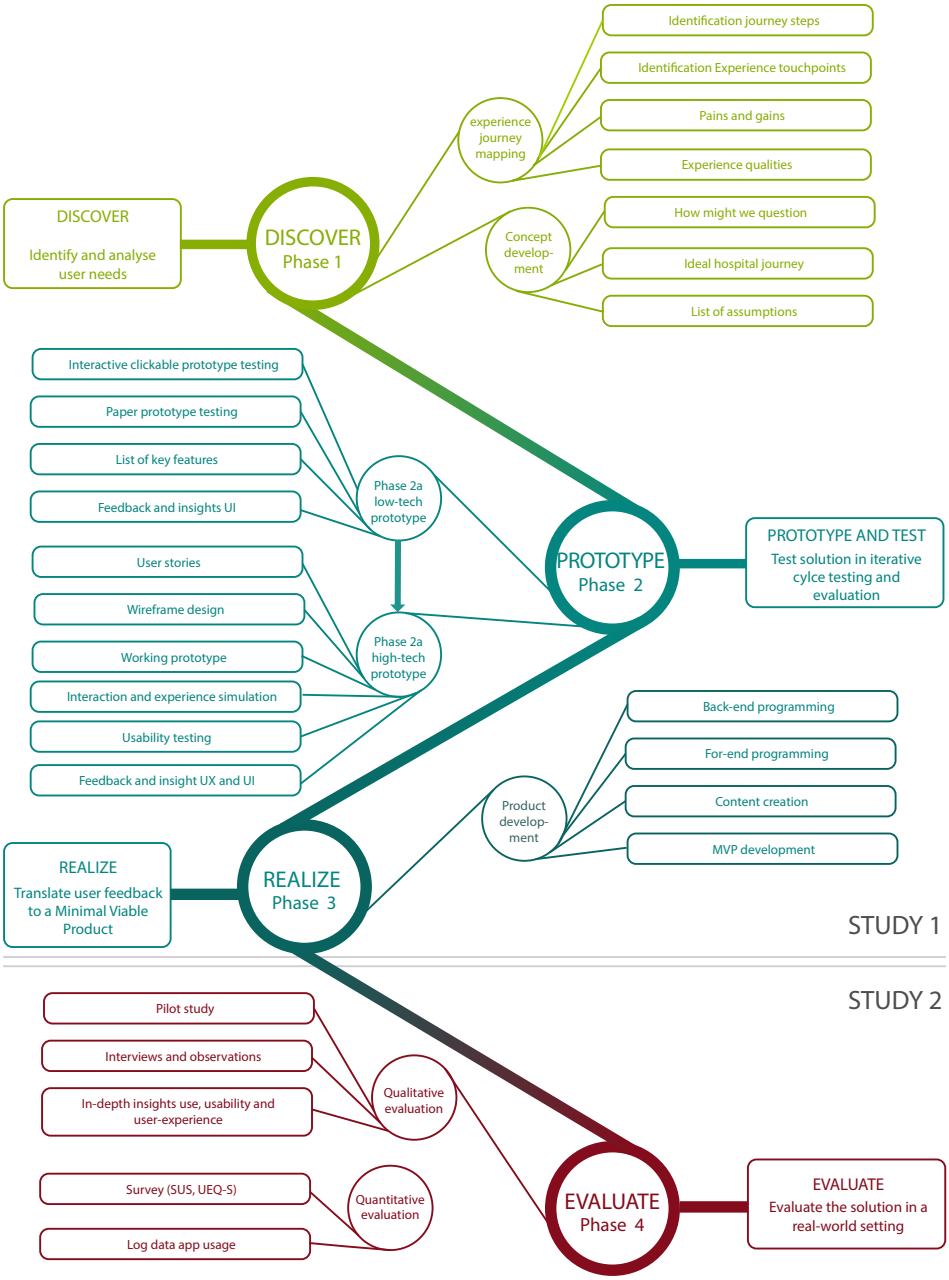

Figure 1. Schematic overview of study design of study 1 and study 2, mapped onto participatory design phases. UX, user-experience; UI, user-interaction; SUS, system usability scale; UEQ-S, User Experience Questionnaire Short version;

Study 1

Method

Design and context

The study followed the first three phases of the participatory design cycle. It was conducted between February 2020 and July 2020 in an outpatient clinic of the academic paediatric hospital in Leiden, the Netherlands. An initial idea, initiated by two paediatric nurses, formed the starting point of this study. The idea, given the name Hospital Hero, included elements of distraction, game play and an animal or hero theme.

Participants and procedures

Phase 1: discover

An experience journey session was held with stakeholders to identify user needs and potential touchpoints where a stress-reducing app would be of value (20). Stakeholders were those involved in paediatric outpatient care (e.g., paediatric doctor, paediatric nurse, child psychologist, doctor's assistant) and those important for the realization of the app and content developers (i.e., app developers, educational content development experts, eHealth experts). Considering the explorative nature of the session, a patient advocate youngster was invited to participate in this early stage instead of young children. The experience journey session was facilitated by an experienced participatory (service) designer (author AB) and consisted of three parts. First, the separate process steps of a visit to the outpatient department were mapped out, including the moments at home and to and from the hospital. Second, experience touchpoints from the child, caregiver and professional were identified, mapped on the journey map and used to identity critical moments within the journey. Experience touchpoints included "pains" (moments that contribute to (pre)procedural stress and anxiety) and "gains" (moments where design could alleviate the stress and anxiety). Third, pains and gains were used to identify design opportunities and ideas for solutions and experience qualities (i.e., properties the designed service or product must have to fulfil the user's needs in terms of desired experience) were brought in by all participants using the "how might we" question technique. A final voting round on the most important experience qualities resulted in a selection of properties that the concept should embody and that led to the ideal journey.

Phase 2: prototype – iteration 1

A multi-disciplinary development team was installed, consisting of two paediatric nurses, a paediatric doctor, an eHealth expert, an app developer and a user experience designer. This team translated experience qualities into a concept for the app and low-cost clickable prototype and accompanying paper prototypes. This approach ensured that the concept fits with the users' needs and could be convincingly communicated to all stakeholders while circumventing full development

costs. The prototypes embodied the essential user interactions. Assumptions on user interaction and user experience were formulated a priori. The prototypes and the assumptions were tested with children and caregivers at the outpatient clinic of the Willem-Alexander Children's Hospital in Leiden, the Netherlands, during two observation days. Children who had an appointment during the testing days were selected following purposive sampling to ensure a variation in gender, age (between 4 and 10 years old), type of visit and prior hospital experience. A letter was sent to all participants two days prior to the observation day to test the entire concept, including the process taking place at home (i.e., informing children and caregivers about the app, preparing for the visit with the app), and to provide a realistic experience. The letter included a QR code with which the participants could download the app and a form on which caregivers could indicate their interest to participate in the study. Two of the eight invited caregivers indicated that their child did not experience stress or anxiety. In total, six caregivers and eight children participated in the prototype testing day. This number was deemed sufficient to test the assumptions (21). During the prototype testing day, observations were held, followed by a short semi-structured interview with the child and caregiver. The interviews were guided by a topic list covering the a priori assumptions.

Phase 2: prototype – iteration 2

Findings from the prototype testing were discussed with the development team. A list of necessary features was drafted and translated into user stories (i.e., stories describing the needed functionality from a user's perspective) which were used to guide and prioritize the development process. A working prototype was developed, which included essential features for the app and acted as a real app (e.g., user interaction, navigation, visual designs). Due to COVID-19 measures, the prototype could not be tested at the outpatient clinic. Instead, a hospital setting was built in an external setting where a hospital visit was simulated (e.g., waiting room, consultation room). Children from the development team's social network were invited for the simulation testing day. The aim of the test was to evaluate user-interactions with the app (e.g., can the user navigate through the app, are there functionalities the user does not understand) and basic user-experiences (e.g. does the user enjoy key activities in the app such as selecting a favourite animal, what does the user like/dislike). Therefore, it was not necessary that the children visited the outpatient clinic and/or had any hospital experience. Two developers observed how the participants performed. An observation list was used to take notes on users' errors/problems and users' expressions for each task. Findings were discussed with the development team and used to identify necessary features and improvements.

Phase 3: realize

Improvements were made and the app's functionalities and design were further refined based on input from the development team. This resulted in a first version (minimum viable product, MVP) of the Hospital Hero app ready to be pilot-tested and evaluated further in practice.

Ethical considerations

Informed consent from all participants was given prior to study activities. Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by all participations prior to study activities. In the case of children, informed consent was provided by the participants' legal guardian/next of kin.

Results

Phase 1: discover

The experience journey mapping session (identifying the process steps and experience touchpoints) resulted in a visual representation of the experience journey with ten distinct steps: (1) At home; (2) to the hospital; (3) at hospital registration; (4) at the outpatient registration desk; (5) In the big waiting room; (6) weighing and measuring; (7); in the consultation room; (8) blood drawing; (9) leaving the hospital; (10) back home. There were multiple (potential) stress and anxiety experience touchpoints, although it became apparent that touchpoints differed strongly between children, possibly due to character traits or prior experience. In general most prominent stress and anxiety experience touchpoints were when entering the building, in the waiting room, taking of the clothes for weighing or physical examination, "giving" their arm for blood drawing, and seeing the needle or attributes (e.g., arm cuff) associated with prior (painful) experiences. Healthcare professionals also noted that caregivers might unwillingly project their stress on the child. As blood drawing is the most common invasive procedure, it was decided to focus on reducing stress and anxiety surrounding blood drawing visits. Finally, the most important experience qualities (e.g., child should be distracted during waiting, app should be engaging during multiple visits, child should be in charge) were identified and resulted in a description of the ideal hospital journey for children with the desired experience qualities (see Figure 2).

Phase 2: iteration 1

The Hospital Hero concept

The desired experience qualities, such as children are distracted with searching, were translated into the Hospital Hero concept. The Hospital Hero concept is based on three core elements: (1) preparation, (2) distraction and (3) supporting caregivers in supporting their children. The Hospital Hero app supports and guides children in their journey through the hospital using a "discovery map" in the app. The map visualizes the different rooms in the outpatient clinic (waiting room, weigh and measure room, consultation room, blood drawing room). It also includes the steps at home, going to and leaving the hospital. Children can download the app already at home and watch short videos in the different steps together with their caregiver, such that they become informed about the different procedures (preparation and parental

support). Children can search for and collect animals in the hospital by scanning QR codes (distraction). Every three months, the children can search for new animals, found at new hiding places to keep the app engaging over time. The concept was visualized into the Hospital Hero journey scheme. For each step in the journey, the scheme included a detailed description of the desired interaction moments between child and app, child and caregiver, and child and healthcare provider, as well as a set of assumptions (see Figure 2 for an exert of the concept Hospital Hero journey and Additional File 1 for the full concept and assumptions).

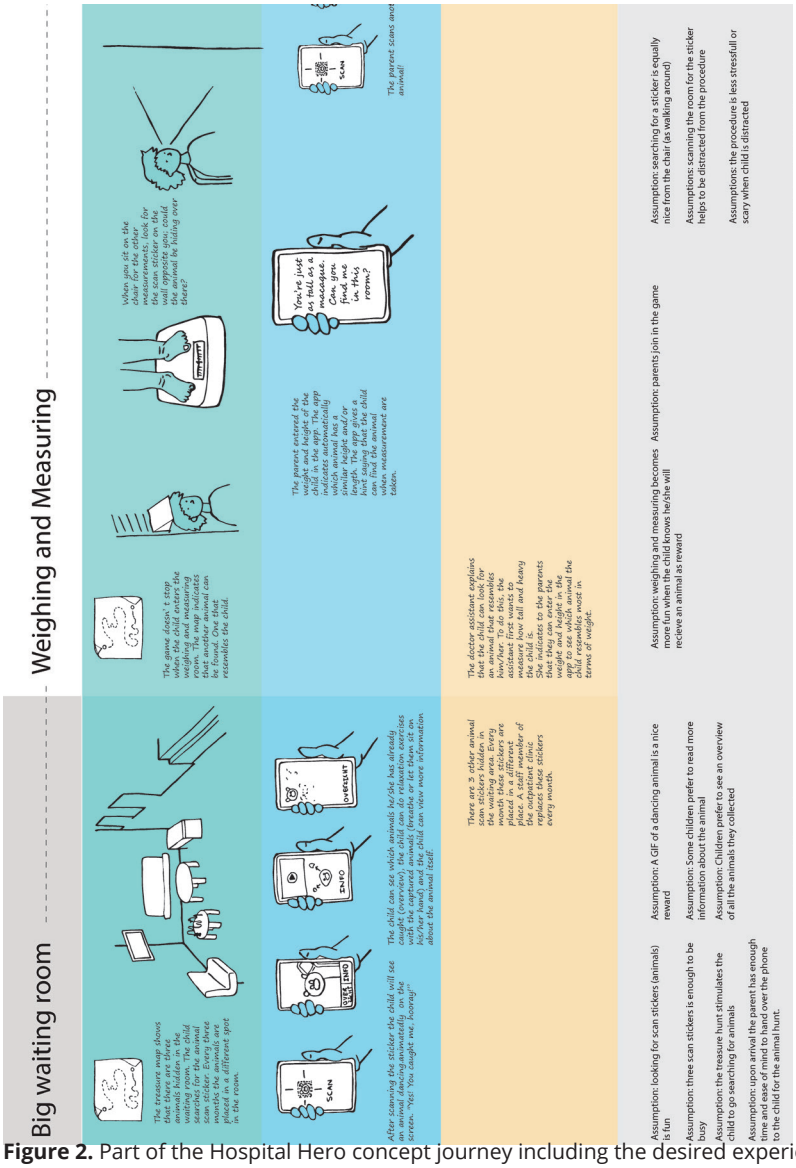

Figure 2. Part of the Hospital Hero concept journey including the desired experience qualities and design assumptions.

Low-fidelity prototype testing

To test the assumptions and the Hospital Hero concept as a whole, the concept was translated into a clickable prototype of the app, including a schematic representation of the different steps of an outpatient visit and a short animation video on blood drawing. In addition, a paper-prototype version of the discovery map was created that simulated the animal collection game and experience. Children could use the paper discovery map to collect animal stickers. Prototype testing showed that children enjoyed looking for animals and collecting animals and that it distracted them while they were waiting. Searching for animals was less suitable in the physicians' consultation room and could be disturbing. Caregivers rather focused on the conversation with the physician. Due to logistical difficulties, not all caregivers had received the invitation letter with the link to download the app, so they had not used it in preparation for the visit. Caregivers however did indicate that they thought it could help them and their child to prepare for the visit by for example knowing what to say. Some caregivers who received the letter did not feel that it addressed their needs (reducing stress and anxiety) as their child was not anxious. They suggested to include the fun and play element in the invitation letter as that was considered of value to them.

Phase 2: iteration 2

Prototype testing resulted in several key functionalities which were translated into user stories (see Table 1) and wireframes that visualized the flow of the app. Both user stories and wireframes were discussed with the development team and used to develop a first working prototype. The prototype was tested with children on usability, user-interaction (e.g., does the child understand how to collect an animal, can the child navigate to the animal collection) and basic user experience (e.g., does the child enjoy collecting the animal, selecting a favourite animal) in a hospital simulation setting. Overall, children understood how to scan a QR code and collect an animal. Younger children (<6 years) needed additional instructions and an adult who demonstrated the scanning process, but they were able to continue playing the app afterward. Children liked searching for animals, and enjoyed receiving the animation of a dancing monkey as a reward token when all animals were found. Children noted that the "reward tune" could give away the animal's location to other children. On the other hand, it also encouraged children to search together. We observed that children missed feedback regarding the number of animals that could be found and that the majority of the children did not read the text beneath the animal picture presenting fun facts about the animal. The user test results were discussed with the development team and resulted in three important improvements: 1) users should receive a small reward after each animal found, 2) the screen with animal facts should be less text-heavy with bigger and more pictures and 3) users should be able to see how many animals can be found per step.

Table 1. List of key functionalities and user stories of the Hospital Hero app

Key functionalities	User stories
Onboarding	Onboarding screens explain the setup of the app (journey map and hidden animals) to the child in visual way.
Journey map	Children can see the separate steps of the (anticipated) hospital journey and navigate between them.
Information per step	Children can read information on what to expect at each step in the map and see a picture of the room or another relevant image.
Preparation video	Children and caregivers have the option to watch a short animation video explaining what happens during the blood drawing procedure, what the child can expect and certain preference they may have (e.g. sit on caregivers lap or alone).
Animal search game	Children can collect animals by scanning QR codes which are hidden in the waiting room, in the room where the child is measured, in the consultation room and in the blood drawing room.
	Children can scan a QR code using the smartphone's camera. Children hear a happy tune when the animal is collected. The animal is automatically added to their animal collection.
Animal collection	Children can access their animal collection any time and read fun facts about the animals they collected. A silhouette indicates that the animal still needs to be found.
Favourite animal game	Children can select their favourite animal from a list of animals. The favourite animal joins them on their journey through the hospital.
General information about the app	Caregivers can read general information about the Hospital Hero app, Hospital Hero's mission and the privacy policy.

Phase 3: realize

To use resources efficiently, it was decided to only develop the app for Android in this phase of the project. To ensure efficient development of the iOS version, it was ensured that all functionalities were equally compatible for iOS. Final refinements were made, resulting in a first version of the Hospital Hero app (minimum viable product, MVP). The final content of the app was drafted with experts on comfort talk. See Figure 3 for a visual presentation of the key features and designs of the Hospital Hero app. Parallel to the app development, a content management system was developed that could, in the future, be used by the hospital staff themselves to manage the app's content and thereby tailor it to their own hospital context.

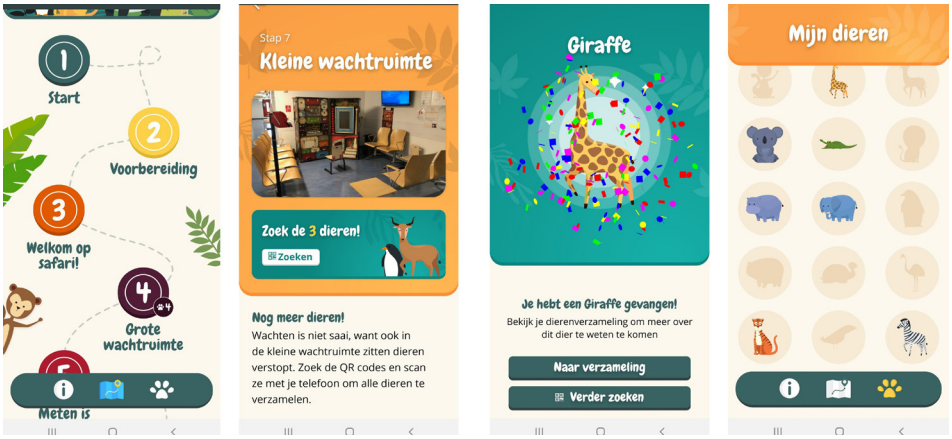

Figure 3. Visuals of the final version of the Hospital Hero app.
From left to right: 'Journey map' home screen, waiting room step, new animal collected, animal collection overview.

Study 2 – pilot study

Method pilot study

Study design and theoretical framework

The first version of the Hospital Hero app was pilot-tested and evaluated during an eight weeks pilot study at the outpatient clinic of an academic paediatric hospital in Leiden, the Netherlands. We conducted a prospective observational study using a concurrent mixed-method approach (i.e. simultaneous collection of qualitative and quantitative data) to gain in-depth insight and provide generalizable results to inform future use. Data was collected in January and February 2021. Quantitative data were collected through an online questionnaire. Observations, online semi-structured interviews and open questions in the online questionnaire were used to collect qualitative data.

Our study design, research materials and analyses were inspired by the ISO norms for "Systems and software Quality Requirements and Evaluation"; ISO/IEC 9126-1 '. Key constructs were usability and user experience. The construct usability can be defined as "the capability of the software product to be understood, learned, used and satisfying to use". As such, it can be subdivided into user- friendliness (i.e., degree to which the software is adapted to the skills and experience of the user) clarity (i.e., the degree to which the software is considered coherent, logical and consistent) operability (i.e. the time it takes the user to learn how to use a function and perform a task efficiently) and customization (i.e. the degree to which the software system can be customized to the needs of the user (e.g., default settings). The construct user-experience was defined as "every emotion, belief, perception, psychological reactions

and behaviour during and after the use of a product" (22). As such, user-experience can be categorized into pragmatic experiences (i.e., task oriented aspects such as efficiency, learnability etc.) and hedonic experiences (i.e., non-task oriented aspect such as aesthetics, stimulation etc.) (see Figure 4) (23).

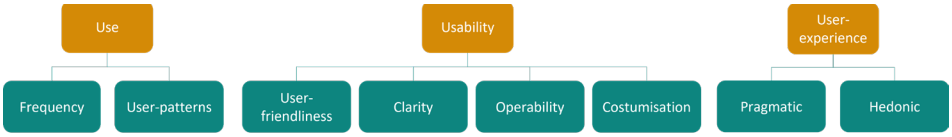

Figure 4. Theoretic framework on use, usability and user-experience.

Participants and procedures

All children between 4 and 12 years old and their caregivers who had an appointment during the pilot study period were eligible for participation. Caregivers received an information folder together with their appointment letter prior to the appointment. The folder contained information on the Hospital Hero app as well as information on study participation. Caregivers could indicate if they were interested in study participation on the included reply card. They could also indicate if they wanted to participate in the online questionnaire, interview, or both. Caregivers and children could also download and play with the app without participating in study activities. Upon expressing interest in study participation, caregivers received an informed consent form. Informed consent was signed prior to all study activities. Due to capacity issues among postal delivery services as a result of the COVID-19 pandemic, not all eligible participants received the invitation letter. Consequently, initial response rates were low. To increase the response rate, we extended our recruitment strategy with a more personal approach, such that two research assistants invited eligible participants face-to-face at the outpatient clinic. Caregivers who expressed interest followed the same informed consent procedures as outlined above. Children and their caregivers had to meet the following inclusion criteria: 1) the child's age between 4 and 12 years old, (2) the child was able to speak, write and understand the Dutch language, (3) the caregiver was able to speak, write and/or understand the Dutch or English language. Caregivers who were not able to express themselves in Dutch or English were unable to participate.

Caregivers who expressed interest in participating in the interview were asked to fill out an observational booklet during the hospital visit, which was returned to the investigators (see Additional File 2).Participants were selected purposively to represent diversity in gender, age, medical background and whether they had to draw blood during the appointment. The sample size was determined by the principle of a priori and inductive thematic saturation which we expected to achieve with 20 children and their caregivers.

Data collection

After the hospital visit, caregivers received an online questionnaire assessing use, user-experience and usability. In addition, demographic data were collected on gender, age, frequency of hospital visits within the past 24 months and whether the visit included a blood draw. The questionnaire was directed to and developed for children. Caregivers were invited to provide help with filling out the questionnaire if necessary. Children could indicate if they had received help with filling out the questionnaire.

Usability

Usability was assessed using the System Usability Scale (SUS)(24). This is a generic instrument to measure the usability of a technology or service. It contains ten items rated on a 5-point Likert scale from 1 = 'strongly disagree' to 5 = 'strongly agree'. An additional free text field allowed for commenting on usability.

User-experience

User-experience was assessed with the short version of the User-Experience Questionnaire (UEQ-S), which was made age-appropriate and tailored to the Hospital Hero app. The UEQ-S consists of eight items rated on a 7-point Likert scale from -3 and 3, with 0 as neutral) in the two dimensions of pragmatic and hedonic quality (25). Responses to the UEQ-S items included an open text field to argue the response given. All the UEQ scales have a good to high reliability of .69 or higher (22).

We aimed to also assess user-experience with the Pick-A-Mood (PAM) tool, a cartoon-based pictorial instrument to measure self-reported mood states (26). A tablet was installed at different locations at the outpatient clinic on which, following instructions by the staff, children could select the pictogram that represented their mood at that moment. Due to the increased COVID-19-related care burden on the hospital staff, the PAM data was not collected consistently enough to acquire reliable data and were therefore disregarded from quantitative data analysis.

Use

Use and user patterns were assessed based on the question 'did you play with the app' in the online questionnaire and from interview and observation data.

Qualitative data collection

Qualitative data was collected through semi-structured interviews. The interviews were held online due to COVID-19 measures, using the video conference software Microsoft Teams and were held within five days after the hospital appointment. In addition, caregivers were asked to fill in an observational booklet during the visit, as observations by the researchers were not possible to due to COVID-19 restrictions. Semi-structured interviews were guided by a topic list, which was developed with a remedial educationalist and a paediatric nurse and followed the theoretical framework. The topic list consisted of main and probing questions and was tailored

to the age of the participating child (see Additional file 3). Only the topic list for older children included temporal questions (e.g. when was that, how did you feel at that moment). An interview toolbox was developed containing screenshots of the app, photographs of the outpatient clinic and the PAM tool. These were used, if deemed helpful, to help retrieve memories and as conversation starters. Interviews were conducted by an experienced qualitative researcher and a remedial educationalist in training. After each interview, field notes were taken, including reflective notes of one's role.

Data analysis and data handling

Quantitative data were analysed using descriptive statistics on the SUS and UEQ-S scores (SPSS version 25; IBM, Amonk, NY, USA). A-priori defined subgroup analyses were performed among subgroups for age (dichotomized into age 4 till 8 years and 9 till 12 years) and gender. Considering the fact that our evaluation was formative by design (i.e. gain understanding for improvements) instead of summative (i.e. to measure performance or specific end-points), we did not perform a power calculation. We did consider the size of the study population (20 – 25 appointments per day), an expected participation rate of 0.2 and recommendations by developers of the UEQ who recommend 51 and 70 participants for pragmatic and hedonic scale respectively (sampling confidence level 95%, margin of error = 0.01) (25). Responses to the online questionnaire were used to triangulate the qualitative findings (e.g., to find out how many participants indicated difficulties operating the app and to inform understanding of use and user feedback). Interviews were audio recorded and transcribed verbatim and anonymised. Qualitative data were analysed following the Framework Method (27). Data were coded inductively and deductively, guided by constructs of the ISO norm but also leaving room for newly emerging codes (Atlas.ti, version 7.5.15). Codes were explored, recoded and used to identify categories (i.e. group of codes around similar and interrelated ideas or concepts). Categories were mapped and discussed, which resulted in the formulation of themes.

Ethical considerations

The study was cleared for ethics by the Medical Ethical Review Committee of the Leiden University Medical Centre (No N20.199). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Children were verbally informed about participations in the study. Information was tailored to the age of the child.

Results pilot study

In total, 44 child-caregiver pairs expressed their interest in participating in the semi-structured interview. In the end, we included 21 child-caregiver pairs for the semi-structured interview and received the observational booklet from 31 caregivers. Children had diverse ages (range 4 to 11 years), gender and medical background (see Additional File 4). In addition, we sent out the online questionnaire to 71 child-

caregiver pairs, of which 50 returned the questionnaire (four questionnaires were excluded because of missing data (i.e. >27 questions unanswered). The overall mean age was 8.2 years (SD 2.8), the majority was boy (n = 28; 61%) and most children had to draw blood during the appointment (n = 26; 57%) Children who did not need to draw blood had other physical examinations (e.g. ECG or cardiac ultrasound) or only a consultation.

Five key themes were identified from our qualitative data, which were then triangulated and complemented with the quantitative descriptive data from the questionnaires. Each theme is described below, integrating both qualitative and quantitative data. Descriptive statistics for usability and user-experience are displayed in Table 2 and Figure 5

Table 2. Descriptive statistics (n=46) on overall score on the system usability scale (SUS) and User-experience Questionnaire short version (UEQ_S)

	Min	Max	mean ± SD
SUS	25	100	71.32 ±17.80
UEQ_S	-.49	2.63	1.49 ± .95
Pragmatic	-2.50	3.00	1.31 ± 1.28
Hedonic	-2.75	3.00	1.49 ± 1.37

SUS, System Usability Scale; UEQ_S: User-Experience Questionnaire Short version; SD, standard deviation

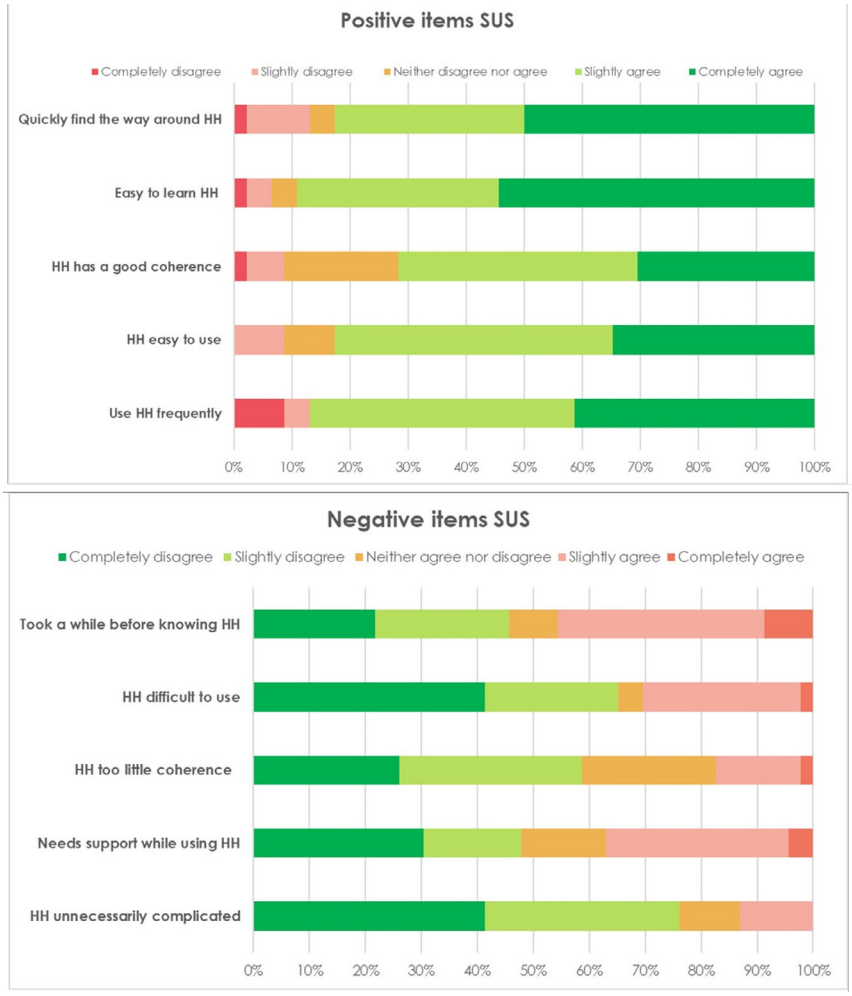

Figure 5. Results SUS item scores divided in negative and positive formulated items. SUS, system usability scale.

Theme 1: user-friendliness

Overall, children and their caregivers were positive about the user-friendliness and usability of the app. This observation was supported by the SUS total score from the questionnaire, which averaged 71.32 (SD = 17.80). Benchmark comparison indicated an overall 'good' usability. 87% of all respondents indicated that they would use the app more frequently ('completely agree' or 'slightly agree').

However, younger children and their caregivers mentioned that the child sometimes needed help from their parents, especially in understanding how to scan the QR codes and navigate between the different screens. Children aged 4 or 5 years also

asked for help with reading the texts. The problems with difficulties of use were also observed in the SUS item scores. Almost 35% of all children needed support while using the HH app ('completely agree' or 'slightly agree'). Comparison of the SUS score showed that older children had a statistically significantly higher overall SUS score (73.13 ± 15.92). However, two-way ANOVA analysis of the overall SUS score on age and gender only showed a main effect for gender ($F(1) = 3.89$, $p = .05$) but not for age ($F(1) = 0.36$, $p = .57$) nor the interaction between the effect of gender and age ($F(1) = 0.23$, $p = .64$). When asked if the usability problems hindered the playing, some children indicated that they enjoyed the interaction with their parents, whereas other children wanted complete control.

> *"I did not see that [explanation screens on QR scanning], but I did notice that mom had to point out certain things to me. Also, she searched with me, but I thought: ´this is for children." – Boy, 10 years old.*

Caregivers added that they enjoyed the interaction moments with their child and the app.

Theme 2: coherence and power of storytelling

SUS scores on items on coherence (HH has good coherence and HH has little coherence) showed that around 40% of the children found that the app lacked good coherence. The lack of good coherence was also observed in the qualitative data, which suggested that children did not find the storyline explicit enough in the app. Also, while children enjoyed choosing their favourite animal in the beginning and searching for the QR codes, only one child referred to elements of the storyline such as going on a safari with their favourite animal. Two children suggested another way to strengthen the storyline in the app, for example, by having a more central character that they repeatedly meet in the app:

> *'Maybe there should be a more adventurous story put into it. As if, for example, you come to a village of monkeys. And then maybe you come across the owner of a mine, who will say: 'my worker is gone'. Then you must find the QR code that belongs to him. You get it?' – Boy, 10 years old.*

Next to the storyline in the app, children and caregivers missed that some healthcare professionals did not ask about the game or seem to be involved. This detracted somewhat from the overall experience and suggests that it is important that healthcare professionals engage in creating an immersive imaginative safari story. Likewise, healthcare professionals that did engage with the story facilitated engagement and improved the overall experience.

> *"No, the doctor did not help. The blood sampling nurse, she was super excited about HH and searched everywhere with her. But the doctor did not, he said sort of: 'well, good luck searching'' – Mother of 8 year old girl.*

When asked how to improve the healthcare professionals' engagement, caregivers

indicated that healthcare professionals could for example give hints and show interest in the child's animal collection. Two caregivers also suggested adding the possibility for the child to add in how they feel before the appointment or to write down questions for the doctor, all to facilitate interaction between child and doctor.

Theme 3: motivation and reward

All interviewed children indicated they were motivated to engage with the app. They were attracted by the design and liked the vibrant colours and animals. Some children above ten years old found the app a bit ' childish' due to the drawing style of the animals and the difficulty level of the animal searching game. They wanted more challenging games such as puzzles, riddles, assignments, or animal quiz. They could imagine it to be fun for younger children. A comparison of scores of the UEQ- hedonic scale showed that boys and younger children scored statistically higher than girls and older children, respectively, indicating that they found the app more appealing.

When asked if they had collected animals, all children indicated that they had collected some or all animals. The majority of the children however did not understand that the animals indicated as silhouettes in the animal collection could only be collected during the next visit. Children felt demotivated, 'disappointed' and confused as they could not collect all animals.

Children did like reward elements such as the virtual confetti rain, and the funny GIF when all animals were collected. They suggested to add additional reward elements such as winning clothes to dress the animal, money, tokens , points or extra assignments.

> *"But also that if you played a game, you receive money. And with that money you can buy clothes for your animals" – Boy, 9 years old.*

Theme 4: fit with the real hospital journey.

An important recurring theme throughout all interviews was the fit with the hospital journey. This could be seen in two different ways. First, the alignment of the true hospital journey with the journey portrayed in the app (map) should be as optimal as possible. The map used a fixed number and sequence of steps. However, not all children needed to draw blood and thus engage with the step. Some children did not mind, however, two children mentioned that this step was confusing and caused more anxiety.

Second, the alignment in terms of timing is important for the overall experience. According to the participants, there should be sufficient time to search for all the animals and enough time to devote attention to playing instead of waiting. One child explained:

> *"I did not watch the videos because I thought, I did not know how much time I had. So I just went ahead and did the fun part, seek the animals." - Boy, 10 years old.*

Also, it should be clear to children and caregivers where the children can engage with the app. Caregivers were sometimes unsure if children were 'allowed' to play in the consultation room or during the weighing and measuring.

Theme 5: procedural comfort

Though not part of the initial research question and not explicitly asked, most of the caregivers indicated that the children were more at ease as they were distracted from the waiting. The children were focused on the animal search and caregivers observed positive emotions such as enjoyment and pride upon finding another animal. Two caregivers reported that they enjoyed seeing their child searching with another child. One mother noted that seeing her child be at ease helped her to relax. However, the distraction was only temporary, as illustrated by the following quote:

> *"The distraction was due to the QR codes. She was just seeking through the blood sample room. But we found the code the moment she was poked. The nurse said, 'look how mom is scanning, look what will happen'. At this moment, the monkey came out. So it gets the pressure off of her. But the needle needs to stay in her arm for a while to take three vials of blood. So yes, within a second, she started screaming 'take the needle out, the needle must come out, I feel it, it is hurting!" – Mother of 6 year old daughter.*

While almost all respondents experienced some distraction, one mother indicated that the app disrupted her standard routine used to help her child cope:

> *'..if I am honest, we had a kind of a routine and this interrupted it a little bit. She is comfortable in her own expectation pattern. Besides that, she is also a bit shy with unfamiliar people, which I really noticed in the waiting room with all the people sitting there.' – Mother of 6 year old daughter.*

Regarding the preparation part, it should be noted that due to COVID-related postal delays, most respondents had not downloaded the app at home but in the hospital. Hence, they had not engaged with the app at home nor used it as a preparation tool. Also, caregivers did not know about the animation video explaining the blood drawing procedure.

When asked if caregivers would think it would help the children prepare, caregivers indicated that they thought it was helpful. Those who visited the hospital regularly added that they wished they could have had the app for the first hospital visit.

Recommendations

Children and caregivers were asked for suggestions how to improve the app during the interview and with an open question in the online survey. Suggestions were clustered into four domains: age differentiation, usability, tailored and immersive journey and others. All recommendations are depicted in Table 3.

Table 3. Design recommendations by children and parents

Age differentiation	
•	Content differentiation for younger children (between 4 and 7 years old) and older children (between 7 and 12 years old)
•	Spoken text for younger children
•	Quiz or challenges for older children
•	More reward elements (e.g. reward tokens to ' purchase' clothes for the animals'
Usability	
•	Cue that all animals are collected and step is completed
•	Notification that animal can be found in another room
•	Interactive instruction screens
•	More clear instructions on how to use and navigate app for younger children
•	Automatic play of video's
Tailored and immersive journey	
•	Possibility to select route or procedure
•	Possibility to indicate first visit or follow-up visit
•	Storyline stronger integrated within app and physical world
Other recommendations	
•	Distraction during blood drawing procedure
•	Include more smaller games
•	Make QR codes more appealing (e.g. integrate the animal theme)

Discussion

This paper described the development and evaluation of an eHealth solution to reduce pre-procedural stress and anxiety following a PD service design approach, which resulted in the Hospital Hero app. The Hospital Hero app guides children in their journey to and through the hospital. By helping children prepare in their familiar environment in a fun and appealing way through gamification, the Hospital Hero app engages and empowers children and informs them about medical procedures. Children can continue their journey at the hospital by searching and collecting animals through QR code scanning, creating an overall more positive and engaging experience. The pilot study of the Hospital Hero app in practice showed that the app is positively evaluated on usability and user-experience and is considered feasible.

We adopted a PD approach, involving children, caregivers, healthcare professionals, and other stakeholders throughout the process. This approach allowed us to develop a novel intervention that is child-centred, takes into account the perspective of child, caregiver and healthcare professional and integrates state-of-the-art knowledge from all stakeholders (i.e. knowledge on procedural comfort, children, education,

psychological preparation). Hence, by involving multiple stakeholders, we were able to develop an intervention focusing on optimizing the experience for children and caregivers while working with available resources and requiring minimal efforts from healthcare professionals.

Patient-centered outcomes

This study demonstrated how a PD service design approach can help to develop interventions to improve paediatric patient experience by taking the experiences of the child, caregiver and healthcare provider as a starting point. Using this approach, we were able to identify critical moments in a child's journey that add to the build-up of stress and anxiety, find ways how to alleviate these moment and benefit the overall patient experience. Increasingly, medical academics acknowledge that overall patient experience is important in creating more beneficial patient-centred outcomes, such as satisfaction of care, self-efficacy and trust in healthcare, and clinical outcomes, such as recovery time (28). As such, patient experiences are increasingly adopted in paediatric and adult care as important indicators for the quality of healthcare. The Hospital Hero app improves the overall experience by taking the patient's experience journey as a starting point and by intervening in the potentially anxiety-heightening moments. These moments do not only involve interactions between child and healthcare professionals, but also entering the hospital building and waiting in the weighing room. Both are equally critical for the overall experience.

Effective mechanisms in the Hospital Hero app

Evaluation of the Hospital Hero in practice helped us to gain in-depth insight in the user experiences and interactions and identify effective mechanisms. The pilot study showed that children specifically enjoyed searching for animals, and this took their attention away from waiting or negative emotions and feelings (in the case of children who experience pre-procedural stress and anxiety). With the animal search, children are given a task (searching for and collecting animals) that they actively engage in. These more active ways of distraction are powerful as they actively divert the focus from negative emotions and the (anticipated) procedure (29). These findings correspond with studies evaluating the use of VR in which children are actively distracted by playing games (30). Moreover, the animal search requires problem-solving skills which help to empower children and give them a feeling of autonomy (I can do it myself) if performed successfully (31). By regularly changing the animals and hiding places, children can endeavour on the search each time they visit the hospital. Based on previous research, the connection of the game world with the physical world (i.e. physical QR codes as game tokens) promises to be especially powerful in transferring the child's acquired coping skills to the real-world and is absent in preparations platforms such as 'Xploro' (14, 32).

The feeling of autonomy and control is strengthened by the fact that the app is child-centred and directed towards the child (i.e. speaking to the child instead of about the child) without requiring active involvement from a caregiver. However, parental involvement and more specifically, their level of stress and anxiety is pivotal

in reducing (pre)procedural distress in children. Parental involvement has even been considered an important moderator of pain perception and stress response (13). Research has shown that children experience more distress and more intense pain during medical procedures if their caregivers show certain distress-related behaviours, such as (unconscious) projection of own psychological distress, provision of reassurance, empathic comments and excessive explanations and apologies to their children, whereas use of humour and talking about topics other than the medical procedure are associated with increases in a child's adaptive coping (33, 34). The Hospital Hero can support caregivers by acting as a conversation tool and introduce stress-reducing terminology (i.e. comfort talk) that they can use. Future developments should explore how to enhance parental guidance within the Hospital Hero app and take the moderating effects of parental involvement into consideration.

Finally, three design opportunities can be identified: 1) tailored journey, 2) differentiation and 3) timing of engagement. Whereas the current Hospital Hero app is built of fixed steps and focused on blood drawing only, future developments should be focused on the possibility to tailor a child's journey to the specific procedures involved. Second, the app's content should be differentiated according to age and medical experience of children. Children between four and seven generally liked the app, found it engaging and fitted their problem-solving skill levels. To appeal to older children it is important to differentiate in age and include more challenging activities (35). Use of, for example artificial intelligence, could be useful in tailoring and deriving the content to the knowledge level of each individual child, as applied to the 'Xploro' platform (14).

Third, the timing of when and how long to engage with the app should fit with the particular hospital visit. For example, there should be no additional distraction during the consultation and children should be distracted long enough during the waiting to reach optimal effects on anxiety levels.

Implications for practice and research

Our study demonstrated multiple critical moments outside of the consultation room where stress and anxiety are present (e.g. anticipation of pain, new environment), some which have been described before (36). Future comfort care strategies should look beyond the hospital walls and explore how to diminish the build-up of stress. This asks for nurses and doctors to be more mindful of the entire experience journey of their patients (e.g. the child's preparations, expectations, and previous experiences).

While this study took the patient journey of children visiting the Willem-Alexander children's hospital as starting point, the Hospital Hero application was built in a modular way. This allows the app to be tailored to other hospitals and to be extended with additional preparation modules (e.g. preparation game for weighing and measuring or spirometry). A modular build is important to create a product that transcends the medical silos and prevents the introduction of an app for every specialism or medical procedure. In addition, the modular build supports scale-up potentials and the adaptation to other healthcare settings where children undergo

(medical)procedures and experience stress and anxiety, such as primary care practices, dentist practices and within vaccination programs (37-39).

Limitations

Both studies had some methodological challenges. First, we were restricted in our data collection methods due to COVID-19 measures. In the first study, we were unable to test the working prototype with children and caregivers at the outpatient clinic and set up a simulated hospital instead. Early testing in the outpatient clinic could have improved our understanding of the user experience earlier in the process (e.g. preferences during consultation). In the second study, we were unable to perform observations at the hospital and interviews were held online, a necessity many researchers reverted to to continue data collection during the pandemic. Although a review of online interviews and focus groups showed that the online setting does not compromise the quality of the data (40), it is unknown if this also goes for interviews with children. Nonetheless, we undertook multiple measures to ensure good quality data. We used an interview toolkit with photos and pictorial images to facilitate the conversation, had caregivers fill in an observation booklet during the appointment, which was used during the interview, and made use of screenshots of the app. Also, to minimize the burden on the healthcare professionals we decided not to collect their experiences in the evaluation. By evaluating the use of the Hospital Hero in practice we were however able to shed light on potential implementation issues (e.g. engagement of all healthcare providers, management of QR codes, reaching and activating caregivers to download the app) that need to be addressed in future research and implementation.

Second, due to COVID-19 pandemic related postal capacity problems, not all participants received the invitation letter and did not download the app. Consequently, the onboarding process (being informed and activated to download the app) could not be properly evaluated. Interviews did give insight into how the onboarding process could be improved. Third, children and caregivers who participated in the study may have been more positive about the application overall. We tried to minimize this by setting out a broad recruitment strategy, approaching caregivers that showed no initial interest in the application in the face-to-face recruitment and emphasizing the importance of hearing all opinions during the interview.

Future directions

Real-world evaluation allowed us to identify important implementation issues that should be addressed in the future, like how to activate caregivers to download the app at home and how to engage all staff in the safari story. Hence, follow-up research should focus on how best to implement the Hospital Hero in practice, setting up an implementation strategy and evaluating the implementation efforts. Implementation and scaling efforts should be directed at being minimally disruptive to daily practice, creating stakeholder support and demonstrating impact for all stakeholders involved.

Finally, we demonstrated that the app was evaluated positively by children and

caregivers and has the potential to diminish stress and anxiety. This pilot evaluation study should thus be considered a first step in the eHealth evaluation cycle (41). Future research should be directed at assessing the app's impact on patient outcomes (i.e. stress and anxiety, procedural knowledge, patient satisfaction), healthcare professionals (i.e. satisfaction) and healthcare as a whole (i.e. cost-benefit). The impact method guided by the Quadruple Aim framework could be a useful way to evaluate impact on the short and long term for all stakeholders (42).

Conclusion

Applying a PD approach, we developed a novel child-centred eHealth intervention that was evaluated positively on use and user experience and has the potential to reduce pre-procedural stress and anxiety by focusing on all anxiety-heightening moments before and during an outpatient visit. The real-world pilot setting helped us to identify three important design improvement opportunities. It also helped us to understand the interaction between the child, caregiver and the Hospital Hero app and provided in-depth insight into implementation issues to address in future research and implementation. As such, the Hospital Hero app can be considered an important addition to the toolbox that healthcare professionals use in their comfort care.

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethical Review Committee of the Leiden University Medical Centre. Written informed consent to participate in this study was provided by the participants' legal guardian/ next of kin.

Author contributions

AB conceptualized and designed study 1 and coordinated data collection and the overall process. CP, EM, MV and NV conceptualized and designed study 2 and CP and MV coordinated data collection and the overall process. AB, CP and MV analysed the data. NV, ND and VvN contributed to data collection, analysis of the data and the overall process. CP wrote the manuscript and EM and AB provided feedback at each version of the manuscript. AR and NC provided advice in multiple stages of the research. EM, AB, MV, NV, NC and AR critically reviewed the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The Hospital Hero app and the interest from other hospitals led to foundation of the non-profit foundation Hospital Hero (founded August 2022). Authors Charlotte Poot and Nicole Donkel are the co-founders and board members of the foundation. Authors Eline Meijer and Arno Roest are members of the advisory board.

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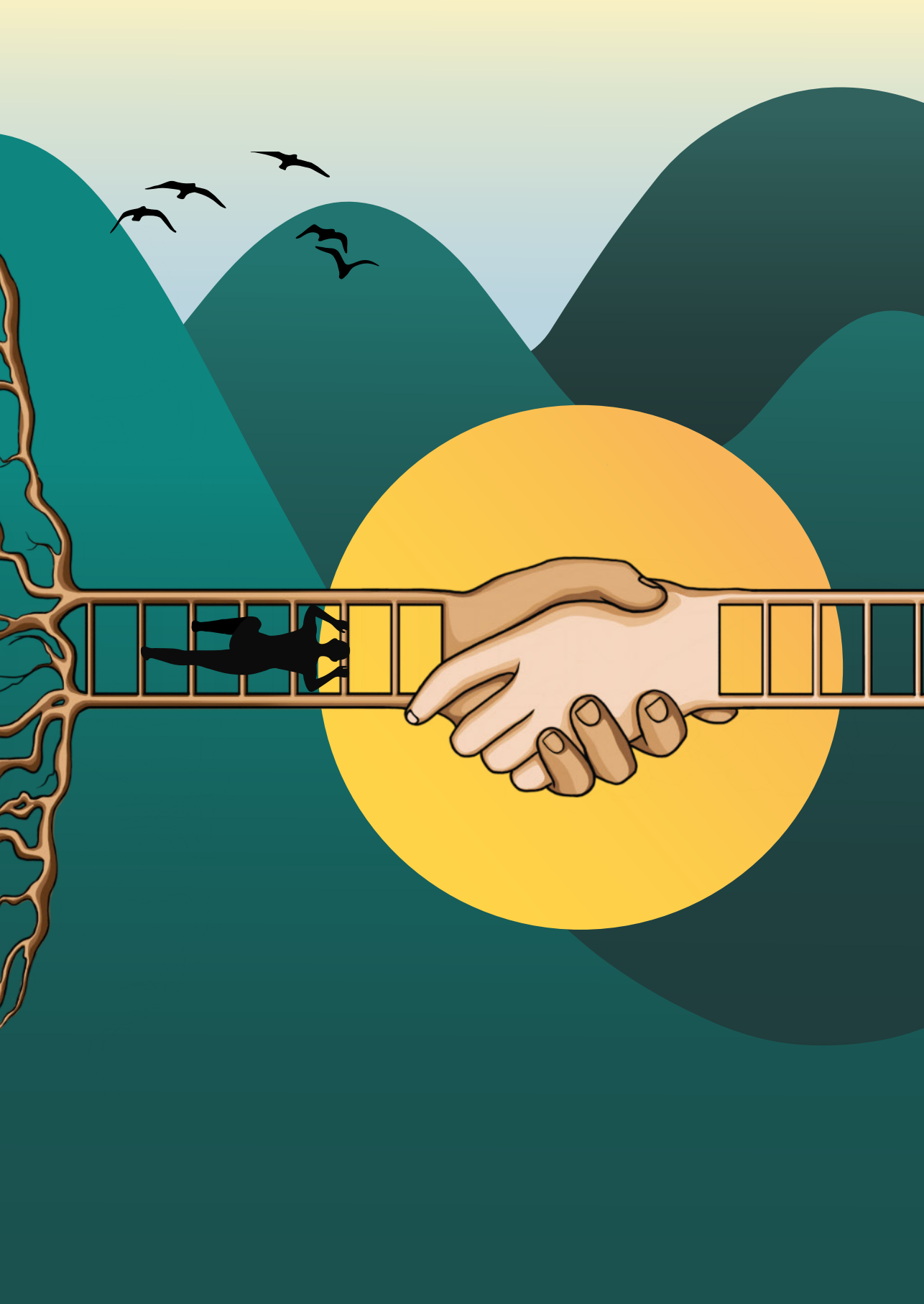
Supplementary materials

Scan the QR code to view supplementary materials

PART 2

EFFECTIVENESS ASSESSMENT



Chapter 5

ACCEPTANCE protocol

Effectiveness, usability and acceptability of a smart inhaler programme in patients with asthma: protocol of the multicentre, pragmatic, open-label, cluster randomised controlled ACCEPTANCE trial

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Abstract

Introduction

Suboptimal asthma control is associated with incorrect inhaler use and poor medication adherence, which could lead to unfavourable clinical and economic outcomes. Smart inhaler programmes using electronic monitoring devices (EMDs) could support self-management and increase medication adherence and asthma control. However, evidence on long-term benefits and acceptability is scarce. This study aims to investigate the effectiveness of a smart inhaler asthma self-management programme on medication adherence and clinical outcomes in adults with uncontrolled asthma, to evaluate its acceptability and to identify subgroups who would benefit most based on patient characteristics.

Methods and analysis

This open-label cluster randomised controlled trial of 12 months will be conducted in primary care in the Netherlands. General practices will be randomly assigned to either intervention or control group. We aim to include 242 patients. The intervention consists of (1) an EMD attached to the patient's inhaler that measures medication use; (2) a smartphone application to set medication reminders, receive motivational messages and track asthma symptoms; and (3) a portal for healthcare professionals to view data on medication use.

The control group is passively monitored by the EMD but cannot view their inhaler data or receive feedback. Eligible patients are adults with suboptimal controlled asthma (Asthma Control Questionnaire score ≥0.75) with evidence of non-adherence established by the EMD during a 6-week run-in period. Primary outcome is the difference in mean medication adherence between intervention and control group.

Secondary outcomes include asthma control, asthma-related quality of life, exacerbations, acceptance, cost-effectiveness and whether the effect of the intervention on medication adherence and asthma control is modified by patient characteristics (e.g., self-efficacy, medication beliefs and eHealth literacy).

Ethics and dissemination

This study has been approved by the Medical Research Ethics Committee (BEBO, Assen, the Netherlands, reference NL69909.056.19). Results will be submitted for publication in peer-reviewed journals.

Trial registration number

NL7854 (Netherlands Trial Register)

Background and rationale

Asthma is characterised by chronic inflammation of the airways and affects more than 300 million adults and children worldwide (1). Despite the availability of effective treatment, nearly half of all asthma patients remain inadequately controlled (2). Suboptimal control is associated with increased symptom burden, increased risk of exacerbations and reduced quality of life, and may lead to short-acting β-2 agonist (SABA) overreliance (3-7). Furthermore, an increased economic burden in terms of direct costs (healthcare utilisation and medication) and indirect costs (loss of productivity and absenteeism) is associated with poor control (8,9). Poor medication adherence and incorrect inhaler use could lead to suboptimal asthma control (10-13). Globally, medication adherence ranges from 13% to 52% (14,15). Numerous factors contribute to poor medication adherence, including illness perceptions, medication beliefs (e.g. concerns about side effects), forgetfulness, difficulty understanding specifics of the regimen (i.e. inhaler technique), attitude towards the illness (i.e. the patient's willingness to work with physicians to manage the disease) and self-efficacy (i.e. the patient's confidence in his or her ability to contribute to the management of the disease) (16,17). As such, medication adherence interventions ask for a comprehensive and personalised approach; one that is tailored towards reasons of non-adherence (18).

Having objective data on medication adherence is essential to inform interventions. Electronic monitoring devices (EMDs) can provide real-time data on medication adherence to both patients and healthcare professionals (HCPs). Insight in adherence data can support clinical decision making, for example, by being able to identify sub-optimal adherence as reason for poor treatment response (19). By combining the EMD with an application on the patient's smartphone there is increasing potential for use in self-management of asthma (20,21). These so called "smart inhalers" are able to upload real-time data to the patient's smartphone. As such, patients can receive tailored audio-visual medication reminders and motivational messages, and gain insight in inhaler use. The use of an app makes it possible to integrate multiple self-management components such as the possibility to track symptoms and triggers over time. In addition, it is possible to provide tailored self-management care that can be delivered outside of office hours and scheduled appointments on a more timely manner.

Various studies have found that smart inhalers increase medication adherence (19, 22-26), but an improvement in asthma control is only shown in children (27). However, those studies only evaluated the short-term effects (≤ 6 months) of smart inhalers. Also, evidence on the cost-effectiveness of smart inhaler based self-management programmes is lacking. Furthermore, acceptance and eHealth usage have not been evaluated in prior studies on smart inhalers, whereas it is known that the effectiveness of an asthma smart inhaler based self-management programme may be compromised by adoption failure and poor adherence to the intervention (28). Acceptance and eHealth usage depend on multiple patient characteristics, including illness perception, beliefs about medication and eHealth literacy (29,30). By

evaluating how these factors interact in affecting medication adherence and clinical outcomes, we will be able to identify which patients would benefit most from the use of a smart inhaler based self-management programme. To our knowledge, this is the first pragmatic randomised trial to evaluate the long-term effects of a smart inhaler based asthma self-management programme on medication adherence and clinical outcomes, to collect data on patient characteristics and acceptance, and to perform a cost-effective analysis.

Aims

The primary objective of our study is to evaluate the effectiveness of a smart inhaler programme on medication adherence in adults with uncontrolled asthma compared with control (i.e., passive monitoring with an EMD) over 12 months. Secondary objectives are to evaluate clinical outcomes (i.e., asthma control, reliever use, exacerbations, and asthma-related quality of life), to evaluate which patient groups would benefit most based on baseline patient characteristics (i.e., self-efficacy and attitude, beliefs about medicine, illness perception, eHealth literacy); to evaluate usability and acceptability of the programme by patients and HCPs, and to evaluate the cost-effectiveness of a smart inhaler programme. The purpose of this paper is to describe the rationale and design of the trial.

Methods

Study design

This is a pragmatic, multi-centre, open-label cluster randomised controlled trial (RCT) of 12 months in primary care in the Netherlands. Primary care practices are eligible if they have access to a computer and internet. Eligible primary care practices that provided consent are randomised to either intervention (smart inhaler programme) or control (usual care + passive electronic monitoring). Participating patients receive either intervention or control depending on the allocation of the cluster. Each patient is screened for eligibility and has follow-up measurements at 3, 6, 9 and 12 months from baseline. The baseline is preceded by a 6-week run-in period to assess whether patients are non-adherent. The study is run by three centres in the Netherlands (Leiden University Medical Centre, General Practitioners Research Institute and University Medical Centre Groningen). Practices and patients are recruited throughout the Netherlands. Since inclusion is ongoing during the COVID-19 pandemic, a number of amendments were made to continue inclusion, warrant the safety of the patients and the research team and increase recruitment pace. All protocol amendments with reason are enlisted in Supplementary Table E1. The design of the study and flow of practices and patients is depicted in Figure 1. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (31). The SPIRIT checklist is provided in Supplementary Table E2.

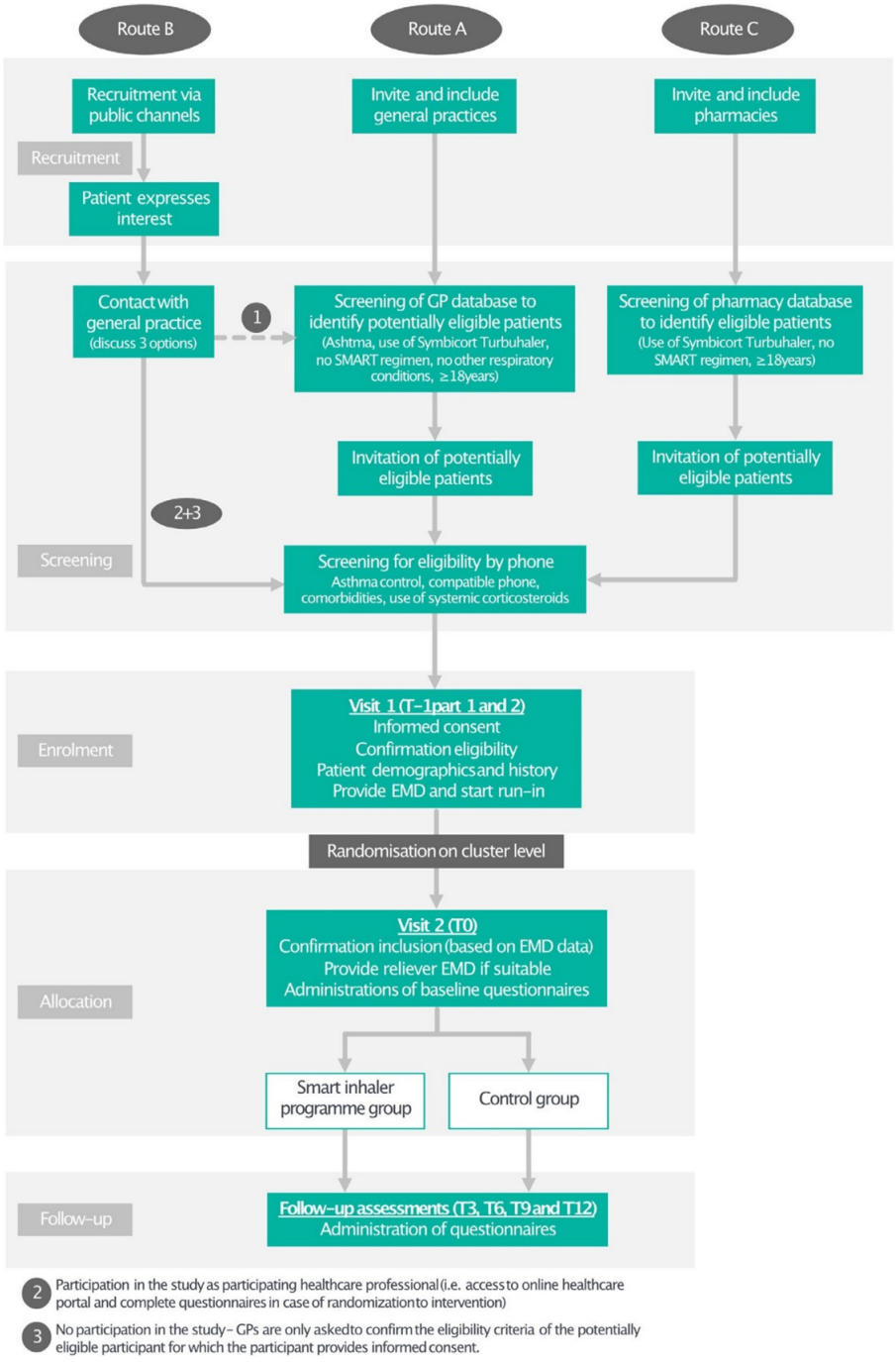

Figure 1. Study flow diagram. EMD, electronic monitoring device; GP, general practice; SMART, Symbicort as maintenance and reliever therapy.

Practice recruitment

Practices are identified via a database search of all primary care practices in the Netherlands. Practices are invited to participate via a letter containing study information and an information folder. Practices are followed-up via telephone contact and email. In addition to invitations, indirect approaches such as presentations at conferences, professional development events for HCPs and word of mouth are used to recruit practices. Before enrolment, practices sign a data processing agreement which allows selection and invitation of potentially eligible patients on behalf of the practice by research staff. This approach allows us to keep the burden for general practices to a minimum, and at the same time to reach an adequate patient sample.

Patient recruitment

Initially, patients are recruited only from enrolled practices. However, due to low inclusion numbers, mainly caused by the increased workload in primary care practices during the COVID-19 pandemic, we broadened the recruitment strategy with recruitment via public channels (i.e., social media and newspaper advertisement) and recruitment via pharmacies. Adding these two alternative recruitment strategies means that eligible patients recruited via these routes do not need to be registered at participating practices but do need to meet all further eligibility criteria. Also, inclusion criteria are checked by the general practitioner in each route. As such, patients can be recruited via the following three routes (partly overlapping at some stages).

Route A (recruitment via general practices)

Eligible patients are selected through electronic record screening by a research assistant or by the practice following an instruction sheet. Invitation letters with an expression of interest form and a reply envelope are sent on behalf of the general practitioner to all eligible patients. Patients can also express their interest via the study website with an identification code included in the letter. Non-responders are sent a reminder letter after two to three weeks. Furthermore, general practices are asked to contact non-responders.

Route B (recruitment via public channels)

Potentially eligible patients are recruited via public channels including (local) newspapers, social media channels and patient organisations by using a visual advertisement including a link to the study website containing more details on the study. Potentially eligible patients expressing their interest to participate are contacted and screened telephonically on eligibility. The general practice where the potential patient is registered is contacted to discuss participation of the general practice (i.e., inviting all eligible patients from the practice following 'route A'). Practices that are not interested in study enrolment are asked to check the inclusion criteria only.

Route C (recruitment via pharmacies)

Pharmacies are identified via a database search of all pharmacies in the Netherlands. Pharmacies are invited to participate via email and are followed-up via telephone or email. Pharmacies are also recruited via word of mouth. Potentially eligible patients are identified via pharmacy records. Pharmacies are asked to select and invite these patients following the steps outlined in route A. Patients who express their interest are screened on eligibility. Since pharmacies cannot identify patients by asthma diagnosis, the inclusion criterion 'doctor-diagnosed asthma' is checked by the general practice. The general practice is not asked to participate as a cluster, as we want to alleviate the burden that general practitioners face due to the COVID-19 pandemic (i.e., an increase in absenteeism due to illness and a postponement of care due to several lockdowns). For the same reason, the inclusion criterion doctor-diagnosed asthma will be checked at 12 months of follow-up instead of at inclusion.

Inclusion and exclusion criteria

On expression of interest, all potentially eligible patients are screened by a research assistant telephonically for further eligibility. Patients aged 18 years and older, who have uncontrolled asthma (defined as an Asthma Control Questionnaire (ACQ)-5 score of ≥0.75), use budesonide/formoterol Symbicort Turbuhaler as maintenance therapy for at least 8 weeks before entering the run-in period, have a doctor diagnosed asthma and are in the possession of a Turbu+ Insights application compatible smartphone (i.e., Android or iOS as mobile operating system) are eligible for inclusion. Patients can receive asthma treatment in primary care or (temporarily) in secondary care, and must provide digital (i.e., via DocuSign) or written informed consent. Furthermore, patients should be classified as 'non-adherent', as observed during the run-in period, during which inhalation actuations are electronically monitored. Non-adherent is defined as an adherence rate of below 80% over the third and fourth weeks of the 6-week run-in period. The adherence rate is defined as the number of adherent days as a proportion of the total number of days. An adherent day is considered a day on which the patient takes at least the number of inhalations prescribed (less inhalations than prescribed means a non-adherent day). Validity of inhalation data can be compromised by change in adherence behaviour due to the knowledge on participating in a trial. To minimise impact, inhalation actuations from the first, second, fifth and sixth weeks of the run-in period are disregarded.

Patients who meet one or more of the exclusion criteria are excluded. Exclusion criteria are (1) use of Symbicort as Symbicort Maintenance and Reliever Therapy (SMART) (to be able to draw valid conclusions on the effect on the primary outcome medication adherence); (2) change in inhaled corticosteroids (ICSs) dose in the 4 weeks prior to the run-in period; (3) use of systemic corticosteroids in the 4 weeks prior to the run-in period, including maintenance therapy (i.e., to exclude patients recovering from an exacerbation at study start); (4) current use of biologics, including anti-interleuking (IL)-5, anti-IL-4Rα or anti-IgE; (5) diagnosis of chronic obstructive pulmonary disease, interstitial lung diseases, bronchiectasis or other significant respiratory conditions; (6) malignancy with life expectancy of < 1 year; (7) pregnancy;

and (8) inability to understand Dutch. Patients with any other condition which, at the general practioner's and/or investigator's discretion, is believed to potentially present a safety risk or impact the study results are also excluded from study participation.

Randomisation, sequence generation and allocation concealment

Primary care practices are block-randomised using a computer-generated permuted block scheme with random block sizes of 4 and 6, stratified by practice size (≤2500 patients or >2500 patients). The randomisation code is recorded in the randomisation database which is accessible only to the coordinating researcher and research assistants. Randomisation at practice level minimises the risk of contamination across intervention and control groups, as patients from the same practice are managed by the same HCPs. Randomisation takes place when the first patient of the general practice has finished the run-in period and will start the smart inhaler programme or enter the control group. Subsequently, practice staff are notified of the allocation of their practice. From this point no additional patients from the same practice can be recruited. This minimises the risk of recruitment bias by practices based on knowledge on allocation. All patient participants that are registered to a participating practice receive the intervention or control depending on the allocation of the practice. Each individual patient participant that is not registered in a participating practice (i.e., part of the patients recruited via route B and all patients recruited via route C) is considered a separate cluster. The cluster will be randomised using the same randomisation scheme and procedures. Randomisation takes place after 6 weeks run-in period when patients fulfil all inclusion criteria.

Study groups

All patients receive usual care according to the Dutch National primary care asthma Guidelines (32).

Intervention (smart inhaler programme)

Patients randomised to the smart inhaler programme will use an EMD, Turbu+ Device (medical devices class I, manufactured by Adherium (NZ), CE marked), which is a small battery-powered electronic data logger. The EMD has previously been used in a research context in the Netherlands (25). The EMD is attached to the patient's inhaler (Symbicort Turbuhaler). The device automatically logs inhaler actuation data including an event stamp and time-and-date stamp. A validation study on the detection of inhaler events as recorded by the Turbu+ device found an accuracy of 99.9% by bench testing over a 12-week period (33). Logged actuation data are sent to an application on a smartphone (Turbu+ Insights). To enable upload of stored actuation data, the app needs to be installed on a smartphone and the device must be paired with the phone using a Bluetooth connection (instructions provided in the app). The upload of new data from the device to the app occurs automatically if the device is within range (<5 meters) of the phone. When the phone is out of range, data will be stored on the device and uploaded to the app when the phone is within range. It is also possible to manually upload data to the app. The battery light-emitting

diode (LED) on the device indicates the battery level. Battery life of the device is approximately 1 year. The app consists of several features which are detailed further. Patients in the intervention group receive instructions on how to use the EMD and how to download, log-in and navigate within the app. No specific instructions on the interaction with the device and application are given (i.e., patients decide which features of the application they use and do not use, and the frequency of interacting with the app) because we aim to mimic a real world situation in which a wide range of user interactions is possible.

Logging and visualisation of actuation events

The app receives and stores inhaler actuation events recorded by the EMD and visualises inhaler use over time. Patients randomised to the intervention group are registered in the Turbu+ system. Registration includes medication regimen (e.g., two inhalations two times a day). Changes in medication regimen are updated in real time and are visible for the patient in the app. Actuation events are plotted against the prescribed medication regimen on a timeline. In addition, patients can view the actuation events over a certain period (e.g., last week or month).

Automatic reminder and messaging

The patient can opt in to receive medication reminder messages as push notifications that pop up on the screen. The application also provides preconfigured missed dose-engaging voice messages (30 minutes after a 'missed dose'). These short messages are based on known drivers and barriers of treatment engagement and treatment perceptions (34). The application also sends overuse messages and weekly targeted motivational messages (e.g., 'Great week. You've been following your prescription this week! Keep it up!').

Symptom and triggers

Patients can record their symptoms and triggers daily in the app by indicating the severity or presence of the symptom or trigger on a 5-point scale. The separate items are projected in the form of a flower (i.e., a full flower is analogous to a happy flower, meaning a minimal presence of symptoms and triggers). The data can be viewed over time.

Web-based HCP portal

Inhaler actuation data are uploaded to the smartphone application and electronically linked to an online web portal (Turbu+ webportal), which can be accessed by the patient's HCP. Within the portal, HCPs can view real time actuation data, including a date-and-time stamp. HCPs from participating practices receive a log in code to be able to set and change the medication regimen and to view the adherence data of their patients participating in the study. Furthermore, they receive instructions on how to access the online healthcare portal and navigate within the portal, but they do not receive specific instructions on the interaction with the healthcare portal and on the use of EMD data during or before patient consultations. Patients who are not

registered in a participating practice (i.e., part of the patients recruited via route B and all patients recruited via route C) can use the app without participation of the HCP.

Control group (passive electronic monitoring)

Patients in the control group attach the same EMD (Turbu+) to their inhaler (Symbicort Turbuhaler) as the intervention group. However, the EMD is connected to a different smartphone application (Hailie Lite). Actuation data are not visible to patients in this app; the app only shows when the EMD last synchronised data with the smartphone (i.e., 'Last synced: (date), (time)'). Inhalation data uploaded to the smartphone application will automatically be uploaded to an online portal (Hailie web portal) which is only accessible to the research team. As inhaler actuations are objectively monitored, without patients and HCPs being able to view their inhaler data, this is called 'passive electronic monitoring'.

EMD for reliever inhalers

A subgroup of patients, regardless of study arm, are provided with an EMD which is compatible with their reliever inhaler (Hailie sensor, medical device class I, manufactured by Adherium (NZ), CE marked). Compatible relievers are Bricanyl Turbuhaler (containing terbutaline) or Ventolin aerosol (containing salbutamol). As in the control group, the EMD will be attached to the patient's inhaler and passively monitor inhaler actuation data using the Hailie Lite smartphone application. Again, actuation data uploaded to the online Hailie portal will only be accessible to the research team.

Data collection and follow-up

Practices

Baseline data from the participating practices are collected at the time of enrolment using a standard data collection form. Data include information on practice size, number of patients and number of staff.

Patients

Considering the pragmatic nature of the study, data are collected during study visits at baseline, and at 6 and 12 months after randomisation. At 3 and 9 months, data are collected via questionnaires sent to the patients. Initially, the study visits took place at the patient's home. Due to the COVID-19 pandemic we decided to change to remote study visits using video consulting software, to be able to continue the study and avert the risk of COVID-19 infection. As remote study visits allow a large flexibility and are perceived as useful by patients (i.e., remote study visits could be easily combined with work), the remote study set up is continued after social distancing measurements are lifted. In case of technical difficulties (e.g., synchronisation problems) which cannot be solved remotely, or when it is impossible for the patient to videocall, the visit proceeds via a home visit (only when COVID-19 measurements allow for home visits).

T-1 (first visit) and run-in period

During the first visit, electronic or handwritten informed consent will be provided. Electronic signature was initiated during the COVID-19 pandemic and proceeds via DocuSign, and electronic signature software that meets all legal requirements for eSignatures according to the European Union (EU) law 'electronic Identification, Authentication and trust services'. After signing the informed consent, initial eligibility is confirmed according to the inclusion and exclusion criteria. Subsequently, demographics (date of birth, sex, education level, smoking history and pack years), medical history (age of asthma onset, number of exacerbations, asthma-related hospital admissions and emergency department visits in the prior year, and other comorbidities) and self-reported asthma medication use will be collected. Patients are provided the EMD (Turbu+ device), instal the app (Hailie Lite) on their smartphone following instructions from the researcher and then enter the 6-week run-in period in which inhaler actuations are objectively monitored.

T0 (baseline visit)

After the run-in period, final eligibility will be confirmed based on the actuation data collected with the EMD during the run-in period. Patients who are classified as non-adherent (see 'the Inclusion and exclusion criteria' for definition) will continue study participation. Before giving informed consent, patients are informed that an additional selection takes place after the run-in period, but they are not informed about what the additional selection entails (i.e., selection based on the level of medication adherence). Awareness of patients hereof probably affects the adherence behaviour of patients and could lead to biased results, especially because the primary outcome measures of this study is medication adherence. During the baseline visit, baseline data are collected through questionnaires and structured interviews (see Table 1). Furthermore, patients are informed of their assigned randomised condition (i.e., intervention or control). The EMD of patients in the intervention group is replaced, to ensure data collected in the run-in period are not visible in the intervention app, and instructions on how to download and use the intervention app are provided.

Follow-up visits (T6 and T12)

At visits T6 and T12, data are collected through structured interviews and questionnaires (see Table 1), as this helps to keep patients involved, retain participation and reduce the amount of missing data. All patients receive a new EMD prior to visit T6 to ensure sufficient battery throughout the study.

Table 1. Overview of measurements

	Run-in	**Intervention**				
	1	**2**	**3**	**4**	**5**	**6**
	T-1	**T0**	**T3**	**T6**	**T9**	**T12**
	Remote visit	**Remote visit**		**Remote visit**		**Remote visit**
Patient assessments						
Informed consent	X					
Eligibility assessment	X					
Demographic characteristics	X					
Medical history	X					
Provide EMD	X					
Confirmation inclusion		X				
Randomisation		X				
Asthma medication regimen	X	X		X		X
Healthcare use*		X		X		X
Exacerbations	X	X	X	X	X	X
(Severe) adverse events		X		X		
Paper administered questionnaires						
Health use assessment*			X		X	
ACQ-5	X	X	X	X	X	X
Mini-AQLQ		X	X	X	X	X
WPAI Questionnaire		X	X	X	X	X
Electronic administered questionnaires						
KASE-AQ		X				X
BMQ-Specific		X				X
Brief IPQ		X				X
eHLQ		X				X
TAQ†			X			X
SUS†			X			X

	Run-in	Intervention				
	1	2	3	4	5	6
	T-1	T0	T3	T6	T9	T12
Non-patient assessments						
Log data						X
Inhaler actuations (EMD)	Data collected over time interval T-1–T12					
Reliever inhalation actuations (EMD)‡	Data collected over time interval T0–T12					
Medication use§						X
Healthcare professional assessments						
TAQ†¶			X			X
SUS†¶			X			X

*At T0, T6, T12 structured interview, at T3 and T9 paper questionnaires (same questions). Healthcare use data covering the study period will be retrieved from the patient's general practice electronic health record system at study end.

†Questionnaires only administered to the intervention group.

‡Only patients that use an EMD compatible reliever inhaler.

§Medication use data during the study and the year prior to the study will be retrieved from the patient's main pharmacist dispense system.

¶Only for HCPs that participate in the study (option A, option B1 and B2).

ACQ, Asthma Control Questionnaire; BMQ-Specific, Beliefs about Medicine Questionnaire–Specific; eHLQ, eHealth Literacy Questionnaire; EMD, electronic monitoring device; IPQ, Illness Perception Questionnaire; KASE-AQ, Knowledge Attitude Self Efficacy-Asthma Questionnaire; Mini- AQLQ, Mini Asthma-Related Quality of Life Questionnaire; SUS, System Usability Scale; TAQ, Technology Acceptance Questionnaire; WPAI, Work Productivity and Activity Impairment.

Study outcomes

Primary outcome

The primary outcome of this study is medication adherence over 12 months, as measured objectively by electronic monitoring of inhaler actuations. The treatment effect will be expressed as the mean absolute difference in medication adherence between the smart inhaler programme group and the control group. Medication adherence is defined as the percentage of daily inhalations taken as prescribed (number of recorded inhalations per day/number of maintenance inhalations prescribed per dayx100), corrected for dose dumping. Dose dumping is defined as ≥6 actuations within a 5 minute period. Daily adherence will be capped at 100% (i.e., to avoid falsely increased values).

Secondary outcomes

Asthma control

Asthma control is measured with the ACQ-5 (35). The ACQ-5 is developed as a self-report measure to assess asthma control. The five items of the ACQ are each rated on a 7-point scale (0 - 6 points). The items assess sleep deprivation, symptoms on waking, activity impairment, dyspnoea and wheezing during the previous week. Patients with a score of ≤0.75 are considered as having controlled asthma; patients with a score of ≥1.5 are considered as having uncontrolled asthma (36). A change of ≥0.5 is considered the minimal clinically important difference (MCID)(37).

Asthma-related quality of life

Asthma-related quality of life is assessed with the self-administered mini Asthma-Related Quality of Life Questionnaire (Mini-AQLQ). Each of the 15 items is rated on a 7-point scale (1-7 points), and the questions cover four domains (symptoms, activities, emotions and environment)(38). A higher score indicates better asthma-related quality of life. The MCID is considered to be 0.5 (39).

Reliever use

Reliever use (SABA) is electronically monitored in a subgroup of patients, who are in possession of a reliever inhaler which is compatible with an EMD. Reliever prescription data are retrieved from the patient's pharmacy at study end for all participating patients.

Exacerbations

The total number of severe exacerbations is collected through self-report (interview during visits and questionnaires at T3 and T9) and through the patient's pharmacist and general practice electronic health record system. The definition of a severe exacerbation is either the use of systemic corticosteroids or an increase from a stable inhaler maintenance dose for at least 3 days, or hospitalisation or an emergency department visit because of asthma requiring systemic corticosteroids.

Acceptance and usability of the smart inhaler programme

The usability and acceptance of the smart inhaler programme are assessed among patients and practices allocated to the intervention group, using two questionnaires.

Acceptance is measured with the Technology Acceptance Questionnaire, which consists of 22 items (e.g., 'using Turbu+ makes it easier to manage my asthma' and 'I find Turbu+ easy to use') which are scored on a 5-point Likert-scale. The items are based on the technology acceptance model (TAM) and the Unified theory of acceptance and use of technology (UTAUT) and address the intended use and different factors determining the behavioural intention to use the smart inhaler programme (40,41). Usability is assessed using the System Usability Scale (SUS) (42). This is a generic instrument to measure usability of a technology or service and contains 10 items which are adapted to the specific technology or service. The items

are rated on a 5-point Likert scale from 1 ('strongly disagree') to 5 ('strongly agree'). An additional free text field allows for commenting on usability.

Patient characteristics

Asthma attitude and self-efficacy

The Knowledge, Attitude and Self Efficacy-Asthma Questionnaire (KASE-AQ) is used as a comprehensive tool to measure various aspects of attitude and self-efficacy regarding controlling asthma symptoms and disease (43). Each domain consists of 20 questions with scores ranging from 20 to 100. Higher scores on the Self-Efficacy Scale indicate more confidence in managing and controlling asthma. Higher scores on the Attitude Scale indicate a more positive attitude towards asthma. The Knowledge Scale will be omitted as it is oriented to the United States and is not in line with the current Dutch medical guidelines on asthma management. The KASE-AQ without the knowledge domain has successfully been used in previous studies (44,45).

Medication beliefs

The Beliefs about Medicine Questionnaire- Specific (BMQ-Specific) is used to measure beliefs about asthma medication (46). The BMQ-Specific consists of 10 items about the necessity and concerns of a patient's prescribed medication. The items are rated on a 5-point Likert scale from 1 ('strongly disagree') to 5 ('strongly agree').

Illness perception

Illness perception specific to asthma will be measured using the Brief Illness Perception Questionnaire (Brief-IPQ). The Brief-IPQ assesses the emotional and cognitive representation of illness and consists of nine items rated on a 11-point scale (47-49).

eHealth literacy

eHealth literacy is assessed using the eHealth Literacy Questionnaire (eHLQ), which is based on the eHealth Literacy Framework (50). This framework consists of seven domains which include individual factors that are necessary to use eHealth (e.g., engagement in own health), system factors (e.g., access to digital services that work) and user–system interaction factors (e.g., motivation to engage with digital services). The questionnaire consists of 35 items which are rated on a 5-point Likert scale from 1 ('strongly disagree') to 5 ('strongly agree'). The eHLQ has been used in international research to help understand people's interaction with eHealth devices and has been translated into seven different languages. As validation studies of the eHLQ into Dutch were ongoing at study start, the initial translated and culturally adapted version was used.

Healthcare use

Healthcare use is assessed at baseline (T0) and during all follow-up moments. Self-report data will be complemented with healthcare use data covering the study period, retrieved from the patients' general practice electronic health record system at study end. Use data include asthma-specific hospital admissions including intensive

care unit days and length of stay, emergency department visits because of asthma, asthma-related visits and phone calls to the general practice, and medical specialist visits because of asthma. Data on medication use will be retrieved from the patients' main pharmacist dispense system at T12.

Absenteeism and presenteeism

The Work Productivity and Activity Impairment instrument (WPAI) will be completed by patients to measure absenteeism and presenteeism. The questionnaire consists of nine questions in three domains (work impairment, school impairment and activity impairment)(51,52). Outcomes on absenteeism, presenteeism, work productivity loss and activity impairment are expressed as percentages, with higher numbers indicating greater impairment and/or less productivity.

Cost-effectiveness analysis

The cost-effectiveness of the smart inhaler programme will be assessed by comparing the costs and benefits of the programme (i.e., intervention group) with usual care (i.e., control group) in a cost-effectiveness analysis.

Sample size

The power calculation is based on the primary outcome: medication adherence over 12 months, as measured by electronic monitoring of inhaler actuations. The treatment effect is expressed as the absolute difference in mean medication adherence between the intervention group and the control group. The sample size is based on an absolute difference in mean medication adherence between the groups of 15% (effect size), based on an expected adherence rate of 65% in the control group (22,53,54), and the target of a mean adherence of 80% in the intervention group. A SD of 0.30 is used (22). A design effect of 1.075 is used, which is based on an intra-cluster correlation coefficient of 0.025 (55), the INCA® (INhaler Compliance Assessment), and a cluster size of 4. The cluster size is based on (1) the average number of asthma patients in a Dutch general practice; (2) data on age, asthma control level and medication use (56); (3) the assumption that 40% of the patients is non-adherent; and (4) recruitment rates in previous primary care asthma trials.

To detect an absolute difference of 15% in mean medication adherence with 90% power and a 5% significance level, a sample size of 242 patients (121 per arm) across approximately 30 clusters in each arm is needed. Given the COVID-19 circumstances and the substantial impact on recruitment pace and strain on healthcare, it is difficult to predict recruitment and drop-out rates. Therefore, we explored different scenarios based on a power of 80% and varying drop-out rates based on literature (Table 2).

Table 2. Scenario power calculations

	Drop-out rate			
	25%	18%	16%	10%
Power 90%	121 per arm	111 per arm	108 per arm	101 per arm
Power 80%	91 per arm	83 per arm	81 per arm	76 per arm

Statistical analysis

The statistical analysis plan is presented in Supplementary File E3. Data will be analysed using the intention-to-treat principle. In addition, a per-protocol analysis will be performed for the primary outcome. Baseline demographic and clinical characteristics will be summarised using means and SD, or medians and IQRs, where appropriate. To test the effect of intervention condition on medication adherence and on changes in medication adherence over time, a multilevel linear mixed-model analysis will be performed. The model will include weekly adherence rates per patient from baseline to T12 (i.e., recorded as a percentage). A precise definition and of medication adherence and how it is calculated is provided in the statistical analysis plan (Supplementary File E3). Medication adherence data around visits will be disregarded to minimise bias. The mixed-model will include a random intercept per general practice. A correlation structure will be chosen for the repeated measurements on the level of patients by selecting the best fitting variance-covariance matrix. The model will include fixed effects for treatment (intervention or control), time, their interaction, age and baseline adherence. Assumptions for mixed models will be investigated beforehand to check that these are met. The mixed-effect model will provide valid statistical inferences in the presence of missing outcome data, which can be explained by covariates in the model (i.e., treatment, age, time). To analyse the effect of intervention on secondary outcomes over time, a similar approach as for the primary outcome will be used. A linear mixed model will be used to assess whether the effect of the intervention on medication adherence and asthma control at 12 months is modified by patient characteristics (i.e., self-efficacy, attitude, medication beliefs, illness perception and eHealth literacy). Sensitivity analysis will be performed using all medication adherence data (i.e., including medication adherence data measured around follow-up moments) and including patients with doctor diagnosed asthma only (see the Route C (recruitment via pharmacies) section). No interim analysis will be performed. Statistical analyses will be carried out using R version 4.1.1.(57 and the R Studio IDE version 1.3.1073 (or higher versions of the programmes)(58). P-values below 0.05 are considered statistically significant.

Cost-effectiveness analysis

A cost-effectiveness analysis will be performed alongside the trial to compare the costs and outcomes of the smart inhaler programme with the control group. A cost-effectiveness model will be used to explore long-term effects. Cost-effectiveness will

be assessed following the Dutch Guideline for Economic Evaluations in healthcare (59).

Blinding (performance and outcome assessment)

Due to the nature of the study, patients cannot be blinded to allocation. As unblinding may introduce performance bias (i.e., a change in patient's behaviour caused by awareness of participation in a trial, especially around visits), the medication adherence data of 1 week before and 1 week after follow-up moments are disregarded to minimise the risk of bias. Outcome assessors cannot be blinded as it is important to carefully instruct patients on how to download and use the intervention app and to provide training to intervention practices on use of the online portal. The statistician who performs the data analyses and validates the results will be blinded to group allocation to avoid bias.

Data management

Data will be pseudonymised by using a code list during data collection. Collection of indirect and direct identifiable information will be minimised, and will be only collected for the purpose of this study. Identifiable information will be stored separately from pseudonymised data. All data collected on paper are stored in locked filling cabinets at the study sites. Electronic data is collected using Castor EDC, an electronic data capture and management application (60). Only investigators and research staff involved in the trial have access to participant data. For the logistic management of participants and the trial, a secured access database is used. Data handling and storage comply with the General Data Protection Regulation. Source documents, informed consent forms and investigator files are archived for 15 years at the study sites, according to the Dutch Medical Treatment Act. Video consulting software used during remote visits comply with security standards set by the study sites and applicable laws and features two-factor authentication and encrypted data. Data that are stored in the apps used in this study are encrypted, as well as data that are stored in a local database on the phone. This prevents other apps on the phone from accessing the data. Data are also encrypted when data are in transit, to protect personal information. All the information supplied through the Turbu+ Insights application will be stored on secure servers in the EU (Ireland) and managed by the Turbu+ Insights programme administrators. Data are pseudonymised when exported from the system. All data collected by Hailie Sensors and transmitted by Hailie Lite App, as well as data entered into the Hailie web portal in the course of the ACCEPTANCE study (Asthma Control through Cost Effective Primary care Treatment: AdhereNCe and E-Health feedback) by the study site personnel, are stored on secure servers in the USA: (1) on AWS servers, from study start date to 17 December 2020 and (2) on MS Azure SQL servers, from 17 December 2020 to the present, under data processing addendums including standard contractual clauses. Further data management procedures and operational details are specified in the data management plan.

Monitoring and quality assurance

The study will be monitored on annual basis according to a monitor plan, by a monitor of the Leiden University Medical Centre who works in a department from the research staff. A structured risk analysis is performed, whereby the risk of this study is considered negligible. Based on this risk, a data monitoring committee is not deemed necessary.

Trial status

The trial is in the recruitment phase at the time of manuscript submission. The first patient was enrolled on 16 December 2019. End of data collection is expected in March 2023.

Dissemination

Results of the trial will be submitted to peer-reviewed journals and presented at both national and international conferences, where possible. In addition, we plan to disseminate during public events for patients with asthma and caregivers.

Public and patient involvement

We set up a patient advisory panel consisting of four trained patient representatives with diverse backgrounds and experience as representatives. The patient advisory panel gives advice during several stages of the research. We received input from the advisory panel on study design, study materials, patient information, recruitment plans and burden to the patient. Alle study materials involving patients such as the smart inhaler programme and videoconference systems, were checked and tested by the panel members. Regular meetings are held with the advisory panel to inform, seek advice, and evaluate the collaboration. No patients were involved in setting the research question or the outcome measures. We plan to disseminate the results of the research to all study participants and to interested audience during public events for people with asthma.

Discussion

This study protocol details the evaluation of the effectiveness and cost-effectiveness of a smart asthma inhaler programme in primary care in the Netherlands. With a follow-up of 12 months, it is the first study to provide evidence on and insight in the effectiveness of a smart inhaler programme on the long term. To our knowledge, this is also the first RCT that longitudinally assesses the use of a smart inhaler programme in a real-world setting. It becomes increasingly acknowledged that eHealth and health innovations should be investigated in a real-world setting, meaning that the study resembles real practice as much as possible. In this trial, that means that study inclusion is inclusive and patients and participating HCPs do not receive instructions on how often to use the smart inhaler programme, allowing patients and HCPs to interact with the programme in a way it suits their needs. The outcomes of this large multi-centre trial will add to the evidence on the effectiveness of EMDs in the

treatment of asthma. Because of the pragmatic trial design, it will give important insights in the practical use and acceptability of a smart inhaler programme in clinical practice from the perspective of patients and HCPs. The study will also contribute to the existing knowledge regarding the role of patient characteristics in medication adherence and the use of eHealth based self-management interventions.

In the early months of the COVID-19 pandemic, study inclusion was paused for six months. In order to proceed with study activities and continue study inclusion, the study continued as remote research. Remote research methods, including video conference systems and postal delivery of questionnaires and devices are innovative ways of performing research. As such, this study provides insight in how remote studies can be performed in an efficient way and how they may benefit participants and the research as a whole (e.g., remote visits allow more flexibility and can easily fit into the participant's daily schedules), thereby adding to limited evidence on remote or decentralised trials (61).

This study has some methodological challenges. First, due to the nature of the intervention, blinding of patients and participating practices is not possible, introducing the possibility of performance bias (i.e., improved adherence behaviour due to knowledge on allocation). This challenge is often encountered in adherence trials. Changes in behaviour are mostly seen at study start and around study visits and result in increased medication adherence in both intervention and control groups. EMD data from the SYGMA two study showed an average improvement in adherence 1 - 2 weeks before and after a study visit, which normalised after a visit (62). Consequently, frequent study visits may increase medication adherence, which can subsequently improve asthma control over a longer period of time (i.e., more than 6 months). In order to reduce the impact of bias and improve internal validity, the study has a follow-up of 12 months and has a minimal number of research visits (i.e., every 6 months), resembling the check-up frequency of patients with suboptimal asthma in the Netherlands). In addition, medication adherence data around visits will be excluded from the analysis to minimise the potential impact of performance bias.

Second, different modes of recruitment and study participation may have an influence on intervention compliance and delivery of the intervention (i.e., delivered to one patient and delivered to all patients of the practice). However, having multiple recruitment strategies increases the reach and enhances the recruitment rate, which is necessary to reach the required study power. Sensitivity analysis will be performed where possible to identify any effects of recruitment ways on outcomes.

Finally, it is uncertain what proportion of patients will fulfil all inclusion criteria, especially the inclusion criteria 'having uncontrolled asthma' and 'being non-adherent'. In general, people with limited health literacy and/or a lower socioeconomic position are known to be less adherent to their medication and at higher risk of having suboptimal controlled asthma (63-65). However, this patient population is also known to be less willing to participate in research, have difficulties understanding study content and be anxious towards research or the research team (66). Hence, while asthma patients with lower socioeconomic positions would probably benefit

most from the intervention, people with lower socioeconomic positions are less likely to participate and complete participation in a clinical trial (67). We attempt to deal with this by providing financial compensation for their time spent, by involving the practice nurse, whom patients are familiar with, in recruitment, by creating a familiar face for the patients (i.e., having the same research assistant perform all study visits with one patient) and through public recruitment channels which the target group interacts with on a daily basis.

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Authors' contributions

SJvdH and CCP contributed equally to this paper. SJvdH, CCP, EM, JFMvB, MJP, LNvdB, BMJF-dB, NHC and JWHK made substantial contributions in the conception and design of the study. SJvdH and CCP wrote the first version and subsequent versions of this manuscript. All authors reviewed the article critically for important intellectual content and gave final approval of the version to be published.

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Competing interests statement

JWHK reports grants, personal fees and non-financial support outside the submitted work from AstraZeneca, grants, personal fees and non-financial support from Boehringer Ingelheim and GSK; grants and personal fees from Chiesi Pharmaceuticals and TEVA; grants from Mundi Pharma and personal fees from MSD and COVIS Pharma; JWHK also holds 72.5% of shares in the General Practitioners Research Institute. JFMVB received grants and/or consultancy fees from AstraZeneca, Chiesi, European Commission COST (COST Action 19132), GSK, Novartis, Teva and Trudell Medical, outside the submitted work and all paid to his institution. BFdB was employed by General Practitioners Research Institute (GPRI) at the time of the study. In the past three years (2019-2021), GPRI conducted investigator-initiated and sponsor-initiated research funded by non-commercial organisations, academic institutes, and pharmaceutical companies (including AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis, and Teva).

Patient and public involvement

Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and was approved by the medical research ethics committee of the Foundation 'Evaluation of Ethics in Biomedical Research' (BEBO, Assen, the Netherlands (reference NL69909.056.19). Results will be submitted for publication in peer-reviewed journals. Participants gave informed consent to participate in the study before taking part. The study was registered in the Netherlands Trial Register (NL7854) on 3 July 2019. In case of protocol modifications, the medical research ethics committee (and the study participants if necessary) will be notified. Since the smart inhaler programme is additional to usual care and patients will use their inhalation medication as prescribed, we do not expect any risk of participation for patients. Also, no risks on the use of the electronic monitoring devices have been reported previously nor are expected. Adverse events are recorded in the study database. Serious adverse events are reported to the sponsor and the medical research ethics committee without undue delay. Participants are informed that they can withdraw from the study at any time without giving a reason. Due to the pragmatic set-up of the study, participants may continue study participation when they switch from Symbicort to other inhaler medications during the study. Switching of inhalers will be documented and data collection will be continued, with the exception of medication adherence data. To promote participation and retention, patients will be financially compensated for their participation with a gift voucher. The compensation will be proportional to the number of visits completed (€20 per visit, maximum of €80). Participating general practices will be reimbursed with €200 for study participation and an additional €100 per patient (intervention group) or €34 (control group). Pharmacies will be reimbursed with €400 for study participation when the invitation letters to potential eligible patients are sent, and an additional €25 for each patient that is eligible. This compensates for the anticipated time a general practice and pharmacy will spend performing study-related activities and answering questions from patients regarding the study.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

No data are available.

Supplemental material

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Supplementary materials

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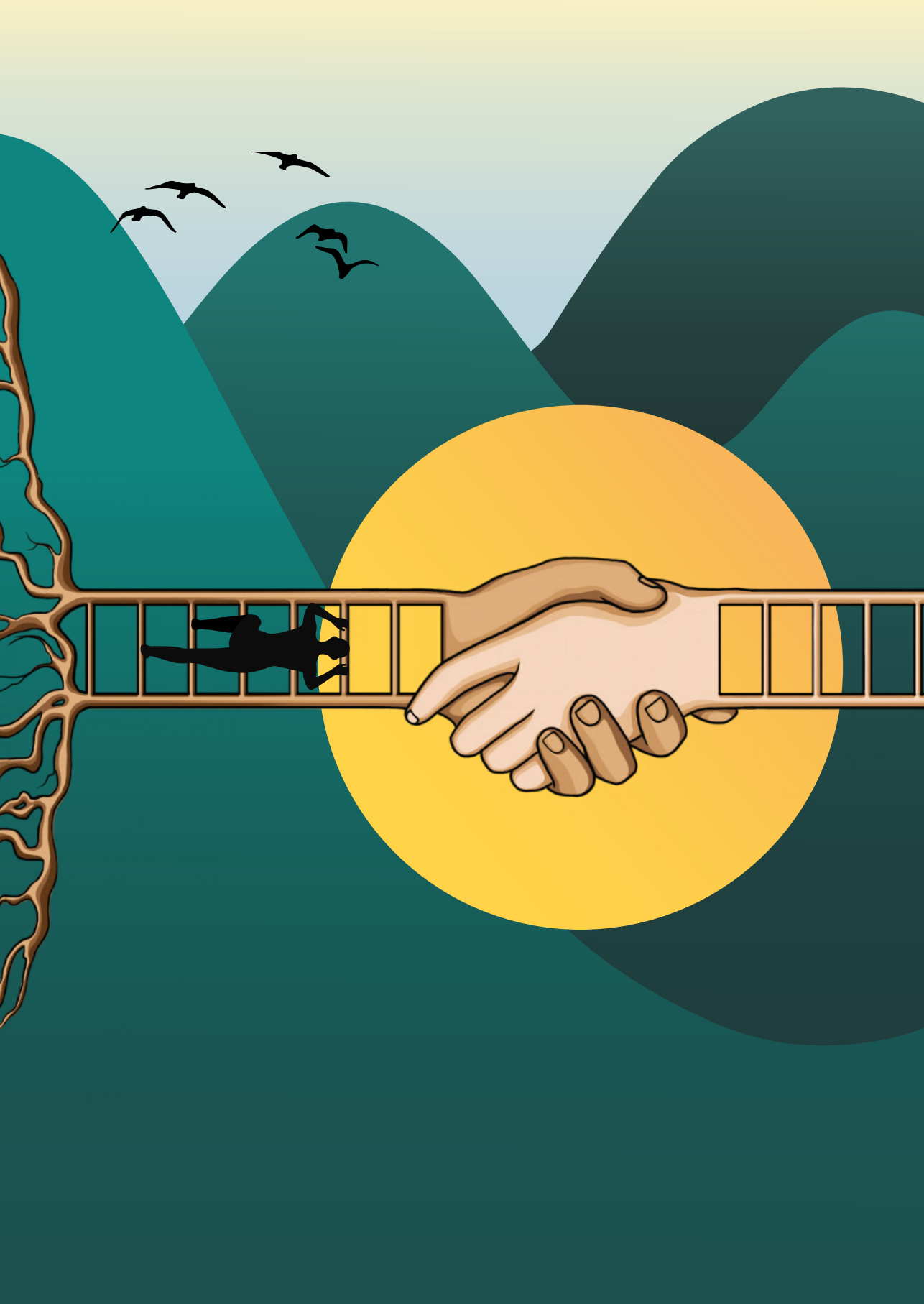

Chapter 6

Cochrane review on integrated disease management for COPD

Integrated disease management interventions for patients with chronic obstructive pulmonary disease (Review)

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Abstract

Background

People with chronic obstructive pulmonary disease (COPD) show considerable variation in symptoms, limitations, and well-being; this often complicates medical care. A multi-disciplinary and multi-component programme that addresses different elements of care could improve quality of life (QoL) and exercise tolerance, while reducing the number of exacerbations.

Objectives

To compare the effectiveness of integrated disease management (IDM) programmes versus usual care for people with chronic obstructive pulmonary disease (COPD) in terms of health-related quality of life (QoL), exercise tolerance, and exacerbation-related outcomes.

Search methods

We searched the Cochrane Airways Group Register of Trials, CENTRAL, MEDLINE, Embase, and CINAHL for potentially eligible studies. Searches were current as of September 2020.

Selection criteria

Randomised controlled trials (RCTs) that compared IDM programmes for COPD versus usual care were included. Interventions consisted of multi-disciplinary (two or more healthcare providers) and multi-treatment (two or more components) IDM programmes of at least three months' duration.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. If required, we contacted study authors to request additional data. We performed meta-analyses using random-effects modelling. We carried out sensitivity analyses for the quality of included studies and performed subgroup analyses based on setting, study design, dominant intervention components, and region.

Main results

Along with 26 studies included in the 2013 Cochrane Review, we added 26 studies for this update, resulting in 52 studies involving 21,086 participants for inclusion in the meta-analysis. Follow-up periods ranged between 3 and 48 months and were classified as short-term (up to 6 months), medium-term (6 to 15 months), and long-term (longer than 15 months) follow-up. Studies were conducted in 19 different countries. The mean age of included participants was 67 years, and 66% were male. Participants were treated in all types of healthcare settings, including primary (n = 15), secondary (n = 22), and tertiary care (n = 5), and combined primary and secondary care (n = 10). Overall, the level of certainty of evidence was moderate to high.

We found that IDM probably improves health-related QoL as measured by St. George's Respiratory Questionnaire (SGRQ) total score at medium-term follow-up

(mean difference (MD) -3.89, 95% confidence interval (CI) -6.16 to -1.63; 18 RCTs, 4321 participants; moderate-certainty evidence). A comparable effect was observed at short-term follow-up (MD -3.78, 95% CI -6.29 to -1.28; 16 RCTs, 1788 participants). However, the common effect did not exceed the minimum clinically important difference (MCID) of 4 points. There was no significant difference between IDM and control for long-term follow-up and for generic QoL.

IDM probably also leads to a large improvement in maximum and functional exercise capacity, as measured by six-minute walking distance (6MWD), at medium-term follow-up (MD 44.69, 95% CI 24.01 to 65.37; 13 studies, 2071 participants; moderate-certainty evidence). The effect exceeded the MCID of 35 metres and was even greater at short-term (MD 52.26, 95% CI 32.39 to 72.74; 17 RCTs, 1390 participants) and long-term (MD 48.83, 95% CI 16.37 to 80.49; 6 RCTs, 7288 participants) follow-up.

The number of participants with respiratory-related admissions was reduced from 324 per 1000 participants in the control group to 235 per 1000 participants in the IDM group (odds ratio (OR) 0.64, 95% CI 0.50 to 0.81; 15 RCTs, median follow-up 12 months, 4207 participants; high-certainty evidence). Likewise, IDM probably results in a reduction in emergency department (ED) visits (OR 0.69, 95%CI 0.50 to 0.93; 9 RCTs, median follow-up 12 months, 8791 participants; moderate-certainty evidence), a slight reduction in all-cause hospital admissions (OR 0.75, 95%CI 0.57 to 0.98; 10 RCTs, median follow-up 12 months, 9030 participants; moderate-certainty evidence), and fewer hospital days per person admitted (MD -2.27, 95% CI -3.98 to -0.56; 14 RCTs, median follow-up 12 months, 3563 participants; moderate-certainty evidence).

Statistically significant improvement was noted on the Medical Research Council (MRC) Dyspnoea Scale at short- and medium-term follow-up but not at long-term follow-up. No differences between groups were reported for mortality, courses of antibiotics/prednisolone, dyspnoea, and depression and anxiety scores. Subgroup analysis of dominant intervention components and regions of study suggested context- and intervention-specific effects. However, some subgroup analyses were marked by considerable heterogeneity or included few studies. These results should therefore be interpreted with caution.

Authors' conclusions

This review shows that IDM probably results in improvement in disease-specific QoL, exercise capacity, hospital admissions, and hospital days per person. Future research should evaluate which combination of IDM components and which intervention duration are most effective for IDM programmes, and should consider contextual determinants of implementation and treatment effect, including process-related outcomes, long-term follow-up, and cost-effectiveness analyses.

Background

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a heterogeneous, systemic condition characterised by restricted airflow that is not fully reversible. It is a major cause of morbidity because people with COPD experience chronic and progressive respiratory symptoms (i.e. dyspnoea and coughing) (GOLD 2020). The prevalence of COPD is currently estimated at 11.7% and is expected to increase substantially in the coming decades due to ageing of the world's population, continued use of tobacco, and exposure to indoor biomass pollution (GOLD 2020; Lopez 2006; Lozano 2012). According to the World Health Organization (WHO), COPD is the fourth leading cause of death in the world (Lopez 2006; WHO 2020). Additionally, COPD has important financial consequences, with high reported direct costs (e.g. healthcare resources, medication prescriptions) and indirect costs (e.g. absence from paid work, consequences of disability) (Britton 2003; FIRS 2017; Guarascio 2013).

Optimal management of COPD is complex as it is a multi-component disease. Clinical, functional, and radiological presentations vary greatly from patient to patient, although patients may have a similar degree of airflow limitation (Agusti 2010; GOLD 2009; GOLD 2020; Wedzicha 2000). Previously, the sole focus in disease management lay on the degree of airflow limitation as a measure of disease severity (in the 2007 Global initiative for Chronic Obstructive Lung Disease (GOLD) classification of disease severity). This turned out to be a poor predictor of other important negative features of COPD, including health-related quality of life (HRQoL) and exercise tolerance (Agusti 2010; Burgel 2010). These patient-oriented outcomes are more important for people with COPD, given that COPD has a profound impact on HRQoL and exercise tolerance, even among those with modest airflow limitation (Engstrom 1996). Furthermore, impaired HRQoL (as shown in Domingo-Salvany 2002 , Fan 2002 , and Martinez 2006) and exercise tolerance (as reported in Gerardi 1996 and Pinto-Plata 2004) are associated with mortality (Cote 2009).

Some people are more prone than others to episodes of acute exacerbation, which is an important additional cause of morbidity, mortality, hospital admission, and impaired health status (Calverley 2003; Seemungal 1998; Wedzicha 2000). Although exacerbations become more severe and occur more frequently with increased severity of COPD, this is not always the case. There is evidence for a 'frequent-exacerbation' phenotype (or group of people) with exacerbation more often than would be expected given disease 'severity' as predicted by lung function testing (Hurst 2010; Le Rouzic 2018).

Description of the intervention

Given that COPD is a disease with a clinically heterogeneous picture characterised by multiple disease components, treatment of patients with COPD requires that these different components of the disease be addressed in a comprehensive programme known as integrated disease management (IDM).

In the previous decade, the concept of IDM was introduced as a means of improving quality and efficiency of care for patients with chronic non-communicable diseases such as COPD, heart failure, and diabetes mellitus. IDM interventions are aimed at reducing symptoms and avoiding fragmentation of care while containing costs. However, although IDM programmes are generally believed to be cost-effective, evidence shows inconclusive results. Several systematic reviews have shown (partly) beneficial results for people with chronic heart failure (Gonseth 2004; Roccaforte 2005), diabetes (Bongaerts 2017; Knight 2005; Norris 2002; Pimouguet 2010), depression (Badamgarav 2003; Neumeyer-Gromen 2004), and COPD (Cronin 2017).

It is important to note that there is no consensus in the literature about the definition of IDM. Several definitions have been proposed since the concept of 'disease management' was introduced. To facilitate communication between researchers, policy makers, and IDM program leaders, Schrijvers proposed a definition based on earlier reported definitions (Faxon 2004): "disease management consists of a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities. The goal of chronic disease management is to identify persons at risk for one or more chronic conditions, to promote self-management by patients, and to address the illness or conditions with maximum clinical outcome, effectiveness, and efficiency regardless of treatment setting(s) or typical reimbursement patterns" (Schrijvers 2009). Peytremann-Bridevaux and Burnand adapted the definition as follows: "chronic disease prevention and management consist of a group of coherent interventions, designed to prevent or manage one or more chronic conditions using a community-wide, systematic, and structured multi-disciplinary approach potentially employing multiple treatment modalities. The goal of chronic disease prevention and management is to identify persons with one or more chronic conditions, to promote self-management by patients, and to address the illness or conditions according to disease severity and patient needs and based on the best available evidence, maximising clinical effectiveness and efficiency regardless of treatment setting(s) or typical reimbursement patterns. Routine process and outcome measurements should allow feedback to all those involved, as well as to adapt the programme" (Peytremann- Bridevaux 2009).

Over the years, IDM programmes combining patient-related, professional-directed, and organisational interventions were developed with the goal of improving effectiveness and economic efficiency of long-term care delivery (Lemmens 2009; Norris 2003; Wagner 2001). Since the previous version of this review of IDM for COPD patients (Kruis 2013), we have seen the advent of technology in IDM programmes, which potentially allows for continuously available and personalised types of patient guidance and monitoring (Kruse 2019).

Technology can be integrated into IDM programmes in different ways, such as use of SMS services, websites, apps, or home monitoring devices. Consequently, several different names are used to describe concepts within this area, such as telehealth, telemonitoring, telerehabilitation, eHealth, and mHealth, which have

features that overlap. For the purposes of this systematic review, we adopted the term 'telemonitoring', defined as use of information and communication technologies to monitor and transmit items related to patient health status between geographically separated individuals (Maric 2009). Telemonitoring best describes the different interventions used in clinical studies, and is the term most studies have used themselves to describe their intervention. Hence, for this update, we have added telemonitoring as a possible additional component of IDM.

How the intervention might work

There is great variation in the symptoms, functional limitations, and degrees of psychological well-being of patients with COPD, as well as in the speed of progression of COPD towards more severe stages (Agusti 2010). This calls for a multi-faceted response, including different elements (e.g. smoking cessation, physiotherapeutic reactivation, self-management, optimal medication adherence) targeted at the patient, the professional, and/or the organisation.

Ideally, COPD care is based on active self-management to slow down progression of the disease, including daily self-care, patient-physician collaboration, and exacerbation management. Information should be tailored to patients' needs, knowledge level, and clinical profile and should be accessible to patients when they need it most (Bourbeau 2013; Tiep 1997).

Another potential benefit of IDM is that without proper self-management, patients often refrain from reporting episodes of exacerbation to healthcare providers (Seemungal 2000). An important reason for this is fear of being sent to the hospital. Unfortunately, neglecting worsening of COPD leads to a negative spiral of increasing dyspnoea, deconditioning, and social deprivation. Eventually, this avoidant behaviour can lead to a respiratory crisis, which necessitates urgent referral to the hospital and might cause further damage to the lungs. To break through this self-reinforcing negative spiral, healthcare professionals must collaborate with their patients. This requires focus on improving and maintaining self-management skills, for example, by urging patients to respond rapidly and seek help to prevent further worsening (Chavannes 2008).

More recently, it has been argued that the addition of telemonitoring to IDM programmes allows for more continuous guidance and might lead to detection of deterioration earlier because of the potential for more frequent assessments. This could lead to more personalised management and prevention of exacerbations (Kruse 2019). However Kruse 2019 also concluded that it is unclear whether this approach enables people with COPD to self-manage more easily. Telemonitoring for pulmonary rehabilitation showed effects similar to those seen with conventional face-to-face, centre-based pulmonary rehabilitation for numerous outcomes (Cox 2021).

Why it is important to do this review

Review authors undertook the original version of this Cochrane Review in 2013 following a number of other (systematic) reviews that described beneficial effects of IDM for the health status of patients with COPD but were unable to draw firm conclusions due to large heterogeneity among interventions, study populations, outcome measurements, and methodological quality. This original review included 26 studies (Kruis 2013), and review authors concluded that IDM improved disease-specific QoL and exercise capacity while reducing hospital admissions and hospital days per person.

An update of the review is required because since that time, many new studies have been conducted to evaluate the effects of IDM programmes on quality of life, exercise capacity, lung function, and exacerbation-related outcomes such as respiratory-related hospital admissions and emergency department (ED) visits. Also, COPD care globally has advanced tremendously. Advancements include greater financial reimbursement for pulmonary rehabilitation programmes and use of technological and digital opportunities. These have altered and potentially improved usual care and have resulted in new studies on the effectiveness of different types of IDM programmes, including telemonitoring interventions. Furthermore, the introduction of telemonitoring has allowed better assessment of actual adherence to IDM programmes due to logging of data entry in apps. This has reinforced the importance of long-term follow-up of outcomes, given that rates of adherence to the IDM programme vary widely and subsequently observed effects can be short-lived (Cheikh-Moussa 2020; Herbert 2018). Finally, the studies included in the previous review provided insufficient data to permit firm conclusions about the long-term effectiveness of IDM.

In summary, in this update of the review, we aimed to summarise and assess evidence of short-, medium-, and long-term effectiveness of IDM compared to usual care among patients with COPD.

Objectives

To compare the effectiveness of integrated disease management (IDM) programmes versus usual care for people with chronic obstructive pulmonary disease (COPD) in terms of health-related quality of life (QoL), exercise tolerance, and exacerbation-related outcomes.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and cluster-randomised trials in which IDM programmes or interventions were compared with control (i.e. usual care) in people with COPD. We excluded non-randomised controlled trials and other intervention studies.

Types of participants

People with a clinical diagnosis of COPD according to the GOLD criteria were included: people with chronic respiratory symptoms (i.e. coughing, sputum, or dyspnoea) and a limited post-bronchodilator forced expiratory volume in one second (FEV1)-to-forced vital capacity (FVC) ratio < 0.7. Severity of airflow obstruction was classified by the GOLD stages of 2009 (GOLD 2009). All GOLD stages were accepted. Studies including participants with diagnoses other than COPD were only eligible if results for participants with COPD were available separately.

Types of interventions

We included studies in which the IDM intervention consisted of strategies to improve care for patients with COPD including organisational, professional, patient-directed (e.g. self-management, education), and financial interventions. We classified these according to the Cochrane Effective Practice and Organisation of Care Group (EPOC) taxonomy of interventions (EPOC 2008), complemented with patient-directed interventions. To be included in the review, a study had to include at least two of the following components of the IDM intervention.

- Education/self-management: education, self-management, personal goals and/or action plan, exacerbation management.
- Exercise: (home) exercise training and/or strength and/or endurance training.
- Psychosocial component: cognitive-behavioural therapy, stress management, other psychological assessment and/or treatment.
- Smoking cessation.
- Medication: optimisation medication regimen/prescription of medication adherence.
- Nutrition: dietary intervention.
- Follow-up and/or communication: structural follow-up and/or communication, case management by nurses, optimal diagnosis.
- Multi-disciplinary team: active participation and formation of teams of

professional caregivers from different disciplines, revision of professional roles, integration of services, local team meetings.

- Financial intervention: fees/payments/grants for providing IDM.

Furthermore, as IDM included different components, as mentioned above, different healthcare disciplines should be involved in delivery of the IDM programme. Hence, we included a study only if at least two different disciplines of healthcare providers were actively involved in the IDM programme.

Finally, a study should have a minimum duration of the IDM intervention of three months.

For all studies, we determined the dominant component of the programme by verifying with the study authors. If this was not possible, we decided based on the duration and intensity of each component. With the emergence of telemonitoring studies, we added telemonitoring as a separate dominant component post hoc.

Types of outcome measures

We specified the following outcomes a priori.

Primary outcomes

1. Health-related quality of life (HRQoL), as reported by a validated disease-specific questionnaire (e.g. St. George's Respiratory Questionnaire (SGRQ) - Jones 1991; Jones 2005; Clinical COPD Questionnaire (CCQ) - Kocks 2006 , van der Molen 2003; Chronic Respiratory Questionnaire (CRQ) - Guyatt 1987; Guyatt 2011; COPD Assessment Test (CAT) - Jones 2009) or a generic quality of life questionnaire (e.g. Short Form-36 (SF- 36) - Ware 1992 EuroQol-5D (EQ-5D) - EuroQol Group 1990)

2. Maximal or functional exercise capacity, as reported by peak capacity measured in the exercise laboratory by an incremental exercise test defined according to results of the 6-minute walking distance test (6MWD) - Redelmeier 1997 - or the shuttle run test - Singh 1992

3. Exacerbation-related outcomes, as reported by one of the following: all-cause hospital admissions, respiratory-related hospital admissions, all-cause hospital days, emergency department (ED) visits, patients with at least one exacerbation and patients with at least one prescription for prednisone and at least one for antibiotics. These outcomes follow the latest definitions of moderate and severe COPD exacerbations in the GOLD guideline and are also used in the two latest Cochrane Reviews assessing exacerbations as a primary outcome (GOLD 2020; Threapleton 2019; Walsh 2019)

Secondary outcomes

Clinical outcomes

1. Dyspnoea, as measured by the Medical Research Council (MRC) Dyspnea Scale - Bestall 1999 - or the Borg Scale - Borg 1970
2. Survival (mortality)
3. Lung function (FEV_1, FVC)
4. Depression, as measured by the Hospital Anxiety and Depression Scale (HADS) - Zigmond 1983 - or the Beck Depression Inventory (BDI) - Beck 1961

Process-related outcomes

1. Coordination of care (e.g. accessibility of care, rate of patient participation in the disease management programme, patients' and healthcare professionals' satisfaction with the programme, extent to which disease management was implemented, from the perspective of the patient (PACIC) - Glasgow 2005)

We evaluated outcomes at (1) short-term (up to 6 months), (2) medium-term (6 to 15 months), and (3) long-term (longer than 15 months) endpoints, if possible.

Search methods for identification of studies

Electronic searches

The previously published version of this review included studies up to April 2013. For the current update, we identified studies using the Cochrane Airways Group Register of trials; the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; MEDLINE (Ovid SP); Embase (Ovid SP); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO).

We used specific medical subject headings (from MeSH) and additional keywords to identify all trials on IDM in COPD patients. The search strategy was developed and conducted in collaboration with the Cochrane Airways Information Specialist. The initial strategy was developed for MEDLINE and was adapted for use in the other databases.

Complete search strategies for the database searches are provided in the appendices (MEDLINE - Appendix 1; Embase - Appendix 2; CINAHL - Appendix 3; CENTRAL - Appendix 4; Airways Register - Appendix 5). The search period for this update covers April 2013 to September 2020. This includes an initial search on 4 January 2017 and updates in March 2018 and March 2019. We ran a final update search in September 2020.

Searching other resources

To identify all possible studies, we carried out an additional search for systematic reviews in the Cochrane Database of Systematic Reviews. We also screened reference lists of included studies and systematic reviews for potential studies for inclusion in the current review. To identify ongoing or new studies, we searched databases of ongoing

studies, including ClinicalTrials.gov (up to September 2020) and the WHO International Clinical Trials Registry Platform (ICTRP) (up to March 2019). See Appendix 6 for those search terms.

Data collection and analysis

Selection of studies

The lead review author (CP) and one of two other review authors (EM, PH) independently assessed the title and abstract of each identified citation. If there was any doubt, we retrieved the full-text article and examined it for inclusion eligibility. Disagreements were discussed during a consensus meeting. When consensus could not be reached, the third review author (AK - the first author of the original 2013 review) adjudicated. Subsequently, the full text of the potential eligible abstract was read by two review authors (CP and EM or PH) before a decision was made regarding its inclusion in the review.

Data extraction and management

For the current update, we used Covidence to extract data and assess risk of bias for each included study (Covidence). The lead review author (CP) extracted data from all papers identified for inclusion using a digital data extraction form. Two other review authors (EM, PH) independently extracted data from an equal share of the same studies. We collected the following information: (1) study design (e.g. randomisation method, sample size, blinding); (2) participant characteristics (e.g. age, sex, COPD diagnosis); (3) interventions (i.e. setting, number of professionals involved, elements of IDM programme/intervention, frequency and duration of intervention); (4) outcome measures and timing of outcome assessment; and (5) results (e.g. loss to follow-up, outcomes). Any discrepancies in data extraction between review authors were resolved through discussion. In case of missing data, we contacted the authors of these studies to request additional information or clarification.

Assessment of risk of bias in included studies

The lead review author (CP) assessed the risk of bias for all included studies using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Two other review authors (EM, PH) independently assessed risk of bias for an equal share of the same studies. Disagreements were resolved through discussion. The following risk of bias items were assessed.

1. Random sequence generation.
2. Concealment of allocation.
3. Blinding of participants and personnel, in relation to the intervention.
4. Blinding of outcome assessment (i.e. patient-reported outcome, other outcomes).
5. Incomplete outcome data.
6. Selective outcome reporting.

7. Other bias.

As cluster-randomised trials were also included, we added the following design-related domains for these types of studies.

1. Recruitment bias (i.e. whether individuals were recruited after clusters had been randomised).
2. Baseline imbalance between groups (i.e. whether risk of baseline differences was reduced by using stratified or pair-matched randomisation of clusters).
3. Loss of follow-up of clusters (i.e. whether missing clusters and missing outcomes for individuals within clusters could lead to a risk of bias in cluster-randomised trials).
4. Methods of analysis adequate for cluster-randomised controlled trials (i.e. whether clustering was taken into account in the analysis) (Higgins 2011).
5. We judged all items as having high, low, or unclear risk of bias and provided a quote from the study and/or a justification for our decision.

Measures of treatment effect

We analysed results of the studies in RevMan 5, using random-effects modelling. We used forest plots to compare results across trials. When possible, results were related to the minimum clinically important difference (MCID) for the respective variable. We undertook meta-analysis only when this was meaningful, that is, when treatment, participants, and the underlying clinical question were similar enough for pooling to make sense, and when the results of at least two RCTs were available.

We used intention-to-treat data or the 'full analysis set' whenever reported. We used per-protocol analysis when neither was reported. Normally, outcome measures that have been adjusted for baseline differences produce the most reliable outcomes. However, these can be analysed only by generic inverse variance (GIV). Also, we noted significant variation in the number of parameters adjusted for between studies. Hence, we used unadjusted values in our random-effects modelling for studies with an RCT design, and values adjusted for potential clustering effects for studies with a cluster-RCT design.

When multiple trial arms were reported in a single study (e.g. hospital-based pulmonary rehabilitation and home-based pulmonary rehabilitation), we included all relevant trial arms. We halved the control group in these cases to avoid double-counting, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 16.5.4) (Higgins 2019a).

Unit of analysis issues

When a study used a cluster-RCT design, we calculated the estimate of effect by using the GIV whenever possible. We used the mean difference (MD) and the 95% confidence interval (CI) reported by study authors when the appropriate analyses were used and authors had adjusted for cluster effect. We calculated a dummy mean change and standard deviation (SD) based on the MD and its 95% CI for cluster-RCT studies, as

recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 23.1.3) (Higgins 2019b).

In case of a unit of analysis error in cluster-RCTs, we adjusted for the design effect by reducing the size of the trial to its "effective sample size" (Rao 1992). The effective sample size of a single intervention group in a cluster-randomised trial is its original sample size divided by a quantity called the 'design effect'. The design effect is 1 + (M - 1) * ICC, where M is the average cluster size, and ICC is the intra-cluster correlation coefficient. For dichotomous data, both the total number of participants and the number of participants experiencing the event were divided by the design effect. For continuous data, for which the GIV method could not be used, only sample sizes were reduced, and means and SDs were left unchanged (Higgins 2011).

Dealing with missing data

When a study paper missed important statistical information required for analysis, or required additional calculations that needed to be clarified, we attempted to contact study authors to gather the required information. When authors had not calculated relevant statistics but presented supporting data, we conducted calculations using methods described in the 2019 Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019a). When studies did not report SDs for change from baseline but did provide information on means, standard errors (SEs), 95% CIs, P values, and population sizes across groups, we calculated SDs for change from baseline using the RevMan 5 internal calculator.

When we could not directly calculate the SD for change from baseline, we imputed the SD using a correlation coefficient as described in the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 6.5.2.8) (Higgins 2019a). We calculated the correlation coefficient by using the weighted mean (based on size of the study) of two or more studies that reported results for the respective variable in sufficient detail.

In the case that fewer than two studies provided sufficient information, a weighted mean correlation coefficient could not be calculated. In that case, we used data on post-intervention measurements, as they are considered to be more precise.

For studies that reported a median instead of a mean, we estimated the mean and the SD using the method and open-access calculator provided in Wan 2014 .

Assessment of heterogeneity

We assessed heterogeneity in each meta-analysis both visually through inspection of forest plots and statistically using tau², I², and the T statistic (Higgins 2019). We regarded heterogeneity as substantial when I² was greater than 50% or a low P value (< 0.10) was reported for the Chi² test for heterogeneity. We reported heterogeneity and explored the possible causes. In cases of substantial ($I^2 > 50\%$) or considerable ($I^2 > 75\%$) heterogeneity, we investigated sources for heterogeneity by conducting subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

The likelihood of publication bias was investigated by preparing a funnel plot only if ten or more studies were included in the meta-analysis. Based on visual inspection, the likelihood of publication bias was evaluated. When asymmetry was observed, we attempted to identify possible reasons by considering the quality of the studies, the particular interventions included, and the contexts in which interventions were implemented.

Data synthesis

We performed statistical analyses using Review Manger software 5.3 (RevMan 5) and RevMan Web 2019 (RevMan Web 2019).

We pooled study results using the random-effects model. For continuous data, we recorded mean change from baseline to endpoint and SD for each group and calculated the MD. For dichotomous data, we recorded the number of participants with each outcome event and calculated the odds ratio (OR). We used all results reported at short-, medium-, and/or long-term follow-up. Given that all interventions had a duration of 12 weeks at minimum, we analysed available data at 6 months for the short term. We analysed data measured most medial to the other time points (i.e. for medium term, we used results at 12 months when 9 and 12 months were given). When possible, we discussed the intervention effect estimate in the context of its MCID. If the meta-analysis led to statistically significant overall estimates, we transformed these results back into measures that are clinically useful in daily practice, such as the number needed to treat for an additional beneficial outcome (NNTB).

Subgroup analysis and investigation of heterogeneity

To explain heterogeneity among study results, we planned the following subgroup analyses a priori (when data were available) to determine if outcomes differed among:

1. settings of the IDM intervention (e.g. primary, secondary, or tertiary care);
2. study designs (individually randomised patients versus cluster-randomised patients); and
3. intervention groups, with regard to different components as listed by the EPOC classification (EPOC 2008).

We performed an additional post-hoc subgroup analysis based on the region in which the study was conducted (i.e. North America, South America, Northwestern Europe, Southern Europe, East Asia, Central Asia) to account for regional differences in usual care and customs regarding hospitalisation, which proved to be large in Kessler 2018. The previous review authors planned to include an additional subgroup on disease severity (Kruis 2013), but they were unable to do so due to the poor quality of reporting. Also, Kruis 2013 performed an additional subgroup analysis based on control group (i.e. no treatment, treatment with one healthcare provider, treatment with one component, other disease management interventions). In the past decade, regular care has evolved in such a way that multiple individual 'intervention components' (e.g. exercise advice,

educational flyers) are delivered to patients with COPD; therefore, classification would be too ambiguous, depending largely on what is reported. Hence, this review does not include different control groups as a subgroup analysis.

Sensitivity analysis

We performed sensitivity analyses on the basis of the methodological quality of studies. We did so by repeating our analysis among only studies judged to be of 'high quality'. For the purposes of this review, 'high-quality studies' were defined as studies with low or unclear risk of bias due to allocation concealment, low or unclear risk of bias due to incomplete outcome data, and, in the case of cluster-RCTs, studies with adequate analysis methods.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of this review in a 'Summary of findings' table, which includes an overall rating of the evidence using the GRADE approach, in accordance with recommendations laid out in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). This involves making separate ratings for quality of evidence for each patient-important outcome by identifying five factors that can lower the quality of evidence, including study limitations, indirectness of evidence (also called clinical heterogeneity with regard to study population, intervention, control group, and outcomes), unexplained heterogeneity or inconsistency of results (i.e. statistical heterogeneity), imprecision of results (i.e. due to small sample sizes and few events), and high probability of publication bias. However, other factors can increase the quality of evidence; these include large magnitude of effect; plausible confounding, which could reduce the demonstrated effect; and the dose-response gradient (GRADE Working Group 2004). We have presented footnotes to justify decisions made and have provided comments to support readers' understanding of this review.

We intended to present short-, medium-, and long-term outcomes for all of our primary outcomes in the 'Summary of findings' table. However, because we were limited to a maximum of seven outcomes, we decided to present dichotomous outcomes for all time points and continuous outcomes for medium-term follow-up only, being most clinically relevant. For all outcomes, we presented the range and the median follow-up.

Results

Description of studies

See Characteristics of included studies.

Results of the search

Our literature search yielded 6900 citations after duplicates were removed with potential for inclusion (see Figure 1). We excluded 6543 citations during the initial screening of titles and abstracts and assessed full texts of 357 citations. Eleven

studies were ongoing at the time of this review (Ali 2020; Bourne 2017; Ding 2019; Drennan 2014; Foot 2017; Hajizadeh 2020a; Hansen 2017; NCT04136418; NCT04416295; NCT04533412; Steed 2017). One study had finished data collection, but as the results were not yet published, study authors wished to withhold results until after publication (Bourne 2017). A further seven provided insufficient detail to allow a decision on eligibility. We were unable to establish contact with the study authors, so some studies are still awaiting classification (Baumann 2012; Borji, 2018; Carcereny, 2016; Mao 2020; NCT04256070; Reguera 2017; Xu 2010). Thus, 26 new studies (57 citations) were added to this review, in addition to the 26 studies already included in the previous version of the review.

Figure 1. Study flow diagram

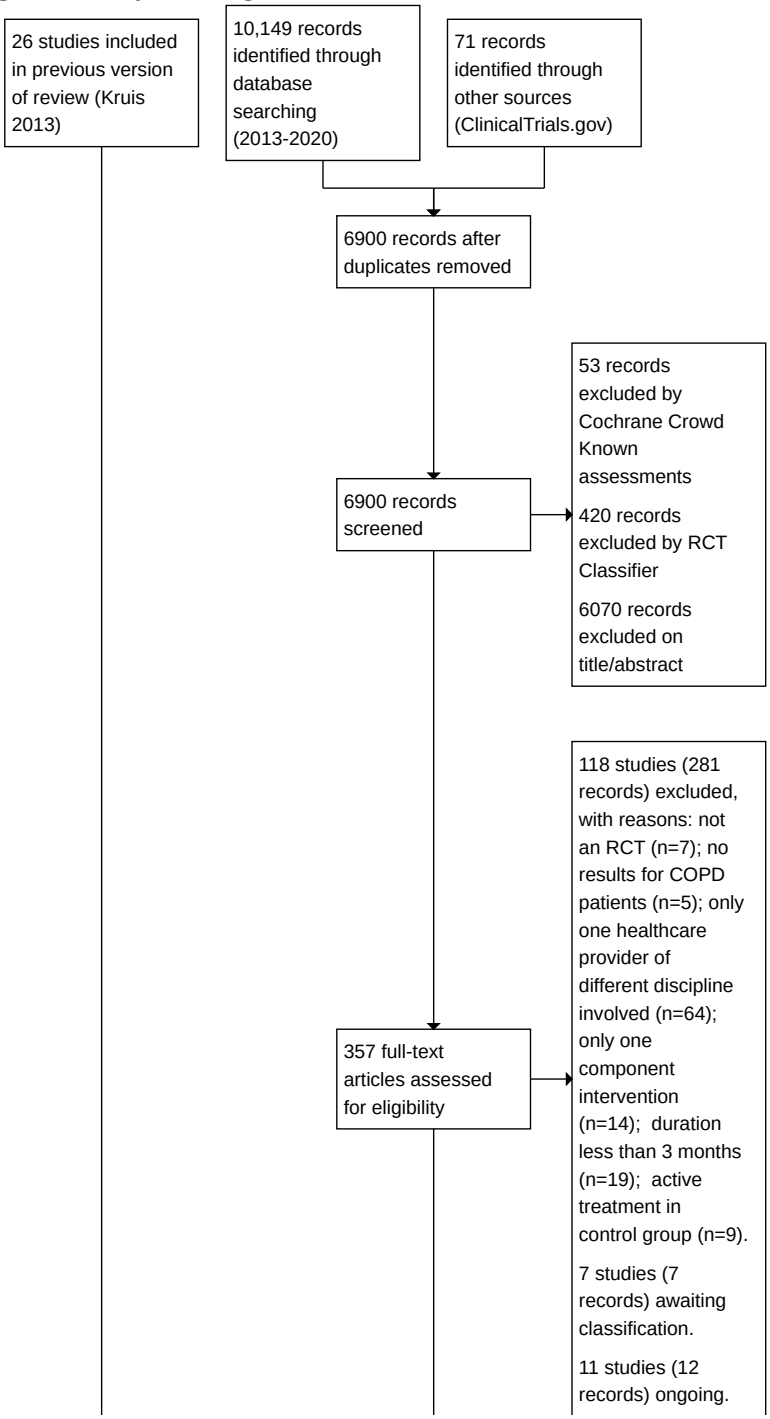
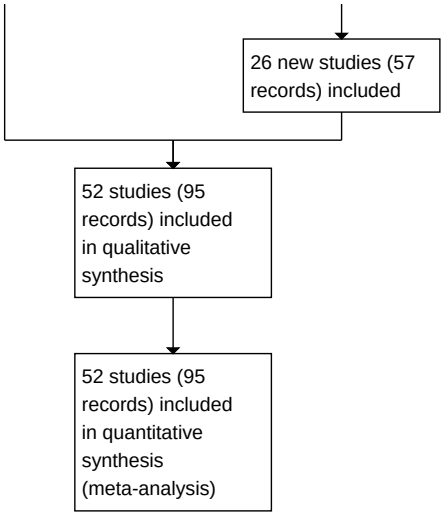


Figure 1. Study diagram (continued)



Included studies

We included the 26 RCTs from the 2013 version of the Cochrane Review (Kruis 2013). A total of 52 studies (represented by 95 citations) contributed to the current meta-analysis, including 26 new studies (Aboumatar 2019; Bernocchi 2017; Fan 2012; Freund 2016; Haesum 2012; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Kennedy 2013; Kessler 2018; Khan 2019; Ko 2016; Kruis 2014; Lenferink 2019; Lilholt 2017; Lou 2015; Öztürk 2020; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Tabak 2014; Titova 2017; Vasilopoulou 2017; Vianello 2016; Wang 2017; Zhang 2020; Zwar 2016). The newly included studies were published between 2014 and 2020 and originated from across the globe. Four studies originated from China (Ko 2016; Lou 2015; Wang 2017; Zhang 2020), three from the USA (Aboumatar 2019; Fan 2012; Silver 2017), and one from Canada (Rose 2017). A total of nine studies were performed in Northwestern Europe - three in the Netherlands (Kruis 2014; Lenferink 2019; Tabak 2014), two in Denmark (Haesum 2012; Lilholt 2017), and one each in Germany (Freund 2016), the UK (Kennedy 2013), and Norway (Titova 2017). Kessler 2018 was a multi-national multi-centre study performed in Germany, France, Italy, and Spain. Five studies were performed in Southern Europe - Italy (Bernocchi 2017; Vianello 2016), Spain (Jimenez-Reguera 2020; Sanchez-Nieto 2016), and Greece (Vasilopoulou 2017). Three studies were performed in Western Asia - one in Israel (Kalter-Leibovici 2018), one in Pakistan (Khan 2019), and one in the Asian part of Turkey (Öztürk 2020). One study originated from Australia (Zwar 2016).

Of the 52 studies that met eligibility criteria, nine used a cluster-RCT design, with general practices or healthcare regions as the unit of randomisation (Freund 2016; Kennedy 2013; Khan 2019; Kruis 2014; Lilholt 2017; Lou 2015; Rea 2004; Wood-Baker

2006; Zwar 2016). All but two trials randomly assigned participants to either IDM or usual care. The other two trials had two different intervention groups and one usual care group (Vasilopoulou 2017; Wijkstra 1994). We included both intervention groups as separate comparisons and split the usual care group in half.

A description of the included studies is provided in Table 1, Table 2 , and Characteristics of included studies.

Participants

A total of 21,086 COPD patients were randomised in the 52 studies, with a range of 29 to 8171 patients per study. Of these, 16,390 (84%) patients completed the studies (range 23% to 100%). At the moment of inclusion, the mean age of the intervention population was 67.1 years (SD 9.27), with 65% male (range 25% to 99%). In the usual care group, mean age was 67.2 years (SD 9.26) and 67% (range 30 to 100%) were male.

Interventions

Patients were treated in all types of healthcare settings: primary care (15 studies), secondary care (22 studies), tertiary care (5 studies), and a combination of primary and secondary health care (10 studies). The numbers of healthcare professionals involved ranged from 2 to 7, with a mean number of 3. The number of components per programme ranged from 2 to 8, with a mean number of 4. Interventions also varied in terms of duration - between 3 and 48 months- with varying intensity of separate intervention components. Some interventions consisted of a clearly defined intensive intervention period and a subsequent maintenance or structural follow-up period (Bourbeau 2003; Fan 2012; Gottlieb 2011; Güell 2000; Jimenez-Reguera 2020; Ko 2016; Sridhar 2008; van Wetering 2010; Vasilopoulou 2017). One study had an intervention with a variable duration of 2 years minimum and 5 years maximum (Kalter-Leibovici 2018).

Following the subgroup analysis performed in the previous version of this review, we determined the dominant component of the IDM programme from all newly included studies. The dominant component could be determined directly from the objective or title of the study for eight studies (Aboumatar 2019; Bernocchi 2017; Fan 2012; Haesum 2012; Kruis 2014; Öztürk 2020; Vasilopoulou 2017; Zwar 2016). For the remaining 18 studies, we contacted study authors to ask what they considered the dominant intervention component. Eleven study authors did not provide a response. Of the seven who responded, three indicated that the intervention did not have a dominant component. To perform a subgroup analysis on types of interventions, we chose the dominant component as the component with the greatest intensity in terms of duration. Given the increased use of telemonitoring and its distinguished features to monitor patients from a distance, we decided to include telemonitoring as a separate dominant component. In Vasilopoulou 2017, usual care was compared to two types of interventions: home-based and hospital-based pulmonary rehabilitation. As interventions were characterised by different dominant

components (telemonitoring and structural follow-up, respectively), we included both as separate interventions

Including the dominant components identified by Kruis 2013, we arrived at the following categories of dominant components of IDM programmes:

1. Exercise (13 studies: Bendstrup 1997; Boxall 2005; Cambach 1997; Engstrom 1999; Fernandez 2009; Gottlieb 2011; Güell 2000; Güell 2006; Mendes 2010; Strijbos 1996; Theander 2009; van Wetering 2010; Wijkstra 1994).
2. Self-management with an exacerbation action plan (12 studies: Aboumatar 2019; Bourbeau 2003; Jimenez-Reguera 2020; Kennedy 2013; Koff 2009; Kruis 2014; Lenferink 2019; Öztürk 2020; Rice 2010; Sanchez-Nieto 2016; Trappenburg 2011; Wood-Baker 2006).
3. Structured follow-up with healthcare professionals, including case management (15 studies: Aiken 2006; Dheda 2004; Farrero 2001; Freund 2016; Kalter-Leibovici 2018; Kessler 2018; Khan 2019; Ko 2016; Lilholt 2017; Littlejohns 1991; Rose 2017; Smith 1999; Titova 2017; Vasilopoulou 2017; Zhang 2020).
4. Individualised educational sessions (5 studies: Fan 2012; Lou 2015; Silver 2017; Wakabayashi 2011; Zwar 2016).
5. Telemonitoring (6 studies: Bernocchi 2017; Haesum 2012; Tabak 2014; Vasilopoulou 2017; Vianello 2016; Wang 2017).

In addition, Kruis 2013 identified two studies that each had two dominant components. Sridhar 2008 included two components on which most of the intervention time was spent (i.e. exercise and self-management with action plan). Rea 2004 included two dominant components: self-management with action plan and structured follow-up. Therefore we included these two studies in separate categories, namely, exercise and self-management and self-management and structural follow-up.

Outcomes

We combined the outcomes of 26 recently included studies with the 26 already included studies. We recorded the number of studies reporting a specific outcome as follows.

1. Quality of life (46 studies).
2. Exercise capacity (28 studies).
3. Exacerbation-related outcomes: measured by numbers of exacerbations, hospital admissions, hospitalisation days, emergency department (ED) visits, prednisolone or antibiotics courses (32 studies).
4. Lung function (21 studies).
5. Survival, mortality (15 studies).

6. Depression (10 studies).
7. Dyspnoea (13 studies).
8. Process-related outcomes (14 studies).

Details of the included studies and outcomes are provided in Characteristics of included studies, Table 3, Table 4, Table 5, and Table 6.

We requested additional data from 21 study authors; 14 (67%) responded. Nine studies provided additional data that we used in the analysis (Bernocchi 2017; Kalter-Leibovici 2018; Kennedy 2013; Kessler 2018; Khan 2019; Lenferink 2019; Titova 2017; Vasilopoulou 2017; Wang 2017) . Seven studies provided sufficient data for calculation of correlation coefficients used to impute missing data (Aboumatar 2019; Engstrom 1999; Fan 2012; Kalter-Leibovici 2018; Lilholt 2017; Sridhar 2008; Vasilopoulou 2017) (see Dealing with missing data).

Excluded studies

We excluded 118 full-text articles from the current update during the full-text screening process. The Characteristics of excluded studies table provides full details on reasons for exclusion.

Risk of bias in included studies

Results of the risk of bias assessment are presented in Figure 2. All but one of the included studies were judged to be at high risk of bias for blinding of participants, which is a result of the nature of the intervention. With regard to the other domains, the likelihood that bias was present (high risk of bias) varied across studies, from 4% for random sequence generation (selection bias) to 27% for blinding of outcome assessment (detection bias).

Allocation

We judged 43 included studies as having low risk of bias in sequence generation (Aboumatar 2019; Aiken 2006; Bernocchi 2017; Bourbeau 2003; Boxall 2005; Cambach 1997; Fan 2012; Fernandez 2009; Freund 2016; Gottlieb 2011; Haesum 2012; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Kennedy 2013; Kessler 2018; Khan 2019; Ko 2016; Koff 2009; Kruis 2014; Lenferink 2019; Lilholt 2017; Littlejohns 1991; Mendes 2010; Öztürk 2020; Rea 2004; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Smith 1999; Sridhar 2008; Tabak 2014; Theander 2009; Trappenburg 2011; van Wetering 2010; Vasilopoulou 2017; Vianello 2016; Wakabayashi 2011; Wang 2017; Wijkstra 1994; Wood-Baker 2006; Zhang 2020; Zwar 2016). Information from eight studies was insufficient to permit a decision (Bendstrup 1997; Dheda 2004; Engstrom 1999; Farrero 2001; Güell 2000; Güell 2006; Lou 2015; Strijbos 1996). One study was judged to have high risk of bias, as participants were randomised based on district (Titova 2017). With regard to allocation bias, we judged 27 studies as having low risk of bias and five studies as having high risk of bias. For the remaining 20 studies, provided information was insufficient to permit a firm conclusion (unclear risk of bias).

Blinding

The nature of the intervention makes blinding of participants and healthcare providers delivering the intervention impossible. Hence, we judged all studies, except Trappenburg 2011 , which kept patients unaware of the primary study aim (postponed information), as having high risk of performance bias. Although blinding of patients and/or healthcare providers is impossible, outcome assessors in some cases could be blinded to participants' allocation. Twenty-five studies were judged as having low risk. These studies had outcome assessors that were adequately blinded for allocation, reported only on outcomes that were objective (i.e. mortality, hospitalisations), or had an outcome committee judging the outcomes. This made risk of detection bias highly unlikely. Outcome assessors were unblinded in 15 studies (Boxall 2005; Cambach 1997; Farrero 2001; Kalter-Leibovici 2018; Khan 2019; Koff 2009; Lenferink 2019; Lilholt 2017; Öztürk 2020; Rea 2004; Smith 1999; Tabak 2014; Theander 2009; Titova 2017; Vianello 2016), posing a high risk of bias. Twelve studies provided insufficient information and were judged as having unclear risk (Bendstrup 1997; Dheda 2004; Fernandez 2009; Gottlieb 2011; Kennedy 2013; Littlejohns 1991; Lou 2015; Mendes 2010; Sridhar 2008; Strijbos 1996; Wijkstra 1994; Wood-Baker 2006). For the remaining 25 studies, outcome assessors were blinded to group allocation.

Incomplete outcome data

We judged 35 studies as having low risk of bias, as they had low dropout rates, or dropout rates were balanced across groups for similar reasons. We considered 13 studies to have high risk of bias (Bendstrup 1997; Bernocchi 2017; Cambach 1997; Farrero 2001; Gottlieb 2011; Kessler 2018; Lilholt 2017; Lou 2015; Mendes 2010; Smith 1999; Tabak 2014; Vianello 2016; Wang 2017). Four of these 13 studies had larger dropout in the control group than in the intervention group. In Lou 2015, 1217 participants dropped out from the control group compared to 779 from the intervention group. Reasons were death and inability to perform the walking test. In Bernocchi 2017 , larger dropout rates in the control group were due to increased hospitalisations as a result of heart failure.

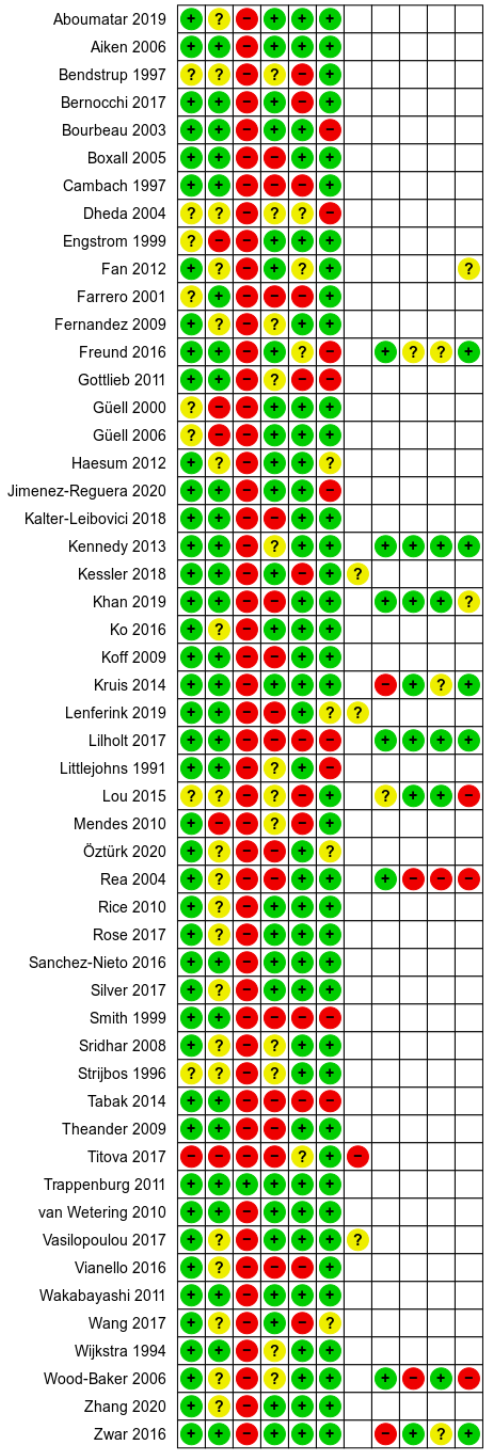
Selective reporting

We judged 39 studies to have low risk of reporting bias, meaning that all outcomes mentioned in the protocol or the clinical trial register were reported. Nine studies selectively reported outcomes specified in the protocol and/or in the methods section (Bourbeau 2003; Dheda 2004; Freund 2016; Gottlieb 2011; Jimenez-Reguera 2020; Lilholt 2017; Littlejohns 1991; Smith 1999; Tabak 2014), or they changed operationalisation of the outcome (i.e. Physical Component Summary (PCS) subscore instead of SF-36 score to measure QoL) (Lilholt 2017). In three studies (Bourbeau 2003; Dheda 2004; Öztürk 2020), the authors observed no statistically significant differences in outcomes and therefore did not present data. In Tabak 2014, outcomes were reported for only 3 months - not for 6 and 9 months - in contrast to the study protocol. This all points to the risk of selective outcome reporting. With the

exception of one outcome (hospital admission (in days)), funnel plots did not indicate that publication bias is likely. Observed asymmetry of the funnel plot for hospital admission is probably caused by the poor methodological quality of Farrero 2001 .

Other potential sources of bias

We included nine cluster-randomised trials, three of which introduced bias (Lou 2015; Rea 2004; Wood-Baker 2006). In Wood-Baker 2006, there was noticeable imbalance in differences between groups at baseline. Wood-Baker 2006 and Lou 2015 did not account for clustering in statistical analyses of dichotomous outcomes. This may lead to over-precise results and can result in much more weight in a meta-analysis (Higgins 2011). Therefore, in our meta-analyses, we adjusted for the design effect by reducing the size of the trial to its "effective sample size" for all dichotomous outcomes (Rao 1992), and we used the adjusted MD via the GIV approach for all continuous outcomes. In Rea 2004, there was loss to follow-up of five clusters (four control and one intervention cluster). Other potential sources of bias were found in Titova 2017 Kessler 2018 Lenferink 2019 Vasilopoulou 2017 Vianello 2016, and Lou 2015. Lou 2015 was performed across four geographically distinct regions and based randomisation on geographical location, thereby potentially introducing cluster effects.



Legend

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias): all outcomes
4. Blinding of outcome assessment (detection bias): all outcomes
5. Incomplete outcome data (attrition bias): all outcomes
6. Selective reporting (reporting bias)
7. Other bias
8. Recruitment bias
9. Baseline imbalance between groups
10. Loss to follow-up clusters
11. Adequate analysis methods for cluster RCT

Figure 2. 'Risk of bias' summary: review author's judgement about each risk of bias for each individual study.

Effects of interventions

Primary outcomes

1. Quality of life

Of the 52 studies included, 46 studies measured quality of life, that is, health-related quality of life (34 studies), generic quality of life (four studies), or both (eight studies). In total, 11 different instruments were used (see Table 3).

Health-related quality of life

1. St. George's Respiratory Questionnaire (SGRQ) (25 studies)
2. Chronic Respiratory Questionnaire (CRQ) (nine studies)
3. Clinical COPD Questionnaire (CCQ) (three studies)
4. COPD Assessment test (CAT) (six studies)
5. Body mass index (BMI), airflow obstruction, dyspnoea, and exercise capacity index (BODE) (six studies)
6. Barthel score (one study)
7. Dartmouth Primary Care Co-operative Quality of Life Questionnaire (COOP) (one study)

Generic quality of life

1. Short Form-36 (SF-36) or Short Form-12 (SF-12) (eight studies)
2. EQ-5D (four studies)
3. Sickness Impact Profile (SIP) (two studies)
4. York Quality of Life Questionnaire (YGLQ) (one study)

We performed a meta-analysis combining the results of some or all of these questionnaires. The SGRQ and the CRQ are respiratory-specific quality of life questionnaires and have become the recognised standards of HRQoL assessment amongst patients with COPD. However, pooling of these instruments into a meta-analysis was impossible, as the CRQ is more responsive than the SGRQ (Puhan 2006). Furthermore, the included generic quality of life questionnaires (SF-36, SIP, and COOP) measure other dimensions of generic quality of life; therefore combining these data in a meta-analysis across tools is not recommended.

1.1. SGRQ total score (medium-term)

Eighteen studies with a total population of 4321 participants provided data on the SGRQ total score with follow-up between 6 and 15 months (Bourbeau 2003; Boxall 2005; Engstrom 1999; Fan 2012; Fernandez 2009; Gottlieb 2011; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Ko 2016; Kruis 2014; Rice 2010; Rose 2017; Titova 2017; Vasilopoulou 2017; Wakabayashi 2011; Wang 2017; Wood-Baker 2006; Zwar 2016). Kessler 2018 used a COPD-specific SGRQ, which could not be pooled. The pooled MD

in SGRQ total score (MD -3.89, 95% CI -6.16 to -1.63) favoured IDM (Analysis 1.2; Figure 3). In other words, those treated with IDM reported 3.89 out of 100 points for improved quality of life. Pooling did indicate considerable heterogeneity (I^2 = 83%). Sensitivity analysis performed on high-quality studies still showed a statistically significant effect in favour of IDM (MD -3.95, 95% CI -6.06 to -1.84). This effect was even more pronounced, indicating the robustness of our results. Sensitivity analysis of high-quality studies only did not change the level of heterogeneity (I^2 = 79%). Pre-defined and post-hoc subgroup analyses were performed to investigate heterogeneity (see below).

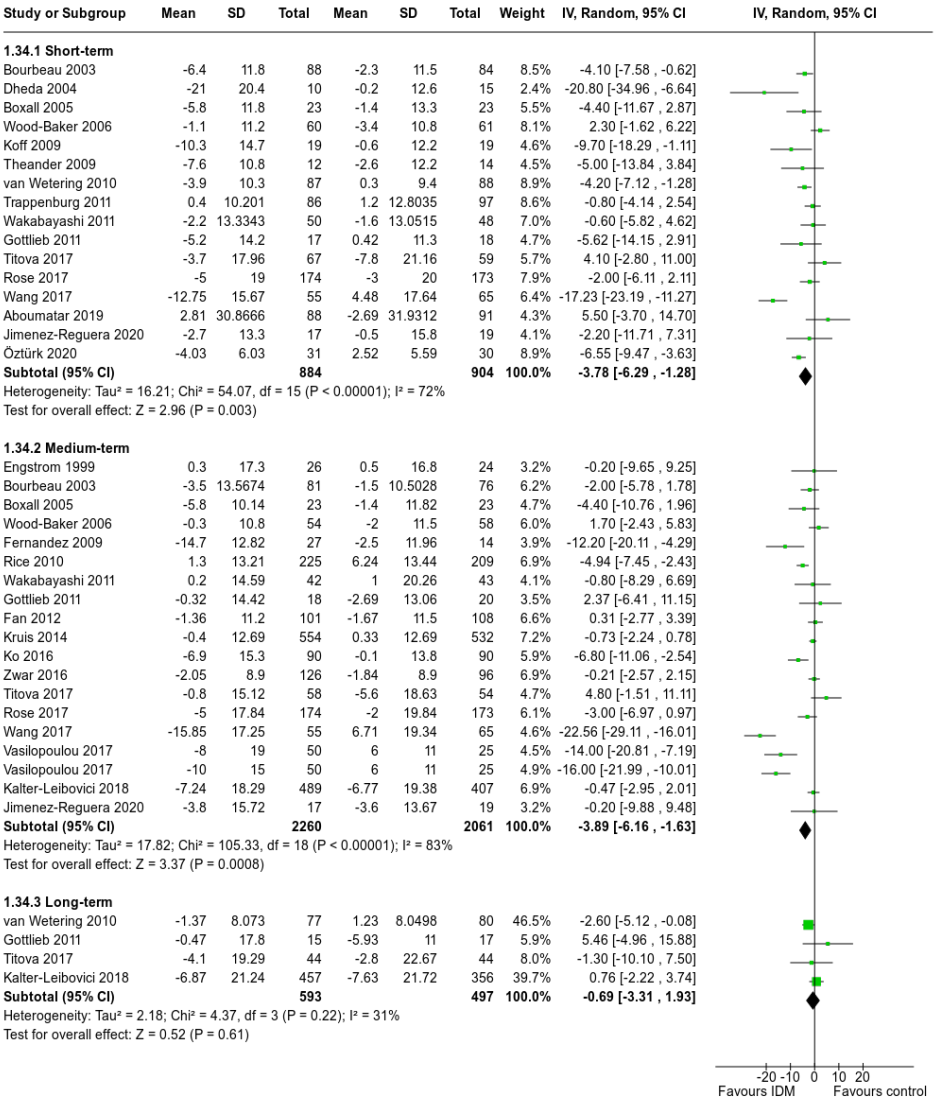


Figure 3. Forest plot of comparison: 1 integrated disease management versus control, update, outcome: 1.34 SGRQ total score.

1.1.1. Subgroup analysis based on setting

Six studies reporting on SGRQ total score were performed in primary care (Boxall 2005; Fernandez 2009; Gottlieb 2011; Kruis 2014; Wood-Baker 2006; Zwar 2016), nine studies in secondary care (Bourbeau 2003; Engstrom 1999; Fan 2012; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Rice 2010; Rose 2017; Titova 2017; Wakabayashi 2011), and three studies in tertiary care (Ko 2016; Vasilopoulou 2017; Wang 2017). A test for subgroup differences showed a statistically significant difference between subgroups (P = 0.001). Studies performed in primary and secondary care showed no statistically significant differences between IDM and control, and pooling of tertiary care studies showed a clinically and statistically significant improvement in favour of IDM (MD -14.58, 95% CI -21.56 to -7.61; Analysis 1.4). However, pooling indicated considerable heterogeneity for all three subgroups. Hence, results of the subgroup analysis should be interpreted with caution.

1.1.2. Subgroup analysis based on study design

We performed subgroup analysis based on study design and compared RCTs (total 2865 participants) with cluster-RCTs (total 1420 participants) (Analysis 1.5). Tests for differences showed a statistically significant difference between both groups. Heterogeneity within the RCT remained considerable (I^2 = 83%).

1.1.3. Subgroup analysis based on dominant component of the programme

Two studies (total 294 participants) included individualised education as the dominant component (Fan 2012; Wakabayashi 2011), five studies (total 1825 participants) included self-management as the dominant component (Bourbeau 2003; Jimenez-Reguera 2020; Kruis 2014; Rice 2010; Wood-Baker 2006), four studies (total 175 participants) included exercise as the dominant component (Boxall 2005; Engstrom 1999; Fernandez 2009; Gottlieb 2011), and five studies (total 1610 participants) included structural follow-up as dominant component (Kalter- Leibovici 2018; Ko 2016; Rose 2017; Titova 2017; Vasilopoulou 2017). Post hoc, we identified telemonitoring as an important dominant component in two studies (Vasilopoulou 2017; Wang 2017). Tests for subgroup differences showed a statistically significant result (Chi^2 = 17.89, df = 4, P = 0.001) indicating differences in effect between subgroups based on the dominant component. A statistically significant difference was found only in the group with telemonitoring as the dominant component (MD -18.33, 95% CI -26.72 to -9.94) (Analysis 1.6). However, the subgroup included only two studies. Also, heterogeneity remained moderate within subgroups. Hence, results should be interpreted with caution.

1.1.4. Subgroup analysis based on region of study

Four studies (total 1147 participants) were performed in North America (Bourbeau 2003; Fan 2012; Rice 2010; Rose 2017), four in Northwestern Europe (total 1286 participants) (Engstrom 1999; Gottlieb 2011; Kruis 2014; Titova 2017), three in Southern Europe (total 227 participants) (Fernandez 2009; Jimenez-Reguera 2020; Vasilopoulou 2017), three in Oceania (total 380 participants) (Boxall 2005; Wood-Baker 2006; Zwar 2016), three in East Asia (total 385 participants) (Ko 2016; Wakabayashi 2011; Wang

2017), and one in Western Asia (total 896 participants) (Wakabayashi 2011). Tests for subgroup differences showed a statistically significant difference in effect between groups ($Chi^2 = 16.88$, df = 5, P = 0.005) (Analysis 1.7). Closer inspection of the subgroups showed no differences between IDM and control for the Northwest Europe and Oceania subgroups. Heterogeneity remained substantial in the North America subgroup (I^2 = 56%) and the Southern Europe subgroup (I^2 = 61%) and were considerable in the East Asia subgroup (I^2 = 91%). Results for these subgroups should therefore be interpreted with caution.

1.2. SGRQ total score - long-term

Four studies including 1090 participants measured the long-term effect on SGRQ total score at 18 months (Gottlieb 2011), or at 24 months (Kalter-Leibovici 2018; Titova 2017; van Wetering 2010). No statistically significant difference was noted between IDM and usual care (MD -0.69, 95% CI -3.31 to 1.93; I^2 = 31%) (Analysis 1.3; Figure 3).

1.3. SGRQ domain scores - short-term

Eleven studies with a total population of 1320 to 1327 participants reported scores on the SGRQ domains of symptoms, activity, and impact. For all domains, heterogeneity was substantial (I^2 between 46% and 71%) (Analysis 1.1). We found the following results: symptoms domain (MD -1.56, 95% CI -6.66 to 2.53), activity domain (MD -3.04, 95% CI -5.80 to -0.28), and impact domain (MD -3.76, 95% CI -5.94 to -1.57). Sensitivity analysis with only high-quality studies showed a statistically significant effect in favour of IDM for the activity domain (MD -3.63, 95% CI -5.66 to -1.61; I^2 = 0%) and for the impact domain (MD -4.1, 95% CI -6.30 to -1.90; I^2 = 31%) of the SGRQ. There was no significant effect on the SGRQ symptoms domain (MD -1.94, 95% CI -5.26 to 1.38; I^2 = 41%). A portion of the heterogeneity could be explained by the difference in quality of studies, as heterogeneity decreased significantly across all domains when only high-quality studies were pooled (Table 7).

1.4. SGRQ domain scores - medium-term

Twelve studies with a total population of 2608 to 2628 participants reported scores on the SGRQ domains after 6 to 15 months' follow-up. We found the following results: symptoms domain: MD -3.88, 95% CI -7.75 to -0.02; I^2 = 79%; activity domain: MD -2.57, 95% CI -5.53 to 0.38; I^2 = 71%; and impact domain: MD -3.34, 95% CI -6.26 to -0.41; I^2 = 0%.

Sensitivity analysis did not explain the heterogeneity observed (I^2 between 71% and 79%) but did show a statistically significant effect in favour of IDM. Effects were statistically significant for all domains (Analysis 1.2; Table 7).

1.5. SGRQ domain scores - long-term

Three studies measured the long-term effect on SGRQ domains at 18 months (Gottlieb 2011), or at 24 months (Titova 2017; van Wetering 2010). As with the SGRQ total score,

pooled effects did not show a statistically significant long-term difference between both groups (Analysis 1.3).

1.6. CRQ domain scores - short-term

The Chronic Respiratory Disease Questionnaire (CRQ), with a scale from 0 to 7 and MCID of 0.5, was reported in nine studies (Bendstrup 1997; Cambach 1997; Farrero 2001; Güell 2000; Güell 2006; Lenferink 2019; Rea 2004; Sridhar 2008; Wijkstra 1994). Farrero 2001 administered the CRQ only to the first 40 consecutive patients, and therefore outcomes were not published. Bendstrup 1997 and Rea 2004 reported insufficient data to compute an estimation of effect and therefore were not included in the meta-analysis. Wijkstra 1994 did not report on the dyspnoea dimension of the CRQ and compared two IDM interventions with usual care. We included both study arms in the meta-analysis. Pooled results for the CRQ up to 6 months included 277 participants for the CRQ Dyspnea dimension and 314 for the other domains. There was no statistically significant difference between IDM and control for any dimension (Analysis 1.8). Heterogeneity was substantial for all dimensions (I^2 between 72% and 86%). Sensitivity analysis for CRQ Dyspnoea was not performed, as this would include only one high-quality study. Sensitivity analysis for the other CRQ dimensions did not change the results but smaller heterogeneity was observed (I^2 between 0% and 35%). Thus, heterogeneity could be explained in part by the quality of the studies (see Table 7).

1.7. CRQ domain scores - medium-term

Three of the four studies that reported CRQ up to 6 months also reported CRQ outcomes after 6 months (Güell 2000; Lenferink 2019; Wijkstra 1994). Pooled results, including 2 studies and 219 participants for the CRQ dyspnoea dimension, showed no statistically significant differences between IDM and control groups (MD 0.29, 95% CI -0.88 to 1.46). There also were no statistically significant differences between groups for the CRQ fatigue domain (MD 0.37, 95% CI -0.53 to 1.26), the CRQ emotion domain (MD 0.36, 95% CI -0.84 to 1.57), and the CRQ mastery domain (MD 0.76, 95% CI -0.41 to 1.94) (Analysis 1.9).

1.8. CRQ domain scores - long-term

Three studies reported on long-term effects on the CRQ at 24 months' follow-up, with a total of 184 participants (Güell 2000; Sridhar 2008; Wijkstra 1994) (Analysis 1.10). Pooled data showed no differences between groups on the CRQ dyspnoea domain (MD 0.47, 95% CI -0.31 to 1.25). In contrast, pooled data on the CRQ fatigue domain showed a statistically significant difference in favour of IDM (MD 0.46, 95% CI 0.06 to 0.85). Also, a significant difference in favour of IDM was observed for CRQ emotion (MD 0.53, 95% CI 0.10 to 0.95) and CRQ mastery (MD 0.83, 95% CI 0.41 to 1.26). With an MCID of 0.5, the differences were also clinically significant. Sensitivity analysis revealed that when Güell 2000 was excluded due to inadequate concealment of allocation, pooled differences on CRQ fatigue, emotion, and mastery remained in favour of IDM; however CRQ fatigue was not statistically significant (MD 0.42, 95% CI -0.05 to 0.89) (Table 7).

1.9. General health-related QoL

General HRQoL was measured with the SF-36 in six studies (Aiken 2006; Kruis 2014; Lilholt 2017; Öztürk 2020; Rea 2004; Vianello 2016), or with the shorter SF-12 in two studies (Fan 2012; Kalter-Leibovici 2018). Aiken 2006 did not provide us with sufficient information and did not respond to our emails. Rea 2004 and Öztürk 2020 reported only on the separate dimensions of the SF-36 and therefore could not be used for pooling. For the remaining studies, we pooled composite scores from the SF-36 and the SF-12. Hence, we pooled the data from studies for the Mental Component Summary (MCS) score with a total population of 3699 participants and of the Physical Component Summary (PCS) score with a total population of 3704 participants. Pooled MD on the MSC score showed no significant differences between both groups (MD 0.36, 95% CI -0.38 to 1.11; I^2 = 0%). Also no significant differences were observed on the PCS score (MD 1.06, 95% CI -0.67 to 2.79; I^2 = 84%). Substantial heterogeneity observed for the PCS score was due in part to differences in the quality of the studies. Sensitivity analysis excluding Vianello 2016 and Lilholt 2017 showed similar non-significant effects (see Table 7). Two studies measured QoL with the Sickness Impact Profile (SIP) (Engstrom 1999; Littlejohns 1991) (Analysis 1.12). No between-group differences were found in any domain of the SIP.

2. Exercise capacity

Twenty-eight studies measured functional or maximum exercise capacity. Functional exercise capacity was measured through the 6MWD (26 studies) or the shuttle test (one study). Maximal exercise capacity was measured using the cycle ergometer test expressed as W-max (five studies), leg fatigue score (one study), and grip strength (one study). The MCID on the 6MWD is estimated at 35 meters (Puhan 2008). No MCID for the cycle ergometer test is reported in the current literature. Results are shown in Figure 4 .

2.1 Functional exercise capacity - short-term

We pooled data from 17 studies using the 6MWD including 1390 participants (Bendstrup 1997; Bernocchi 2017; Boxall 2005; Cambach 1997; Gottlieb 2011; Güell 2000; Güell 2006; Jimenez-Reguera 2020; Khan 2019; Mendes 2010; Tabak 2014; Theander 2009; van Wetering 2010; Wakabayashi 2011; Wang 2017; Wijkstra 1994; Zhang 2020). One study could not be pooled, as study authors reported no data because there was no significant difference between groups at 12 months' follow-up (Bourbeau 2003). The pooled MD on the 6MWD outcome was 52.56 in favour of IDM (95% CI 32.39 to 72.74) and exceeded the MCID of 35. In other words, patients treated in an IDM programme were able to walk 52 meters more, on average, than those who received usual care. Pooling did indicate considerable heterogeneity (I^2 = 90%). Sensitivity analysis performed on high-quality studies showed a smaller but still statistically and clinically significant effect in favour of IDM (MD 41.00, 95% CI 4.40 to 77.60, I^2 = 92%).

2.2 Functional exercise capacity - medium-term

Thirteen studies with a total population of 2071 participants provided data on the 6MWD after a medium-term follow-up period (between 6 and 15 months) (Engstrom 1999; Fernandez 2009; Gottlieb 2011; Güell 2000; Jimenez- Reguera 2020; Kalter-Leibovici 2018; Kessler 2018; Ko 2016; Littlejohns 1991; Vasilopoulou 2017; Wakabayashi 2011; Wang 2017; Zhang 2020). Pooled MD showed a statistically and clinically significant effect of 44.69 in favour of IDM. The observed effect was statistically significant (95% CI 24.01. to 65.37) and exceeded the MCID of 35 meters. Sensitivity analysis showed that our results were robust (MD 40.49, 95% CI 9.71 to 71.27). However, heterogeneity remained substantial (I^2 = 92%). The heterogeneity among high-quality studies and the large confidence interval for the pooled results of all studies indicate there may be substantial methodological or clinical differences between studies. Pre-defined and post-hoc subgroup analyses were performed to further investigate the existing heterogeneity (see below).

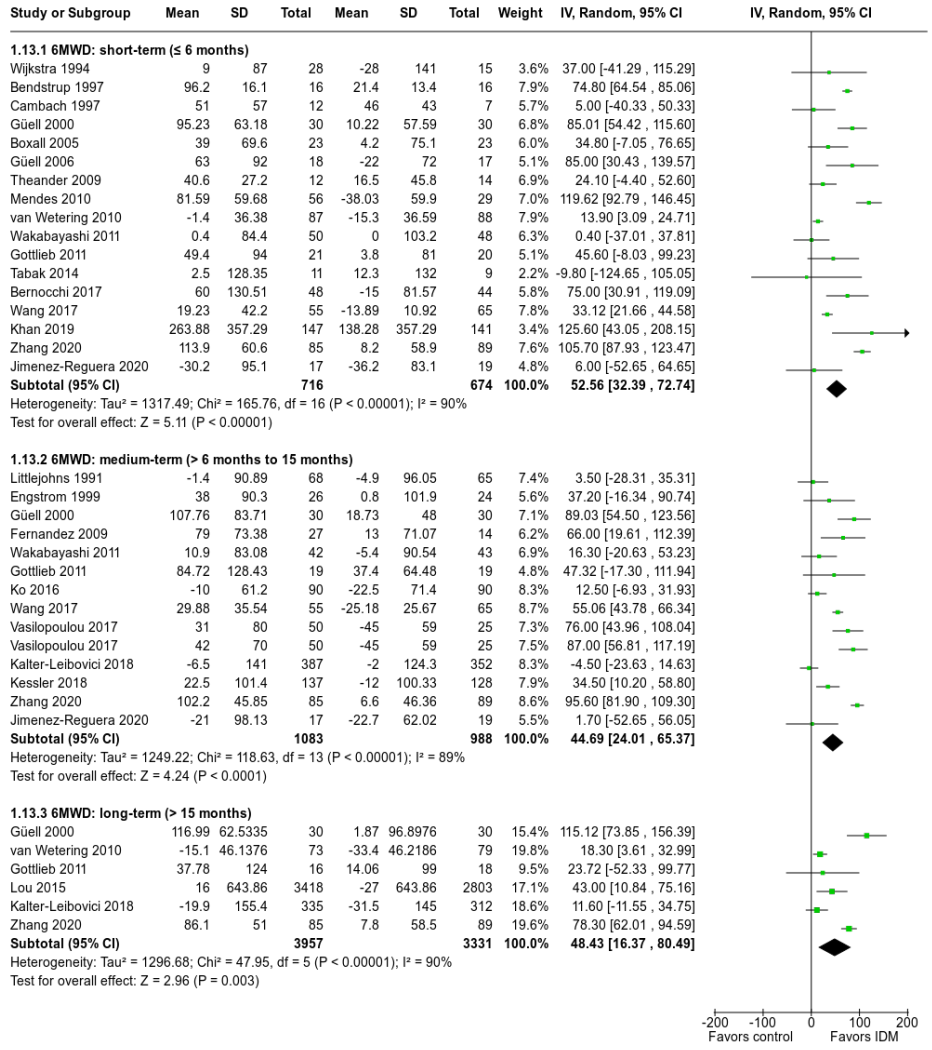


Figure 4. Forest plot of comparison: 1 integrated disease management versus control, update, outcome: 1.13 Functional exercise capacity: 6MWD.

2.2.1 Subgroup analysis based on type of setting

Of the studies reporting 6MWD at 12 months, two were conducted in primary care (Fernandez 2009; Gottlieb 2011), seven in secondary care (Engstrom 1999; Güell 2000; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Kessler 2018; Littlejohns 1991; Wakabayashi 2011), and four in tertiary care (Ko 2016; Vasilopoulou 2017; Wang 2017; Zhang 2020). Tests for subgroup differences showed no difference in effect based on setting ($Chi^2 = 4.49$, df = 2, P = 0.11). However, heterogeneity remained considerable for the secondary care subgroup ($I^2 = 80\%$) and for the tertiary care subgroup ($I^2 = 87\%$).

Therefore, results for these groups should be interpreted carefully (Analysis 1.14).

2.2.2 Subgroup analysis based on dominant component of intervention

Four studies (102 participants) reporting on the 6MWD had some kind of exercise training as their dominant component (Engstrom 1999; Fernandez 2009; Gottlieb 2011; Güell 2000). In six studies, structural follow-up was considered the dominant component (Kalter-Leibovici 2018; Kessler 2018; Ko 2016; Littlejohns 1991; Vasilopoulou 2017; Zhang 2020). One study provided individualised education as the dominant component (Wakabayashi 2011), and another study included self-management as the dominant component (Jimenez-Reguera 2020). Therefore, these could not be pooled. A test for subgroup differences showed a statistically significant difference ($Chi^2 = 10.56$, df = 4, P = 0.03; Analysis 1.14).

Subgroup analysis for exercise training as the dominant component showed that the 6MWD improved by 68.21 metres (95% CI 44.75 to 91.68; $I^2 = 3\%$). This effect was almost twice the MCID of 35 metres. Also, studies with telemonitoring as the dominant component showed a large improvement of 59.94 metres (95% CI 42.59 to 77.29; $I^2 = 32\%$). Studies with structural follow-up as the dominant component showed statistically significant differences in favour of IDM (MD 35.14, 95% CI 2.83 to 67.45). However, heterogeneity remained substantial.

2.2.3 Subgroup analysis based on region of study

Three studies reporting on 6MWD with medium-term follow-up were performed in Northwestern Europe (Engstrom 1999; Gottlieb 2011; Littlejohns 1991), five in Southern Europe (Fernandez 2009; Güell 2000; Jimenez-Reguera 2020; Kessler 2018; Vasilopoulou 2017), four in East Asia (Ko 2016; Wakabayashi 2011; Wang 2017; Zwar 2016), and one in Western Asia (Kalter-Leibovici 2018). A test for subgroup differences indicated statistically significant differences in effect between subgroups ($Chi^2 = 19.09$, df = 3, P = 0.00003).

Pooling of studies performed in Northwestern Europe showed no statistically significant difference between IDM and control (MD 18.18, 95% CI -7.87 to 44.24; $I^2 = 4\%$). A statistically significant difference was found for the Southern Europe subgroup (MD of 61.73) and the East Asia subgroup (MD of 42.67). Pooling indicated considerable heterogeneity in the subgroup of studies from Southern Europe ($I^2 = 68\%$) and East Asia ($I^2 = 90\%$); results for these subgroups should therefore be interpreted carefully (Analysis 1.16).

2.3 Functional exercise capacity - long-term

Six studies on 7288 participants published long-term results on the 6MWD (Gottlieb 2011; Güell 2000; Kalter- Leibovici 2018; Lou 2015; van Wetering 2010; Zhang 2020). The MD was 48.83 metres in favour of IDM and was of statistically and clinically significant relevance (95% CI 16.37 to 80.49; $I^2 = 90\%$) (Analysis 1.13). Sensitivity analysis could not explain heterogeneity and showed a smaller non-statistically significant mean difference (MD 36.4; $I^2 = 94\%$; Analysis 1.13) noted by a wide CI (95% CI -6.43.97 to 79.24).

2.4 Maximal exercise capacity

Four studies on 298 participants assessed maximum exercise capacity (in Watts) using the cycle ergometer test (Engstrom 1999; Strijbos 1996; van Wetering 2010; Wijkstra 1994). Pooling showed that IDM statistically significantly improved maximal exercise capacity by 7 Watts (MD 6.99, 95% CI 2.96 to 11.02; Analysis 1.17).

3. Exacerbation-related outcomes

3.1 Respiratory-related admissions

Fifteen studies including a total of 4207 participants reported on the number of patients with at least one respiratory-related admission, which could be COPD-related, exacerbation-related, or of a respiratory nature in general. Pooling showed an effect in favour of the IDM intervention (OR 0.64, 95% CI 0.50 to 0.81). In other words, per 1000 patients, 89 fewer (range 131 fewer to 44 fewer) patients had a respiratory-related (re-) hospitalisation compared to patients given usual care (Analysis 1.18; Figure 5).

Figure 5. In the usual care group, 32 out of 100 people had a respiratory-related hospital admission over a period of 3 to 36 months, compared to 23 (95% CI 19 to 28) out of 100 people in the integrated disease management group.

3.2 Respiratory-related admissions - short-term

We pooled data from three studies with 377 patients measuring respiratory-related admissions until 6 months' follow- up (Bernocchi 2017; Koff 2009; Trappenburg 2011). There were no statistically significant differences in the risk of respiratory-related hospital admissions in the short term (OR 0.60; 95% CI 0.30 to 1.22). Studies were homogeneous, but the number of events was too small (ranging from 1 to 11) to allow firm conclusions based on the data.

3.3. Respiratory-related admissions - medium-term

Nine studies with a total of 2449 participants reported on the number of patients with at least one respiratory-related admission at 6 to 15 months' follow-up (Bourbeau 2003; Fan 2012; Lenferink 2019; Rea 2004; Rice 2010; Sanchez-Nieto 2016; Silver 2017; Smith 1999; Vasilopoulou 2017). Pooled estimates showed a statistically significant reduction in admissions in favour of IDM (OR 0.60, 95%CI 0.44 to 0.81). Data showed considerable heterogeneity (I^2 = 57%) (Analysis 1.18). Sensitivity analysis of only high-quality studies showed similar results, with only a small reduction in heterogeneity (I^2 = 48%) (see Table 7). To further explore the reasons for heterogeneity, we performed three subgroup analyses.

3.3.1. Subgroup analysis based on setting

Heterogeneity remained substantial or considerable when we pooled all studies in which the intervention was delivered in a primary care setting (I^2 = 84%) and secondary or tertiary care settings combined (I^2 = 48%). A test for subgroup differences showed no differences between groups (Chi^2 = 0.38, df = 1, P = 0.54). In other words, there seems to be no convincing difference between primary care and secondary or tertiary care that can explain the observed heterogeneity (Analysis 1.19).

3.3.2. Subgroup analysis based on dominant component of the programme

In five studies with a total of 1353 participants, the dominant component was self-management (Bourbeau 2003; Lenferink 2019; Rea 2004; Rice 2010; Sanchez-Nieto 2016). Two studies included education (Fan 2012; Silver 2017), two studies structural follow-up (Smith 1999; Vasilopoulou 2017), and one study telemonitoring as the dominant intervention component (Vasilopoulou 2017). A test for subgroup difference showed no differences between groups (Chi^2 = 3.65, df = 3, P = 0.30). However, these results should be interpreted carefully, as only the self- management subgroup pooled more than two studies, while the other subgroups pooled two or fewer studies. Among studies with self-management as the dominant component, the effect on respiratory-related admissions favoured IDM ((OR 0.55, 95% CI 0.43 to 0.71; I^2 = 0%) (Analysis 1.20).

3.3.3. Subgroup analysis based on region

Four of the nine studies, with a total of 1788 participants, originated in North America (Bourbeau 2003; Fan 2012; Rice 2010; Silver 2017), two studies in Southern Europe (Sanchez-Nieto 2016; Vasilopoulou 2017), one study in Northwestern Europe (Lenferink 2019), and one study in Oceania (Smith 1999). The effect estimate differed

significantly between subgroups (Chi^2 = 10.93, df = 3, P = 0.01). Pooling of studies conducted in North America showed a significant reduction in respiratory-related hospital admissions (OR 0.69, 95% CI 0.50 to 0.94; I^2 = 44), as did pooling of studies conducted in Southern Europe (OR 0.35, 95% CI 0.18 to 0.68; I^2 = 25%). Pooling of studies from Northwestern Europe and Oceania was not possible due to the small numbers (Analysis 1.21) (Lenferink 2019; Smith 1999). In addition to regional differences in effects of IDM on respiratory-related hospital admissions, there was a marked difference in the mean rate of respiratory-related hospital admissions per patient. Among IDM groups, the mean rate per patient was 0.19 admissions per patient in studies from North America, 0.21 per patient from Northwestern Europe, 0.59 per patient for Southern Europe, and 0.70 per patient from Oceania. Similarly, for controls, the rate from North America was 0.26 per patient, from Northwestern Europe 0.26 per patient, from Southern Europe 0.64 per patient, and from Oceania 0.56 per patient.

3.4. Hospital admissions, all causes

We were able to pool ten studies that reported on patients experiencing at least one hospital admission for all causes and included a total of 9030 participants. Pooling showed an overall statistically significant effect in favour of IDM (OR 0.75, 95% CI 0.57 to 0.98). This means that compared with usual care, there were 72 fewer (range 138 fewer to 5 fewer) hospitalisations per 1000 with IDM. Pooling based on follow-up period indicated slight differences in short-, medium-, and long-term effects (Analysis 1.22).

3.5. Hospital admissions, all causes - short-term

Only one study including 112 participants reported on the number of hospital admissions for all causes after 6 months' follow-up and therefore could not be pooled (Bernocchi 2017). Study authors reported a significant reduction in the number of patients having at least one hospital admission, in favour of the intervention group (OR 0.31, 95% CI 0.14 to 0.67).

3.6. Hospital admissions, all causes - medium-term

Five studies with a total of 1212 participants provided data on the number of participants admitted at least one time for all causes at 6 to 15 months' follow-up (medium-term) (Fan 2012; Kessler 2018; Lenferink 2019; Littlejohns 1991; Rea 2004). Kessler 2018 did not directly report the number of participants, so the number was approximated based on the percentage of people with 0 hospitalisation days. Pooling showed that results were homogeneous and there was no significant difference between groups (OR 0.93, 95% CI 0.71 to 1.21; I^2 = 14%). A sensitivity analysis of only high-quality studies showed a similar result (OR 0.91, 95% CI 0.66 to 1.26; I^2 = 0%).

3.7. Hospital admissions, all causes - long-term

Four studies including a total of 7706 participants assessed the number of participants admitted after 15 months' follow-up (Kalter-Leibovici 2018; Lou 2015; Sridhar 2008; van

Wetering 2010). Numbers of events and total numbers are lower for Lou 2015, as we reduced the size of the study to its 'effective sample size' to adjust for clustering effects. Pooled meta-analysis showed no significant differences between groups (OR 0.72, 95% CI 0.45 to 1.16). Pooled results showed considerable heterogeneity (I^2 = 75%) and differences in direction of effect. Although Lou 2015 and van Wetering 2010 showed positive effects in favour of IDM, Kalter-Leibovici 2018 and Sridhar 2008 showed no statistically significant differences. The different findings could have resulted from variation in follow-up duration which ranged from 24 months in Sridhar 2008 and van Wetering 2010 to 36 months in Kalter-Leibovici 2018 to 48 months in Lou 2015. Finally, heterogeneity could be explained by the large differences in study size ranging from 104 participants in Sridhar 2008 to 6221 participants (435 effective sample size) in Lou 2015. Sensitivity analysis including only high-quality studies did not show a statistically significant effect (OR 0.88, 95% CI 0.61 to 1.27; I^2 = 38%).

3.8. Hospital days per patient

We were able to pool 14 studies that reported on the number of hospital days among those (3563 participants) hospitalised during the study. Pooling showed an overall reduction of 2.27 days spent in the hospital in favour of IDM; this finding was statistically significant (MD -2.27, 95% CI -3.98 to -0.56; I^2 =7 8%) (see Figure 6).

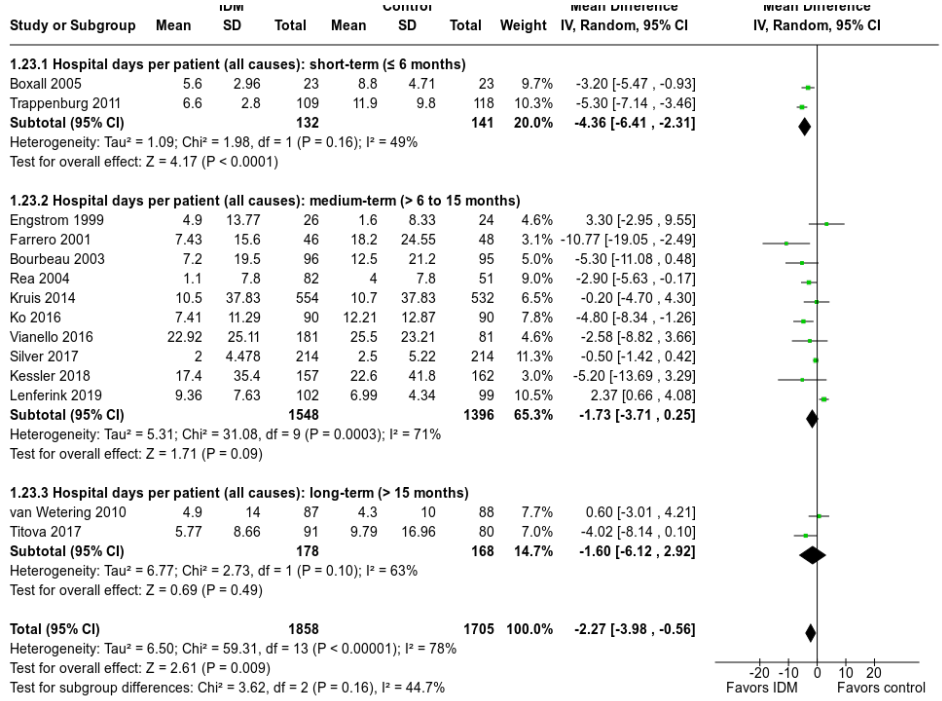


Figure 6. Forest plot of comparison: 1 Integrated disease management versus control, update, outcome: 1.24 Hospital days per patient (all causes).

3.9. Hospital days per patient - short-term

Two studies with a total of 273 participants reported on the difference in mean hospitalisation days per patient per group within the first 6 months (Boxall 2005; Trappenburg 2011). Pooling showed a significant reduction in days spent in the hospital per patient in favour of IDM (MD -4.36, 95% CI -6.41 to -2.31) (Analysis 1.23).

3.10. Hospital days per patient - medium-term

Ten studies including 2994 participants assessed the difference in mean hospitalisation days per patient per group from 6 to 15 months' follow-up (Bourbeau 2003; Engstrom 1999; Farrero 2001; Kessler 2018; Ko 2016; Kruis 2014; Lenferink 2019; Rea 2004; Silver 2017; Vianello 2016). Pooling showed a non-significant reduction in hospitalisation days in favour of IDM (MD -1.73, 95% CI -3.71 to 0.25), with moderate heterogeneity (I^2 = 71%). Heterogeneity could not be explained by differences in the quality of studies. Three studies showed a significant effect in favour of IDM (Farrero 2001; Ko 2016; Rea 2004), and one study showed a significant effect in favour of control (Smith 1999). Smith 1999 reported increased attention to disease and symptoms by the COPD nurse as a possible explanation. Mean hospitalisation days also varied substantially between studies and within the IDM study groups, with an average hospital stay ranging from 2 days in Silver 2017 to 25.5 days in Vianello 2016 (Analysis 1.23).

3.11 Hospital days per patient - long-term

Two studies with 346 participants reported the difference in mean hospitalisation days after 15 months' follow-up (Titova 2017; van Wetering 2010). There was no significant difference between groups (MD -1.60, 95% CI -6.12 to 2.92) (Analysis 1.23).

3.12 Emergency department

Twelve studies assessed the number of participants with at least one ED visit (Bourbeau 2003; Fan 2012; Farrero 2001; Lou 2015; Rea 2004; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Smith 1999; Trappenburg 2011; Wakabayashi 2011). To account for clustering, we reduced the study size in Lou 2015 to its 'effective sample size'. We were able to pool the data from nine studies with 8791 participants (Bourbeau 2003; Fan 2012; Lou 2015; Rea 2004; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Silver 2017; Smith 1999), which revealed a significant reduction in the number of participants with at least one ED visit in favour of IDM, with considerable heterogeneity (OR 0.69, 95% CI 0.50 to 0.93; I^2 = 68%) (Analysis 1.24). A sensitivity analysis including only high-quality studies showed that the risk of an ED visit was still significantly reduced with IDM (OR 0.69, 95% CI 0.50 to 0.94; I^2 = 64%) but could not explain the heterogeneity. Further exploration to assess reasons for heterogeneity revealed that seven trials had decreased risk of ED visits in favour of IDM (Bourbeau 2003; Fan 2012; Lou 2015; Rea 2004; Rice 2010; Sanchez-Nieto 2016; Silver 2017), of which three were statistically significant (Bourbeau 2003; Lou 2015; Rice 2010). Two studies showed a non-significant increase in risk of ED visits for the IDM group (Rose 2017; Smith 1999). Silver 2017 reported in the discussion that lack of effect on ED visits "may be due to the emergency department functioning

as an out-patient or rescue clinic for patients with exacerbations of their disease". The fact that most of the participants enrolled in the study lacked access to a primary care provider could explain the observation that the effect was non-significant.

3.13. Number of patients experiencing at least one exacerbation

Seven studies reported on the number of patients experiencing at least one exacerbation during follow-up. The definition of exacerbation differed slightly between studies. Trappenburg 2011 and Bourbeau 2003 defined an exacerbation as an increase in symptoms with deterioration of dyspnoea or purulent sputum. Lenferink 2019 used a similar definition (clear negative change in two symptoms classified as major symptoms (dyspnoea, sputum purulence, sputum volume) or in one major and one minor symptom (coughing, wheezing, fever) from baseline, for 2 or more consecutive days). Vasilopoulou 2017, Kruis 2014, and Sridhar 2008 defined exacerbation as an "unscheduled need for healthcare, or need for steroid tablets, or antibiotics for worsening of their COPD". Vasilopoulou 2017 and Kruis 2014 defined exacerbation based on a visit to the general practitioner or the respiratory physician in combination with a prescription of antibiotics and/or prednisolone; Kruis 2014, Vasilopoulou 2017, and Kessler 2018 made a distinction between moderate and severe exacerbations. If provided, we included the results for severe exacerbations.

Pooling of all studies reporting on the number of participants experiencing at least one exacerbation during follow-up showed no statistically significant difference between groups (OR 0.96, 95% CI 0.65 to 1.42). Pooling based on follow- up periods showed consistent non-significant results for medium-term effects (OR 0.72, 95% CI 0.90 to 1.27; I^2 = 47%) and long-term effects (OR 1.53, 95% CI 0.90 to 2.60; I^2 = 0%; Analysis 1.25). Trappenburg 2011, which reported results at 6 months' follow-up, indicated that although exacerbation rates did not differ between groups, exacerbations within the IDM group were perceived as substantially milder by patients. Sridhar 2008 , reporting on the number of participants experiencing at least one exacerbation at 24 months' follow-up (long-term), stated that patients in the intervention group were more likely to have exacerbations treated with oral steroids alone or oral steroids and antibiotics than patients in the control group. The initiator of treatment in the control group was statistically more likely to be the patient rather than the GP, and this could explain the absence of an effect.

3.14. Patients using at least one course of oral steroids

We pooled data from four studies including 433 participants reporting on the number of patients using at least one course of oral steroids during follow-up (12 months) (Farrero 2001; Littlejohns 1991; Rea 2004; Sanchez-Nieto 2016). Pooling showed homogeneity between studies and no differences between groups (OR 1.05, 95% CI 0.66 to 1.64; I^2 = 27%; Analysis 1.26).

3.15. Patients using at least one course of antibiotics

Three studies with 321 participants reported on the number of patients using at least

one course of antibiotics (Littlejohns 1991; Rea 2004; Sanchez-Nieto 2016). The number of patients using at least one course of antibiotics was not statistically different between groups (OR 1.46, 95% CI 0.51 to 4.18; I^2 = 53%; Analysis 1.27). A sensitivity analysis of high-quality studies showed decreased heterogeneity (I^2 = 53%) and significantly increased risk when a course of antibiotics was received by people in the IDM group (OR 2.35, 95% CI 1.02 to 5.42). Further exploration of these studies revealed that they provided the same follow-up (12 months) but represented very different settings, as Rea 2004 was a cluster-randomised trial in a primary care setting, and Littlejohns 1991 and Sanchez-Nieto 2016 were RCTs conducted in a secondary care setting.

Secondary outcomes

4. Dyspnoea

Fifteen studies reported on modified MRC Dyspnoea Scale scores as an outcome for dyspnoea (Bernocchi 2017; Gottlieb 2011; Kalter-Leibovici 2018; Khan 2019; Ko 2016; Kruis 2014; Lenferink 2019; Lou 2015; Mendes 2010; Öztürk 2020; van Wetering 2010; Vasilopoulou 2017; Wakabayashi 2011; Wang 2017; Zhang 2020). Gottlieb 2011 did not publish any results, and results from Wang 2017 could not be included due to a reporting error. Outcomes were reported after 3 months, 4 months, 6 months, 12 months, and/or 24 months. The data allowed us to calculate the MRC Dyspnoea Scale score at short-, medium-, and long-term follow-up. Pooling showed significant improvement in favour of IDM for short-term follow-up (MD -0.33, 95% CI -0.52 to -0.15). Pooling of mMRC Dyspnoea Scale scores at medium- and long-term follow-up showed heterogeneity (I^2 = 96%) too large to be permit conclusions based on the results (Analysis 1.28). Dyspnoea as measured by Borg Scale score in three studies showed no differences between groups (MD 0.14, 95% CI -0.70 to 0.98; I^2 = 39%) (Boxall 2005; Gottlieb 2011; Güell 2000).

5. Mortality

Fifteen studies assessed mortality as an outcome or as part of patient safety assessment. Of these studies, two assessed mortality at 6 months' follow-up (Aboumatar 2019; Bernocchi 2017), nine at 12 months' follow-up (Fan 2012; Farrero 2001; Kessler 2018; Littlejohns 1991; Rice 2010; Rose 2017; Sanchez-Nieto 2016; Smith 1999; Vianello 2016), and four after more than 15 months' follow-up (Kruis 2014; Lou 2015; Sridhar 2008; Titova 2017). The numbers for Lou 2015 are lower, taking clustering into account. Fan 2012 was temporarily stopped because all-cause mortality was higher in the intervention group than in the usual care group. A thorough investigation of the circumstances of death by an independent and blinded panel showed that death was unrelated to the intervention, and a minority of deaths were due to COPD. Pooling of death events in IDM and control groups across all studies showed a non-statistically significant effect in favour of the intervention (OR 0.86, 95%CI 0.59, to 1.25). Heterogeneity was substantial and could not be explained by duration of follow-up, as outcomes were comparable after medium-term (OR 0.80, 95% CI 0.45 to 1.43) and long-term follow-up (OR 0.87, 95% CI 0.48 to 1.57) (Analysis 1.30).

6. Lung function

Lung function was expressed as FEV1 in litres and as FEV1% predicted. Following Kruis 2013 , we pooled data from a total of six studies for FEV1 (litre) (Bourbeau 2003; Kalter-Leibovici 2018; Öztürk 2020; Sridhar 2008; Wood- Baker 2006; Zhang 2020), and from 14 studies for FEV1% predicted (Farrero 2001; Fernandez 2009; Güell 2000; Jimenez-Reguera 2020; Kalter-Leibovici 2018; Khan 2019; Ko 2016; Lenferink 2019; Littlejohns 1991; Lou 2015; van Wetering 2010; Wakabayashi 2011; Wood-Baker 2006; Zhang 2020). Wang 2017 and Wood-Baker 2006 reported on short-term effects on FEV1 in litres, but data from Wang 2017 could not be pooled due to reporting error. Pooling of FEV1 in litres showed no differences between groups for medium- and long-term follow-up (Analysis 1.31). Pooled MDs in FEV1% predicted showed a short-term effect in favour of the IDM group (MD 2.88, 95% CI 1.35 to 4.40). This effect was statistically significant but was not clinically significant. Medium-term effects were less pronounced and were not statistically significant (MD 0.95, 95% CI -0.20 to 2.11). After 24 months, there was no difference between groups (MD 1.18, 95% CI -0.82 to 3.18). Results were homogeneous across studies (Analysis 1.32). However, except for Lou 2015 , 95% confidence intervals for the different studies were consistently large, suggesting large between-patient variation.

7. Anxiety and depression

Ten studies assessed depression, anxiety, or both as an outcome (Engstrom 1999; Güell 2000; Kessler 2018; Lenferink 2019; Littlejohns 1991; Öztürk 2020; Rose 2017; Titova 2017; Trappenburg 2011; Vianello 2016). Engstrom 1999 used the Mood Adjective Check List (MACL), and Güell 2006 used a Revised Symptom Checklist. Kessler 2018 used the Hospital Anxiety and Depression Scale (HADS) but reported only the combined score. The other studies reported depression and anxiety scores from the HADS, and results were pooled. Pooled data from the anxiety domain of the HADS showed no differences between groups (MD 0.09, 95% CI -0.30 to 0.47; I^2 = 38%). Pooled data for the depression domain of the HADS showed a non-significant effect in favour of the intervention group (MD -0.20, 95% CI -0.45 to 0.05; I^2 = 38%: Analysis 1.33).

8. Process-related outcomes

8.1 Compliance/Adherence

Patient adherence to the programme or to intervention uptake was evaluated in five studies by review of programme attendance rate and programme completers (Bernocchi 2017; Rose 2017; Tabak 2014; Vasilopoulou 2017; Zwar 2016). Bernocchi 2017 reported a high adherence rate, with 93% of participants performing activities at home as part of the programme. Rose 2017 reported that 29% of participants were fully compliant and 22% were non-compliant (< 50% compliant with separate components). In addition, only 7% of study participants attended respiratory rehabilitation despite this being a component of usual care. Study authors also noted that 38% of intervention group participants who met the eligibility criteria for pulmonary rehabilitation were unable to attend due to unavailability of classes. Tabak 2014 monitored use of the web

portal and separate intervention modules and observed that use of the web portal differed greatly among participants; some used the diary almost every day, others used it on only half of the days. Varying levels of implementation were also reported by Kennedy 2013 and Zwar 2016 . Zwar 2016 particularly reported low implementation rates by practitioners and low response to questionnaires caused by limited time.

8.2 Satisfaction

Eight studies assessed patient satisfaction with the IDM programme in some way (Bernocchi 2017; Fan 2012; Koff 2009; Kruis 2014; Littlejohns 1991; Rose 2017; Tabak 2014; Zwar 2016). Various questionnaires, either validated or self-developed, were used to measure patient satisfaction; this made pooling impossible. Rose 2017 and Tabak 2014 used the eight-item Client Satisfaction Questionnaire (CSQ-8) (Attkisson 2004). Tabak 2014 measured lower satisfaction with the telehealth programme compared to usual care, and Rose 2017 found no differences between groups. Likewise, Fan 2012 found no differences between groups on the 21-item Seattle Outpatient Satisfaction Questionnaire, and Littlejohns 1991 found no differences on its self-developed questionnaire. Both Bernocchi 2017 and Koff 2009 reported high satisfaction scores for IDM, except for use of the pedometer, but did not compare satisfaction scores with those of the control group. Bernocchi 2017 saw that patients reported high satisfaction on all items of the self-developed questionnaire, including service as a whole, use of the devices, and healthcare professionals' willingness to respond to patient needs. Zwar 2016 included patient satisfaction as a secondary outcome in its protocol paper but for unknown reasons did not report on this.

8.3 Co-ordination of care

Two studies assessed co-ordination of care (Kruis 2014; Zwar 2016). Kruis 2014 measured the level of care integration from the view of patients using the Patient Assessment Chronic Illness Care (PACIC) and found a statistically significant increase and difference in favour of the IDM group (Glasgow 2005). Zwar 2016 included in its protocol the Collaborative Practice Scale to assess 'interactions between nurses and GPs that enable synergistic influence of patient care' (WEISS 1985). For unknown reasons, these results were not reported.

Discussion

Summary of main results

This review summarised and meta-analysed the results of 52 studies involving 21,086 participants with chronic obstructive pulmonary disease (COPD) who were randomly allocated to usual care or to an integrated disease management (IDM) programme with a minimum duration of 12 weeks. This review is an update of the review performed in 2013 (Kruis 2013). Studies were conducted in 19 different countries across multiple healthcare settings. All studies investigated an IDM programme. Studies differed in terms of intervention components, duration of intervention, healthcare professional

involvement, follow-up window, number of participants, and outcome reporting. Nonetheless, we were able to pool data on all primary outcomes for short-term (up to 6 months), medium-term (6 to 15 months), and long-term (longer than 15 months) follow-up. Results of the previous review support IDM for management of COPD. Results of this update reinforce these findings, providing evidence of higher certainty and including evidence on long-term effects (up to 48 months).

First, this review showed that IDM probably improves health-related quality of life (HRQoL) as indicated by a change in St. George's Respiratory Questionnaire (SGRQ) overall score by 3.89 points after 12 months without reaching the minimum clinically important difference (MCID) of -4 points. This improvement was more pronounced among high- quality studies only, indicating the robustness of our conclusions. This effect was not observed after 15 months (mean difference (MD) -0.69). IDM probably leads to improvement after 12 months in the symptoms domain (MD -3.88) and in the impact domain (MD- 3.34) but not in the activity domain of the SGRQ. Across all outcomes, we observed considerable heterogeneity, which could be explained in part by differences in the quality of studies. Subgroup analysis suggested context-specific effects with no differences among studies performed in Northwestern Europe and Oceania. Pooling of data from the Chronic Respiratory Questionnaire (CRQ), another measurement for HRQoL, showed statistically significant long-term effects in favour of IDM in fatigue (MD 0.46), emotion (MD 0.53), and mastery (MD 0.83) domains. No significant effects were found for short- and medium-term follow-up, nor for generic quality of life.

Second, IDM probably results in a large improvement in maximum and functional exercise capacity as measured by the six-minute walking distance test (6MWD), which exceeds the MCID of 35 metres. At short-term follow-up, pooling showed improvement of 48 metres. This effect was sustained over time, as shown by pooled data after 12 months (MD 44.69) and after 15 months' follow-up (MD 60.41). Subgroup analysis indicated a considerable intervention-specific effect, with a larger effect in studies with exercise, structural follow-up, or telemonitoring as the dominant intervention component.

Third, the total number of patients with at least one respiratory-related hospital admission receiving an IDM programme, after median follow-up of 12 months, was on average 235 per 1000 patients compared to 324 per 1000 receiving usual care. Likewise the number of all-cause hospital admissions decreased from 517 per 1000 for usual care to 445 per 1000 for IDM. Within the group of patients admitted to the hospital, IDM likely reduces the length of stay by 2.3 days after median follow-up of 12 months. However, length of stay differed considerably between studies, ranging from a reduction of 10.8 days to an increase of 3.5 days in the IDM group compared to the usual care group. In terms of the number of emergency department (ED) visits, IDM probably reduces the number of visits by 86 per 1000 ED visits.

Effects on the aforementioned primary outcomes and details on level of certainty are summarised in Summary of findings Table 1. In addition to effects on our primary outcomes, we found a statistically significant improvement in lung function parameters

without clinical relevance and in dyspnoea. We found no statistically significant differences between IDM and usual care in terms of generic quality of life (i.e. Short Form (SF)-12/36 score), courses of antibiotics/prednisolone, mortality, or depression and anxiety scores.

Overall completeness and applicability of evidence

With the addition of 26 new studies resulting from the search update for the 2020 review, the number of people with COPD in this review increased from 2997 to 21,086. The large increase in terms of studies and participants has resulted in better precision and better generalisability of findings. In addition, we were able to distinguish short-, medium-, and long-term effects. Unfortunately, we observed large heterogeneity within the primary analysis for almost all primary outcomes. Although part of the observed heterogeneity could probably be explained by variation in the quality of studies in some cases, our results are also marked by large clinical and methodological variations. Accordingly, the applicability of our evidence warrants some comments.

The COPD population in the included studies ranged from those with mild to very severe COPD, and trials were conducted across all types of healthcare settings in a range of different countries, each with a unique healthcare system. This improves generalisability and makes (parts of) the results of this review applicable to a large proportion of COPD patients worldwide. However, one should bear in mind that the precise applicability will depend on the context of the specific healthcare setting and the type of COPD patient. The IDM programmes included in this review also differed in types of healthcare providers involved, types of intervention components, and intervention duration and intensity, reflecting the diversity of daily practice. Overall, with subgroup analysis, we noticed intervention-specific effects, that is, IDM programmes focused mainly on exercise probably result in greater improvement in exercise capacity, and programmes with self-management as the dominant component probably led to fewer respiratory- related hospital admissions.

Besides clinical heterogeneity, our review also deals with significant methodological heterogeneity. We included studies with differences in duration and intensity of follow-up. By dividing the follow-up duration into short-, medium-, and long-term follow-up, we aimed to assess groups of studies with sufficient homogeneity. However, the intensity of the intervention could still differ between included studies. Also, it should be noted that an observed effect at long term does not necessarily indicate a sustained effect of the intervention because for some studies, the interventions continued throughout the study. Hence, further research is required to define the optimal combination, intensity, and duration of components of IDM programmes, taking into account the importance of methodological factors.

Our subgroup analysis results point towards beneficial effects among telemonitoring-based IDM interventions in terms of health-related quality of life, exercise capacity, and respiratory-related hospital admissions. However, given the small number of studies (5 studies) including telemonitoring, no decisive conclusions or recommendations can be made regarding the overall beneficial effects of telemonitoring as an IDM programme.

Future research should shed light on the beneficial effects of telemonitoring and its use in practice.

Also, the applicability of evidence depends on the healthcare context in which the IDM programme is implemented, which differed greatly among studies included in this review. Studies were conducted in many different countries across five different continents. Subgroup analysis pointed towards a context-specific effect. This is in line with recent findings from the COMET study performed in Germany, France, Italy, and Spain (Kessler 2018), which reported significant country-specific differences between study settings. Kessler attributed these to differences in routine care, such as country-specific differences in baseline hospitalisation practices, admission criteria, and bed availability. Hence, effectiveness varying between study regions is likely related to variations in usual care that occur over time and are driven by national changes in policy and healthcare financing.

Also, country-specific differences in terms of cultural and societal norms may play a role in terms of implementation fidelity and therefore outcomes (Marsiglia 2015). For example, the four-year study in which the IDM group received a monthly one-hour health lecture, performed by Lou 2015 in China, reported dropout (other than death) of only 7%, and noted that 87% of the study population attended all 48 COPD lectures.

Furthermore, the period in which included studies were published spanned 30 years, with the earliest published in 1991 and the latest in 2020. The clinical applicability of more recent studies is larger, given the embedding of IDM programmes into the healthcare system and the evolution of healthcare systems nationally and internationally. Hence, it would be worthwhile to investigate the relationship between advancements in usual healthcare over time and additional beneficial effects of IDM. Furthermore, it would be interesting to explore ways in which more weight could be given to more recent studies or older studies with limited applicability for current health care could be left out in a legitimate way.

Quality of the evidence

There was clinical and methodological heterogeneity among studies, which likely results (at least in part) from the complexity of IDM interventions. We have incorporated heterogeneity into estimated effects by using random-effects analyses. Using the GRADE approach, we specified levels of quality of the evidence (high, moderate, low, and very low) in our 'Summary of findings' table. According to this approach, we checked whether included trials had limitations in terms of design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. Such limitations may impact the certainty of evidence for all outcomes that are relevant to guideline formation, health policy development, and clinical guidance.

We deemed the quality of evidence for HRQoL (as measured by the SGRQ) as moderate, and we observed a consistent effect in favour of the intervention group for all SGRQ domains at medium-term follow-up. We downgraded the quality of evidence due to

large heterogeneity between studies. For outcomes of functional and maximum exercise capacity, we downgraded the certainty of evidence owing to large heterogeneity that may be caused by an intervention-specific effect (i.e. IDM programmes with exercise as the dominant component showed more positive results for exercise capacity). We deemed the quality of evidence for respiratory-related hospital admissions as high. We downgraded one level for all-cause hospital admissions because of considerable heterogeneity and inconsistency in direction of effect. We also downgraded the certainty of evidence for outcomes of hospital days per patient and ED visits due to inconsistency in effects.

Potential biases in the review process

Several methodological strengths minimised the risk of bias in this review. As definitions of IDM are still under debate, we strictly determined the inclusion criteria for an IDM programme a priori and published this in our review protocol (Kruis 2011). Our definition was derived from definitions published in the literature (Peytremann-Bridevaux 2009; Schrijvers 2009). Overall, researchers reported on "multiple interventions, designed to manage chronic conditions, with a focus on a multidisciplinary approach". Furthermore, these definitions suggest that IDM interventions should "focus on maximum clinical outcome, regardless of treatment setting(s) or typical reimbursement patterns". As a result, we chose to include all interventions, independent of treatment setting, and to keep our definition as simple as possible, to be easily understandable for readers and easy to use when readers check on all relevant literature. Therefore, we restricted included trials to multi-component, multi-disciplinary programmes of at least 12 weeks' duration. Furthermore, we performed comprehensive searches to identify possible studies, leading to identification of more than 10,000 potentially relevant abstracts. Subsequently, three different assessors assessed the abstracts. We reached consensus on all included studies. Final decisions of course are open to interpretation or criticism. However, we have applied a systematic approach to including and excluding studies in this review, have followed the criteria pre-specified in the protocol, and have used robust methods for data collection and 'Risk of bias' assessment.

We were able to retrieve additional data from 17 study authors but did not receive a response from eight authors despite multiple reminders. This may have introduced bias. Another limitation of this review is inconsistent reporting in the included studies, in terms of adjusting for baseline differences. We decided on a conservative approach, using unadjusted mean differences for all randomised controlled trials (RCTs) and adjusted only values corrected for clustering effects, to overcome inconsistency between study authors' corrections. Inconsistency in reporting also resulted in the need for computing standard deviations of the mean change using appropriate analysis methods. Last, there may have been large heterogeneity in control groups, resulting from country-specific healthcare systems and COPD regulations for COPD treatment (i.e. reimbursements). Because the level of detail in reporting usual care varied greatly between studies (possibly also due to journal guidelines), we decided it was more informative to further investigate differences between regions instead of differences between types of usual care, as was performed in the previous version of

this review (Kruis 2013).

Agreements and disagreements with other studies or reviews

This review adds to the results of six earlier systematic reviews analysing IDM for COPD patients (Adams 2007; Lemmens 2009; Lemmens 2013; Niesink 2007; Peytremann-Bridevaux 2008; Peytremann-Bridevaux 2014). The current review brings together new trials that were not included in any of these reviews, and it provides an overview of multiple outcomes. Adams 2007 examined the effectiveness of programmes for COPD patients, including chronic care model components, and pooled six trials including at least two components. Pooled results did not demonstrate statistically significant differences on the SGRQ. Adams 2007 showed lower rates of hospitalisation and shorter length of stay in the intervention group, comparable to our results. Lemmens 2009 pooled data based on the number of components used in IDM and compared these to usual care. The effect on the SGRQ was optimal if three components of IDM were used (MD -4.69), which is comparable to our effect in the medium term (MD -3.89). Review authors also showed a decrease in the number of respiratory-related hospitalisations for studies with multiple intervention components, with a pooled odds ratio (OR) of 0.58, which is comparable to the OR of 0.64 found in the current review. Niesink 2007 described the results of several studies that evaluated quality of life in IDM programmes among COPD patients. Five out of 10 studies showed clinically relevant improvement in quality of life. Peytremann-Bridevaux 2008 examined the effectiveness of IDM in COPD patients for exercise tolerance, quality of life, hospital admissions, and mortality. Only data on hospital admissions and exercise tolerance were pooled. In line with the current review, positive effects on exercise capacity were found, but no significant effects were found for hospital admissions. Review authors demonstrated mean improvement of 32 metres on the 6MWD in five studies. Although we found overall improvement of 45 metres, this is largely attributable to the IDM programmes with a dominant exercise component.

Furthermore, the pooled odds ratio of 0.85 (95% confidence interval (CI) 0.54 to 1.36) for mortality reported by review authors is comparable to that in our review (OR 0.86, 95% CI 0.59 to 1.25). Lemmens 2013 performed a meta-analysis on existing reviews that focused on IDM programmes with two or more components for adult patients with COPD. They showed statistically significant improvements on the SGRQ in favour of IDM ($P < 0.01$) with moderate heterogeneity. In contrast to our review, these review authors did not find any significant changes in all-cause hospitalisations (OR 0.95, 95% CI 0.76 to 1.14) or in numbers of ED visits (OR -0.11, 95% CI -0.26 to 0.04). Peytremann-Bridevaux 2014 performed an additional analysis of studies in the previous version of this Cochrane systematic review, in which they specifically assessed potential differences in mortality between IDM and usual care. They found no effects of IDM on mortality (OR 1.00, 95% CI 0.79 to 1.28), which is in line with our current findings. Some of the observed differences can be explained by the fact that nearly all reviews used different definitions of IDM. Also, all aforementioned systematic reviews included study designs other than RCTs, except Peytremann-Bridevaux 2014.

In addition to other reviews that assessed the effectiveness of IDM in COPD as

described above, multiple systematic reviews have assessed the effectiveness of different components of IDM programmes.

Exercise

Two Cochrane Reviews examined pulmonary rehabilitation programmes for COPD patients in which the dominant component is generally exercise training. McCarthy 2015 assessed the effectiveness of pulmonary rehabilitation for COPD in general, although Puhan 2016 specifically assessed the effectiveness of pulmonary rehabilitation following an exacerbation of COPD. Similar to our review, McCarthy 2015 demonstrated statistically significant improvement in quality of life and exercise capacity (6MWD) in favour of pulmonary rehabilitation (SGRQ overall score MD -6.89; 6MWD MD 43.93 metres). Only one study in our review, Ko 2016, is also included in Puhan 2016, probably because of its selection of COPD patients with a recent exacerbation. The review authors also showed significant improvement in quality of life and exercise capacity in favour of pulmonary rehabilitation (SGRQ MD 7.80; 6MWD MD 62 metres) and a reduction in hospital admissions (OR 0.44).

Telemonitoring

The effectiveness of telemonitoring among COPD patients was assessed in a systematic review and meta-analysis of 27 studies (Hong 2019). In contrast to results from our subgroup analysis with telemonitoring as the dominant component, Hong 2019 found no difference in SGRQ (MD -0.21; our review MD -18.33) or in hospitalisations (all-cause and respiratory-related). However, our analyses are based on a small number of studies, which makes it impossible to draw firm conclusions. Another recent systematic literature review showed inconclusive results for the effectiveness of telemonitoring in COPD (Kruse 2019). These review authors did not perform a meta-analysis but described 29 articles, of which 13 (45%) showed favourable results, five (17%) negative outcomes, and 11 (38%) no differences in outcomes.

Self-management

Two Cochrane systematic reviews reported on self-management-based interventions in COPD. Zwerink 2014 assessed self-management training, which should allow patients to successfully manage their own disease. Follow-up ranged between 2 and 24 months. Lenferink 2017 focused on self-management interventions that are personalised and included action plans for the management of exacerbations. In line with our results, both reviews found significant improvement in HRQoL in favour of the intervention (Zwerink 2014 SGRQ overall score MD -3.51; Lenferink 2017 MD -2.69). In these reviews, respiratory-related hospital admissions were assessed as the number of people with at least one respiratory-related hospital admission. Still, both studies showed similar significantly reduced risk in favour of the intervention (Zwerink 2014 OR 0.57; Lenferink 2017 OR 0.69). It is interesting to note that in our review, we did not find a difference in the number of people prescribed at least one course of oral corticosteroids (OR 1.05), whereas in both of the other reviews, odds ratios appeared to be much higher in the intervention group, albeit with non-statistically significant

findings (Zwerink 2014 number of courses of steroids OR 4.42; Lenferink 2017 OR 4.38). This might have to do with the nature of the action plans incorporated into self-management programmes, which stimulate patients to start a course of prednisolone in case of increased symptoms.

Education

A Cochrane systematic review from 2016 assessed the effectiveness of action plans with brief patient education for exacerbations in COPD (Howcroft 2016). Review authors showed that the intervention reduced the combined rate of hospitalisations and ED visits (rate ratio 0.59, 95% CI 0.44 to 0.79) and led to small but significant improvement in quality of life (SGRQ MD -2.8. 95% CI -4.8 to -0.8). One recent systematic review explored the effects of health coaching for people with COPD (Long 2019). According to the definition used in this review, health coaching programmes aim to improve self-management and healthy behaviour by teaching and motivating patients to achieve personalised goals. Long 2019 showed that health coaching had a significantly positive effect on the SGRQ (MD -0.69). These review authors also found a significant reduction in COPD-related hospital admissions (OR 0.45). In contrast to both of these reviews, our subgroup analysis on studies with education as the main component did not find significant differences in SGRQ (MD 0.15) nor in respiratory-related hospital admissions (OR 0.83). This might be related to the content of the education, suggesting that action plans need to be an integral part of any educational component in IDM to be of benefit for patient outcomes. Additionally, as shown by Long 2019, education has a larger beneficial effect when it is personalised and includes motivational techniques and goal-setting.

It is hard to draw conclusions on our subgroup analysis of the dominant component and the findings of earlier reviews because of the limited number of studies per dominant component and considerable variation among studies in terms of intervention duration. However, our findings suggest that to improve exercise capacity, IDM programmes with an exercise focus or with use of telemonitoring components are best suited. IDM programmes using telemonitoring can provide large benefit with regard to respiratory-related admissions by monitoring the patient's symptoms, providing tailored and individualised self-management support (i.e. delivery of coping skills), and managing unexpected patient hospitalisations. For quality of life, most reviews on different components show improvement. Overall, this suggests that a multi-component approach, such as that used in IDM programmes, should result in optimal benefit for multiple important outcomes.

Finally, when compared to pharmaceutical treatments such as long-acting beta-agonist (LABA)/long-acting muscarinic antagonist (LAMA) treatment or use of phosphodiesterase-4 inhibitors, our findings from the SGRQ showed improvement of comparable magnitude. Our review showed that IDM resulted in improvement of 3.89 points on the SGRQ compared to 4.08 points for LABA/LAMA treatment (Maqsood 2019), as well as 1.06 points for phosphodiesterase-4 inhibitors (Janjua 2020). Although the confidence interval for IDM was wider (95% CI -6.16 to -1.63) compared to the confidence interval for LABA/LAMA treatment (95% CI -4.80 to -3.36), our results

indicate clinical significance of the effects of IDM for a large group of patients.

Authors' conclusions

Implications for practice

This review and meta-analysis provides evidence that integrated disease management (IDM) programmes of at least 12 weeks' duration are generally effective for people with chronic obstructive pulmonary disease (COPD) and result in clinically beneficial outcomes. Effects are most pronounced on the short term and in the medium term. For the long term only, effects on six-minute walking distance (6MWD) persist, although this may be explained in part by the smaller number of studies. Also, the effect size differs between studies and interventions. In practice, this means there is no one size fits all solution, and interventions should always be carefully designed and evaluated.

We calculated that 89 hospital admissions related to respiratory problems can be prevented for every 1000 patients treated with IDM, leading to a number needed to treat for additional beneficial outcome (NNTB) of 12 patients to prevent one from being admitted over follow-up of 12 months. Although the numbers of patients admitted to hospital for all causes differed slightly between groups, time spent in the hospital decreased by two days in patients treated with IDM compared to those receiving usual care. This is of utmost importance, as hospitalisations contribute to the highest burden and costs among patients with COPD.

In our review, we do not provide the ideal combination of components that represent the optimal IDM programme. Rather, our results indicate that different dominant components of IDM have beneficial effects for specific outcomes. Our dominant component analysis showed that telemonitoring improves quality of life, whereas exercise tolerance is improved by IDM programmes with a dominant component of exercise, structural follow-up, or telemonitoring, and respiratory-related admissions are improved by self-management. This means that IDM programmes should consist of several different components to reach the highest potential. Ideally, components of the IDM programme should be linked to personal goals of the patient.

Previously, Kessler 2018 and Marsiglia 2015 showed important differences in usual care between countries, and our review also found differences between regions. These differences might stem from a disparity in local availability of different components, from differences in the healthcare system, or from different customs. Furthermore, they are dependent on available resources and costs of interventions. Therefore, we suggest that policy makers and healthcare leaders should assess local needs and available interventions and use this overview to develop and implement an IDM programme in a context-sensitive manner. This review suggests that an IDM programme with a combination of exercise

Implications for research

Well-designed and appropriately conducted studies are still needed to minimise bias,

to allow measurement of the true intervention effect. Specifically, consistent reporting on exacerbation outcomes and on severity of exacerbations may overcome the difficulties we encountered in this review, for which we found a myriad of exacerbation definitions. Researchers are encouraged to use recent Global initiative for Chronic Obstructive Lung Disease (GOLD) guidelines to provide unambiguous definitions of disease severity and to evaluate effects of IDM programmes on mild, moderate, and severe exacerbations (GOLD 2020).

Subgroup analyses undertaken as part of this update stimulate new questions in relation to IDM and its contextual embedding. Differences in subgroups based on the dominant intervention component call for further research to identify which intervention component, or which combination of components, is most effective in IDM programmes, and for which patient groups. Similarly, the context-specific effects we observed in the subgroup analysis suggest that the country in which the IDM programme is embedded and the level of usual care it is compared to greatly impact the magnitude of effect. This still means that the individual components of IDM programmes are important and will improve patient outcomes, as shown in this review. However, the contrast of a new IDM programme versus usual care becomes smaller when usual care itself already routinely contains several of the components. Other factors that remain uncertain are the optimal duration and intensity of the intervention and the combination of healthcare providers involved. These questions can be examined in a meta-regression analysis, which could shed light on the contribution of each individual factor or combination of factors to observed treatment effects.

Although the observed effect of - 3.89 on the SGRQ did not reach the proposed MCID of -4 points for medium-term follow-up, there could be a proportion of patients in the intervention group that does exceed the 4 points of improvement. These so called 'responders' would clinically benefit more from IDM than from usual care. In our review, only Bourbeau 2003 reported the proportion of people who improved by 4 points or more on the SGRQ. Hence, we echo Cates 2015 and urge trialists to also report, besides the mean difference, the spread of individual responses to the intervention or treatment. This information can be used for more complete assessment of clinical importance and helps to reveal the population benefit.

Last, process-related outcomes raised issues that require consideration beyond this current review. For example, special attention should be given to evaluating the actual implementation of IDM programmes in existing healthcare structures, which should include outcomes related to patient satisfaction, feasibility, programme compliance, and assessment of personal and contextual determinants of implementation and treatment effects. Pragmatic, real-life RCTs including both clinical and process-related outcomes and qualitative assessment with long-term follow-up are needed to evaluate IDM programmes as comprehensive packages in routine primary and secondary care practice. As part of this, cost-effectiveness remains an important outcome, to allow for reimbursement and to inform health policy development and clinical guidance.

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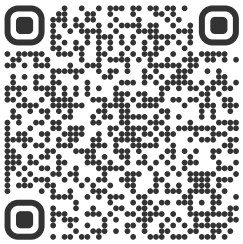
Additional tables, analysis and appendices

Scan the QR code to view characteristics of included studies table



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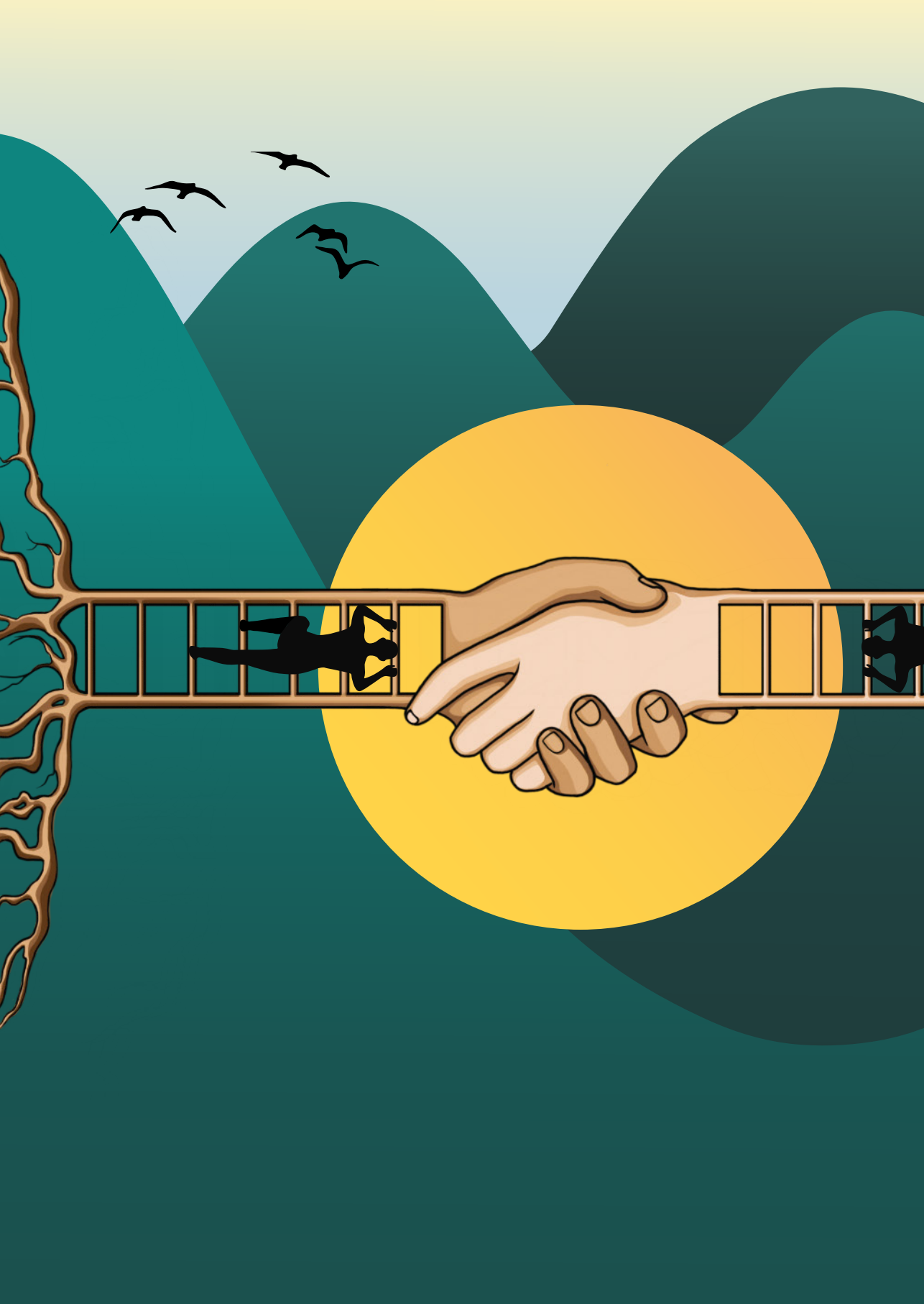
PART 3

TOOLS AND INSTRUMENTS



Chapter 7

Dutch version of the eHealth Literacy Questionnaire

Translation, cultural adaptation and validity assessment of the Dutch version of the eHealth Literacy Questionnaire: a mixed-method approach

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Abstract

Background

The digitalization of healthcare requires users to have sufficient competence in using digital health technologies. In the Netherlands, as well as in other countries, there is a need for a comprehensive, person-centred assessment of eHealth literacy to understand and address eHealth literacy related needs, to improve equitable uptake and use of digital health technologies.

Objective

We aimed to translate and culturally adapt the original eHealth Literacy Questionnaire (eHLQ) to Dutch and to collect initial validity evidence.

Method

The eHLQ was translated using a systematic approach with forward translation, an item intent matrix, back translation, and consensus meetings with the developer. A validity-driven and multi-study approach was used to collect validity evidence on 1) test content, 2) response processes and 3) internal structure. Cognitive interviews (n =14) were held to assess test content and response processes (Study 1). A pre-final eHLQ version was completed by 1650 people participating in an eHealth study (Study 2). A seven-factor Confirmatory Factor Analysis (CFA) model was fitted to the data to assess the internal structure of the eHLQ. Invariance testing was performed across gender, age, education and current diagnosis.

Results

Cognitive interviews showed some problems in wording, phrasing and resonance with individual's world views. CFA demonstrated an equivalent internal structure to the hypothesized (original) eHLQ with acceptable fit indices. All items loaded substantially on their corresponding latent factors (range 0.51-0.81). The model was partially metric invariant across all subgroups. Comparison of scores between groups showed that people who were younger, higher educated and who had a current diagnosis generally scored higher across domains, however effect sizes were small. Data from both studies were triangulated, resulting in minor refinements to eight items and recommendations on use, score interpretation and reporting.

Conclusion

The Dutch version of the eHLQ showed strong properties for assessing eHealth literacy in the Dutch context. While ongoing collection of validity evidence is recommended, the evidence presented indicate that the eHLQ can be used by researchers, eHealth developers and policy makers to identify eHealth literacy needs and inform the development of eHealth interventions to ensure that people with limited digital access and skills are not left behind.

Background

Digitalization of healthcare

The use of digital technologies for health, also called eHealth, is revolutionizing the way we diagnose, treat and manage health and disease. eHealth, defined as "the use of information and communications technology in support of health and health-related fields" spans a range of different digital health technologies and services, including smartphone apps, remote monitoring, smart wearables, patient portals and electronic patient records (1). Given the wide application and spectrum of eHealth, eHealth is often presented as a solution to relevant healthcare challenges, including challenges posed by the ageing population, the increased number of chronic and multi-morbidities and the growing resource gap (2, 3). As a result, eHealth has been stimulated and has shaped the way people engage with their health and how information is exchanged and shared between patients, healthcare providers and across health ecosystems.

eHealth literacy

This changing healthcare landscape has added complexity in the way community members, healthcare professionals and digital technologies interact. For example, healthcare portals and telehealth systems allow people to remotely communicate with healthcare professionals and caregivers, electronic health records based on cloud storage allow patients to manage diagnostic data with clinicians, and wearables and apps can help people to self-manage their condition. However, this increased complexity requires additional skills and competences from people using eHealth, including patients and people without a medical diagnosis. In the early days of the internet (web 1.0) the additional set of needed skills to navigate the web was introduced as eHealth Literacy: "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem." However, with the increased complexity of the digital health landscape scholars have called for a more comprehensive view and included elements related to users' cognitive skills, communication elements, social and cultural context or system level attributes (4-6). Since the web 1.0, eHealth literacy and its association with health outcomes has been investigated extensively (7, 8). However, eHealth literacy as evolved concept in the new digital (health)landscape and its impact on health is a relatively new area that needs to be further investigated (9, 10).

eHealth, COVID-19 pandemic and digital divide

eHealth literacy has gained attention with the accelerated uptake of eHealth due to the COVID-19 pandemic, mainly with the use of telehealth and remote monitoring systems (11-13). While large scale studies are lagging behind, smaller scale studies indicate that people who have low digital literacy and health literacy have difficulties comprehending and navigating through the information on the internet, downloading and using teleconsultation software, and understanding the already complex security safeguards and privacy policies necessary to effectively interact with telehealth devices (14, 15). Also, studies evaluating use of telehealth during the pandemic observed a lower

usage among people who were lower educated (16, 17). This so-called digital divide in which digital systems are more frequently used by people with higher education is of particular concern as people with lower education and fewer resources generally more often need ongoing medical care (11, 18). As such, academics have expressed concerns that ongoing digitalization of the health landscape may ultimately result in increasing health inequities and exclusion of those who are digitally disadvantaged (15, 19, 20). This issue is not new (20-22). In fact, the WHO has recognized the digital divide with risk of digital exclusion and unequal access as one of the biggest challenges posed by the digital transformation of healthcare (23).

Measuring eHealth literacy

Adequate assessment of eHealth literacy is instrumental in bridging the digital divide. Over the years, several instruments have been developed to measure eHealth literacy (24-28), with the eHealth Literacy Scale (eHEALS) the most commonly used (25, 28) due to its early development. The eHEALS measures perceived skills in finding, evaluating, and applying electronic health information related to health problems using first-generation internet based health services (25, 29). The instrument does, however, not fit with the evolving concept of eHealth literacy and today's broad scope of digital technologies which requires a wider range of competences (30, 31), like entering data in patient portals or health apps on a smartphone (30, 32). The Digital Literacy Instrument (DLI) was developed to overcome these limitations. Data collected have shown validity and reliability in a Dutch sample (24, 28). However, the instrument is performance-based and covers individual skills in digital health technology use, without capturing broader interactions with health technologies and services, including motivation to engage with digital health technologies.

The eHealth Literacy Questionnaire

To overcome the shortcomings of the eHEALS, the eHealth Literacy Questionnaire (eHLQ) was developed. The 35-item eHLQ is based on the eHealth Literacy Framework (eHLF), developed in 2012 with patients and medical professionals during a systematic concept mapping process (33). This framework includes individual factors that are necessary to use eHealth (e.g., engagement in own health), system factors (e.g., access to digital services that work) and user–system interaction factors (e.g., motivation to engage with digital services). The constructs were conceptualized into seven conceptually distinct dimensions that present a multifaceted understanding of eHealth literacy and are measured by the eHLQ (34, 35):

1. Using technology to process health information (five items)
2. Understanding of health concepts and language (five items)
3. Ability to actively engage with digital services (five items)
4. Feel safe and in control (five items)
5. Motivated to engage with digital services (five items)
6. Access to digital services that work (six items)

7. Digital services that suit individual needs (four items)

Each item is scored on a 4-point scale (strongly disagree, disagree, agree, strongly agree). The questionnaire was developed in Danish and English simultaneously "to support researchers, developers, designers, and governments to develop, implement, and evaluate effective digital health interventions" (35). As such, the eHLQ has been used to understand people's interaction with eHealth devices (34, 36, 37), to evaluate the association between eHealth literacy and health outcomes (38) and to inform the adaptation of health technologies (39). The eHLQ has been shown to have strong construct validity, reliability, is easy to use (35, 40, 41) and is intended to be used by policy makers, eHealth developers and researchers. It can be used in a wide range of settings including community health or hospitals and was designed for self-administration by pen and paper or by interview to ensure inclusion of persons with visual, reading or other difficulties. The questionnaire is supported by an instruction page including an explanation of terms used in the questionnaire.

Validity assessment

Use of a questionnaire in a novel linguistic setting requires translation, cultural adaption and validity assessment of the questionnaire, in order to determine that its properties have not been compromised and are equivalent to the original instrument (42). In the field of questionnaire validity testing, there is a growing acceptance of the view that the validity testing of self-reported instruments is as an accumulation and evaluation of different sources of validity evidence (43). As such, validation includes several supportive arguments on validity, rather than relying on factor analysis or regression analysis only (44, 45). The standards for Educational and Psychological Testing (in short, 'the Standards') are a set of guidelines which can be used to guide evaluation of validity evidence (46). The Standards, considered best practice in the field of psychometrics, proposes five sources of evidence: 1) test content; 2) response process (i.e., respondents' cognitive processes when responding to the items, such as understanding the instructions, interpreting the items as intended); 3) internal structure (i.e., the extent to which the items conform to constructs and constructs are conceptually comparable across subgroups and with repeated administration); 4) relations to other variables, and 5) consequences of testing (i.e., the robustness of the proposed instrument use including intended benefits, indirect effect and unintended consequences). By using evidence on content, response and internal structure as a framework, we build upon previous validation studies of the original instrument and systematically use different sources of validity. We used this evidence to inform the development of a Dutch version of the eHLQ and assess its properties. Relations to other variables (4) and consequences of testing (5) remain beyond the scope of this study.

Relevance and study aim

In line with global developments, the Netherlands is transforming its healthcare system and investing in various forms of eHealth. Accelerated by the COVID-19 pandemic, eHealth is increasingly adopted and implemented across various disciplines in primary

care (47) and secondary care (48, 49). Despite eHealth gaining ground, a comprehensive Dutch person-centred instrument to measure eHealth literacy is lacking. Hence, the aim of this study was to translate and culturally adapt the original eHLQ into a Dutch version, and to examine validity of the translated instrument.

Method

Overall study design

In this paper we report on the translation of the original eHLQ, and two studies performed to assess the initial validity evidence that was used to inform the final translation and cultural adaption. Our research was guided by the Standards to assess validity evidence. Figure 1 provides a schematic outline of the study design and the relation between the two studies. In Study 1, evidence on 1) content validity and 2) response process was collected using cognitive interviewing. In Study 2, the initial eHLQ was tested in a large sample and evidence on 3) internal structure validity was collected. Studies in cross-cultural adaptation of instruments often first perform cognitive interviews, then change wordings or phrasings, and subsequently evaluate psychometric properties of the final instrument (50, 51). We instead performed Study 1 and 2 simultaneously, which allowed us to use results from both studies in the decision on item revision and final translation, instead of changing items based on cognitive interview data only. In the final consensus stage, more weight was given to the cognitive interview data over psychometric data, considering the richness of qualitative data. As such, this study had a nested mixed-method design (52, 53). We formulated validity evidence arguments per source of validity evidence (see Table 5). The Dutch and other translations of the eHLQ are available upon request from the original developers and authors (LK, RHO)(54).

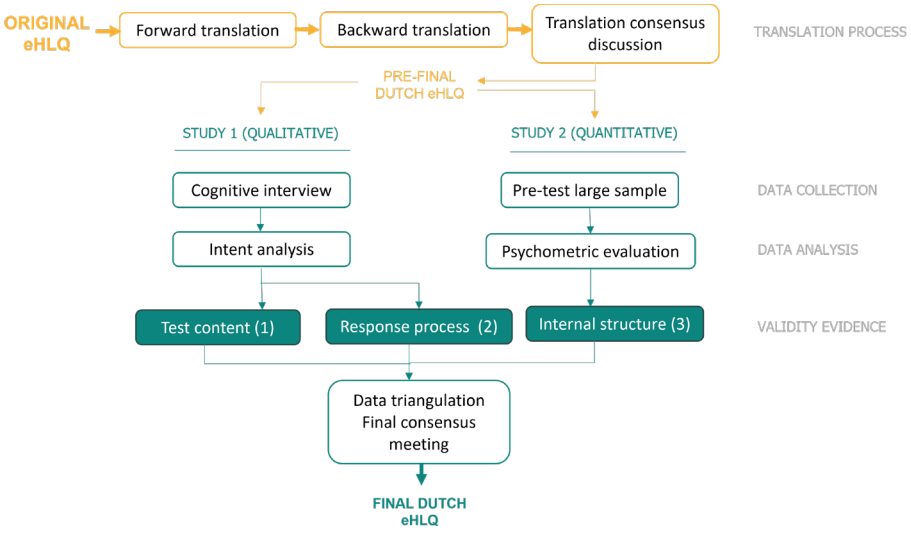

Figure 1. Schematic overview study design: a concurrent mixed-method design

Translation process

The original English eHLQ was translated into Dutch following the Translation Integrity Procedure (TIP) set up by the developers. The TIP is a documented systematic translation method that includes the careful specification of descriptions of item intent (55). It includes an item intent matrix describing the intended meaning and conceptual basis of each individual item, and a translation management grid that can be used by the translation team to guide the translation process. Both documents were used to track ambiguities, guide discussions on the nuances of item meanings and identify focus points for further evaluation. The steps are detailed below.

Forward translation

Two bilingual translators independently translated the original English eHLQ to Dutch, following the item intent guide. The first translator (CP), affiliated to the Leiden University Medical Center and the National eHealth Living Lab (NeLL) was knowledgeable about health and eHealth. The second translator (AR), a certified translator with rich expertise in medical research translation. The individual versions were compared and consensus on an initial translation was reached through discussion.

Back translation

The initial translation was then translated back to English by an independent translator (MS) who was blinded to the original English version of the questionnaire. The back-translator was a native English speaker, fluent in Dutch and a linguistic expert.

Translation consensus discussion

During a first translation consensus team meeting, the back and initial forward translations were compared against the original questionnaire and the item intent. The consensus team was composed of both forward translators (CP and AR), the backward translator (MS), the developer (LK) and an expert team, including two bilingual representatives (EM and PH), both working in health innovation, and a field worker (IM) experienced in questionnaire administration. Any ambiguities and discrepancies were documented and resolved during the meeting. The consensus meeting resulted in a version that was ready for pre-testing and generated a list of items to examine more closely during pre-testing.

Study 1: qualitative study

The first study aimed to assess validity evidence on test content and response process. Cognitive interviews were performed with a diverse sample of individuals who were considered potential future respondents of the Dutch eHLQ.

Method Study 1

Participants

Fourteen people participated (see Additional file 1 for demographics). This sample size was deemed sufficient to identify the most important problems (56). Inclusion criteria were able to read and express their thoughts in Dutch, and being 18 years of age or older. The Dutch eHLQ is meant to be used among the general Dutch population. While the 'general Dutch population' is an ambiguous definition we used purposive sampling, to ensure a wide variation in terms of demographics, health condition and prior experience with eHealth. Participants were recruited via various channels including posters in public areas of Leiden University Medical Center, various sports clubs in the region, patient organizations and the co-author's personal network.

People interested in participation were contacted by telephone to confirm their interest, to explain the study, and to schedule the interview. The interview was held at a quiet location (mostly the participant's home). Prior to data collection, written informed consent was collected.

Data collection

Cognitive interview

Cognitive interviews were held to assess the 1) test content and 2) response process. We adopted the validity arguments formulated by Cheng et al. in a validity study on the original eHLQ (41). The validity arguments for test content included themes, wording, format of items, administration and scoring. Assessment of the response process includes assessing whether the items were understood by the respondents as intended by the developers, whether items were understood similarly across subgroups, and whether the number of items, response format and instructions were appropriate.

The cognitive interviews were performed by an experienced qualitative researcher (CP) and a research assistant trained in cognitive interviewing, and lasted between 1.5 - 2 hours. The interviews followed a think-aloud approach in which respondents were asked to verbalize their thoughts while completing the questionnaire. This helps to understand the mental processes of respondents as they interpret questions and formulate answers, with minimal interference of the interviewer (57). In addition, problems regarding memory retrieval, ambiguities or unclear perspectives can be elucidated. The think-aloud exercise was complemented by spontaneous and scripted probing (58). Spontaneous probes were used based on a respondent's response such as signs of hesitation (e.g., responses to certain items taking longer than to other items) and included questions such as 'I saw you hesitate while answering item [X]. Could you explain why?'. Scripted probing helped to explore items which needed further exploration according to the consensus teams. Scripted probes were 'what does [word or phrasing] mean to you?'. The subsequent structured part of the interview was guided by a manual containing items and scripted probes. The combination of a respondent-driven approach (think aloud) and an interviewer-driven approach (scripted probing)

shows the cognitive processes of the interviewee, while also being able to reflect on ambiguous or problematic items in detail (58, 59). To minimize the cognitive burden on participants, the interview was divided in 3 parts. Participants first completed the first 11 items, thinking aloud, and then responded to scripted probes. This process was repeated for the next two sets of 11 items. Participants received a 20-euro gift card for their participation.

Debriefing sessions were held among the researchers to reflect on the interviews and the interview guide, and to include emergent probes (scripted probes) based on previous interviews. For example, if multiple participants felt an item was ambiguous or unclear, a scripted probe was added to the interview guide to examine the item further.

Data analysis

Interviews were analysed through an item-to-item review, guided by the first three stages of Hacomb's six-stage model (60). We audio recorded the interview and took notes during the interview (step 1), held debriefing sessions after a set of three interviews (step 2), and had three researchers familiarize themselves with the data (step 3). Responses relevant to item interpretation were then transcribed, organized per item, compiled for all participants and reviewed item-per-item. For the item-per-item review, responses were compared to the item-intent guide, carefully examining whether the items were understood as intended. Item response problems were coded following the problem item classification coding scheme by Knafl and colleagues, classifying problematic items based on the type of problem encountered (61). The coding scheme included the following code categories: (a) limited applicability; referring to a comment on groups of people or situations for which the item is or would not be appropriate (b) unclear reference; referring to lack of clarity regarding what aspect, condition or situation the item is intended to address, (c) unclear perspective; pointing towards problems in clarity regarding the perspective from which the items should be answered and (d) problems with wording or tone. We also assessed clarity of response options, recall problems and resonance with local worldview (57).

Results study 1

Cultural adaptation during translation process

During the translation process several items required cultural adaption to appropriately reflect their meaning in Dutch. First, English expressions such as 'make technology work for me', 'works together' 'find my way' and 'have good conversation' lack meaningful direct translation into Dutch. Alternative translations were tested and included as scripted probing during the cognitive interviews. Second, nuances between 'sure' and 'confident' and 'good conversations about health' and 'take part in conversations about health' were discussed and explored further during the cognitive interviews, to ensure content validity and sufficient contrast between the items. Third, back translation deviated somewhat from the original wording, as more common phrasings were

preferred to literal translations (i.e., 'those who need it', 'measurements about my body', 'organise'). Content validity was explored using scripted probes. Lastly, cultural adaptation was needed for some terms included in the terminology list.

Results on test content and response process

Fourteen cognitive interviews were held. The age of the participants ranged between 27 and 73 years old (median age 61); ten participants were male; six were considered low educated; six indicated that they did not have affinity with digital technology. Their previous eHealth experiences were mainly smartphone and computer use. Some also had a digital blood pressure device or used an online patient portal from their healthcare provider (see Additional file 1 for an overview of respondent's characteristics).

Respondents' comprehension of the Dutch eHLQ was satisfactory as they were able to adequately comment on their responses with respect to each item. Respondents generally understood the response options and were able to distinguish among them, although some participants desired additional scoring option 'not applicable' for items referring to 'problems with my health' and 'all the health technology I use'.

Respondents commented on limited applicability, unclear reference and problems with wording or tone for 12 items. In addition, a problem in resonance with local worldviews was found in four items. No problems were found regarding unclear perspective, recall problems or clarity of response options (see Additional file 4).

Wording or tone. From the items marked for additional exploration based on the cultural adaption in the translation phase, four items were classified as problematic due to problems with wording or tone. The Dutch word for the word 'organise' (NL 'ordenen') in the item 'organise my health information' was confused with 'sorting things in/on colour or shape'. Other wording problems included 'take care of my health', 'work together' and 'monitor'.

Limited applicability. Limited applicability was seen in two ways 1) items concerning health problems (i.e., people without health problems), 2) items on use of digital health services (i.e., people not using digital health services).

Unclear reference. Four items were marked by an unclear reference. Participants were unsure whether an item referred to their own health or health in general (i.e., 'health problems in general or my health problems'; item 11 and 20). The majority also struggled with the word 'nuttig' in item 6 (English translation 'work for me'), indicating that it was too vague. Despite the terminology list, participants who were less familiar with eHealth were unsure what health technology and health technology services included, and wondered whether it also included telephone and email.

Resonance with local worldviews. Cognitive interviews also revealed a problem in resonance with worldviews in 8 items. Participants who frequently used eHealth privately or professionally, expressed their wish to have 'all technology work together' (item 23) and have information about their health always 'available to those who need it' (item 3), but had had no such experience. Participants less familiar with eHealth

had difficulties responding to these items and with understanding the items within their references and knowledge on digital health technologies. Some participants also had difficulties responding to three items from domain 7 on 'digital services that suit individual needs' (items 28,31 and 34) as they found it difficult to envision how technology services can adapt to someone's skills. Only two respondents, who were professionally involved in eHealth, responded with thinking of 'self-learning machines' and 'artificial intelligence', thereby voicing the items' intent most closely. The dissonance with local worldviews can point to differences in how items of the eHLQ are interpreted across subgroups. Differences were mainly observed based on having a current diagnosis, previous eHealth experience and educational level.

Besides the above-mentioned issues, we noted that all respondents remarked on similarity of items 19 and 20, and items 22 and 30. Although there were no intent or content problems (i.e., respondents noted the nuance differences), some respondents noted that having very similar items could cause irritation and advised to include a remark on having similar items in the instructions.

Study 2 – quantitative study

Study 2 was performed to perform psychometric evaluation and assess internal structure of the pre-final eHLQ. The pre-final eHLQ was administered among the 1650 people participating in the FitKnip study. The size of the sample was conform the sample size requirements for factor analysis and deemed sufficient (62).

Method Study 2

Participants

The eHLQ was administered online among participants of the FitKnip study, as part of its baseline measurements. The FitKnip study evaluated the use of a digital health budget as an innovative way to improve population health. Participants received a digital health budget of 100 euro to purchase preselected mobile or web applications offered on the online FitKnip library. People were recruited via municipality teams and various institutions, including healthcare insurance companies, an organization for vital and healthy neighbourhoods, and patient organizations. People had to be 18 years or older, able to understand, read, and speak the Dutch language and have access to the internet, but no other in- or exclusion criteria were applied.

Data collection

The eHLQ was included in a battery of six questionnaires on mental and physical health, general wellbeing and health awareness, and administered online among the FitKnip participants. Participants provided digital informed consent for the entire study prior to completing the questionnaire. The questionnaire battery was sent to 2562 participants and returned by 1650 respondents within 1 month (response rate 64%). There was no missing data among the 1650 returned eHLQ questionnaires. Participants received

access to their digital health budget after completing all six questionnaires. Within the study demographic data, age, gender and educational background were collected. Educational level was categorised as low (no education to lowest high school degree), middle (vocational training to highest high school degrees) and high (university of applied sciences degree and research university degree). People were also asked to indicate whether they had a current medical, physical or psychological diagnosis.

Data analysis

Preparatory analyses

Descriptive statistics were used to describe the means and standard deviations of individual items, and to identify floor or ceiling effects. Internal consistency for the seven domains was evaluated using a Cronbach's alpha, with a Cronbach's alpha of at least 0.7 considered acceptable (35).

Confirmatory factor analysis

We conducted confirmatory factor analysis (CFA) to assess the internal structure of the translated eHLQ. CFA was performed as the eHLQ has a pre-specified factor structure. We evaluated the extent to which the items loaded on the seven hypothesized scales (i.e., the latent factors) based on the seven dimensions that the eHLQ intends to measure. CFA was performed using the R package Lavaan in R version R-3.6.1 (63). We fitted a seven-factor CFA model allowing for correlation between latent factors. The Diagonally Weighted Least Squares estimator was used, which is the recommended estimation for ordinal data (64). The CFA provided the standardized and unstandardised factor loadings between item responses and the underlying latent variables. In line with the original eHLQ development study, we report on the robust indexes Comparative Fit Index (CFI), Tucker-Lewis index (TLI), Standard Root Mean Square Residual (SRMR) and Root Mean Square Measure of Approximation (RMSEA). We used the following threshold values for the test of good model fit; CFI >0.95, TLI >0.95, SRMR<0.08 and RMSEA <0.06 and the thresholds: CFI >0.90, TLI >0.90, and RMSEA< 0.08 as indicators for reasonable fit (65). We deemed an item factor loading of 0.4 substantial (66). Items that performed poorly on the above criteria were flagged. To further examine the flagged items, possible model improvements were performed.

Invariance testing and multi group comparison

Based on previous studies on health literacy and eHealth literacy, and the cognitive interviews, we hypothesized that the demographic characteristics age, gender, educational background and self-reported current diagnosis may affect how the items are interpreted and thus introduce measurement invariance. Hence, we defined the following subgroups prior to performing CFA: Age ≤45 years versus >45 years (median split), gender, high vs. middle and low educational background, and diagnosis yes vs. no. Of the 1650 participants, 467 (28.3%) were male, 1307 (79.2%) were highly educated, and 595 (35.9%) reported to currently have a diagnosis. To investigate measurement invariance within these subgroups we performed invariance testing.

From a measurement perspective, the use of multiple-item composite scales for group comparisons depends on the demonstration that: (a) the same factor structure underlies the item responses in all groups of interest (configural invariance); (b) the factor loadings are equivalent across groups (metric invariance); and (c) item intercepts (thresholds in the case of ordered categorical variables) are also equivalent across the groups (scalar invariance) (67, 68). We performed a series of nested model comparisons with increasingly stringent equality constraints each time. The fit of each model was compared with the fit of the previous (less restricted) model. When invariance could be obtained, we moved on to the next, more restricted model. We adhered to the rule of thumb to interpret differences in CFI of >0.01 as significant differences (69) and maintained a significance level of $p<0.05$. For items with insufficient endorsement (≤2) of the response category "completely disagree", this category was collapsed with the "disagree" category.

We performed exploratory analyses to identify patterns of eHLQ scale scores (i.e., total observed scores for each domain) across a range of sociodemographic variables. We performed post-hoc tests for differences between groups based on gender, age, education and having a current diagnosis using independent t-tests and ANOVAs. Effect sizes were calculated using Cohen's d with the interpretation of effect size as: small < 0.20 to 0.50; medium between 0.50 and 0.80 and large > 0.80.

Ethical considerations

The cognitive interview study and the FitKnip study were cleared for ethics by the Medical Ethical Review Committee of the Leiden University Medical Centre (No. 19 – 078 and P20.001, respectively). Written informed consent was obtained from each participant prior to study activities.

Results study 2

Participants Demographics

Participant characteristics are depicted in **Table 1**. The majority was female (71%) and between 35 and 54 years old (mean (SD); 45.05 (13.28). 1556 (94.3%) of the participants had a Dutch Nationality. The large majority (78.2%) reported having finished a high education, was employed full-time (43,8%) and lived with a partner and children (35.1%) or only with a partner (33.1 %). About one third (30.1%) of the participants had a BMI above 25, indicative of overweight and 18% had a BMI above 30, indicative of obesity. In total 592 (35.9%) reported having a current medical, physical or psychological diagnosis, and over one third (38.4%) had used a form of healthcare the past month. Details concerning the study design and data collection are provided elsewhere (70).

Preparatory analyses

For each eHLQ item, the distribution of responses, the mean and standard deviation, and Cronbach's alpha are reported in Additional file 2. Alpha values show acceptable to good internal consistency for all seven scales (range 0.66 to 0.80).

Table 1. Characteristics of participants in study 2 (n = 1650)

	n (%)
Gender	
Male	467 (28.3)
Female	1177 (71.3)
Gender neutral	6 (0.4)
Age (years)	
Mean ± SD	45.05 ± 13.28
18 t/m 34	447 (27.1)
35 t/m 54	776 (47.0)
55 t/m 74	406 (24.6)
75 and older	21 (1.3)
Nationality	
Netherlands	1556 (94.3)
Suriname	16 (1.0)
Germany	10 (0.6)
Belgium	8 (0.5)
Morocco	6 (0.4)
Other	51 (3.1)
Missing/unknown	3
BMI (kg/m2) 1	
Mean ± SD	25.80 ± 5.05
Education	
Low	58 (3.5)
Middle	285 (17.3)
High	1307 (79.2)
Living situation	
Living with partner	547 (33.1)
Living with partner and child(ren)	580 (35.1)
Living alone	316 (19.1)
Others	207 (12.5)
Employment status	
Student	58 (3.5)
Employed full-time	722 (43.8)
Employed part-time	450 (27.3)
Volunteering or retired	156 (9.5)
Unemployed. on sick leave	173 (10.5)

Table 1. Characteristics of participants in study 2 (n = 1650) (continued)

	n (%)
Other	91 (5.5)
Self-reported diagnosis	
Yes	592 (35.9)
No	1058 (64.1)
Utilisation healthcare past month	
Yes	365 (38.4)

Construct validity

A seven factor CFA model was fitted to the 35 eHLQ items, allowing correlation between latent factors. Standardized factor loadings were 0.51 or higher (range 0.51 to 0.84). The CFI and TLI indicated acceptable model fit (0.936 and 0.930, respectively). The RMSEA and SRMR (0.088 and 0.085, respectively) indicated that the model fit was not acceptable. However, it is not uncommon for fit indexes to show less than optimal values with large numbers of observed variables, like in the current study. Similar values for fit indices have also been reported for the closely related Health Literacy Questionnaire (71). Closer inspection of correlation matrices indicated substantial residual correlations between items 4, 6, 7, 20 and 26. We inspected whether goodness of fit improved when allowing correlation between these items. Goodness of fit indices improved for the CFI and SRMR, exceeding the cut-off value for good fit. Considering that item 26 ('I use measurements about my body to help me understand my health') showed strong residual correlation with seven other items and goodness-of fit improved, item 26 was flagged for discussion (see Table 2). Correlation matrices are provided in Additional file 2.

Table 2. Model fit indices for the seven-factor confirmatory factor analysis of the Dutch version of eHealth Literacy Questionnaire

	Chi square	DF	CFI	TLI	RMSEA (95% CI)	SRMR	Goodness of fit
Seven factor model	7429.201	539	0.936	0.930	0.088 (0.086 -0.09)	0.085	Acceptable fit
Seven factor model – improved model	5960.518	527	0.950	0.943	0.079 (0.077-0.081)	0.077	Good fit

DF, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker-Lewis index ; RMSEA, Root Mean Square Measure of Approximation; SRMR, Standard Root Mean Square Residual

Invariance testing

Invariance testing for subgroups based on age, gender, education and current diagnosis showed configural invariance, indicating that the overall factor structure of the eHLQ is the same between subgroups. We did not obtain full metric invariance in any of the subgroup comparisons (**Table 3**). Following the significant $\Delta\chi 2$ tests, we examined the univariate test scores and identified the item loadings which showed the strongest lack of invariance, indicated by larger chi-square values. Lifting between-group equality restrictions on these loadings, we obtained models of partial metric invariance: We lifted restrictions on loadings of items 15, 21, 23 and 26 for comparison of age groups; items 20, 19 and 29 for gender; items 10, 14, 22, 30 and 31 for educational level and items 11, 19, 23 and 25 for current diagnosis and. All models improved and partial metric invariance was supported, indicating that the model is partially metric invariant (see **Table 3**). Next, we applied between-group equality restrictions to item thresholds, which proved tenable according to the non-significant decreases in $\Delta\chi 2$ tests (**Table 3**). Closer examination of the non-invariant items showed comparable factor loadings between groups and standard errors below 0.1, except for item 19, hence we concluded that the items were sufficient invariant to allow comparison of scores between groups (See Additional file 3).

Comparison of scores between groups

Comparison of mean scores between subgroups are presented in **Table 4**. The group of people with people 45 years or older consistently had lower scores than the younger age group. Statistically significant differences were found for domains '2. Engagement in own health', '3. Ability to actively engage with digital services' and ' 7. Digital services that suit individual needs, however effect sizes were small (range 0.38 to 0.12). Comparison of mean scores across educational level (low vs. high) showed moderate effect sizes on the domain scores domains 2. 'Engagement in own health', 3. 'Ability to actively engage with digital services', 6. 'Access to digital services that work' and 7. 'Digital services that suit individual needs', with people with lower education scoring lower for all, except domain 4. 'Feel safe and in control'. People with a current diagnosis scored significantly higher on domain 1. 'Using technology to process health information', 2. 'Engagement in own health' and 6. 'Access to digital services that work' but again effect sizes were small (range 0.13 to 0.26).

Table 3. Results of invariance testing among a priori subgroups (n=1650)

	X^2	DF	CFI	TLI	RMSEA (95% CI)	SRMR	ΔX^2	ΔDF	P-value significance level
Age (18-45 yr vs ≥ 45 yr)									
Configural invariance	8040	1078	0.939	0.932	0.089	0.088			
Metric invariance	8348	1106	0.936	0.931	0.089 (0.089 - 0.091)	0.090	80.919	28	<.001
Partial metric invariance [a]	8186	1102	0.938	0.933	0.088 (0.087-0.089)	0.089	41.310	24	<.05
Scalar invariance	8402	1168	0.936	0.935	0.087(0.085 – 0.088)	0.088	68.921	62	n.s.
Gender (male vs female)									
Configural invariance	8004	1078	0.937	0.930	0.088 (0.087 -0.090)	0.089			
Metric invariance	8252	1006	0.935	0.934	0.086 (0.084 - 0.088)	0.089	54.740	28	<.001
Partial metric invariance [b]	8136	1103	0.936	0.930	0.088 (0.086 - 0.090)	0.089	34.861	25	n.s.
Scalar invariance	8237	1167	0.935	0.934	0.086 (0.084 -0.088)	0.089	12.720	61	n.s.
Education (low and middle vs high)									
Configural invariance	7733	1078	0.940	0.933	0.087 (0.085-0.088)	0.085			
Metric invariance	8026	1106	0.937	0.933	0.087 (0.085 - 0.089)	0.087	51.676	28	< .01
Partial metric invariance [c]	7891	1103	0.938	0.933	0.087 (0.085 - 0.088)	0.086	36.055	25	n.s.

Table 3. Results of invariance testing among a priori subgroups (n=1650) (continued)

	X^2	DF	CFI	TLI	RMSEA (95% CI)	SRMR	ΔX^2	ΔDF	P-value significance level
Diagnosis (yes vs no)									
Configural invariance	8080	1078	0.937	0.93	0.089 (0.087 -0.091)	0.088			
Metric invariance	8382	1106	0.935	0.930	0.089 (0.088 - 0.091)	0.090	73.577	28	<.001
Partial metric invariance [d]	8198	1102	0.936	0.931	0.088 (0.087 - 0.090)	0.089	32.745	24	n.s.
Scalar invariance	8343	1168	0.935	0.934	0.086 (0.085 - 0.088)	0.089	18.489	62	n.s.

CFI, comparative fit index; CI, 90% confidence interval; DF, degrees of freedom; RMSEA, root mean squared error of approximation; SRMR, standardised root mean squared residual; df, degrees of freedom; n.s., non-significant

a lifted restrictions on loadings of items 15, 21, 23 and 26;

b lifted restrictions on loadings of items 20, 19 and 29

c lifted restrictions on loadings of items 10, 14, 22, 30 and 31;

d lifted restrictions on loadings of items 11, 19, 23 and 25.

Table 4. Comparison of mean domain scores between a priori subgroups (n=1650)

	1. Using technology to process health information	2. Engagement in own health	3. Ability to actively engage with digital services	4. Feel safe and in control	5. Motivated to engage with digital services	6. Access to digital services that work	7. Digital services that suit individual needs
Age							
18 - 45 yr (n=447) (ref)	2.83	3.07	3.24	2.79	2.89	2.52	2.59
≥45 yr (n=776)	2.83	3.02*	3.06***	2.78	2.88	2.54	2.50***
Cohen's d (95% CI)	0.00 (-0.10 -0.10)	0.12 (0.02 -0.21)	0.38 (0.28 -0.47)	0.02 (-0.08 -0.12)	0.03 (-0.07 -0.12)	-0.04 (-0.14 -0.06)	0.19 (0.09 -0.29)
Gender							
Men (n=467) (ref)	2.82	3.02	3.18	2.78	2.96	2.52	2.55
Women (n=1177)	2.83	3.06	3.14	2.79	2.86***	2.53	2.55
Cohen's d (95% CI)	0.00 (-0.11 -0.11)	-0.10 (-0.21 – 0.00)	0.10 (-0.01 – 0.21)	-0.02 (-0.13 – 0.09)	0.26 (-0.14 – 0.08)	-0.03 (-0.14 -0.08)	0.00(-0.10 – 0.11)
Educational level							
Low (n=58) (ref)	2.72	2.81	2.90	2.98	2.83	2.74	2.66
Middle (n=285)	2.85	2.94	3.09**	2.94	2.92	2.71	2.67
High (n=1307)	2.83	3.08***	3.17***	2.74**	2.88	2.48***	2.52
Cohens' d (low vs middle)	-0.32 (-0.60 –0.04)	-0.34 (-0.62 - -0.05)	-0.44(-0.73 –0.16)	0.10 (-0.19 – 0.38)	-0.23 (-0.52 -0.05)	0.05 (-0.23 -0.33)	-0.03 (-0.31 -0.25)
Cohen's d (low vs high)	-0.24(-0.50 – 0.02)	-0.67 (-0.93 –0.41)	-0.60(-0.86— 0.34)	0.50 (0.24-0.76)	-0.14 (-0.40- 0.12)	0.58(0.32-0.84)	-0.28 (0.02-0.55)

Table 4. Comparison of mean domain scores between a priori subgroups (n=1650) (continued)

	1. Using technology to process health information	2. Engagement in own health	3. Ability to actively engage with digital services	4. Feel safe and in control	5. Motivated to engage with digital services	6. Access to digital services that work	7. Digital services that suit individual needs
Age							
18 - 45 yr (n=447) (ref)	2.83	3.07	3.24	2.79	2.89	2.52	2.59
≥45 yr (n=776)	2.83	3.02*	3.06***	2.78	2.88	2.54	2.50***
Cohen's d (95% CI)	0.00 (-0.10 -0.10)	0.12 (0.02 -0.21)	0.38 (0.28 -0.47)	0.02 (-0.08 -0.12)	0.03 (-0.07 -0.12)	-0.04 (-0.14 -0.06)	0.19 (0.09 -0.29)

Ref: reference group; CI: confidence interval

***p < .001, **p < .01, *p < .05

Data triangulation study 1 and study 2 and final revision

Evidence from both studies and all sources was collected, combined and triangulated. Table 5 presents a summary of the evidence collected for the three sources of validity evidence (i.e., test content, response process and internal structure). Overall, no large response process problems were found, the items were interpreted as intended, and the internal structure was equivalent to the original eHLQ with acceptable to good model fit indices. The items which were flagged based on the cognitive interviews were compared with the results from the CFA and invariance testing and discussed during a final consensus meeting.

Closer examination of the items contributing to non-invariance among the subgroups for current diagnosis showed that item 11 ('I often use technology to understand health problems') had the largest contribution. Two other items were identified as 'problem resonance worldview' based on the cognitive interviews, indicating that people with a diagnosis probably interpret the item as referring to their own health, whereas those without a diagnosis probably interpret the item as referring to 'health in general'. As such, interpretation of these items may depend on presence of a current diagnosis or not. Likewise, the items contributing to non-invariance between the age subgroup could be differently interpreted based on healthcare use as the older group probably had more healthcare use experience overall. Closer examination of the non-invariance among the subgroups showed that four of the five items load to domain 4 'feel safe and in control'. While no problems were encountered in the cognitive interviews, the observed partial invariance and inconsistency in scoring patterns could point towards a difference in interpretation.

Eight items were amended following discussion of the findings and flagged items with the consensus team and developers. In addition, we formulated several recommendations for those using the eHLQ that can support the use, administration and interpretation of the eHLQ (see Table 6).

Table 5. Summary of the three sources of validity evidence for the eHealth Literacy Questionnaire

Validity argument	Evidence collected
1. Test content	
1.1 The items are clear and understandable to everyone without any technical jargon	No evidence of major misunderstanding observed during cognitive interviewing. The wording or tone of four items were amended based on cognitive interviews and CFA results.
1.2. The number of items is appropriate and will not cause unnecessary burden on respondents	No missing values were reported in study 2, indicative of not being overly burdensome for respondents. Number of items was deemed appropriate.
1.3. The eHLQ can be administered in various formats to ensure respondents with varied skills can participate	Paper-based format (study 1), face-to-face interviews (study 1) and web-based format were administered. No problems were encountered among any of the formats.
1.4 The paper-based or web-based formats of items allow for easy response to items	Some issues were identified in responding to the items during cognitive interviews. The issues related to discordance in resonance with worldviews.
2. Response process	
2.1 The response option of a four-point ordinal scale is appropriate	Four participants desired an additional response option for the items identified as problems with limited applicability.
2.2. Formats of administration do not affect the cognitive process of responding to the items	Not evaluated. Prior studies show no difference in administration formats (41)
2.3 The items are understood by respondents as intended by the test developers	Twelve items showed problems in limited applicability, unclear reference and problems with wording or tone. Comparison to CFA results and discussion with the consensus team led to the revision of eight items.
2.4 The items are understood in the same way by respondents as intended across subgroups.	Differences in interpretation were seen during cognitive interviews based on (digital) healthcare use. Eight items were identified as having problems with 'limited applicability' or 'resonance with worldview'. This observation was confirmed by invariance tests demonstrating partial invariance between groups based on current diagnosis.
	Differences in interpretation can be the result of prior experience with digital health technology use. We recommend administers of the eHLQ to collect contextual information on prior and current eHealth use and diagnosis.
	Also recommend collecting eHLQ validity evidence in different settings and populations and perform invariance testing based on eHealth experience.

Table 5. Summary of the three sources of validity evidence for the eHealth Literacy Questionnaire (continued)

3. Internal structure	
3.1 The items of each construct reflect a spectrum of the relevant construct such that the resulting score is a good indicator of the construct	Only item 26 showed strong residual correlation with seven other items, indicating that the item relates strongly to other items and the underlying latent factor.
3.2 The eHLQ is a multidimensional tool consisting of seven independent constructs with 4 to 6 relevant items for each construct and such items are related only to the designated construct	CFA confirmed adequate model fit for the seven-factor model. Model and fit indices were acceptable. Standardized factor loadings were 0.51 or higher (range 0.51 to 0.84). No significant cross-loadings were identified.
3.3. The eHLQ demonstrates measurement equivalence across subgroups and settings	eHLQ is partially invariant for subgroups age, gender, educational level and current diagnosis. Items displaying potential non-invariance were revised, triangulated with cognitive interview data and resulted in amendment of four items.
3.4 The eHLQ produces stable and consistent results	Cronbach alpha levels were acceptable. Pre-testing was not performed

a validity argument adopted from Cheng et al (40).

Table 6. Recommendations for future eHLQ use, score interpretation and reporting by researchers and others

Recommendations	
1.	Collect contextual information such as prior eHealth experience, and current diagnosis, depending on purpose of use and use in score interpretation.
2.	Perform validity analysis in new contexts to build further validity arguments for use of the Dutch eHLQ
3.	Perform cognitive interviews when used in a new context to test if intended interpretation of data is valid for the new context and reason for testing
4.	Include description of local or national digital healthcare context, depending on context and purpose of use.

Discussion

This paper reported on the systematic translation of the eHLQ into Dutch and initial validity evidence. We used evidence on test content, response process and internal structure to further refine and culturally adapt the Dutch eHLQ. This validity-driven approach created an in-depth understanding on content, response process and internal structure of the Dutch eHLQ. Our study builds on a well-established line of research and strengthens the continuous strand on validity evidence of the eHLQ as

a global instrument to measure eHealth literacy.

The translated and culturally adapted eHLQ items were found to be highly coherent with the original intended item meanings and demonstrated good internal structure, comparable with the original eHLQ (35). All 35 items loaded strongly or moderately on their respective factor. After one modification (i.e., allowing residual correlations with item 26 'I use measurements about my body to help me understand my health'), the model showed good fit with the data. Item 26 showed similar residual correlation issues in a validity study in an Australian population (41) and in Taiwan using a Mandarin version (72). In fact, both studies found a lower factor loading (factor loading 0.36 and 0.56 respectively) than our study (factor loading 0.61). Hence, it is unlikely that the observed validity issue with item 26 results from translation or cultural adaption, but rather is a characteristic of the item that is notable across settings and languages. We also tested invariance of item loadings and thresholds between age, gender, education and current diagnosis groups, and found that only a small subset of loadings differed between groups, indicating that the eHLQ measures largely the same construct in the same manner, in different groups.

Multi-group comparison showed that, overall, people who were younger scored higher across domains. This is in line with other literature demonstrating that older age is associated with lower eHealth literacy (73). We also observed that people with a lower education overall scored lower than those with a higher education. This is in line with previous eHLQ studies and with the notion that, generally, people with lower education use eHealth less often (72, 73). Interestingly, and contrasting with previous studies, in our study, people with lower education scored higher on the domain 'feel safe and control'. At the same time, items that loaded on this domain showed metric non-invariance based on education. Hence, the higher score could potentially result from a difference in interpretation between people with low and high education, rather than reflect true differences in domain 4 'feel safe and control'. Future research should explore these observed differences further.

Our approach of collecting and combining the three sources of validity evidence to inform the final translation and cultural adaption of a questionnaire is a new, highly disciplined and transparent approach to validity testing, informed by contemporary validity testing theory (45). By combining the insights from the cognitive interviews with results from CFA and invariance testing, we were able to leverage both the depth of qualitative data as well as the quantitative power of large sample analysis and psychometric evaluation methods. While cognitive interviews were successful in identifying items which demonstrated potential problems (in wording, phrasing, or resonance with world views), CFA helped to understand if and how interpretation issues may affect the internal structure. Vice versa, the qualitative data helped to interpret CFA results, such as lower standardized factor loadings in some subgroups, that may indicate interpretation difficulties. However, low factor loadings on itself do not provide information of where the problem lies. Therefore, in-depth exploration of response process and how items are interpreted using cognitive interviewing was important. Hence, with our approach, we were able to better understand the

source and impact of these intricacies and make well-substantiated amendments to eight items. In addition we formulated several recommendations to support the use, administration and interpretation of the eHLQ (see Table 6).

Our approach can be considered an amalgamation of an ideographic approach (i.e., the participant is considered a unique individual with a unique life history) and a nomothetic approach (i.e., the participant is an exemplar of a population with corresponding traits). From an ideographical perspective, the qualitative component of cognitive interviewing is used to understand how items are interpreted by an individual and how this is affected by previous experiences in medical and psychosocial domains (e.g., previous positive experience in using eHealth, previous diagnosis, healthcare use, etc.). From a nomothetic perspective, items scores and latent factor structures are a result of subjects being an exemplar of a given population with (assumed) corresponding personal traits and behaviours and whose behaviour can at least partially be explained following certain rules. This strong nomothetic approach forms the foundation of psychometric evaluation, with use of standardized methods and statistical analysis as the basis. As such, our combined approach allows us to understand in more depth how items are interpreted by individuals, and to combine this information with generalized findings from the CFA to inform the final instrument. Hence, this mixed-method approach creates a conjunction between ideographic and nomothetic perspectives in instrument design and underlines the importance of considering both approaches in the understanding of complex constructs such as eHealth literacy.

An important strength of our research is that we followed a systematic, uniform translation approach and aligned our validity assessment with initial validation studies. This uniform process facilitated international comparison and helped to understand whether a validity issue has arisen during the translation process or can be considered an item characteristic and deemed acceptable. We undertook several steps to ensure validity during the translation and cultural adaption process. First, the translation process followed a rigorous translation procedure including forward and backward translations. Second, we used the Translation Integrity Protocol developed by the developers of the original instrument, using detailed specification of item intents and consensus meeting with the consensus team and developers. With this we ensured that the items in the Dutch version captured the same meaning and difficulty level compared to the original questionnaire and the subsequent translations into twenty other languages. Third, we carefully documented all steps of the process, and ensured that both the developers and people with clinical, research and linguistic expertise were engaged in the translation process. Fourth, we analysed the cognitive interviews following an analysis framework and discussed results with the consensus team.

Limitations and strengths

A drawback of our study is that the study sample from study 2 is drawn from an existing study population. Although using an existing sample is a cost-effective sampling method and has resulted in a large sample to draw conclusions, using an existing sample has some limitations. First of all, the single administration of the eHLQ did not allow for a test-retest comparison to provide further evidence on the stability

and consistency of results. Second, given that the study focuses on health budget and health apps, study participants were probably more highly sensitised to eHealth than the general population. However, given that eHLQ scores were comparable with previous eHLQ studies, it is unlikely that this has biased our results. The sample was also not fully representative in terms of educational level and nationality, with an over representation of high education and Dutch nationality. Nonetheless, we encourage researchers to be aware of the multi-cultural Dutch populations when evaluating eHealth Literacy in a Dutch setting and considering the most appropriate language based on the study population. Importantly, our population included both people with a current diagnosis as well as without (72). This increases the generalizability and applicability of our findings as the eHLQ has been developed to be used in a wide range of settings.

Another limitation may be the use of cognitive interviewing to assess response process and test content. Cognitive interviewing has been criticized and considered inappropriate for people who are less articulate and find it difficult to verbalize their thought process. Consequently, this could result in overestimation or underestimation of response difficulties (i.e., difficulties in articulation of thoughts interpreted by the investigator as response process issues or the other way around, when people are unable to accurately articulate the problems, they encounter). We tried to minimize this limitation by combining think-aloud as a primarily respondent-driven with scripted-probing as a more interviewer-driven approach. Finally, a limitation of our approach is that we have not evaluated the eight items we improved on validity. Considering the minor changes made in wording we expect that the internal structure validity will remain equivalent to the original. Nonetheless, in line with The Standards and the establishment that tests, or instruments are themselves not valid or invalid, but rather are valid for a particular use, we encourage researchers to use this initial validity evidence, build on it and always consider validity of the eHLQ in the context of the particular use and intended purpose.

Implications for practice and research

Our findings have implications for future use of the eHLQ by policy makers, eHealth developers and researchers in understanding people's eHealth literacy. Researchers should collect relevant contextual data (e.g., experience with technology, current diagnosis) to aid the interpretation of eHealth literacy scores and understand score differences between groups. For example, we noticed differences in the interpretation of 'health technology' and 'health technology services' depending on former experience with eHealth. Also, contextual information on current diagnosis and/or extent of healthcare usage can aid score interpretation.

Next to the use of contextual information of the individual, researchers should interpret their eHLQ scores in light of the local or national digital healthcare context (macro context) (74). Understanding of the digital landscape from a macro perspective, in terms of the delivery, access, integration, and (inter)connectivity of systems and services is particularly important in the interpretation of scores for domain 6 'Access to digital services that work' and domain 7 'Digital services that suit individual needs'.

While the items touch upon the maturity of healthcare systems and services, response processes may be country specific and affected by the national advancement in the health technology infrastructure (e.g., access to a national infrastructure for telehealth solutions, use of centralized health databases) (74). Building on the existing literature that explores the link between relatable concepts such as motivation, engagement, trust, activation and health literacy, we propose that future studies should investigate the relationship between eHealth literacy and related concepts (75, 76). In addition we suggest that future research should investigate the role of these constructs in determining health outcomes and how they can be incorporated in the design of health interventions to foster meaningful patient engagement in the digital health landscape.

The eHLQ's large number of items makes the questionnaire less suitable for use in practice. There is a need among healthcare professionals to assess the eHealth literacy needs of their patients (77). To address their needs, the eHealth Literacy Assessment toolkit (eHLA) was developed in parallel to the eHLQ (34). The toolkit employs a combination of existing and newly developed scales to assess individuals' health literacy and digital literacy across the seven dimensions of the eHLQ (78) . Our findings could inform the development of a Dutch version of the eHLA, which could assist in the implementation and evaluation of digital health technologies and services.

Conclusion

We systematically performed and combined several procedures to generate comprehensive validity evidence of the eHLQ and conducted informed further refinement of the eHLQ. The objective of this study was to provide initial evidence on the validity and use of the eHLQ as a Dutch person-centred instrument to measure eHealth literacy, rather than to provide a complete picture of all aspects of validity. This study demonstrates that the Dutch version of the eHLQ can be considered a robust instrument which can be used by policy makers, eHealth developers and researchers to understand people's ability to engage with and use technology so that these systems can be developed, evaluated, and redesigned to meet the eHealth Literacy need of their communities. Ultimately, this is necessary to provide appropriate support and work towards an inclusive, equitable digital healthcare landscape.

Ethics approval and consent to participate

The cognitive interview study and the FitKnip study were cleared for ethics by the Medical Ethical Review Committee of the Leiden University Medical Centre (No. 19 – 078 and No. P20.001, respectively). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent to participate in the study was obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

Individual de-identified participant data supporting findings of study 1 are available from corresponding author on reasonable request. The raw data that support the findings of study 2 are available from the FitKnip study but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the FitKnip study investigators at the Leiden University Medical Centre (fitknip@lumc.nl)

Competing interests

The authors declare that they have no competing interests

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Authors contribution

CP and EM conceptualized and designed the study. CP, EM and LK contributed to the translation. CP coordinated data collection and the overall process. CP analysed the data. MF provided statistical advice and support. CP wrote the manuscript and EM and MF and MF provided feedback at each version of the manuscript. LK and NC provided advice in multiple stages of the research. EM, MF, NC, RHO and LK critically reviewed the paper. All authors gave input to the manuscript and approved the last version.

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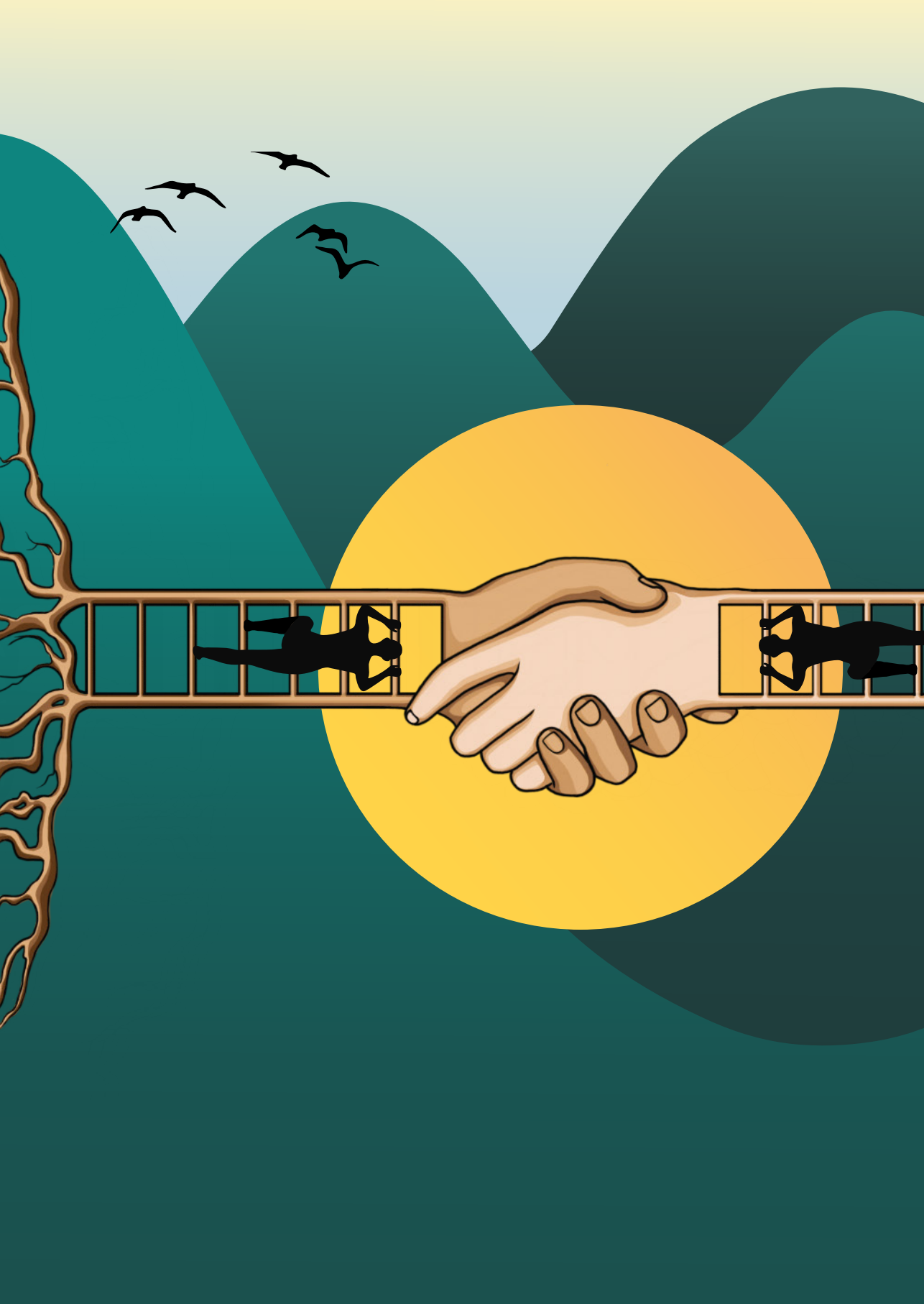
Abbreviations

CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
DLI	Digital Literacy Instrument
eHEALS	eHealth Literacy Scale
eHLF	eHealth Literacy Framework
eHLQ	eHealth Literacy Questionnaire
NeLL	National eHealth Living Lab
RMSEA	Root Mean Square Measure of Approximation
SRMR	Standard Root Mean Square Residual
TIP	Translation Integrity Procedure
TLI	Tucker-Lewis Index
The *Standards*	The Standards for Educational and Psychological Testing
WHO	World Health Organization

Supplementary materials

Scan the QR code to view supplementary materials



Chapter 8

A knowledge creation study

From research to evidence-informed decision making: a systematic approach

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Abstract

Background

Knowledge creation forms an integral part of the knowledge-to-action framework aimed at bridging the gap between research and evidence-informed decision making. Although principles of science communication, data visualisation and user-centred design largely impact the effectiveness of communication, their role in knowledge creation is still limited. Hence, this article aims to provide researchers a systematic approach on how knowledge creation can be put into practice.

Methods

A systematic two-phased approach towards knowledge creation was formulated and executed. First, during a preparation phase the purpose and audience of the knowledge were defined. Subsequently, a developmental phase facilitated how the content is 'said' (language) and communicated (channel). This developmental phase proceeded via two pathways: a translational cycle and design cycle, during which core translational and design components were incorporated. The entire approach was demonstrated by a case study.

Results

The case study demonstrated how the phases in this systematic approach can be operationalised. It furthermore illustrated how created knowledge can be delivered.

Conclusion

The proposed approach offers researchers a systematic, practical and easy-to-implement tool to facilitate effective knowledge creation towards decision-makers in healthcare. Through the integration of core components of knowledge creation evidence-informed decision making will ultimately be optimized.

Background

Building upon a knowledge translation framework

Knowledge translation (KT) aims to fill the evidential gap between knowledge and practice; a process that is considered by the World Health Organization (WHO) to be one of the most important public health challenges of this century (1). The knowledge gap has often been referred to as the knowledge-to-action (KtA) gap. This term implies a broader application of knowledge, involving decision-makers, health practitioners, patients and the public.

Using this broader definition of KT, Graham et al. developed a knowledge-to-action (KtA) framework that conceptualizes the process of KT (2). This framework, comprises two distinct but related components. The 'Action Cycle' represents the activities that are needed to apply evidence-based knowledge to practice. This includes tailoring interventions to the local context and identifying and evaluating barriers and facilitators to implementation. The 'Knowledge Creation funnel', on the other hand, refers to the simultaneous process of the generation of the tools and key messages that aid in the Action Cycle. These are created by distilling and tailoring core messages from research knowledge to the needs of the knowledge user. In its broadest definition, knowledge users include, policy-makers, health practitioners and the general public. This article will focus on KT to decision-makers (In this article decision-makers include managerial decision-makers (e.g., managers in hospital, community organisations and private business) as well as policy decision-makers at the national, provincial, district and local levels (7) as they are in the best position to influence health decisions and benefit public health through evidence-informed decision making.

Even though the action process and the knowledge creation process must form part of any KT model, it remains ambiguous how these processes should be executed. Large inconsistencies can especially be identified in the knowledge creation process due to a lacking systematic approach on how to put the process into practice (3). This article strives to provide a systematic approach on how the knowledge creation process can be put into practice. More specifically it focuses on what, based on the literature, are the core components of the knowledge creation process that every researcher engaging with KT should consider. The use of a case-study will demonstrate how the systematic approach can be used by researchers to effectively establish evidence-informed decision making.

With the focus shifting from knowledge dissemination to KT, the role of reciprocity between decision-makers and researchers in facilitating evidence-informed decision making has become widely acknowledged (4). Whereas the traditional and more linear model – 'the science push model'- underlines the supply of evidence to inform evidence-informed decision making, the interaction model reflects the need of reciprocity and partnership building. The latter, suggests that the more sustained the interaction between researchers and policy-makers is, the larger the impact of evidence-informed decision making becomes (5-9). This interactive KT model is

however, a complex, time-consuming step that is hampered by political instability, high turn-over of policy-making staff (6) and perceived cultural differences between researchers and policy-makers (10, 11). Consequently, the traditional, linear approach remains the most common used approach.

Pitfalls in knowledge creation

Despite the less complex nature of the traditional science push model, in practice, researchers and policy-makers rarely speak the same language. Evidence provided to decision-makers is generally considered to be too complex, too detailed, too technical or lacking in timeliness (6, 12, 13). Aside from these substantive elements, inattentiveness to design and structure of a research report can also trouble the communication from researchers to decision-makers (14).

Tailored communication: a conceptual framework

In order to avoid these pitfalls, it is paramount to tailor knowledge to the level of understanding, needs and demands of the target audience. Guided by Lavis' extension of Lasswell's communication model effective communication depends on tailoring what is being said (content), how it is being said (language), how it is communicated (channel) to whom (audience) and with what purpose (intended effect) (7,15). Although the 'who', the 'what' and the 'to whom' are often taken into consideration, the 'how' is often overlooked in communication to decision-makers (7, 16). Strikingly, it is precisely this 'how' aspect of the communication process that might be crucial in influencing evidence-informed decision making. Drawn from the literature on the field of science communication, visual communication and user-centred design, we formulated a number of core components approaching this 'how' aspect (see Figure 1). These components can be divided in translational components and design components, determining how the content is said, or how the content is communicated, respectively.

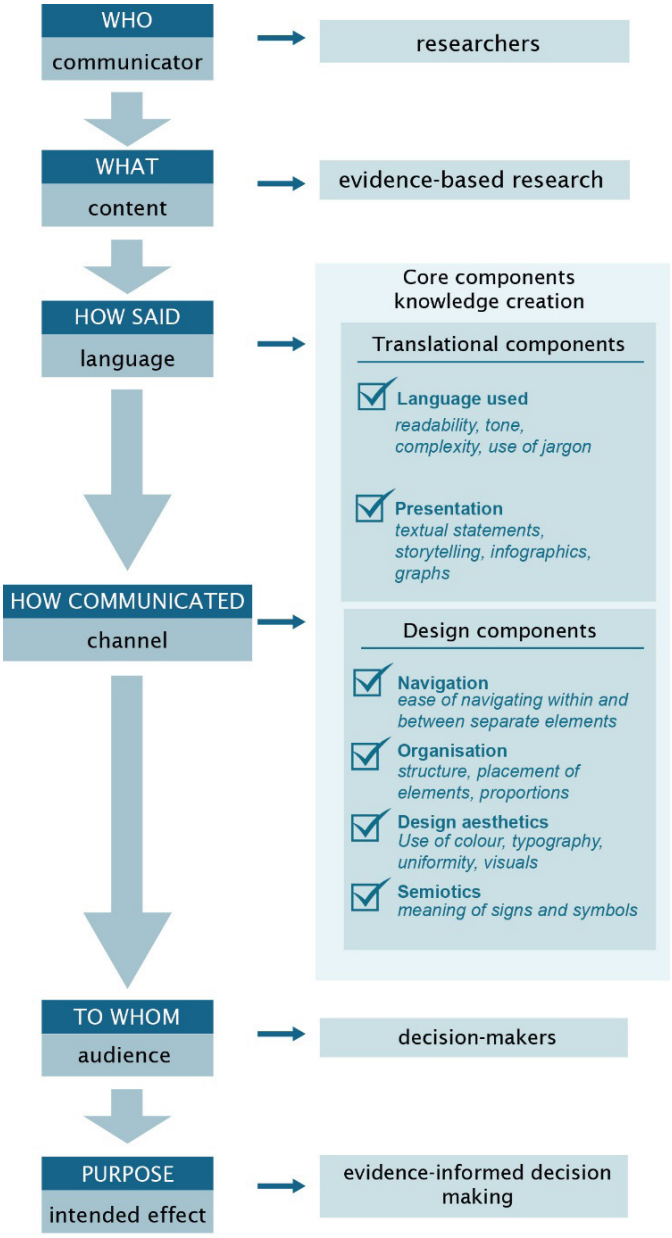


Figure 1. Conceptual framework adopted from Lasswell's communication model and its extension by Lavis et al. Each step in the sequence represents further interpretations of the framework when communicating evidence- based research (content) to decision-makers (audience) with the purpose to influence evidence-informed decision making. Core components on knowledge creation provide elaborate interpretation of how the content is said and communicated.

Core components on how the content is said

The first core component, the translational component, entails that content should be target-audience appropriate and packaged in a mode of communication that is familiar to the target audience. Information should be concise and understandable, adapted in terms of length and complexity of grammar (6, 14). In addition, messages that are meant to prompt action should be expressed as an actionable message. This can be established by integrating concepts of applicability (i.e. feasibility of an intervention), and transferability (i.e. likelihood that the intervention will equally benefit health in this specific setting)(17).

Knowledge should moreover be represented in a form that facilitates understanding (18). Representation forms include common used textual statements, compelling narratives (storytelling) or the visualisation of data into graphs or infographics. Visualisation of data is an effective means of representing complex ideas of information in a format that is quickly understood (18-20). Storytelling, an increasingly used tool in public health communication (21, 22), provides context to the situation by anchoring a problem in the real world (14, 23). The power of storytelling lies therefore, beside the transfer of explicit knowledge, in the transfer of tacit knowledge.

Core components on how the content is communicated

Apart from the choice on language and representation one should tailor how content is being communicated to the target audience. Simply communicating information in a form and language tailored to the needs and demands of decision-makers does not sufficiently influence evidence-informed decision making (24, 25). The majority of research evidence is consumed by decision-makers via a written channel (12, 13). Therefore, elements of design, including navigation, organisation (25, 26), design aesthetics (27), and semiotics should also be taken into account (14, 28).

This means that navigation between information should be intuitive and information should be presented in an orderly way (28). Online repositories such as the 'HealthCOMpass' (29) and 'Science for Environment Policy' (30) are generally effective in transferring knowledge by presenting information in separate self-contained 'chunks' of information, enabling decision-makers to access the information in the order they choose. Furthermore, it is important to create and incorporate design aesthetics. An appealing exterior can be accomplished through the use of complementing colours, a polished house style, simple typography and the appropriate use of visual aids (31, 32). Ultimately, visual aids can become more meaningful via the utilisation of semiotics. Semiotics refers to the interpretation of a visual into the meaning that goes with it. Pictograms can be ideal to communicate a subject as they derive their meaning from an iconic relation with what they refer to and are understood universally (33, 34).

This article takes one approach in how researchers can communicate knowledge to decision-makers with the purpose of influencing evidence-based decision making. It should be noted that this article does not attempt to cover all aspects of KT to decision-makers. Rather, takes a starting point in how to create knowledge (tools and

key messages) in such a way that it fits the needs and demands of decision-makers. In the following section, using a case study we provide an approach on how core components of knowledge creation can be integrated in an easy-to-implement tool.

Method

A case study

The knowledge gap is apparent in all areas of public health. However, it may be even more evident in low- and middle- income countries (LMICs) (35-37). LMICs are generally characterized by suboptimal primary care standards, general poor health and significant challenges in implementing clinically and cost-effective interventions (35, 36, 38, 39). There is a growing recognition of the need to improve the translation of evidence into practice in these LMICs and to adapt evidence-based interventions proven to be effective in developed settings to the local context (35, 40, 41). The FRESH AIR study, aimed at addressing the need to prevent, diagnose and treat non-communicable lung diseases (NCLDs) in LMICs is considered an ideal case study. Exploring barriers and facilitators to the implementation of evidence-based interventions in low-resources settings and tailoring them to the context are key elements to reach the FRESH AIR aim. Due to this implementation design, KT and creation were included as an integral part of the FRESH AIR study. The protocol has been published elsewhere (42). This case study elucidates one of the methods FRESH AIR is using to create knowledge tailored to decision-makers.

A systematic approach to knowledge creation

The approach to knowledge creation was guided by Lasswell's adapted communication model and consisted of two phases: a preparation and a developmental phase. Both are schematically depicted in Figure 2. Creating a knowledge platform requires the developer to think and approach the subject matter from multiple angles, making use of scientific and analytical knowledge as well as editorial reasoning. Due to the complexity of this iterative process, one should therefore keep in mind that Figure 2 is a simplification of the developmental process.

Preparation and developmental phase

During the preparation phase the purpose of the knowledge platform was defined through the formulation of the main objectives. A main audience was defined to specify the 'to whom' aspect. Both the objective and the audience were decisive in 'what' was to be communicated. Subsequently, the 'what' led to the development of a framework of the knowledge platform, comprising all topics the knowledge platform should address.

The second phase, the developmental phase, provides an approach towards the "how" aspect of the communication model. The approach to "how it is said" and "how it is communicated" were guided by two separate pathways, respectively the translational cycle and the design cycle. The translational cycle involves the

translation of scientific data and information into tailored content. Whereas, the design cycle is the incorporation of core components on navigation, organisation, design aesthetics and semiotics. For conceptual and illustrative purposes, we made a clear distinction between the approaches. In practice however, the two approaches are complex and intertwined with each other.

Translational cycle

During the translational cycle research findings (non-translated knowledge) generated during the FRESH AIR project were passed through a number of consecutive steps. Through the integration of the translational core components this resulted in the generation of content tailored to decision-makers (translated knowledge). As individual studies rarely provide sufficient evidence for decision making, evidence was also synthesized from other sources (43).

Evidence acquired per topic (Step 1) was synthesized and critically appraised (Step 2). Critical appraisal, defined as the examination of research evidence on the level of evidence and relevance, is an important step within the translational process (44). Critical appraisal was performed using a flow-chart like tool. The flow-chart integrated multiple appraisal tools on grey literature with the Scottish Intercollegiate Guidelines Network (SIGN) grading system on scientific evidence to create a tool that can be applied to all types of evidence (45, 46). The level of evidence and relevance was categorized into five categories. Scientific evidence that was based on meta-analysis, rigorous systematic reviews or RCT with very low risk of bias according to the SIGN grading system (Grade A), was extracted (Step 3). In the case of disputable evidence (Grade E or D) due to either a high risk of bias, low level of evidence or evidence-based on non-analytical studies such as expert opinion or a case report, an annotation was added.

Based on the extracted data key message were formulated (Step 4) and data was aggregated into explorative or explanatory overview charts, infographics, visuals, textual statements or narratives (Step 5). Before incorporation into the knowledge platform the product was run through a set of criteria to determine whether all core translational components were sufficiently integrated (see checklist in Figure 2). When the translated knowledge product scored insufficiently, it re-entered the translational cycle.

Design cycle

Parallel to the translational cycle the communication channel was designed. Core components on navigation, organisation, design aesthetics and semiotics were integrated into so called ‘proof of concepts’ (trial products) which were subsequently tested on the experience of the user (user-experience analysis). ‘Proof of concepts’ allow for iterative amendments during several moments of evaluation, thereby warranting feasibility and sustainability early on (47, 48).

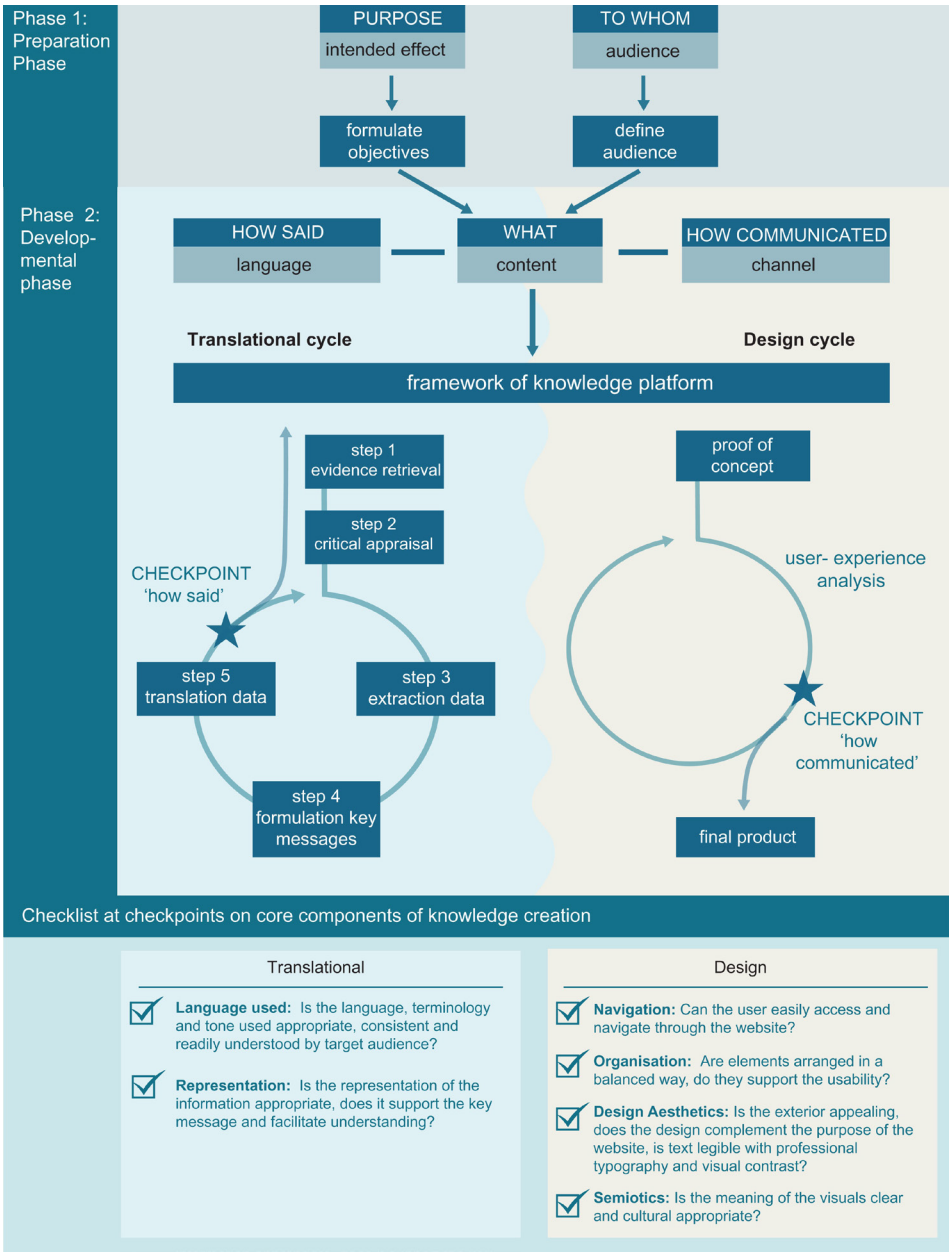


Figure 2. Methodological approach towards knowledge creation Integrating Laswell's adapted communication model with Graham's knowledge-to-action framework. Separate phases provide a step-by-step approach towards knowledge creation

Results

Study deliverables

The following section presents how the systematic knowledge creation approach was put into practice within the FRESH AIR project.

Preparation phase

In the FRESH AIR knowledge dissemination strategy several objectives of the knowledge platform have been formulated. The first objective is to inform decision-makers and other stakeholders about the prevalence of NCLD diseases, risk factors and present feasible context-specific solutions. The second objective is to share materials that assist in the implementation of these context-specific solutions. Since purpose and audience determine the knowledge that is to be communicated, two separate channels were created, each serving one of the above mentioned objectives. A public website serves the first objective whereas a linked knowledge base serves the second. A knowledge base offers access to a large range of documents, including scientific publications, translated policy briefs, protocols and educational materials. Since the knowledge base complements the website as a source of information the following section will focus on the development of the public website.

Developmental phase

The translational- and design cycle served as a template to develop the public website. Figure 3 depicts an example of how the translational cycle was operationalised. After retrieval of evidence (Step 1) and critical appraisal of evidence (Step 2), relevant data was extracted (Step 3). This was then used to formulate key messages and create visualisations (Steps 4 and 5). Correct interpretation of the visualisations was supported by adding a simplification of the key messages (Step 5).

Figure 4 illustrates a concept of the home-page of the FRESH AIR public website, demonstrating the integration of the core components of knowledge creation. As the development of the website is an on-going project and has not yet been delivered, intermediate results are presented and complemented by future ideas.

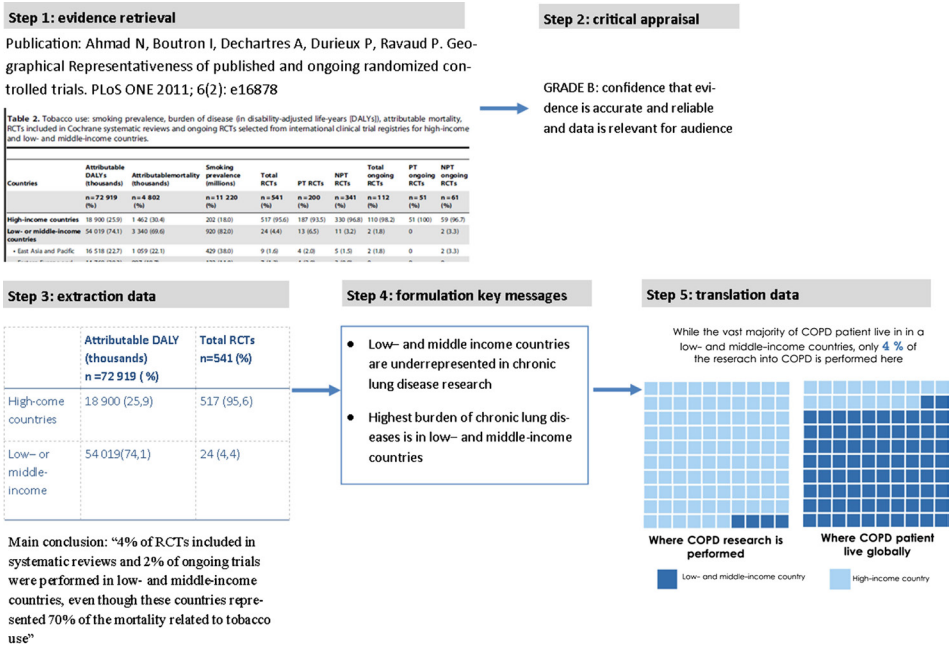


Figure 3. From evidence to visual representation of data in five steps. A case study example providing interpretation of the different steps of the translational cycle.

Future plans

Novel knowledge is continuously generated during the FRESH AIR project. Hence, core components of knowledge creation will be integrated in several additional ways. Information will be presented in various forms. Global prevalence of disease will be expressed in a bubble chart. Bubble charts are explorative rather than explanatory, allowing comparison between settings and different measures.

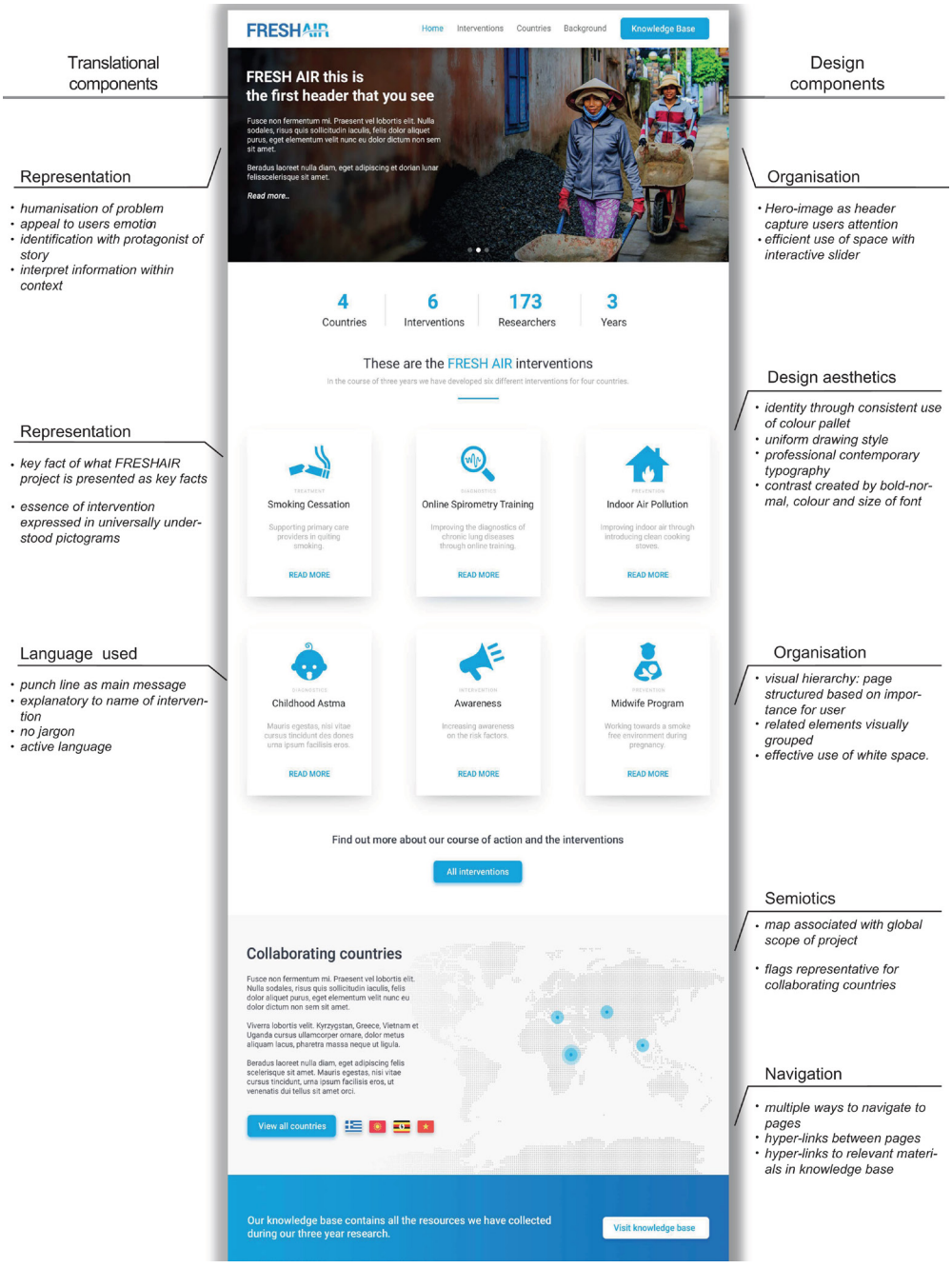
Furthermore, storytelling will be used to trigger action or share knowledge by presenting successful implementation stories. Excessive detail will be avoided to permit the reader to be able to imagine a comparable solution within their own situation. Composite stories will be created from interview narratives derived from the qualitative FRESH AIR data.

Warranting sustainability and outreach

Elements regarding sustainability, outreach and dissemination will furthermore be taken into account. Sustainability will be warranted by basing the website on a WordPress platform. This free content-management software does not require programming skills and allows for content management independent of a web designer. Outreach to a non-academic audience, including decision-makers, will be

maximized through the integration of several social media channels and hyperlinks to leading health institutions.

Figure 4. Core components of knowledge creation integrated into the home page of the website



Discussion

In this article we presented a systematic approach towards knowledge creation- the tailoring of research knowledge to decision-makers to facilitate evidence-informed decision making. We elaborated on the knowledge creation cycle, an integral part of the KtA framework by Graham et al (49). Guided by Lasswell's widely known communication model, we formulated an approach that incorporates how content should be communicated–an overlooked but essential component. The approach integrates two core components: 1) the translation of knowledge towards the audience and 2) the design of knowledge created. Through a case study we demonstrated how these two core components can be put into practice.

This systematic approach is, to our knowledge, the first to provide a practical approach to knowledge creation. A systematic approach to knowledge creation was urgently needed for two reasons. Firstly, the vast amount of literature covering the question on how to communicate scientific evidence to a target audience, indicates a lack of an overall effective approach (31, 50, 51). Secondly, the European Commission increasingly emphasizes to include strategies on knowledge dissemination to a non-academic audience in project proposals (52). Consequently, researchers are expected to engage in knowledge creation; a skill that they have generally not been trained in.

Whereas decision-makers have been equipped with multiple tools to assist in using research evidence for evidence-informed decision making (53, 54), researchers have hardly been provided with any. The SUPPORT tool, developed for decision-makers and researchers presents a variety of activities on KT, but does not provide a practical approach on how these activities can be operationalized (16, 55). Our approach complements herein, as it provides researchers engaging in knowledge creation with a simple, easy-to-implement tool that does not require advanced training.

As previously noted, this article only covers a small portion of the broad and complex process KT entails. While we have proposed a strategy to warrant that researcher and policy makers 'speak the same language', our approach should not be considered a stand-alone solution, but one embedded within the KtA cycle. As suggested by Graham et al., knowledge has to go through a number of phases before it can shape practice. These phases include adaptation to the local context, assessing barriers to implementation and monitoring knowledge use (49, 56). Furthermore, researchers should build capacity for implementation by formulating, implementing and evaluating capacity building plans.

Even though our approach was developed towards communicating research evidence to decision-makers, it may be widely applicable as the approach integrates essential and universal components of science communication, data visualization and user-centered design. Regardless of the specific audience, the questions concerning "how something is said" and "how it is communicated" should always be given full attention in the process of communicating research-evidence.

Conclusion

To conclude, this approach offers researchers a tool to facilitate effective knowledge creation towards decision-makers in healthcare. The tool complements existing approaches; it is systematic, practical and designed to be easily implemented by researchers engaging in KT. However, it should not be considered a stand-alone communication tool, but rather a tool within the communication process of KT. Nonetheless, through the integration of core components on knowledge creation an approach has been established that may be widely applicable to similar projects, ultimately optimizing evidence-informed decision making.

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Conflicts of interest

The authors declare no conflict of interest. All authors have contributed to writing and revision of the article.

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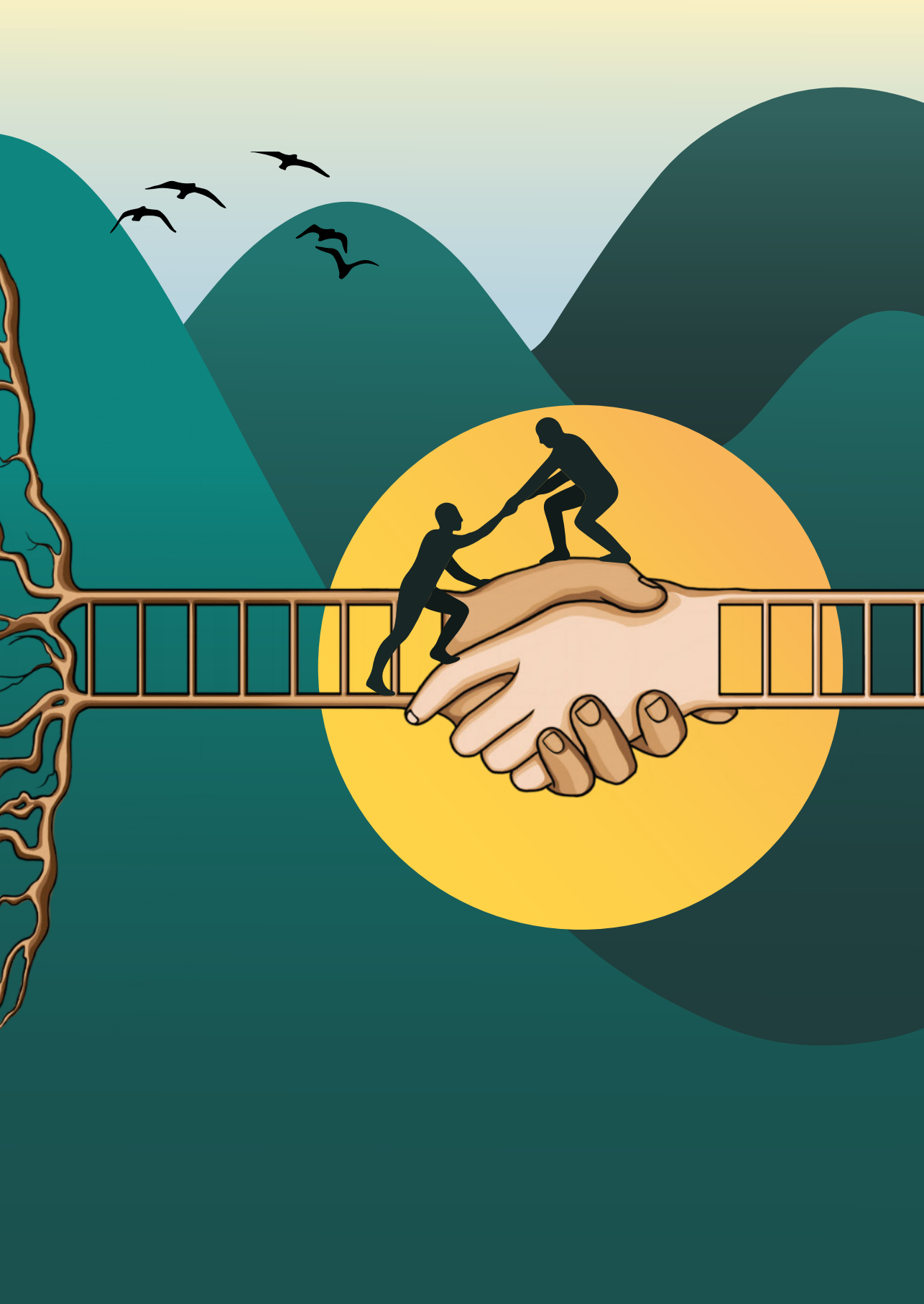
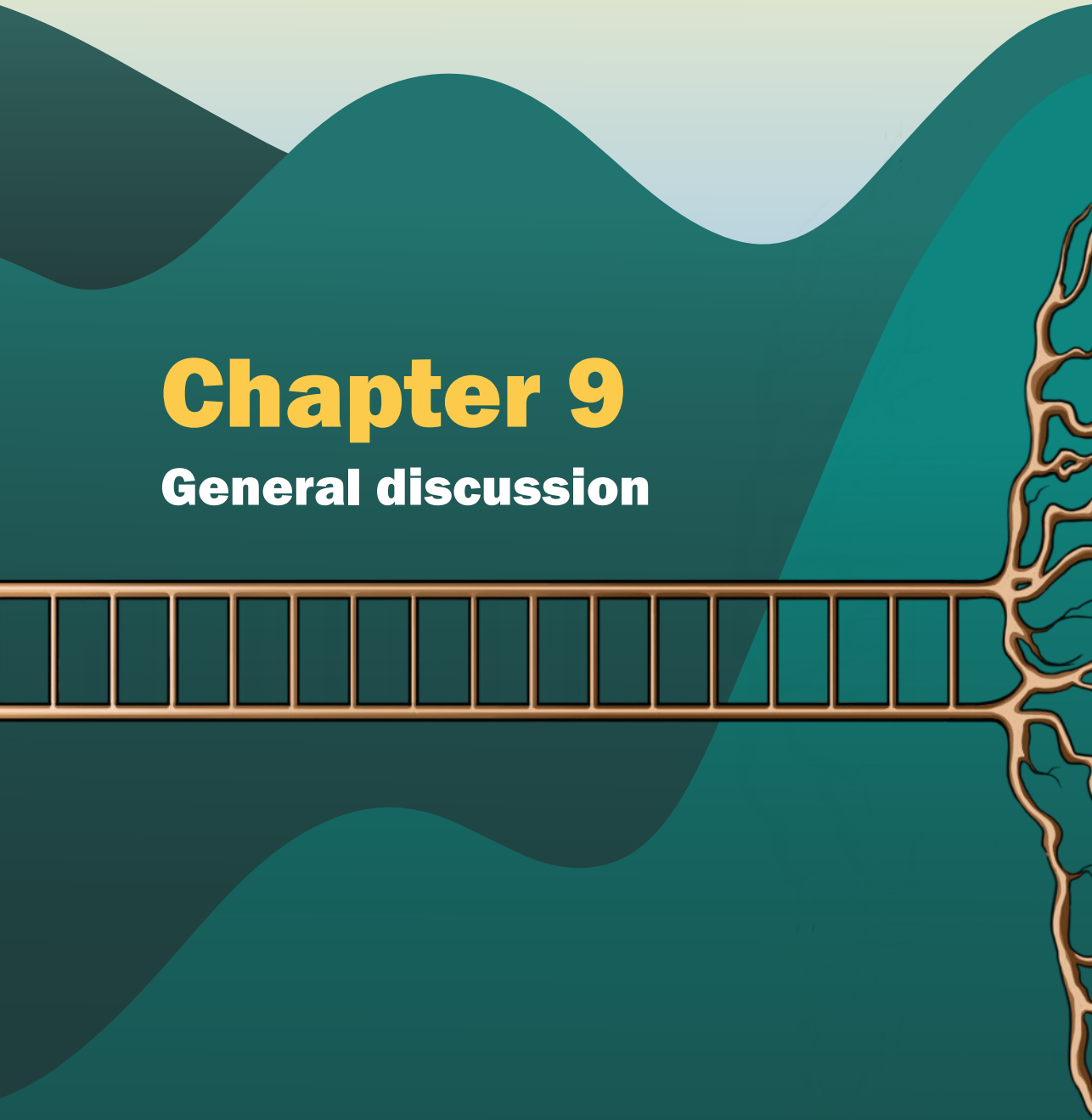


Chapter 9

General discussion



General discussion

In accordance with the adage, "with the wisdom of hindsight", a consistent observation emerges: embarking on the same journey for a second time is invariably easier. This dissertation encompasses a collection of distinct studies, each presenting a unique journey, involving different contexts, disciplines, approaches, and methodologies. While some journeys were pre-defined, others were discovered along the way, making this dissertation a co-production between different disciplines, following different paths, and offering different perspectives. As such, our journey has yielded several new insights and helped us gain new knowledge along the way. Knowledge and insights that reinforce our decisions made and provide alternative perspectives when considering the broad context of eHealth development, evaluation, implementation, and sustainment.

This closing chapter serves as a reflection on the road travelled, the knowledge acquired along the way and the lessons learned by embarking on this journey with designers, behavioural change experts, persuasive game design experts, various healthcare developers, patient advocates, app developers and statistical advisors. Drawing inspiration from the words "the journey matters more than the destination" we believe that these journeys were necessary to acquire these lessons on development, evaluation, and implementation of eHealth. The lessons learned tap into the five challenges presented in the introduction, thereby offering a wider perspective on the intricate relationship between patient empowerment and eHealth literacy, meaningful patient and public involvement, the road toward sustainable implementation, the challenges and implication of evaluation of eHealth and the importance of creating a favourable academic climate in creating societal impact with eHealth. These lessons learned have been clustered into five themes, each of which concludes with key messages intended for fellow (prospective) eHealth researchers, healthcare professionals and academic institutions who play a vital role as knowledge brokers in the field of knowledge dissemination.

THEME 1 – SELF MANAGEMENT, PATIENT EMPOWERMENT AND eHEALTH LITERACY

Within the ongoing transformation and digitalisation of healthcare in the Netherlands, people are expected to participate in and take responsibility for their own health (1). This entails fostering shared decision making and empowering patients to participate in their healthcare choices (2). Patient empowerment focuses on increasing a patient's capacity to think critically and make autonomous, informed decisions about their health and has been associated with improved health outcomes, greater healthcare satisfaction, better treatment adherence and reduced healthcare costs (3, 4). This is particularly of importance for individuals with chronic conditions, who continuously self-manage their health regardless of their interaction with the healthcare system or specific professionals (5). Recognizing the significance of patient empowerment and self-management, numerous eHealth interventions for chronic diseases, such as asthma and COPD, focus on empowering patients to enhance their self-management

skills (6, 7).

However, it is essential to acknowledge that in this digital era patient empowerment must be accompanied by adequate health and eHealth literacy to enable individuals to make well-informed decisions (6). Patients who possess a high degree of empowerment but lack adequate health or eHealth literacy may make risky health choices, leading to adverse outcomes and increased healthcare costs (8). For instance, a patient with asthma monitoring their lung function using a peak flow meter to self-monitor might decide to use their reliever medication when their peak flow values are low. While this decision reflects patient empowerment, the patient may lack understanding of the distinction between a reliever and a maintenance inhaler, potentially causing harm in the long run (8).

We integrated empowerment principles in the design of the persuasive game 'Ademgenoot' to support people with asthma in their medication adherence, alongside patient education on the difference between maintenance and reliever inhaler (**chapter 2**). We applied personal goal attainment in combination with a behaviour feedback mechanism to motivate patients to adhere to their maintenance inhaler and thereby empower them in doing so. In **chapter 3** we focused on people with asthma and limited health literacy, to improve their understanding and organization of medication intake by visualizing the medication's effects on the body and the relationship between usage and symptoms.

Hence, eHealth interventions should incorporate principles of empowerment, but at that same time be mindful of differences in health and eHealth literacy that enable people to make well-informed and reasoned choices. In **chapter 7**, we adapted a widely used instrument for measuring eHealth literacy to the Dutch context, providing a valuable tool for understanding users' eHealth literacy needs in the design, development, and evaluation of eHealth solutions (**Challenge one, General introduction**). Also in our design research for people with asthma and limited health literacy (**chapter 3**), we were mindful of their eHealth literacy needs, as people with limited health literacy generally have little experience with digital health technologies and services (9). We carefully addressed their eHealth literacy needs through co-constructing stories, experience prototyping, and utilizing simplified visuals and illustrations to explain complex physiological processes in the final prototype of the app.

In summary, while patient empowerment and the use of eHealth to support self-management have the potential to improve health outcomes and reduce healthcare costs, it is crucial to be mindful of individuals' health and eHealth literacy needs. Tools like the eHLQ can help identify eHealth literacy needs and provide tailored support to individuals with limited eHealth literacy. This support can include training and education to enhance eHealth literacy, assistance from healthcare professionals in effectively utilizing eHealth resources, technology-enabled learning experiences (e.g., an interactive game used to teach people to navigate a patient portal) and involving individuals with limited eHealth literacy in the development of eHealth solutions.

TAKE HOME MESSAGES | THEME 1

- Patient empowerment has the potential to improve health outcomes and increase patient satisfaction. However, it must be accompanied by sufficient health literacy to ensure informed decision-making. Lack of health or eHealth literacy can lead to risky choices and negative outcomes, despite patient empowerment.
- While eHealth has the potential to empower people in self-managing their disease, digital health technologies or services should fit people's eHealth literacy needs.
- The eHLQ Dutch version can be a useful tool to understand the eHealth literacy needs of people in a Dutch healthcare or research setting and guide the design, development, and evaluation of eHealth solutions.

THEME 2 - MEANINGFUL INVOLVEMENT OF END-USERS AND THE PUBLIC

The continuously evolving digital landscape has led to the general consensus among academics and health innovators that involving end-users should be standard practice in the development and evaluation of eHealth solutions (10). This agreement is rooted in the understanding that solutions are more likely to meet end-users' needs and benefit them when they are actively involved in the design process. Meaningful involvement, however, requires that end-users are able to articulate their needs. A seemingly logical requirement, but one that is often overlooked by medical and healthcare researchers, and prompted the question: "how can we help people articulate their needs?" (**Challenge one, General introduction**).

How can we reveal the deeper levels of knowledge?

In current healthcare research and intervention design, medical researchers often rely on qualitative methods such as interviews of focus groups discussions to identify end-users' needs. Qualitative researchers are generally trained to be good observers and listeners. They interpret what is being said or what they observe into what it means. However, their source of data strongly depends on how well people can articulate themselves or verbalise their needs, or the observation of behaviour at the specific moment in time. As mentioned in the beginning of this dissertation, needs, motivations and desires are often concealed in deeper knowledge layers. Knowledge that people can act upon but not readily express in words (tacit knowledge) and knowledge people are not aware of yet (latent knowledge). These types of knowledge do not necessarily manifest themselves in the present in order to be observed (11). However, these deeper knowledge layers can be revealed using participatory design methods (12, 13) .

This dissertation (**chapters 2,3 and 4**) exemplified various approaches to using participatory design methods. It demonstrated how design and creative practices can help people articulate their needs, thereby granting them a voice in the design

process. In **chapter 2**, participatory design methods were employed to elicit the needs of people with asthma, which led to the design of a persuasive game to motivate individuals with mild asthma to adhere to their maintenance medication (**Challenge two, General introduction**). In **chapter 3**, people with limited health literacy were actively involved, and participatory design tools helped to gain an understanding of their specific needs and preferences. Lastly, **chapter 4** demonstrated how participatory design can be used to include children in the design of an app to reduce pre-procedural stress and anxiety.

Given the enormous possibilities of participatory design tools and techniques, selection and tailoring of participatory design tools and techniques is a delicate process and should be based on 1) the purpose and 2) the context in which they are utilized (14). Purpose can be priming participants (i.e. immersing participants in the domain of interest), probing (i.e. revealing participants personal perspectives), understanding or generating ideas or design concepts (12, 14). Context can be described along the four dimensions: group size, group composition, face-to-face versus online, venue in which the participator design activity is held, and stakeholder relationship (14).

In this dissertation we carefully selected and applied participatory design tools that aligned with the purpose and context of their usage, customizing them accordingly. To prime participants we developed an introduction video featuring the design researcher himself (**chapter 3**) and providing sensitizing materials to stimulate self-reflection and collection of lived experiences on dealing with asthma (**chapter 2**). To gain an understanding of end-users' needs, experiences, and motives we used personas (**chapter 2 and 3**), co-creating stories (**chapter 3**) and experience journey mapping (**chapter 4**). To generate new ideas or design concepts, we employed paper-prototypes (**chapter 2 and 4**), think aloud exercises and mock-up or clickable prototypes (**chapter 2, 3 and 4**). Throughout all projects, we opted for a face-to-face approach, selected home environments as the preferred venue, and carefully managed stakeholder-participant relationships, incorporating a trust officer (**chapter 3**) or parents (**chapter 4**).

Furthermore, we made a deliberate effort to tailor our participatory design tools to accommodate the characteristics of the end-users, consider their cognitive abilities, communication skills, and any potential barriers they may face regarding participation (e.g., risk of stigmatization, mistrust, financial barriers). This is especially important when including people who can be considered vulnerable or have difficulties verbalizing their needs, such as those with limited health literacy (**Challenge three, General introduction**). People with limited health literacy may struggle with abstract thinking or understanding the content of the study, may experience language or literacy problems or feelings of anxiety towards research or the research team.

In **Chapter 3,** we demonstrated the active involvement of individuals with limited health literacy in participatory design. Through the careful selection and tailoring of appropriate participatory design tools and techniques, we effectively engaged these individuals and fostered mutual understanding during the research process. The

utilization of the co-creating stories method enabled individuals with limited health literacy and asthma to reflect upon their experiences with adhering to their asthma medication regimen. By using relatable fictional stories, participants were able to share their own experiences, connect with different characters, and contemplate their own behaviour and motivations for non-adherence. Experience prototype sessions, involving physical interaction with multiple prototypes, further facilitated the expression of preferences, needs, and attitudes toward the prototypes by end-users. Similarly, the design process involving children (**chapter 4**) necessitated the customization of participatory design tools. To address children's difficulty in envisioning the final product, visual elements, such as a colourful animal theme, were incorporated into the prototype and a hospital setting was simulated.

While the toolbox for participatory design offers an extensive array of tools and techniques, it is not practical nor comprehensive to provide a complete repertoire in this dissertation. Nonetheless, the studies in this dissertation successfully illustrate several ways in which participatory design tools can be effectively employed for different purposes, within diverse contexts, and involving a range of end-users thereby adding to the knowledge base on the use and application of participatory design tools and methods in eHealth design.

Prerequisites for meaningful end-user involvement in design

The active involvement of end-users and granting them a voice in the development and evaluation of eHealth solutions, are not only crucial for increasing the likelihood of successful adoption but also aligns with ethical principles of justice and inclusiveness. It is our ethical responsibility to value individuals' lived experiences, listen to their narratives and involve them in the design process. Also from a societal stance, it can be considered a human right for those affected by the digital transformation now and in the future to have a say in the design solution to the complex issues and societal challenges that awaits us. Consequently, we are obligated to make every effort to include individuals and communities most in need, ensuring that eHealth solutions benefit everyone and do not contribute to widening the digital divide (**Challenge three, General introduction**).

In **chapter 3** we concentrated on how to involve people with limited health literacy in the design of eHealth interventions and give them a voice. However, meaningful involvement of people with limited health literacy or lower socio-economic position requires also other important consideration to assure meaningful involvement. Several of these considerations have also been described in the context of including socio-economically disadvantaged population as study participants in randomized controlled trials (15, 16).

Firstly, research should be planned and structured in a manner that accommodates the needs of the participants, such as employing a flexible study design and considering participants' competing demands like childcare or other family responsibilities. In the eHLQ translation study (**chapter 7**) we included recruitment with posters at various familiar (public) spaces such as sport clubs and community centres to reach

more socio-economically disadvantaged individuals. In the ACCEPTANCE study protocol, we included follow-up telephone calls by the patient's general practice as a recruitment strategy, to minimize the risk of including only those with controlled asthma en generally more willing to participate in clinical trials (**chapter 5**).

Secondly, maintaining a collaborative team is crucial to foster and ensure effective communication (17). This can be achieved through regular communication with participants, having a familiar point of contact (e.g., a research assistant performing all study activities, **chapter 5**) and by providing transparency in design decisions. The design researcher (**chapter 3**) visited a community centre multiple times to first build trust before inviting people to participate in the study. People who were invited by their practice nurse to participate received a video with the design researcher introducing himself and explain in plain terms the purpose and set-up of the study activity. This helped establish familiarity and build trust (**chapter 3**).

Lastly, it is important to take into account potential socio-economic barriers such as lack of transportation, financial constraints or limited access to healthcare facilities (15). We accommodated for this by performing the study activities at people's houses (**chapter 5 and 7**) or at the neighbourhood's community centre (**chapter 3, chapter 5, and chapter 7**), or by providing a financial compensation when study budget allowed it (**chapter 5 and chapter 7**). Thus, before embarking on a journey including socio-economically disadvantaged people as study participants or as active contributors, researchers should invest time, budget, and effort in establishing a meaningful collaboration and trust. Throughout the process, it is essential to report on and reflect upon the execution, documenting best practices and lessons learned. By doing so, we can ensure that eHealth solutions are designed with the needs and preferences of those who would benefit the most in mind and are evaluated with them. This is a vital step in working towards an equitable and inclusive digital health landscape, reducing health disparities, and improving health outcomes (**Challenge Three, General introduction**).

Creating meaningful patient and public involvement

Besides meaningful involvement of people in the design of eHealth, the importance of the involvement of patients (and public) in the set-up and execution of clinical research has become increasingly evident in the past two decades (18). This is reflected by the growing body of evidence on its value, the publication of guidelines on patient and public involvement (PPI), reporting standards and the inclusion of PPI as requirements by funding bodies and journals (19, 20).

In our cluster RCT evaluating the effectiveness of an asthma inhaler programme (**chapter 5**), we established a patient advisory panel to provide input throughout the research process. Recognizing the novelty and complexity of the intervention, involving patients was crucial. The patient advisors provided valuable insights into study design, materials, and feasibility. They also contributed to improving communication, recruitment (e.g., through social media), and retention strategies. By involving patient advisors from the early stages, setting clear expectations, defining

their roles, and maintaining regular communication and evaluation, we established a mutually beneficial collaboration. Our experiences were compiled into a short video in collaboration with a leading patient involvement institute, which is now used for researcher training.

Throughout this dissertation, we actively engaged individuals in various aspects, whether in the design of new concepts or the design and execution of clinical effectiveness studies. We witnessed first-hand the value it brings to research. Consequently, we identified six questions that eHealth researchers should consider to attain meaningful involvement of patients or individuals and its relevance to the research as a whole (see Box 1). While addressing all questions in detail goes beyond the scope of this dissertation, we encourage eHealth researchers to carefully consider these aspects and set-up a plan accordingly, before engaging in PPI or participatory design.

Box 1. Six questions researchers should ask themselves to achieve meaningful patient and public involvement (PPI) in eHealth research

1.	In which phase of the eHealth evaluation cycle is our project?
2.	Who is our target population (e.g., end-user, individuals that would benefit from the studied intervention?)
3.	What do we aim to achieve with PPI (i.e., identify specific needs, understand lived experiences for design purposes)?
4.	How will we implement PPI (e.g., what participatory design or PPI tools to use)?
5.	What are possible conditions and challenges (e.g., planning, funding)?
6.	How will we evaluate the impact of PPI on the project?

Lastly, we emphasize the importance of reporting best practices in research. Clear reporting guidelines with standardized approaches for reporting and reflecting on strategies to include and involve people, patients, and the public facilitates an understanding of good practices. The reporting should include how people were involved in the research, a detailed description of their roles in each phase, the participatory design of PPI tools, techniques, and methods used to elicit their needs, values, and preferences, a description of the study setting and how certain barriers were accommodated for (15). Most importantly, it should highlight what worked and what did not, serving as a guidepost for future research endeavours.

‘Users are experts of their own experience; designers are experts of the innovation process’

End-user involvement is crucial for participatory design, but the involvement of designers is equally important. This dissertation includes three participatory design projects (**Chapter 2, 3, and 4**), all of which were conducted in close collaboration with designers, without whom they would not have been possible. While users are experts in their own experiences, designers are experts in the innovation and design process. They possess a wide range of skills that are invaluable to healthcare innovation,

including problem understanding and identification, empathizing with users, clear and effective communication of ideas and concepts, and creative thinking focused on the "why" and "how" of solutions.

However, collaboration between two distinct disciplines—medical research and design research—brings its own challenges. Groeneveld et al. identified several challenges that designers face when working in healthcare (21). These challenges stem from the relative unfamiliarity of design research within healthcare research and the medical research culture, which may not always be favourable for the fast-paced, iterative, and flexible design process.

As such, collaborating effectively with designers in healthcare requires establishing mutual understandings as the foundation for collaboration. First, both disciplines need to communicate and understand each other's standards. For example, healthcare researchers should inform designers about the need to obtain medical ethical clearance early in the process, while designers should communicate the iterative nature of the design process and its associated phases (22). Second, both parties should be aware of the regulated environment in which research takes place, which allows little room for improvisation. Establishing contact with patients directly within healthcare settings, without the involvement of treating physicians, can be challenging due to the inherent patient-physician relationship. To overcome this, we recruited people with asthma outside of healthcare clinics (**Chapter 2**) and utilized social media channels (**Chapter 2, Chapter 5).** Third, both parties should clearly communicate their expectations regarding the outcomes of the design project, which may not be always a ready to be implemented end-product, from the outset. This begins with understanding the value of the design process as a whole.

While presented as distinct challenges, they are all interconnected, stemming from a lack of mutual understanding. Therefore, prior to embarking on a design journey, designers and healthcare researchers and professionals involved should invest time and effort to learn each other's language, involve academics with experience in both design and medical research, understand the research context and appreciate the value that participatory design brings to the project.

Changes in clinical ethics approval and governance

To foster a more favourable research environment for participatory design institutional changes are necessary, particularly in clinical ethics approval and governance. Current medical ethical approval practices in the Netherlands primarily focus on 1) the protection of the autonomy and rights of individuals participating in clinical research and 2) the pre-specified study protocols and other documents to assess the potential harm to the participants (23, 24). This approach ensures that studies such as our cluster RCT **(chapter 5)** and the RCTs included in our Cochrane Review (**chapter 6**) are conducted in a way that is ethical, safe, reproducible and protects the rights and welfare of the participants. However, this linear approach in which people are considered as subjects on whom research is done and should be protected, is in stark contrast with the co-creative and iterative approach of

participatory design in which people's lived experience, expertise and personal perspective are considered as a source of knowledge which informs the next design steps and for which reciprocity and equal power between researcher and participant is required (25). Consequently, definitions of 'benefits and risks' differ between a classical medical and participatory design viewpoint. Participatory design approaches 'benefits' as a right to have a seat at the table and ensure a fair chance to participate and 'risk' of not being able to participate. Conversely, classical medical viewpoints perceive study procedures as potentially harmful to an individual (25). Hence, for participatory design to benefit healthcare, clinical ethics approval should provide room for adaptation, facilitating a fast-paced and iterative process of data collection, analysis, and reflection. Thus, medical ethical review approvals should establish the framework within which participatory design research can be performed, leaving sufficient room for flexibility, deviations from initial plans and adaptation of study methods and procedures to benefit the overall objective. Essentially, this would broaden the view on 'participants' from an individual on whom research is 'done', to an individual who is actively engaged in designing and implementing the research or design process. We believe that this viewpoint benefits the individuals involved, enhances the socio-cultural movement of involving patients in clinical research, and promotes empowerment and ownership, an essential aspect of modern healthcare.

To bring about changes in clinical ethics approval and governance, ethical principles of respect for persons, risk and harms should be evaluated in a new light. As such, we echo Goodyear's words and encourage medical ethical committees to acknowledge and embrace the diversity of research (22). This can be achieved by training ethics board members on various research study designs, including professional expertise in the review process, fostering discussions and debates among review boards, researchers, and research participants, and helping board members understand the empowering and reciprocal relationship between researchers and the people involved (22, 25).

TAKE HOME MESSAGES | THEME 2

- Healthcare researchers have a responsibility to do their absolute best to help end-users to articulate their needs. These often reside in the deeper layers of knowledge. This means going beyond the traditional methods of interviews and observations.
- Participatory design methods and tools are useful methods to reveal deeper layers of knowledge and help people articulate their needs. Researchers should decide on what tools and techniques to use based on the purpose and the context and tailored to fit the target population.
- Meaningful involvement requires accommodating the characteristics and potential barriers of participants, especially those with limited health literacy or difficulties verbalizing their needs.

TAKE HOME MESSAGES | THEME 2 (Continued)

- Multidisciplinary collaborations between medical researchers and designers requires both parties to invest time and effort to learn each other's language, the healthcare context in which the research is performed, and the value of design and its process.

- The governance and protocols of medical ethical committees are not favourable for participatory design research projects as these are based on a linear approach, require pre-specification of study procedures and documents, and consider people solely as participants that can be harmed by research activities.

THEME 3 –IMPORTANCE OF CREATING VALUE FOR ALL STAKEHOLDERS FOR SUSTAINABLE IMPLEMENTATION

The importance of involving other stakeholders, such as various healthcare professionals, in eHealth design is also becoming more evident (26). Especially considering the fact that current healthcare problems often involve complex and interconnected challenges, known as "wicked problems," which are characterised by stakeholders having additional needs or conflicting needs compared to end users. Stakeholder involvement ensures that the intervention aligns with the existing work processes and thinking of those who will interact with the technology or health service, or in another way will experience impact of the intervention on themselves or their work. For example, nurses should incorporate the Hospital Hero animals (**chapter 4**) in their interaction with children to create an immersive safari experience. Additionally, involving developers, such as those working on smart asthma inhaler programs, is necessary to align with their business strategy (**chapter 2**).

To facilitate effective stakeholder involvement, the first step is to identify all relevant stakeholders. Tools like stakeholder identification and analysis and stakeholder mapping (27) help identify all individuals affected by a given technology, their responsibilities, interdependencies and what is at stake for whom (28). Second, the needs of stakeholders should be identified. This can be achieved by involving them directly in the participatory design activities such as experience journey mapping sessions (**chapter 4**) or through separate meetings to discuss insights, align thoughts and plan subsequent steps collaboratively (**chapter 2**)**.** Strategies like prototyping can be employed to communicate early ideas and identify areas of agreement and disagreement.

Besides identification and prioritisation of all stakeholders' needs, early stakeholder involvement is important for implementation. Stakeholders play an important and often influential role in the decision-making process, particularly in the context of purchasing decisions (29). Moreover, when stakeholders perceive that their input has been heard and incorporated into the design, they are more likely to support the innovation and advocate for its adoption (30, 31). As such, late or no stakeholder involvement has been found to form a barrier for the uptake and implementation of digital health interventions (31, 32). Throughout our research, we strived to involve

various stakeholders and capture their needs through participatory design activities, such as experience journey sessions (**chapter 4**), structured brainstorm sessions, prototyping, simulations, and visualizations (**chapters 3 and 4**). While we mainly involved internal stakeholders (i.e. individuals directly involved in the development or implementation in daily practice) it is equally important to include external stakeholders such as top-management as they play a relevant role in supporting the innovation process, championing it and protecting it from short-term pressures (32, 33).

When involving stakeholders, it is important to recognize that development and implementation of eHealth is an ongoing journey, wherein the value of these technologies for each stakeholder within their specific usage context needs to be understood. Stakeholder can be involved in different phases accordingly. This entails involving internal stakeholders, such as healthcare professionals and developers, earlier in the process, while engaging external stakeholders such as decision makers, regulators, financiers, and suppliers later on when addressing issues like feasibility, sustainability, and cost-benefit (27).

The importance of early business development exploration

Besides implementation challenges caused by lack of early stakeholder involvement, large scale implementation of eHealth faces challenges related to funding, uncertainties regarding effectiveness and scalability (**Challenge four, General introduction**). Unfortunately, the majority of all eHealth initiatives fail to reach the implementation and scale-up phase and stop when project or research subsidies have dried up (34).

To mitigate the risk of implementation failure, it is crucial to define a suitable implementation strategy as an integral part of the eHealth development process. One critical aspect of the strategy is defining who will pay for the eHealth technology or service. Currently, many innovations fail to scale-up because of the inability to find a sustainable funding model (35). This is of particular concern in innovating within the Dutch healthcare system (in which all studies described in **chapters 2 till 4** were conducted) as the end-users are rarely the payers. Instead, healthcare insurance companies, healthcare institutions or hospitals bear the costs. Therefore, for an eHealth technology or service to succeed, it must bring value to the payer. In other words, the payer should in some way benefit from the technology. This can be achieved as the technology reduces costs, improves workflow efficiency, or enhances healthcare and employee satisfaction. It is important to note that an eHealth technology that meets the needs of end-users (e.g., patients) does not necessarily guarantee willingness to pay from the intended payer (e.g., insurance companies, hospital boards).

The CeHRes roadmap can be a valuable tool in addressing these considerations early in the development process. It takes a holistic approach by integrating eHealth design with implementation and business development frameworks. By addressing questions about the value created by the technology and who benefits from it, the

roadmap ensures a better fit among humans (meeting their needs), organizations (aligning with their digital strategy), and technology (being technically feasible and compatible with existing infrastructure). It emphasizes a value-driven approach and considers the needs of all stakeholders (36). Currently, development teams often define the value proposition and business model post-development, rather than integrating them into the development process. However, having the potential payers involved from the start can help co-create value to the eHealth technology and inform the business model (27), which is necessary for adoption and sustained funding (37).

Therefore, we recommend that researchers adopt frameworks like the CeHRes roadmap to systematically identify all relevant stakeholders, understand their needs, explore value propositions, and actively incorporate business modelling in the development and implementation process. While defining a business case or launching a business is generally not considered a primary focus for academics, start-up incubator programs can provide university spin-offs with the necessary resources, support, and guidance to establish themselves a business and gain traction in the market, moving beyond project funding. Although beyond the scope of this dissertation, paediatric nurse Nicole Donkel and myself decided to spin-off the Hospital Hero app (**chapter 4**) and participate in an incubator program for start-up companies after its development. This program offered us valuable insights for defining our business case and advancing the implementation and scale-up of the Hospital Hero app.

Lastly, both public and private funding bodies play significant roles in catalysing the development and implementation of eHealth solutions. However, few public and private funding parties provide specific funding for activities such as market or business validation. Funding opportunities that do encourage for example stakeholder identification and analysis are still outcome driven, requiring a finished product as output, making value identification a secondary objective. The complex system of payments or reimbursements, typically coming from third parties like the government or private insurance companies, further complicates funding issues (35). Moreover, there are differences in perception of value, financial incentives and the intricate interplay between economics of insurers and healthcare providers to consider (38).

TAKE HOME MESSAGES | THEME 3

- Stakeholders, such as healthcare professionals and developers, and their needs should be identified and considered early in the eHealth development process, in order to ensure that the intervention aligns with existing work processes and thinking, and to support its implementation.
- Incorporating business development exploration early in the eHealth development process is crucial for finding sustainable funding models, addressing implementation challenges, and ensuring the technology brings value to payers and other stakeholders.
- The CeHRes framework can be used to identify and address questions on implementation, value proposition and the underlying business case early in the process.
- Funding bodies can facilitate sustainable implementation by providing funding schemes aimed at validating the business model and investigating commercial feasibility.

THEME 4 – SUMMATIVE AND FORMATIVE EVALUATION OF EHEALTH

In previous themes we focused on the development process of eHealth and emphasized the importance of involving end-users and stakeholders in the developmental process of eHealth. In the following theme we address the need for proper evaluation, present various evaluation methodologies, and discuss the challenges associated with applying traditional research designs like RCT and meta-analysis in the context of eHealth (**Challenge Four, General introduction**).

This dissertation includes several eHealth evaluation studies that employ different methodologies based on what is being evaluated and the purpose of the evaluation (39). Evaluation can be categorized into three types: process evaluation, impact evaluation and outcome evaluation (39). In **chapter 2 and 3** we performed multiple small scale evaluation studies (process evaluation) to assess whether the prototype of the eHealth solution met the design requirements (e.g., does the design visualise the effect of inhaler use in a compelling way? Does the participant feel motivated to perform the desired behaviour?). Based on the findings, adjustments were made to improve the design. In **chapter 4** we performed a pilot study (impact evaluation) to assess the Hospital Hero app on use, user-experience, and usability. **Chapter 5** presented a study protocol for evaluating a smart asthma inhaler program, focusing on multiple clinical and patient outcomes (outcome evaluation), while in **chapter 6** we performed a meta-analysis to examine the overall effect of different integrated disease management programs, including eHealth-based programs, on clinical outcomes (outcome evaluation).

Clearly, the evaluation studies had different objectives. **Chapter 2, 3 and 4** aimed to gain understanding of user experience and user-interactions with the digital health technology to inform design improvements and implementation. This type

of evaluation, known as formative evaluation, draws its roots from educational assessment where it is used to assess students' learning process and to adjust learning and teaching practices accordingly, rather than solely judging students' performance. In the development of eHealth, formative evaluation, which involves continuous evaluation, adaptation, and re-evaluation, plays a central role. On the other hand, summative evaluation aims to assess whether the desired endpoints have been reached. In educational assessment, it would determine whether students pass the test. The cluster RCT ACCEPTANCE protocol in **chapter 5** is a form of summative evaluation, aimed at investigating the effectiveness of a smart inhaler asthma self-management programme on medication adherence and clinical outcomes. By also assessing usability, acceptability, and cost-effectiveness the study results provide a comprehensive understanding of clinical and patient benefits the meta-analysis presented in **chapter 6** is another form of summative evaluation as it aims to demonstrate a pooled effect of comparable interventions on multiple clinical outcomes.

Unique challenges in the summative evaluation of eHealth with RCTs and meta-analysis

As mentioned before, one of the critical challenges of large-scale eHealth uptake and implementation is the uncertainty surrounding the effectiveness of eHealth interventions, particularly in terms of health benefit (40). Therefore, evaluating the effectiveness of eHealth interventions (summative evaluation) is essential to provide evidence of their impact on patients and healthcare systems. However, determining what outcomes should be included and considered important can be challenging, as stakeholders (patients, healthcare professionals, payers) may have differing perspectives. Having a clear value proposition helps prioritize outcomes and endpoints. Additionally, involving end-users in the design of the evaluation study facilitates the inclusion of outcomes that are meaningful to them, such as disease-related quality of life (**chapter 5**).

Randomized controlled trials (RCTs) have long been considered the golden standard for evaluating interventions (41). Based on the principles of randomization and creating controlled settings, RCTs are able to isolate the impact of an intervention and ensure comparable groups from the start, thereby minimizing the potential for systematic bias affecting the results. Similarly, meta-analysis as conducted **in chapter 6**, is considered the golden standard for synthesizing, and summarizing the results of multiple studies and forms the cornerstone of evidence-based medicine. By pooling, meta-analysis enhances statistical power and provides more accurate estimates of the interventions' effect (42). However, eHealth presents unique challenges that make RCTs less suitable for evaluating their effectiveness and poses difficulties in performing and interpreting meta-analysis results.

One challenge is that eHealth interventions are often complex interventions that are difficult to standardize and replicate across various healthcare settings. RCTs, typically conducted in tightly controlled settings with a highly selected study population and with additional resources, may fail to consider the complex healthcare context in

which the eHealth intervention is implemented. Consequently, RCT results may have limited applicability to patient outcomes once the trial has ended (43, 44).

Another challenge is the multiple component nature of eHealth interventions, which rely on an interplay between technology, human characteristics (e.g., patient behaviour, engagement with technology) and socioeconomic factors (e.g., reimbursement schemes). This complexity makes it difficult to attribute observed effects within an RCT to a specific component of the intervention. This is important to determine what works for whom to derive the effective components. In the case of the smart asthma inhaler programme **(chapter 5**) we indeed cannot solely deduce from results of our primary endpoint (medication adherence over 12 months follow up) which components of the programme (e.g., reminders and symptom tracker, patient portal) contributed to the potential beneficial effect.

The multi-component nature of eHealth interventions also presents comparability issues in meta-analysis. Meta-analyses are based on the premises that interventions are comparable (e.g., drug 'A' versus drug 'B'). Hence, problems arise when interventions are not comparable as is often the case with complex health interventions such as eHealth and the integrated disease management programs studied in **chapter 6** (40)**.** While we attempted to address this issue in **chapter 6** by performing subgroup analyses based on the dominant intervention component, the substantial heterogeneity observed in some subgroup comparisons indicates that comparison issues may persist, and no definitive conclusions can be drawn regarding the most effective components of an integrated disease management program. Moreover, interpreting the overall estimate of effect can be challenged by the interaction of the components with each other.

Alternative designs and recommendations

Alternative study designs, such as stepped-wedge trials or hybrid designs incorporating process outcomes, may be better suited to evaluate the effectiveness of eHealth interventions. These designs provide flexibility and adaptability, accommodating the complexities inherent to eHealth interventions (45). Factorial design and realist reviews should be considered as means to identify working components of eHealth technologies (46, 47) and more advanced meta-analytical techniques like meta regression (48), Network Meta Analysis (47) or Individual patient data meta-analysis can be deployed as alternative to traditional meta-analysis to identify working mechanisms of complex health interventions using pooled data.

Pragmatic trials (**Chapter 5**), performed in a real-world clinical practice setting, overcome some limitations of traditional RCTs. They resemble routine care as closely as possible and incorporate the natural variation observed among patients, including heterogeneity in study samples and co-morbidities. Consequently, the results are more applicable to the target population of the intervention (44). As with all study designs, the research process is a balancing act between maintaining internal validity while maximizing external validity (44, 49). To facilitate the design of a pragmatic trial and ensure alignment with the intended goals and purposes, researchers can

employ the PRECIS-2 tool, which allows for purposeful decision-making regarding trial design (50). Given that pragmatic trials, like most trials, can be financially demanding, researchers should consider performing a pilot study. This pilot study serves to refine study procedures, optimize recruitments strategies, minimize drop-out rates and inform decisions related to the allocation of time and budgetary resources (51).

Historically, meta-analysis has paid little attention to the role of context in the observed effect, typically including RCTs in tightly controlled settings. However, pragmatic RCTs often vary strongly in context (e.g., national healthcare system), and these contextual differences may impact the observed effects. Our subgroup analysis based on study country (as described in **chapter 6**) indicated that the context in which the intervention is implemented may be crucial for overall inference. Given the growing use of pragmatic trails to address the aforementioned challenges in eHealth evaluation, we propose that leading institutions like the Cochrane Library include an explanatory-pragmatic assessment in their quality assessment. This assessment would not only evaluate the quality of evidence using tools like GRADE-2, but also consider the external validity and generalizability of study results. This information can aid policymakers and healthcare leaders in assessing the applicability of the meta-analysis results to their specific context, considering factors such as study population, available resources, local needs, and adapting the intervention accordingly in a context-sensitive manner.

Finally, collecting qualitative data is crucial for evaluating eHealth interventions as it provides valuable insights into the human experience of using these interventions in real-world settings. Qualitative data complements the quantitative data by providing contextual information and a deeper understanding of the reasons behind observed outcomes. While clinical outcomes such as asthma control and medication adherence (**chapter 5**) offer an objective measure of the impact of the eHealth intervention, they do not shed light on the underlying reasons for those outcomes. In addition, qualitative data can provide insight in potential acceptance or implementation issues (52, 53).

To conclude, eHealth evaluation should be considered a continuous process which should include formative and summative evaluation moments throughout the development and implementation phase (10). In doing so, we recommend that researchers consider alternative designs as better options for evaluating eHealth interventions and include process outcomes and qualitative data for a comprehensive understanding of the impact of the eHealth interventions on health benefits.

TAKE HOME MESSAGES | THEME 4

- Evaluation of eHealth should be considered a continuous process and include formative (i.e., to gain understanding for improvements) and summative (i.e., to measure performance or specific endpoints) evaluation moments.
- Researchers should be mindful of specific challenges related to eHealth (i.e., multicomponent, difficult to standardize and replicate across settings) that make RCTs less suitable for evaluating the effectiveness of eHealth and consider alternative designs.
- Pooling of effects of complex health interventions to give an overall estimate of effect is challenged by heterogeneity of the interventions and complicated by interaction between intervention components and contextual factors.
- Collecting qualitative data alongside quantitative data is essential for evaluating eHealth interventions. Qualitative data provides valuable insights into the human experience, contextual information, and deeper understanding of observed outcomes.

THEME 5 EFFECTIVE SCIENCE COMMUNICATION AND SOCIETAL IMPACT

Transferring knowledge on for example evidence on effectiveness of eHealth is essential to benefit patients and impact society as a whole. However, a substantial gap exists between knowledge and practice **(Challenge five, General introduction**). Science communication plays a vital role in bridging this gap by communicating complex scientific knowledge in an accessible way, thereby promoting understanding, facilitating engagement between public and scientists, and fostering informed decision-making based on evidence (54). These are prerequisites in creating societal impact (55). Science communication also plays a significant role in building trust in science, fostering open dialogue and countering misinformation (56).

The process of translating knowledge, as discussed in **chapter 8,** is pivotal for effective science communication to the public. Knowledge translation and dissemination is complex and entails many distinct aspects (i.e., knowledge synthesis, creation, dissemination, exchange, and application). In **chapter 8** we focused on the knowledge creation process and provided a systematic approach to facilitate effective knowledge creation in healthcare. By offering a step-by-step approach we help academics in navigating the complex process of translating research evidence in practice or policy. This approach facilitates evidence-informed decision-making, enhances the uptake of research findings, and ultimately leads to societal impact. It is particularly relevant that academics have the right tools at their disposal, as they are increasingly expected to disseminate their research findings outside the scientific community and engage in societal impact. However, translating research knowledge into societal impact requires skills, experience, and practices that are often absent from doctoral programs and academic discourse (57, 58).

Recognizing the importance of societal impact, significant changes have taken place over the past decade in the academic reward and evaluation system, at both system and disciplinary level. Examples include the installation of U.K.'s Research Excellence Framework (i.e. reward system that rewards universities that demonstrate impact) and the inclusion of societal impact in research proposal evaluation schemes by funding bodies (59). In the Netherlands, academic discourse has embraced societal impact through the New Recognition and Reward system (60). As a result, efforts in science communication, public engagement and societal impact align more closely with academic reward structures (57). This recognition opens up opportunities for individuals to pursue different career paths based on their aspirations, qualities and opportunities, thereby 'redefining the balance between rewards for research, education, societal impact and leadership' (60). However, there is room for improvement in the weight given to societal impact and non-scientific outreach efforts in the assessment of PhD students if we are to really perpetuate the current system, thereby offering full room for differentiation in academic (early) career paths. By doing so, we - at the same time - recognize that non-scientific communication and directly engaging in societal impact may not be for everyone and requires specific skills, experience, and interest.

Finally, to promote societal impact and effective science communication, universities should institutionalize support for impact design and non-scientific communication, similar to how they provide support for data management or statistical analysis (52). By doing so, institutions can stimulate and facilitate societal impact, ensuring that effective science communication becomes an integral part of academic endeavours.

TAKE HOME MESSAGES | THEME 5

- Effective science communication is crucial for promoting public and patient involvement in science. It bridges the gap between scientists and the general public, promotes understanding, and facilitates informed decision-making based on evidence.
- Translating scientific knowledge into societal impact requires effective knowledge creation and dissemination. Providing a systematic approach to knowledge creation in healthcare enhances evidence-informed decision-making and may benefit its societal impact. Doctoral programs and academic discourse should include training in these skills.
- Newly implemented Reward and Recognition systems provide room to participate in science communication and public engagement with performances being more closely aligned with academic reward structures. However, more weight should be given to non-scientific outreach efforts in the assessment of PhD students.

CONCLUDING REMARKS

This dissertation demonstrated how end-users and stakeholders can be actively involved in the development and evaluation of eHealth. It emphasized the importance of facilitating the expression of people's needs and including the voices of those who stand to benefit the most from eHealth but are often overlooked. Through participatory design, we successfully demonstrated how to design eHealth solutions to meet people's needs, foster mutual understanding, and promote reciprocity. Additionally, we explored the potential of persuasive game in facilitating behaviour change and highlighted the importance of stakeholder involvement for sustainable implementation. Finally, we provided future researchers with a tool to identify eHealth literacy needs and ways to include individuals with limited health literacy in eHealth design, which are essential components for achieving equitable eHealth.

In conclusion, we must keep in mind the proverbial wisdom that "A journey of thousand miles begins with a single step." The digitalisation of healthcare is an ongoing process which requires us to take different viewpoints in how we develop and evaluate digital health interventions and consider ethical perspectives. It necessitates a critical examination of the research paradigms guiding the development and evaluation of eHealth. Reflecting on our work, this dissertation does not provide a simple solution for how to develop and evaluate eHealth interventions, but rather builds upon the knowledge and scholarships of those who have preceded us in this rapidly evolving field. Above all, we invite and encourage discussions and open dialogues among researchers, designers, ethics, and most importantly those directly impacted by these eHealth technologies.

It is Saturday afternoon, June 20, 2020. Mrs. V sits in her garden. Next to her lies her new smartphone. With a satisfied smile, she gazes at the screen. After four instruction sessions with her buddy from 'Blijf in Beeld', she has managed to video call her friend in the eastern part of the country. It took effort and did not come naturally, but through practice, perseverance, and simply giving it a try, she succeeded.

She glances at the time on her smartphone. It's a quarter past five. The doctor's office is closed, but she realizes that she might be able to schedule an appointment through the online patient portal.
As a little bird flies by, she contemplates on how good it feels to be connected once more and decides that it is a fantastic feeling to have the sense of fully participating in society again.

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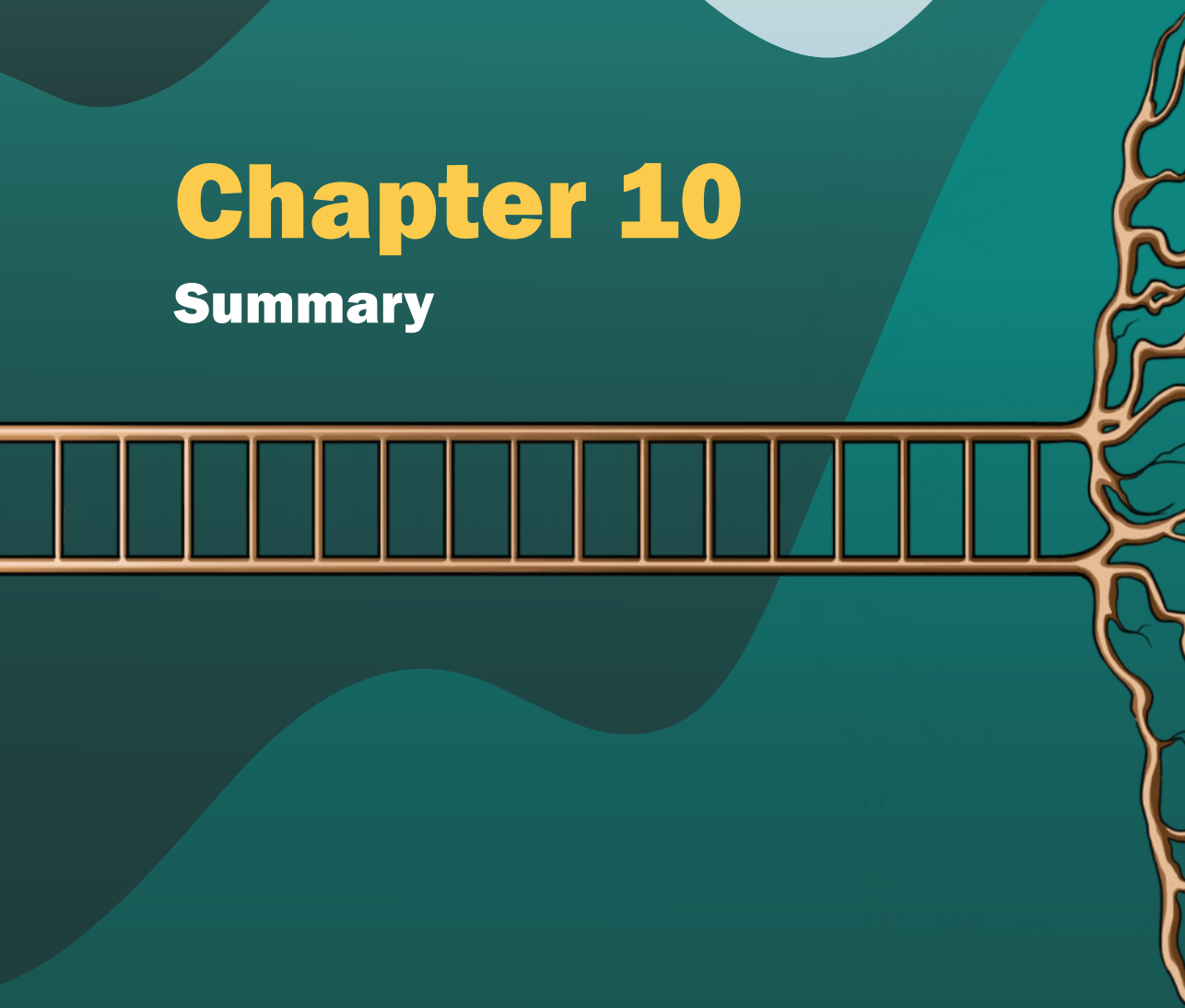
9

Chapter 10

Summary



Summary

The Dutch healthcare system is facing multiple challenges which have put a strain on the healthcare system in terms of finances and workforce shortages. eHealth offers innovative and promising ways of providing healthcare, including remote and digital care. However, despite the potential of eHealth to transform healthcare and improve patient outcomes, its wide-spread adoption and implementation have been limited.

In the general introduction of this dissertation, five challenges in the development, implementation and evaluation of eHealth were identified:

1. Misalignment with end-user needs due to the lack of active involvement of end-users in the design process.
2. Non-adherence caused by a lack of user engagement to the eHealth solution.
3. Missing those who benefit most in the development and evaluation of eHealth, risking a widening of the digital divide.
4. Limited real-world evidence on the effectiveness of eHealth and the need for alternative study designs.
5. Disconnection between evidence and its application, and the need for a practical guide to translate knowledge into practice.

Targeting and overcoming the above-mentioned challenges is essential to work toward meaningful eHealth that benefits patient, healthcare professionals and the healthcare system as whole. By addressing these challenges, eHealth has the potential to revolutionize healthcare and improve health outcomes for individuals and populations.

This dissertation addressed the above-mentioned challenges by presenting and discussing real-world case studies on the development and evaluation of various eHealth technologies using participatory design tools and generating real-world evidence, respectively. It also presented a study on the translation and validity assessment of the Dutch version of the eHealth Literacy questionnaire, and a step-by-step approach to guide the translation of research to inform evidence to inform decision-making.

Part 1 – Participatory design

In the first part of this dissertation, we demonstrated how participatory design can be used to actively involve end-users and other stakeholders in early stages of eHealth development). **Chapter 2** described the design of the persuasive game design 'Ademgenoot' to motivate people with asthma to be medication adherent. Through early involvement of end-users and use of participatory design tools we were able to identify several reasons for non-adherence and needs which led to the design of 'Ademgenoot'. User testing showed that Ademgenoot was engaging and has the potential to influence inhaler use behaviour by fostering motivation and

combining personal goal setting and continuous direct visual feedback on medication use with game elements such as narrative and rewards.

In **chapter 3** we focused our participatory design efforts on people with limited health literacy and delved deeper into the application and tailoring of participatory design methods for people with limited health literacy. Through a study aimed at enhancing medication adherence, we presented strategies to overcome challenges specific to working with individuals with limited health literacy and asthma. We demonstrated how participatory design tools can be carefully selected, tailored, and applied to actively involve people with limited health literacy in eHealth design, identify their needs and foster mutual understanding during the design process.

In **chapter 4** we presented a multiple study report in which we described the development and pilot study of the 'Hospital Hero' app, an app aimed to reduce pre-procedural stress and create a more positive hospital experience for children. In the first study we employed participatory design, taking the experience of the user (child) as starting point to develop an application that supports children in their entire hospital journey, by providing preparation and distraction. A first version of the Hospital Hero app was subsequently evaluated in practice. Using a mixed-method approach, we evaluated the Hospital Hero app on use, usability, and user-experience. As such, we were able to demonstrate how children, as end-users, can be actively involved in the development of eHealth and emphasized the importance of evaluating eHealth solutions in practice to assess their value for children, parents, and healthcare providers.

Part 2 – Effectiveness assessment

Chapter 5 continued on the significance of evaluating eHealth interventions in real-world settings. It presented a protocol for a cluster RCT to evaluate a smart inhaler asthma self-management programme. The study aimed to provide real-world evidence on clinical outcomes, acceptance, and usability, while also considering patient characteristics such as beliefs about medication and eHealth literacy. The chapter also highlighted how patients can be involved in the design and execution of clinical trials, and ways to overcome limitations of traditional RCTs in studying effectiveness of eHealth.

The equivalent of the RCT as golden-standard study design for the evaluation of effectiveness, is the meta-analysis for the overall the effectiveness of multiple studies. **Chapter 6** presented a meta-analysis and systematic review on the effectiveness of integrated disease management programmes (IDM) for people with chronic obstructive pulmonary disease (COPD). The review pooled fifty-two studies on IDM interventions, performed across 19 different countries, and compared these with usual care on a number of health-related and clinical outcomes. The findings indicated that IDM programs probably improve disease-specific quality of life, exercise capacity, respiratory-related hospital admissions, and hospital days per person. No significant differences were found for mortality, courses of antibiotics/prednisolone, dyspnoea, and depression and anxiety scores.

Integrated disease management programmes (IDM) are complex interventions, consisting of multiple components. Since eHealth interventions are also often also multi- component these can be considered complex health interventions as well. Consequently, challenges in meta-analysis of IDM programs can provide important insights and considerations in the evaluation of eHealth.

Part 3 – Tools and instruments

The third part of this dissertation presented two different tools. The first tool is a Dutch version of the eHealth Literacy Questionnaire (eHLQ) (**Chapter 7**). The tool can be used by researchers, eHealth developers and policy makers to identify eHealth literacy needs and inform the development of eHealth interventions to ensure that people with limited digital access and skills are not overlooked. **Chapter 7** described the translation, cultural adaptation, and validity assessment of the Dutch eHLQ using a validity-driven and multi-study approach. Validity was assessed on test content, response process and internal structure performing cognitive interviewing, confirmatory factor analysis, invariance testing and multi-group comparison. The Dutch version of the eHLQ showed strong properties for assessing eHealth literacy in the Dutch context. However, ongoing collection of validity evidence was recommended as validity should not be considered a characteristic of the instrument but depends on the context and purpose of use.

The second tool, a tool to facilitate effective knowledge creation towards decision-makers in healthcare to help bridge the knowledge-to-action gap, was presented in **Chapter 8.** By integrating principles of science communication, data visualisation and user-centred design, a step-by-step process was outlined for translating scientific research into actionable messages, focusing on 'how something is said' and 'how it is communicated.'

General discussion

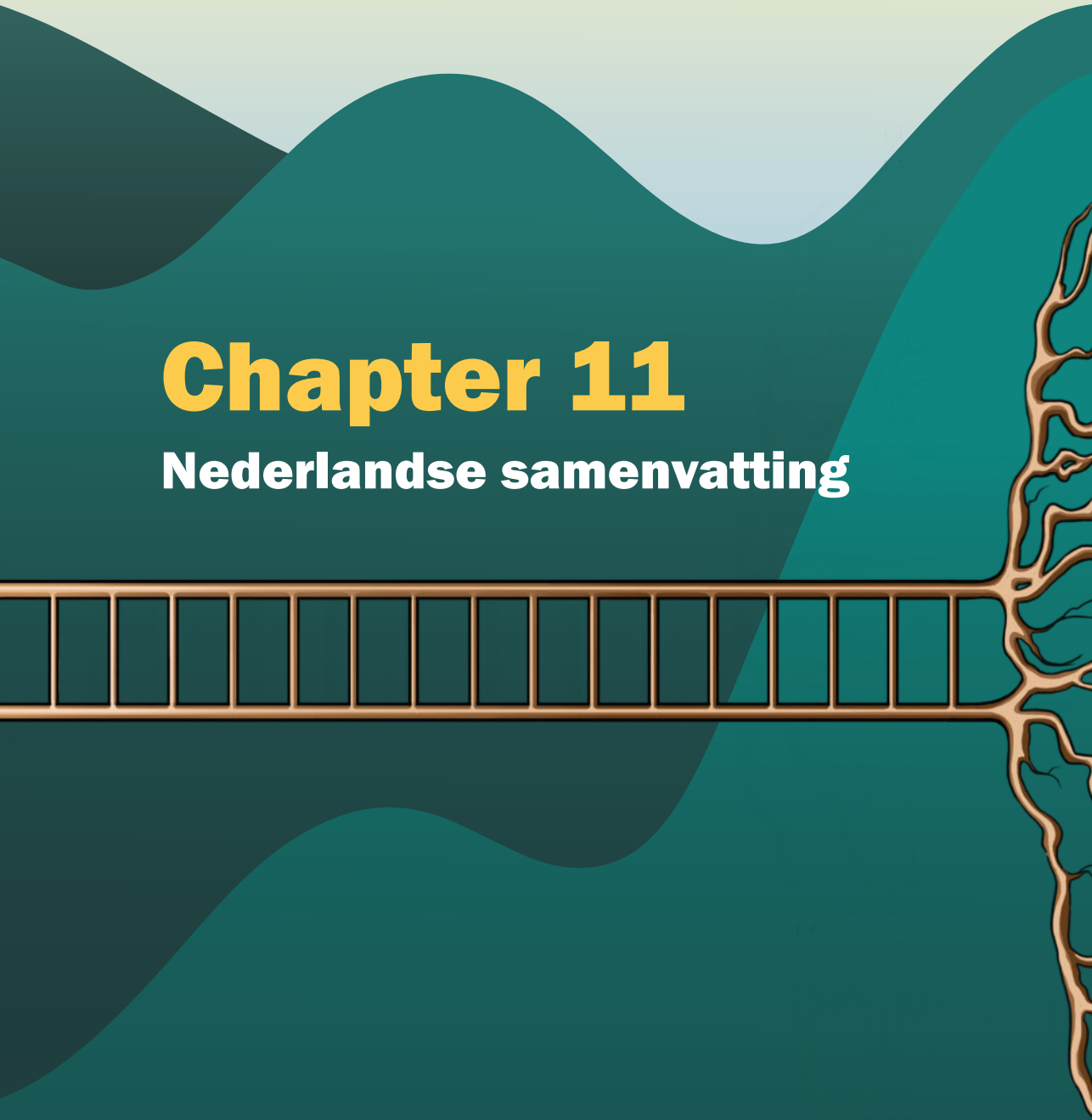
In the closing chapter we reflected on the separate studies, placing them in a wider perspective on the development, evaluation and implementation of eHealth and sharing our lessons learned. We discussed the importance of empowering patients to participate in their healthcare choices but emphasized that differences in patients' eHealth literacy needs should be taken into account (**Theme 1**). Moreover, we discussed conditions that should be met when involving socio-economically disadvantaged groups in the development and evaluation of eHealth (**Theme 2**). We tapped into the importance of early stakeholder involvement, as stakeholders are important actors within the development and sustained use and implementation of eHealth technologies (**Theme 3**) and presented ways to identify stakeholders, their needs and how to create value, including taking a more business viewpoint on value. We furthermore discussed why evaluation of eHealth should be considered a continuous process, including formative (i.e., to gain understanding for improvements) and summative (i.e., to measure performance or specific endpoints) evaluation moments (**Theme 4**). By doing so we touched upon the need to create a more favourable

research environment for eHealth research, in terms of medical ethical procedures, governance and academic reward structures (**Theme 5**).

This dissertation advocated for the early involvement of end-users and other stakeholders in the development and evaluation of eHealth. It underscored the importance of facilitating the expression of people's needs and inclusion of voices from socio-economically disadvantaged individuals who, when eHealth solution fit their needs, can benefit the most from eHealth. Moreover, it called for a critical examination of existing research paradigms that are to effectively guide the development and evaluation of eHealth solutions to create.

Chapter 11

Nederlandse samenvatting



Nederlandse samenvatting

De Nederlandse gezondheidszorg staat voor diverse uitdagingen, voornamelijk door de dubbele vergrijzing, de toename van chronische ziekten en de vooruitgang in medische behandelingen en technologie. Dit heeft geleid tot aanzienlijke financiële druk en een tekort aan personeel binnen het huidige zorgstelsel. Om deze problemen aan te pakken is het Integraal Zorg Akkoord (2023-2026) opgesteld. In het akkoord is er nadrukkelijk aandacht voor de integratie en het gebruik van digitale zorgtechnologieën (eHealth), bijvoorbeeld voor het aanbieden van zorgdiensten en informatie. Daarmee biedt eHealth een alternatieve en innovatieve benadering voor het leveren van gezondheidszorg, zoals zorg op afstand en digitale zorg. Ondanks de potentie van eHealth om de gezondheidszorg te transformeren en klinische uitkomsten te verbeteren, is de wijdverspreide adoptie en implementatie ervan beperkt.

De beperkte adoptie van eHealth interventies kan deels worden toegeschreven aan het gebrek aan actieve betrokkenheid van eindgebruikers, zoals patiënten, in de vroege ontwerp- en ontwikkelfase van interventies (**eerste uitdaging).** Dit resulteert vaak in matige bruikbaarheid en gebruikerservaring, en een gebrek aan afstemming van de interventie op de behoeftes van de gebruiker. Participatief ontwerpen, waarbij gebruikers als 'experts van hun eigen ervaringen' worden betrokken, is daarom steeds belangrijker geworden. Deze ontwerpaanpak is gericht op het aanboren van kennis van gebruikers en het bevorderen van wederzijds begrip tijdens het ontwerpproces. Het gebruik van participatieve ontwerp tools is echter vaak beperkt of slecht onderbouwd. Daarom zijn uitgebreide casestudies nodig om een solide kennisbasis op dit gebied op te bouwen.

eHealth interventies die wel worden gebruikt, worden veelal maar voor een korte periode gebruikt en hebben vaak te lijden onder kortstondig gebruik, vaak meestal als gevolg van een gebrek aan betrokkenheid van de gebruiker bij de interventie (**tweede uitdaging**). Betrokkenheid omvat een breed scala aan psychologische en gedragsfactoren die de interactie van gebruikers met, en hun gebruik van, digitale gezondheidstechnologieën beïnvloeden. Om de adoptie en het gebruik van eHealth oplossingen te bevorderen is het derhalve van belang dat de eHealth interventie boeiend is. Het inzetten van zogenaamde 'Persuasive games', waarbij spelelementen worden geïntegreerd om gebruikers aan te moedigen een bepaald gedrag of attitude aan te nemen, kan de betrokkenheid van gebruikers vergroten en het gebruik van eHealth op de langer termijn bevorderen.

Langdurig gebruik van eHealth hangt daarnaast samen met kenmerken van de gebruiker zelf. Bepaalde gebruikerskenmerken zoals leeftijd, chronische aandoeningen, een lagere sociaaleconomische positie en beperkte gezondheidsvaardigheden, worden geassocieerd met een lager gebruik van eHealth. Dit resulteert in een digitale kloof, waarbij personen met beperkte digitale toegang en vaardigheden obstakels ondervinden bij het gebruik van digitale gezondheidstechnologieën (derde uitdaging). Het overbruggen van deze kloof vereist niet alleen toegang tot digitale technologieën, maar ook de bevordering van digitale gezondheidsvaardigheden en

de betrokkenheid van deze personen bij de ontwikkeling van eHealth oplossingen. Het effectief betrekken van achtergestelde groepen, zoals mensen met beperkte gezondheidsvaardigheden, bij participatief ontwerp wordt echter belemmerd door verschillende factoren. Praktijkvoorbeelden en leidraden zijn nodig om inzicht te krijgen in hoe deze barrières te overkomen.

Bovendien wordt wijdverspreide adoptie en implementatie belemmerd door een gebrek aan bewijs van de effectiviteit van eHealth interventies. Hoewel gerandomiseerde klinische studies vaak worden gebruikt om de effectiviteit van interventies te onderzoeken, houden ze over het algemeen onvoldoende rekening met de complexiteit van de context waarin de interventie wordt toegepast (**vierde uitdaging**). Daarom zijn alternatieve onderzoeksontwerpen en -methoden vereist om robuuste 'real-world evidence' (d.w.z. bewijs dat in de praktijk wordt gegenereerd) te verkrijgen.

Tot slot, wordt niet alle gegenereerde kennis toegepast in de praktijk, wat zorggebruikers en de samenleving niet ten goede komt. Het vertalen van wetenschappelijk bewijs naar begrijpelijke en bruikbare kennis voor belanghebbenden en besluitvormers is een essentieel proces, dat ook wel bekend staat als kenniscreatie. Dit proces is van groot belang om de zogenaamde "kennis-naar-actie kloof" te overbruggen. Helaas ontbreken momenteel richtlijnen voor het praktisch toepassen van dit kenniscreatie proces.

Het aanpakken en overbruggen van de bovengenoemde uitdagingen is essentieel om toe te werken naar zinvolle eHealth die gebruikers, zorgverleners en het zorgsysteem als geheel ten goede komt. Als we deze uitdagingen het hoofd bieden, kan eHealth een revolutie teweegbrengen in de gezondheidszorg en gezondheidsuitkomsten voor individuen en populaties verbeteren.

Het doel van dit proefschrift was dan ook om de genoemde uitdagingen aan te pakken door middel van praktijkgerichte onderzoeksprojecten. Deze hadden betrekking op de ontwikkeling van verschillende eHealth interventies met behulp van participatieve ontwerptools, en het genereren van real-world evidence om deze interventies te evalueren. Daarnaast bevat het proefschrift een studie naar de vertaling en evaluatie van de validiteit van de Nederlandse versie van de eHealth Literacy-vragenlijst (d.w.z. een vragenlijst naar digitale gezondheidsvaardigheden) en biedt het een stapsgewijze aanpak voor het vertalen van wetenschappelijke kennis naar bruikbare informatie voor besluitvorming.

Deel 1 – Participatief ontwerpen

In het eerste deel van dit proefschrift hebben we aan de hand van drie praktijkgerichte onderzoeken als casussen, laten zien hoe participatief ontwerpen kan worden gebruikt om eindgebruikers en andere belanghebbenden actief te betrekken in de vroege fase van de ontwikkeling van eHealth (**eerste uitdaging**). **Hoofdstuk 2** beschreef het ontwerp van het persuasive game 'Ademgenoot' om mensen met astma te motiveren hun medicatie te gebruiken zoals voorgeschreven (casus 1). We

konden verschillende redenen voor slechte medicatietrouw en specifieke behoeften identificeren door eindgebruikers in een vroeg stadium te betrekken en gebruik te maken van participatieve ontwerptools zoals persona's en paper-prototyping. Gebaseerd op deze inzichten met betrekking tot redenen en behoeften hebben we 'Ademgenoot' ontworpen. Dit innovatieve spel combineert de monitoring van inhalator gebruik met behulp van een elektronisch apparaat en integreert gedragsveranderingstechnieken en persuasieve spelontwerpelementen. Het spel werd positief ontvangen door mensen met milde astma en heeft de potentie om het gebruik van inhalatoren positief te beïnvloeden. Motivatie voor dagelijks inhalatorgebruik werd gestimuleerd door verschillende strategieën voor gedragsverandering te combineren, waaronder het stellen van persoonlijke doelen en voortdurende directe visuele feedback over inhalatorgebruik, aangevuld met spelelementen zoals een boeiend verhaal en beloningen.

In **hoofdstuk 3** richtten we onze participatieve ontwerpinspanningen op mensen met beperkte gezondheidsvaardigheden en zijn we dieper ingegaan op het aanpassen en toepassen van participatieve ontwerpmethoden voor deze doelgroep (casus 2). In dit onderzoek, gericht op het verbeteren van medicatietrouw, hebben we strategieën ontwikkeld om de specifieke uitdagingen bij het ontwerpen voor en met mensen met beperkte gezondheidsvaardigheden en astma te ondervangen. We hebben laten zien hoe participatieve ontwerptools zorgvuldig geselecteerd, aangepast en toegepast kunnen worden om mensen met beperkte gezondheidsvaardigheden actief te betrekken bij het ontwerpen van eHealth oplossingen, met als doel het identificeren van hun behoeften en bevorderen van wederzijds begrip gedurende het ontwerpproces.

In **hoofdstuk 4** presenteerden we een derde praktijkcasus. In dit hoofdstuk beschreven we de ontwikkeling en pilotstudie van de 'Hospital Hero' app, een app die tot doel heeft om pre-procedurele stress te verminderen en een positievere ziekenhuiservaring te creëren voor kinderen. In de eerste studie hebben we participatief ontwerp toegepast door de ervaring van de gebruiker, in dit geval het kind, als uitgangspunt te nemen om een applicatie te ontwikkelen die kinderen gedurende hun hele ziekenhuisreis ondersteunt. De Hospital Hero app doet dit door voorbereiding en afleiding te bieden. Een eerste versie van de Hospital Hero app is vervolgens geëvalueerd in de praktijk tijdens een pilotstudie van twee maanden. Met behulp van een mixed-method aanpak, waarbij kwalitatieve en kwantitatieve data gelijktijdig werd verzameld, hebben we met kinderen, ouders en zorgverleners de Hospital Hero app geëvalueerd op gebruik, bruikbaarheid en gebruikerservaring. Met deze studie konden we aantonen hoe kinderen, als eindgebruikers, actief betrokken kunnen worden bij de ontwikkeling van eHealth. Bovendien benadrukten we het belang van het evalueren van eHealth oplossingen in de praktijk om hun waarde voor kinderen, ouders en zorgverleners te beoordelen.

Deel 2 – Beoordeling van effectiviteit

Hoofdstuk 5 ging verder in op het belang van het evalueren van eHealth interventies in real-world settings (**vierde uitdaging**). In dit hoofdstuk werd een protocol

gepresenteerd voor een cluster gerandomiseerde studie (RCT) om een zelfmanagementprogramma voor astma met een slimme inhalator te evalueren. Het onderzoek had als doel om real-world evidence te verschaffen met betrekking tot klinische uitkomsten (o.a. therapietrouw en astma controle), acceptatie en bruikbaarheid van de slimme inhalator. Hierin werden ook patiëntkenmerken zoals overtuigingen over medicatie en digitale gezondheidsvaardigheden meegenomen. Het hoofdstuk belichtte tevens manieren om patiënten te betrekken bij zowel het ontwerp als de uitvoering van klinische studies, en bood inzicht in het omgaan met beperkingen die traditionele RCTs kunnen hebben bij het onderzoeken van de effectiviteit van eHealth interventies.

De tegenhanger van de RCT, die wordt beschouwd als 'gouden standaard studieopzet' voor onderzoek naar effectiviteit, is de meta-analyse van meerdere onderzoeken om het totale effect te beoordelen. **Hoofdstuk 6** presenteerde een meta-analyse en systematische review naar de effectiviteit van geïntegreerde zorgprogramma's voor mensen met chronisch obstructieve longziekte (COPD). De review omvatte tweeënvijftig onderzoeken naar geïntegreerde zorgprogramma's, uitgevoerd in negentien verschillende landen, en vergeleek deze met gebruikelijke zorg op verschillende gezondheid gerelateerde - en klinische uitkomsten. De resultaten toonden aan dat geïntegreerde zorgprogramma's waarschijnlijk zorgen voor een verbetering in ziekte-specifieke kwaliteit van leven, inspanningsvermogen, ziekenhuisopnames gerelateerd aan luchtwegen, en ziekenhuisdagen per persoon. Er werden geen significante verschillen gevonden voor sterfte, antibioticakuren/prednison, kortademigheid en depressie- en angstscores.

Geïntegreerde zorgprogramma's zijn complexe interventies, gekenmerkt door hun opbouw uit verschillende componenten en de betrokkenheid van diverse gezondheidsdisciplines. Aangezien eHealth interventies vaak ook uit meerdere componenten bestaan en gekenmerkt worden door de betrokkenheid van meerdere belanghebbenden, kunnen ze eveneens beschouwd worden als complexe gezondheidsinterventies. Daarom kunnen de uitdagingen die we hebben geïdentificeerd in de meta-analyse van geïntegreerde zorgprogramma's waardevolle inzichten bieden en overwegingen aandragen voor de evaluatie van eHealth interventies (**vierde uitdaging**).

Deel 3 - Instrumenten

In het derde deel van dit proefschrift hebben we twee verschillende instrumenten gepresenteerd. Het eerste instrument betreft de Nederlandse versie van de eHealth Literacy Questionnaire (eHLQ) (**hoofdstuk 7**). Met dit instrument kunnen onderzoekers, eHealth-ontwikkelaars en beleidsmakers de behoeften op het gebied van digitale gezondheidsvaardigheden identificeren en de ontwikkeling van eHealth-interventies begeleiden. Hierdoor blijven mensen met beperkte digitale toegang en vaardigheden niet achter in de digitale transformatie van de gezondheidszorg (**derde uitdaging**). **Hoofdstuk 7** beschreef de vertaling, culturele aanpassing en het validatie onderzoek van de Nederlandse eHLQ. Dit onderzoek bestond uit twee studies en omvatte validatie op testinhoud, antwoordproces en interne structuur door middel van cognitief interviewen, confirmatieve factoranalyse (CFA), invarian-

tietesten en vergelijking tussen verschillende groepen. De Nederlandse versie van de eHLQ toonde sterke eigenschappen voor het beoordelen van digitale gezondheidsvaardigheden in de Nederlandse context. We bevolen echter ook aan om voortdurend bewijs van validiteit te verzamelen, aangezien validiteit niet moet worden beschouwd als een eigenschap van het instrument, maar afhangt van de context en het doel van gebruik.

Het tweede instrument, gepresenteerd in **hoofdstuk 8**, is een tool die de effectieve overdracht van wetenschappelijke kennis naar besluitvormers in de gezondheidszorg moet vergemakkelijken, met als doel de kloof tussen kennis en actie te overbruggen (**vijfde uitdaging**). Door het integreren van principes van wetenschapscommunicatie, datavisualisatie en gebruikersgericht ontwerpen, werd een stappenplan beschreven om wetenschappelijke kennis te vertalen naar bruikbare boodschappen, met nadruk op 'hoe iets wordt gezegd' en 'hoe het wordt gecommuniceerd'. Een casestudy naar interventies voor chronische longaandoeningen in lage- en middeninkomenslanden illustreerde deze aanpak.

Algemene discussie

In het laatste hoofdstuk reflecteerden we op de individuele studies en plaatsten we ze in een bredere context met betrekking tot de ontwikkeling, evaluatie en implementatie van eHealth. Belangrijke inzichten en leerlessen zijn gedeeld, waarbij de volgende kernpunten zijn besproken:

- Het belang om patiëntempowerment samen te laten gaan met voldoende (digitale) gezondheidsvaardigheden in een tijdperk van toenemende digitalisering (Thema 1).
- Het betrekken van sociaaleconomisch achtergestelde groepen bij de ontwikkeling en evaluatie van eHealth (Thema 2).
- De noodzaak van vroegtijdige betrokkenheid van belanghebbenden als cruciale actoren bij de ontwikkeling, duurzaam gebruik en implementatie van eHealth interventies (Thema 3).
- Het benadrukken van de noodzaak om belanghebbenden en hun behoeften te identificeren, evenals het creëren van waarde voor alle belanghebbenden, inclusief het aannemen van een meer zakelijk perspectief op waarde gedurende de hele ontwikkelingscyclus van eHealth (Thema 4).
- Het belang om de ontwikkeling van eHealth als een continu proces te beschouwen, met formatieve evaluatiemomenten voor verbeteringen en summatieve evaluatiemomenten om prestaties, specifieke uitkomsten of eindpunten te meten. (Thema 4).
- De noodzaak van een gunstigere onderzoeksomgeving met betrekking tot medisch-ethische procedures, bestuur en beleid en de noodzaak voor nieuwe academische beloningsstructuren, waarin publieke

betrokkenheid, leiderschap en educatie beter in lijn worden gebracht met academische beloningen en positie (Thema 5).

Met dit proefschrift illustreer ik hoe belangrijk het is om er voor te zorgen dat mensen hun behoeftes kunnen uitdrukken en delen. Hierin is er speciale aandacht voor de stemmen van sociaaleconomisch achtergestelde individuen die het meest kunnen profiteren van vooruitgang in digitale zorgtechnologieën. Daarnaast roep ik op tot een kritische evaluatie van bestaande onderzoek paradigma's, die van cruciaal belang zijn voor de effectieve ontwikkeling en evaluatie van digitale zorgtechnologieën, zodat we betekenisvolle en impactvolle eHealth kunnen bereiken.

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Presentations at (inter)national conferences

14. eHealth in pediatrics - beyond the hospital walls, 29th European Pediatirc Rheumatology Congress 2023, Rotterdam, The Netherlands (invited oral presentation)
15. Hospital Hero - beyond the hospital walls, International Pediatric Chest Conference 2023, Rotterdam, The Netherlands (invited oral presentation)
16. Ademgenoot' – a serious game to motivate and empower asthma patients in adherence to their maintenance medication, European Respiratoyr Society Research Seminar (invited) 2022, Lissabon, Portugal (oral presentation)
17. Hospital Hero – an app to support children and their families in the child's hospital journey The Association of Researchers in Psychology and Health 2022, Boemendaal aan zee (oral presentation, **best oral award**)
18. An innovative eHealth solution developed with and for asthma patients with low (health) literacy, ESPACOMP 2020 (online oral presentation)
19. 'Ademgenoot ' - a serious game to motivate and empower asthma patients to adhere to their maintenance medication, IPCRG 10th World Conference 2020 (online oral presentation)
20. An innovative solution 2019 developed with and for asthma patients with low (health) literacy, Longdagen 2019, Ermelo, The Netherlands (poster presentation, **nominated for public award**)
21. Rocky Road - from complex health problems to evidence based eHealth, UXD Healthcare 2019, Amsterdam, The Netherlands (key note)
22. Ademgenoot' – a serious game to motivate and empower asthma patients in adherence to their maintenance medication: a user-centered design study, ESPACOMP 2019, Porto, Portugal (poster presentation; **poster award)**
23. Ontwikkeling van een innovatieve zelfmanagement applicatie voor astmapatiënten - de gebruiker centraal, Longdagen 2019, Ermelo, The Netherlands (post presentation, **nominated for public award**)
24. Development of an innovative self-management app for asthma patients, Conference European Society Research internet innovations 2018, Dublin, Ireland (oral presentation)
25. Communicatie van onderzoek naar praktijk - een praktische aanpak in kenniscreatie, Nederlandse Huisartsen Genootschaps Wetenschapsdag 2018, Amsterdam, the Netherlands (oral presentation)

26. Development of an innovative self-management app for asthma patients based on a user-centred approach - a study protocol, IPCRG 9th World Conference, Porto, Portugal (oral presentation)

Curriculum Vitae

Charlotte Poot was born on December 30th 1992 in Leiden, the Netherlands. She spent her childhood time in England and Germany, attending the ACS International School Hillingdon and the Hofenfels Gymnasium in Zweibrücken. Her secondary education was completed at the Rijnlands Lyceum Oegstgeest, where she graduated in 2010 with a bilingual atheneum diploma and an International Baccalaureate Higher Level English. In that same year she started the bachelor studies Biomedical Science at the Leiden University Medical Centre. During her undergraduate years, she actively engaged with International Federation Medical Student Association (IFMSA) and was a committee member of the Standing Committee on Reproductive Health, including Aids. Her interest in public and global health was ignited during this period. She successfully completed her bachelor's degree in 2014 and started working as a research assistant at the Department of Public Health and Primary Care, as well as at the Centre for Human Drug Research.

The following year, she pursued her master's degree in Biomedical Sciences, specializing in science communication. During her master Charlotte performed a research internship in Heidelberg, at the German Cancer Research Center and at the Department of Neurology at the Leiden University Medical Centre. Charlotte commenced her masters with a research project centred on 'Factors That Enhance or Inhibit Scientists' Engagement In Knowledge Transfer Activities', under the supervision of Dr E. Meijer and Prof. N.H. Chavannes. During this period Charlotte worked as project manager assistant, and collaborated with members of the FRESH AIR consortium on mixed-method research pertaining to local beliefs, perceptions and behaviours regarding chronic lung disease. Charlotte played an integral role in the collection of qualitative data during fieldwork in Kyrgyzstan, Greece and Vietnam, providing training and supervision to the local teams.

In 2017, Charlotte embarked on a doctoral journey at the department of Public Health and Primary Care and the National eHealth Living Lab, under the supervision of Prof. N.H Chavannes and Dr. E. Meijer. Her research project initially focused on the evaluation of a self-management app linked to a smart asthma inhaler. However, due to the COVID-19 pandemic, the study coordination was transferred to a colleague. Charlotte therefore initiated a range of other research projects which now constitute her PhD thesis. During her PhD trajectory, Charlotte was involved in the minor Global Health Cuba and actively contributed to the organisation of PhD journal club, the department PhD committee and social activities. She presented her work at (inter)national conferences and made several appearances in the local and national media, including RTL nieuws, 'M' and Koffietijd. Because of her dedication and participative work with people with asthma, she was awarded the 'Sterk Participatie Prijs' by the National Lung Foundation.

In 2022, Charlotte founded, together with paediatric nurse Nicole Donkel, the non-profit foundation 'Stichting Hospital Hero' as a spin-off of the Hospital Hero project which she performed during her PhD period. Stichting Hospital Hero's mission is to reduce stress and anxiety among children undergoing medical procedures, by providing the Hospital Hero app to hospitals. Charlotte currently serves as the foundation's chair and has successfully secured multiple grants. In addition to her entrepreneurial endeavours, Charlotte holds the position of senior researcher at the Universitair Netwerk voor de Care-sector Zuid Holland.