e-Exercise

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The integration of face-to-face physiotherapy with a web-application

for patients with osteoarthritis of hip and knee

Corelien Kloek

e-Exercise: the integration of face-to-face physiotherapy with a web-application for patients with osteoarthritis of hip and knee

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e-Exercise:

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	Prof. dr. M.R. Vollenbroek-Hutten

The greatest medicine of all

Is teaching people how not to need it.

-Hippocrates (Attrib, 460-377 BC)-

Contents

1

General introduction and thesis outline

Changes in Healthcare

Over the past century, we saw a transformation of healthcare within the Netherlands as well as in other developed countries. In the beginning of the 20th century, our healthcare system was mainly focused on the treatment of life-threatening infectious diseases like diphtheria, cholera and tuberculosis [1]. Thanks to the access to clean drink water and sanitation, but also due to the introduction of antibiotics and vaccines, most infectious diseases have been conquered. As a result, our life expectancy has increased with more than 30 years [2]. However, these extra life years have also introduced new challenges within healthcare. Aging is an important risk factor for the onset of noncommunicable diseases like Alzheimer, cardiovascular diseases and osteoarthritis. Nowadays, one out of three adults live with one or more chronic diseases, which consequently results in an increasing demand on the healthcare system [3]. The rising prevalence of chronic disease has led to an alteration from acute to chronic care. Whereas the Dutch healthcare system, like most other healthcare systems, in the twentieth century was developed as a system to treat (infectious) diseases, in the last decades we saw a paradigm shift in healthcare focused on promoting health and improving management of chronic diseases [4].

Managing chronic diseases

Within the management of chronic diseases, healthcare has become more patient-centered with the aim to stimulate patients to be actively involved within their own care team [5]. This transformation within healthcare fits the new purposed definition of health [6]. Health is no longer defined as a static situation but as the "ability to adapt and to self-manage, in the face of social, physical, and emotional challenges". This new definition subscribes the importance of self-management, which refers to individuals' management of the chronic condition (i.e. symptoms, treatment, physical-, psychological- and social consequences, as well as related changes in lifestyle) so that the condition is optimally incorporated into someone's daily life [7-9]. From previous studies we know that better self-management is effective in reducing clinical symptoms and improving quality of life for different types of chronic diseases [10-13]. For example, in respiratory and cardiovascular disorders, it appeared that supporting self-management can reduce health service utilization, without losing quality of care [14]. Within self-management, five core skills are distinguished: problem solving, decision-making, resource utilization, taking action, and partnerships with health care providers [7]. These points illustrate that promotion of self-management requires not only new skills and behavior for the patient, but also a

different role for the healthcare professional. Instead of traditional one-way paternalistic decision making, there is a shift to shared decision making, in which there is a mutual dialogue between caregivers and patients. The healthcare professional emerges to a coach, partner or supervisor which plays a key role in providing education, promoting healthy behavior and motivating patients [10].

Electronic Health in chronic care management

One emerging way for healthcare professionals to fulfill their new coaching role and support patients in self-managing their chronic condition, is by using electronic health (eHealth) [15]. Websites and apps can, for example, provide patients tailored information and assignments to change behavior and manage their disease adequately, or facilitate remote monitoring. The combination of websites and apps within healthcare provided by a professional (e.g. face-to-face or telephonic) is called "blended care", or "technology supported care" [16, 17]. An example of a blended intervention is Return@Work, developed for sick-listed employees with mental disorders. Within this Dutch intervention, an eHealth module for the employee is embedded within the face-to-face guidance from an occupational physician [18]. Both treatment modalities are complementing to each other, since the physician can tailor the eHealth module to individuals' needs and uses online progress monitoring for optimal treatment and referral options [18].

The added value of blended care

Blended care is promising in many ways. Three main advantages of blended care are: 1) patients are offered a tool which can support self-management and trigger them 24/7 in changing their health behavior; 2) the healthcare provider can provide irreplaceable human support, tailored to patients' individual needs; and 3) part of the face-to-face care might be substituted by online guidance, resulting in reduced healthcare expenditures. Each advantage will be described in more detail below.

1) *Self-management and behavior change support regardless of time and place*

One of the biggest challenges in chronic care management is patients' compliance to the behavior change recommendations. Within physiotherapy, for example, 45-70% of the patients do not (completely) follow their exercise recommendations [19, 20]. To

illustrate the difficulty of treatment compliance and behavior change, Box 1 describes a case of a patient with osteoarthritis (OA) which consulted her physiotherapist.

Box 1. Case of patient with hip osteoarthritis

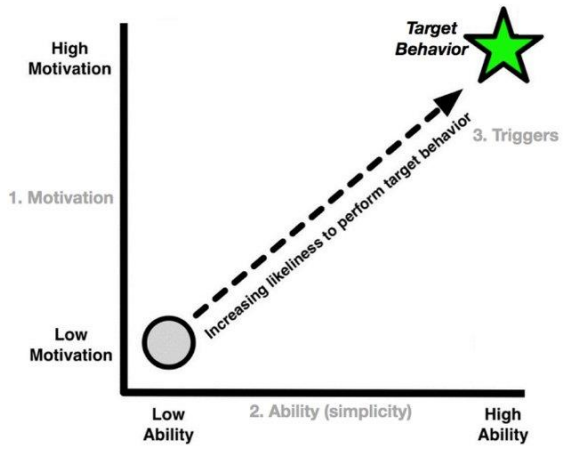
Miss Jacobson is 64 years old, has a BMI of 27 and is two years ago diagnosed with OA in her left hip. Because of worsening pain and stiffness, she consulted her physiotherapist. Her physiotherapist instructed Miss Jacobson about the importance of physical activity, despite OA related symptoms. Miss Jacobson shifted from cycling towards car using one year ago, since she always believed that cycling deteriorated her complaints. Since Miss Jacobson is informed and reassured by her physiotherapist, she is motivated to cycle again and formulated her goal: going to the library in the nearest town by bike (approximately 40 minutes of cycling). Although she is still not completely convinced about her ability to reach this goal, her physiotherapist ensured her that, despite her OA, she will be able to reach this goal within a few months. The physiotherapist and Miss Jacobson meet each other again after 4 weeks, since Miss Jacobson does not want to spend all her physiotherapy sessions (which are covered by her health insurance) in the beginning of the year. Unfortunately, after 4 weeks it appeared that Miss Jacobson cycled only once per week instead of the scheduled three times. As she said: "I'm so sorry, I just forgot to follow your recommendations in the daily hustle and bustle. Maybe I should put my indoor cycle in the middle of the living, instead of in the shed, since I consequently forget to exercise on my indoor!"

The difficulty of Miss Jacobson in changing her behavior can be illustrated by the Fogg Behavioral Model (Figure 1) [21]. This model describes behavior as a product of three factors: 1) having sufficient motivation for changing the central behavior; 2) having the ability to perform the central behavior; and 3) being triggered, or reminded, to perform the behavior.

All factors must be present in order to succeed in changing or maintaining a target behavior, however, the quantity in which each factor is present may vary. Within the case of Miss Jacobson, sufficient motivation is available, caused by the pain and her hope to go cycling again. The physiotherapist confronts Miss Jacobson with maladaptive behavior and thoughts, and helps her to change her coping style and increase her physical load ability with a personalized exercise schedule. However, the

trigger to perform the desired behavior is missing. As a solution, Fogg promotes the use of technology to provide this trigger [21]. Persuasive design features like personalized announcements and assignments on phone or computer are hypothesized to support Miss Jacobson in her OA management [17]. The technology can also be used to remind Miss Jacobson to her preset goal, or to provide information about coping with OA, in order to keep her motivated. All in all, an important advantage of blended care compared to conventional face-to-face care is the accessibility of technology regardless of time and place, whereas professional guidance is restricted to a certain amount of sessions.

Figure 1. The Fogg Behavioral Model



2) Irreplaceable guidance by a professional, tailored to individual needs

A second advantage is related to patients' interaction with a healthcare professional. Up to now, a lot of research has focused on unguided web-applications to change behavior. The effectiveness of these web-applications appeared to be small and usage was often disappointing [17, 22]. One of the recommendations to improve the effectiveness and usage of web-application is by integrating online guidance with professional guidance which can provide support, but also empathy, attention and warmth [17, 22, 23]. From the perspective of the healthcare professional, remote monitoring can provide valuable information to tailor the treatment to patients' individual needs [24]. For example, when the web-application can provide insight in patients experienced difficulty in executing physiotherapeutic exercises, a physiotherapists can use this information to adapt patients' exercise schedule, or provide extra instruction.

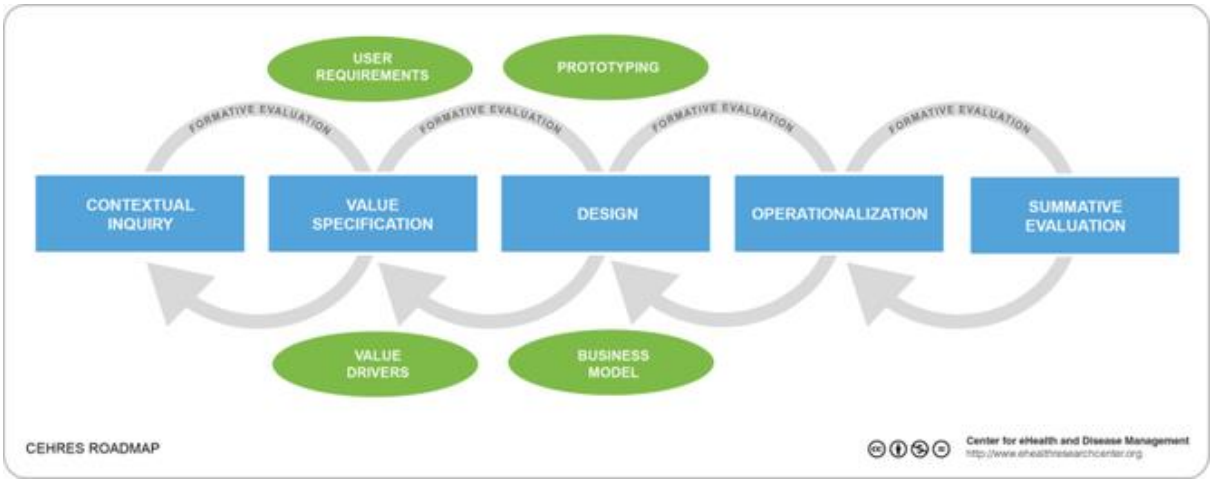
3) Reducing healthcare costs

The last important advantage of integrating web-applications within usual care is its potential to reduce healthcare costs [14]. In some patients, online care might substitute part of the face-to-face contacts and reduce healthcare utilization, which might result in reduced healthcare costs. With respect to the increasing number of patients with one or more chronic diseases, there is a need for affordable and cost-effective interventions in chronic care.

The participatory development of eHealth

The use of web-applications within healthcare have been a field of interest since the beginning of the 21th century. Web-applications from the "first generation" were often developed using a technology-driven approach, which frequently resulted in applications which did not meet the values of the end-user. To solve this problem, and to ensure uptake and acceptance of the intervention, participatory development is highly recommended [25]. Participatory development consists of co-creation between developers, stakeholders and end-users. A framework which can be used for the participatory development, evaluation and implementation of eHealth is the Center for eHealth Research (CeHRes) Roadmap (Figure 2) [25, 26]. The roadmap consists of five steps: 1) *contextual inquiry* in which the design team makes an investigation of current health problem and its context; 2) *value specification* in which the values and requirements of different end-users and stakeholders are investigated; 3) *design*: based on the values of the end-users and stakeholders a prototype of the intervention can be built. A first prototype is tested on usability; 4) *operationalization* in which the technology is launched in daily practice; and 5) *summative evaluation,* an evaluation how the application is used, as well as the effects on clinical and economic outcome measures. Each step should be based on participatory approach. Alongside the process, business modelling is seen as crucial factor for the sustainability and effectiveness of eHealth. This business modelling should consist of an implementation strategy in an early stage of the project [27]. Next, the framework describes not a linear process, but an iterative process in which formative evaluations aim to provide ongoing information about how the intervention can be improved [28].

Figure 2. The CeHRes Roadmap



The case: osteoarthritis of hip and/or knee

This thesis focuses on a blended care intervention for patients with osteoarthritis (OA) of the hip and/or knee. OA is the most common chronic joint disease and mostly affects the hip and knee [29]. Prevalence of OA increases with age. Based on radiographical diagnosis, hip OA is seen in approximately 5-15% of people of 55 years and older [30], knee OA in 10-30% [31]. The prevalence of OA is expected to increase due to the aging population and the growing number of people with obesity [29]. Most common symptoms of OA are pain, stiffness, crepitation, reduced range of motion and sometimes inflammation [32]. Due to these symptoms, daily activities become difficult. As a result, some patients with OA tend to avoid daily activities. In these patients, pain sensations are misinterpreted and patients have the idea that physical activity might worsen their symptoms. However, a negative spiral of physical inactivity may lead to muscle weakness and reduced confidence or anxiety in the long-term, resulting in even more limitations in daily activities [33]. A physiotherapist can guide these patients replacing useless thoughts and increasing patients' daily activities.

Physiotherapy in osteoarthritis of hip and knee

Physiotherapy is seen as the most recommended non-surgical and non-pharmacological treatment for patients with OA [34, 35]. Effective physiotherapeutic modalities in reducing levels of pain and improving physical functioning consist of patient education, muscle strengthening exercises and aerobic exercises [30, 31]. A well-known approach to increase activity levels among patients with OA is graded

activity [36]. Graded activity is a behavioral approach in which levels of physical activity, in a time-contingent way, are gradually increased to a preset goal. Within this approach, positive reinforcement of performed physical activity and withdrawal of attention to pain are essential elements. The final goal of graded activity is that physical activity is integrated in individuals' daily life in order to reach a physically active lifestyle [36, 37]. However, an important challenge within the physiotherapy is patients' adherence to exercise recommendations, both in the short- as in the long-term. It appeared that between 45-70% of the patients do not (completely) follow their exercise recommendations which hamper the effectiveness of physiotherapy [19, 20].

Aim of this thesis

Within this thesis, the CeHRes Roadmap will be used as a framework for the development, evaluation and implementation of a blended physiotherapeutic intervention for patients with hip and/or knee OA. The first aim of this thesis was to develop a blended intervention (e-Exercise, Box 2) for patients with OA of the hip and/or knee, that values the needs of patients, physiotherapists and other stakeholders. The second aim was to investigate the feasibility and the (cost-) effectiveness of e-Exercise in comparison to usual physiotherapy for patients with hip and/or knee OA.

Outline of the thesis

Chapter 2 describes a systematic review about the characteristics and effectiveness of blended interventions to change behavior in patients with a chronic somatic disorder. The results of this systematic review were used in the development of e-Exercise for patients with OA of the hip and/or knee. This participatory development-process, as well as the feasibility study for the first prototype of e-Exercise, are described in *Chapter 3*. Based on the results of the pilot-study, adaptations were made to improve e-Exercise. *Chapter 4* describes the study-protocol of the multicenter randomized controlled trial study to study the (cost-)effectiveness of e-Exercise in patients with OA of the hip and/or knee. The results of effectiveness of e-Exercise compared to usual physiotherapy are presented in *Chapter 5*. The cost-effectiveness study, which includes both the societal- as well as the healthcare perspective, is presented in *Chapter 6*. Patients usage of the web-application of e-Exercise and an investigation of which patient-, intervention- and environmental factors were related to program usage, are presented in the mixed-methods study in *Chapter 7*. A second mixed-

methods study is presented in C*hapter 8,* which describes the factors that were related to physiotherapists' usage or non-usage of e-Exercise. Both mixed-methods provided valuable information for the implementation of e-Exercise on a broader scale. Finally, *Chapter 9* presents a general discussion of the entire e-Exercise project and our findings, methodological considerations and recommendations for future research as well as implications for daily physiotherapeutic practice. This dissertation ends with a summary in English and Dutch.

Box 2. The e-Exercise Osteoarthritis intervention

E-Exercise is a blended physiotherapeutic intervention for patients with hip and/or knee osteoarthritis. Within this 12-week intervention, five face-to-face physiotherapeutic sessions are integrated within a web-application. The web-application, with a log-in for both the patient and the physiotherapist, consists of 1) a graded activity module in which assignments for an individually chosen activity, like walking or cycling gradually, is increased until a personal short-term goal is reached; 2) strength & stability exercises, selected by the physiotherapists with instructions in text and video on the website; and 3) a weekly new information text and video about an osteoarthritis related theme like etiology, pain management or the importance of a physical active lifestyle. Patients were asked to evaluate their assignments weekly. Based on this evaluation, the web-application provided automatic tailored feedback. Physiotherapists could monitor patients' evaluations and accordingly tailor the treatment to individual needs.

References

1. Sheingold BH, Hahn JA: The history of healthcare quality: The first 100 years 1860–1960. *International Journal of Africa Nursing Sciences* 2014, 1:18-22.
2. Riley JC: Estimates of Regional and Global Life Expectancy, 1800–2001. *Population and Development Review* 2005, 31(3):537-543.
3. World Health Organization. Global status report on noncommunicable diseases 2010 http://www.who.int/nmh/publications/ncd_report_full_en.pdf [Checked on 28-07-2015].
4. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A: Improving chronic illness care: translating evidence into action. *Health Aff (Millwood)* 2001, 20(6):64-78.
5. Karazivan P, Dumez V, Flora L, Pomey MP, Del Grande C, Ghadiri DP, Fernandez N, Jouet E, Las Vergnas O, Lebel P: The patient-as-partner approach in health care: a conceptual framework for a necessary transition. *Acad Med* 2015, 90(4):437-441.
6. Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, Leonard B, Lorig K, Loureiro MI, van der Meer JW *et al*: How should we define health? *BMJ* 2011, 343:d4163.
7. Lorig KR, Holman H: Self-management education: history, definition, outcomes, and mechanisms. *Ann Behav Med* 2003, 26(1):1-7.
8. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J: Self-management approaches for people with chronic conditions: a review. *Patient Educ Couns* 2002, 48(2):177-187.
9. CBO: Zorgmodule Zelfmanagement 1.0. Het ondersteunen van eigen regie bij mensen met één of meerdere chronische ziekten. . 2014.
10. Kivela K, Elo S, Kyngas H, Kaariainen M: The effects of health coaching on adult patients with chronic diseases: a systematic review. *Patient Educ Couns* 2014, 97(2):147-157.
11. Hill JC, Whitehurst DG, Lewis M, Bryan S, Dunn KM, Foster NE, Konstantinou K, Main CJ, Mason E, Somerville S *et al*: Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet* 2011, 378(9802):1560-1571.
12. Czupryniak L, Barkai L, Bolgarska S, Bronisz A, Broz J, Cypryk K, Honka M, Janez A, Krnic M, Lalic N *et al*: Self-monitoring of blood glucose in diabetes: from evidence to clinical reality in Central and Eastern Europe--recommendations from the international Central-Eastern European expert group. *Diabetes Technol Ther* 2014, 16(7):460-475.
13. Chodosh J, Morton SC, Mojica W, Maglione M, Suttorp MJ, Hilton L, Rhodes S, Shekelle P: Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med* 2005, 143(6):427-438.
14. Panagioti M, Richardson G, Small N, Murray E, Rogers A, Kennedy A, Newman S, Bower P: Self-management support interventions to reduce health care utilisation

without compromising outcomes: a systematic review and meta-analysis. *BMC Health Serv Res* 2014, 14:356.
15. Gee PM, Greenwood DA, Paterniti DA, Ward D, Miller LM: The eHealth Enhanced Chronic Care Model: a theory derivation approach. *J Med Internet Res* 2015, 17(4):e86.
16. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JE: Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. *JMIR mental health* 2016, 3(1):e9.
17. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE: Persuasive system design does matter: a systematic review of adherence to web-based interventions. *J Med Internet Res* 2012, 14(6):e152.
18. Volker D, Zijlstra-Vlasveld MC, Anema JR, Beekman AT, Brouwers EP, Emons WH, van Lomwel AG, van der Feltz-Cornelis CM: Effectiveness of a blended web-based intervention on return to work for sick-listed employees with common mental disorders: results of a cluster randomized controlled trial. *J Med Internet Res* 2015, 17(5):e116.
19. Friedrich M, Gittler G, Halberstadt Y, Cermak T, Heiller I: Combined exercise and motivation program: effect on the compliance and level of disability of patients with chronic low back pain: a randomized controlled trial. *Arch Phys Med Rehabil* 1998, 79(5):475-487.
20. Sluijs EM, Kok GJ, van der Zee J: Correlates of exercise compliance in physical therapy. *Phys Ther* 1993, 73(11):771-782; discussion 783-776.
21. Fogg BJ: A behavior model for persuasive design. In: *Proceedings of the 4th international Conference on Persuasive Technology: 2009*: ACM; 2009: 40.
22. Macea DD, Gajos K, Daglia Calil YA, Fregni F: The efficacy of Web-based cognitive behavioral interventions for chronic pain: a systematic review and meta-analysis. *J Pain* 2010, 11(10):917-929.
23. Brouwer W, Kroeze W, Crutzen R, de Nooijer J, de Vries NK, Brug J, Oenema A: Which intervention characteristics are related to more exposure to internet-delivered healthy lifestyle promotion interventions? A systematic review. *J Med Internet Res* 2011, 13(1):e2.
24. Coulter A, Entwistle VA, Eccles A, Ryan S, Shepperd S, Perera R: Personalised care planning for adults with chronic or long-term health conditions. *Cochrane Database Syst Rev* 2015(3):CD010523.
25. van Gemert-Pijnen J, Peters O, Ossebaard HC: Improving eHealth: Eleven international publishing Den Haag, The Netherlands; 2013.
26. van Gemert-Pijnen JE, Nijland N, van Limburg M, Ossebaard HC, Kelders SM, Eysenbach G, Seydel ER: A holistic framework to improve the uptake and impact of eHealth technologies. *J Med Internet Res* 2011, 13(4):e111.
27. van Limburg M, van Gemert-Pijnen JE, Nijland N, Ossebaard HC, Hendrix RM, Seydel ER: Why business modeling is crucial in the development of eHealth technologies. *J Med Internet Res* 2011, 13(4):e124.

28. Kensing F BJ: Participatory design: Issues and concerns. Computer Supported Cooperative Work (CSCW) 1998 Sep;, 7(3-4):167–85.
29. Zhang Y, Jordan JM: Epidemiology of osteoarthritis. *Clinics in geriatric medicine* 2010, 26(3):355-369.
30. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S: Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev* 2014(4):CD007912.
31. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL: Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2015, 1:CD004376.
32. Bijlsma JW, Berenbaum F, Lafeber FP: Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011, 377(9783):2115-2126.
33. Bossen D, Veenhof C, Dekker J, de Bakker D: The usability and preliminary effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis. *BMC Med Inform Decis Mak* 2013, 13:61.
34. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H *et al*: OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and cartilage* 2014, 22(3):363-388.
35. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM: A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Seminars in arthritis and rheumatism* 2014, 43(6):701-712.
36. Veenhof C, Koke AJ, Dekker J, Oostendorp RA, Bijlsma JW, van Tulder MW, van den Ende CH: Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial. *Arthritis Rheum* 2006, 55(6):925-934.
37. Pisters MF, Veenhof C, de Bakker DH, Schellevis FG, Dekker J: Behavioural graded activity results in better exercise adherence and more physical activity than usual care in people with osteoarthritis: a cluster-randomised trial. *Journal of physiotherapy* 2010, 56(1):41-47.

2

Blended interventions to change behavior in patients with chronic somatic disorders: systematic review

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Abstract

Background: Blended behavior change interventions combine therapeutic guidance with online care. This new way of delivering health care is supposed to stimulate patients with chronic somatic disorders in taking an active role in their disease management. However, knowledge about the effectiveness of blended behavior change interventions and how they should be composed is scattered.

Objective: This comprehensive systematic review aimed to provide an overview of characteristics and effectiveness of blended behavior change interventions for patients with chronic somatic disorders.

Methods: We searched for randomized controlled trials published from 2000 to April 2017 in PubMed, Embase, CINAHL, and Cochrane Central Register of Controlled Trials. Risk of bias was assessed using the Cochrane Collaboration tool. Study characteristics, intervention characteristics, and outcome data were extracted. Studies were sorted based on their comparison group. A best-evidence synthesis was conducted to summarize the effectiveness.

Results: A total of 25 out of the 29 included studies were of high quality. Most studies (n=21; 72%) compared a blended intervention with no intervention. The majority of interventions focused on changing pain behavior (n=17; 59%), and the other interventions focused on lifestyle change (n=12; 41%). In addition, 26 studies (90%) focused on one type of behavior, whereas 3 studies (10%) focused on multiple behaviors. A total of 23 studies (79%) mentioned a theory as basis for the intervention. The therapeutic guidance in most studies (n=18; 62%) was non face-to-face by using email, phone, or videoconferencing, and in the other studies (partly), it was face-to-face (n=11; 38%). In 26 studies (90%), the online care was provided via a website, and in 3 studies (10%) via an app. In 22 studies (76%), the therapeutic guidance and online care were integrated instead of two separate aspects. A total of 26 outcome measures were included in the evidence synthesis comparing blended interventions with no intervention: for the coping strategy catastrophizing, we found strong evidence for a significant effect. In addition, 1 outcome measure was included in the evidence synthesis comparing blended interventions with face-to-face interventions, but no evidence for a significant effect was found. A total of 6 outcome measures were included in the evidence synthesis comparing blended interventions with online interventions, but no evidence for a significant effect was found.

Conclusions: Blended behavior change interventions for patients with chronic somatic disorders show variety in the type of therapeutic guidance, the type of online care, and how these two delivery modes are integrated. The evidence of the effectiveness of blended interventions is inconsistent and nonsignificant for most outcome measures. Future research should focus on which type of blended intervention works for whom.

Introduction

An important challenge of today's health care is the management of patients with chronic somatic disorders. In addition, 1 out of 3 European adults deal with consequences of conditions such as heart failure, diabetes, asthma, or rheumatism [1]. Roughly, 50 million of them have even more than one chronic disorder (ie, multimorbidity) [2]. Patients' behavior can influence the progression of their disorder and their perceived health, particularly when it concerns a lifestyle-related chronic disorder [3]. For those who need support in taking actions related to their lifestyle, a behavior change intervention can be helpful [4]. Examples are an education program for patients with rheumatoid arthritis [5] or an intervention for patients with chronic obstructive pulmonary disease (COPD) focused on physical activity, smoking, disease knowledge, and emotional wellbeing [6].

Blended Interventions

An upcoming and new delivery mode for behavior change interventions is the use of Internet technologies, such as websites and apps. Although traditional behavior change interventions in primary care are restricted to face-to-face sessions, websites and apps are available at any time and place and can act as an extension of care provided by the professional. Online interventions without therapeutic guidance, however, struggle with disappointing adherence rates [7]. Therefore, it is recommended to combine online interventions with therapeutic guidance. The combination of online care and therapeutic guidance is called blended care, also known as technology supported care [7,8]. Bringing together the personal attention of a professional and the accessibility of an online tool is seen as a highly promising combination, which can stimulate patients to take an active role in their disease management [9]. The potential of integrating online care and technology within regular care for patients with chronic somatic disorders is also described in the recently developed eHealth Enhanced Chronic Care Model. The authors extended the original Chronic Care Model with eHealth tools to promote an informed and activated patient, to create productive interactions with the health care provider, and to increase patients' self-management [10,11].

Characteristics of Blended Interventions

Present blended interventions have in common that they consist of an online element complemented with therapeutic guidance; however, they show a wide variety in how

both elements are delivered and combined. For example, the online part can be delivered via a website with solely information texts, but supplementary videos, games, and links can be used as well. In addition, the guidance by a therapist can be delivered in various ways, for example, by providing traditional face-to-face sessions, contact by email, or by videoconferencing [12]. One of the challenges in delivering blended care is the integration of online care and therapeutic guidance instead of two separate components [8]. When integrated properly, the website or app is not only supportive to the usual therapeutic guidance but is also a substantial element of the intervention as a whole [13].

Although blended care is seen as promising in terms of effectiveness and improving health care access, the actual usage in daily primary care practice is lagging behind [14]. More knowledge about the characteristics and the effectiveness of blended behavior change interventions may support the usage in daily health care practice. However, to our knowledge, a clear overview of blended behavior change interventions is missing in literature. We conducted a systematic literature review to investigate the characteristics and the effectiveness of blended behavior change interventions for patients with chronic somatic disorders. Chronic somatic disorders are defined as health conditions that are persistent or long-lasting [15]. Mental illnesses were excluded from this review. The first goal was to investigate the varieties of intervention characteristics of behavior change interventions in terms of type of online care, type of therapeutic guidance, the extent of online and therapeutic integration, and the theoretical basis of the intervention [16]. The second aim was to study the effectiveness of blended interventions for behavior change. The following questions were studied:

- Which types of blended behavior change interventions for patients with chronic somatic disorders are available in literature?
- What is the effectiveness in comparison with no intervention, face-to-face behavior change interventions, and online behavior change interventions without therapeutic guidance?

Methods

Search Strategy

A comprehensive literature search was conducted using PubMed, Embase, CINAHL, and Cochrane Central Register of Controlled Trials from January 2000 to April 2017. Studies published before 2000 were excluded because of the rapid developments

within the field of eHealth. A combination of the following constructs was used: chronic somatic disorder, eHealth, behavior change intervention, and intervention study. Multimedia Appendix 1 shows the full range of keywords used for each construct. Keywords were adapted to control vocabularies for different databases. Additionally, reference lists of included studies and other systematic reviews [13-18] were hand-searched for potentially relevant studies.

Study Selection and Eligibility Criteria

First step of the study selection consisted of the screening of titles and abstracts of all retrieved studies on eligibility. This was performed by 2 researchers (CK and DB). Subsequently, full texts of all initially relevant studies were independently checked for inclusion by the same researchers. Disagreements about study inclusion were discussed until consensus was reached. Inclusion criteria are provided in Box 1. Studies on decision support systems or interventions using solely reminder messages as online component were excluded. Interventions in which the online component primarily consisted of health tracking technology or self-monitoring (eg, accelerometer or glucose meter) were also excluded, unless the tracking technology was integrated in a behavior change intervention with information /or assignments.

Box 1. Inclusion criteria for this study

Inclusion criteria

- randomized controlled trial published in the English language
- the patient sample comprised adults (≥18 years) with chronic somatic disorders
- the study included an intervention aimed to change one or more of the following behaviors: physical activity, dietary intake, pain coping, and time spent in sedentary activity
- the intervention consisted of a combination of online care provided through a website, app, or automatic email and contains at least two episodes of contact with a health care professional (either face-to-face, personal emails, telephone, or videoconference)
- the blended intervention was compared with waiting list or usual care, a face-to-face intervention, or an online intervention

Data Extraction

Data were extracted from studies that met the inclusion criteria. These data comprised study characteristics (type of study, year of publication, type of control group, outcome measures, and timing of outcome assessment), study population (number of participants, age, sex, and type of chronic disorder), intervention

characteristics (target behavior, described theoretical basis, duration of intervention, delivery mode and frequency of Internet-based element, delivery mode and frequency of therapeutic guidance, integration of online care, and therapeutic guidance), and type of control intervention. A modified version of the delivery coding schemes of Webb et al [16,17] was used for coding the Internet-based element: (1) assignments, (2) information, (3) enriched information environment (eg, supplementary content and links, videos, and games), (4) automated tailored feedback based on individual progress monitoring (eg, comparison with norms or goals, reinforcing messages, or coping messages), (5) automated follow-up messages (reminders, tips, and encouragement). Coded delivery modes for the therapeutic guidance were as follows: (1) option to request for advice (ask the expert, expert-led discussion board or chat sessions), (2) face-to-face contact, (3) email contact (scheduled), (4) phone calls,(5) short messaging service, (6) videoconferencing, and (7) discussion forum with peers. For the integration of therapeutic guidance and online care, we distinguished: (a) an integrated blended delivery mode for studies which mentioned that the therapeutic guidance was related to the content of the online care, for example, by discussing assignments or program progress, and (b) a nonintegrated blended delivery mode that was defined when the online care and the therapeutic guidance were described as two separate aspects or nothing was mentioned in the description of the therapeutic guidance about discussing or using a website or an app. Interventions in which the therapist only provided technical support and did not have access to online assignments and progress were also seen as nonintegrated.

Studies were sorted based on their type of control intervention: (1) no intervention, (2) face-to-face behavior change intervention, and (3) online behavior change intervention without therapeutic guidance.

All outcome measures were distracted and grouped into the following five constructs: (1) symptoms and signs, (2) limitations, (3) dealing with the chronic condition (cognitive and behavioral), (4) emotional outcomes, and (5) quality of life. Means and standard deviations for all outcome measurements (pre- and postvalues) were extracted. A *P* value of <.05 was considered a significant indication for effectiveness.

Quality Assessment

All articles were independently assessed on methodological quality by 2 researchers (CK and DB). For this assessment, the risk of bias criteria list of the Cochrane collaboration was used [18]. A total of 10 dimensions were assessed, namely, random

sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective reporting of results (reporting bias), group similarity at baseline (selection bias), cointerventions (performance bias), compliance (performance bias), intention-to-treat analysis, and timing of outcome assessments (detection bias). The criteria of blinding of participants and personnel (performance bias) were not used, as blinding is not possible in the types of intervention investigated in this review. Each study was rated as low risk, high risk, or unclear when there were no data to assess this criterion. Dimensions scored as low risk received 1 point. Dimensions scored as high risk or unclear received 0 points. Points were counted and summarized as a risk of bias score (range 0-10, where 10 indicates low risk of bias for all 10 dimensions). Studies with a score of ≥6 were judged as high methodological quality. Interobserver agreement was expressed as the percentage of agreement on bias dimensions between CK and DB.

Data Analysis

A best-evidence synthesis was conducted to summarize the effectiveness of blended behavior change interventions, using the same method used by Proper et al [19]. For this synthesis, the number of studies, methodological quality, and consistency of findings were all taken into account. A distinction was made for each of the 3 types of control conditions. Outcome measurements that were measured 3 times or more were sorted on level of evidence: strong evidence, moderate evidence, and inconsistent evidence (Table 1). When there were at least three high methodological quality studies, studies with low quality were disregarded from the evidence synthesis. When at least 75% of the studies showed results in the same direction, results were considered consistent. In case of 3-arm studies, all eligible between-group comparisons were included and treated as different studies.

Table 1. Best-evidence synthesis

Level of evidence	Description
Strong evidence	Consistent findings in multiple (≥3) high-quality RCTs[a]
Moderate evidence	Consistent findings in at least one high-quality study and at least one low-quality study, or consistent findings in multiple low-quality studies
Inconsistent evidence	Inconsistent findings in multiple studies
Insufficient evidence	Only one or two studies available

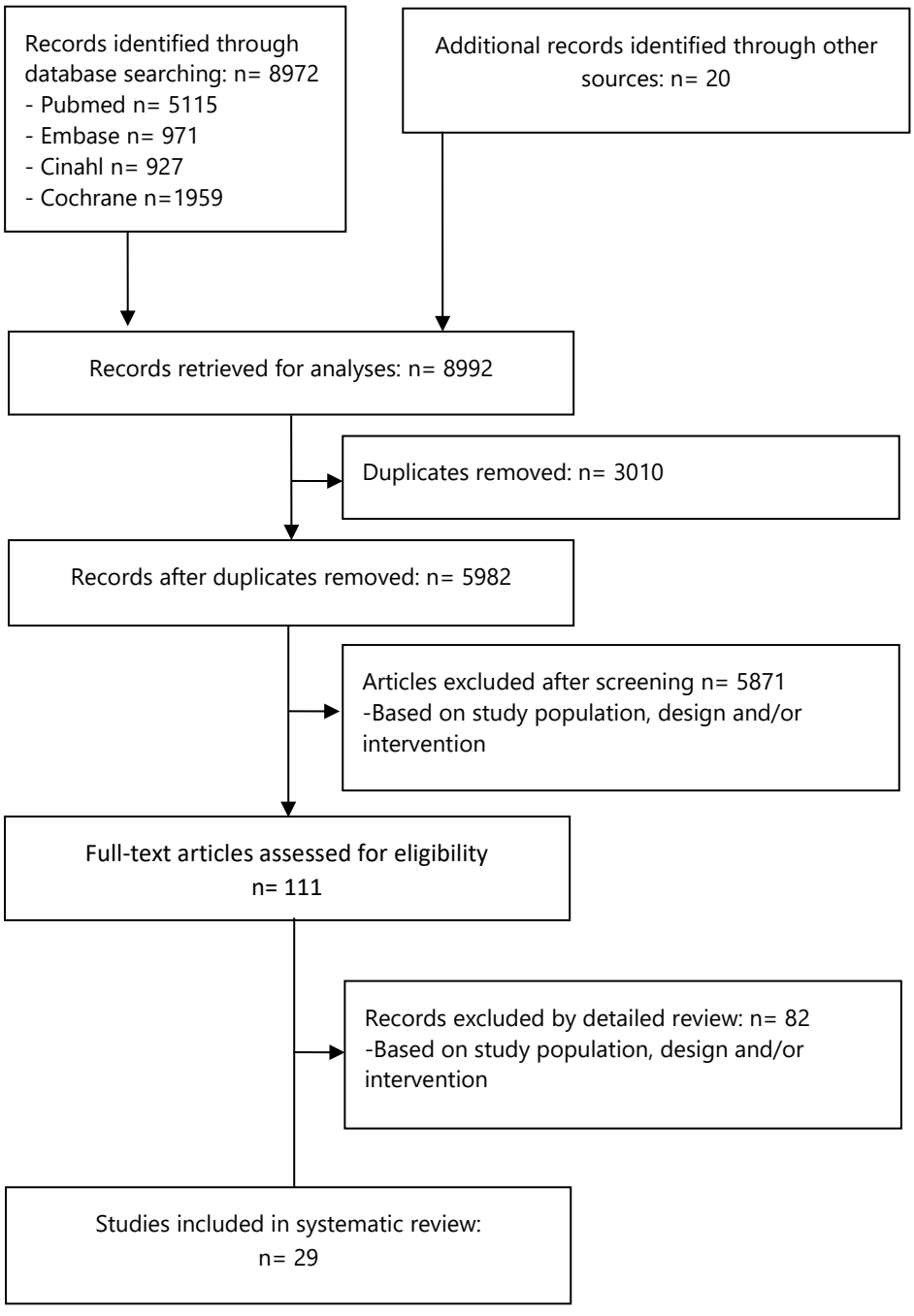
[a]RCTs: randomized controlled trials.

Results

Search Results and Study Characteristics

The initial literature search resulted in 8992 articles. After deleting duplicates, 6192 unique articles were screened on title and abstract. A total of 111 selected articles were studied on full text, whereof 29 articles met the inclusion criteria. An overview of the selection procedure is shown in Figure 1.

Figure 1. Flow-chart of selection procedure



Characteristics of Selected Studies

An overview of study characteristics is shown in Multimedia Appendix 2. Sample size ranged from 45 to 463 participants. A total of 17 interventions were targeted on changing pain thinking and pain behavior related to chronic pain [20,27], irritable bowel syndrome [28,29], chronic tinnitus [30], diabetes mellitus [31], multiple sclerosis [32], rheumatoid arthritis [33], fibromyalgia [34], psoriasis [35], and cancer [36]. Furthermore, 12 studies were targeted on changing lifestyle behavior (ie, physical activity, nutrition, and sedentary behavior) for patients with obesity [37,39], diabetes mellitus [40,44], chronic obstructive pulmonary disease [44], multiple sclerosis [45,46], and rheumatoid arthritis [47]. Moreover, 1 study was targeted on asthma self-management skills [48]. Out of all 29 included randomized controlled trials, 21 studies had 2 study arms, 5 studies had 3 study arms, and 3 studies used a 4-arm design. Divided per control group, 21 studies compared the blended intervention with no intervention, 5 studies made a comparison with a face-to-face intervention, and 10 studies compared a blended intervention with an online self-guided intervention. The number of outcome measures per study ranged from 1 to 21.

Methodological Quality

Ten different sources of bias were rated to assess the methodological quality of the studies (Multimedia Appendix 3). There was 87% agreement between the reviewers. After discussion, consensus was reached and no third reviewer had to be consulted.

In total, 25 studies were rated as high quality [20,22-27,29-45,47,49] and 4 studies as low quality [21,28,46,48]. The most frequent sources of bias were not reporting blinding of the outcome assessor (90% of studies) and information about patients' use of cointerventions (93% of studies).

Characteristics of Blended Behavior Change Interventions

An overview of intervention characteristics is shown in Multimedia Appendix 2. The length of the interventions ranged from 5 weeks to 12 months. Most interventions focused on one target behavior [20-36,38,39,41,42,44-48], and 3 interventions were focused on multiple behaviors (ie, nutrition and physical activity) [37,40,43]. A total of 23 studies mentioned a theory as basis for the intervention, most frequently the principles of cognitive behavior therapy [20,24,25,27,28,30,32-36,39], social cognitive theory [37,41,46], and acceptance and commitment therapy [22,26,29]. In contrast, 6 studies did not mention any theory [38,43-45,47,48]. In 11 studies, the therapeutic guidance was delivered through face-to-face contact[27,36-40,47,48], mostly in

combination with email or phone communication [33,35,36,38-40,44,47,48]. In 18 studies, the therapeutic guidance was non face-to-face [20-26,28-32,34,41-44,48]. In 12 studies, patients had the option to request for advice at a random moment [29-31,33,36,38,39,41-44,48]. Frequency of therapeutic guidance varied from weekly contact to bimonthly. A total of 22 studies delivered online care through a website, and the other 3 studies via an app [37,43,44]. Furthermore, 21 interventions were enriched with videos, links, games, automated tailored feedback r automated reminder messages, and in 8 studies, the online care consisted solely of assignments and information [21,28-30,35,38,41,47]. In 7 studies, nothing was mentioned about the use of the website or app during the therapeutic guidance, and therefore, they were classified as nonintegrated [27,30,35-37,43,47]. In all other interventions, the online care and the therapeutic guidance were described to be integrated. For example, in the study of De Boer et al [20], the psychologist emailed personal feedback on homework assignments. In the study of Buhrman et al [24], the therapist tailored the online care by selecting treatment modules that were in line with the individual needs of the patient.

Effectiveness of Blended Care Versus no Intervention

Multimedia Appendix 4 demonstrates 21 studies that compared a blended behavior intervention with no intervention. A complete overview with levels of evidence is given in Table 2. Within the construct of symptoms and signs, strong evidence for a nonsignificant effect was seen for pain reduction [21-26,33,34,36], fatigue reduction [33-36], and body weight reduction [38,39]. Within the construct of limitations, inconsistent evidence was found for disability improvement [24-26,29]. With regard to the construct dealing with the chronic condition: cognitive measures, strong evidence for a significant effect was found for reducing catastrophizing thoughts [21-24,26,28,34]. Inconsistent evidence was found for improving acceptance of the chronic condition [25,30], reducing fear of movement [25,34], improving pain self-efficacy [25,34], and the coping strategy praying or hoping [21-24]. Strong evidence for a nonsignificant effect was found for the coping strategies diverting attention, reinterpret pain sensations, coping self-statements and ignorance of pain sensations, perceived life control, perception of support received from others, perception of received punishing responses, perception of received solicitous responses, and perception of received distracting responses [21-24]. Within the construct dealing with the chronic condition: behavioral measures, strong evidence for a nonsignificant effect was found for pain interference with daily activities [21-24,26,34] and strong evidence for a nonsignificant effect was found for the coping strategy increasing

activity level [21-24]. Within the construct emotional outcomes, inconsistent evidence was found for reducing anxiety [21-26,28,30,32-35], depression [21-26,30,32-36], and affective distress [21-24]. Inconsistent evidence was also found for the improvement of generic quality of life [22-24] and emotional and physical health-related quality of life [33-35,44].

Effectiveness of Blended Care Versus Face-to-Face

Multimedia Appendix 5 demonstrates 5 studies that compared a blended behavior intervention with a face-to-face behavior change intervention. A complete overview with levels of evidence is given in Table 2. Within the construct limitations, inconsistent evidence was found for increasing levels of physical activity [37,44]. All other outcome measures were measured less than 3 times, indicating insufficient evidence.

Effectiveness of Blended Care Versus Online Care

Multimedia Appendix 6 shows 10 studies that compared a blended behavior intervention with an online behavior change intervention. A complete overview with levels of evidence is given in Table 2. Within the construct symptoms and signs, inconsistent evidence was found for reduction of pain [25,26] and body mass index [37,40]. Strong evidence for a nonsignificant effect was found for body weight reduction [37,39,40]. Within the construct limitations, strong evidence for a nonsignificant effect was found for improving physical activity levels [37,40-42,47]. Within the construct emotional outcomes, strong evidence for a nonsignificant effect was found for reducing anxiety [25,26] and depression [25,26,31,42].

Table 2. Effectiveness of blended behavior change interventions compared to 1) no intervention, 2) face-to-face behavior change intervention, 3) online behavior change intervention

	Outcome construct
Control condition "no intervention"	
Construct 'symptoms and signs'	
Pain [21-26, 33, 34, 36]	Strong evidence for a non-significant effect
Fatigue [33-36]	Strong evidence for a non-significant effect
Body weight [38, 39]	Strong evidence for a non-significant effect
Construct 'limitations'	
Disability [24-26, 29]	Inconsistent evidence
Construct 'dealing with the chronic condition: cognitive measures'	
Coping strategy: Catastrophizing [21-24, 26, 28, 34]	Strong evidence for a significant effect

Acceptance [25, 30]	Inconsistent evidence
Coping strategy: Praying or hoping [21-24]	Inconsistent evidence
Fear of movement [25, 34]	Inconsistent evidence
Pain self-efficacy [25, 34]	Inconsistent evidence
Coping strategy: Diverting attention [21-24]	Strong evidence for a non-significant effect
Coping strategy: Reinterpret pain sensation [21-24]	Strong evidence for a non-significant effect
Coping strategy: Coping self-statements [21-24]	Strong evidence for a non-significant effect
Coping strategy: Ignore pain sensations [21-24]	Strong evidence for a non-significant effect
Perceived life control [21-24]	Strong evidence for a non-significant effect
Perception of support received from others [21-24]	Strong evidence for a non-significant effect
Perception of received punishing responses [21-24]	Strong evidence for a non-significant effect
Perception of received solicitous responses [21-24]	Strong evidence for a non-significant effect
Perception of received distracting responses [21-24]	Strong evidence for a non-significant effect
Construct 'dealing with the chronic condition: behavior measures'	
Coping strategy: Increase activity level [21-24]	Strong evidence for a non-significant effect
Pain interference with daily activities [21-24, 26, 34]	Strong evidence for a non-significant effect
Construct 'emotional outcomes'	
Anxiety [21-26, 28, 30, 32-35]	Inconsistent evidence
Depression [21-26, 30, 32-36]	Inconsistent evidence
Affective distress [21-24]	Inconsistent evidence
Construct 'quality of life'	
Generic quality of life [22-24]	Inconsistent evidence
Health related quality of life: emotional role impairment [33-35, 44]	Inconsistent evidence
Health related quality of life: emotional role impairment [33-35, 44]	Inconsistent evidence
Control condition "face-to-face behavior change intervention"	
Construct 'limitations'	
Physical activity [37, 44]	Inconsistent evidence
Control condition "online behavior change intervention"	
Construct 'symptoms and signs'	
Pain [25, 26]	Inconsistent evidence
Body mass index [37, 40]	Inconsistent evidence
Body weight [37, 39, 40]	Strong evidence for a non-significant effect
Construct 'limitations'	
Physical activity [37, 40-42, 47]	Inconsistent evidence
Construct 'emotional outcomes'	
Anxiety [25, 26]	Strong evidence for a non-significant effect
Depression [25, 26, 31, 42]	Inconsistent evidence

Discussion

Principal Findings

This review provides an overview of the intervention characteristics of a new and promising field within health care for patients with chronic somatic disorders. The characteristics of the included blended behavior change interventions showed a wide heterogeneity. For example, length of interventions ranged from 5 weeks to 12 months. A previous systematic review that studied factors related to online adherence showed that shorter interventions are related to higher usage rates [50]. On the other hand, it is also known that long-term maintenance of behavior change is challenging [51] and that an extension of the intervention with follow-up booster sessions improves the overall effectiveness of face-to-face interventions [52]. The majority of interventions focused on one type of behavior. As many people have multiple unhealthy behaviors linked to risk factors for different chronic diseases, studies should focus on changing multiple behaviors [4]. Such holistic programs have a great potential for targeting complete health profiles and stimulating patients to take an active role in their health management.

The theoretical basis of the intervention content was most frequently based on the principles of cognitive behavior therapy. The aim of the cognitive behavior therapy is to change individuals' unhelpful thoughts, beliefs, and behaviors [53]. In less than half of the studies, the therapeutic guidance was delivered face-to-face, whereas in the other studies, it was delivered completely at distance. Future research is needed to investigate whether face-to-face contact, guidance at distance, or a combination of multiple delivery modes are more or less effective for the overall effectiveness of a blended intervention. The review of Webb et al [16] showed that an "ask the expert" facility is related to higher effectiveness. This additional option was used in 12 out of 29 studies. Furthermore, it is known that the use of an enriched information environment is related to higher effectiveness [16]. Such supplementary content, such as videos and links to informative websites, was used in most interventions. In summary, we can conclude that a wide diversity was seen in the characteristics or ingredients of blended interventions. Given the considerable heterogeneity in the interventions, it was difficult to isolate subtypes of blended interventions for patients with chronic somatic disorders. Future research should focus on which type of blended intervention works for whom, for example, by using subgroup analyses and comparing different types of blended care.

Almost all included studies described that the therapeutic guidance and the online care were integrated with each other. Examples of integration of therapeutic

guidance and online care were the provision of therapeutic feedback on online assignments or tailoring of the online intervention by the therapist. This high number of integrated blended interventions surprised us, as in literature, the interconnection of the therapeutic and the Web-based part is described as one of the biggest challenges of blended care [8,54]. When Web-based apps are integrated within health care, online care is often used as an additional component to usual care, instead of being a substantial element of the intervention as a whole [8]. Although the interventions were described as interconnected, analyses of user experiences are needed to draw conclusions about actual experienced integration.

A wide range of outcome measures were included in our evidence synthesis comparing blended interventions with no interventions or online blended interventions without therapeutic guidance. For some outcome measures, we found inconsistent evidence, and for other outcome measures, we found strong evidence for a nonsignificant effect. The lack of evidence for blended interventions, even when comparing with no intervention, is surprising. Although blended care is described as best of both worlds [8], results of this systematic review do not support this expectation. Before broad-scale implementation of blended behavior change interventions in daily practice, further investigation of how blended interventions should be composed is needed.

A minority of studies compared blended interventions with face-to-face interventions. The evidence synthesis of this comparison showed inconsistent evidence for improvement in physical activity. Particularly, for the comparison of blended behavior change interventions with face-to-face interventions, it would be interesting to investigate cost-effectiveness, long-term effectiveness, and patient satisfaction. The potential added value of blended care above face-to-face care may be found in these outcome measures instead of outcome measures related to symptoms and signs, limitations, behavior, emotions, and quality of life. To illustrate, if face-to-face sessions are substituted by online care, blended interventions may be cheaper than usual care [55]. Another advantage of blended interventions over face-to-face care is the possibility to overcome geographical barriers, as therapeutic guidance in these interventions can be served by a computer or mobile phone.

Limitations

A methodological limitation of our evidence synthesis is the use of multiple outcome measures and multiple comparisons. This multiplicity may result in an increased risk of false-positive statistically significant indications of the effectiveness of blended behavior change interventions [56]. Moreover, 4 studies were conducted by the same

research group [21-24]. These 4 studies investigated interventions targeted on the same behavior and generally used the same measurement instruments. The predominance of these 4 studies within the evidence synthesis may also lead to false-positive statistically significant indications of the effectiveness of blended behavior change interventions.

Implications for Future Research

This review investigated a huge heterogeneity in how blended interventions were composed. For future research, we suggest investigating the effectiveness of different intervention components such as intervention duration, type of face-to-face guidance, and type of online care. Studies included in this review provided the same intervention, with the same amount of ingredients to the entire group of included patients. However, with respect to individual differences, it is presumed that different patients benefit from different blended interventions. For example, considering the ratio between online care and therapeutic guidance, one patient may benefit from more online support, whereas others need more therapeutic guidance. To determine the most optimal ratio in the treatment of patients with depression, the Fit for blended care instrument was recently developed [8]. Future studies could investigate whether such an instrument is useful in the treatment of patients with chronic somatic disorders.

Next, there is a substantial need for studies that compare blended interventions with face-to-face interventions. Only 5 studies compared a blended intervention with face-to-face care [20,30,37,40,44], which hampered drawing conclusions for this comparison. For future trials, we recommend to compare blended behavior change interventions with a control group that receives face-to-face treatment and also to include cost-effectiveness outcomes, patient satisfaction, self-management skills, attrition, or reach of the intervention. This will provide more clinically relevant information about the additional value of integrating therapeutic guidance and online care.

Conclusions

To our knowledge, this is the first comprehensive overview of characteristics of blended behavior change interventions in patients with chronic somatic disorders. The wide variety of intervention characteristics, in terms of type and dose of therapeutic guidance, the type and dose of online care, and how these two delivery modes are integrated, hampered the investigation of intervention subtypes within the entire spectrum of blended behavior change interventions. Overall, within this

heterogenic sample of studies, we found no evidence for the effectiveness of blended behavior change interventions in patients with chronic somatic disorders compared with no intervention, face-to-face behavior change interventions, or with online interventions without face-to-face support. With respect to the potential of blended behavior change interventions, we suggest investigating which type of blended intervention works for whom to come to personalized blended care for patients with chronic somatic disorders.

Conflicts of Interest
None declared.

Abbreviations
COPD: chronic obstructive pulmonary disease

References

1. Eurostat data http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_silc_04&lang=en [Checked on 27-07-2015].
2. Ginneken MRVSMDMGMSREv: CARE4EU: Improving care for people with multiple chronic conditions in Europe. E. *Eurohealth 2013* 2013, 19(3):29-31.
3. World Health Organization. Global status report on noncommunicable diseases 2010 http://www.who.int/nmh/publications/ncd_report_full_en.pdf [Checked on 28-07-2015].
4. Prochaska JJ, Prochaska JO: A Review of Multiple Health Behavior Change Interventions for Primary Prevention. *American journal of lifestyle medicine* 2011, 5(3).
5. Niedermann K, Buchi S, Ciurea A, Kubli R, Steurer-Stey C, Villiger PM, De Bie RA: Six and 12 months' effects of individual joint protection education in people with rheumatoid arthritis: a randomized controlled trial. *Scandinavian journal of occupational therapy* 2012, 19(4):360-369.
6. Mitchell KE, Johnson-Warrington V, Apps LD, Bankart J, Sewell L, Williams JE, Rees K, Jolly K, Steiner M, Morgan M *et al*: A self-management programme for COPD: a randomised controlled trial. *The European respiratory journal* 2014, 44(6):1538-1547.
7. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE: Persuasive system design does matter: a systematic review of adherence to web-based interventions. *Journal of medical Internet research* 2012, 14(6):e152.
8. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JE: Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. *JMIR Ment Health* 2016, 3(1):e9.
9. van der Vaart R, Witting M, Riper H, Kooistra L, Bohlmeijer ET, van Gemert-Pijnen LJ: Blending online therapy into regular face-to-face therapy for depression: content, ratio and preconditions according to patients and therapists using a Delphi study. *BMC Psychiatry* 2014, 14:355.
10. Gee PM, Greenwood DA, Paterniti DA, Ward D, Miller LM: The eHealth Enhanced Chronic Care Model: a theory derivation approach. *Journal of medical Internet research* 2015, 17(4):e86.
11. Siminerio LM: The role of technology and the chronic care model. *J Diabetes Sci Technol* 2010, 4(2):470-475.
12. Barak A, Klein B, Proudfoot JG: Defining internet-supported therapeutic interventions. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2009, 38(1):4-17.
13. Anderson NB, Bulatao RA, Cohen B: Critical Perspectives on Racial and Ethnic Differences in Health in Late Life. In., edn. Washington (DC); 2004.
14. Krijgsman J PJ, Burghouts A, Brabers A, Jong J, Beenkens F. Nictiz. ; [2015-08-18]. : Op naar meerwaarde! eHealth-monitor 2014. http://www.nictiz.nl/module/360/1110/Rapport In. Den Haag en Utrecht: Nictiz en het NIVEL.
15. Hoeymans N, Van Oostrom, S.H., Gijsen, R. Schellevis, F.C. : Selectie van chronische ziekten. In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, <http://www.nationaalkompas.nl> Nationaal

Kompas Volksgezondheid\Gezondheidstoestand\Ziekten en aandoeningen\Chronische ziekten en multimorbiditeit, 14 november 2013.
16. Webb TL, Joseph J, Yardley L, Michie S: Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *Journal of medical Internet research* 2010, 12(1):e4.
17. Webb TL, Sniehotta FF, Michie S: Using theories of behaviour change to inform interventions for addictive behaviours. *Addiction* 2010, 105(11):1879-1892.
18. Collaboration C: Cochrane handbook for systematic reviews of interventions version 5.1. 2011 [2017-03-31]. http://handbookcochraneorg/.
19. Proper KI, Singh AS, van Mechelen W, Chinapaw MJ: Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. *American journal of preventive medicine* 2011, 40(2):174-182.
20. Boer MJ, Versteegen GJ, Vermeulen KM, Sanderman R, Struys M: A randomized controlled trial of an Internet-based cognitive-behavioural intervention for non-specific chronic pain: An effectiveness and cost-effectiveness study. In: *European Journal of Pain (United Kingdom)*. vol. 18; 2014: 1440-1451.
21. Buhrman M, Fältenhag S, Ström L, Andersson G: Controlled trial of Internet-based treatment with telephone support for chronic back pain. In: *Pain*. vol. 111; 2004: 368-377.
22. Buhrman M, Fredriksson A, Edström G, Shafiei D, Tärnqvist C, Ljótsson B, Hursti T, Gordh T, Andersson G: Guided Internet-delivered cognitive behavioural therapy for chronic pain patients who have residual symptoms after rehabilitation treatment: randomized controlled trial. In: *European journal of pain (London, England)*. vol. 17; 2013: 753-765.
23. Buhrman M, Nilsson-Ihrfeldt E, Jannert M, Ström L, Andersson G: Guided internet-based cognitive behavioural treatment for chronic back pain reduces pain catastrophizing: a randomized controlled trial. In: *Journal of rehabilitation medicine*. vol. 43; 2011: 500-505.
24. Buhrman M, Syk M, Burvall O, Hartig T, Gordh T, Andersson G: Individualized Guided Internet-delivered Cognitive-Behavior Therapy for Chronic Pain Patients With Comorbid Depression and Anxiety: A Randomized Controlled Trial. *Clinical Journal of Pain* 2015, 31(6):504-516 513p.
25. Dear BF, Gandy M, Karin E, Staples LG, Johnston L, Fogliati VJ, Wootton BM, Terides MD, Kayrouz R, Perry KN *et al*: The Pain Course: a randomised controlled trial examining an internet-delivered pain management program when provided with different levels of clinician support. *Pain* 2015, 156(10):1920-1935.
26. Trompetter HR, Bohlmeijer ET, Veehof MM, Schreurs KM: Internet-based guided self-help intervention for chronic pain based on Acceptance and Commitment Therapy: a randomized controlled trial. In: *Journal of behavioral medicine*. vol. 38; 2015: 66-80.
27. Nordin CA, Michaelson P, Gard G, Eriksson MK: Effects of the Web Behavior Change Program for Activity and Multimodal Pain Rehabilitation: Randomized Controlled Trial. *Journal of medical Internet research* 2016, 18(10):e265.
28. Hunt MG, Moshier S, Milonova M: Brief cognitive-behavioral internet therapy for irritable bowel syndrome. *Behaviour research and therapy* 2009, 47(9):797-802.
29. Ljotsson B, Hedman E, Andersson E, Hesser H, Lindfors P, Hursti T, Rydh S, Ruck C, Lindefors N, Andersson G: Internet-delivered exposure-based treatment vs. stress

management for irritable bowel syndrome: a randomized trial. *The American journal of gastroenterology* 2011, 106(8):1481-1491.
30. Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstauber M: Internet-based guided self-help versus group cognitive behavioral therapy for chronic tinnitus: a randomized controlled trial. *Psychother Psychosom* 2014, 83(4):234-246.
31. Nobis S, Lehr D, Ebert DD, Baumeister H, Snoek F, Riper H, Berking M: Efficacy of a web-based intervention with mobile phone support in treating depressive symptoms in adults with type 1 and type 2 diabetes: a randomized controlled trial. In: *Diabetes care*. vol. 38; 2015: 776-783.
32. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L: A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. *Behaviour research and therapy* 2012, 50(6):415-421.
33. Ferwerda M, van Beugen S, van Middendorp H, Spillekom-van Koulil S, Donders AR, Visser H, Taal E, Creemers MC, van Riel PC, Evers AW: A tailored-guided internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care: results of a randomized controlled trial. *Pain* 2017.
34. Friesen LN, Hadjistavropoulos HD, Schneider LH, Alberts NM, Titov N, Dear BF: Examination of an Internet-Delivered Cognitive Behavioural Pain Management Course for Adults with Fibromyalgia: A Randomized Controlled Trial. *Pain* 2016.
35. van Beugen S, Ferwerda M, Spillekom-van Koulil S, Smit JV, Zeeuwen-Franssen ME, Kroft EB, de Jong EM, Otero ME, Donders AR, van de Kerkhof PC *et al*: Tailored Therapist-Guided Internet-Based Cognitive Behavioral Treatment for Psoriasis: A Randomized Controlled Trial. *Psychother Psychosom* 2016, 85(5):297-307.
36. Steel JL, Geller DA, Kim KH, Butterfield LH, Spring M, Grady J, Sun W, Marsh W, Antoni M, Dew MA *et al*: Web-based collaborative care intervention to manage cancer-related symptoms in the palliative care setting. *Cancer* 2016, 122(8):1270-1282.
37. Allen JK, Stephens J, Dennison Himmelfarb CR, Stewart KJ, Hauck S: Randomized controlled pilot study testing use of smartphone technology for obesity treatment. *Journal of obesity* 2013, 2013:151597.
38. Bennett GG, Herring SJ, Puleo E, Stein EK, Emmons KM, Gillman MW: Web-based weight loss in primary care: a randomized controlled trial. *Obesity (Silver Spring, Md)* 2010, 18(2):308-313.
39. Yardley L, Ware LJ, Smith ER, Williams S, Bradbury KJ, Arden-Close EJ, Mullee MA, Moore MV, Peacock JL, Lean MEJ *et al*: Randomised controlled feasibility trial of a web-based weight management intervention with nurse support for obese patients in primary care. In: *International journal of behavioral nutrition and physical activity*. vol. 11; 2014.
40. Glasgow RE, Kurz D, King D, Dickman JM, Faber AJ, Halterman E, Wooley T, Toobert DJ, Strycker LA, Estabrooks PA *et al*: Outcomes of minimal and moderate support versions of an internet-based diabetes self-management support program. *J Gen Intern Med* 2010, 25(12):1315-1322.
41. Liebreich T, Plotnikoff RC, Courneya KS, Boule N: Diabetes NetPLAY: A physical activity website and linked email counselling randomized intervention for individuals with type 2 diabetes. *The international journal of behavioral nutrition and physical activity* 2009, 6:18.

42. McKay HG, King D, Eakin EG, Seeley JR, Glasgow RE: The diabetes network internet-based physical activity intervention: a randomized pilot study. *Diabetes care* 2001, 24(8):1328-1334.
43. Torbjornsen A, Jenum AK, Smastuen MC, Arsand E, Holmen H, Wahl AK, Ribu L: A Low-Intensity Mobile Health Intervention With and Without Health Counseling for Persons With Type 2 Diabetes, Part 1: Baseline and Short-Term Results From a Randomized Controlled Trial in the Norwegian Part of RENEWING HEALTH. *JMIR Mhealth Uhealth* 2014, 2(4):e52.
44. van der Weegen S, Verwey R, Spreeuwenberg M, Tange H, van der Weijden T, de Witte L: It's LiFe! Mobile and Web-Based Monitoring and Feedback Tool Embedded in Primary Care Increases Physical Activity: A Cluster Randomized Controlled Trial. *Journal of medical Internet research* 2015, 17(7):e184.
45. Dlugonski D, Motl RW, Mohr DC, Sandroff BM: Internet-delivered behavioral intervention to increase physical activity in persons with multiple sclerosis: sustainability and secondary outcomes. *Psychology, health & medicine* 2012, 17(6):636-651.
46. Klaren RE, Hubbard EA, Motl RW: Efficacy of a behavioral intervention for reducing sedentary behavior in persons with multiple sclerosis: a pilot examination. *American journal of preventive medicine* 2014, 47(5):613-616.
47. Berg MH, Ronday HK, Peeters AJ, Cessie S, Giesen FJ, Breedveld FC, Vliet Vlieland TP: Using internet technology to deliver a home-based physical activity intervention for patients with rheumatoid arthritis: A randomized controlled trial. In: *Arthritis and rheumatism*. vol. 55; 2006: 935-945.
48. Meer V, Bakker MJ, Hout WB, Rabe KF, Sterk PJ, Kievit J, Assendelft WJ, Sont JK: Internet-based self-management plus education compared with usual care in asthma: a randomized trial. In: *Annals of internal medicine*. vol. 151; 2009: 110-120.
49. Dear BF, Titov N, Perry KN, Johnston L, Wootton BM, Terides MD, Rapee RM, Hudson JL: The Pain Course: a randomised controlled trial of a clinician-guided Internet-delivered cognitive behaviour therapy program for managing chronic pain and emotional well-being. *Pain* 2013, 154(6):942-950.
50. Cugelman B, Thelwall M, Dawes P: Online interventions for social marketing health behavior change campaigns: a meta-analysis of psychological architectures and adherence factors. *Journal of medical Internet research* 2011, 13(1):e17.
51. Kwasnicka D, Dombrowski SU, White M, Sniehotta F: Theoretical explanations for maintenance of behaviour change: a systematic review of behaviour theories. *Health Psychol Rev* 2016, 10(3):277-296.
52. Pisters MF, Veenhof C, van Meeteren NL, Ostelo RW, de Bakker DH, Schellevis FG, Dekker J: Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. *Arthritis Rheum* 2007, 57(7):1245-1253.
53. AT BJaB: Cognitive behavior therapy: Basics and beyond. New York: Guilford Publication; 2011.
54. De Vries H, Kloek, C., Bossen, D., Veenhof, C.: Physiotherapeutic use of a blended e-health-intervention; why is e-health (not) being used? (article in Dutch). *FysioPraxis* 2016.
55. Elbert NJ, van Os-Medendorp H, van Renselaar W, Ekeland AG, Hakkaart-van Roijen L, Raat H, Nijsten TE, Pasmans SG: Effectiveness and cost-effectiveness of ehealth

interventions in somatic diseases: a systematic review of systematic reviews and meta-analyses. *Journal of medical Internet research* 2014, 16(4):e110.
56. Jakobsen JC, Wetterslev J, Lange T, Gluud C: Viewpoint: taking into account risks of random errors when analysing multiple outcomes in systematic reviews. *Cochrane Database Syst Rev* 2016, 3:ED000111.

Appendix 1. Keywords per construct (PubMed version)

	Aspect Chronic disorder
1	"chronic disease"[MeSH Terms] OR "chronic disease"[tiab] OR "chronic diseases"[tiab] OR "chronic illness"[tiab] OR "chronic illnesses"[tiab] OR "chronic condition"[tiab] OR "chronic conditions"[tiab] OR "chronically ill"[tiab] OR disability[tiab] OR "pulmonary disease, chronic obstructive"[MeSh Terms] OR asthma[tiab] OR copd[tiab] OR "chronic obstructive pulmonary disease"[tiab] OR neoplasms[MeSh Terms] OR leukemia[MeSh Terms] OR neoplasms[tiab] OR neoplasm[tiab] OR cancer [tiab] OR leukemia[tiab] OR "coronary artery disease"[MeSh Terms] OR "coronary artery disease"[tiab] OR stroke[MeSH Terms] OR stroke[tiab] OR "heart failure"[MeSh Terms] OR "heart failure"[tiab] OR "cardiovascular disease"[tiab] OR hypertension[MeSh Terms] OR hypertension[tiab] OR "blood pressure"[MeSH Terms] OR "blood pressure"[tiab] OR "cardiovascular diseases"[MeSH Terms] OR "cardiovascular diseases" [tiab] OR "cardiovascular disease"[tiab] OR "cardiovascular risk"[tiab] OR "cardiovascular risks"[tiab] OR "peripheral vascular diseases"[MeSh Terms] OR "vascular disease"[tiab] OR "vascular diseases"[tiab] OR "liver diseases"[MeSh Terms] OR "liver diseases"[tiab] OR "liver disease"[tiab] OR "liver failure"[tiab] OR "liver dysfunction"[tiab] OR "diabetes mellitus" [MeSh Terms] OR "diabetes mellitus"[tiab] OR diabetes[tiab] OR obesity[MeSh Terms] OR obesity[tiab] OR "headache disorders"[MeSH Terms] OR "migraine disorders"[MeSh Terms] OR migraine [tiab] OR headache [tiab] OR "back pain"[MeSH Terms] OR "back pain"[tiab] OR backache[tiab] OR "arthritis, rheumatoid" [MeSh Terms] OR "musculoskeletal diseases"[MeSH Terms] OR musculoskeletal [tiab] OR arthritis [tiab] OR osteoarthritis [tiab] OR fibromyalgia [tiab] OR osteoporosis [tiab] OR rheumatism [tiab] OR arthrosis [tiab] OR "multiple sclerosis"[MeSh Terms] OR "multiple sclerosis" [tiab] OR epilepsy[MeSH Terms] OR epilepsy [tiab] OR "HIV infections" [MeSH Terms] OR aids [tiab] OR "HIV infections" [tiab] OR "immunodeficiency syndrome"[tiab] OR hiv[tiab] OR "vision disorders"[MeSH Terms] OR "vision disorders"[tiab] OR "vision disorder"[tiab] OR "hearing disorders"[MeSH Terms] OR "hearing disorders"[tiab] OR "hearing disorder"[tiab] OR "neck pain"[MeSh Terms] OR "neck pain"[tiab] OR neckache[tiab] OR "parkinson disease"[MeSH Terms] OR parkinson[tiab] OR "chronic pain"[MeSh Terms] OR somatic[tiab] OR "chronic pain"[tiab] OR "Fatigue syndrome, chronic"[MeSh Terms] OR "chronic fatigue" [tiab]
	Aspect e-Health
2	telemedicine [MeSH Terms] OR telemedicine [tiab] OR internet [MeSH Terms] OR internet [tiab] OR website [tiab] OR "world wide web"[tiab] OR web-based [tiab] OR internet-based [tiab] OR e-health [tiab] OR ehealth[tiab] OR blended [tiab] OR "smart phone" [tiab] OR "mobile health" [tiab] OR Mhealth [tiab] OR M-health [tiab] OR tele-health [tiab] OR telehealth[tiab] OR technology[tiab]
	Aspect behavior change intervention
3	Behavior[MeSH Terms] OR behavior[tiab] OR behaviour[tiab] OR behavioral[tiab] OR self-management[tiab] OR "selfmanagement"[tiab] OR lifestyle[tiab] OR behavioural[tiab] OR "behavior change"[tiab] OR "behaviour change"[tiab] OR "motor activity"[MeSH Terms] OR "physical activity"[tiab] OR "Nutrition therapy"[MeSH Terms] OR nutrition [tiab] OR dietary[tiab]
	Aspect intervention study
4	"intervention studies"[MeSH Terms] OR "intervention studies"[tiab] OR "intervention study"[tiab] OR intervention[tiab] OR experimental[tiab] OR effect[tiab] OR effectiveness[tiab] OR evaluation[tiab] OR RCT[tiab] OR CCT[tiab] OR trial[tiab] OR random*[tiab]
	Combined aspects
	#1 AND #2 AND #3 AND #4 NOT child*[tiab]

Appendix 2. Risk of bias assessment

Author, year of publication	Random sequence generation	Allocation concealment	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Group similarity at baseline	Co-intervention	Compliance	Intention-to-treat analysis	Timing outcome assessments	Score (0-10)*	Total: Low or high quality
Allen, 2013	L	U	U	L	L	L	U	L	H	L	6	High
Bennett, 2010	L	U	U	L	L	L	U	L	L	L	7	High
De Boer, 2014	L	L	U	L	L	U	U	L	L	L	7	High
Buhrman 2004	L	U	U	L	L	L	U	U	H	L	5	Low
Buhrman 2011	L	U	U	L	L	L	U	U	L	L	6	High
Buhrman 2013	L	L	U	L	L	L	U	U	L	L	7	High
Buhrman, 2015	L	L	U	L	L	L	U	U	L	L	7	High
Dear, 2015	L	L	U	L	L	L	U	U	U	L	6	High
Dlugonski, 2012	L	H	U	L	L	L	U	L	L	L	7	High
Ferwerda, 2017	L	L	U	H	L	L	U	H	L	L	6	High
Friessen, 2017	L	L	H	L	L	L	U	L	L	L	8	High
Glasgow, 2010	L	U	U	L	L	L	U	L	L	L	7	High
Hunt, 2009	L	H	U	H	L	L	U	U	H	L	4	Low
Jasper, 2014	L	L	U	L	L	L	U	L	L	L	8	High
Klaren, 2014	L	L	U	U	H	H	U	U	L	L	4	Low
Liebreich, 2009	L	U	U	L	L	H	U	L	L	L	6	High
Ljotsson, 2011	L	L	U	L	L	L	U	L	L	L	8	High
McKay, 2001	L	L	U	L	L	L	U	L	L	L	8	High
Moss Morris 2012	L	U	U	L	L	H	L	L	L	L	7	High
Nobis, 2015	L	U	U	L	L	L	U	L	L	L	7	High
Nordin, 2016	L	L	U	L	H	L	U	L	L	L	7	High
Steel, 2016	L	L	L	L	L	L	U	L	L	L	9	High
Torbjørnsen 2014	L	L	U	L	H	L	U	U	L	L	6	High
Trompetter 2015	L	U	U	L	L	L	U	L	L	L	7	High
V. Beugen 2016	L	L	U	H	L	L	U	L	L	L	7	High
Vd Berg 2006	L	L	L	L	L	L	L	L	L	L	10	High
Vd Meer 2009	L	H	U	H	L	L	U	U	H	L	4	Low
Vd Weegen '15	L	L	L	L	L	H	U	U	L	L	7	High
Yardley '14	L	H	H	L	H	L	H	L	L	L	6	High

L=Low Risk; H=High; U=Unclear
Total score: low risk=1 point; unclear or high risk=0 points; Low quality= 0-5 points, High quality= 6 points or more

Appendix 3. Characteristics of studies, participants, and interventions.							
Author, year of publication	**Study population (n, mean age in years, F: females [%])**	**Chronic disorder**	**Target behavior, duration of intervention**	**Theoretical basis**	**Description of blended intervention (therapeutic delivery mode and frequency; Internet-based delivery mode and frequency)**	**Therapeutic guidance (T[a]), online care (O[b]), and blended integration (B[c])**	**Type of control intervention (C)[d]**
Allen et al, 2013 [37]	n=68, mean age=45, F=78%	Obesity	Weight loss (nutrition and physical activity), 6 months	Social cognitive theory	T1: 9 face-to-face sessions with counselor; T2: 7 face-to-face sessions with counselor; O: app with weekly assignments and (feedback) messages	T: b O: a, d, e B: b	C1: c C2: b
Bennett et al, 2010 [38]	n=101, mean age=54, F=48%	Obesity and hypertension	Obesogenic behavior (individual selected), 3 months	No	T: 2 face-to-face sessions and 2 phone calls with dietitian, ask-the-expert option, and forum with peers; O: website with weekly assignments and information	T: a, b, d, g O: a, b B: a	C: a
De Boer et al, 2014 [20]	n=72, mean age=52, F=64%	Chronic pain	Pain thinking, feeling, and behaving; 4 months	Cognitive behavioral therapy	T: weekly email contact with a cognitive behavior therapist; O: website with weekly assignments, enriched information, and messages	T: c O: a, b, c, e B: a	C: b
Buhrman et al, 2004 [21]	n=56, mean age=45, F=63%	Chronic back pain	Pain thinking, feeling, and behaving, 6 weeks	Fear avoidance model	T: weekly phone calls with a therapist; O: website with weekly assignments and information	T: d O: a, b B: a	C: a
Buhrman, 2011 [23]	n=54, mean age=43, F=69%	Chronic back pain	Pain thinking, feeling, and behaving, 11 weeks	Fear avoidance model	T: weekly email contact with psychologist; O: website with weekly assignments and messages	T: c O: a, e B: a	C: a
Buhrman et al, 2013 [22]	n=76, mean age=49, F=59%	Chronic pain	Pain thinking, feeling, and behaving, 7 weeks	Acceptance and commitment therapy	T: weekly email contact and 2 phone calls with clinical psychology graduate student; O: website with weekly assignments, enriched information, and messages	T: c, d O: a, b, c, e B: a	C: a
Buhrman et	n=52, mean	Chronic pain	Pain thinking,	Cognitive	T: weekly email contact and 2 phone calls with	T: c, d	C: a

al, 2015 [24]	age=51, F=85%		feeling, and behaving, 8 weeks	behavioral therapy	clinical psychology graduate student; O: website with weekly assignments, information, and messages	O: a, b, e B: a	
Dear et al, 2015 [25]	n=490, mean age=50, F=80%	Chronic pain	Pain thinking, feeling, and behaving, 8 weeks	Cognitive behavioral therapy	T1: weekly telephone or email contact with psychologist; T2: optional telephone and email contact with psychologist; O: website with 7 assignments, information, and automatic (feedback) messages	T: c, d O: a, b, d, e B: a	C1: a C2: c
Dlugonski, 2012 [45]	n=45, mean age=47, F=87%	Multiple sclerosis	Physical activity, 12 weeks	No	T: 7 videoconferencing sessions with health behavior coach; O: website with weekly assignments, information, and messages	T: f O: a, b, e B: a	C: a
Ferwerda et al, 2017 [33]	n=133, mean age=56, F=64%	Rheumatoid arthritis with heightened distress	Coping with symptoms, 9-65 weeks	Cognitive behavioral therapy	T: 1 face-to-face session with therapist, followed by weekly or biweekly email contact; O: website with assignments and psychoeducational texts	T: a, b, c O: a, b, c B: a	C: a
Friessen et al, 2017 [34]	n=60, mean age=48, F=95%	Fibromyalgia	Coping with pain, 8 weeks	Cognitive behavioral therapy	T: weekly telephone contact with trained student and email contact; O: website with weekly assignments, enriched information, and automated messages	T: c, d O: a, b, c, e B: a	C: a
Glasgow et al, 2010 [40]	n=463, mean age=58, F=50%	Diabetes Mellitus type II	Nutrition, physical activity, and medication taking, 4 months	Social ecological theory, 5 A's self-management model	T: 2 phone calls with therapist, 3 group sessions, and forum with peers; O: website with weekly assignments, enriched information, and automatic telephonic (feedback) messages	T: b, d, g O: a, b, c, e B: a	C: c
Hunt et al, 2009 [28]	n=54, mean age=39, F=80%	Irritable bowel syndrome	Stress management and catastrophic thinking, 5 weeks	Cognitive behavioral therapy	T: weekly email contact with therapist; O: website with weekly assignments and information	T: c O: a, b B: a	C: a

Jasper et al, 2014 [30]	n=128, mean age=51, F=40%	Chronic tinnitus	Relaxation, positive thinking, and cognitive restructuring, 10 weeks	Cognitive behavioral therapy	T: weekly chat session and email contact with cognitive behavior therapist; O: website with weekly assignments and information	T: a, c O: a, b B: b	C1: b C2: a
Klaren et al, 2014 [46]	n=70, mean age=50, F=78%	Multiple sclerosis	Sedentary behavior, 6 months	Social cognitive theory	T: 13 videoconferences with coach; O: website with 13 assignments and enriched information	T: f O: a, b, c B: a	C: a
Liebreich, Plotnikoff et al, 2009 [41]	n=49, mean age=54, F=59%	Diabetes Mellitus type II	Physical activity, 12 weeks	Social cognitive theory	T: weekly email contact with counselor and ask-the-expert option, and forum with peers; O: website with weekly assignments and information	T: a, c, g O: a, b B: a	C: c
Ljotsson, Hedman et al, 2011 [29]	n=61, mean age=35, F=74%	Irritable bowel syndrome	Avoidance behavior, 10 weeks	Acceptance and commitment therapy	Cognitive behavioral intervention; T: weekly email contact with psychologist, ask-the-expert option, and forum with peers; O: website with weekly assignments and information	T: a, c, g O: a, b B: a	C: a
McKay et al, 2001 [42]	n=78, mean age=52, F=53%	Diabetes Mellitus type II	Physical activity, 8 weeks	Multilevel social ecological model of diabetes self-management	Behavioral intervention to increase physical activity; T: weekly email contact with occupational therapist, ask-the-expert option, and forum with peers; O: website with weekly assignments	T: a, c, g O: a, b, c, d B: a	C: c
Moss Morris et al, 2012 [32]	n=40, mean age=41, F=80%	Multiple sclerosis	Fatigue behavior, 10 weeks	Cognitive behavioral therapy	T: 3 phone sessions of 30-60 min with assistant psychologist; O: website with weekly assignments and information	T: d O: a, b, c, e B: a	C: a
Nobis et al, 2015 [31]	n=256, mean age=51, F=63%	Diabetes Mellitus type I and II	Depressive symptoms, 8 weeks	Systematic behavioral activation and problem solving	T: weekly email or phone contact with psychologist or graduate student; O: website with weekly assignments, information, and automatic text messages	T: a, c, d, e O: a, b, e B: a	C: c

Nordin, et al, 2016 [27]	n=99, mean age=43, F=85%	Persistent musculoskeletal pain	Pain behavior, 4 months	Cognitive behavioral therapy	T: treatments from at least three different occupations according to an individualized treatment plan; O: website with assignments, enriched information, and automated messages	T: b O: a, b, c, e B: b	C: b
Steel et al, 2016 [36]	n=261, mean age=61, F=27%	Advanced cancer	Pain, fatigue, and depression, 6 months	Cognitive behavioral therapy	T: email contact every 2 weeks, face-to-face contact with care coordinator every 2 months, and forum with peers; O: website with assignments and enriched information	T: a, b, c, g O: a, b, c B: b	C: a
Torbjørnsen et al, 2014 [43]	n=151, mean age=57, F=41%	Diabetes Mellitus type II	Nutrition and physical activity, 4 months	No	T: 5 phone sessions with a diabetes specialist nurse and ask-the-expert option; O: app with daily assignment, enriched information, and (feedback) messages	T: a, d O: a, b, c, d, e B: b	C1: c C2: a
Trompetter et al, 2015 [26]	n=238, mean age=53, F=76%	Chronic pain	Pain behavior, 3 months	Acceptance and commitment therapy	T: weekly email contact with counselor; O: website with weekly assignments and enriched information	T: c O: a, b, c B: a	C1: c C2: a
van Beugen et al, 2016 [35]	n=131, mean age=53, F=49%	Psoriasis	Pain, fatigue, and negative mood, 25 weeks	Cognitive behavioral therapy	T: 2 face-to-face sessions with therapist, telephonic instruction, and weekly feedback emails; O: website with information and assignments	T: b, c, d O: a, b B: b	C: a
van der Berg et al, 2006[47]	n=160, mean age=50, F=76%	Rheumatoid arthritis	Physical activity, 12 months	No	T: weekly email contact with physical therapist, 4 group meetings, and forum with peers; O: website with weekly assignments	T: b, c, g O: a B: b	C: c
Van der Meer et al, 2009 [48]	n=200, mean age=31, F=69%	Asthma	Asthma control: measuring FEV1 and inhaler technique, 12 months	No	T: 1 group session and optional phone calls and email contact with a respiratory nurse; O: website with weekly assignments, enriched information, and automatic (feedback) messages	T: a, b, c, d, e O: a, b, d, e B: a	C: a
Van der Weegen et al,	n=199, mean age=58, F=51%	COPD or Diabetes	Physical activity, 4-6 months	No	T: 4 face-to-face sessions with nurse and mail contact, and option to request for advice; O:	T: a, b, c O: a, d, e	C1: a C2: b

2015 [44]		Mellitus type II			activity tracker, mobile app and website with assignments, and automated tailored feedback messages	B: a	
Yardley et al, 2014 [39]	n=179, mean age=51, F=66%	Obesity	Weight management and nutrition, 6 months	Cognitive behavioral therapy	T1: 3 face-to-face, phone, or email contacts with a nurse and ask-the-expert option; T2: 7 face-to-face, phone, or email contacts with a nurse and ask-the-expert option; O: website with weekly assignments, enriched information, and (feedback) messages	T: a, b, c, d O: a, b, c, d, e B: a	C1: a C2: c

[a]T: therapeutic guidance: (1) option to request for advice, (2) face-to-face contact, (3) email, (4) phone calls, (5) short messaging service, (6) videoconferencing, and (7) discussion forum with peers.

[b]O: online care: (1) assignments, (2) information, (3) enriched information environment, (4) automated tailored feedback, and (5) automated messages.

[c]B: blended integration: (1) online care and therapeutic guidance are integrated and (2) online care and professionals are two separate elements.

[d]C: control conditions: (1) no intervention, (2) face-to-face behavior change interventions, and (3) online behavior change intervention.

Appendix 4. Outcome measures of studies with "no intervention" as control condition

Author, year of publication	Outcome measure	Instrument	Time of measurement (pre- and post-treatment)	Pre-treatment mean (SD)	Post-treatment mean (SD)	Significant effect
Symptoms and Signs						
Bennett, 2010	Body weight	Weighing scale	0, 12 weeks	I:101.0 (15.4) C: 97.3 (10.9)	I: 98.7 (3.2) C: 97.6 (0.6)	No
	BMI	Scale and meter	0, 12 weeks	I: 35.0 (3.5) C: 34.6 (3.2)	I: 34.1 (1.2) C: 34.5 (0.8)	No
Buhrman, 2004	Pain	Scale 0-100, average score of 3 daily assessments	0, 8 weeks	I: 37.4 (18.2) C: 44.4 (14.2)	I: 34.3 (16.8) C: 39.6 (16.3)	No
	Pain	Multidimensional Pain Inventory: subscale pain severity	0, 8 weeks	I: 3.8 (1.9) C: 5.0 (1.7)	I: 2.4 (1.1) C: 3.2 (0.8)	No
Buhrman, 2011	Pain	Multidimensional Pain Inventory: subscale pain severity	0, 12 weeks	I: 3.5 (2.5) C: 3.2 (2.2)	I: 3.2 (2.2) C: 3.4 (2.6)	No
Buhrman, 2013	Pain	Multidimensional Pain Inventory: subscale pain severity	0, 8 weeks	I: 4.51 (0.80) C: 4.35 (0.88)	I: 4.30 (1.04) C: 4.29 (1.00)	No
Buhrman, 2015	Pain	Multidimensional Pain Inventory: subscale pain severity	0, 8 weeks	I: 3.81 (1.14) C: 3.90 (0.89)	I: 3.75 (1.05) C: 3.95 (0.93)	No
Dear, 2015 *regular contact group	Pain	Wilcinson Brief Pain Questionnaire	0, 8 weeks	I: 5.74 (1.72) C: 5.98 (1.53)	I: 4.86 (1.79) C: 5.71 (1.50)	Yes
Dear, 2015 *optional contact group	Pain	Wilcinson Brief Pain Questionnaire	0, 8 weeks	I: 5.54 (1.74) C: 5.98 (1.53)	I: 4.85 (1.73) C: 5.71 (1.50)	Yes
Ferwerda, 2017	Pain	Impact of Rheumatic Diseases on General Health and Lifestyle	0, post-intervention	I: 14.78 (4.76) C: 15.77 (3.88)	I: 14.60 (4.50) C: 15.68 (3.73)	No

	Fatigue	Checklist Individual Strength	0, post-intervention	I: 35.98 (11.49) C: 38.24 (10.06)	I: 32.13 (11.46) C: 35.88 (10.71)	No
	Disease activity	Rheumatoid Arthritis Disease Activity Index	0, post-intervention	I: 3.31 (1.99) C: 3.84 (1.75)	I: 3.19 (2.10) C: 3.62 (1.68)	No
Friessen, 2017	Severity and symptoms of fibromyalgia	Revised Fibromyalgia Impact Questionnaire	0, 8 weeks	I: 65.19 (13.07) C: 67.75 (13.51)	I: 53.39 (18.94) C: 64.59 (12.75)	Yes
	Pain	Brief Pain Inventory – subscale pain severity	0, 8 weeks	I: 5.45 (1.10) C: 6.02 (1.39)	I: 4.99 (1.66) C: 6.28 (1.28)	Yes
	Fatigue	Fatigue Symptom Inventory	0, 8 weeks	I: 44.30 (12.83) C: 49.20 (14.29)	I: 39.69 (15.10) C:47.87 (12.75)	No
Hunt, 2009	Abdominal symptoms: pain, bloating, constipation, diarrhea and satiety	Gastrointestinal Symptom Rating Scale	0, 5 weeks	I: 57 (13) C: 61 (14)	I: 35 (12) C: 52 (14)	Yes
Ljotsson, 2011	Abdominal symptoms: pain, bloating, constipation, diarrhea and satiety	Gastrointestinal Symptom Rating Scale	0, 10 weeks	I: 44.6 (11.1) C: 39.8 (12.0)	I: 31.0 (10.2) C: 40.9 (14.5)	Yes
Van der Meer, 2009	Forced expiratory volume in 1 second (FEV1)	Handheld electronic spirometer	0, 12 months	I: 3.08 (NM) C: 3.13 (NM)	I: 3.32 (NM) C: 3.12 (NM)	Yes
Steel, 2016	Fatigue	Functional Assessment of Cancer Therapy-Fatigue	0, 6 months	I: 36.8 (7.9) C: 35.4 (7.1)	I: 28.3 (9.4) C: 31.1 (11.4)	No
	Pain and impact on functioning	Brief Pain Inventory	0, 6 months	I: 5.8 (1.2) C: 6.1 (1.6)	I: 4.7 (1.5) C: 6.1 (2.6)	No
Torbjørnsen, 2014	Hemoglobin	DCA Vantage Analyzer	0, 4 months	I: 8.2 (1.08) C: 8.3 (1.08)	I: 7.8 (1.44) C: 8.0 (1.44)	No
Trompetter, 2015	Pain	Pain NRS	0, 3 months	I: 6.3 (1.6) C: 6.2 (1.6)	I: 5.4 (2.2) C: 5.6 (2.1)	No

Van Beugen, 2016	Fatigue	Checklist Individual Strength	0, post-treatment	I: 37.70 (10.68) C: 34.31 (10.30)	I: 30.77 (12.46) C: 33.8 (9.19)	Yes
	Itch	Impact of chronic Skin Disease on daily Life – itch subscale	0, post-treatment	I: 9.44 (3.50) C: 9.06 (3.75)	I: 7.09 (3.51) C: 7.44 (3.67)	No
	Psoriasis severity – clinician rated	Psoriasis Area and Severity Index	0, post-treatment	I: 5.99 (5.61) C: 4.20 (2.87)	I: 5.04 (4.59) C: 3.79 (2.94)	No
	Psoriasis severity – self-reported	Psoriasis Area and Severity Index	0, post-treatment	I: 5.27 (3.29) C: 4.48 (2.41)	I: 4.61 (5.39) C: 3.95 (2.26)	No
Yardley, 2014 *basic nurse support	Body weight	Weighing scale	0, 6 months	I: 103.43 (25.23) C: 103.27 (20.09)	I: 97.92 (5.80) C: 99.38 (5.75)	No
Yardley, 2014 *regular nurse support	Body weight	Weighing scale	0, 6 months	I: 100.36 (19.38) C: 103.27 (20.09)	I: 97.14 (5.74) C: 99.38 (5.75)	No

Limitations in daily activities						
Buhrman, 2015	Disruption of daily activities by chronic pain	Pain Disability Index	0, 8 weeks	I: 36.71 (9.96) C: 36.96 (10.25)	I: 32.13 (9.64) C: 36.65 (9.91)	Yes
Dear, 2015 *regular contact group	Backpain associated disability in daily activities	Roland-Morris Disability Questionnaire	0, 8 weeks	I: 13.47 (5.23) C: 13.93 (5.22)	I: 11.05 (5.63) C: 13.97 (5.17)	Yes
Dear, 2015 *optional contact group	Backpain associated disability in daily activities	Roland-Morris Disability Questionnaire	0, 8 weeks	I: 13.24 (5.60) C: 13.93 (5.22)	I: 10.95 (5.84) C: 13.97 (5.17)	Yes
Dlugonski, 2012	Walking mobility	Multiple Sclerosis Walking Scale-12	0, 3 months	I: 27.4 (22.0) C: 24.9 (25.0)	I: 30.9 (22.1) C: 27.0 (25.6)	No
	Physical activity	Godin Leisure-Time Exercise Questionnaire	0, 3 months	I: 13.6 (11.6) C: 16.1 (14.2)	I: 28.2 (15.6) C: 15.4 (13.9)	Yes
Ferwerda, 2017	Self-care	Impact of Rheumatic Diseases on General Health and Lifestyle	0, post-intervention	I: 27.39 (5.72) C: 25.04 (6.52)	I: 27.35 (5.94) C: 24.41 (6.92)	No
	Mobility	Impact of Rheumatic Diseases on General Health and Lifestyle	0, post-intervention	I: 22.00 (5.78) C: 19.82 (6.40)	I: 22.30 (5.55) C: 19.37 (6.55)	No
Jasper, 2014	Insomnia	Insomnia Severity index	0, 10 weeks	I: 12.68 (5.91) C: 11.25 (6.51)	I: 8.70 (5.80) C: 10.91 (7.21)	Yes
Klaren, 2014	Sedentary behavior	International Physical Activity Questionnaire	0, 6 months	I: 550 (233) C: 412 (193)	I: 429.2 (201.2) C: 528.2 (200.7)	Yes
Ljotsson, 2011	Functional impairment in work/school, social life and family	Sheehan Disability Scales	0, 10 weeks	I: 11.9 (8.1) C: 6.4 (6.7)	I: 8.7 (6.3) C: 7.8 (7.6)	Yes
Trompetter, 2015	Disruption of daily activities by chronic pain	Pain Disability Index	0, 3 months	I: 36.0 (12.7) C: 36.1 (12.7)	I: 30.6 (14.5) C: 33.0 (14.0)	No
Van der Weegen, 2015	Physical activity	Pam accelerometer	0, post-intervention	I: 39.29 (18.1) C: 44.13 (20.3)	I: 48.16 (23.8) C: 39.16 (19.5	Yes

Dealing with the chronic condition: cognitive measures						
Buhrman, 2004	Coping strategy: diverting attention	Coping Strategy Questionnaire: subscale diverting attention	0, 8 weeks	I: 11.6 (5.7) C: 12.3 (7.4)	I: 12.3 (5.2) C: 11.9 (6.9)	No
	Coping strategy: reinterpret pain sensation	Coping Strategy Questionnaire: subscale reinterpret pain sensation	0, 8 weeks	I: 3.6 (3.5) C: 5.4 (6.5)	I: 4.4 (3.6) C: 4.6 (5.9	No
	Coping strategy: coping self-statements	Coping Strategy Questionnaire: subscale coping self-statements	0, 8 weeks	I: 18.4 (6.5) C: 18.3 (6.6)	I: 19.1 (5.8) C: 17.3 (6.7)	No
	Coping strategy: ignore pain sensations	Coping Strategy Questionnaire: subscale ignore pain sensations	0, 8 weeks	I: 13.1 (13.7) C: 13.5 (6.6)	I: 13.7 (7.0) C: 12.9 (6.5)	No
	Coping strategy: praying or hoping	Coping Strategy Questionnaire: subscale praying or hoping	0, 8 weeks	I: 12.0 (6.9) C: 10.4 (6.7)	I: 9.8 (5.1) C: 8.5 (6.0)	No
	Coping strategy: catastrophizing	Coping Strategy Questionnaire: subscale catastrophizing	0, 8 weeks	I: 13.6 (7.7) C: 13.7 (6.9)	I: 8.6 (5.2) C: 12.3 (7.2)	Yes
	Coping strategy: control over pain	Coping Strategy Questionnaire: subscale control over pain	0, 8 weeks	I: 2.8 (1.0) C: 2.9 (1.1)	I: 3.9 (0.7) C: 2.9 (1.0)	Yes
	Coping strategy: ability to decrease pain	Coping Strategy Questionnaire: subscale ability to decrease pain	0, 8 weeks	I: 3.0 (0.8) C: 2.6 (1.0)	I: 3.9 (0.9) C: 2.9 (1.0)	Yes
	Perceived life control	Multidimensional Pain Inventory: subscale life control	0, 8 weeks	I: 3.1 (1.1) C:2.7 (0.9)	I: 3.9 (1.0) C: 3.1 (0.9)	No
	Perception of support received from others	Multidimensional Pain Inventory: subscale	0, 8 weeks	I: 4.0 (1.6) C: 3.9 (1.5)	I: 4.2 (1.3) C: 3.8 (1.6)	No
	Perception of received punishing responses	Multidimensional Pain Inventory: subscale punishing responses	0, 8 weeks	I: 1.0 (1.4) C:1.5 (1.4)	I: 0.7 (1.1) C: 1.2 (1.3)	No
	Perception of received solicitous responses	Multidimensional Pain Inventory: subscale solicitous responses	0, 8 weeks	I: 2.3 (1.4) C: 2.1 (1.4)	I: 2.3 (1.2) C: 1.9 (1.5)	No
	Perception of received distracting responses	Multidimensional Pain Inventory: subscale distracting responses	0, 8 weeks	I: 2.5 (1.7) C: 2.7 (1.7)	I: 2.5 (1.6) C: 2.5 (1.7)	No
Buhrman, 2011	Beliefs and attitudes associated with chronic pain	Pain and Impairment Relationship Scale	0, 12 weeks	I: 53.3 (10.4) C: 48.3 (13.7)	I: 49.1 (11.0) C: 46.1 (18.7)	No
	Coping strategy: diverting attention	Coping Strategy Questionnaire: subscale diverting attention	0, 12 weeks	I: 11.2 (5.9) C: 11.4 (5.7)	I: 11.5 (6.5) C: 10.8 (5.5)	No
	Coping strategy:	Coping Strategy Questionnaire:	0, 12 weeks	I: 5.3 (5.2)	I: 6.2 (4.5)	No

	reinterpret pain sensation	subscale reinterpret pain sensation		C: 5.4 (3.9)	C: 6.1 (5.1)	
	Coping strategy: coping self-statements	Coping Strategy Questionnaire: subscale coping self-statements	0, 12 weeks	I: 21.0 (5.9) C: 18.3 (6.7)	I: 19.1 (7.6) C: 19.4 (7.5)	No
	Coping strategy: ignore pain sensations	Coping Strategy Questionnaire: subscale ignore pain sensations	0, 12 weeks	I: 15.4 (6.0) C: 15.3 (7.0)	I: 17.6 (7.7) C: 14.7 (7.4)	No
	Coping strategy: praying or hoping	Coping Strategy Questionnaire: subscale praying or hoping	0, 12 weeks	I: 11.0 (7.4) C: 10.8 (5.9)	I: 10.8 (7.0) C: 9.2 (5.9)	No
	Coping strategy: catastrophizing	Coping Strategy Questionnaire: subscale catastrophizing	0, 12 weeks	I: 14.3 (6.1) C: 12.0 (8.2)	I: 9.5 (5.5) C: 11.6 (8.2)	Yes
	Coping strategy: control over pain	Coping Strategy Questionnaire: subscale control over pain	0, 12 weeks	I: 3.3 (1.3) C: 2.9 (1.4)	I: 3.0 (1.1) C:2.8 (1.5)	No
	Coping strategy: ability to decrease pain	Coping Strategy Questionnaire: subscale ability to decrease pain	0, 12 weeks	I: 3.1 (0.9) C: 3.0 (1.0)	I: 3.3 (0.8) C: 3.0 (1.2)	No
	Perceived life control	Multidimensional Pain Inventory: subscale life control	0, 12 weeks	I: 3.1 (1.1) C: 2.7 (0.9)	I: 3.9 (1.0) C: 3.1 (0.9)	No
	Perception of support received from others	Multidimensional Pain Inventory: subscale	0, 12 weeks	I: 4.0 (1.6) C: 3.9 (1.5)	I: 4.2 (1.3) C: 3.8 (1.6)	No
	Perception of received punishing responses	Multidimensional Pain Inventory: subscale punishing responses	0, 12 weeks	I: 1.0 (1.4) C: 1.5 (1.4)	I: 0.7 (1.1) C:1.2 (1.3)	No
	Perception of received solicitous responses	Multidimensional Pain Inventory: subscale solicitous responses	0, 12 weeks	I: 2.3 (1.4) C: 2.1 (1.4)	I: 2.3 (1.2) C: 1.9 (1.5)	No
	Perception of received distracting responses	Multidimensional Pain Inventory: subscale distracting responses	0, 12 weeks	I: 2.5 (1.7) C: 2.7 (1.7)	I: 2.5 (1.6) C: 2.5 (1.7)	No
Buhrman, 2013	Beliefs and attitudes associated with chronic pain	Pain And Impairment Relationship Scale	0, 8 weeks	I: 60.89 (10.27) C: 59.79 (9.93)	I: 55.88 (12.43) C: 59.24 (10.29)	No
	Coping strategy: diverting attention	Coping Strategy Questionnaire: subscale diverting attention	0, 8 weeks	I: 15.01 (6.15) C: 14.87 (6.10)	I: 14.54 (6.08) C: 14.76 (6.48)	No
	Coping strategy: reinterpret pain sensation	Coping Strategy Questionnaire: subscale reinterpret pain sensation	0, 8 weeks	I: 9.03 (5.65) C:8.29 (5.57)	I: 9.39 (6.97) C: 7.88 (5.25)	No
	Coping strategy: coping self-statements	Coping Strategy Questionnaire: subscale coping self-statements	0, 8 weeks	I: 17.79 (5.58) C: 18.18 (6.43)	I: 18.66 (6.23) C: 19.20 (6.24)	No

	Coping strategy: ignore pain sensations	Coping Strategy Questionnaire: subscale ignore pain sensations	0, 8 weeks	I: 13.66 (5.85) C: 14.26 (5.20)	I: 14.40 (5.59) C: 15.50 (5.33)	No
	Coping strategy: praying or hoping	Coping Strategy Questionnaire: subscale praying or hoping	0, 8 weeks	I: 12.00 (7.42) C: 11.34 (6.73)	I: 11.93 (7.96) C: 13.96 (6.33)	Yes
	Coping strategy: catastrophizing	Coping Strategy Questionnaire: subscale catastrophizing	0, 8 weeks	I: 17.82 (5.78) C: 18.58 (6.42)	I: 16.08 (5.91) C: 19.00 (5.56)	Yes
	Perceived life control	Multidimensional Pain Inventory: subscale life control	0, 8 weeks	I: 2.62 (0.96) C: 2.41 (1.21)	I: 2.96 (1.67) C: 2.54 (1.22)	No
	Perception of support received from others	Multidimensional Pain Inventory: subscale	0, 8 weeks	I: 4.06 (1.55) C: 4.11 (1.38)	I: 3.69 (1.66) C: 4.05 (1.33)	No
	Perception of received punishing responses	Multidimensional Pain Inventory: subscale punishing responses	0, 8 weeks	I: 2.17 (1.38) C: 2.25 (1.52)	I: 1.84 (1.49) C: 2.15 (1.40)	No
	Perception of received solicitous responses	Multidimensional Pain Inventory: subscale solicitous responses	0, 8 weeks	I: 2.72 (1.60) C:2.73 (1.25)	I: 2.44 (1.64) C: 2.72 (1.34)	No
	Perception of received distracting responses	Multidimensional Pain Inventory: subscale distracting responses	0, 8 weeks	I: 2.55 (1.36) C: 2.19 (1.03)	I: 2.60 (1.43) C: 2.18 (1.16)	No
Buhrman, 2015	Fear of symptoms	Anxiety Sensitivity Index	0, 8 weeks	I: 24.57 (2.61) C:18.87 (8.16)	I: 18.90 (12.23) C: 17.37 (7.50)	No
	Pain-related catastrophizing	Pain Catastrophizing Scale	0, 8 weeks	I: 22.71 (8.58) C: 24.58 (9.20)	I: 14.49 (9.49) C:22.94 (11.65)	Yes
	Coping strategy: diverting attention	Coping Strategy Questionnaire: subscale diverting attention	0, 8 weeks	I: 13.69 (5.06) C: 11.87 (5.41)	I:13.07 (6.09) C: 12.41 (4.84)	No
	Coping strategy: reinterpret pain sensation	Coping Strategy Questionnaire: subscale reinterpret pain sensation	0, 8 weeks	I: 6.25 (5.43) C: 6.54 (6.09)	I: 7.10 (6.22) C: 5.75 (5.73)	No
	Coping strategy: coping self-statements	Coping Strategy Questionnaire: subscale coping self-statements	0, 8 weeks	I: 17.25 (5.68) C: 16.70 (5.00)	I: 19.04 (6.63) C: 18.86 (6.08)	No
	Coping strategy: ignore pain sensations	Coping Strategy Questionnaire: subscale ignore pain sensations	0, 8 weeks	I: 13.86 (8.98) C: 14.96 (6.13)	I: 15.36 (7.64) C: 16.73 (5.84)	No
	Coping strategy: praying or hoping	Coping Strategy Questionnaire: subscale praying or hoping	0, 8 weeks	I: 9.68 (6.56) C:10.58 (7.91)	I: 10.77 (7.49) C: 9.62 (8.00)	No
	Coping strategy: catastrophizing	Coping Strategy Questionnaire: subscale catastrophizing	0, 8 weeks	I: 16.36 (7.12) C: 17.83 (6.84)	I: 10.06 (6.35) C: 16.36 (5.64)	Yes
	Perceived life control	Multidimensional Pain Inventory:	0, 8 weeks	I: 2.41 (0.87)	I: 3.48 (1.42)	No

		subscale life control		C: 2.51 (0.79)	C: 2.94 (0.74)	
	Perception of support received from others	Multidimensional Pain Inventory: subscale	0, 8 weeks	I: 3.36 (1.57) C:3.61 (1.36)	I: 3.26 (1.70) C: 3.89 (1.31)	No
	Perception of received punishing responses	Multidimensional Pain Inventory: subscale punishing responses	0, 8 weeks	I: 2.05 (1.51) C: 2.10 (1.73)	I: 2.13 (1.72) C: 2.13 (1.72)	No
	Perception of received solicitous responses	Multidimensional Pain Inventory: subscale solicitous responses	0, 8 weeks	I: 2.57 (1.56) C:2.41 (1.30)	I: 2.17 (1.44) C: 2.50 (1.38)	No
	Perception of received distracting responses	Multidimensional Pain Inventory: subscale distracting responses	0, 8 weeks	I: 3.42 (5.35) C:2.29 (1.16)	I: 2.41 (1.05) C: 2.48 (1.30)	No
Dear, 2015 *regular contact group	Pain self-efficacy	Pain Self-efficacy Questionnaire	0, 8 weeks	I: 28.86 (12.93) C: 28.63 (12.10)	I: 35.94 (12.98) C: 29.68 (12.11)	Yes
	Fear of movement	TAMPA Scale of Kinesiophobia	0, 8 weeks	I: 38.59 (7.99) C: 39.56 (8.67)	I: 34.48 (7.00) C: 37.65 (8.60)	Yes
	Acceptance of pain	Chronic Pain Acceptance Questionnaire	0, 8 weeks	I: 22.58 (7.53) C: 22.67 (7.52)	I: 26.79 (6.69) C: 23.66 (7.66)	Yes
Dear, 2015 *optional contact group	Pain self-efficacy	Pain Self-efficacy Questionnaire	0, 8 weeks	I: 28.61 (14.08) C: 28.63 (12.10)	I: 33.60 (13.83) C: 29.68 (12.11)	Yes
	Fear of movement	TAMPA Scale of Kinesiophobia	0, 8 weeks	I: 37.60 (8.40) C:39.56 (8.67)	I: 34.88 (7.80) C: 37.65 (8.60)	Yes
	Acceptance of pain	Chronic Pain Acceptance Questionnaire	0, 8 weeks	I: 23.30 (7.72) C: 22.67 (7.52)	I: 25.40 (8.01) C: 23.66 (7.66)	No
Friessen, 2017	Fear of movement	TAMPA Scale of Kinesiophobia	0, 8 weeks	I: 38.35 (7.39) C: 40.57 (5.55)	I: 33.87 (6.25) C: 42.73 (4.64)	No
	Pain self-efficacy	Pain Self-Efficacy Questionnaire	0, 8 weeks	I: 22.93 (9.78) C: 19.83 (10.25)	I: 29.99 (11.10) C: 22.00 (10.18)	No
	Pain coping	Pain Responses Self-Statements: subscale coping	0, 8 weeks	I: 29.73 (5.94) C: 23.77 (8.22)	I: 31.99 (5.72) C: 23.75 (7.74)	No
	Pain catastrophizing	Pain Responses Self-Statements: subscale catastrophizing	0, 8 weeks	I: 21.52 (7.37) C: 24.53 (9.77)	I: 17.23 (9.26) C: 24.09 (9.51)	No
Hunt, 2009	Catastrophizing	Consequences of Physical Sensations Questionnaire	0, 5 weeks	I: 2.1 (0.51) C: 2.1 (0.57)	I: 1.25 (0.39) C: 2.1 (0.56)	Yes
Jasper, 2014	Acceptance	Tinitis Acceptance Questionnaire	0, 10 weeks	I: 42.07 (11.70) C: 42.84 (13.48)	I: 47.91 (11.70) C: 43.99 (13.51)	Yes
Ljotsson, 2011	Fear of irritable bowel	Visceral Sensitivity Index	0, 10 weeks	I: 32.5 (18.0)	I: 14.1 (15.1)	Yes

	syndrome symptoms			C: 27.5 (16.3)	C: 26.2 (17.9)	
Moss Morris, 2012	The impact of fatigue on patient's daily life	Modified fatigue impact scale	0, 10 weeks	I: 13.17 (3.81) C: 12.69 (3.89)	I: 9.00 (3.75) C: 12.88 (3.89)	Yes
Trompetter, 2015	Mindfulness skills	Five Facet Mindfulness Questionnaire-Short Form	0, 3 months	I: 81.4 (10.7) C: 80.4 (10.7)	I: 86.7 (12.2) C: 83.3 (11.7)	No
	Avoidance of pain and cognitive fusion with pain	Psychological Inflexibility in Pain Scale	0, 3 months	I: 55.0 (11.6) C: 54.5 (11.6)	I: 40.7 (13.8) C: 48.8 (13.1)	Yes
	Pain catastrophizing	Pain Catastrophizing Scale	0, 3 months	I: 18.6 (9.5) C: 19.1 (9.6)	I: 13.5 (11.3) C: 17.8 (11.0)	Yes
Van der Weegen, 2015	General self-efficacy	General Self-Efficacy Scale	0, post-intervention	I: 3.2 (0.5) C: 3.1 (0.5)	I: 3.3 (0.4) C: 3.2 (0.4)	No
	Exercise self-efficacy	Exercise Self-Efficacy Scale	0, post-intervention	I: 55.4 (17.0) C: 54.0 (19.2)	I: 59.7 (17.3) C: 54.5 (17.4)	No
Dealing with the chronic condition: behavioral measures						
Buhrman, 2004	Coping strategy: Increase activity level	Coping Strategy Questionnaire: subscale increase activity level	0, 8 weeks	I: 14.4 (5.0) C: 17.3 (6.1)	I: 14.8 (5.6) C: 16.9 (6.3)	No
	Pain interference with daily activities	Multidimensional Pain Inventory: subscale pain interference	0, 8 weeks	I: 3.6 (1.2) C: 3.9 (1.3)	I: 3.2 (1.4) C: 3.5 (1.2)	No
Buhrman, 2011	Coping strategy: Increase activity level	Coping Strategy Questionnaire: subscale increase activity level	0, 12 weeks	I: 16.0 (6.0) C: 15.6 (4.5)	I: 14.3 (5.4) C: 15.9 (5.7)	No
	Pain interference with daily activities	Multidimensional Pain Inventory: subscale pain interference	0, 12 weeks	I: 3.6 (1.2) C:3.9 (1.3)	I: 3.2 (1.4) C: 3.5 (1.2)	No
Buhrman, 2013	Coping Strategy: Increase activity level	Coping Strategy Questionnaire: subscale increase activity level	0, 8 weeks	I: 16.32 (6.41) C: 16.05 (5.15)	I: 15.76 (5.56) C: 18.07 (4.60)	No
	Coping Strategy: Pain behavior	Coping Strategy Questionnaire: subscale pain behavior	0, 8 weeks	I: 18.26 (4.85) C: 18.71 (4.67)	I: 18.07 (4.60) C: 18.69 (5.39)	No
	Coping Strategy: the extent to which a person follows their activities regardless of pain	Chronic pain acceptance questionnaire: subscale activities engagement	0, 8 weeks	I: 22.84 (11.02) C: 21.18 (9.70)	I: 28.62 (11.15) C: 22.22 (11.17)	Yes
	Coping Strategy: the extent to which a	Chronic pain acceptance questionnaire: subscale pain	0, 8 weeks	I: 18.13 (8.85) C: 20.61 (8.68)	I: 23.53 (8.32) C: 21.53 (7.94)	Yes

	person believes that avoiding activities prevents pain	willingness				
	Pain interference with daily activities	Multidimensional Pain Inventory: subscale pain interference	0, 8 weeks	I: 4.76 (0.88) C: 4.85 (0.89)	I: 4.37 (1.09) C:4.94 (0.93)	Yes
Buhrman, 2015	Coping Strategy: Increase activity level	Coping Strategy Questionnaire: subscale increase activity level	0, 8 weeks	I: 14.93 (5.13) C: 15.92 (5.23)	I: 16.40 (5.69) C: 15.76 (5.07)	No
	Coping Strategy: Pain behavior	Coping Strategy Questionnaire: subscale pain behavior	0, 8 weeks	I: 17.07 (5.00) C: 17.67 (4.14)	I: 17.64 (5.38) C:18.33 (5.50)	No
	Coping Strategy: the extent to which a person follows their activities regardless of pan	Chronic pain acceptance questionnaire: subscale activities engagement	0, 8 weeks	I: 38.00 (11.45) C: 38.54 (11.68)	I: 45.11 (12.03) C: 40.37 (9.16)	Yes
	Coping Strategy: the extent to which a person believes that avoiding activities prevents pain	Chronic pain acceptance questionnaire: subscale pain willingness	0, 8 weeks	I: 30.46 (8.00) C: 31.58 (7.76)	I: 34.73 (7.15) C: 32.38 (5.72)	No
	Pain interference with daily activities	Multidimensional Pain Inventory: subscale pain interference		I: 3.91 (1.20) C: 4.14 (1.03)	I: 3.31 (1.29) C: 3.80 (1.21)	No
Ferwerda, 2017	Compliance to standard rheumatological care	5-point Likert scales for rheumatologic care	0, post-intervention	I: 4.15 (0.92) C: 4.20 (0.89)	I: 4.43 (0.67) C: 4.28 (0.71	No
Friessen, 2017	Pain interference with daily activities	Brief Pain Inventory: subscale interference	0, 8 weeks	I: 6.56 (1.90) C: 7.48 (1.71)	I: 5.46 (2.11) C: 7.32 (1.58)	No
Van der Meer, 2009	Adequacy of asthma control	Asthma Control Questionnaire	0, 12 months	I: 1.12 (NM) C:1.11 (NM)	I: 0.59 (NM) C: 1.04 (NM)	Yes
Torbjørnsen, 2014	Self-management: skills and technique acquisition	Hei-Q	0, 4 months	I: 2.87 (0.43) C: 2.92 (0.34)	I: 3.04 (0.52) C: 2.92 (0.56)	Yes
	Self-management: Health service navigation	Hei-Q	0, 4 months	I: 3.08 (0.43) C: 3.13 (0.40)	I: 3.27 (0.56) C: 3.20 (0.54)	Yes

Trompetter, 2015	Awareness of personal values and the degree to which this guide person's actions in daily life	Engaged Living Scale	0, 3 months	I: 51.5 (10.4) C: 49.8 (9.1)	I: 55.1 (12.4) C: 52.8 (11.8)	No
	Pain interference with daily activities	Multidimensional Pain Inventory: subscale pain interference	0, 3 months	I: 32.3 (9.8) C: 33.3 (9.8)	I: 28.7 (12.0) C: 32.1 (11.5)	No
Emotional outcomes						
Buhrman, 2004	Anxiety	Hospital Anxiety and Depression Scale	0, 8 weeks	I: 7.4 (4.5) C: 7.0 (3.3)	I: 7.2 (4.0) C: 6.0 (3.3)	No
	Depression	Hospital Anxiety and Depression Scale	0, 8 weeks	I: 6.9 (4.8) C: 6.6 (4.1)	I: 6.0 (4.7) C: 5.4 (4.0)	No
	Affective distress	Multidimensional Pain Inventory: subscale affective distress	0, 8 weeks	I: 2.9 (0.9) C: 3.0 (0.6)	I: 2.8 (0.9) C: 3.1 (0.6)	No
Buhrman, 2011	Anxiety	Hospital Anxiety and Depression Scale	0, 12 weeks	I: 7.6 (3.7) C: 7.6 (5.1)	I: 5.8 (3.5) C: 7.0 (6.0)	No
	Depression	Hospital Anxiety and Depression Scale	0, 12 weeks	I: 6.3 (4.2) C: 6.3 (4.5)	I: 4.9 (3.6) C: 6.3 (5.2)	No
	Affective distress	Multidimensional Pain Inventory: subscale affective distress	0, 12 weeks	I: 2.9 (0.9) C: 3.0 (0.6)	I: 2.8 (0.9) C: 3.1 (0.6)	No
Buhrman, 2013	Anxiety	Hospital Anxiety and Depression Scale	0, 8 weeks	I: 9.89 (4.19) C: 9.13 (4.26)	I: 8.97 (4.33) C: 9.67 (3.50)	Yes
	Depression	Hospital Anxiety and Depression Scale	0, 8 weeks	I: 9.58 (4.57) C: 9.63 (4.04)	I: 8.85 (4.40) C: 10.52 (3.77)	Yes
	Affective distress	Multidimensional Pain Inventory: subscale affective distress	0, 8 weeks	I: 3.32 (0.78) C: 3.14 (0.73)	I: 3.08 (0.74) C: 3.31 (0.64)	Yes
Buhrman, 2015	Anxiety	Beck Anxiety Inventory	0, 8 weeks	I: 20.36 (9.54) C:17.83 (7.56)	I: 11.99 (8.13) C: 14.57 (6.81)	Yes

	Depression	Montgomery Asberg Depression Rating Scale	0, 8 weeks	I: 23.14 (6.94) C: 20.83 (6.19)	I: 15.77 (7.79) C: 17.95 (6.51)	Yes
	Affective distress	Multidimensional Pain Inventory: subscale affective distress	0, 8 weeks	I: 3.25 (0.61) C: 3.26 (0.81)	I: 3.17 (0.56) C:3.31 (0.64)	No
Dear, 2015 *regular contact group	Depression	Patient Health Questionnaire 9-item	0, 8 weeks	I: 11.55 (5.88) C: 10.37 (5.47)	I: 6.30 (4.57) C: 11.11 (5.51)	Yes
	Anxiety	Generalized Anxiety Disorder 7-item	0, 8 weeks	I: 8.40 (5.52) C: 8.21 (5.92)	I: 4.91 (4.40) C: 7.89 (5.29)	Yes
Dear, 2015 *optional contact group	Depression	Patient Health Questionnaire 9-item	0, 8 weeks	I: 10.60 (5.33) C: 10.37 (5.47)	I: 7.20 (5.25) C: 11.11 (5.51)	Yes
	Anxiety	Generalized Anxiety Disorder 7-item	0, 8 weeks	I: 7.98 (4.67) C: 8.21 (5.92)	I: 5.66 (4.94) C: 7.89 (5.29)	Yes
Ferwerda, 2016	Depression	Beck Depression Inventory	0, post-intervention	I: 11.53 (6.99) C: 13.38 (6.46)	I: 8.16 (5.67) C: 12.27 (5.97)	Yes
	Negative mood	Impact of Rheumatic Diseases on General Health and Lifestyle	0, post-intervention	I: 4.07 (2.56) C: 5.42 (4.21)	I: 3.25 (2.39) C: 4.95 (4.17)	Yes
	Anxiety	Impact of Rheumatic Diseases on General Health and Lifestyle	0, post-intervention	I: 20.82 (4.85) C: 21.40 (4.85)	I: 18.12 (4.13) C: 20.61 (4.99)	Yes
Friessen, 2017	Anxiety	Generalized Anxiety Disorder 7-item (GAD7)	0, 8 weeks	I: 10.87 (4.65) C: 9.93 (4.88)	I: 7.83 (5.70) C: 9.98 (5.15)	Yes
	Depression	Patient Health Questionnaire 9-item(PHQ9)	0, 8 weeks	I: 14.07 (4.66) C: 14.07 (4.93)	I: 10.13 (5.30) C: 14.00 (5.44)	Yes
	Anxiety	Hospital Anxiety and Depression Scale	0, 8 weeks	I: 11.60 (4.00) C: 10.17 (3.98)	I: 9.22 (4.33) C: 10.43 (4.69)	Yes
	Depression	Hospital Anxiety and Depression Scale	0, 8 weeks	I: 9.90 (3.37) C: 9.97 (3.82)	I: 7.97 (3.55) C: 10.17 (3.42)	Yes
Hunt, 2009	Anxiety	Anxiety Sensitivity Index	0, 5 weeks	I: 2.9 (0.91) C: 2.7 (0.99)	I: 1.9 (0.93) C: 2.5 (0.95)	Yes

Jasper, 2014	Tinnitus associated distress	Mini-Tinnitus Questionnaire	0, 10 weeks	I: 12.20 (4.58) C: 12.50 (4.83)	I: 7.44 (5.30) C: 11.09 (5.77)	Yes
	Tinnitus associated distress	Tinnitus Handicap Inventory	0, 10 weeks	I: 40.34 (17.64) C: 40.23 (20.54)	I: 26.67 (20.75) C: 37.46 (18.94)	Yes
	Anxiety	Hospital Anxiety and Depression Scale	0, 10 weeks	I: 7.41 (3.56) C: 8.00 (4.24)	I: 5.44 (3.23) C: 7.67 (4.68)	Yes
	Depression	Hospital Anxiety and Depression Scale	0, 10 weeks	I: 5.95 (4.21) C: 6.43 (4.48)	I: 4.41 (3.72) C: 5.88 (4.41)	No
Moss Morris, 2012	Anxiety	Hospital Anxiety and Depression Scale	0, 10 weeks	I: 8.26 (4.31) C: 9.56 (4.50)	I: 6.44 (3.91) C: 11.65 (5.26)	Yes
	Depression	Hospital Anxiety and Depression Scale	0, 10 weeks	I: 7.96 (3.64) C: 6.75 (2.72)	I: 5.18 (3.38) C: 8.73 (3.62)	Yes
Steel, 2016	Depression	Center for Epidemiologic Studies Depression Scale	0, 6 months	I: 25.9 (9.8) C: 25.49 (6.9)	I: 15.3 (10.5) C: 24.7 (15.1)	No
Trompetter, 2015	Anxiety	Hospital Anxiety and Depression Scale	0, 3 months	I: 7.2 (3.3) C: 6.9 (3.3)	I: 6.0 (3.8) C: 6.1 (3.6)	No
	Depression	Hospital Anxiety and Depression Scale	0, 3 months	I: 6.1 (3.4) C: 6.1 (3.4)	I: 5.1 (3.7) C: 5.8 (3.5)	No
	Positive mental health	Mental Health Continuum-Short Form	0, 3 months	I: 52.6 (11.8) C:49.9 (12.8)	I: 54.7 (12.2) C: 52.6 (14.3)	No
Van Beugen, 2016	Negative mood	Impact of chronic Skin Disease on Daily Life	0, post-treatment	I: 5.29 (3.77) C: 5.39 (3.72)	I: 3.69 (3.36) C: 4.60 (3.21)	No
	Anxiety	Impact of chronic Skin Disease on Daily Life	0, post-treatment	I: 21.85 (4.61) C: 22.10 (4.58)	I: 19.36 (4.37) C: 21.02 (5.74)	No
	Depression	Beck Depression Inventory	0, post-treatment	I: 12.78 (7.50) C: 11.50 (6.23)	I: 8.46 (5.34) C: 8.89 (6.82)	No
Quality of life						
Buhrman, 2011	Generic quality of life	Quality Of Life Inventory	0, 12 weeks	I: 1.2 (1.4) C: 1.8 (1.5)	I: 1.7 (1.4) C: 1.1 (1.6)	Yes
Buhrman, 2013	Generic quality of life	Quality Of Life Inventory	0, 8 weeks	I: 0.26 (2.18) C: 0.15 (1.97)	I: 0.56 (2.07) C: 0.39 (1.77)	No
Buhrman, 2015	Generic quality of life	Quality of Life Inventory	0, 8 weeks	I: 0.65 (1.65) C: 0.70 (1.39)	I: 1.38 (1.78) C: 1.39 (1.59)	No

Dlugonski, 2012	Multiple Sclerosis-specific health related quality of life: physical impact	Multiple Sclerosis Impact Scale	0, 12 weeks	I: 44.3 (19.8) C: 38.3 (19.0)	I: 44.8 (21.2) C: 41.1 (20.6)	No
	Multiple Sclerosis-specific health related quality of life: psychological impact	Multiple Sclerosis Impact Scale	0, 12 weeks	I: 20.0 (8.2) C: 18.5 (8.0)	I: 19.5 (7.9) C: 19.6 (9.2)	No
Ferwerda, 2017	Health related quality of life: Role impairment (physical)	RAND-36 subscale Role impairment (physical)	0, post-intervention	I: 39.58 (39.94) C: 26.49 (38.65)	I: 48.91 (45.02) C: 33.19 (39.84)	No
	Health related quality of life: Role impairment (emotional)	RAND-36 subscale Role impairment (emotional)	0, post-intervention	I: 69.44 (39.91) C: 58.82 (46.47)	I: 83.33 (28.76) C: 62.15 (45.26)	Yes
Friessen, 2017	Quality of life, physical component	Medical Outcomes Study Short Form (SF 12)	0, 8 weeks	I: 30.81 (7.82) C: 32.17 (7.35)	I: 34.70 (7.94) C: 32.82 (8.20)	Yes
	Quality of life, mental component	Medical Outcomes Study Short Form (SF 12)	0, 8 weeks	I: 34.42 (8.52) C: 36.12 (7.60)	I: 39.62 (11.22) C: 38.95 9.16)	No
Hunt, 2009	Irritable bowel-specific health related quality of life	Irritable Bowel Syndrome Quality of Life Impairment	0, 5 weeks	I: 122 (27) C: 84 (26)	I: 123 (26) C: 111 (25)	Yes
Ljotsson, 2011	Irritable bowel-specific health related quality of life	Irritable Bowel Syndrom Quality of Life Instrument	0, 10 weeks	I: 67.4 (20.9) C: 76.1 (18.8)	I: 82.6 (13.4) C: 67.4 (23.1)	Yes
Van Beugen, 2016	Health related quality of life: Role impairment (physical)	RAND-36 subscale Role impairment (physical)	0, post-intervention	I: 53.02 (41.90) C: 58.89 (43.09)	I: 72.09 (36.68) C:73.94 (40.03)	Yes
	Health related quality of life: Role impairment (emotional)	RAND-36 subscale Role impairment (emotional)	0, post-intervention	I: 78.16 (35.07) C: 67.54 (39.89)	I: 86.6 (23.09) C: 76.09 (38.27)	No
Van der Meer 2009	Asthma-specific health related quality of life	Asthma Quality of Life Questionnaire	0, 12 months	I: 5.73 (NM) C: 5.79 (NM)	I: 6.29 (NM) C: 5.97 (NM)	Yes

Van der Weegen, 2015	Health related quality of life: Role impairment (physical)	RAND-36 subscale Role impairment (physical)	0, post-intervention	I: 42.5 (11.1) C: 45.8 (9.4)	I: 45.2 (9.5) C: 47.0 (10.0)	No
	Health related quality of life: Role impairment (emotional)	RAND-36 subscale Role impairment (emotional)	0, post-intervention	I: 48.2 (10.3) C: 50.1 (9.5)	I: 48.8 (10.6) C: 47.7 (9.8)	Yes
Steel, 2016	Cancer-specific health related quality of life	Functional Assessment of Cancer Therapy-General	0, 6 months	I: 67.2 (17.1) C: 65.8 (16.9)	I: 82.4 (15.2) C: 63.2 (21.5)	Yes

Appendix 5. Outcome measures of studies with control conditions "face-to-face behavior change intervention

Author, year of publication	Outcome measure	Instrument	Time of measurement (pre- and post-treatment)	Pre-treatment mean (SD)	Post-treatment mean (SD)	Significant effect
Symptoms and signs						
Allen, 2013 * intensive counseling	Body weight	Weighing scale	0, 6 months	I: 100.3 (16.5) C: 96.0 (17.4)	I: 94.9 (4.0) C: 93.5 (4.1)	No
	BMI	Scale and meter	0, 6 months	I: 34.3 (3.9) C: 34.1 (4.1	I: 32.5 (1.3) C: 33.3 (1.4)	No
	Male waist circumference	Measuring tape	0, 6 months	I: 119.4 (11.6) C: 117.3 (15.5)	I: 112.4 (2.6) C: 114.3 (2.4)	No
	Female waist circumference	Measuring tape	0, 6 months	I: 109.7 (11.4) C: 106.4 (14.5)	I: 104.0 (3.7) C: 103.2 (7.4)	No
Allen, 2013 *less intensive counseling	Body weight	Weighing scale	0, 6 months	I: 96.8 (14.8) C:96.0 (17.4)	I: 93.5 (5.9) C: 93.5 (4.1)	No
	BMI	Scale and meter	0, 6 months	I: 33.5 (3.5) C: 34.1 (4.1)	I: 32.4 (2.0) C: 33.3 (1.4)	No
	Male waist circumference	Measuring tape	0, 6 months	I:116.4 (4.6) C: 117.3 (15.5)	I: 109.9 (0.35) C: 114.3 (2.4)	No
	Female waist circumference	Measuring tape	0, 6 months	I: 108.7 (8.4) C: 106.4 (14.5)	I: 105.1 (7.9) C: 103.2 (7.4)	No
De Boer, 2014	Pain-intensity	Visual analogue scale	0, 4 months	I: 6.59 (1.94) C: 5.61 (1.94)	I: 5.19 (2.53) C: 5.49 (2.32)	No
	Extend of fatigue	Visual analogue scale	0, 4 months	I: 6.34 (2.28) C: 6.63 (2.23)	I: 5.91 (2.44) C: 6.88 (2.32)	No
	Mean arterial blood pressure	Blood pressure test	0, 4 months	I: 95.1 (0.8) C: 95.4 (0.8)	I: 94.4 (0.9) C: 94.6 (0.9)	Yes

Nordin, 2016	Pain	Visual Analogue Scale (average of 7 days)	0, 4 months	I: 66.1 (16.7) C: 64.7 (16.2)	I: 59.6 (21.0) C: 54.8 (21.9)	No
Daily activity related limitations						
Allen, 2013 * intensive counseling	Self-reported activity	Stanford 7-Day Physical Activity Recall	0, 6 months	I:4.9 (5.7) C:5.0 (5.2)	I: 2.9 (5.4) C: 3.6 (7.1)	No
Allen, 2013 *less intensive counseling	Self-reported activity	Stanford 7-Day Physical Activity Recall	0, 6 months	I: 5.3 (5.4) C:5.0 (5.2)	I:1.7 (5.5) C: 3.6 (7.1)	No
Jasper, 2014	Insomnia	Insomnia Severity Index	0, 10 weeks	I: 12.68 (5.91) C: 12.40 (6.08)	I: 8.70 (5.80) C: 9.03 (6.75)	No
Van der Weegen, 2015	Physical activity	Pam accelerometer	0, post-intervention	I: 39.29 (18.1) C: 47.47 (26.5)	I: 48.16 (23.8) C: 46.28 (30.8)	Yes
Dealing with the chronic condition: cognitive measures						
De Boer, 2014	Pain-related catastrophizing	Pain catastrophizing scale	0, 4 months	I: 19.82 (13.9) C: 20.38 (11.38)	I: 11.00 (11.49) C: 16.10 (11.56)	Yes
	Catastrophizing	Pain coping and cognition list	0, 4 months	I: 3.12 (0.72) C: 3.19 (0.89)	I: 2.57 (0.86) C: 3.11 (0.88)	Yes
	Pain coping	Pain coping and cognition list	0, 4 months	I: 3.17 (0.96) C: 3.00 (0.64)	I: 3.72 (0.79) C: 3.14 (0.61)	Yes
	Internal pain management	Pain coping and cognition list	0, 4 months	I: 3.55 (0.67) C: 3.15 (0.98)	I: 4.30 (0.73) C: 3.57 (0.84)	Yes
	External pain management	Pain coping and cognition list	0, 4 months	I: 2.23 (0.86) C: 2.59 (0.94)	I: 1.99 (0.63) C: 2.40 (0.92)	Yes
Jasper, 2014	Acceptance	Tinitis Acceptance Questionnaire	0, 10 weeks	I: 42.07 (11.70) C: 40.26 (11.87)	I: 47.91 (11.70) C: 46.31 (11.96)	No
Nordin, 2016	Self-efficacy pain	Arthritis Self-Efficacy Scale: pain subscale	0, 4 months	I: 45.8 (21.6) C: 49.0 (20.4)	I: 50.0 (23.4) C: 49.3 (21.9)	Yes
	Self-efficacy other symptoms	Arthritis Self-Efficacy Scale: pain subscale	0, 4 months	I: 52.6 (19.2) C: 52.0 (16.7)	I: 58.1 (21.5) C: 56.1 (19.8)	No

	Self-efficacy general	General Self-Efficacy Scale	0, 4 months	I: 2.90 (0.60) C: 2.97 (0.46)	I: 2.88 (0.58) C: 3.06 (0.53)	No
	Coping strategy: diverting attention	Coping Strategy Questionnaire: subscale diverting attention	0, 4 months	I: 2.9 (1.4) C: 2.8 (1.5)	I: 3.2 (1.4) C: 2.9 (1.7)	No
	Coping strategy: reinterpret pain sensation	Coping Strategy Questionnaire: subscale reinterpret pain sensation	0, 4 months	I: 1.8 (1.4) C: 1.7 (1.4)	I: 2.1 (1.3) C: 1.8 (1.4)	No
	Coping strategy: catastrophizing	Coping Strategy Questionnaire: subscale catastrophizing	0, 4 months	I: 3.2 (1.4) C: 2.8 (1.2)	I: 2.8 (1.4) C: 2.8 (1.4)	Yes
	Coping strategy: ignore pain sensations	Coping Strategy Questionnaire: subscale ignore pain sensations	0, 4 months	I: 2.7 (1.2) C: 2.8 (1.2)	I: 2.9 (1.1) C: 2.9 (1.3)	Yes
	Coping strategy: praying or hoping	Coping Strategy Questionnaire: subscale praying or hoping	0, 4 months	I: 2.7 (1.6) C: 2.6 (1.5)	I: 2.8 (1.6) C: 2.5 (1.7)	No
	Coping strategy: self-statements	Coping Strategy Questionnaire: subscale ignore pain sensations	0, 4 months	I: 3.1 (1.1) C:3.1 (1.3)	I: 3.0 (1.2) C: 2.9 (1.3)	No
Van der Weegen, 2015	General self-efficacy	General Self-Efficacy Scale	0, post-intervention	I: 3.2 (0.5) C: 3.2 (0.5)	I: 3.3 (0.4) C: 3.3 (0.5)	No
	Exercise self-efficacy	Exercise Self-Efficacy Scale	0, post-intervention	I: 55.4 (17.0) C: 53.1 (21.3)	I: 59.7 (17.3) C: 59.7 (19.6)	No
Dealing with the chronic condition: behavioral measures						
De Boer, 2014	Pain interference with daily activities	Visual analogue scale	0, 4 months	I: 5.89 (2.14) C: 5.93 (2.40)	I: 5.13 (2.52) C: 6.33 (2.21)	No
Nordin, 2016	Coping strategy: Increased behavioral activities	Coping Strategy Questionnaire: subscale praying or hoping	0, 4 months	I: 3.3 (1.1) C: 3.1 (1.3)	I: 3.4 (1.0) C: 2.9 (1.3)	No

Emotional outcomes						
Jasper, 2014	Tinnitus associated distress	Mini-Tinnitus Questionnaire	0, 10 weeks	I: 12.20 (4.58) C: 14.19 (4.51)	I: 7.44 (5.30) C: 8.09 (4.93)	No
	Tinnitus associated distress	Tinnitus Handicap Inventory	0, 10 weeks	I: 40.34 (17.64) C: 44.33 (19.17)	I: 26.67 (20.75) C: 27.70 (21.93)	No
	Anxiety	Hospital Anxiety and Depressiona Scale	0, 10 weeks	I: 7.41 (3.56) C: 7.79 (3.73)	I: 5.44 (3.23) C: 5.84 (3.82)	No
	Depression	Hospital Anxiety and Depressiona Scale	0, 10 weeks	I: 5.95 (4.21) C: 6.02 (3.79)	I: 4.41 (3.72) C: 4.41 (3.92)	No
Quality of life						
Van der Weegen, 2015	Health related quality of life: Role impairment (physical)	RAND-36 subscale Role impairment (physical)	0, post-intervention	I: 42.5 (11.1) C: 46.1 (9.8)	I: 45.2 (9.5) C: 46.8 (10.0)	No
	Health related quality of life: Role impairment (emotional)	RAND-36 subscale Role impairment (emotional)	0, post-intervention	I: 48.2 (10.3) C: 48.6 (11.7)	I: 48.8 (10.6) C: 51.6 (11.3)	No

Appendix 6. Outcome measures of studies with control conditions "online behavior change intervention"

Author, year of publication	Outcome measure	Instrument	Time of measurement (pre- and post-treatment)	Pre-treatment mean (SD)	Post-treatment mean (SD)	Significant effect
Symptoms and signs						
Allen, 2013 *intensive counseling	Body weight	Weighing scale	0, 6 months	I: 100.3 (16.5) C:96.4 (16.9)	I: 94.9 (4.0) C:94.6 (3.7)	No
	BMI	Scale and meter	0, 6 months	I: 34.3 (3.9) C: 35.3 (4.1)	I: 32.5 (1.3) C: 34.7 (1.3)	No
	Male waist circumference	Measuring tape	0, 6 months	I: 119.4 (11.6) C: 113.8 (23.0)	I: 112.4 (2.6) C: 110.4 (8.3)	No
	Female waist circumference	Measuring tape	0, 6 months	I: 109.7 (11.4) C: 105.5 (11.1)	I: 104.0 (3.7) C: 110.4 (8.3)	No
Allen, 2013 *less intensive counseling	Body weight	Weighing scale	0, 6 months	I: 96.8 (14.8) C: 96.4 (16.9)	I: 93.5 (5.9) C: 94.6 (3.7)	No
	BMI	Scale and meter	0, 6 months	I: 33.5 (3.5) C: 35.3 (4.1)	I: 32.4 (2.0) C: 34.7 (1.3)	No
	Male waist circumference	Measuring tape	0, 6 months	I: 116.4 (4.6) C: 113.8 (23.0)	I: 109.9 (0.35) C: 110.4 (8.3)	No
	Female waist circumference	Measuring tape	0, 6 months	I: 108.7 (8.4) C: 105.5 (11.1)	I: 105.1 (7.9) C: 110.4 (8.3)	No
Dear, 2015 *regular contact group	Average pain	Wilcinson Brief Pain Questionnaire	0, 8 weeks	I: 5.74 (1.72) C: 5.72 (1.63)	I: 4.86 (1.79) C: 5.20 (1.80)	No
Dear, 2015 *optional contact group	Average pain	Wilcinson Brief Pain Questionnaire	0, 8 weeks	I: 5.54 (1.74) C: 5.72 (1.63)	I: 4.85 (1.73) C: 5.20 (1.80)	No
Glasgow, 2010	BMI	Scale and meter	0, 4 months	I: 35.2 (6.78) C: 34.5 (6.28)	I: 35.1 (6.83) C: 34.4 (6.27)	Yes
	Hemoglobin	Bio-Rad Variant II Turbo liquid by high pressure liquid	0, 4 months	I: 8.26 (1.75) C: 8.01 (1.85)	I: 8.05 (1.48) C: 7.84 (1.67)	No

		chromatography				
	Lipid ratio (total / HDL)	Modular chemistry analyzer, Abell Kendall method	0, 4 months	I: 4.04 (1.11) C: 4.00 (1.25)	I: 3.94 (1.16) C: 3.84 (1.06)	No
	Mean arterial blood pressure	Blood pressure meter	0, 4 months	I: 95.12 (10.54) C: 95.42 (10.40)	I: 94.58 (10.50) C: 94.27 (10.20)	No
Torbjørnsen, 2014	Hemoglobin	Blood test	0, 4 months	I: 8.2 (1.08) C: 8.1 (1.09)	I: 7.8 (1.44) C: 7.8 (0.91)	No
Trompetter, 2015	Pain	Pain NRS	0, 3 months	I: 6.3 (1.6) C: 6.1 (1.6)	I: 5.4 (2.2) C: 5.9 (2.3)	Yes
Van den Berg, 2006	Disease activity: pain, swelling and tenderness	Reumatoid Arthritis Disease Activity: DAS28	0, 12 months	I: 3.5 (2.3) C: 3.3 (2.1)	I: 3.1 (1.6) C: 2.8 (2.0)	No
Yardley, 2014 *basic nurse support	Body weight	Weighing scale	0, 6 months	I: 103.43 (25.23) C: 98.25 (18.11)	I: 97.92 (5.80) C: 99.00 (5.75)	No
Yardley, 2014 *regular nurse support	Body weight	Weighing scale	0, 6 months	I: 100.36 (19.38) C: 98.25 (18.11)	I: 97.14 (5.74) C: 99.00 (5.75)	No
Daily activity related limitations						
Allen, 2013 * intensive counseling	Self-reported activity	Stanford 7-Day Physical Activity Recall	0, 6 months	I:4.9 (5.7) C:3.5 (3.7)	I: 2.9 (5.4) C:3.3 (5.1)	No
Allen, 2013 *less intensive counseling	Self-reported activity	Stanford 7-Day Physical Activity Recall	0, 6 months	I: 5.3 (5.4) C:3.5 (3.7)	I:1.7 (5.5) C:3.3 (5.1)	No
Van den Berg, 2006	Functional ability	MACTAR	0, 12 months	I: 51.0 (4.0) C: 50.0 (4.0)	I: 55.2 (8.1) C: 52.5 (10.1)	Yes
	Rheumatoid related disabilities	Health Assessment Questionnaire	0, 12 months	I: 0.75 (1.13) C: 0.75 (0.75)	I: 0.66 (0.35) C: 0.71 (0.16)	Yes
Dear, 2015 *regular contact group	Backpain associated disability in daily activities	Roland-Morris Disability Questionnaire	0, 8 weeks	I: 13.47 (5.23) C: 13.92 (5.06)	I: 11.05 (5.63) C: 11.36 (5.22)	No

Dear, 2015 *optional contact group	Backpain associated disability in daily activities	Roland-Morris Disability Questionnaire	0, 8 weeks	I: 13.24 (5.60) C: 13.92 (5.06)	I: 10.95 (.84) C: 11.36 (5.22)	No
Glasgow, 2010	Physical activity	CHAMPS instrument	0, 4 months	I: 3664 (2959) C: 4294 (3054)	I: 3697 (3272) C: 4146 (3578)	No
Liebreich, 2009	Leisure-time Physical activity	Modified version Godin Leisure-Time Exercise Questionnaire	0, 3 months	I: 483 (620) C: 501 (582)	I: 654 (659) C: 490 (562)	Yes
McKay, 2001	Moderate-to-vigorous exercise	Behavioral Risk Factor Surveillance system	0, 2 months	I: 5.6 (6.2) C: 7.3 (6.2)	I : 17.6 (15.3) C : 18.0 (17.3)	No
	Walking	Behavioral Risk Factor Surveillance system	0, 2 months	I: 6.4 (6.2) C: 8.4 (8.4)	I: 12.5 (9.5) C: 16.8 (22.8)	No
Van den Berg, 2006	Meeting physical activity recommendations	Self-reported, percentage of total sample	0, 12 months	I: 0 (0) C: 0 (0)	I: 19 (26) C: 11 (15)	No
	Physical activity score	Number of acceleration per 5-minute period throughout the day, Actilog V3.0 activity monitor	0, 12 months	I: 72.0 (33.5) C: 79.0 (25.8)	I: 72.3 (34.0) C: 80.7 (30.6)	No
Trompetter, 2015	Disruption of daily activities by chronic pain	Pain Disability Index	0, 3 months	I: 36.0 (12.7) C: 36.4 (12.7)	I: 30.6 (14.5) C: 34.6 (14.3)	No
Dealing with the chronic condition: cognitive measures						
Dear, 2015 *regular contact group	Pain Self-efficacy	Pain Self-efficacy Questionnaire	0, 8 weeks	I: 28.86 (12.93) C: 26.80 (11.52)	I: 35.94 (12.98) C: 33.21 (11.97)	Yes
	Fear of movement	TAMPA Scale of Kinesiophobia	0, 8 weeks	I: 38.59 (7.99) C: 39.35 (7.37)	I: 34.48 (7.00) C: 34.59 (6.80)	No
	Pain acceptance	Chronic Pain Acceptance Questionnaire	0, 8 weeks	I: 22.58 (7.53) C: 22.26 (7.19)	I: 26.79 (6.69) C: 25.76 (6.65)	No
Dear, 2015 *optional contact group	Pain Self-efficacy	Pain Self-efficacy Questionnaire	0, 8 weeks	I: 28.61 (14.08) C: 26.80 (11.52)	I: 33.60 (13.83) C: 33.21 (11.97)	No
	Fear of movement	TAMPA Scale of Kinesiophobia	0, 8 weeks	I: 37.60 (8.40) C: 39.35 (7.37)	I: 34.88 (7.80) C: 34.59 (6.80)	No
	Pain acceptance	Chronic Pain Acceptance Questionnaire	0, 8 weeks	I: 23.30 (7.72) C: 22.26 (7.19)	I: 25.40 (8.01) C: 25.76 (6.65)	No
Liebreich, 2009	Self-efficacy in performing regular physical activity	Self-efficacy 12-item scale, Plotnikoff et al.	0, 3 months	I: 3.00 (0.74) C: 3.01 (0.71)	I: 2.99 (0.84) C: 2.82 (0.84)	No

	Outcome expectations of engaging in physical activity	Modified version of the Decisional Balance Scale and Physical Activity Expectations Scale	0, 3 months	I: 4.66 (0.87) C: 4.62 (0.37)	I: 4.57 (0.54) C: 4.57 (0.42)	No
	The perceived importance of outcome expectations	Perceived importance of the Outcome Expectations	0, 3 months	I: 2.73 (0.29) C: 2.71 (0.34)	I: 2.69 (0.39) C: 2.65 (0.36)	No
	The degree to which participants rewarded themselves ans set realistic goals	Reinforcement 4-item scale, Marcus et al.	0, 3 months	I: 2.73 (0.66) C: 2.58 (0.84)	I: 2.83 (0.74) C: 2.70 (0.91)	No
	Emotional coping response	Emotional well-being subscale	0, 3 months	I: 2.93 (0.76) C: 2.78 (0.67)	I: 2.90 (0.67) C: 2.90 (0.67)	No
	Participants'indication of how true a variety of reasons to exercise were (e.g. 'I value the benefits of exercise')	Subscale of Behavior Regulation in Exercise Questionnaire	0, 3 months	I: 3.81 (0.54) C: 3.94 (0.53)	I: 3.56 (0.91) C: 3.75 (1.05)	No
	Experienced confidence in performing physical activity	Behavioral capacity 4-item scale, Rogers et al.	0, 3 months	I: 3.10 (1.18) C: 3.25 (0.98)	I: 3.23 (1.32) C: 2.97 (0.98)	Yes
	Indication of how often external situations prevented participants from getting a physical active lifestyle	Situation 17-item scale, Rogers et al.	0, 3 months	I: 2.41 (0.66) C: 2.11 (0.55)	I: 2.35 (0.67) C: 2.16 (0.59)	No
	Experienced social support in getting a physical active lifestyle	Social support 2-item scale, Cournya et al.	0, 3 months	I: 5.06 (1.52) C: 4.58 (1.99)	I: 4.18 (2.10) C: 4.27 (2.05)	No
	The degree to which participants observed others being physical active	Observational learning 2-item scale, Plotnikoff et al.	0, 3 months	I: 4.14 (0.78) C: 3.25 (0.98)	I: 3.96 (0.92) C: 2.97 (0.98)	No
Trompetter, 2015	Positive mental health	Mental Health Continuum-Short Form	0, 3 months	I: 52.6 (11.8) C: 53.1 (11.8)	I: 54.7 (12.2) C: 55.9 (15.2)	No
	Avoidance of pain and cognitive fusion with pain	Psychological Inflexibility in Pain Scale	0, 3 months	I: 55.0 (11.6) C:55.1 (11.6)	I: 40.7 (13.8) C: 46.3 (14.1)	Yes

	Mindfulness skills	Five Facet Mindfulness Questionnaire-Short Form	0, 3 months	I:81.4 (10.7) C:83.2 (10.7)	I:86.7 (12.2) C: 88.8 (12.5)	No
	Pain catastrophizing	Pain Catastrophizing Scale	0, 3 months	I: 18.6 (9.5) C: 17.6 (10.2)	I: 13.5 (11.3) C: 15.6 (11.7)	No
Dealing with the chronic condition: behavioral measures						
Nobis, 2015	Coping with diabetes	Acceptance and Action Diabetes Questionnaire	0, 2 months	I: 36.93 (8.96) C: 36.56 (10.27)	I: 34.13 (8.45) C: 36.11 (9.86)	Yes
	Diabetes specific self-management	Diabetes Self-Management Questionnaire	0, 2 months	I: 4.78 (0.65) C:4.68 (0.65)	I: 4.76 (0.55) C: 4.72 (0.62)	No
Torbjørnsen, 2014	Self-management: skills and technique acquisition	Hei-Q	0, 4 months	I: 2.87 (0.43) C: 2.95 (0.46)	I: 3.04 (0.52) C: 2.98 (0.62)	No
	Self-management: Health service navigation	Hei-Q	0, 4 months	I: 3.08 (0.43) C: 3.14 (0.51)	I: 3.27 (0.56) C: 3.21 (0.60)	Yes
Trompetter, 2015	Awareness of personal values and the degree to which this guide person's actions in daily life	Engaged Living Scale	0, 3 months	I:51.5 (10.4) C: 51.5 (9.9)	I: 55.1 (12.4) C: 56.1 (12.8)	No
	The degree to which pain interferes with daily activities	Multidimensional Pain Inventory	0, 3 months	I: 32.3 (9.8) C: 32.2 (9.8)	I: 28.7 (12.0) C: 32.7 (12.3)	Yes
Emotional outcomes						
Dear, 2015 *regular contact group	Depression	Patient Health Questionnaire 9-item	0, 8 weeks	I: 11.55 (5.88) C: 10.90 (4.76)	I: 6.30 (4.57) C: 6.96 (4.29)	No
	Anxiety	Generalized Anxiety Disorder 7-item		I: 8.40 (5.52) C: 8.28 (4.60)	I: 4.91 (4.40) C: 5.16 (3.91)	No
Dear, 2015 *optional contact group	Depression	Patient Health Questionnaire 9-item	0, 8 weeks	I: 10.60 (5.33) C: 10.90 (4.76)	I: 7.20 (5.25) C: 6.96 (4.29)	No
	Anxiety	Generalized Anxiety Disorder 7-item		I: 7.98 (4.67) C: 8.28 (4.60)	I: 5.66 (4.94) C: 5.16 (3.91)	No
McKay, 2001	Depression	10-item version of the Center for Epidemiologic Studies Depression scale	0, 2 months	I: 16.9 (11.6) C: 17.6 (10.4)	I: 14.9 (12.5) C: 19.9 (14.2)	No
Nobis, 2015	Depressive symptom	Center for Epidemiologic Studies	0, 2 months	I: 32.7 (6.95)	I: 21.08 (8.84)	Yes

	severity	Depression Scale		C:32.53 (7.51)	C: 28.90 (8.65)	
	Depressive symptoms	Hospital Anxiety and Depression Scale	0, 2 months	I: 11.99 (3.23) C: 11.69 (3.08)	I: 8.12 (3.92) C: 11.26 (3.72)	Yes
	Emotional distress related to living with DM	Problem Areas in Diabetes Scale	0, 2 months	I: 10.24 (4.27) C: 10.57 (4.52)	I: 8.35 (3.94) C: 10.87 (4.67)	Yes
Trompetter, 2015	Anxiety	Hospital Anxiety and Depression Scale	0, 3 months	I: 7.2 (3.3) C: 6.5 (3.4)	I: 6.0 (3.8) C: 5.7 (3.8)	No
	Depression	Hospital Anxiety and Depression Scale	0, 3 months	I: 6.1 (3.4) C: 7.5 (3.3)	I: 5.1 (3.7) C: 5.9 (3.9)	No
Quality of life						
De Boer, 2014	Health related quality of life: Physical functioning	RAND-36 subscale Physical functioning	0, 4 months	I: 50.10 (17.20) C: 52.50 (22.94)	I: 58.50 (22.37) C: 55.88 (22.35)	Yes
	Health related quality of life: Social functioning	RAND-36 subscale Social functioning	0, 4 months	I: 49.34 (23.74) C: 47.92 (23.79)	I: 65.79 (26.95) C: 54.17 (27.00)	Yes
	Health related quality of life: Role impairment (physical)	RAND-36 subscale Role impairment (physical)	0, 4 months	I: 15.79 (29.12) C: 15.63 (24.24)	I: 37.24 (41.89) C: 22.19 (34.89)	No
	Health related quality of life: Role impairment (emotional)	RAND-36 subscale Role impairment (emotional)	0, 4 months	I: 59.65 (42.42) C: 57.97 (44.06)	I: 71.93 (41.96) C: 67.39 (40.97)	No
	Health related quality of life: Mental health	RAND-36 subscale Mental health	0, 4 months	I: 62.74 (18.95) C: 65.83 (18.80)	I: 70.11 (20.76) C: 66.17 (17.61)	No
	Health related quality of life: Vitality	RAND-36 subscale Vitality	0, 4 months	I: 41.32 (15.35) C: 39.79 (16.84)	I: 52.63 (20.30) C: 40.63 (14.69)	Yes
	Health related quality of life: Pain	RAND-36 subscale Pain	0, 4 months	I: 37.16 (14.73) C: 38.76 (17.87)	I: 50.70 (18.60) C:39.80 (19.35)	Yes
	Health related quality of life: General health appraisal	RAND-36 subscale General health appraisal	0, 4 months	I: 49.33 (23.35) C: 42.50 (22.84)	I: 56.63 (27.69) C: 43.54 (20.51)	No
	Health related quality of life: Perceived health change	RAND-36 subscale Perceived health change	0, 4 months	I: 28.75 (24.70) C: 38.54 (30.38)	I: 51.25 (23.61) C: 38.54 (34.56)	Yes

Van den Berg, 2006	Disease related quality of life	Rheumatoid Arthritis Quality of Life	0, 12 months	I: 10.0 (10.2) C: 10.0 (9.5)	I: 8.7 (6.1) C: 9.4 (3.6)	Yes
	Quality of life: physical summary scale	RAND-36: physical summary	0, 12 months	I: 52.8 (40.1) C: 54.4 (42.8)	I: 47.9 (17.6) C: 50.4 (18.2)	Yes
	Quality of life: mental summary	RAND-36: mental summary	0, 12 months	I: 75.1 (26.2) C: 73.0 (30.5)	I: 74.9 (21.0) C: 72.2 (12.2)	No

3

A blended intervention for patients with knee and hip osteoarthritis in the physical therapy practice: development and a pilot study

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Abstract

Background: Blended care, a combination of online and face-to-face care, is seen as a promising treatment option. However, actual use of blended interventions in practice is disappointing. The objective of this study was two folded.
Objective: The first aim was to develop a blended exercise therapy intervention for patients with knee and hip osteoarthritis that matches the values of the users and which can be implemented in the daily routine of physical therapists. The second aim was to investigate the feasibility through interviews and a pilot study.
Methods: In this paper, we employed the first three steps of the CeHRes roadmap to develop a blended intervention for patients with knee and hip osteoarthritis. We used interviews, a focus group and discussions with stakeholders to explore the needs, values and requirements with respect to our to-be-developed blended intervention. The first version of e-Exercise was tested in a pre- and post-test pilot study. Feasibility outcomes, including recruitment rates within each practice, website usage (assignments completed and website visits), health related outcomes (physical activity, physical functioning pain and fatigue) and user satisfaction, were measured. In addition, therapists and patients from the pilot study were interviewed to investigate users' experiences.
Results: The study captured important information about stakeholders' needs and perspectives. Based on our findings, we created a first version and attuned the application's content, functionality and structure. Patients and, to lesser extent, physical therapists were satisfied with the e-Exercise intervention. Eight patients were recruited by eight physical therapists. Six out of the eighth patients completed more than seven of twelve modules. Results from the pilot study showed small but non-significant improvements for the outcomes physical functioning, pain and tiredness. No improvements were found in physical activity levels.
Conclusion: This study outlines the development and feasibility of a blended exercise therapy intervention for patients with knee and hip osteoarthritis. E-Exercise offers an alternative approach in the physical therapy treatment of knee and hip osteoarthritis. This study provides valuable information to conduct a further trial to evaluate the (cost) effectiveness of e-Exercise compared to usual physical therapy.

Introduction

Knee and hip osteoarthritis (OA) are leading causes of disability in older people [1]. In the upcoming years, the number of people with knee and hip OA will grow due to the aging population and escalating risk factors, such as obesity [2]. Since there is no cure for OA, exercise, education and medication are considered to be cornerstones in the treatment of knee and hip OA [3,4].

Although generally patients with knee and hip OA tend to avoid physical activity [5], physical exercise is one of the most effective and recommended treatment modalities [3,4]. Exercise therapy, generally provided by a physical therapist, is a regimen of physical activities with the aim to change patient's lifestyle behavior and improve patients' overall function [6].
Therapeutic exercise therapy consists of strengthening, aerobic, flexibility and/or functional exercises. Multiple studies have demonstrated beneficial effects of exercise therapy in patients with knee and hip OA. Exercise therapy has positive effects on pain perception and self-reported physical function [7,8]. However, therapeutic exercise therapy is labor-intensive, costly and often not covered by the healthcare insurances, especially over the long term. So, although helpful, physical therapy is not accessible for many OA patients. According current estimates, only 7% of all patients with knee and hip OA seen in general practice is actually referred to a physical therapist [9].

There is a clear need for more feasible and easy accessible strategies in order to regulate therapeutic costs and make exercise therapy attainable for a broader range of OA patients. This can be accomplished through self-management support. Self-management implies individuals' ability to manage symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic disease [10]. The use of eHealth has the potential support self-management in patients with OA treatment beyond the walls of the physical therapy practice. Examples include, but are not limited to, web-based interventions and mobile health interventions which can help to improve patients' health behavior and corresponding health outcomes [11,12]. The 24/7 availability of information may improve treatment compliance which is critical for the success of physical therapy [13]. Moreover, embedding e-Health within daily practice has also the potential to substitute a part of the face-to-face contacts and alleviate the pressure on health services. Furthermore,

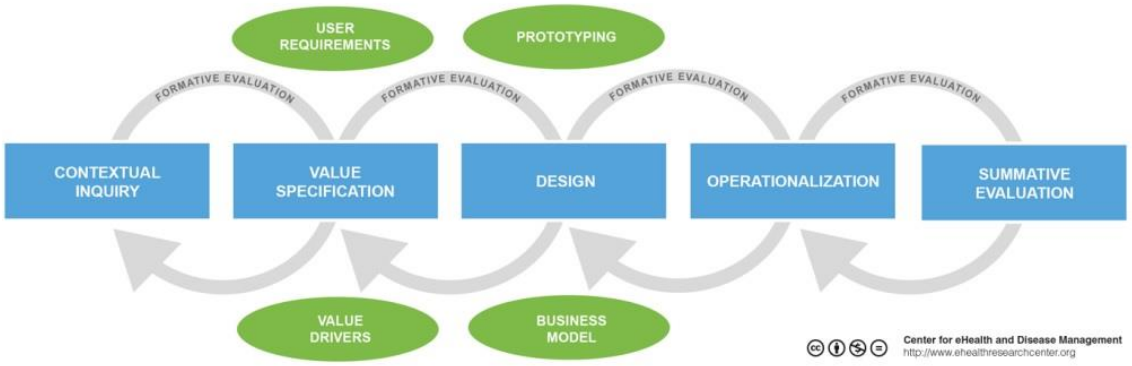
eHealth opens up new avenues to reach new patient groups, especially for those who have minimal or no coverage for physical therapy expenses.
Although promising in terms of evidence and accessibility, the adoption of eHealth technologies is disappointing [14]. Embedding eHealth technologies in daily practice is a complex and time-consuming process, more than initially anticipated [15]. So far, eHealth interventions are primarily used outside the healthcare setting and rarely integrated as part of the treatment. To illustrate, only 1% of all patients in the physical therapy practice use therapeutic-provided eHealth interventions, such as online self-management treatments or online exercises [16]. The uptake and implementation of eHealth innovations in practice is dependent on various factors which can be broadly divided into four categories: (i) characteristics of the technology itself, such as ease-of-use and quality of the intervention; (ii) characteristics of the end-users, such as perceived usefulness, perceived support from family/colleagues, skills and knowledge; (iii) characteristics of the organization, such as formal endorsement and costs; and (iv) policy and legislation, such as privacy issues and reimbursement schemes for eHealth services [17].

The success of eHealth is hampered by insufficient attention paid to abovementioned determinants during the development process. The majority of eHealth technologies is created through ad-hoc procedures without a thoughtful approach [18]. High rates of non-usage and implementation difficulties are normative phenomena in eHealth [14, 19, 20]. The peripheral position of end-users and inadequate input of other stakeholders lead to a mismatch between technology and context which explains why eHealth do not reach its full potential in practice [21]. The involvement of stakeholders, such as healthcare providers, policy makers and health insurers, provides direction for the development of eHealth technologies. Co-creation, the engagement of users and other stakeholders throughout the development process, is an important strategy in order to meet the values and needs of stakeholders.

The Centre for eHealth Research and Disease management (CeHRes) roadmap is a development approach in which co-creation plays a central role [21]. This CeHRes roadmap anticipates on the needs and values of stakeholders and consists of five steps (figure 1). In this article, we employed the CeHRes roadmap to develop a new blended intervention for patients with knee and/or hip OA. This intervention, which will be a combination of eHealth and face-to-face care, will be integrated in the daily physical therapy practice. This proposed program aims to promote a physically active lifestyle among patients with knee and hip OA. The objective of this study was two folded. The first aim of this study is to develop a human-centred eHealth physical activity intervention that matches the values of users and which can be implemented

in the daily routine of physical therapists. The second aim was to investigate the feasibility through interviews and a pilot study. To our knowledge this is the first study investigating a blended exercise therapy intervention for physical therapists.

Figure 1. CeHRes roadmap



Methods & Results

In the following section we describe the first three steps of the CeHRes roadmap, namely the contextual inquiry, the value specification and design. In addition, we conducted a pilot study in order to determine the feasibility of the blended intervention. The first three stages of the CeHRes roadmap and the pilot study provide the basis for step four (operationalization) and five (summative evaluation), which will be conducted in a later phase of the project. In order to enhance clarity and optimize the execution of each step, we have chosen to present the methods and results sections together. The study has been approved by the Medical Ethical Committee of the St. Elisabeth hospital Tilburg, the Netherlands (Dutch Trial Register NTR4224).

Contextual inquiry and value specification

Methods

During the contextual inquiry and value specification we aimed to establish stakeholders' most important needs, values and requirements with respect to our to-be-developed blended intervention. The input of this phase was mainly based on

another project, executed by the same authors [22]. In this previous work, we developed and evaluated the web-based intervention Join2move. Join2move is a self-

Figure 2. Stakeholders' needs and perspectives

	Stakeholder 1	Stakeholder 2	Stakeholder 3	Stakeholder …
Why are you participating in this committee?				
What is your added value to the team?				
Is there a need for a blended intervention for your organization? Please explain				
Potential advantages of the blended intervention				
Potential disadvantages of the blended intervention				
Potential facilitators for implementation				
Potential barriers for implementation				

guided intervention and contains automatic functions without human support. The 9-week program is directed at increasing the level of physical activities in a time-contingent manner (fixed time points). More information about the intervention and used methods can be found elsewhere [22]. For the development of e-Exercise, a focus group among seven physical therapists was conducted. Physical therapists, who had an extensive experience in the field of OA, were recruited through the website of The Royal Dutch Society for Physical Therapy to participate. The focus group was facilitated by two moderators (CK and DB) and lasted approximately 120 minutes. During the focus group, we used a topic guide that contained questions related to the content needs of the intervention, reimbursement and frequency of face-to-face contact. The focus group discussion was audio-taped and subsequently summarized. An implementation committee was formed with different stakeholders. The stakeholder committee consisted of patients with knee and/or hip OA, the Royal Dutch Society for Physical Therapy, two rehabilitation centers, the Dutch arthritis

foundation, an eHealth entrepreneur and a health insurer. The committee meetings were held three times and were led by the last author (CV). At each meeting, stakeholder members were encouraged to discuss and share their thoughts about the development and implementation process of the blended intervention. The results from these discussions provided direction for further development of the blended intervention. We created a matrix in order to summarize and analyze needs and perspectives of the individual committee members (see figure 2).

Results

The interviews showed that patients have a positive attitude towards the idea that eHealth will be integrated as a part of their treatment, especially for information and education purposes. These findings were also found in a previous study by Pietrzak et al. [23]. In accordance with the patients, physical therapists in the focus group also indicated that a blended intervention will be a useful instrument in the treatment of OA patients. The 24/7 availability of information and exercises, the possibility to extent the physical therapy treatment in the home environment and the potential to enhance the adherence of home exercises were mentioned as possible advantages. On the other hand, the fact that the proposed blended intervention aims to substitute conventional visits may lead to reduced revenues per patient. According to physical therapists, this lack of financial incentive was seen as a potential barrier to use the proposed intervention in practice. The stakeholder committee was also positive towards the to be developed blended intervention. As a stakeholder from a rehabilitation institute cited: “Patients will benefit from the blended intervention because it is cheap, independent of time or place and promotes self-management in the home environment of OA patients”. Another facilitator for implementation is the potential reduction in treatment costs. An employee of a health insurance company summarized this by: “The proposed blended intervention will possibly result in lower costs since the average number of sessions will be decreased. This will lead to a cost reduction of the OA treatment”.

Design

Methods

E-Exercise is a combination of (i) visits with a physical therapist, and (ii) a web-based physical activity intervention. The technical functionality of the web-based part is based on a previously developed physical activity intervention [24]. This initial web-

based intervention contained only self-directed features without the integration of physical therapy sessions. To investigate whether and how the initial web-based intervention fits the day-to-day requirements and routines of physical therapists, different content scenarios were presented during a second focus group session with physical therapists. These scenarios concentrated on several themes, such as the number of face-to-face visits, extent of (online) interaction between patient and physical therapist and website content such as videos, design and education topics. Results were used to change the first web-based intervention and create the blended intervention e-Exercise. This first blended version of e-Exercise was tested in a pilot study.

Results

Over the course of a half year, a team of experts from the NIVEL developed the e-Exercise program. The starting point of the development process was a previously developed web-based exercise intervention [25] and the Dutch guideline for physical therapists [26]. The intervention is delivered over a period of 12 weeks. During the 12 weeks, patients receive four face-to-face sessions with a physical therapist and are supposed to complete 12 online assignments (see figure 3). The physical therapists were encouraged to follow a fixed treatment protocol. The website has a portal for both patients and physical therapists and contains text- and video-based information. The core element of the website activities is the promotion of moderate physical activities, such as cycling, walking or swimming in the home environment of patients. Every week, automatic generated physical activity exercises are posted on a password-secured website in which a self-chosen physical activity is gradually increased in a time contingent manner (i.e. fixed time points). Time-contingency means that physical activities are increased on fixed time quotas rather than guided by OA related symptoms such as pain and fatigue. This strategy is derived from the behavioral graded activity intervention and concepts of operant conditioning [27]. The homepage is shown in figure 4. Screenshots with illustrative screenshots of the e-Exercise website are presented in Multimedia appendix 1.

Figure 3. Overview of the 12-week e-Exercise treatment

Figure 4. E-Exercise homepage

Pilot study

Methods

Study design and objective:

This pilot study employed a multicentre one-group pre-and post-test design. The purpose was to evaluate the feasibility of the e-Exercise treatment in the daily practice of physical therapists.

Procedures and participants:

Physical therapists working in a private practice were recruited through the website of the Royal Dutch Society for Physical Therapy and the social network of the authors. Eventually, eight physical therapists were included in the pilot study. All participating physical therapists received a half day training about the study procedures and how to use e-Exercise in their practice. Eligible patients, who visited a participating centre during the study period, were enrolled by the physical therapists. Enrolment started on March 3, 2014, and ended May 6, 2014. Participants were suitable for inclusion if they (i) were aged 40 to 80 age and (ii) had the diagnosis OA of the knee and/or hip according to the clinical criteria of the American College of Rheumatology [28]. Participants were not suitable if they (i) were on a waiting list for a hip or knee replacement surgery, (ii) had contra-indications for physical activity without supervision, (iii) had a physically active lifestyle (iv) participated in a physical therapy for OA and/or PA program in the last six months (v) had no access to internet and (vi) were unable to understand the Dutch language. Interested patients who were willing to participate and met the eligibility criteria were sent an information letter about the study and an informed consent. Once written informed consent was obtained, participants were invited to fill out an online baseline questionnaire. After baseline completion, participants were included in the study. Follow-up testing for post-intervention results was performed 12 weeks after the baseline assessment.

Feasibility:

Feasibility measures included website usage, user satisfaction with the website and recruitment rates of participants within each practice. Program use was measured by the number of modules completed. User satisfaction was measured through the System Usability Scale [29]. Moreover, participating physical therapists and participants were invited for interviews to obtain experiences with respect to e-Exercise. Semi-structured interviews were conducted on a sub-sample of five physical therapists and four patients. Interviews were audio-recorded and transcribed with interviewee's permission. An interview guide with open questions was employed to provide structure to the interviews (see Appendix 1). Transcribed texts were read and thematic trend analysis was conducted to identify, analyze and report recurrent patterns. Themes were discussed by CK and DB to gain an overall understanding of the usability and user satisfaction.

Health measurements:
Self-reported online questionnaires were used to investigate the potential effectiveness of e-Exercise. Physical functioning was assessed the Hip Osteoarthritis Outcome Score (HOOS) [30] and/or the Knee Injury and Osteoarthritis Outcome Score (KOOS) [31]. Recreational physical activity was assessed by the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) [32]. Pain and fatigue were examined with a 10-point numerical rating scale (0 is no pain/not tired, 10 is worst possible pain/extremely tired). Descriptive statistics were used to analyze the data. Analyses were conducted using SPSS Statistics 20.0.

Results

Feasibility:
Overall, patients and, to a lesser extent, physical therapists were satisfied with the e-Exercise intervention. Results from the system usability scale among patients revealed an average score of 79 points (SD 8.7) on a 100-point scale questionnaire, which can be considered as a good score [33]. Usability scores from physical therapists were considerably lower, namely 64 (SD 7.7). This rating can be interpreted as 'fairly' good [33]. Login-analyses showed that six out of the eighth patients completed more than seven of the twelve modules. Over the twelve week intervention period, patients visited the website 33 times on average. Prior the study, we intended to recruit two patients per participating physical therapist. However, during the 10-week enrollment period, only five of the eight physical therapists recruited eight patients in total. Physical therapists reported that e-Exercise is only suitable for a small subset of patients. Most of the patients with knee and hip OA prefer traditional face-to-face treatments over the blended intervention or did not meet the study inclusion criteria. One physical therapist said: "*Most of the patients with knee or hip osteoarthritis that I have seen were not interested in participating in e-Exercise because they preferred face-to-face guidance. Other patients did not have a computer or had an already physically active lifestyle*".Overall, interviewees were satisfied with the intervention. One patient summarized this sentiment by saying: *"I have told many friends and family that this is a great program because the program motivates you to perform exercises in your own time. I would therefore definitely recommend e-Exercise to others"*. Physical therapists expressed also positive feedback regarding the content of e-Exercise. To cite one therapist: *"I am especially pleased with the information about osteoarthritis provided by the videos. More insight into the disease and the role of pain is important prerequisite to encourage a physically active lifestyle".* Although physical therapists were generally

satisfied, they stressed that e-Exercise must be adapted for suitable integration into practice. As one physical therapist commented:*"The program provides no insight which modules patients receive. This was a truly downside of the program because I had little or no control over patients' progress"*. It was also reported by some patients that they liked effective approach of e-Exercise. One patient commented: "*I liked the effective approach of the intervention. You need only a few face-to-face treatments to get on track. The provision of weekly physical therapy sessions is not useful because you have to exercise yourself*".

Health measurements:

After all, eight eligible OA patients were included by the nine participating physical therapists. Patients were on average 62 years old, had one or more comorbidities (88%) and most of them were female (75%). None of the participants withdrew from the study. An overview of the sample characteristics are presented in Table 1. Over the twelve week intervention period, total minutes spent on physical activity decreased from 2123 to 1727 min/week. Knee and hip functioning scores, measured with the HOOS and KOOS, showed in most cases a small improvement. Overall, patients reported lower levels of pain and fatigue compared to the baseline (from 5,9 to 4,9 and 5,5 to 5,1. An overview of investigated outcome measures is provided in Table 2.

Table 1. Baseline demographics and characteristics OA patients

Participants (n=8)		
Gender, n (%)	Female	6 (75)
	Male	2 (25)
Mean age (years, (SD)		61.88 (14.53)
Location OA, n	Knee	4
	Hip	3
	Both	1
Duration of symptoms, n	< 1 year	2
	1-3 year	1
	3-7 year	2
	≥7 year	3
Education, n	Low	2
	Middle	2
	High	4
Comorbidity, n	None	1
	One	4
	Two or more	3

OA, osteoarthritis; SD, standard deviation.

Table 2.Outcome measurements

	Baseline, mean (SD)	12 weeks, mean (SD)
Physical activity		
Total PA (min)	2123 (969)	1727.5 (907)
Light PA (min)	1446 (796)	1124.4 (909)
Moderate PA (min)	676 (342)	603.1 (451)
Vigorous PA (min)	0	0
Knee function		
Symptoms (0-100)	61.0 (4.2)	62.0 (17.9)
Stiffness (0-100)	37.5 (23.4)	50.0 (29.3)
Pain (0-100)	43.1 (10.7)	54.4 (21.0)
ADL (0-100)	58.2 (17.4)	60.9 (24.1)
Sport (0-100)	15.0 (22.4)	36.0 (32.7)
QOL (0-100)	30.0 (16.2)	37.5 (21.2)
Hip function		
Symptoms (0-100)	37.5 (14.4)	43.8 (23.9)
Stiffness (0-100)	56.3 (23.9)	62.5 (30.6)
Pain (0-100)	63.1 (21.0)	61.8 (15.4)
ADL (0-100)	69.1 (24.1)	65.4 (18.5)
Sport (0-100)	46.9 (15.8)	43.8 (30.2)
QOL (0-100)	53.1 (18.8)	53.1 (13.0)
Pain (0-10)	5.9 (2.8)	4.9 (3.0)
Tiredness (0-10)	5.5 (3.0)	5.1 (3.6)

SD, standard deviation;PA, Physical Activity; ADL, activities of daily life; QOL, Quality of life For physical activity, knee
function and hip function, a higher score indicates an improvement. For pain and tiredness, a lower score indicates an improvement.

Discussion

Provision of blended care requires a harmonious integration of technology into practice, combining complementary face-to-face treatments with eHealth technology. Implementing a blended intervention into healthcare is a complex process that changes existing routines, relationships and budgets. Developers and researchers have to anticipate on these implementation difficulties. While research supports the effectiveness of health technology, healthcare professionals often lack time, skills and resources to integrate eHealth in their daily practice. Input of end-users and others stakeholders throughout the development process is prerequisite for successful implementation of blended interventions into practice [21]. The aim of this study was to develop and investigate the feasibility of a blended exercise therapy intervention for patients with knee and hip OA which can be implemented in the daily routine of physical therapists.

The involvement of patients, physical therapists and other stakeholders was extremely valuable throughout the development process. The first three phases of the CeHRes roadmap yielded unique insights into different needs and values of end-users and various stakeholders. Steps from the CeHRes model were not purely sequentially executed but involved a continuous process. For instance, the identification of needs and problems was mainly derived from experiences with a previous eHealth project, rather than a separate phase in the current project. Results from the post-pilot interviews demonstrated that e-Exercise is feasible in the treatment of patients with knee and hip OA. Users considered the usability of e-Exercise as 'good'. Interviews with physical therapists and patients revealed a beneficial impact on the organization process of care. The possibility to stimulate exercises in the home environment and to enhance exercise adherence were cited as major advantages. However, the inability to monitor patients' progress between consultations seemed to be a drawback. Monitoring was therefore added in the latest version of e-Exercise. Another sign that demonstrated the feasibility of e-Exercise were the usage rates. Six of the eight participants completed more than seven of the twelve modules. These usage rates can be reasonable high when compared with a previous study [22]. Results from the pilot study showed small non-significant improvements for the outcomes physical functioning, pain and tiredness. However, patients reported a small decrease in the amount of physical activity. To explore the unexpected decrease of physical activity

levels, a combination of questionnaires and accelerometers will be used in an ongoing randomized controlled trial.

The visit-based method of recruitment was challenging. Over the 10-week enrollment period, we intended to recruit two patients per participating physical therapist. However, only eight eligible patients were recruited by eight physical therapists. Others have reported similar challenges with the recruitment of patients[34-36]. The lack of remuneration may have contributed to the disappointing recruitment rates since there is no financial incentive to adopt e-Exercise in practice. In the contrary, the use of e-Exercise might even lead to reduced revenues per patient. Another possible explanation for the poor recruitment rates is the small pool of eligible OA patients. Primary care data from the Netherlands shows that only 2% of all patients seen in the physical therapy practice have OA [37]. General practitioners, the gatekeepers of the Dutch healthcare system, have a strong influence on the influx of patients into physical therapy setting. General practitioners should therefore be informed of the availability and possibilities of blended interventions. This might influence the referral behavior of general practitioners positively.

Limitations

The findings of the pilot study need to be interpreted in light of several limitations. The small number of participants and the absence of a control group are major limitations of the current study. It is worth noting, however, that this small pilot study (n=8) was not meant to investigate the actual effectiveness of e-Exercise. Moreover, the generalizability might be limited by the self-selected sample in this study. Obviously, included physical therapists are techno-enthusiasts who are more willing to adopt technology in their practice than others.

Implications for future research

Results from this study are valuable to set up a follow-up study to compare e-Exercise with usual physical therapy. We have planned to conduct a larger, adequately powered, randomized controlled trial to investigate the (cost)effectiveness of e-Exercise [38]. The recruitment of patients was a true challenge in this study. We therefore need to pay extra attention to the recruitment process and find additional avenues to increase recruitment rates for the randomized controlled trial. Given the 1:1 recruitment ratio of this pilot study, we should aim to recruit at least 200 physical therapists. We should use strategies to encourage physical therapists to include

participants and we also have planned to engage general practitioners in the recruitment of patients and extent the inclusion period of patients.

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Conflict of interests

The authors declare that they have no competing interests.

References

1. European Commission. Europe's population is getting older. How will this affect us and what should we do about it? 2005. http://europa.eu/rapid/press-release_IP-05-322_en.pdf. Archived at: http://www.webcitation.org/6as6yyFsk
2. The 2009 aging report. European Commision, 2009. http://www.ec.europa.eu/economy_finance/publications/publication14992_en.pdf. Archived at: http://www.webcitation.org/6as6gDqPZ
3. Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, Conaghan PG, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Paediatr Rheumatol. 2013;72(7):1125-35. PMID: 23595142.
4. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis and cartilage. 2010;18(4):476-99. PMID: 20170770.
5. Hootman JM, Macera CA, Ham SA, Helmick CG, Sniezek JE. Physical activity levels among the general US adult population and in adults with and without arthritis. Arthritis Rheum.. 2003;49(1):129-35. PMID: 12579604
6. Medical Subject Headings (MeSH). National Library of Medicine. [cited 2015 Jul 10]. Available from: http://www.ncbi.nlm.nih.gov/mesh/?term=exercise+therapy.Archived at: http://www.webcitation.org/6as6WcGoz
7. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. J Rheumatol.. 2009;36(6):1109-17. PMID: 19447940
8. Dekker J, Peter W, van der Leeden M, Lems WF. Exercise therapy in hip or knee osteoarthritis. Ned Tijdschr Geneeskd. 2011;155(30-31):A3462. PMID: 22085510
9. Barten DJ, Swinkels LC, Dorsman SA, Dekker J, Veenhof C, de Bakker DH. Treatment of hip/knee osteoarthritis in Dutch general practice and physical therapy practice: an observational study. BMC Fam Pract. 2015;16:75. PMID: 26116374
10. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. Patient Educ Couns. 2002;48(2):177-87. PMID: 12401421
11. Kuijpers W, Groen WG, Aaronson NK, van Harten WH. A systematic review of web-based interventions for patient empowerment and physical activity in chronic diseases: relevance for cancer survivors. J Med Internet Res. 2013;15(2):e37. PMID: 23425685
12. Bossen D, Veenhof C, Dekker J, de Bakker D. The Effectiveness of Self-Guided Web-Based Physical Activity Interventions Among Patients with a Chronic Disease: A Systematic Review. J Phys Act Health. 2013. PMID: 23493018

13. Mazieres B, Thevenon A, Coudeyre E, Chevalier X, Revel M, Rannou F. Adherence to, and results of, physical therapy programs in patients with hip or knee osteoarthritis. Development of French clinical practice guidelines. Joint Bone Spine. 2008;75(5):589-96. PMID: 18805033
14. May CR, Finch TL, Cornford J, Exley C, Gately C, Kirk S, et al. Integrating telecare for chronic disease management in the community: what needs to be done? BMC Health Serv Res. 2011;11:131. PMID: 21619596
15. Watson R. European Union leads way on e-health, but obstacles remain. Bmj. 2010;341:c5195. PMID: 20858645
16. Krijgsman J, Peeters J, Burghouts A, Brabers A, Jong Jd, Beenkens F, et al. Op naar meerwaarde! eHealth-monitor 2014. Den Haag en Utrecht: Nictiz en het NIVEL, 2104. http://www.nictiz.nl/module/360/1110/Rapport. Archived at: http://www.webcitation.org/6as6P24mm
17. Fleuren MA, Paulussen TG, Van Dommelen P, Van Buuren S. Towards a measurement instrument for determinants of innovations. Int J Qual Health Care. 2014;26(5):501-10. PMID: 24951511
18. Dunne S, Cummins NM, Hannigan A, Shannon B, Dunne C, Cullen W. A method for the design and development of medical or health care information websites to optimize search engine results page rankings on Google. J Med Internet Res. 2013;15(8):e183. PMID: 23981848
19. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res. 2012;14(6):e152. PMID: 23151820
20. Murray E, Burns J, May C, Finch T, O'Donnell C, Wallace P, et al. Why is it difficult to implement e-health initiatives? A qualitative study. Implement Sci.2011;6:6. PMID: 21244714
21. van Gemert-Pijnen JE, Nijland N, van Limburg M, Ossebaard HC, Kelders SM, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. Med Internet Res. 2011;13(4):e111. PMID: 22155738
22. Bossen D, Buskermolen M, Veenhof C, de Bakker D, Dekker J. Adherence to a web-based physical activity intervention for patients with knee and/or hip osteoarthritis: a mixed method study. Med Internet Res. 2013;15(10):e223. PMID: 24132044
23. Pietrzak E, Cotea C, Pullman S, Nasveld P. Self-management and rehabilitation in osteoarthritis: is there a place for internet-based interventions? Telemed J E Health. 2013;19(10):800-5. PMID: 24003979
24. Bossen D, Veenhof C, Dekker J, de Bakker D. The usability and preliminary effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis. BMC Med Inform Decis Mak. 2013;13:61.
25. Bossen D. Join2move. A web-based physical activity intervention for patients with knee and hip osteoarthritis. PhD [dissertation].Tilburg University; 2014. PMID: 23714120

26. Peter W, Bloo H, Dekker L, Dilling R, Hilberdink W, Kersten C, et al. KNGF-richtlijn Artrose heup-knie. Ned Tijdschr voor Fysiotherapie 2010. http://www.cebp.nl/media/m156.pdf. Archived at: http://www.webcitation.org/6as6A8YXb
27. Veenhof C, Koke AJ, Dekker J, Oostendorp RA, Bijlsma JW, van Tulder MW, et al. Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial. Arthritis Rheum. 2006;55(6):925-34. PMID: 17139639
28. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-49. PMID: 3741515
29. Bangora A, Kortumb P, Millerc J. An Empirical Evaluation of the System Usability Scale. Intl Journal of Human-Computer Interaction. 2008;24:574-94. DOI:10.1080/10447310802205776
30. de Groot IB, Reijman M, Terwee CB, Bierma-Zeinstra S, Favejee MM, Roos E, et al. Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. Osteoarthritis and cartilage. 2009;17(1):132. PMID: 18620874
31. de Groot IB, Favejee MM, Reijman M, Verhaar JA, Terwee CB. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. Health Qual Life Outcomes. 2008;6:16. PMID: 18302729
32. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. Journal of clinical epidemiology. 2003;56(12):1163-9. PMID: 14680666
33. Bangor AK, P.; Miller, J. Determining What Individual SUS Scores Mean: Adding an Adjective Rating Scale Journal of usability studies. 2009;4(3):114-23.
34. Kristjansdottir OB, Fors EA, Eide E, Finset A, van Dulmen S, Wigers SH, et al. Written online situational feedback via mobile phone to support self-management of chronic widespread pain: a usability study of a Web-based intervention. BMC Musculoskelet Disord. 2011;12:51. PMID: 21352516
35. Danaher BG, Seeley JR. Methodological issues in research on web-based behavioral interventions. Ann Behav Med. 2009;38(1):28-39. PMID: 19806416
36. Codagnone CL-VF. Benchmarking Deployment of eHealth among General Practitioners. European Commission, 2013. https://ec.europa.eu/digital-agenda/en/news/benchmarking-deployment-ehealth-among-general-practitioners-2013-smart-20110033. Archived at: http://www.webcitation.org/6as5UZPVN.
37. Leemrijse CJ BJ KM, Verberne LDM, Veenhof C, Swinkels ICS. . Omvang en kenmerken fysiotherapeutische zorg bij patiënten met artrose. Uit: NIVEL Zorgregistraties eerste lijn. http://www.nivel.nl/node/3336. Archived at: http://www.webcitation.org/6as4KtHJb.

38. Kloek CJ, Bossen D, Veenhof C, van Dongen JM, Dekker J, de Bakker DH. Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: study protocol of a randomized controlled trial. BMC Musculoskelet Disord. 2014;15:269. PMID: 25103686

4

Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: study protocol of a randomized controlled trial

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Abstract

Background: Exercise therapy in patients with hip and/or knee osteoarthritis is effective in reducing pain, increasing physical activity and physical functioning, but costly and a burden for the health care budget. A web-based intervention is cheap in comparison to face-to-face exercise therapy and has the advantage of supporting in home exercises because of the 24/7 accessibility. However, the lack of face-to-face contact with a professional is a disadvantage of web-based interventions and is probably one of the reasons for low adherence rates. In order to combine the best of two worlds, we have developed the intervention e-Exercise. In this blended intervention face-to-face contacts with a physical therapist are partially replaced by a web-based exercise intervention. The aim of this study is to investigate the short- (3 months) and long-term (12 months) (cost)-effectiveness of e-Exercise compared to usual care physical therapy. Our hypothesis is that e-Exercise is more effective and cost-effective in increasing physical functioning and physical activity compared to usual care.

Methods/design: This paper presents the protocol of a prospective, single-blinded, multicenter cluster randomized controlled trial. In total, 200 patients with OA of the hip and/or knee will be randomly allocated into either e-Exercise or usual care (physical therapy). E-Exercise is a 12-week intervention, consisting of maximum five face-to-face physical therapy contacts supplemented with a web-based program. The web-based program contains assignments to gradually increase patients' physical activity, strength and stability exercises and information about OA related topics. Primary outcomes are physical activity and physical functioning. Secondary outcomes are health related quality of life, self-perceived effect, pain, tiredness and self-efficacy. All measurements will be performed at baseline, 3 and 12 months after inclusion. Retrospective cost questionnaires will be sent at 3, 6, 9 and 12 months and used for the cost-effectiveness and cost-utility analysis.

Discussion: This study is the first randomized controlled trial in the (cost)-effectiveness of a blended exercise intervention for patients with osteoarthritis of the hip and/or knee. The findings will help to improve the treatment of patients with osteoarthritis.

Trial registration: NTR4224

Background

Osteoarthritis (OA) is worldwide one of the leading causes of pain and disability. Most common affected sites are the hip and knee joints [1]. In the United States, prevalence of knee OA for patients of 45 years or older is 17 percent and prevalence of hip OA 10 percent [2]. In the Netherlands, it is estimated that 312.000 persons suffer from knee OA (19.1/1000) and 238.000 from hip OA (14.5/1000) [3]. Presumably, these prevalence rates are underestimated since these data are solely based on general practice patients' registrations [3]. OA is an age-related disease and besides pain and disability characterized by morning stiffness, reduced range of motion, instability of the joint and loss of health related quality of life [4, 5]. These symptoms induce that people with hip and/or knee OA are physically less active than the general population [6, 7]. In the long term, physical inactivity may lead to functional decline and psychological problems [8, 9].

Exercise therapy is the widely recommended non-pharmacological intervention in patients with hip and/or knee OA [10–13]. Therapeutic exercise, most of the time provided by a physical therapist, can consist of strengthening exercises, functional task-oriented exercises and/or aerobic training [10]. Many studies have shown the effectiveness of exercise therapy on patients' physical functioning in daily life, for example stair climbing, rising from a chair or getting in or out a car [14, 15]. Besides, exercise therapy is effective in reducing patients' levels of pain and increasing their physical activity [14, 15]. Unfortunately, the face-to-face contacts with a physical therapist are costly and a burden for the health care budget. To illustrate, Dutch healthcare costs related to OA were about 1,112 million euro in 2011 [16]. Likewise, the prevalence of hip and knee OA is expected to increase with 52% in 2040, due to the aging population and an increasing number of obese people [3]. In order to regulate OA costs there is a need for more (cost)-effective strategies to manage hip and/or knee OA.

The internet has created new possibilities to combine face-to-face care with online care, called blended healthcare [17]. The partial substitution of a web-based intervention for exercise therapy sessions is hypothesized to result in a (cost)-effective intervention in many ways. In the first place, a blended intervention will result in lower costs since the average number of physical therapy sessions for patients with OA will decrease. A second advantage of a blended intervention is the 24/7 online support for exercises at home. Support in exercises at home is important since adherence to self-directed exercise is a common problem in exercise therapy

[18, 19]. Research highlighted the importance of adherence to exercises at home, since this positively influences treatment effects on pain and physical functioning [19]. Third, a well-designed web-based intervention in which patients' can report their experiences with home exercises provides physical therapists information about patients' individual needs for guidance.

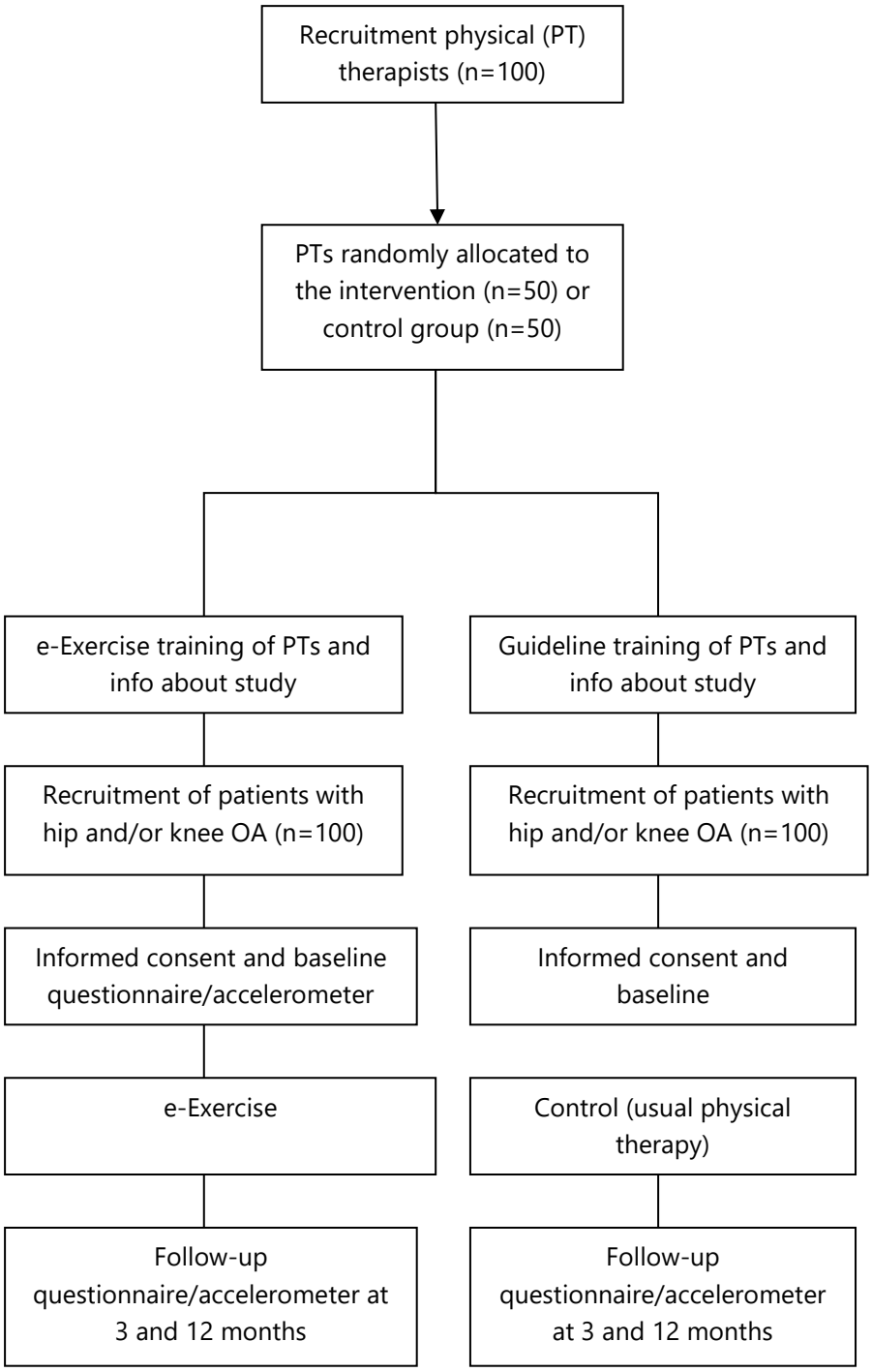
Up till now, previous research in web-based interventions has focused on interventions without human support. Unfortunately, the effects of these interventions are small, especially in the long-term [20–24]. These modest effects can partly be explained by the absence of personal guidance [17]. To illustrate, in the study by Bossen et al. [23], patients cited that the lack of face-to-face contact in a self-guided web-based intervention was an important reason to discontinue. Hence, the combination of a web-based intervention with face-to-face contact has been recommended by several researchers [20, 25, 26]. To date, there are no studies investigating the (cost)-effectiveness of a blended intervention in the physical therapy setting. Therefore, we have developed e-Exercise and have planned to evaluate and implement this blended intervention. The intervention will be based on the Dutch "KNGF guideline OA hip-knee" for physical therapists [10]. The web-based part will be an adapted version of the previously developed and evaluated online PA program Join2Move [24], a web-based intervention for OA patients without support of a physical therapist. The aim of this study is to determine the (cost)-effectiveness of e-Exercise compared to usual care (physical therapy). Our first hypothesis is that e-Exercise will be more effective in terms of increasing PA and improving physical functioning in patients with hip and/or knee OA as compared to usual care. The second hypothesis is that e-Exercise will be cost-effective in comparison to usual care by physical therapists. The research question of this RCT study is: What is the short- (3 months) and long-term (12 months) (cost)-effectiveness of e-Exercise in patients with hip and/or knee OA on PA and physical functioning in comparison to usual care?

Methods/design

Study design

A prospective, single-blinded, multicenter cluster randomized controlled trial (RCT) will be conducted. The study has been approved by the medical ethical committee of the St. Elisabeth hospital Tilburg, the Netherlands (Dutch Trial Register NTR4224). The e-Exercise intervention will be compared with usual care (i.e. physical therapy). A flow diagram of the study protocol is shown in Figure 1.

Figure 1. RCT study procedures



Participants

- *Physical therapists*

A stratified random sample of 800 physical therapy practices in three provinces of the Netherlands (e.g. Noord-Holland, Utrecht and Gelderland) will be invited by letter to participate in the study. Contact information of physical therapy practices will be obtained from the national database for physical therapists of the Netherlands Institute for Health Services Research (NIVEL). Additionally, a recruitment advertisement will be placed in the online newsletter of The Royal Dutch Society for Physical Therapy (KNGF). Each participating physical therapy practice will be asked to enroll one or two physical therapists. The researchers will recruit 100 physical therapists. Inclusion criteria for physical therapists will concern: (i) practicing in primary care, (ii) treating at least six patients with OA of the hip and/or knee each year. Physical therapists practicing in another physical therapy practice participating in the study will be excluded.

- *Patients*

In order to include 200 participants, each physical therapist is requested to recruit about two patients. Since the study of Veenhof et al. [27] showed that recruitment of OA patients in the physical therapy practice is difficult and research has shown that different recruitment strategies do not affect treatment outcomes [28], this study uses various recruitment strategies. First, patients with hip and/or knee OA who visit a physical therapy practice will be invited to participate in the study. Second, recruitment advertisements will be placed in local newspapers. Third, information letters and flyers will be sent to general practitioners. Responders to these articles and flyers will be allocated to the nearest participating physical therapist. Eligibility criteria of patients interested in the study concern: (i) age 40-80 years, (ii) OA of the hip and/or knee according to the clinical criteria of the American College of Rheumatology (ACR) [29]. Exclusion criteria will include: (i) being on a waiting list for a hip or knee replacement surgery, (ii) being contra-indicated for PA without supervision, (iii) being sufficiently physically active according to the physical therapist, (iv) participation in a physical therapy and/or PA program in the last six months, (v) no access to internet, (vi) inability to understand the Dutch language. The diagnostic ACR clinical criteria for knee OA are: knee pain and at least three of the following six criteria: age > 50 years, morning stiffness <30 minutes, crepitation, bony tenderness, bony enlargement and no palpable warmth. Diagnostic ACR clinical criteria for hip OA are: hip pain and hip internal rotation < 15 degree and hip flexion ≤ 115 degree; or hip internal rotation ≥ 15 degree and pain on hip internal rotation and morning

stiffness of the hip ≤ 60 minutes and age > 50 years [29]. Contra-indications for PA will be determined using the adapted Physical Activity Readiness Questionnaire (PAR-Q) [30]. This questionnaire is used to identify patients for whom PA is inappropriate.

Study procedure

Physical therapists willing to participate in the study will be screened on in- and exclusion criteria by a researcher (CK). Cluster randomization will be performed at the level of the participating physical therapy practices that will randomly be assigned to the intervention (e-Exercise) or the control group (usual care) by means of a computer-generated random sequence table. Physical therapists will receive a half day training about e-Exercise and the study procedure (intervention group) or about practicing according to the "KNGF guideline OA hip-knee" [10] and the study procedure (control group). Physical therapists will inform eligible patients about the study and screen them on in- and exclusion criteria. All suitable patients will be stimulated to contact the research team by telephone, e-mail or reply card. After an informative phone call with one of the researchers (CK or DB), interested patients will receive a letter about the trial and a request to complete an informed consent form. Patients recruited by the additional recruitment strategies (i.e. advertisements in newspapers and flyers from the general practitioner) will be informed by the researchers before they visit their physical therapist. Physical therapists in both groups will be asked to record the content of their treatment on a registration form. During the study period, both patient groups will continue their medication and usual care managed by other caregivers.

Blinding

In this single-blind study , the physical therapists are not blinded since they will treat patients according to the randomization. The researchers will be blinded to group allocation until completion of the statistical analyses. Participants will be assigned to a unique digital trial code to ensure that treatment outcome measurement and statistical analysis will be performed blind to treatment allocation. Patient information will be stored in a separate database.

Interventions

- *e-Exercise*

The 3-month program e-Exercise is based on the Dutch guideline for physical therapists (10) and is a combination of (i) maximum five face-to-face sessions with a physical therapist, and (ii) a web-based PA intervention. Table 1 provides an overview of the program content of e-Exercise.

Table 1. Description e-Exercise intervention

Intake	Physical therapist	Anamnesis and physical examination Assessment in- and exclusion criteria Providing information about osteoarthritis, e-Exercise and study Scheduling a follow-up appointment for week 1
	Patient	Reading patient information letter Signing an informed consent Completing baseline measurement
Start e-Exercise		
Week 1	Physical therapist	Providing Information about osteoarthritis and e-Exercise Providing information about the 3-day baseline self-test Instruction of the 4 stability/mobility exercises
	Physical therapist & Patient	Registration on website to participate in e-Exercise Online selection of central activity and 4 stability/mobility exercises Providing information about the 3-day baseline self-test Scheduling a follow-up appointment for week 2
	Patient	Signing online treatment agreement Performance of a 3-day baseline test Performance of 4 stability/mobility exercises
Week 2	Physical therapist	Providing information about physical activity and pain
	Physical therapist & Patient	Evaluation results from the 3-day self-test Determining short-term goal Discussing the gradual increase of the selected activity Evaluation stability/mobility exercises Scheduling a follow-up appointment for week 6
	Patient	Performance of online module 1, each module consists of: - Gradually increase selected activity - Video home exercises - Video/text self-management themes
Week 3-5	Patient	Online modules 2-4
Week 6		Evaluation online modules 1-4
	Physical therapist & Patient	Discussing the upcoming steps and weeks Evaluation stability/mobility exercises
	Patient	If necessary, scheduling an additional treatment between week 7-11

		Scheduling a follow-up appointment for week 12 Online module 5
Week 7-11	Patient	Online modules 5-10
Week 12	Physical therapist	Discussing long-term goals Support to maintain a physically active lifestyle
	Patient	Online module 11

A) Face-to-face sessions

During the first face-to-face session (week 1), physical therapists will provide information about OA, the importance of PA and the relation of PA with pain. Together with their physical therapist, patients choose one physical activity, for example, walking, cycling or swimming. Physical therapists select and instruct four strength & stability exercises. Patients are instructed to perform the first module of the web-based part of the intervention. In this module, the patients will be asked to determine their physical load ability based on a 3-day self-test. The second assignment is the execution of strength & stability exercises. During the second face-to-face session (week 2), patients' physical load ability will be discussed and personal short and long-term goals will be formulated according to the principles of Goal Setting, which is based on the idea that goals can affect action [31]. The strength & stability exercises will be trained again. After the second appointment, patients are instructed to perform four online modules for the duration of four weeks. In week 6, a third face-to-face treatment takes place. Patients' progress will be discussed, based on an online report which is automatically sent to the physical therapists. This report contains a summary of website-visits and patients' experiences with the strength and stability exercises. After the third face-to-face treatment, patients perform another six online modules. The final face-to-face appointment will take place in week 12. In this final treatment physical therapists will support and encourage patients to maintain a physically active lifestyle. If necessary, physical therapists can plan an additional fifth session. This optional session is especially for patients who are less capable to perform unsupervised physical exercises. Physical therapists are recommended to treat patients according to the e-Exercise protocol, however, with respect to their clinical competences, physical therapist are free to deviate from the protocol.

B) Web-based PA intervention

The web-based part of e-Exercise is based on the web-based intervention Join2move [32] and consists of three topics: (i) Graded Activity; the duration of patients' chosen physical activity (e.g. walking, cycling, swimming) will gradually be increased until

patients reach their personal short-term goal. (ii) Strength & Stability; each module contains two exercises. The number of repeats will gradually increase per 4 weeks. (iii) Information; topics about OA, PA, aetiology of OA, pain-management, weight-management, motivation, medication and social influences on pain will be discussed. Automatic emails are generated if participants do not visit the website once a week.

Usual care

Patients in the control group will receive usual care. For the current study, usual care is defined as any treatment provided by physical therapists. Physical therapists will be encouraged to practice according to the "KNGF guideline OA Hip-Knee" [10]. According to the guideline, the physical therapy treatment comprises the same three elements as e-Exercise: (i) information, (ii) physical exercise and (iii) strength and stability exercises. Practical content considerations can be made by therapists themselves. The number of sessions will differ per patient. From the NIVEL Primary Care Database we know that the average number of physical therapy sessions in patients with OA is 17.1 [33].

Measurements

Three online questionnaires (0, 3 and 12 months) will be used for data collection. Participants will receive an accelerometer for the measurement of objective PA (0, 3 and 12 months). The physical therapists will measure physical functioning objectively at baseline and post-treatment (3 months). In addition, online cost questionnaires will be sent (0, 3, 6, 9 and 12 months). We offer no financial incentives to complete questionnaires or to wear accelerometers. Table 2 gives a summary of all measures that will be collected.

Table 2. Summary of measures to be collected

Primary Outcome measures	**Data collection Instrument**	**Collection Points**
Physical functioning	HOOS and/or KOOS	0, 3, 12 months
	Timed "Up & Go" test	0, 3 months,
Physical activity	SQUASH	0, 3, 12 months
	ActiGraph GT3X tri-axial accelerometers	0, 3, 12 months

Secondary Outcome measures		
OA related costs	Cost questionnaire	3, 6, 9, 12 months
Health Related Quality of Life	EQ-5D	0, 3, 12 months
Self-perceived effect	7-point Likert Scale	3, 12 months
Pain	NRS	0, 3, 12 months
Tiredness	NRS	0, 3, 12 months
Self-efficacy	Arthritis Self-efficacy Scale	0, 3, 12 months
Other measures		
Age	Questionnaire	0 months
Sex	Questionnaire	0 months
Height	Questionnaire	0 months
Weight	Questionnaire	0, 3, 12 months
Educational level	Questionnaire	0 months
Location of OA	Questionnaire	0 months
Disease duration	Questionnaire	0 months
Presence of comorbidities	Questionnaire	0 months
Adherence	Completed web-modules	During intervention

Primary outcome measures

-*Physical functioning* will be assessed subjectively with the subscale 'function in daily living' of the Hip OA Outcome Score (HOOS) [34] and/or the Knee Injury and OA Outcome Score (KOOS) [35], depending their affected joint. The HOOS and the KOOS assess 5 indicators: pain, symptoms, physical function, sport and recreation function and quality of life, in relation to patients' hip or knee complaints. Each indicator is scored on a 5-point Likert scale (0=extreme symptoms/problems; 4=no symptoms/problems). A lower score indicates respectively more pain, symptoms, problems in physical functions, problems in sports and recreation activities and a lower quality of life. In addition, objectively physical functioning will be measured by the physical therapist with timed "Up & Go" test (TUG) [36]. In this easily administered test, the patient is requested to rise from an arm chair, walk three meters, turn, walk back again and sit down. Meanwhile, the physical therapist observes the patient and measures the time.

-*Physical activity* will be measured subjectively with the SQUASH [37]. The questionnaire measures habitual PA during a normal week over the last few months. The total score is expressed as minutes per week. In addition, data can also be analysed according to whether the activity is light, moderate or vigorous. Objective PA will be measured through ActiGraph GT3X tri-axial accelerometers. Participants will be instructed to wear the monitor on a belt around their waist for five executive days [38], except during sleeping, showering or swimming. In addition, participants will be requested to fill out a short activity diary. This diary contains questions about wearing time, unusual activities and reasons for device removal. When accelerometers and diaries are returned by post, data can be downloaded, processed and subsequently analyzed. The widely accepted PA thresholds of Freedson et al.[39] will be used: 0-99 counts for sedentary activities, 100-1951 for light PA, 1952-5724 moderate PA, 5725-9498 for vigorous PA and 9499- max for very vigorous activities. The total time spent in light, moderate and vigorous PA will be summed and subsequently divided by the number of days worn to compute the daily average time spent in total activity. For analysis, data will be recorded at 1-minute intervals.

Secondary outcome measures

-Information on the patients' healthcare utilization, (unpaid) productivity losses, and sports costs due to OA will be gathered with four retrospective 3-month cost questionnaires that cover the full 12-months of the program. Healthcare utilization due to OA comprises of visits to a physical therapist, general practitioner, massage therapist, alternative therapist, medical specialist, as well as informal care, hospital care, the use of both prescribed and over the counter drugs and medical devices. Healthcare utilization will be valued using Dutch standards costs [40]. If these are unavailable, prices reported by professional organizations will be used. Medication use will be valued using unit prices derived from the "Royal Dutch Society of Pharmacy" [41]. Unpaid productivity losses will be valued in accordance with the "Dutch Manual of Costing" [40]. Paid productivity losses comprise of both sickness absence and presenteeism (i.e. reduced productivity while at work). Sickness absence will be valued in accordance with the "Friction Cost Approach" (FCA), with a friction period of 23 weeks and an elasticity of 0.8, using age- and gender-specific price weights [40]. The FCA assumes that production losses are confined to the "friction period" (i.e. time needed to replace a sick worker) and that a 100 percent loss of labour input corresponds with an 80 percent reduction in productivity (i.e. an

elasticity of 0.8) [42]. The participants' level of presenteeism will be measured using the "World Health Organization – Work Performance Questionnaire" as well as the "Productivity and Disease Questionnaire", and valued using age- and gender-specific price weights [40, 43–45]. The cost of the e-Exercise intervention will be estimated using a bottom-up micro-costing approach [46].

-*Health Related Quality of Life* will be measured with the EuroQol-5D (EQ-5D) [47]. This questionnaire comprises of 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Per dimension, patients are asked to indicate their health state on a 3-point Likert scale (1=no problems; 3=extreme problems). The questionnaire differentiates between 245 health states. These health states will be converted into utility units by using the Dutch tariff [48]. Utilities represent quality of life into a single number that ranges from 0 (death) to 1(full health). Quality adjusted life years (QALY's) will subsequently be calculated by multiplying the participants' health state utilities by the duration of time they spent in that particular health state.

-*Self-perceived effect* will be assessed by a single question about the degree of change in osteoarthritis symptoms since their previous assessment. Patients will score this effect on a 7-point Likert scale (1=much worse; 7= much better). A higher score indicates a better self-perceived effect.

-*Pain and tiredness* will be measured with a numeric rating scale (NRS; 0 is no pain/not tired and 10 is worst possible pain/very tired). Furthermore, pain will be assessed with the pain subscale of the HOOS and/or the KOOS [34, 35].

-*Self-efficacy* will be measured by the Arthritis Self-efficacy Scale (ASES) [49]. Subscales for the ASES are pain, symptoms and physical functioning, the 19 statements can be scored on a 5 point-Likert scale (1=fully disagree; 5=fully agree). A higher score indicates more self-efficacy.

Other measures

-*Adherence* will be measured objectively by quantitative data about usage which is automatically stored on the backend of the website. Usage is defined as completed week modules. Subjective adherence is measured by a questionnaire about patients' adherence to the Graded Activity modules and Strength & Stability exercises (frequency and intensity).

-*Content of physical therapy sessions* will be measured trough registrations forms, developed by the researchers. The registrations forms collect information about the adherence and content of the sessions.

-*Patient characteristics* i.e. age, sex, height, weight, educational level, location of OA, disease duration and the presence of comorbidities will be assessed at baseline.

Sample Size

The power calculation is based on a previous multicenter cluster RCT study among patients with hip and/or knee OA [27] and performed for the primary outcome measure physical functioning (power 0.8; alpha 0.05). In this current RCT study, the target sample size will be 200 participants to detect a small to medium effect size (0.2-0.4) in physical functioning at a 2-sided significance level of 0.05 and anticipating on maximum loss to follow up of 20%.

Statistical analysis

Descriptive statistics will be used to describe the main characteristics of the study population and to explore baseline comparability (frequencies, t-test, Chi-square). Primary baseline variables between the response and the non-response group will be performed in order to investigate selective attrition. The primary analysis will be performed according to the intention-to-treat principle. In addition, per-protocol analyses that include only adherent patients of the intervention group and the entire control group will be performed. For all analyses, a two-tailed significance level of $p < 0.05$ is considered to be statistically significant. All analyses will be carried out with the statistical package STATA.

Effectiveness

To determine the short (baseline-3 months) and long term (baseline -12 months) effectiveness of e-Exercise on primary and secondary outcomes, multi-level modelling of repeated measures will be performed controlling for baseline values and relevant confounders such as age, OA location and gender. With multilevel modelling of repeated measures it is possible to correct on one side for dependency of observations within subjects and, on the other side, to take into account the variation between physical therapists [50, 51]. The three-level hierarchy will exist of repeated

measurements (level 1), nested within patients (level 2), nested within physical therapists (level 3).

Economic evaluation

A cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA) will be performed from the societal and the healthcare perspective. From the societal perspective all costs will be taken into account irrespective of who pays or benefits, whereas solely those borne by the healthcare sector will be included when the healthcare perspective is applied [40]. For the CUA and CEA, missing cost and effect data will be imputed using multiple imputation [52]. The results of the imputed datasets will be pooled using Rubin's rules [52]. In order to account for the highly skewed nature of cost data, bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% confidence intervals around the mean differences in costs between the study groups. Incremental Cost-Effectiveness Ratios (ICERs) will subsequently be calculated by dividing the differences in costs between study groups by their respective differences in QALYs for the CUA. For the CEA, ICERs will be calculated by dividing the difference in costs by the difference in PA and physical functioning. The uncertainty surrounding the ICERs will be graphically illustrated by plotting bootstrapped incremental cost-effect pairs on cost-effectiveness planes [53]. Moreover, cost-effectiveness acceptability curves (CEACs) will be constructed to provide a summary measure of the joint uncertainty of costs and effects. CEACs indicate the probability of the e-Exercise intervention being cost-effective in comparison to usual care at different willingness-to-pay values [54]. To test the robustness of the study results, several sensitivity analyses will be performed.

Timeline

Recruitment of physical therapy practices begun in May 2014. The trial will start in September 2014. Until December 2014 patients are able to enrol the program. The follow-up will last until December 2015. Analysis of the data will start in January 2016.

Discussion

Scarce health resources and a growing number of patients with OA of the hip and/or knee require cost-effective treatment strategies in patients with OA. The presented RCT will study the (cost)-effectiveness of e-Exercise, an intervention in which face-to-face exercise therapy sessions are partly replaced by a web-based PA intervention. This study is, as far as we know, the first RCT that investigates the (cost)-effectiveness of a blended intervention in patients with knee and hip OA. Therefore, this RCT will provide internationally relevant results regarding the short- and long-term (cost)-effectiveness of an exercise therapy intervention that incorporates modern technologies.

The primary goal of e-Exercise is to improve levels of PA and physical functioning in a cost-effective manner. In addition to our outcome measurements, e-Exercise might have several other benefits beyond the primary scope of this study. First, a number of studies showed that exercise therapy may help to postpone joint replacement surgery [55–57]. For example, in the study of Pisters et al.[56], a 60 month follow-up showed that 20% of the patients from the exercise therapy group underwent total hip surgery, compared to 45% of the patients from the usual care group. The exercise therapy consisted of a 12-week Behavioral Graded Activity treatment [27], which is also incorporated in e-Exercise. Second, it is known that most people with OA of the hip and/or knee suffer from at least one comorbidity, such as cardiovascular diseases and diabetes mellitus. It is presumable that improving PA contribute to patients' general health status, since PA has several health advantages for these comorbidities [58].

Although the study is well-considered, we take into account potential operational issues. First challenge is the recruitment of sufficient numbers of physical therapists. Since e-Exercise is characterized by fewer physical therapy sessions, physical therapists will receive less reimbursement from health insurances compared to usual care. To deal with this challenge, accreditation points for participating physical therapists will be supplied in order to make study participation more attractive. Another incentive is that physical therapists keep their access to the website after the study is finished. The second challenge is the non-usage of the web-based part of e-Exercise. Previous studies have indicated that participants in online interventions are less motivated and feel less pressure to continue compared to traditional face-to-face interventions [59]. However, in order to stimulate website usage, we will incorporate email reminders into the program. But most importantly, since this study concerns a

blended intervention, which is a combination of face-to-face contact with e-health, e-Exercise is expected to maximize adherence compared to self-guided internet interventions [17, 23].

There are several strengths in the design of this study. First, we elaborate on the study results of Joint2Move [24]. This intervention showed to be an effective web-based intervention for patients with OA of the hip and/or knee and will be the fundament for e-Exercise. Second, the primary outcome measurements PA and physical functioning will be measured subjectively (questionnaires) and objectively by means of accelerometers and the timed "Up & Go test". Third, the 12-month follow-up will result in data about long-term effectiveness. The last strength is that e-Exercise will be evaluated in daily physical therapy practice, the setting in which the intervention will be implemented after the presented trial. Therefore, user experiences can be used in order to improve e-Exercise and to facilitate implementation.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

All authors (CK, DB, CV, JvD, JD and DdB) made substantial contributions to the conception of the described protocol. Specifically, CK and DB drafted the manuscript. CV was responsible for the design of the study protocol and coordination of the project. JvD contributed to the design of the economic evaluation. CV, JD and DdB critically revised the manuscript for important intellectual content. All authors have contributed to the final manuscript and have approved it.

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References

1. Issa SN, Sharma L: Epidemiology of osteoarthritis: An update. *Curr Rheumatol Rep* 2006, 8:7–15.
2. Suri P, Morgenroth DC, Hunter DJ: Epidemiology of osteoarthritis and associated comorbidities. *PM R* 2012, 4(5 Suppl):S10–9.
3. Poos M, Gommer A, Uiters E, Zantinge E: Volksgezondheid Toekomst Verkenning. *RIVM, Bilthoven* 2009.
4. Zhang Y, Jordan JM: Epidemiology of osteoarthritis. *Clin Geriatr Med* 2010, 26:355–69.
5. Salaffi F, Carotti M, Stancati A, Grassi W: Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. *Aging Clin Exp Res* 2005, 17:255–63.
6. De Groot IB, Bussmann JB, Stam HJ, Verhaar J a N: Actual everyday physical activity in patients with end-stage hip or knee osteoarthritis compared with healthy controls. *Osteoarthritis Cartilage* 2008, 16:436–42.
7. Rosemann T, Kuehlein T, Laux G, Szecsenyi J: Factors associated with physical activity of patients with osteoarthritis of the lower limb. *J Eval Clin Pract* 2008, 14:288–93.
8. Dunlop DD, Semanik P, Song J, Manheim LM, Shih V, Chang RW: Risk factors for functional decline in older adults with arthritis. *Arthritis Rheum* 2005, 52:1274–82.
9. Pisters MF, Veenhof C, van Dijk GM, Heymans MW, Twisk JWR, Dekker J: The course of limitations in activities over 5 years in patients with knee and hip osteoarthritis with moderate functional limitations: risk factors for future functional decline. *Osteoarthritis Cartilage* 2012, 20:503–10.
10. Peter WFH, Jansen MJ, Bloo H, Dekker-Bakker LMMCJ, Dilling RG, Hilberdink WKHA, Kersten-Smit C, Rooij M de, Veenhof C, Vermeulen HM, Vos I de, Vlieland TPMV: KNGF-richtlijn Artrose heup-knie. *Ned Tijdschr voor Fysiother* 2010, 1.
11. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P: OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008, 16:137–62.
12. Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther K-P, Hauselmann HJ, Herrero-Beaumont G, Jordan K, Kaklamanis P, Leeb B, Lequesne M, Lohmander S, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Swoboda B, Varatojo R, Verbruggen G, Zimmermann-Gorska I, Dougados M: EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2005, 64:669–81.
13. Jordan KM: EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003, 62:1145–1155.
14. Fransen M, McConnell S: Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. *J Rheumatol* 2009, 36:1109–17.
15. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S: Exercise for osteoarthritis of the hip. *Cochrane database Syst Rev* 2014, 4:CD007912.
16. Kosten van ziekten in Nederland 2011. [www.kostenvanziekten.nl]

17. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JEWC: Persuasive system design does matter: a systematic review of adherence to web-based interventions. *J Med Internet Res* 2012, 14:e152.
18. Pisters MF, Veenhof C, van Meeteren NLU, Ostelo RW, de Bakker DH, Schellevis FG, Dekker J: Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. *Arthritis Rheum* 2007, 57:1245–53.
19. Mazières B, Thevenon A, Coudeyre E, Chevalier X, Revel M, Rannou F: Adherence to, and results of, physical therapy programs in patients with hip or knee osteoarthritis. Development of French clinical practice guidelines. *Joint Bone Spine* 2008, 75:589–96.
20. Vandelanotte C, Spathonis KM, Eakin EG, Owen N: Website-delivered physical activity interventions a review of the literature. *Am J Prev Med* 2007, 33:54–64.
21. Davies CA, Spence JC, Vandelanotte C, Caperchione CM, Mummery WK: Meta-analysis of internet-delivered interventions to increase physical activity levels. *Int J Behav Nutr Phys Act* 2012, 9:52.
22. Van Den Berg MH, Schoones JW, Vliet Vlieland TP: Internet-Based Physical Activity Interventions: A Systematic Review of the Literature. *J Med Internet Res* 2007, 9:e26.
23. Bossen D, Buskermolen M, Veenhof C, de Bakker D, Dekker J: Adherence to a Web-Based Physical Activity Intervention for Patients With Knee and/or Hip Osteoarthritis: A Mixed Method Study. *J Med Internet Res* 2013, 15:e223.
24. Bossen D, Veenhof C, Van Beek KE, Spreeuwenberg PM, Dekker J, De Bakker DH: Effectiveness of a Web-Based Physical Activity Intervention in Patients With Knee and/or Hip Osteoarthritis: Randomized Controlled Trial. *J Med Internet Res* 2013, 15:e257.
25. Brouwer W, Kroeze W, Crutzen R, de Nooijer J, de Vries NK, Brug J, Oenema A: Which intervention characteristics are related to more exposure to internet-delivered healthy lifestyle promotion interventions? A systematic review. *J Med Internet Res* 2011, 13:e2.
26. Van Den Berg MH, Ronday HK, Peeters AJ, Voogt-van Der Harst EM, Munneke M, Breedveld FC, Vliet Vlieland TPM: Engagement and satisfaction with an Internet-based physical activity intervention in patients with rheumatoid arthritis. *Rheumatol Oxford Engl* 2007, 49:545–552.
27. Veenhof C, Köke AJA, Dekker J, Oostendorp RA, Bijlsma JWJ, Van Tulder MW, Van Den Ende CHM: Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial. *Arthritis Rheum* 2006, 55:925–934.
28. Veenhof C, Dekker J, Bijlsma JWJ, van den Ende CHM: Influence of various recruitment strategies on the study population and outcome of a randomized controlled trial involving patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2005, 53:375–82.
29. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986, 29:1039–49.
30. Thomas S, Reading J, Shephard RJ: Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Can J Sport Sci* 1992, 17:338–45.
31. Locke EA, Latham GP: Building a practically useful theory of goal setting and task motivation. A 35-year odyssey. *Am Psychol* 2002, 57:705–17.

32. Bossen D, Veenhof C, Dekker J, de Bakker D: The effectiveness of self-guided web-based physical activity interventions among patients with a chronic disease: a systematic review. *J Phys Act Health* 2014, 11:665–77.
33. Amount of treatment of the physiotherapist for patients with osteoarthritis. From: NIVEL Primary Care Database [NIVEL Zorgregistraties eerste lijn] [www.nivel.nl/node/3336]
34. De Groot IB, Reijman M, Terwee CB, Bierma-Zeinstra SMA, Favejee M, Roos EM, Verhaar JAN: Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthritis Cartilage* 2007, 15:104–9.
35. De Groot IB, Favejee MM, Reijman M, Verhaar JAN, Terwee CB: The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health Qual Life Outcomes* 2008, 6:16.
36. Podsiadlo D, Richardson S: The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991, 39:142–8.
37. Wendel-Vos GCW, Schuit AJ, Saris WHM, Kromhout D: Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003, 56:1163–9.
38. Hart TL, Swartz AM, Cashin SE, Strath SJ: How many days of monitoring predict physical activity and sedentary behaviour in older adults? *Int J Behav Nutr Phys Act* 2011, 8:62.
39. Freedson PS, Melanson E, Sirard J: Calibration of the Computer Science and Applications, Inc. accelerometer. *Med Sci Sports Exerc* 1998, 30:777–81.
40. Oostenbrink J, Koopmanschap M, Van Rutten F: *Handleiding Voor Kostenonderzoek. Methoden En Richtlijnprijzen Voor Economische Evaluaties in de Gezondheidszorg. [Handbook for Cost Studies, Methods and Guidelines for Economic Evaluation in Health Care]*. The Hague, the Netherlands: Health Care Insurance Council; 2000.
41. Z-index. G-Standard. *Z-Index BV, Den Haag, Netherlands https//www.z-index.nl/g-standaard* 2009.
42. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L: The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995, 14:171–89.
43. Koopmanschap M, Meeding W, Evers S, Severens J, Burdorf A, Brouwer W: *Handleiding Voor Het Gebruik van PRODISQ Versie 2.1 [Manual for the Use of PRODISQ Version 2.1]*. Erasmus MC Rotterdam - Instituut voor Medical Technology Assessment, Instituut Maatschappelijke Gezondheidszorg, Universiteit van Maastricht – Beleid Economie en Organisatie van de Zorg; 2004.
44. Kessler RC, Ames M, Hymel PA, Loeppke R, McKenas DK, Richling DE, Stang PE, Ustun TB: Using the World Health Organization Health and Work Performance Questionnaire (HPQ) to evaluate the indirect workplace costs of illness. *J Occup Environ Med* 2004, 46(6 Suppl):S23–37.
45. Kessler RC, Barber C, Beck A, Berglund P, Cleary PD, McKenas D, Pronk N, Simon G, Stang P, Ustun TB, Wang P: The World Health Organization Health and Work Performance Questionnaire (HPQ). *J Occup Environ Med* 2003, 45:156–74.
46. Frick KD: Microcosting quantity data collection methods. *Med Care* 2009, 47(7 Suppl 1):S76–81.
47. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990, 16:199–208.

48. Lamers LM, Stalmeier PFM, McDonnell J, Krabbe PFM, van Busschbach JJ: [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. *Ned Tijdschr Geneeskd* 2005, 149:1574–8.
49. Taal E, Riemsma RP, Brus HL, Seydel ER, Rasker JJ, Wiegman O: Group education for patients with rheumatoid arthritis. *Patient Educ Couns* 1993, 20:177–87.
50. Raudenbush SW, Bryk AS: *Hierarchical Linear Models: Applications and Data Analysis Methods (Advanced Quantitative Techniques in the Social Sciences)*. 2nd edition. Newbury Park: Sage Publications; 2001.
51. Goldstein H: *Multilevel Statistical Models*. 4th edition. New York: Halsted Press; 2010.
52. Rubin D: *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons; 1987.
53. Black WC: The CE plane: a graphic representation of cost-effectiveness. *Med Decis Making* 1990, 10:212–4.
54. Fenwick E, O'Brien BJ, Briggs A: Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. *Health Econ* 2004, 13:405–15.
55. Smink AJ, van den Ende CHM, Vliet Vlieland TPM, Swierstra BA, Kortland JH, Bijlsma JWJ, Voorn TB, Schers HJ, Bierma-Zeinstra SMA, Dekker J: "Beating osteoARThritis": development of a stepped care strategy to optimize utilization and timing of non-surgical treatment modalities for patients with hip or knee osteoarthritis. *Clin Rheumatol* 2011, 30:1623–9.
56. Pisters MF, Veenhof C, Schellevis FG, De Bakker DH, Dekker J: Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized controlled trial comparing two different physical therapy interventions. *Osteoarthr Cartil OARS Osteoarthr Res Soc* 2010, 18:1019–26.
57. Svege I, Nordsletten L, Fernandes L, Risberg MA: Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: a long-term follow-up of a randomised trial. *Ann Rheum Dis* 2013.
58. Eckstein F, Hudelmaier M, Putz R: The effects of exercise on human articular cartilage. *J Anat* 2006, 208:491–512.
59. Gunther Eysenbach: The law of Attrition. *J Med Internet Res* 2005, 7:13.

5

Effectiveness of a blended physiotherapy intervention in patients with hip and/or knee osteoarthritis: a cluster randomized controlled trial

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Abstract

Background: Integrating physiotherapy sessions and an online application might support patients with hip/knee osteoarthritis in taking an active role in the management of their chronic condition and may reduce the number of physiotherapy sessions.
Objective: To investigate the short- and long-term effectiveness of e-Exercise compared to usual physiotherapy in patients with hip/knee osteoarthritis.
Design: A prospective, single-blinded, multicenter, superiority, cluster randomized controlled trial.
Setting: 143 primary care physiotherapy practices.
Patients: 208 patients with hip and/or knee osteoarthritis, aged 40-80 years**.**
Intervention: E-Exercise is a 3-month intervention in which about five face-to-face physiotherapy sessions are integrated with an online application consisting graded activity, exercise and information modules. Usual physiotherapy was according to the Dutch physiotherapy guideline.
Measurements: Primary patient-outcomes, measured at baseline, after 3 and 12 months, were physical functioning and free-living physical activity. Secondary outcome measures were pain, tiredness, quality of life, self-efficacy and the number of physiotherapy sessions.
Results: The e-Exercise group (N=109) received on average 5 face-to face sessions, the usual physiotherapy group (N=99) 12. No significant differences in primary outcomes between e-Exercise and usual physiotherapy were found. Within group analyses showed for both groups a significant improvement in physical functioning. After 3 months, the e-Exercise group reported an increase in physical activity, however, no objectively measured physical activity differences were found. With respect to the secondary outcomes, after 12 months sedentary behavior significantly increased in the e-Exercise group compared to usual physiotherapy. Within both groups there were significant improvements for pain, tiredness, quality of life and self-efficacy.
Limitations: The response rate at 12 months was 65%.
Conclusions: The blended intervention e-Exercise was not more effective than usual physiotherapy in patients with hip/knee osteoarthritis.

Introduction

Osteoarthritis (OA) is the most common chronic condition of the joints [1]. Prevalence of this rheumatic disease increases with age and mostly affects the hip and knee. Based on radiographic diagnosis 5-15% of people of 55 years and older are affected with hip OA [2] and 10-30% with knee OA [3]. Due to the aging population and the growing number of people with obesity the prevalence of OA is expected to increase [1], with an extra demand on health services as a consequence. People suffering from OA of the hip and/or knee experience pain, stiffness, crepitation, reduced range of motion and sometimes inflammation [4]. Daily activities become more problematic and in combination with psychological factors people are at risk for a negative spiral of inactivity, resulting in muscle weakness and even more limitations in daily activities [5].

The most recommended non-surgical and non-pharmacological treatment for patients with OA is physiotherapy [6, 7]. Physiotherapy consisting of muscle strengthening exercises, aerobic exercises and patient education has shown to be effective in reducing levels of pain and improving physical functioning [2, 3]. One of the approaches to increase activity levels among patients with OA is graded activity [8]. However, the downside of face-to-face physiotherapy sessions is that they are costly. With the increasing prevalence of OA, there is a need for (cost-) effective interventions to manage hip and knee OA.

Technological developments provide new solutions for guiding patients to a physically active lifestyle. For example internet-based interventions, which are accessible at any time and place, might have the possibility to replace part of physiotherapists' face-to-face guidance. In literature, the integration of therapeutic guidance and online care is called "blended care" [9]. One of the main advantages of blended care is that the online part can support patients 24/7 in exercise at home. Well-designed online applications can be used as a medium for many behavior change techniques like goal setting assignments, monitoring of outcomes and behavior, instruction and providing information [10, 11]. Next, patients' online evaluations of home assignments can provide valuable information for physiotherapists about patients' individual needs for guidance. Whereas online self-guided interventions oftentimes struggle with high rates of non-usage, the combination with therapeutic guidance is seen as highly promising in terms of usage, effectiveness and cost-effectiveness [12, 13].

Given the high potential of blended interventions for OA patients we developed the intervention e-Exercise [14]. In e-Exercise, physiotherapy sessions are combined with an online application to improve free-living physical activity in patients with hip and/or knee OA. The integration of physiotherapy sessions and an online application might replace part of the therapeutic guidance. Next to this, we expect that the online application can support patients in taking an active role in the management of their chronic condition in daily living by providing access to a 24/7 available behavior-change application. Therefore, we hypothesize e-Exercise to be more effective than usual physiotherapy. The aim of this multicenter superiority cluster randomized controlled trial study was to investigate the short- and long-term effectiveness on physical functioning and free-living physical activity of e-Exercise compared to usual physiotherapy in patients with OA of hip and/or knee.

Methods

Design Overview

A prospective, single-blinded, multicenter, superiority, cluster randomized controlled trial (RCT) was conducted. From May 2014 till August 2014 248 physiotherapist, working in 143 primary care physiotherapy practices, were recruited. Half of the physiotherapists were instructed to treat patients with hip and/or knee OA according to the e-Exercise protocol and the other half of the physiotherapist were instructed to treat patients as usual. Enrollment of patients started in September 2014 and ended in March 2015. Study outcomes were assessed at baseline, 3 and 12 months. The study design and protocol were approved by the Medical Ethical Committee of the St. Elisabeth hospital Tilburg, the Netherlands (Dutch Trial Register NTR4224). Since we wanted to prevent for less accurate answers or non-responding, we deleted some secondary outcome measures (i.e. motivation, locus of control, depression and anxiety, subjective adherence, and self-management) which are listed in the trial register, and executed the study as described in the study protocol [15]. The trial is reported according to the CONSORT Cluster Trial checklist (Appendix 1).

Setting and Randomization

Physiotherapists were recruited in two ways. First, an invitational letter was send to a random sample of 800 physiotherapy practices in three provinces of the Netherlands. Second, an advertisement was placed in the online newsletter of The Royal Dutch Society for Physiotherapy (KNGF). Physiotherapy practices could participate with one or two physiotherapists. Inclusion criteria for physiotherapist were: (1) practicing in

primary care; and (2) treating at least six patients with OA of the hip and/or knee per year. Physiotherapist were cluster-randomized on the level of physiotherapy practice using a computer-generated sequence table. To avoid contamination across physiotherapists working in the same practice, randomization of the 248 eligible physiotherapists took place at the level of the physiotherapy practice using an 1:1 allocation ratio. By e-mail they were informed about their allocation. Physiotherapists were not blinded, since they had to treat according to the randomization. The main investigator (CK) was blinded to group assignment until completion of statistical analyses. Participants were assigned to a unique trial code. Patient information was stored separately.

All physiotherapists were invited for a half-day training. Physiotherapists allocated to e-Exercise (N=123) were instructed about the study procedure and how to use the online application. Physiotherapists allocated to "usual physiotherapy" (N=125) were also instructed on the study procedure and received a presentation about the Dutch OA guideline [16]. Physiotherapists who followed the training and recruited at least two patients received accreditation points for the Dutch physiotherapy registration. Physiotherapists from the "usual physiotherapy" group received e-Exercise log in codes and an invitation for an instruction-session after the study period.

Participants

Patients with hip and/or knee OA visiting a participating physiotherapist were invited to participate in the study. Also, recruitment advertisement were placed in local newspapers and information brochures were sent to general practitioners. Physiotherapists verified patient's eligibility for study participation. Eligibility criteria concerned: (1) age 40-80 year, (2) OA of the hip and/or knee according to the clinical criteria of the American College of Rheumatology (ACR) [17]. Exclusion criteria were (1) being on a waiting list for a hip or knee replacement surgery, (2) contraindications for PA without supervision according to the Physical Activity Readiness Questionnaire (PAR-Q), (3) sufficiently physically active according to the physiotherapist, (4) participation in a physiotherapy and/or PA program in the last six months, (5) no access to internet, (6) inability to understand the Dutch language. Eligible patients were informed by their physiotherapist about the study and received an information letter and informed consent form. Patients were blinded to the study hypotheses, but unblinded to the comparator intervention. After an informative phone call with the researcher (CK), patients were asked to return their informed consent form.

Intervention: e-Exercise

The development and pilot study of e-Exercise is described elsewhere [14]. The overall aim of e-Exercise is to stimulate a physical active lifestyle regardless of OA related sensations. The intervention e-Exercise takes 12 weeks and is a combination of (1) about five face-to-face sessions with a physiotherapist and (2) an online application focusing on behavioral graded activity, exercises and information. The e-Exercise protocol is based on the Dutch OA guideline [16]. In patients' first session (week 1), the therapist created an e-Exercise account and provided support in the selection of one type of PA, for example walking or cycling and four strength & stability exercises. The patient was informed about the first online assignment, which was a three-day baseline test to assess patients' physical load ability. The results were discussed during the second face-to-face session and used for the formulation of a short- and long-term goal. During the third session in week 6, patients' progress were discussed using the online progress-reports (i.e. a summary of website-visits and patients' experiences with the exercises). In the last session (week 12), the maintenance of PA was discussed and supported. Although physiotherapists were recommended to treat according the e-Exercise protocol, they were free to deviate from the protocol with respect to their clinical competences.

The online part of e-Exercise consisted of three modules: 1) Graded Activity in which the duration of patients' chosen PA gradually increased until the individual short-term goal. 2) Strength & Stability, each week the patient was asked to perform two video-supported exercises on three different days. The number of repetitions increased gradually per 4 weeks. 3) Information: each week a new video was generated about OA etiology, pain-management, weight-management, motivation, medication and social influences on pain. Weekly automatic emails informed and reminded patients about new assignments and content. At the end of the week patients were asked to evaluate the execution of their assignments. Depending on their answer to the question: "were you able to execute the Graded Activity assignment, or did you do less or more?", automatic tailored feedback was generated. The online application of e-Exercise can be visited at https://www.e-exercise.nl (in Dutch), a promotional video with English subtitles at https://www.youtube.com/watch?v=4l9GoQWWy58.

Intervention: Usual physiotherapy

Usual physiotherapy in the current study was defined as any treatment provided by the physiotherapist. Physiotherapists were encouraged to practice according to the Dutch OA guideline, which recommends the same three elements as e-Exercise: 1)

information, 2) physical exercise and 3) strength and stability exercises [16]. No restrictions were given with regard to the number of face-to-face sessions.

Outcomes and Follow-up
Patients received an online questionnaire and an accelerometer at baseline, after 12 weeks and after 12 months. The physiotherapist measured physical functioning objectively at baseline and post-treatment. No financial incentives were offered to complete the measurements. In case of an unfilled questionnaire, a first reminder was sent after ten days and a second reminder or a phone call after fifteen days. A detailed description of outcome measures and interpretation is given in Appendix 2.

Demographics
Patient characteristics: age, sex, height, weight, educational level, location of OA, duration of OA and the presence of comorbidities was assessed as part of the baseline questionnaire.

Primary outcome measures
-Physical functioning, assessed subjectively with the subscale "function in daily living'' of the Hip OA Outcome Score (HOOS) and/or the Knee Injury and OA Outcome Score (KOOS) [18, 19]. A lower score on the sum-score (0-100) indicates problems in physical functioning. Physical functioning was objectively assessed by the physiotherapists using the Timed Up and Go (TUG) test [20].
Free-living physical activity, assessed subjectively with the SQUASH, a questionnaire that measures habitual PA during the last week [21]. PA was objectively assessed using ActiGraph GT3x tri-axial accelerometers. Patients were instructed to wear the accelerometer on a belt around their waist for five executive days, except during the night, showering or swimming. Accelerometer data were eligible if patients had worn the meter at least 3 days, for 8 hours or more [22]. PA thresholds of Freedson et al. [23] were used to distinguish sedentary activity, light, moderate and vigorous PA. Moderate and vigorous activity were summed and divided by the number of wearing days to calculate a PA score in minutes per day.

Secondary outcome measures
-Other symptoms and functional limitations: The HOOS and the KOOS assesses, next to function in daily living, 4 other subscales: pain, symptoms, sport/recreation function and quality of life [18, 19].
-Self-perceived effect: assessed by a single question about the degree of change in OA symptoms. A score ranged from 1 (=much better) till 6 (much worse).

-Pain and tiredness: assessed with a numeric rating scale ranged from 0 (=no pain/not tired) till 10 (=worst possible pain/very tired).
-Self-efficacy: assessed by the Arthritis Self-efficacy Scale (ASES), using the subscale pain and symptoms [24]. Scores ranged from 1 till 5, a higher score indicates more self-efficacy.

Other measures
-Online adherence: quantitative data about website usage, stored on the backend of the website, was used to analyze adherence to the online application.

-Usability: assessed by the System Usability Scale (SUS). A higher SUS score (range 0-100) indicates better usability. For interpretation a grading system introduced by Sauro and Lews was used [25, 26].

-Content of and number of physiotherapy sessions. Physiotherapists were asked to fill out a registration form about the number and content of face-to-face sessions.

Statistical Analysis
Descriptive statistics were used to describe patients' general characteristics and the number and content of the physiotherapy sessions. Frequencies, t-tests and Chi-squares were used to explore differences in demographics between both groups. Primary analysis were performed according to the intention-to-treat principle. Per-protocol analyses were performed using the adherent e-Exercise patients and the entire usual physiotherapy group. Patients were seen as adherent if they completed at least 8 out of 12 modules [27].

Multilevel repeated measures analyses were used to determine short- (3 months) and long term (12 months) effectiveness of e-Exercise compared to usual physiotherapy on primary and secondary outcome measures. The three-level hierarchy existed of repeated measurements (level 1), nested within patients (level 2) and nested within physiotherapists (level 3). Analyses were controlled for the physiotherapist, baseline values, sex, BMI, level of education and location of OA. Between group effect sizes (ES) were calculated according Cohen's d using the pooled standard deviation. An effect size of 0.2 was considered as a "small" effect, 0.5 as "medium" effect and 0.8 and larger as a "large" effect [28]. According to the recommendations of Twisk et al. about handling missing data in longitudinal mixed-model analyses, no imputation techniques were used [29, 30]. In order to investigate selective attrition, a non-response analyses with t-tests and chi-squares was performed by comparing general

characteristics and primary baseline variables of responders and non-responders at 3 and 12 months. For per-protocol analyses, adherent patients that completed ≥8 modules were compared with the usual physical therapy group. Per-protocol analyses consisted of multilevel analyses controlling for the same variables as the primary analysis.

Sample size

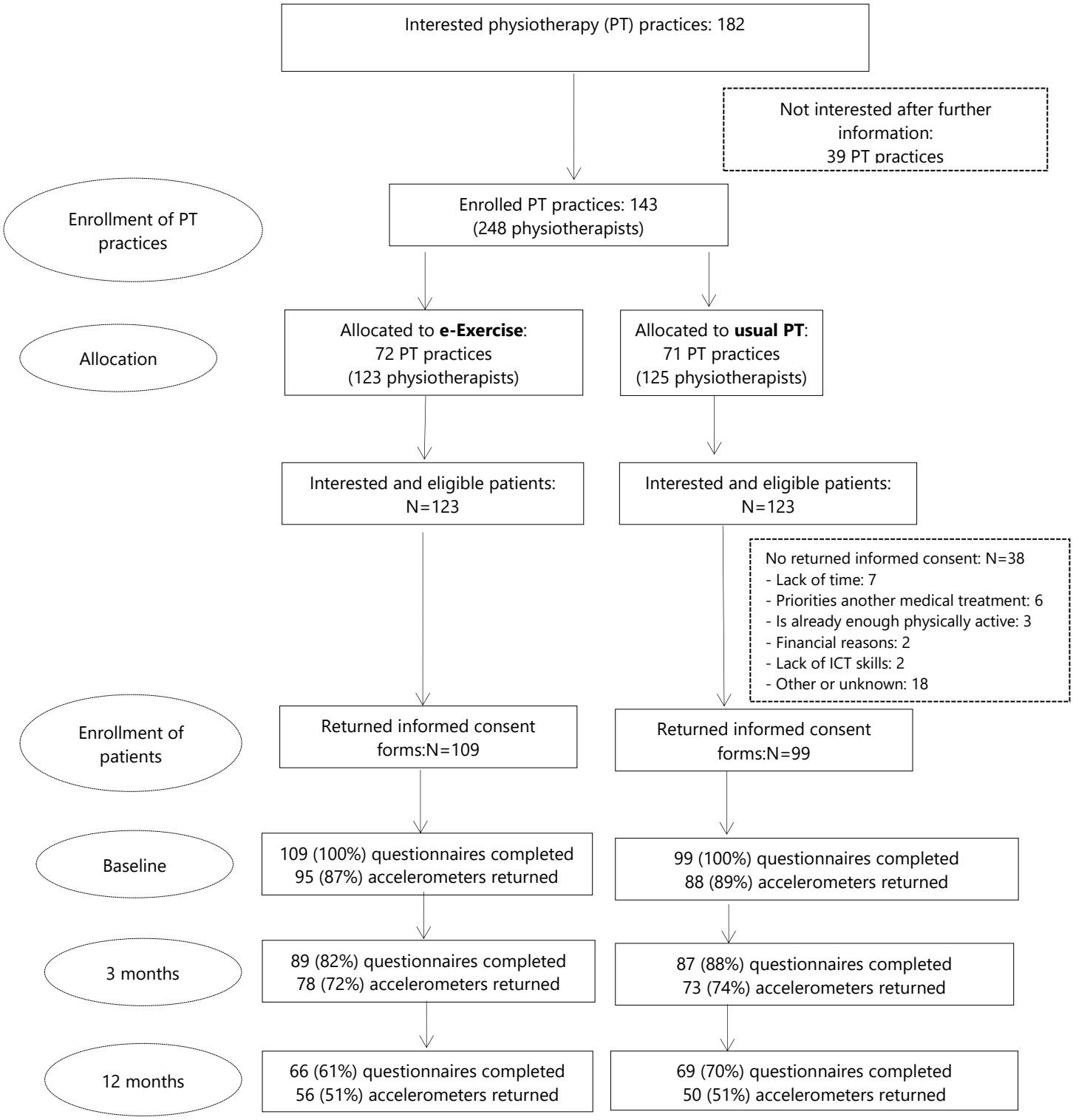
The power calculation was based on a previous multicenter cluster RCT among patients with hip and/or knee OA [8] and performed for the primary outcome measure physical functioning (power 0.8; alpha 0.05). The target sample size was 200 patients to detect a small to medium effect size (0.2-0.4) in physical functioning at a 2-sided significance level of 0.05, anticipating on maximum loss to follow up of 20% over the study period of 12 months. Since we had four primary outcome measures we applied a Bonferroni correction. A two-tailed significance level of 0.05/4=0.0125 was considered as statistically significant. Analyses were carried out using SPSS Statistics 23.0.

Results

Patients

In total, 246 eligible patients were included (Figure 1). A number of 38 patients did not return informed consent after reading the patient information letter because of lack of time (N=7), priority for another medical treatment (N=6), a physically active lifestyle (N=3), financial reasons (N=2), a lack of ICT skills (N=2) or other/unknown reasons (N=18). From the physiotherapy practices allocated to e-Exercise, 109 patients filled out the first questionnaire. From the physiotherapy practices allocated to usual physiotherapy, 99 patients completed the first questionnaire. The response rate for the follow-up questionnaire at 3 months was 85% (e-Exercise N=89; usual PT N=87), and 65% (e-Exercise: N=66; usual PT: N=69) at 12 months. Eligible accelerometer data at baseline, 3 and 12 months were available for respectively 88%, 73% and 51% of the 208 patients. Demographics and characteristics are shown in table 1. The e-Exercise group consisted of more low educated people (e-Exercise 24.8%; usual PT 12.1%; p=0.04) at baseline. No other differences in demographics were seen between groups. Responders after 3 months differed from non-responders in BMI (responders 27.0 (SD 4.1); non-responders 29.0 (4.1); p=0.02). No statistical differences were seen between patients which wore the accelerometer or not.

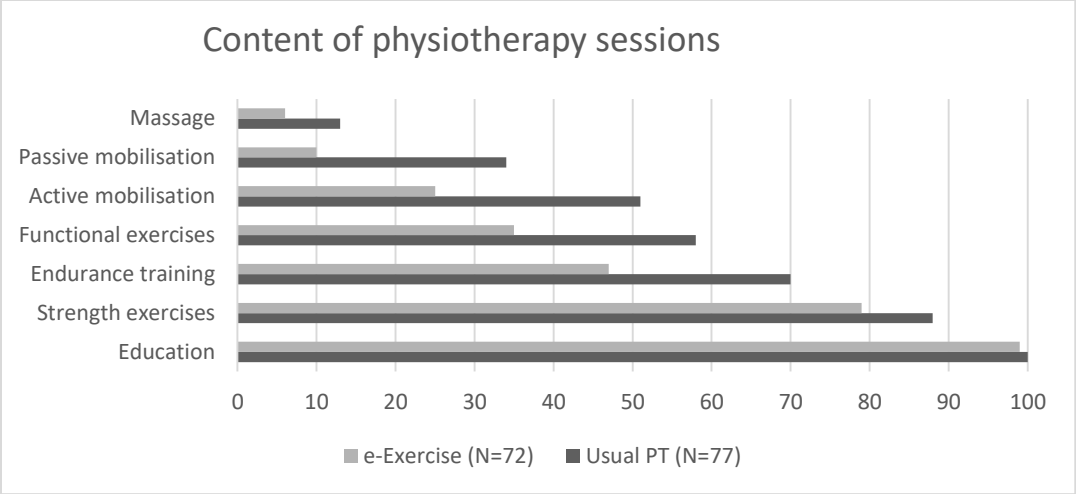
Figure 1. Flow chart



Content and number of physiotherapy sessions

In total, 149 physiotherapist registration forms were returned, 77 about patients which received usual physiotherapy and 72 about patients which received e-Exercise. Figure 2 shows the content of physiotherapy sessions of usual physiotherapy and e-Exercise. Overall, physiotherapists that applied usual physiotherapy provided more often active and passive mobilizations, endurance training, functional- and strength exercises. Patients in the usual physiotherapy group received 12 sessions (range 2-29), patients in the e-Exercise group received on average 5 sessions (range 2-16).

Figure 2. Applied physiotherapy interventions (% of patients that received the given intervention as part of their OA physiotherapy treatment)



Usability and adherence

At 3 months, the average System Usability Score of 85 responders was 73.1 (SD 18.6), which correspondents with a Grade B-usability. For 90 out of 109 patients adherence data was available. Of these patients, 73 (81.1%) completed at least 8 out of 12 modules and were classified as adherent. A detailed overview of adherence to e-Exercise and related factors is published elsewhere [27].

Short-term effectiveness

After 3 months no statistically significant differences were seen between e-Exercise and usual physiotherapy for the primary outcome measures physical functioning and physical activity (table 2) and the secondary outcome measures (table 3). Within the

usual physiotherapy group, significant improvements were seen for physical functioning, the timed up-and-go test, sub-scales of the HOOS and KOOS (pain, sport and quality of life), NRS pain and self-efficacy (subscales pain and symptoms). Within the e-Exercise group, significant improvements were seen for physical functioning, subjective PA, pain (NRS and HOOS/KOOS), tiredness and self-efficacy (sub-scales pain and symptoms). Self-perceived effect of patients in the e-Exercise group was 3.1 (SD 1.2) and in the usual physiotherapy group 3.1 (SD 1.3), a score of 3 means "a little bit better". Results of the per-protocol analyses showed that there were no statistically significant differences between the adherent e-Exercise group and the regular physiotherapy group (results not presented).

Long-term effectiveness

At 12 months follow-up, no statistically significant differences were seen between groups for the primary outcome measures. For secondary outcome measures, a significant difference was seen on changes in sedentary behavior (usual PT group: -29.4 minutes/day; e-Exercise: +8.3 minutes/day; p=<0.01; ES= -0.73). Within the usual physiotherapy group, statistical significant improvements were seen on physical functioning, sub-scales of the HOOS and KOOS (pain and quality of life), NRS pain, NRS tiredness and self-efficacy (subscales pain and quality of life). Within the e-Exercise group, statistical significant improvements were seen on physical functioning, sub-scales of the HOOS and KOOS (pain, symptoms, quality of life), NRS pain, NRS tiredness and self-efficacy (subscales pain and quality of life). Results are reported in table 2 and 3. Self-perceived effect of patients in the e-Exercise group was 3.4 (SD 1.4) and in the usual PT group 3.1 (SD 1.6). Long-term results of the per-protocol analyses showed that there were no statistically significant differences between the adherent e-Exercise group and usual physiotherapy (results not presented). The Intraclass Correlation coefficient (ICC) ranged from 0.0%-1.4%.

Table 1. Demographics and unadjusted primary outcome measures of participants at baseline, 3 months and 12 months

Time of measurement		**Baseline**	**Baseline**	**3 months**	**3 months**	**12 months**	**12 months**
Intervention		**e-Exercise**	**Usual PT**	**e-Exercise**	**Usual PT**	**e-Exercise**	**Usual PT**
Number of respondents		**N=109**	**N=99**	**N=89**	**N=87**	**N=66**	**N=69**
Sex, N (%)	Female	74 (67.9)	67 (67.7)	60 (67.4)	57 (65.5)	44 (66.7)	44 (63.8)
	Male	35 (32.1)	32 (32.3)	29 (32.6)	30 (34.5)	22 (33.3)	25 (36.2)
Age (years), mean (SD)		63.8 (8.5)	62.3 (8.9)	63.6 (8.1)	62.6 (9.1)	64.1 (7.7)	61.7 (8.8)
BMI (kg/m^2), mean (SD)		27.8 (4.2)	27.9 (4.9)	27.4 (4.4)	27.7 (4.8)	26.9 (4.2)	27.7 (4.9)
Location OA, N (%)	Knee	71 (65.1)	67 (67.6)	59 (66.3)	58 (66.7)	45 (68.2)	48 (69.6)
	Hip	21 (19.3)	17 (17.2)	19 (21.3)	16 (18.4)	16 (24.2)	12 (17.4)
	Both	17 (15.6)	15 (15.2)	11 (12.4)	13 (14.9)	5 (7.6)	9 (13.0)
Duration of symptoms, N (%)	< 1 year	21 (19.3)	20 (20.2)	14 (15.7)	19 (21.8)	11 (16.7)	14 (20.3)
	1-5 year	42 (38.5)	38 (38.4)	38 (42.7)	33 (37.9)	31 (47.0)	31 (44.9)
	≥5 year	46 (42.2)	41 (41.4)	37 (41.6)	35 (40.2)	24 (36.4)	24 (34.8)
Education, N (%)	Low	27 (24.8)	12 (12.1)	23 (25.8)	9 (10.3)	17 (25.8)	8 (11.6)
	Middle	41 (37.6)	51 (51.5)	35 (39.3)	46 (52.9)	26 (39.4)	34 (49.3)
	High	41 (37.6)	36 (36.4)	31 (34.8)	32 (36.8)	23 (34.8)	27 (39.1)
Comorbidity, N (%)	0	62 (56.9)	62 (62.6)	47 (52.8)	53 (60.9)	37 (56.1)	40 (58.0)
	1	20 (18.3)	20 (20.2)	16 (18.0)	18 (20.7)	11 (16.7)	15 (21.7)
	≥2	27 (24.8)	17 (17.2)	26 (29.2)	16 (18.4)	18 (27.3)	14 (20.3)
Physical functioning (0-100)		61.3 (18.3)	55.5 (21.4)	66.7 (18.2)	62.2 (20.4)	69.3 (18.7)	65.3 (22.8)
Timed Up and Go test (sec)		8.4 (2.1)	8.6 (5.8)	7.3 (1.7)	7.3 (2.4)		
Physical activity, subjective	Min/day	98.4 (118.4)	107.0 (103.3)	120.4 (111.0)	131.4 (122.2)	105.6 (97.2)	125.8 (123.0)
Physical activity, objective	Min/day	25.2 (23.1)	22.5 (21.8)	25.5 (17.7)	25.5 (23.7)	23.5 (19.9)	25.3 (22.8)

Table 2. Primary adjusted outcome measures: improvements and differences within and between groups

Outcome measures	N	e-Exercise, mean (95% CI)	Within group differences, p-value*	N	Usual PT, mean (95% CI)	Within group differences, p-value*	Difference in difference, mean (95% CI)^	Between group differences, p-value*	Between group effect size
Physical									
Baseline	109	52.7		99	50.7				
3 months	87	56.8	<0.01	87	56.3	<0.01	-1.4 (-5.6;2.8)	0.52	0.01
12 months	65	59.8	<0.01	69	58.0	<0.01	-0.2 (-6.4;6.0)	0.95	0.04
Timed Up and Go									
Baseline	72	9.6 (8.1;11.1)		74	9.8 (8.3;11.3)				
3 months	68	8.5 (7.3;9.7)	0.01	66	8.4 (7.1;9.7)	<0.01	0.3 (-0.8;1.5)	0.58	0.02
Physical activity[#],									
Baseline	109	126.7		99	129.8				
3 months	87	154.2	<0.01	87	141.7	0.26	15.7 (-13.4;44.7)	0.26	0.04
12 months	65	193.1	0.41	69	200.9	0.22	4.6 (-27.9;37.2)	0.78	-0.02
Physical activity[#],									
Baseline	95	35.4		88	33.7				
3 months	79	34.9	0.78	72	35.0	0.52	-1.8 (-7.2;3.6)	0.51	0.00
12 months	56	43.4	0.28	50	44.6	0.89	3.0 (-3.9;10.0)	0.39	-0.02

*adjusted for baseline, sex, BMI, level of education, pain, type of osteoarthritis, physiotherapist

[#] moderate and vigorous intensity

^Difference between baseline and 3 months in e-Exercise vs. usual physiotherapy; difference between baseline and 12 months in e-Exercise vs. usual physiotherapy

Baseline and 3 month data were extracted from short-term analyses, 12 month data from long-term analysis

Table 3. Secondary adjusted outcome measures: improvements and differences within and between groups

Outcome measures	N	e-Exercise, mean (95% CI)	Within group differences, p-value*	N	Usual PT, mean (95% CI)	Within group differences, p-value*	Difference in difference, mean (95% CI)^	Between group differences, p-value*	Between group effect size
Pain (0-100)									
Baseline	109	50.4 (42.1;58.8)		99	43.9 (35.2;52.7)				
3 months	87	55.8 (47.3;64.3)	<0.01	87	48.8 (39.9;57.7)	<0.01	0.5 (-4.1;5.0)	0.84	0.14
12 months	65	65.9 (54.3;77.5)	<0.01	69	61.6 (49.9;73.4)	<0.01	-2.0 (-8.9;4.8)	0.56	0.07
Symptoms (0-100)									
Baseline	109	53.1 (45.9;60.4)		99	51.2 (43.5;58.8)				
3 months	87	54.2 (46.7;61.7)	0.50	87	54.4 (46.5;62.3)	0.05	-2.1 (-6.6;2.4)	0.35	0.00
12 months	65	56.7 (46.3;67.1)	<0.01	69	62.1 (51.6;72.6)	0.03	-7.4 (-13.8;-1.0)	0.73	-0.10
Sport (0-100)									
Baseline	109	36.3 (39.2;50.8)		99	39.7 (29.8;49.6)				
3 months	87	39.3 (42.7;55.4)	0.23	87	46.6 (36.1;57.1)	<0.01	-3.9 (-11.0;3.1)	0.27	-0.16
12 months	65	45.9 (32.5;59.3)	0.05	69	49.1 (35.5;62.6)	0.04	0 (-8.3;8.3)	0.99	-0.05
QOL (0-100)									
Baseline	109	45.0 (39.2;50.8)		99	44.2 (38.1;50.4)				
3 months	87	49.1 (42.7;55.4)	0.02	87	53.0 (46.3;59.7)	<0.01	-4.7 (-9.5;0.2)	0.06	-0.10
12 months	65	52.5 (43.6;61.4)	<0.01	69	56.1 (47.0;65.1)	<0.01	-4.3 (-10.3;1.8)	0.16	-0.08
Sedentary behavior,									
Baseline	95	495.5		88	514.0				
3 months	79	505.8	0.19	72	498.3	0.05	26.0 (3.9;48.1)	0.02	0.03
12 months	56	521.0	0.37	50	501.3	<0.01	29.4 (10.3;48.6)	<0.01	0.08
Pain (0-10)									
Baseline	109	5.4 (4.3;6.4)		99	6.1 (4.9;7.2)				

3 months	87	4.1 (3.0;5.2)	<0.01	87	5.3 (4.1;6.4)	<0.01	-0.5 (-1.1;0.2)	0.16	-0.18
12 months	65	3.8 (2.4;5.2)	<0.01	69	4.0 (2.6;5.5)	<0.01	0.4 (-0.5;1.3)	0.40	-0.03
Tiredness (0-10)									
Baseline	109	6.1 (5.1;7.2)		99	6.1 (5.1;7.2)				
3 months	87	4.8 (3.8;5.8)	<0.01	87	5.6 (4.5;6.7)	0.02	-0.8 (-1.4;-0.1)	0.02	-0.13
12 months	65	5.6 (4.2;7.0)	<0.01	69	5.6 (4.2;7.1)	<0.01	-0.1 (-0.9;0.8)	0.84	0
Self-efficacy pain (1-									
Baseline	109	3.6 (3.3;4.0)		99	3.5 (3.2;3.9)				
3 months	87	3.9 (3.6;4.3)	<0.01	87	4.0 (3.6;4.4)	<0.01	-0.1 (-0.4;0.1)	0.33	-0.05
12 months	65	4.1 (3.6;4.6)	<0.01	69	4.0 (3.5;4.5)	<0.01	0 (-0.3;0.3)	0.99	0.04
Self-efficacy									
Baseline	109	3.5 (3.1;3.8)		99	3.4 (3.0;3.7)				
3 months	87	3.7 (3.4;4.1)	<0.01	87	3.8 (3.4;4.2)	<0.01	-0.2 (-0.4;0.1)	0.20	-0.05
12 months	65	3.7 (3.2;4.2)	<0.01	69	3.7 (3.2;4.3)	<0.01	-0.1 (-0.4;0.1)	0.29	0
Pain reported by PT									
Baseline	72	6.4 (5.5;7.3)		74	6.6 (5.7;7.5)				
3 months	69	4.2 (3.2;5.1)	<0.01	73	4.5 (3.6;5.5)	<0.01	-0.2 (-0.9;0.6)	0.64	-0.06

*adjusted for baseline, sex, BMI, level of education, pain, type of osteoarthritis, physiotherapist

^Difference between baseline and 3 months in e-Exercise vs. usual physiotherapy; difference between baseline and 12 months in e-Exercise vs. usual physiotherapy

Baseline and 3 month data were extracted from short-term analyses, 12 month data from long-term analysis

Discussion

The aim of this multicenter superiority cluster randomized controlled trial study was to investigate the short- and long-term effectiveness of e-Exercise compared to usual physiotherapy in patients with OA of hip and/or knee. Since online applications can support patients in exercise at home [13, 31], we expected that e-Exercise would be more effective than usual physiotherapy. The results of this RCT study showed that there we no significant differences between e-Exercise and usual physiotherapy with respect to physical functioning and free-living physical activity. However, within group differences showed that both interventions were significantly effective with respect to physical functioning and most secondary outcomes, post-treatment and after 12 months. Notably, patients in the e-Exercise group visited the physiotherapist five times, whereas the usual physiotherapy group received on average twelve sessions. This reduction of face-to-face sessions might lead to a reduction of healthcare costs, which will be investigated in a future cost-effectiveness study.

Integrating face-to-face physiotherapy with online applications is an upcoming field and this is the first RCT evaluating the effectiveness of blended care in patients with OA of hip and/or knee compared to usual physiotherapy. The comparison of the average change in both treatment groups show minimal differences with small effect sizes in all primary and secondary outcome measures. To illustrate, patients improved on average 7.2 points on physical functioning (e-Exercise +7.1; usual PT +7.3; ES=0.04; p=0.95) and 16.1 points on pain (e-Exercise +15.5; usual PT +17.7; ES=0.07; p=0.56) as measured with the HOOS and KOOS (scale 0-100). If we would have used a non-inferiority design, we probably would have specified a non-inferiority margin of 0.5x 0.3=0.15 [2, 3, 32]. Since all our between group effect sizes were below this value, e-Exercise and usual physiotherapy are likely to be equally effective. These within group effects of are comparable with other studies in exercise therapy for patients with hip/knee OA [2, 3] and underline the potential of blended care.

Although patients in the e-Exercise group reported a significantly increase of physical activity after 3 months, in both groups no significant improvements in objective physical activity were found. This result is in accordance with a recent meta-analysis that found no consistent evidence for improvement of objective physical activity in lower limb OA [33]. Next to the difficulty of measuring free-living physical activity

[34], an explanation in our trial might be patients' high level of physical activity at baseline. Whereas physical inactivity was set as an inclusion criteria (administered during physiotherapists' anamnesis), baseline data show that patients already met the global recommendations for physical activity [35]. Physiotherapists might have underestimated patients level of physical activity, leading to a physical active study population with less room for improvement. Next to this, a significant increase of sedentary behavior within the e-Exercise group compared to usual physiotherapy was determined. Since sedentary behavior increases the morbidity and mortality risk [36], we will include an information module about this topic within a future e-Exercise intervention. Taking in account the difficulty of changing physical activity and sedentary behavior, we also recommend to combine e-Exercise with wrist worn activity trackers, for self-monitoring. In the same time, these trackers can be used for continuously measurement of intervention compliance [37, 38].

A remarkable difference between e-Exercise and usual physiotherapy is the content of the physiotherapy sessions. Physiotherapists that applied e-Exercise provided in a smaller proportion of patients active and passive mobilizations, endurance training, functional- and strength exercises. A possible explanation is that patients in the e-Exercise group were extensively stimulated to take an active role within their treatment. A detailed description of patients' and physiotherapists' experiences with e-Exercise is published elsewhere [39, 40].

Strengths and limitations

The strength of this study is that we compared e-Exercise with usual physiotherapy. This design made it possible to set up conclusions about the additional value of a blended delivery mode compared to face-to-face physiotherapy. Unfortunately, we had to deal with high dropout rates: 15% after 3 months and 35% after 12 months. Percentages of missing data in our accelerometer data were even higher. Possibly, we might have overloaded the participants with too many measurements. Although we did not find clinical relevant differences in baseline demographics between responders and non-responders, results should be interpreted with caution. It is known that drop-out rates in eHealth studies are accompanied with non-usage attrition [41]. For future studies, we recommend to use in-person survey visits since this might increase response-rates and would also provide the possibility to measure objective physical functioning by an independent researcher [42]. Final limitation is the discrepancy between our intended study population and the actual study

population. Inclusion of patients was done by the physiotherapists and clinical diagnosis of OA was not confirmed by an independent caregiver. Next, physiotherapists assessed patients' level of physical activity during anamneses with one single question. After analyses of the baseline data, it turned out that patients were already sufficient physical active at baseline. On the one hand, it is a limitation that our inclusion strategy resulted in a physical active population which had less room for improvement on this outcome measurement during the intervention. On the other hand, our inclusion strategy has the advantage that it reflects physiotherapists' clinical reasoning process in daily practice. After implementation of e-Exercise, physiotherapists will select patients for e-Exercise in the same way.

Clinical implications and future directions

We recommend to further elaborate on an instrument to determine patients' suitability for a (partly) online intervention. In line with a stepped care strategy that promotes to start with relatively simple treatment modalities [43], patients could start with an unguided internet-delivered intervention like Join2Move [12]. If this simple treatment modality appears to be inadequate, physiotherapeutic guidance can be added (e-Exercise). In case of deterioration of symptoms or unsatisfying results, the frequency of face-to-face contact can be increased [43]. In a future study we will describe the cost-effectiveness of e-Exercise compared to usual physiotherapy from societal perspective.

Conclusions

The blended intervention e-Exercise was not more effective than usual physiotherapy in patients with hip/knee osteoarthritis. Both interventions led to clinical improvements.

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Appendix 2. Detailed overview of outcome measures

PRIMARY OUTCOME MEASURES	
Physical functioning (subjective)	Subjectively assessed with the subscale "function in daily living'' of the Hip OA Outcome Score (HOOS) and/or the Knee Injury and OA Outcome Score (KOOS) [18, 19]. Based on the 17 items a sum score was calculated, ranging from 0 to 100. A lower score indicates problems in physical functioning. Patients with hip OA filled out the HOOS, patients with knee OA the KOOS and patients with hip and knee OA filled out the HOOS and KOOS. In patients with both hip and knee OA the lowest score of the HOOS and KOOS was used for analysis of this primary outcome measure.
Physical functioning (objective)	Objectively assessed by the physiotherapists using the Timed Up and Go (TUG) test [20]. Patients were asked to rise from an arm chair, walk three meters, turn, walk back and sit down. The physiotherapists measured the time.
Physical activity (subjective)	Subjectively assessed with the SQUASH, a questionnaire that measures habitual PA during the last week [21]. A PA score was expressed as minutes of moderate and vigorous PA per day.
Physical activity (objective)	Objectively assessed using ActiGraph GT3x tri-axial accelerometers. Patients were instructed to wear the accelerometer on a belt around their waist for five executive days, except during the night, showering or swimming. Accelerometer data were eligible if patients had worn the meter at least 3 days, for 8 hours or more [22]. PA thresholds of Freedson et al. [23] were used to distinguish sedentary activity, light, moderate and vigorous PA. Moderate and vigorous activity were summed and divided by the number of wearing days to calculate a PA score.
SECONDARY OUTCOME MEASURES	
Other symptoms and functional limitations	The HOOS and the KOOS assesses, next to function in daily living, 4 other subscales: pain, symptoms, sport/recreation function and quality of life [18, 19]. For each subscale a sum score is calculated, ranging from 0 to 100. A lower score indicates respectively more pain, symptoms, problems in sports and recreation activities and a lower quality of life.
Self-perceived effect	Assessed by a single question about the degree of change in OA symptoms. A score ranged from 1 (=much better) till 6 (much worse).
Pain and tiredness	Assessed with a numeric rating scale ranged from 0 (=no pain/not tired) till 10 (=worst possible pain/very tired).
Self-efficacy	Assessed by the Arthritis Self-efficacy Scale (ASES), using the subscale pain and symptoms [24]. Scores ranged from 1 till 5, a higher score indicates more self-efficacy.
OTHER MEASURES	
Online adherence	Quantitative data about website usage, stored on the backend of the website, was used to analyze adherence to the online application.

Usability	Assessed by the System Usability Scale (SUS). A higher SUS score (range 0-100) indicates better usability. For interpretation a grading system introduced by Sauro and Lews was used [25, 26]: Grade F (0–51.7); Grade D (51.8–62.6); Grade C- (62.7–64.9); Grade C (65.0–71.0); Grade C+ (71.1–72.5); Grade B- (72.6–74.0); Grade B (74,1–77.1); Grade B+ (77.2–78.8); Grade A- (78.9–80.7); Grade A (80.8–84.0); Grade A+ (84.1–100).
Content of physiotherapy sessions	Physiotherapists were asked to fill out a registration form about the number and content of face-to-face sessions.
Patient characteristics	Age, sex, height, weight, educational level, location of OA, duration of OA and the presence of comorbidities

References

1. Zhang Y, Jordan JM: Epidemiology of osteoarthritis. *Clinics in geriatric medicine* 2010, 26(3):355-369.
2. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S: Exercise for osteoarthritis of the hip. *The Cochrane database of systematic reviews* 2014(4):CD007912.
3. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL: Exercise for osteoarthritis of the knee. *The Cochrane database of systematic reviews* 2015, 1:CD004376.
4. Bijlsma JW, Berenbaum F, Lafeber FP: Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011, 377(9783):2115-2126.
5. Dekker J: Exercise and Physical Functioning in Osteoarthritis: Medical, Neuromuscular and Behavioral Perspectives. In., edn. New York: Spinger-Verlag; 2013.
6. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H *et al*: OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and cartilage* 2014, 22(3):363-388.
7. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM: A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Seminars in arthritis and rheumatism* 2014, 43(6):701-712.
8. Veenhof C, Koke AJ, Dekker J, Oostendorp RA, Bijlsma JW, van Tulder MW, van den Ende CH: Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial. *Arthritis and rheumatism* 2006, 55(6):925-934.
9. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JE: Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. *JMIR mental health* 2016, 3(1):e9.
10. Webb TL, Joseph J, Yardley L, Michie S: Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *Journal of medical Internet research* 2010, 12(1):e4.
11. Wood CE, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, Michie S: Applying the behaviour change technique (BCT) taxonomy v1: a study of coder training. *Translational behavioral medicine* 2015, 5(2):134-148.
12. Bossen D, Veenhof C, Van Beek KE, Spreeuwenberg PM, Dekker J, De Bakker DH: Effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis: randomized controlled trial. *Journal of medical Internet research* 2013, 15(11):e257.

13. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE: Persuasive system design does matter: a systematic review of adherence to web-based interventions. *Journal of medical Internet research* 2012, 14(6):e152.
14. Bossen D, Kloek C, Snippe HW, Dekker J, de Bakker D, Veenhof C: A Blended Intervention for Patients With Knee and Hip Osteoarthritis in the Physical Therapy Practice: Development and a Pilot Study. *JMIR research protocols* 2016, 5(1):e32.
15. Kloek CJ, Bossen D, Veenhof C, van Dongen JM, Dekker J, de Bakker DH: Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: study protocol of a randomized controlled trial. *BMC musculoskeletal disorders* 2014, 15:269.
16. Peter WFH JM, Bloo H, Dekker-Bakker LMMCJ, Dilling RG, Hilberdink WKHA, Kersten-Smit C, de Rooij M, Veenhof C, Vermeulen HM, de Vos I, Vlieland TPMV. 2010.: KNGF-richtlijn Artrose heup-knie. *Ned Tijdschr voor Fysiotherapie* 2010.
17. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M *et al*: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and rheumatism* 1986, 29(8):1039-1049.
18. de Groot IB, Favejee MM, Reijman M, Verhaar JA, Terwee CB: The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health and quality of life outcomes* 2008, 6:16.
19. de Groot IB, Reijman M, Terwee CB, Bierma-Zeinstra SM, Favejee M, Roos EM, Verhaar JA: Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthritis and cartilage* 2007, 15(1):104-109.
20. Podsiadlo D, Richardson S: The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society* 1991, 39(2):142-148.
21. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D: Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003, 56(12):1163-1169.
22. Hart TL, Swartz AM, Cashin SE, Strath SJ: How many days of monitoring predict physical activity and sedentary behaviour in older adults? *The international journal of behavioral nutrition and physical activity* 2011, 8:62.
23. Freedson PS, Melanson E, Sirard J: Calibration of the Computer Science and Applications, Inc. accelerometer. *Medicine and science in sports and exercise* 1998, 30(5):777-781.
24. Taal E, Riemsma RP, Brus HL, Seydel ER, Rasker JJ, Wiegman O: Group education for patients with rheumatoid arthritis. *Patient education and counseling* 1993, 20(2-3):177-187.
25. Brooke J: Sus—a quick and dirty usability scale. Usability Evaluation in industry 1996.
26. Sauro JL, J.: Quantifying the User Experience: Practical Statistics for User Research. San Francisco, USA; 2012.

27. De Vries HJK, C.J.J.; de Bakker, D.H.; Dekker, J.; Bossen, D.; Veenhof, C.: Determinants of adherence to the online component of a blended intervention for patients with hip- and/or knee osteoarthritis: a mixed methods study embedded in the e-Exercise trial [accepted]. *Telemedicine and e-Health* 2017.
28. Cohen J: Statistical power analysis for the behavioral sciences. *Hillsdale, NJ L Erlbaum Associates* 1988.
29. Twisk J, de Vente, W.: Attrition in longitudinal studies. How to deal with missing data. *J Clin Epidemiol* 2002, 55(4):329-337.
30. Twisk J, de Boer M, de Vente W, Heymans M: Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. *J Clin Epidemiol* 2013, 66(9):1022-1028.
31. Pietrzak E, Cotea C, Pullman S, Nasveld P: Self-management and rehabilitation in osteoarthritis: is there a place for internet-based interventions? *Telemed J E Health* 2013, 19(10):800-805.
32. Greene CJ, Morland LA, Durkalski VL, Frueh BC: Noninferiority and equivalence designs: issues and implications for mental health research. *J Trauma Stress* 2008, 21(5):433-439.
33. Williamson W, Kluzek S, Roberts N, Richards J, Arden N, Leeson P, Newton J, Foster C: Behavioural physical activity interventions in participants with lower-limb osteoarthritis: a systematic review with meta-analysis. *BMJ Open* 2015, 5(8):e007642.
34. Kelly P, Fitzsimons C, Baker G: Should we reframe how we think about physical activity and sedentary behaviour measurement? Validity and reliability reconsidered. *The international journal of behavioral nutrition and physical activity* 2016, 13:32.
35. Organization WH: Global recommendations on physical activity for health.; 2010.
36. Owen N, Healy GN, Matthews CE, Dunstan DW: Too much sitting: the population health science of sedentary behavior. *Exerc Sport Sci Rev* 2010, 38(3):105-113.
37. Cadmus-Bertram L: Using Fitness Trackers in Clinical Research: What Nurse Practitioners Need to Know. *J Nurse Pract* 2017, 13(1):34-40.
38. Mercer K, Li M, Giangregorio L, Burns C, Grindrod K: Behavior Change Techniques Present in Wearable Activity Trackers: A Critical Analysis. *JMIR Mhealth Uhealth* 2016, 4(2):e40.
39. Kloek C; Bossen, D; de Vries, H; de Bakker, DH; Veenhof, C; Dekker, J: Physiotherapists' experiences with a blended osteoarthritis intervention: a mixed methods study. [submitted 2017].
40. De Vries HK, CJJ; De Bakker, DH; Dekker, J; Bossen, D; Veenhof, C: Determinants of adherence to the online component of a blended intervention for patients with hip- and/or knee osteoarthritis: a mixed methods study embedded in the e-Exercise trial. *Telemedicine and e-Health* 2017 [accepted, in press].
41. Eysenbach G: The law of attrition. *Journal of medical Internet research* 2005, 7(1):e11.

42. Christensen AI, Ekholm O, Glumer C, Juel K: Effect of survey mode on response patterns: comparison of face-to-face and self-administered modes in health surveys. *Eur J Public Health* 2014, 24(2):327-332.
43. Smink AJ, van den Ende CH, Vliet Vlieland TP, Swierstra BA, Kortland JH, Bijlsma JW, Voorn TB, Schers HJ, Bierma-Zeinstra SM, Dekker J: "Beating osteoARThritis": development of a stepped care strategy to optimize utilization and timing of non-surgical treatment modalities for patients with hip or knee osteoarthritis. *Clin Rheumatol* 2011, 30(12):1623-1629.

6

Cost-effectiveness of a blended physiotherapy intervention in patients with hip and/or knee osteoarthritis: a cluster randomized controlled trial

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Abstract

Background: Blended physiotherapy, in which physiotherapy sessions and an online application are integrated, might support patients in taking an active role in the management of their chronic condition and may reduce disease related costs. The aim of this study was to evaluate the cost-effectiveness of a blended physiotherapy intervention (e-Exercise) compared to usual physiotherapy in patients with osteoarthritis of hip and/or knee, from the societal as well as the healthcare perspective.

Methods: This economic evaluation was conducted alongside a 12-month cluster randomized controlled trial, in which 108 patients received e-Exercise, consisting of physiotherapy sessions and a web-application, and 99 patients received usual physiotherapy. Clinical outcome measures were quality-adjusted life years (QALYs) according to the EuroQol (EQ-5D-3L), physical functioning (HOOS/KOOS) and physical activity (Actigraph Accelerometer). Costs were measured using self-reported questionnaires. Missing data were multiply imputed and bootstrapping was used to estimate statistical uncertainty.

Results: Intervention costs and medication costs were significantly lower in e-Exercise compared to usual physiotherapy. Total societal costs and total healthcare costs did not significantly differ between groups. No significant differences in effectiveness were found between groups. For physical functioning and physical activity, the maximum probability of e-Exercise being cost-effective compared to usual physiotherapy was moderate (<0.82) from both perspectives. For QALYs, the probability of e-Exercise being cost-effective compared to usual physiotherapy was 0.68/0.84 at a willingness to pay of €10.000,- and 0.70/0.80 at a willingness to pay of €80.000,- per gained QALY, from respectively the societal and the healthcare perspective.

Conclusions: E-Exercise itself was significantly cheaper compared to usual physiotherapy in patients with hip and/or knee osteoarthritis, but not cost-effective from the societal- as well as healthcare perspective. The decision between both interventions can be based on the preferences of the patient and the physiotherapist.

Trial registration: NTR4224 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4224)

Background

Osteoarthritis (OA) is a chronic disease which mostly affects the hip and knee. People with OA experience pain, stiffness and limitations in physical functioning [1]. Worldwide, OA is the most common joint disease [2]. In the Netherlands, the prevalence is 22.5 per 1,000 for hip OA and 32.2 per 1000 for knee OA [3]. In 2011, Dutch healthcare costs related to OA, including primary care, secondary care, alternative medicine and medication expenditures, were estimated to be about 1.1 billion Euros [4]. Due to the rising life expectancy and number of people with obesity, the prevalence of OA is expected to further increase during the next decades [2], which will in turn lead to an extra demand for OA-related healthcare services.

Physiotherapy is the most recommended conservative treatment for patients with hip and knee OA [5,6]. Physiotherapeutic modalities like aerobic exercise, muscle strengthening and education have shown to be effective in reducing pain and improving physical functioning [7,8]. However, face-to-face physiotherapy is costly and the rising number of people with OA requires new solutions to regulate OA-related healthcare costs. A promising strategy for reducing OA-related healthcare costs is the use of web-applications [9]. Websites and apps have the potential to partly replace face-to-face physiotherapy sessions. Next to this, websites and apps provide possibilities to support patients in taking an active role within their disease management. This new way of delivering physiotherapy, in which therapeutic guidance and an online support are integrated, is called “blended care” [10].

To the best of our knowledge, studies on the cost-effectiveness of blended interventions for patients with OA are lacking. Within mental healthcare, however, blended care for anxiety disorders, depression, smoking cessation and alcohol misuse was found to have a high probability of being cost-effective compared with wait-list, face-to-face mental healthcare, telephone counseling or unguided online care [11]. In the field of physiotherapy, a recent study showed that a blended cardiac rehabilitation intervention with minimal therapeutic guidance was cost-effective compared to center-based cardiac rehabilitation [12].

In order to investigate whether the integration of a web-application within physiotherapeutic treatment for patients with hip and/or knee OA can substitute a part of the face-to-face sessions, we developed and evaluated e-Exercise [13-15]. This blended intervention consists of a web-application integrated within regular face-to-face physiotherapy sessions. A recent cluster randomized controlled trial revealed no

differences in effectiveness for physical functioning and physical activity compared to usual physiotherapy. Within group improvements in physical functioning of e-Exercise were somewhat comparable with usual physiotherapy, both at the short- and long-term. Although e-Exercise was not more effective than usual physiotherapy, a difference between both groups was found in terms of the number of face-to-face sessions: i.e. the usual physiotherapy group received twelve face-to-face sessions and the e-Exercise group received five sessions [14]. It is unknown whether this reduction in face-to-face sessions also leads to a reduction of societal and/or healthcare costs and whether e-Exercise is cost-effective compared to usual physiotherapy. Therefore, the aim of this study is to evaluate the cost-effectiveness of e-Exercise compared to usual physiotherapy in patients with OA of hip and/or knee. A primary analysis was performed from the societal perspective and a secondary analysis from that of the healthcare sector.

Methods

Design Overview

This economic evaluation was conducted alongside a prospective, single-blinded, multicenter cluster randomized controlled trial (RCT) [14,15]. The Medical Ethical Committee of the St. Elisabeth hospital Tilburg in the Netherlands approved the study design and protocol (Dutch Trial Register NTR4224 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4224). The trial is reported according to the CONSORT Cluster Trials checklist.

A total of 143 primary care physiotherapy practices from the Dutch provinces Utrecht, Noord-Holland and Gelderland with 248 eligible physiotherapists, which treated at least six OA patients per year, were randomized according to an 1:1 allocation ratio using a computer-generated sequence table. Half of the physiotherapist (N=123) were instructed to treat their patients with OA of the hip and/or knee according to the e-Exercise protocol, the other half (N=125) treated their patients as usual. All physiotherapists received an half-day instruction course about the study procedure. Physiotherapists allocated to e-Exercise also received an account to the website and instructions about the intervention. Physiotherapists allocated to usual physiotherapy received their e-Exercise account and instructions after the study period. Enrollment of patients lasted from September 2014 till March 2015, after which they were followed-up for 12 months.

Participants

Patients who visited a participating physiotherapy practice were invited to participate in the study. The physiotherapist assessed eligibility, which concerned: (1) age 40-80 year, (2) OA of the hip and/or knee according to the clinical criteria of the American College of Rheumatology (ACR) [16], (3) not on a waiting list for hip or knee replacement surgery, (4) no contra-indications for physical activity without supervision according to the Physical Activity Readiness Questionnaire (PAR-Q), (5) being insufficiently physically active according to the physiotherapist, (6) no participation in a physiotherapy and/or physical activity program in the last six months, (7) access to internet, and (8) ability to understand the Dutch language. Interested patients received an information letter, an informative phone call from the main investigator (CK) and were asked to sign informed consent. Gathered patient information was stored separately from study outcomes, using an individual trial code. The main investigator (CK) was blinded to group assignment until completion of the statistical analyses.

Intervention: e-Exercise

E-Exercise is a 12-weeks intervention, in which (1) five face-to-face half-our sessions with a physiotherapist are integrated with (2) a web-application consisting of a graded activity, exercise, and an information module. The e-Exercise intervention is based on cognitive behavioral principles and the Dutch OA guideline [17]. The physiotherapist and patient both have an e-Exercise account. The physiotherapists could adapt the online program to the patients' individual needs and monitor patients' log-in frequencies and assignment evaluations. The patients' online graded activity module started with a baseline-measurement and formulation of a short- and long-term goal. Next, assignments for a self-chosen activity, for example walking or cycling, gradually increased up to the personal short-term goal. The online exercise modules consisted of strength- and stability exercises selected by the physiotherapists. Online information modules provided weekly new content (text and video) about OA etiology, pain-management, and physical activity. Patients were asked to evaluate the execution of their assignments every week, followed by tailored feedback. Automatic emails reminded patients about new assignments and content every week. During the face-to-face physiotherapy sessions, the patients' progress was discussed. The online e-Exercise application can be visited at https://www.e-exercise.nl [in Dutch] and a promotional video with English subtitles can be found at https://www.youtube.com/watch?v=4l9GoQWWy58.

Intervention: usual physiotherapy

Usual physiotherapists were encouraged to treat their patients with OA according to the Dutch OA guideline, which recommends: 1) information, 2) physical exercise, and 3) strength and stability exercises [17]. No restrictions were given with regard to the number of face-to-face sessions.

Clinical outcome measures

Clinical outcomes for this cost-effectiveness analyses included health-related quality of life, physical functioning and physical activity. Outcomes were assessed at baseline, 3 and 12 months using online questionnaires.

-Health-related quality of life was assessed using the EQ-5D-3L [18]. This questionnaire differentiates 245 health states, which were converted into a utility score (0-1), based on the Dutch tariff [19]. Quality-adjusted life years (QALY's) were calculated by multiplying patients' utility score by their time spent in that particular health state.

-Physical functioning was assessed with the subscale "function in daily living'' of the Hip OA Outcome Score (HOOS) for patients with hip OA and/or the Knee Injury and OA Outcome Score (KOOS) for patients with knee OA [20,21]. In patients with hip and knee OA, the lowest score of the HOOS and KOOS was used (0-100).

-Physical activity was assessed with Actigraph GT3x tri-axial accelerometers. Data were eligible if patients wore the meter ≥3 days, for ≥8 hours per day [22]. Sedentary activity, light, moderate and vigorous physical activity were distinguished according to the thresholds of Freedson et al [23]. Moderate and vigorous physical activity were summed and translated into a score of minutes moderate and/or vigorous physical activity/day.

Cost outcome measures

Costs included intervention, healthcare, sports, informal care, absenteeism, presenteeism, and unpaid productivity costs related to OA of hip and/or knee. Cost outcome measures were assessed at baseline, 3, 6 and 12 months using online self-reported questionnaires. All costs were converted to Euros 2015, using consumer price indices [24].

-Intervention costs: Costs of both intervention groups consisted of the self-reported number of face-to-face physiotherapy sessions, valued by Dutch standard costs [25]. For the e-Exercise group, intervention costs also comprised development, hosting, and maintenance costs of the website, divided by the number of patients allocated to e-Exercise.

-Healthcare costs: Patients reported their total number of physiotherapy visits after the intervention period, as well as their total number of visits to a general practitioner, massage therapist, alternative therapist, medical specialist, their hospital use as well as their use of prescribed and over the counter drugs and medical devises during the entire study period. During data-cleaning it appeared that 16 people reported 2 or 3 hip or knee replacements within 1 year. To validate these data, all patients that reported ≥1 surgeries were contacted again in June 2017. Data derived during this contact were used for further analyses. Healthcare volumes were valued using Dutch standard costs [25], prices according to professional organizations, and unit prices of the Royal Dutch Society of Pharmacy [26].

-Sports costs: Patients reported their sports membership costs as well as their expenses on sports equipment (e.g. shoes, clothes, racket).

-Informal care costs: Care by family and other volunteers was valued using a recommended Dutch shadow price of €14.58/h [25].

-Absenteeism costs: Patients were asked to report their total number of sickness absence days due to OA of hip and/or knee. In accordance with the Friction Cost Approach (friction period=60 days), sickness absence days were valued using gender-specific price weights [27].

-Presenteeism costs: Presenteeism was estimated using the Productivity and Disease Questionnaire (PRODISQ), valued using gender-specific price weights [25,28-31].

-Unpaid productivity costs: volunteer and domestic work that patients were not able to perform due to their OA was valued using a recommended Dutch shadow price of €14.58/h [25].

Demographics

Patient characteristics, including age, sex, height, weight, educational level, location of OA, duration of OA and the presence of comorbidities, were assessed at baseline.

Statistical analysis

Statistical analysis were performed according to the intention-to-treat principle. Descriptive statistics were used to describe and compare general characteristics of patients in the e-Exercise group and the usual physiotherapy group, and patients with complete and incomplete data. Missing data were multiply imputed in accordance with the MICE procedure [32]. The imputation model included variables that differed between e-Exercise and usual physiotherapy at baseline, variables that were related to the "missingness" of data, variables related to the outcomes, and all available baseline and follow-up cost and effect measure values. Results of each dataset were analyzed separately as described below, and pooled according to Rubin's rules [32].

A primary analysis was performed from the societal perspective and a secondary analysis from that of the healthcare sector. The societal perspective consisted of all costs related to the intervention under study, irrespective of who paid or benefitted from them. The healthcare perspective included only costs accruing to the healthcare sector.

Effectiveness of e-Exercise on clinical outcomes at 12-month follow-up was analyzed using linear multilevel analyses. Two levels were identified: patients (n=208) and physiotherapists (n=108). Analyses were adjusted for baseline values, sex, BMI, level of education and location of OA. The same analysis were used to compare costs between both groups. The 95%CI's around all cost differences were estimated using bias-corrected bootstrap intervals, with 5000 replications – stratified by physiotherapist. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the differences in costs between both groups by the difference in effects. Bootstrapped incremental cost-effect pairs were plotted on cost-effectiveness planes (5000 replications). Next, cost-effectiveness acceptability curves (CEACs) were constructed to provide a summary measure of the joint uncertainty of surrounding costs and effects. CEACs provide an indication of the probability of e-Exercise being cost-effective compared to usual physiotherapy at different willingness-to-pay values. For QALY's, the probabilities were provided for a willingness-to-pay of €10.000,- and €80.00,- per patient. For physical functioning and physical activity, the maximum probabilities were provided.

Sensitivity analysis

Two sensitivity analysis were performed. The first sensitivity analysis was performed by using only data of complete cases. The second sensitivity analysis was a per-protocol analyses, performed by comparing patients from the e-Exercise group that completed ≥8 modules (out of 12) with the entire usual physiotherapy group.

For the cost and effect differences, a two-tailed significance level of 0.05 was considered as statistically significant. Analyses were carried out using STATA Corp 13.0 and SPSS Statistics 23.0.

Results

Participants

In total, 208 eligible patients participated in this study; 109 in the e-Exercise group and 99 in the usual physiotherapy group (figure 1). At baseline, the e-Exercise group consisted of more low educated people compared to the usual physiotherapy group (e-Exercise 24.8%; usual PT 12.1%; p=0.04). Also, physical functioning was significantly higher in the e-Exercise group compared to the usual physiotherapy group (e-Exercise 61.3 (SD 18.3); usual physiotherapy 55.5 (SD 21.4);p=0.04). Clinical outcome questionnaires were complete in 135 patients (65%), accelerometer data were complete in 106 patients (51%) and cost outcome measures were complete in 113 participants (54%). Demographics and characteristics are shown in table 1.

Figure 1. Flow chart

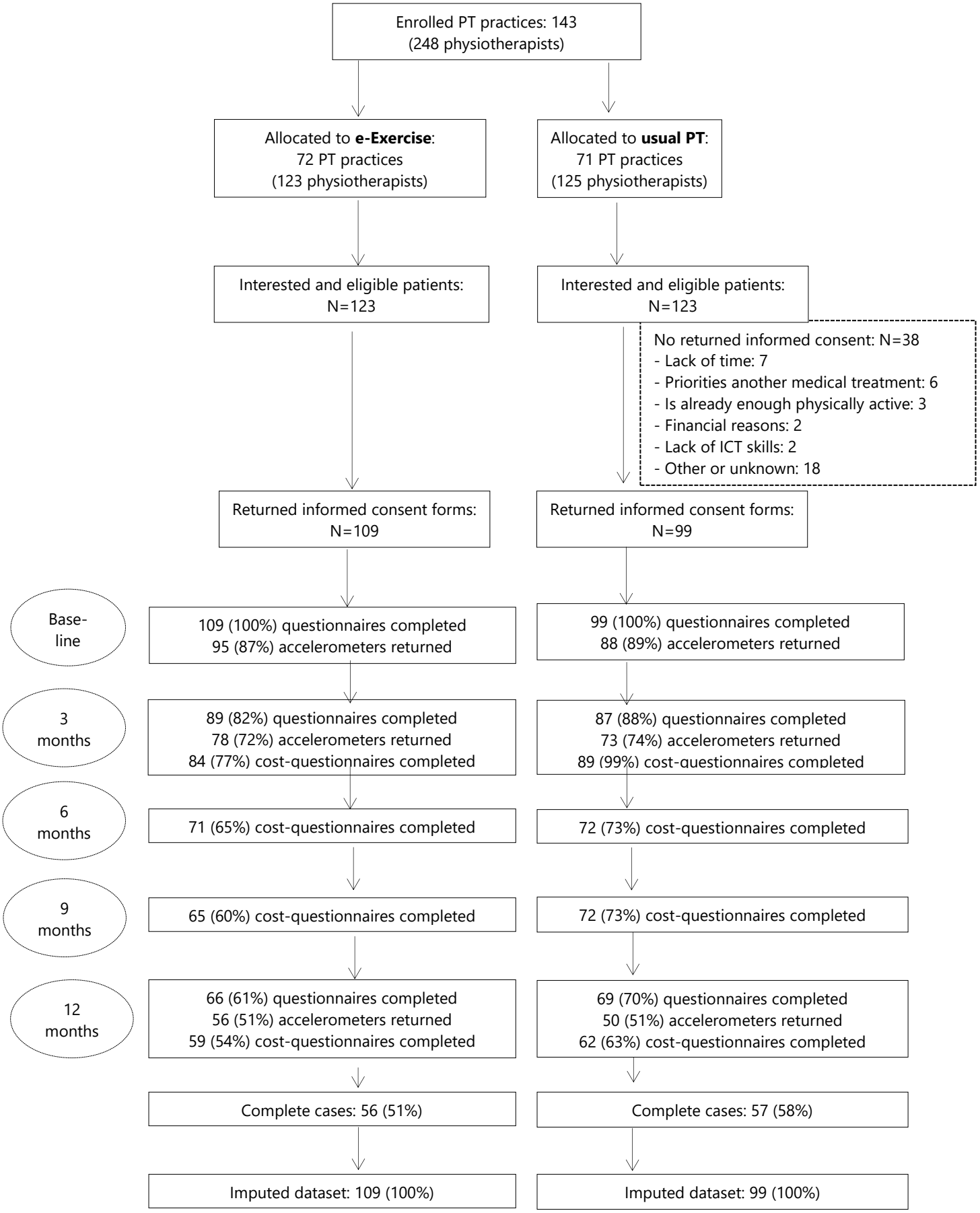


Table 1. Baseline characteristics of e-Exercise and usual physiotherapy (PT) patients

Intervention Number of respondents		e-Exercise All N=109	e-Exercise Complete N=56	e-Exercise Incomplete N=53	Usual PT All N=99	Usual PT Complete N=57	Usual PT Incomplete N=42
Sex, N (%)	Female	74 (67.9)	35 (62.5)	39 (73.6)	67 (67.7)	39	28
	Male	35 (32.1)	21 (37.5)	14 (26.4)	32 (32.3)	18	24
Age (years), mean (SD)		63.8 (8.5)	64.0 (3.9)	63.5 (10.0)	62.3 (8.9)	61.9 (8.8)	62.9 (9.2)
BMI (kg/m^2), mean (SD)		27.8 (4.2)	27.1 (4.2)	28.5 (4.2)	27.9 (4.9)	27.7 (4.9)	28.1 (4.8)
Location OA, N (%)	Knee	71 (65.1)	37 (66.1)	34 (64.2)	67 (67.6)	38 (66.7)	29 (69.0)
	Hip	21 (19.3)	15 (26.8)	6 (11.3)	17 (17.2)	11 (19.3)	6 (14.3)
	Both	17 (15.6)	4 (7.1)	13 (24.5)	15 (15.2)	8 (14.0)	7 (16.7)
Duration of symptoms, N (%)	< 1 year	21 (19.3)	8 (14.3)	13 (24.5)	20 (20.2)	14 (24.6)	6 (14.1)
	1-5 year	42 (38.5)	28 (50.0)	14 (26.4)	38 (38.4)	23 (40.4)	15 (35.7)
	≥5 year	46 (42.2)	20 (35.7)	26 (49.1)	41 (41.4)	20 (35.1)	21 (50.0)
Education, N (%)	Low	27 (24.8)	14 (25.0)	13 (24.5)	12 (12.1)	6 (10.5)	6 (14.3)
	Middle	41 (37.6)	24 (42.9)	17 (32.1)	51 (51.5)	29 (50.9)	22 (52.4)
	High	41 (37.6)	18 (32.1)	23 (43.4)	36 (36.4)	22 (38.6)	14 (33.3)
Comorbidity, N (%)	0	62 (56.9)	29 (51.8)	33 (62.3)	62 (62.6)	31 (54.4)	31 (73.8)
	1	20 (18.3)	11 (19.6)	9 (17.0)	20 (20.2)	15 (26.3)	5 (11.9)
	≥2	27 (24.8)	16 (28.6)	11 (20.8)	17 (17.2)	11 (19.3)	6 (14.3)
Physical functioning, mean (SD)	0-100	61.3 (18.3)	64.8 (15.1)	57.6 (20.7)	55.5 (21.4)	55.9 (21.7)	55.0 (21.2)
Physical activity, mean (SD)	Min/day	25.2 (23.1)	27.3 (26.0)	22.6 (18.8)	22.5 (21.8)	25.8 (23.7)	17.1 (17.3)
Pain, mean (SD)	0-10	5.1 (2.2)	4.7 (2.1)	5.5 (2.3)	5.7 (2.3)	5.8 (2.4)	5.5 (2.1)
Utility score, mean (SD)	0-1	0.8 (0.1)	0.8 (0.1)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)

Effects

At 12 months, no significant differences were seen between the e-Exercise group and the usual physiotherapy group on health-related quality of life (B=0.01; 95%CI: -0.03 to 0.04), physical functioning (B=1.49; 95%CI: -4.70 to 7.69) and physical activity (B=-3.46; 95%CI: -11.66 to 4.73).

Resource use and costs

Patients in the e-Exercise group reported to have had on average 5 face-to-face physiotherapy sessions, whereas patients in the usual physiotherapy group reported to have had on average 12 face-to-face sessions. Consequently, intervention costs of e-Exercise were significantly lower compared to usual physiotherapy. Medication costs and sports costs were also significantly lower in the e-Exercise group compared to the usual physiotherapy group. Primary healthcare costs, secondary healthcare

costs, informal care costs, absenteeism costs, presenteeism costs and unpaid productivity costs did not significantly differ between groups. Overall, total societal costs and total healthcare costs showed no statistical significant differences between groups (Table 2).

Table 2. Mean costs per participant in the e-Exercise group and usual physiotherapy (PT) group and mean differences between both groups during 12 months follow-up

Cost category	e-Exercise (N=109); mean costs (SEM)	Usual PT (N=99); mean costs (SEM)	Unadjusted mean cost difference (95% CI)	Adjusted mean cost difference (95% CI)
Intervention ǂ	241 (37)	451 (55)	-209 (-294 to -128)	-202 (-286 to -120)
Primary healthcare	438 (63)	536 (84)	-98 (-306 to 80)	-107 (-340 to 82)
Secondary healthcare	3143 (711)	3819 (885)	-677 (-2699 to 1138)	-332 (-2134 to 1444)
Medication ǂ	106 (24)	299 (90)	-192 (-436 to -79)	-151 (-340 to -52)
Sport	159 (26)	292 (73)	-133 (-242 to -51)	-126 (-237 to -43)
Informal care	327 (109)	327 (80)	1 (-173 to 156)	46 (-117 to 205)
Absenteeism	927 (434)	743 (304)	184 (-64 to 1092)	368 (-459 to 1365)
Presenteeism	237 (74)	429 (121)	-191 (-533 to 12)	-120 (-411 to 64)
Unpaid productivity	768 (137)	823 (162)	-55 (-397 to 256)	97 (-219 to 413)
Healthcare costs*	3928 (744)	5105 (937)	-1177 (-3340 to 763)	-792 (-2720 to 1100)
Total costs	6348 (1007)	7718 (1292)	-1371 (-4512 to 1240)	-529 (-3315 to 2057)

ǂ Significant difference between e-Exercise and usual PT

*Healthcare costs= intervention costs + primary healthcare costs + secondary healthcare costs + medication costs

Cost-effectiveness analysis

-Primary analysis: societal perspective

For QALYs, the ICER was -52.900, demonstrating that one QALY gained in e-Exercise was on average associated with a societal cost saving of €52.900,- compared to usual physiotherapy (Table 3, Figure 2a). The CEAC (Figure 3a) showed that the probability of e-Exercise being cost-effective compared to usual physiotherapy was 0.68 at a willingness to pay of €10.000,- per QALY gained and 0.70 at a willingness to pay of €80.000,- per QALY gained.

For physical functioning, the ICER was -355, demonstrating that a 1-point improvement on the HOOS or KOOS in e-Exercise was on average associated with a societal cost saving of €355,- compared to usual physiotherapy (Table 3, Figure 2b). The CEAC (Figure 3b) showed that if decision makers are not willing to pay anything

per 1-point improvement on the HOOS/KOOS, the probability of e-Exercise being cost-effective compared to usual physiotherapy was 0.67. At higher willingness to pays, this probability remained about the same.

For physical activity, the ICER was 153, indicating that a decrease of 1-minute moderate or vigorous physical activity per day in e-Exercise was on average associated with a societal cost saving of €153,- compared to usual physiotherapy (Table 3, Figure 2c). The CEAC (Figure 3c) showed that if decision makers are not willing to pay anything per 1-minute improvement of physical activity per day, the probability of e-Exercise being cost-effective compared to usual physiotherapy was 0.67. At higher willingness to pays, this probability decreased.

Overall, from the societal perspective, the maximum probability of e-Exercise being cost-effective compared with usual physical therapy was moderate.

-Secondary analysis: healthcare perspective

The ICER for QALYs was -79.200, indicating that one QALY gained in e-Exercise was on average associated with a healthcare cost saving of €79.200.- compared to usual physiotherapy (Table 3). The CEAC (not shown) indicated that the probability of cost-effectiveness was 0.84 at a willingness to pay of €10.000,- per QALY gained and 0.80 at a willingness to pay of €80.000,- per QALY gained.

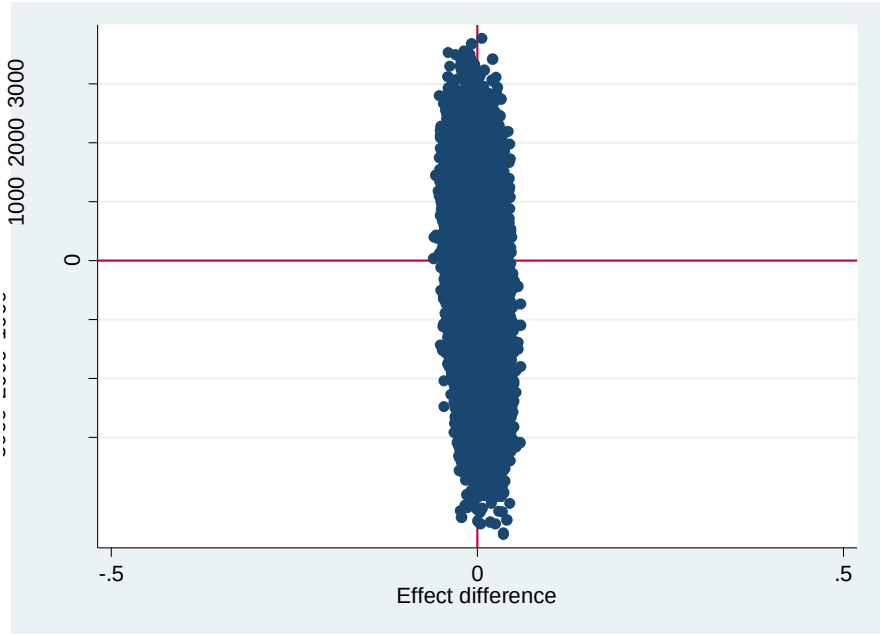
The ICER for physical functioning was -532, indicating that a 1-point improvement on the HOOS or KOOS in e-Exercise was on average associated with a healthcare cost saving of €532,- compared to usual physiotherapy (Table 3). The CEAC (not shown) showed that if decision makers are not willing to pay anything per 1-point improvement on the HOOS/KOOS, the probability of cost-effectiveness was 0.82. At higher willingness to pays, this probability remained about the same.

For physical activity, the ICER was 229, demonstrating that a decrease of 1-minute moderate or vigorous physical activity per day in e-Exercise was on average associated with a healthcare cost saving of €229,- compared to usual physiotherapy (Table 3). The CEAC (not shown) showed that if decision makers are not willing to pay anything per 1-minute improvement of physical activity per day, the probability of cost-effectiveness was 0.82. At higher willingness to pays, this probability remained about the same.

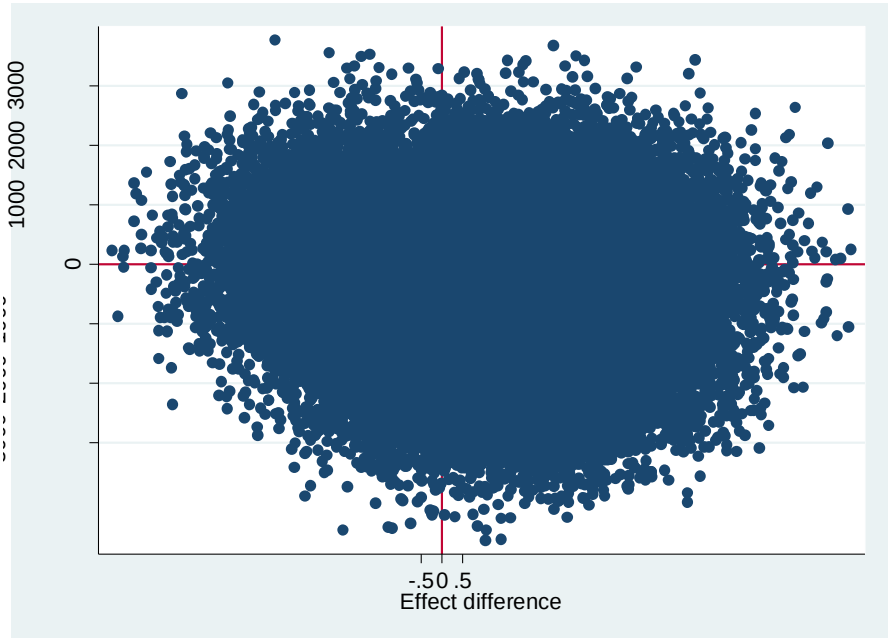
Overall, from the healthcare perspective, the maximum probability of e-Exercise being cost-effective compared with usual physical therapy was moderate.

Figure 2. Cost effectiveness planes from societal perspective

2a Difference in QALY (range 0-1, EQ-5D)



2b. Difference in objectively measured physical functioning (0-100, HOOS or KOOS)



2c. Difference in objectively measured physical activity (min/day, accelerometer)

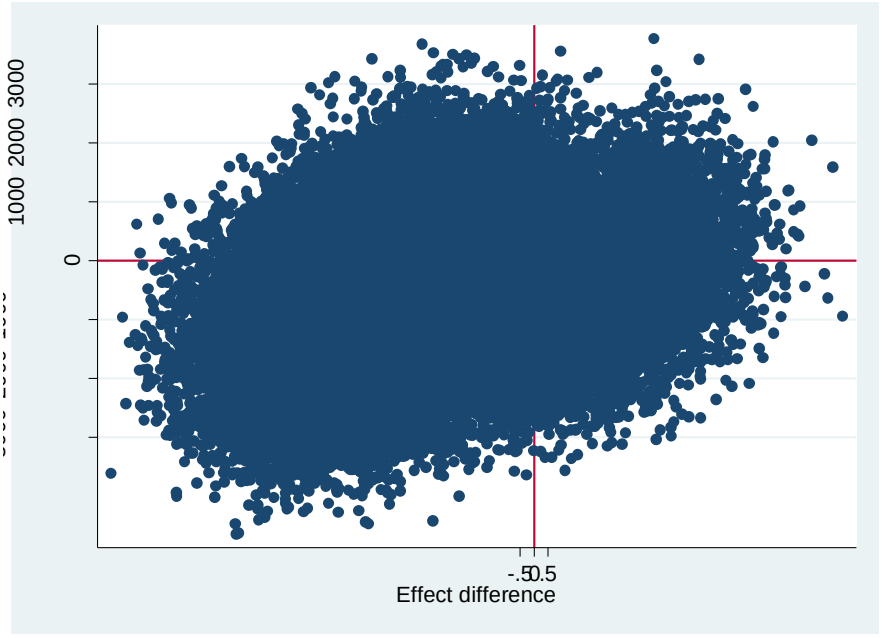
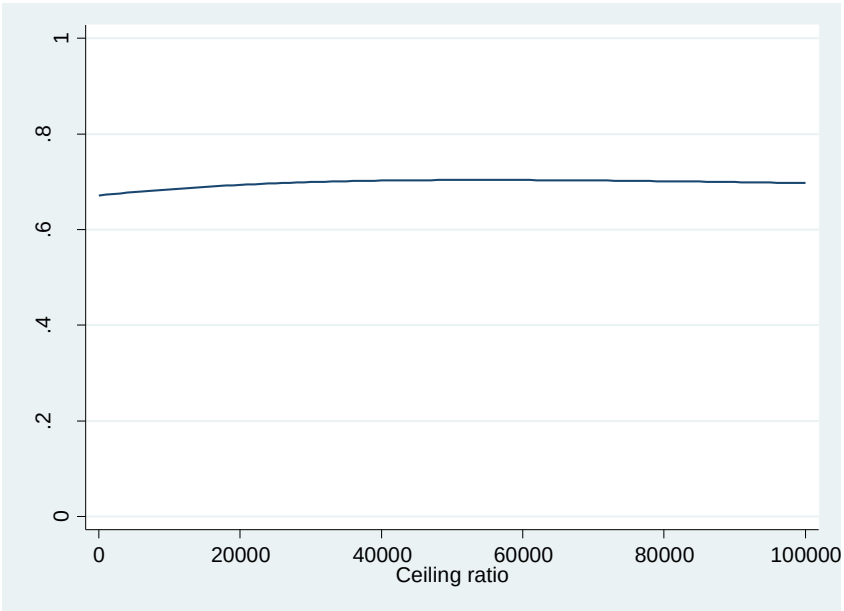
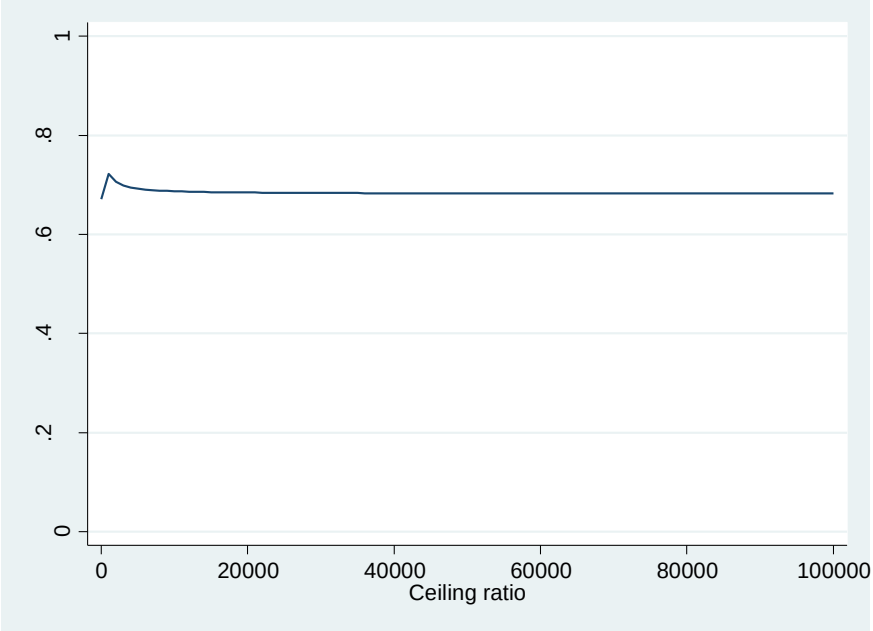


Figure 3. Cost-effectiveness acceptability curves from societal perspective

3a Willingness-to-pay in Euros 2015 for QALY (range 0-1, EQ-5D)



3b Willingness-to-pay in Euros 2015 for physical functioning (0-100, HOOS or KOOS)



3c Willingness-to-pay in Euros 2015 for physical activity (min/day, accelerometer)

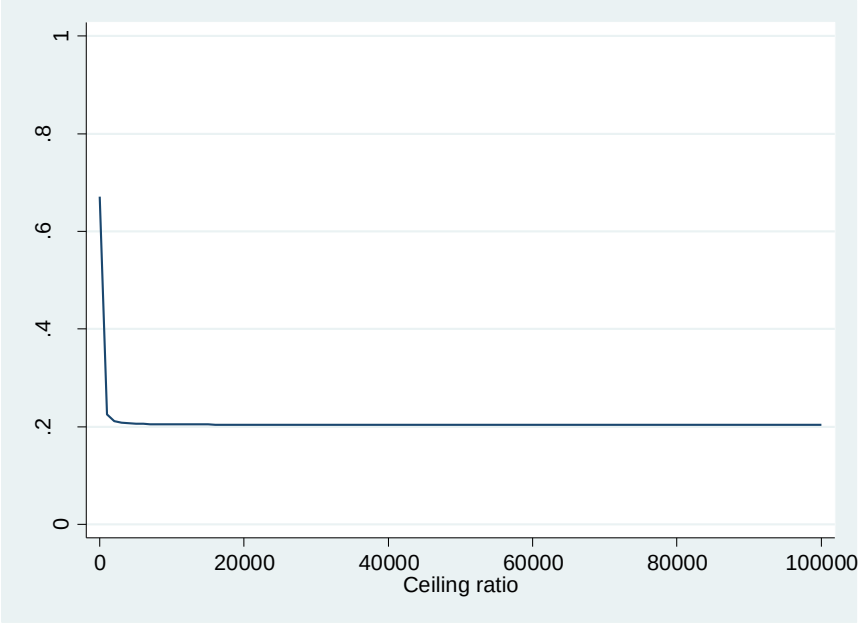


Table 3. Differences in pooled mean costs and effects

Analysis	N e-Exercise	N Usual PT	Outcome	ΔC (95% CI) In euro's	ΔE (95% CI) In points	ICER Euro/point	Distribution CE-plane (%)			
							NE[a]	SE[b]	SW[c]	NW[d]
Main analysis 1:	109	99	QALY's (0-1)	-529 (-2265 to 1268)	0.01 (-0.03 to 0.04)	-52.900	17.8	42.1	23.2	16.9
Total costs and	109	99	Physical functioning (0-100)	-529 (-2265 to 1268)	1.49 (-4.70 to 7.69)	-355	20.5	44.7	20.6	14.2
imputed dataset	109	99	Physical activity (min/day)	-529 (-2265 to 1268)	-3.46 (-11.66 to 4.73)	153	7.7	9.4	55.9	27.0
Main analysis 2:	109	99	QALY's (0-1)	-792 (-2101 to 440)	0.01 (-0.03 to 0.04)	-79.200	13.5	46.4	33.4	6.7
Healthcare costs and	109	99	Physical functioning (0-100)	-792 (-2101 to 440)	1.49 (-4.70 to 7.69)	-532	14.4	50.7	29.2	5.7
imputed dataset	109	99	Physical activity (min/day)	-792 (-2101 to 440)	-3.46 (-11.66 to 4.73)	229	5.2	11.9	67.9	15.0
Sensitivity analysis 1:	42	36	QALY's (0-1)	2211 (701 to 3722)	-0.00 (-0.03 to 0.03)	-22.1100	34.8	0.1	0.1	65.0
Complete cases	42	36	Physical functioning (0-100)	2211 (701 to 3722)	-2.15 (-7.50 to 3.20)	-1.028	18.4	0.0	0.2	81.4
	42	36	Physical activity (min/day)	2211 (701 to 3722)	-1.95 (-7.43 to 3.53)	-1.134	22.0	0.0	0.2	77.8
Sensitivity analysis 2:	39	99	QALY's (0-1)	-592 (-2719 to 1603)	0.02 (-0.01 to 0.06)	-29.600	29.0	65.6	1.4	4.0
Per-protocol and	39	99	Physical functioning (0-100)	-592 (-2719 to 1603)	4.10 (-1.56 to 9.77)	-144	30.7	66.1	0.8	2.4
imputed dataset	39	99	Physical activity (min/day)	-592 (-2719 to 1603)	-1.79 (-8.72 to 5.13)	331	12.8	18.3	48.7	20.2

CI: Confidence Interval; C: Costs; CE-plane: Cost-Effectiveness plane, E: Effects, ICER: Incremental Cost-Effectiveness Ratio; Costs are expressed in 2015 Euros.

[a] The northeast quadrant of the CE plane, indicating that e-Exercise is more effective and more costly than usual physiotherapy

[b] The southeast quadrant of the CE plane, indicating that e-Exercise is more effective and less costly than usual physiotherapy

[c] The northwest quadrant of the CE plane, indicating that e-Exercise is less effective and more costly than usual physiotherapy

[d] The southwest quadrant of the CE plane, indicating that e-Exercise is less effective and less costly than usual physiotherapy

Sensitivity analysis

Results of the sensitivity analyses with complete-cases showed significant higher costs in the e-Exercise group compared to usual physiotherapy, but no significant differences in effects. Results of the per-protocol sensitivity analysis were in line with those of the main analysis (Table 3).

Discussion

Main findings

This study showed that the intervention costs of e-Exercise were significantly lower compared to usual physiotherapy in patients with hip and/or knee OA due to the fact that e-Exercise patients received on average seven face-to-face sessions less than their usual physiotherapy counterparts. Medication costs were also significantly lower in e-Exercise compared to usual physiotherapy, whereas total societal and total healthcare costs did not significantly differ between groups. Effectiveness on clinical outcome measures did not significantly differ. For physical functioning and physical activity, the maximum probability of e-Exercise being cost-effective compared to usual physiotherapy from both perspectives was moderate (<0.82). For QALY, the probabilities of cost-effectiveness were 0.68 and 0.84 at a willingness to pay of €10.000,- per QALY gained and 0.70 and 0.80 at a willingness to pay of €80.000,- per QALY gained, for respectively the societal and the healthcare perspective. These results were confirmed by a per-protocol sensitivity analysis. However, the sensitivity analysis using complete cases only showed significant higher costs in the e-Exercise group compared to the usual physiotherapy group. The latter is probably due to selective drop-out. That is, patients with complete and incomplete data slightly differed in terms of levels of physical functioning and physical activity.

Interpretation of the findings

An explanation for the absence of a significant difference in total societal and healthcare costs between e-Exercise and usual physiotherapy might be the fact that physiotherapeutic sessions are relatively cheap compared to for example secondary healthcare costs, like outpatient clinic visits. Within economic evaluations it is warranted to include all relevant cost categories, instead of only including intervention costs [25]. Although we did find significantly lower intervention and

medication costs within e-Exercise, the share of these cost categories is relatively small (interventions costs 4% of total costs; medication: 2% of total costs) compared to that of secondary healthcare costs (50% of total costs). Taken all healthcare costs together, total costs were still in favor of e-Exercise, albeit not statistically significantly. One should hear in mind, however, that a 12-month follow-up is likely to be too short to investigate whether one of both interventions results in a reduction of secondary healthcare costs at the long-term (e.g. due to joint replacements). Therefore, for future cost-effectiveness analyses of physiotherapeutic interventions, it is recommended to use a longer follow-up periods. With respect to this this study, we recommend to investigate the number of hip and/or knee replacements in both groups five years after baseline.

Another explanation for the finding that e-Exercise was not cost-effective compared with usual physiotherapy might be the fact that differences in effectiveness between both interventions were minimal. For physical activity, this can be explained by the fact that patients already had a high level of physical activity per day at baseline, which resulted in less room for improvement in both groups. Next to this, two mixed-methods studies provided recommendation to improve the effectiveness of e-Exercise [33,34]. Two concrete recommendations were to provide options to tailor the intervention more to individual patient needs and to learn physiotherapists to integrate online care within physiotherapeutic care. Also, knowledge about patients that are more or less suitable for receiving a blended intervention is warranted. Improving the intervention as a whole (i.e. the web-application, the integration within physiotherapeutic care and providing it to the right person) might improve the effectiveness, as well as the cost-effectiveness of e-Exercise. Currently, effectiveness of e-Exercise and usual physiotherapy are somewhat comparable, with significantly lower intervention costs in e-Exercise.

Since from both perspectives, no significant differences were seen in total costs and effects, the decision about which intervention should be applied can be based on the preferences of the patient and the physiotherapist. In the current Dutch healthcare system, however, physiotherapists get paid per session and have no financial incentive to apply an intervention with less face-to-face sessions. Physiotherapists that used e-Exercise, mentioned this financial (dis-)advantage as one of the determinants for not using e-Exercise [34]. In order to stimulate the usage of e-Exercise by physiotherapists, the investigation of new business models (like a shared-savings model) is recommended.

Strengths & limitations

A strength of this economic evaluation is that we analyzed the data both from the societal perspective as well as the healthcare perspective. Next, we not only used QALYs as outcome measure, but also physical functioning and physical activity. These two outcome measures are closely related to the aim of the studied interventions. A limiting factor within the current study was the use of self-reported questionnaires, which were sent every three months. Self-reported questionnaires are a potential source of "social desirability" and/or "recall bias". To illustrate, after analyzing the data, it appeared that 16 participants reported multiple hip and/or knee surgeries, whereas it highly unlikely for patients to have had more than one joint replacement in one year. To validate these data, in June 2017 all patients that reported ≥1 surgeries were sent again the question how often they received a hip or knee replacement in their specific 12 month follow-up. A final limitation is the relatively high percentage of patients with missing data. As a solution, missing costs and effects were multiply imputed. Within economic evaluations, multiple imputation is a widely used method which is considered as highly appropriate since the use of several imputed data sets makes it possible to account for the uncertainty about missing data [32].

Conclusion

Overall, e-Exercise cannot be seen as cost-effective in comparison with usual physiotherapy, from both a societal and a healthcare perspective. From both perspectives, no significant differences were seen in total costs and effects. Therefore, the decision about which intervention should be applied can be based on the preferences of the patient and the physiotherapist. Future research exploring which patients are more or less suitable for blended physiotherapy is warranted.

Declarations

The Medical Ethical Committee of the St. Elisabeth hospital Tilburg in the Netherlands approved the study design and protocol (Dutch Trial Register NTR4224). All datasets used for this manuscript are available from the corresponding authors on reasonable request. The authors declare that they have no competing interests. The study is funded by ZonMw, the Dutch Rheumatoid Arthritis Foundation and the Royal Dutch Society for Physiotherapy.

Authors' Contributions

CK, HvD, DB, DdB, JD and CV were involved in the conception and design of the study. CK was involved with data collection, performed the statistical analysis together with HvD, and drafted the manuscript. CK, HvD, DB, JD and CV were involved in the interpretation of data and have critically reviewed the manuscript and approved the final version submitted for publication.

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References

1. Bijlsma JW, Berenbaum F, Lafeber FP: Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011, 377(9783):2115-2126.
2. Zhang Y, Jordan JM: Epidemiology of osteoarthritis. *Clinics in geriatric medicine* 2010, 26(3):355-369.
3. MMJ. N: Incidentie en prevalentie van gezondheidsproblemen in de Nederlandse huisartsenpraktijk in 2014. Uit: NIVEL Zorgregistraties eerste lijn [internet]. 2017 [Laatst gewijzigd op 23-02-2017; geraadpleegd op 03-05-2017]. URL: www.nivel.nl/node/4309. 2014.
4. RIVM: Kosten van Ziekten database 2013, reference code: kvz_v2l1b1p4r0c0i0t1j0o1y6a-1g0d86s54f0z0w2; URL: www.kostenvanziekten.nl. 2011.
5. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H *et al*: OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014, 22(3):363-388.
6. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM: A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Seminars in arthritis and rheumatism* 2014, 43(6):701-712.
7. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL: Exercise for osteoarthritis of the knee. *The Cochrane database of systematic reviews* 2015, 1:CD004376.
8. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S: Exercise for osteoarthritis of the hip. *The Cochrane database of systematic reviews* 2014(4):CD007912.
9. Elbert NJ, van Os-Medendorp H, van Renselaar W, Ekeland AG, Hakkaart-van Roijen L, Raat H, Nijsten TE, Pasmans SG: Effectiveness and cost-effectiveness of ehealth interventions in somatic diseases: a systematic review of systematic reviews and meta-analyses. *J Med Internet Res* 2014, 16(4):e110.
10. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JE: Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. *JMIR mental health* 2016, 3(1):e9.
11. Donker T, Blankers M, Hedman E, Ljotsson B, Petrie K, Christensen H: Economic evaluations of Internet interventions for mental health: a systematic review. *Psychol Med* 2015, 45(16):3357-3376.
12. Kraal JJ, Van den Akker-Van Marle ME, Abu-Hanna A, Stut W, Peek N, Kemps HM: Clinical and cost-effectiveness of home-based cardiac rehabilitation compared to conventional, centre-based cardiac rehabilitation: Results of the FIT@Home study. *Eur J Prev Cardiol* 2017:2047487317710803.

13. Bossen D, Kloek C, Snippe HW, Dekker J, de Bakker D, Veenhof C: A Blended Intervention for Patients With Knee and Hip Osteoarthritis in the Physical Therapy Practice: Development and a Pilot Study. *JMIR research protocols* 2016, 5(1):e32.
14. Kloek C, Bossen D, Spreeuwenberg P, Dekker J, de Bakker D, Veenhof C: Effectiveness of a blended physiotherapy intervention in patients with hip and/or knee osteoarthritis: a randomized controlled trial. *[in press]* 2017.
15. Kloek CJ, Bossen D, Veenhof C, van Dongen JM, Dekker J, de Bakker DH: Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: study protocol of a randomized controlled trial. *BMC musculoskeletal disorders* 2014, 15:269.
16. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M *et al*: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and rheumatism* 1986, 29(8):1039-1049.
17. Peter WFH JM, Bloo H, Dekker-Bakker LMMCJ, Dilling RG, Hilberdink WKHA, Kersten-Smit C, de Rooij M, Veenhof C, Vermeulen HM, de Vos I, Vlieland TPMV. 2010.: KNGF-richtlijn Artrose heup-knie. *Ned Tijdschr voor Fysiotherapie* 2010.
18. EuroQol-group: EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990, 16:199-208.
19. Lamers LM SP, McDonnell J, Krabbe PFM, van Busschbach JJ: [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. *Ned Tijdschr Geneeskd* 2005, 149:1574-1578.
20. de Groot IB, Favejee MM, Reijman M, Verhaar JA, Terwee CB: The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health and quality of life outcomes* 2008, 6:16.
21. de Groot IB, Reijman M, Terwee CB, Bierma-Zeinstra SM, Favejee M, Roos EM, Verhaar JA: Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthritis Cartilage* 2007, 15(1):104-109.
22. Hart TL, Swartz AM, Cashin SE, Strath SJ: How many days of monitoring predict physical activity and sedentary behaviour in older adults? *The international journal of behavioral nutrition and physical activity* 2011, 8:62.
23. Freedson PS, Melanson E, Sirard J: Calibration of the Computer Science and Applications, Inc. accelerometer. *Medicine and science in sports and exercise* 1998, 30(5):777-781.
24. Netherlands S: Consumer price indices. Url: https://www.cbs.nl/nl-nl/cijfers 2017.
25. Hakkaart-van Roijen LvdL, N; Bouwmans, C; Kanters, T, Tan SS: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. *CVZ* 2015.
26. Z-Index: G-Standaard. Url: www.z-index.nl/zorgverleners. . 2009.

27. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L: The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995, 14(2):171-189.
28. Kessler RC, Ames M, Hymel PA, Loeppke R, McKenas DK, Richling DE, Stang PE, Ustun TB: Using the World Health Organization Health and Work Performance Questionnaire (HPQ) to evaluate the indirect workplace costs of illness. *J Occup Environ Med* 2004, 46(6 Suppl):S23-37.
29. Kessler RC, Barber C, Beck A, Berglund P, Cleary PD, McKenas D, Pronk N, Simon G, Stang P, Ustun TB *et al*: The World Health Organization Health and Work Performance Questionnaire (HPQ). *J Occup Environ Med* 2003, 45(2):156-174.
30. Koopmanschap M MW, Evers S, Severens J, Burdorf A, Brouwer W: Handleiding Voor Het Gebruik van PRODISQ Versie 2.1 [Manual for the Use of PRODISQ Version 2.1]. . *Erasmus MC Rotterdam: Instituut voor Medical Technology Assessment, Instituut Maatschappelijke Gezondheidszorg, Universiteit van Maastricht – Beleid Economie en Organisatie van de Zorg* 2004.
31. Koopmanschap MA: PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. *Expert Rev Pharmacoecon Outcomes Res* 2005, 5(1):23-28.
32. White IR, Royston P, Wood AM: Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011, 30(4):377-399.
33. de Vries HJ, Kloek CJJ, de Bakker DH, Dekker J, Bossen D, Veenhof C: Determinants of Adherence to the Online Component of a Blended Intervention for Patients with Hip and/or Knee Osteoarthritis: A Mixed Methods Study Embedded in the e-Exercise Trial. *Telemed J E Health* 2017.
34. Kloek C; Bossen, D.; de Vries, H.; de Bakker, DH.; Veenhof, C.; Dekker, J.: Physiotherapists' experiences with a blended osteoarthritis intervention: a mixed methods study. [submitted 2017].

7

Determinants of adherence to the online component of a blended intervention for patients with hip- and/or knee osteoarthritis: a mixed methods study embedded in the e-Exercise trial

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Abstract

Background: Embedding web-based interventions within physiotherapy has potential, but knowledge on patient adherence to these interventions is limited.

Introduction: This study explores which patient-, intervention- and environment-related factors are determinants of adherence to the online component of e-Exercise, a twelve-week blended intervention for patients with hip and/or knee osteoarthritis.

Methods: A convergent mixed methods study was performed, embedded within an ongoing trial. Quantitative data of 109 participants that received e-Exercise were used for negative binomial regression analysis. Adherence was defined as the number of online evaluated weeks. Next, semi-structured interviews on factors related to adherence to the online component were analyzed.

Results: Nineteen participants with missing outcome data because their program was not started were excluded. Of the 90 analyzed participants, 81.1% evaluated at least 8 weeks. Adherence was highest for participants with middle education, 1-5 year osteoarthritis duration and participants that were physiotherapist-recruited. The 10 analyzed interviews revealed that sufficient internet-skills, self-discipline, execution of the exercise plan, the intervention's usability, flexibility, persuasive design, added value, acceptable required time and research participation were linked to favorable adherence.

Discussion: It is unknown if patients that adhered to the online component also adhered to their exercise plans. The relationship between adherence to the online component and clinical outcomes will be addressed in a future study.

Conclusions: The majority of the participants adhered to the online component of e-Exercise, illustrating its applicability. The integration within the physiotherapy setting and intervention's persuasive design appear to have an important role in optimizing patient adherence.

Introduction

Osteoarthritis is an age-related joint disease that causes stiffness, reduced range of motion and joint instability that are manifested in pain, disability and loss of health-related quality of life [1, 2]. The hip and knee are the most affected joints [1]. Face-to-face exercise therapy reduces pain levels and increases physical activity in patients with hip and/or knee osteoarthritis [3, 4], but is costly. Cost-effective strategies to manage hip and/or knee osteoarthritis are therefore needed. Web-based interventions (e.g. website with personalized goals, home exercises and educational modules) have potential to enhance patient self-management [5] and lower healthcare costs [6, 7]. Although some web-based interventions are offered without professional guidance, they can also be integrated with professional guidance, which is called blended care [8]. For patients with osteoarthritis, web-based self-management interventions are linked to high acceptance and satisfaction levels and have shown to modestly improve several health outcomes [9].

An example of such a web-based intervention without professional guidance for patients with hip and/or knee osteoarthritis is the 9-week physical activity program Join2Move [10, 11]. Join2Move was found to improve short term (3 months) physical function and long term (12 months) subjective and objective physical activity [11]. However, only 46.0% of the patients were considered adherent [10], defined as the completion of at least 6 completed online week-modules [12]. Since web-based interventions are more effective for patients that adhere [13, 14], Join2Move's effectiveness potentially can be increased if adherence can be improved. Based on semi-structured interviews, lack of human involvement and professional guidance were named as reasons for non-usage amongst participants of the Join2Move study [10].

This led to the development of e-Exercise, a 12-week physical activity program for patients with hip and/or knee osteoarthritis that combines an online component based on Join2Move with offline, face-to-face physiotherapy sessions [12]. Furthermore, the intervention's persuasive design was improved by adding several new features [12]. Both therapeutic contact [15, 16] and persuasive design [16] are intervention-related factors associated with favorable adherence. The (cost)effectiveness of e-Exercise is currently being studied [17].

Since blended care is a new, upcoming treatment option, knowledge on adherence to the online component of these interventions and how that might differ from fully web-based interventions is limited. Insight in patients' adherence to the online

component of e-Exercise will contribute to this body of knowledge, as well as its implementation. By identifying which sub-populations adhere to the program and which factors are related to these possible differences in adherence will help determine which sub-populations can be targeted and how the program can be improved. Therefore, this study explores what patient-, intervention- and environment-related factors are determinants of adherence to the online component of e-Exercise.

Methods

Study Design

A convergent mixed methods study was executed, embedded within a trial on the (cost)effectiveness of e-Exercise [17]. Qualitative and quantitative data were analyzed during the same time span. Quantitative analysis mostly targeted patient-related factors, while qualitative analysis was expected to particularly yield intervention- and environment-related determinants. The e-Exercise trial was approved by the Medical Ethical Committee of the St. Elisabeth hospital Tilburg (NL 46358.008.13) [17].

Participants

Participants of the e-Exercise trial were recruited in Dutch primary care physiotherapy practices or through advertisements from September 2014 to March 2015. Patients were eligible when they (i) were aged 40-80 years and (ii) had osteoarthritis of the hip and/or knee according to the American College of Rheumatology criteria [17]. Patients were excluded when they (i) were on a waiting-list for a hip or knee replacement surgery, (ii) were being contra-indicated for physical activity without supervision, (iii) were sufficiently physically active based on Dutch physical activity guidelines [18], (iv) had received physical therapy for their osteoarthritis in the last six months, (v) did not have internet-access or (vi) were unable to understand the Dutch language [17]. Quantitative data of all 109 participants that were randomized to the intervention group of the e-Exercise trial were used for the current study. To limit recall bias during semi-structured interviews that were executed in October and November 2015, the twenty last included patients were invited. If necessary, additional participants were recruited for telephonic interviews based on purposeful and theoretical sampling until optimal variability in patient characteristics (age,

geographic location, comorbidity, adherence) and data saturation in two consecutive interviews was achieved.

Intervention

The online component of e-Exercise consists of (i) a twelve-week incremental physical activity program based on graded activity, (ii) strength and stability exercises and (iii) information on osteoarthritis-related themes [17]. The offline component consists of up to five face-to-face physiotherapy sessions that comply with the Dutch guideline for hip- and knee osteoarthritis [17, 19].

In the first session, the physiotherapist created an account, instructed the patient on using the e-Exercise website and selected exercises. During the first week, patients submitted their baseline capacity for their central activity through an online form. This baseline capacity was determined by performing the targeted activity on independent three days for as long as acceptable. In the second session, the physiotherapist and patient used this baseline value to set a goal for the short- and long term. The physiotherapist would then press the 'start the program' button, after which the system automatically created an individual activity scheme that gradually increased to the patients' short term goal. Pressing the start button was essential, since the patient otherwise wouldn't receive access to the full intervention, including the weekly graded activity and exercise modules and evaluation forms.

After the program was started, patients received automated weekly e-mails that informed them about new website content and reminded them to evaluate their weekly graded activity and exercise modules. Evaluation of the graded activity modules consisted the question if the participant performed more, less or exactly the assigned minutes of physical activity and an eleven-point Numeric Rating Scale (NRS) for pain during that activity. Evaluation of exercises consisted an eleven point NRS for difficulty of the exercise. During face-to-face sessions, the physiotherapist used these evaluations to discuss the patient's progress and if necessary change the intensity or exercise type. A more detailed description of the intervention can be found in the study protocol [17].

Quantitative Data Collection

Outcome variables

Adherence to the online component of e-Exercise was operationalized as the number of weeks that a participant evaluated either a graded activity or exercise module. The main outcome variable was therefore a discrete (count) variable with a minimum of 1

and a maximum of 12 weeks with an evaluated module. Additionally, to allow comparison to the Join2Move study, participants were labelled adherent to the online component when they evaluated at least eight out of the maximum of twelve modules, using the same ratio as the Join2Move study [10].

Independent variables

The measuring instruments, categories and value ranges of included variables are described in Table 1. The number of treatment sessions were determined after the intervention period. All other variables were measured at baseline. More detailed information can be found in the study protocol [17].

Quantitative Data Analysis

Descriptive statistics for the observed independent and outcome variables were calculated. Depending on their distribution, a percentage (if categorical), a mean and standard deviation (if normal) or a minimum, maximum and median (if non-normal) were described. Negative binomial regression analysis, a method that is appropriate for count data that follow the negative binomial distribution, was performed using the inversed outcome data [20]. First, univariate analyses were performed to screen for potential determinants using a p-value of ≤.2. Second, multivariate analysis was performed with a backward stepwise procedure [21], excluding variables with p-value of p≥.1). To determine the maximum number of independent variables in the final model, a rule-of-thumb that the ratio of participants to independent valuables needed to be 10:1 was applied [22, 23]. The final model's Goodness of Fit was evaluated using the Omnibus Test [24, 25] and the ratio of the deviance and Pearson Chi-Square values to the degrees of freedom, which ideally should be close to 1.

Qualitative Data Collection and Analysis

Initial semi-structured interviews were performed by two research assistants using a topic-list (Online Appendix 1) that was based on a study by Fleuren et al. [26] Interview audiotapes were transcribed verbatim by HdV. HdV and CK performed open coding independently [27, 28]. Investigator triangulation was applied by performing axial and selective coding in co-operation by constant comparison of codes within and between interviews [27, 28]. Codes expressing related concepts were grouped to create themes. Respondent validation was performed through member-checks by e-

mailing participants a summary of the interview. An audit trail including theoretical memos was tracked and inspected by DB [29].

Table 1. Description of the used measurement instrument, categories, value ranges and association with adherence for independent variables used in quantitative analysis

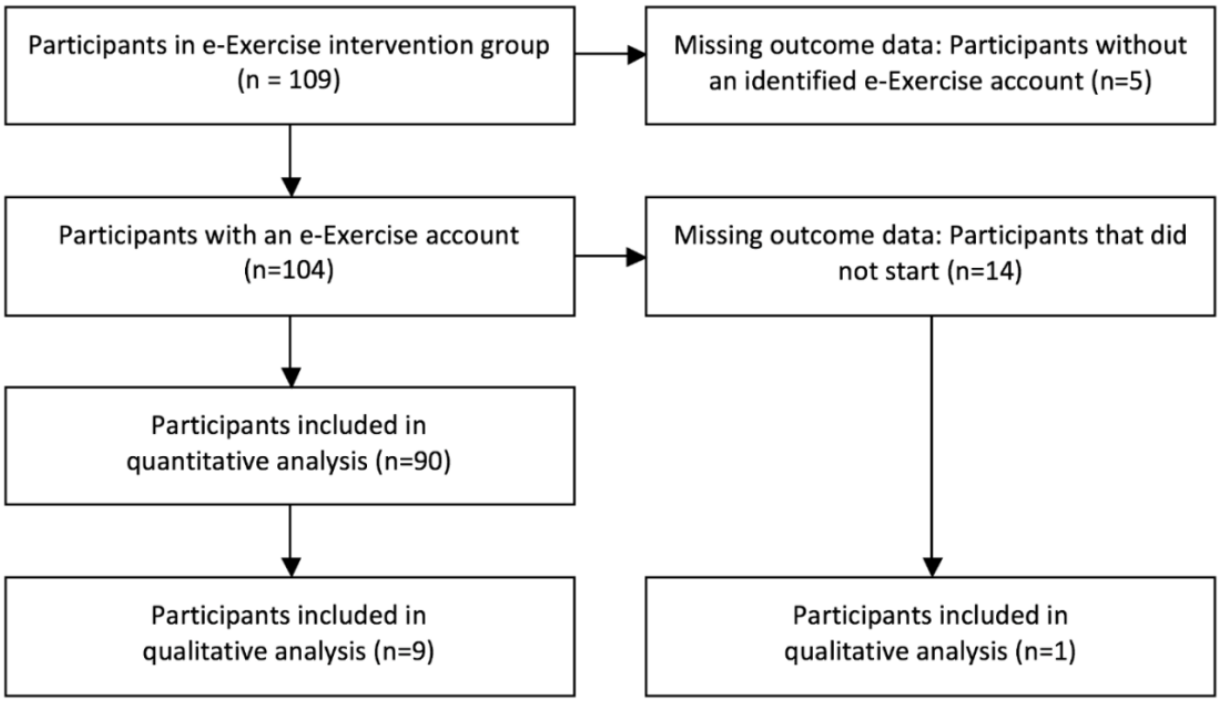
Independent variable	Measurement instrument	Categories	Value range
Patient-related factors			
Gender	Demographic survey	Male, female	-
Education	Demographic survey	Low, middle, high	-
Osteoarthritis location	Demographic survey	Knee, hip, both	-
Osteoarthritis duration	Demographic survey	<1 year, 1-5 years, >5 years	-
Comorbidity	Demographic survey	None, 1, >1	-
Age	Demographic survey	-	0-∞
Body Mass Index (BMI)	Self-reported height, weight	-	0-∞
Physical mobility	Timed Up and Go (TUG) [35]	-	0-∞
Pain	Numeric Rating Scale (NRS)	-	0-10
Tiredness	Numeric Rating Scale (NRS)	-	0-10
Activities in Daily Life (ADL) functioning	ADL subscale of the Hip disability and Osteoarthritis Outcome Score (HOOS) [36, 37] or Knee disability and Osteoarthritis Outcome Score (KOOS) [38, 39]	-	0.0-100.0
Sedentary time	ActiGraph tri-axial accelerometer*	-	0.0-1,440.0
Moderate-to-Vigorous Physical Activity (MVPA)	ActiGraph tri-axial accelerometer*	-	0.0-1,440.0
Perceived health status	EQ-5D [40] Health Index score	-	0.0-100.0

Self-efficacy for pain	Arthritis Self-Efficacy Scale (ASES) [41, 42]	-	0.0-5.0
Self-efficacy for symptoms	ASES [41, 42]	-	0.0-5.0
Intervention-related factors			
Treatment sessions	Physiotherapist-reported	-	0-∞
Environment-related factors			
Recruitment strategy	Demographic survey	Physiotherapist, advertisement	-

* Participants wore the ActiGraph during at least eight hours per day for at least three days. The physical activity thresholds of Freedson et al. [43] were used as cut-off points for physical activity intensity.

Results

For 5 out of the 109 participants that were randomized to the intervention group of e-Exercise, no account was identified. Also, for 14 participants with an account, the 'start the program' button was never pressed by the physiotherapist for unknown reasons. Since no adherence outcome data were available for these 19 participants, they were excluded for quantitative analysis and the remaining 90 (82.6%) were analyzed. No significant differences were found for the baseline characteristics of the 90 participants that were analyzed and the 19 participants that were not. A flowchart of the included participants is depicted in Figure 1.



Quantitative results

For the 90 analyzed participants, values for physical mobility (25.6%) and both sedentary time and MVPA (12.2%) were missing. In total, 81.1% of the analyzed participants evaluated a module during at least eight weeks and were therefore considered adherent to the online component (Figure 2). Based on univariate negative binomial regression analyses, education (p=.092), osteoarthritis symptom duration (p=.109), recruitment strategy (p=.096) and self-efficacy for symptoms (p=.138), were included for multivariate analysis. The final model (Table 3) was significant (Omnibus Test p=.015) and fits the negative binomial distribution well (deviance Value/df 1.010 and Pearson Chi-Square Value/df 0.839). Middle-educated participants were 39.7% more likely to adhere to the online component than low-educated participants and 31.6% more likely than high-educated participants. Also, participants that were recruited by a physiotherapist were 62.7% more likely to adhere than participants recruited by advertisement. Participants that experienced osteoarthritis symptoms for less than one year were 87.3% less likely to adhere than participants with a symptom duration of one to five years and 34.0% less likely to adhere than participants that had symptoms for more than five years.

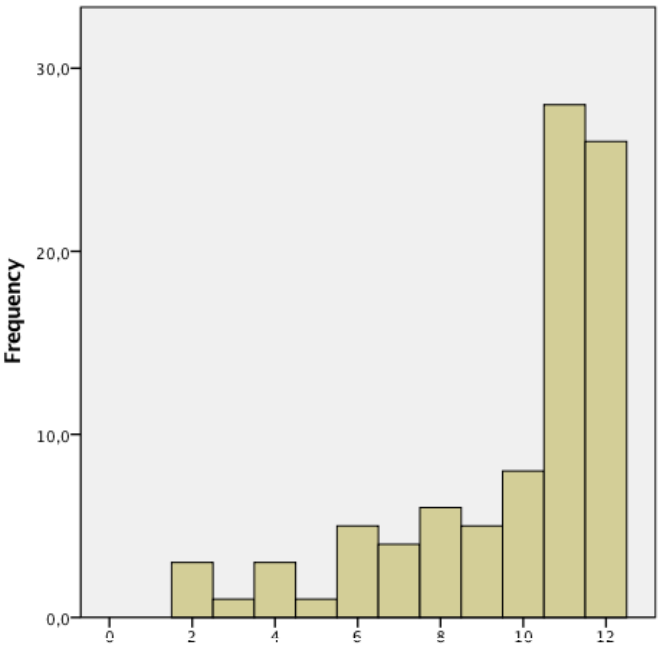


Figure 2.

Qualitative results

Of the twenty invited participants, eight responded and were interviewed. Data saturation appeared after six interviews. All participants confirmed the validity of the member-checks. To obtain optimal variation in patient characteristics, two more interviews were performed, but no new themes were found. The ten interviewed participants were mostly female (70%), without comorbidity (60%), between 51-79 (median: 60) years old, received 0-6 (median: 5) treatment sessions and evaluated a module in 1-12 (median: 10.5) weeks. These characteristics were similar to those of the total sample (Table 2) and were therefore considered representative.

Patient-related determinants

Three patient-related determinants were identified: (i) internet skills, (ii) self-discipline (iii) execution of the exercise plan. Sufficient internet skills and self-discipline were described as a prerequisite to use the online component. A participant with optimal adherence to the online component explained how she was motivated to keep exercising because of the experienced treatment effect: "Life just becomes better by participating in the program."

Table 2. Descriptive statistics for independent and outcome variables for participants that were included in quantitative analysis.

Variable	**Description (n=90)**
Outcomes	
Weeks evaluated; median, min-max (n)	11, 2-12 (90)
Percentage of (non-)adherent participants	
Adherent; % (n)	81.1 (73)
Non-adherent; % (n)	18.9 (17)
Patient-related factors	
Gender	
Male; % (n)	32.2 (29)
Female; % (n)	67.8 (61)
Age, mean ± sd (n)	63.6 ± 8.3 (90)
* Education	
Low education; % (n)	24.4 (22)
Middle education; % (n)	37.8 (34)
High education; % (n)	37.8 (34)
BMI; mean ± sd (n)	27.8 ± 4.4 (90)
Osteoarthritis location	
Knee; % (n)	66.7 (60)
Hip; % (n)	18.9 (17)
Both; % (n)	14.4 (13)
* Osteoarthritis duration	
Less than one year; % (n)	17.8 (16)
One to five years; % (n)	41.1 (37)
More than five years; % (n)	41.1 (37)
Comorbidity	
None, n (%)	53.5 (48)
One, n (%)	20.0 (18)
More than one, n (%)	26.7 (24)
Physical mobility; median, min-max (n)	8.3, 4.0-13.9 (67)
Pain; median, min-max (n)	5, 0-10 (90)

Tiredness; median, min-max (n)	5, 0-9 (90)
ADL functioning; mean ± sd (n)	60.6 ± 18.1 (90)
Sedentary time; mean ± sd (n)	497.4 ± 6.0 (79)
MVPA; median, min-max (n)	21.4, 0.0-107.6 (79)
Perceived health status; median, min-max (n)	71.0, 0.0-97.8 (90)
Self-efficacy for pain; median, min-max (n)	3.6, 1.2-5.0 (90)
* Self-efficacy for symptoms; median, min-max (n)	3.7, 1.5-5.0 (90)
Intervention-related factors	
Treatment sessions; median, range (n)	5, 1-16 (90)
Environment-related factors	
* Recruitment strategy	
Physiotherapist; % (n)	68.9 (62)
Advertisement; % (n)	31.1 (28)

* Independent variable that was a significant predictor of adherence during univariate binomial regression analysis (p≤.2).

Intervention-related determinants

Six intervention-related determinants were identified: (i) website usability, (ii) persuasive design, (iii) flexibility of the exercise schedule, (iv) added value, (v) time required, and (vi) the physiotherapist. Examples of positively evaluated persuasive features were received weekly email reminders and monitoring of behavior. One participant described that she wanted the assignments to be more flexible in adjusting exercises and goals. Also, participants described that the online component needed to have added value over regular therapy options and require little time to use. A well-travelled participant explained: "We went on vacation for three weeks and because of the online program I exercised every morning and evening."

The physiotherapist's role was mostly described as facilitating but sometimes as restricting. One interviewed participant reported that her physiotherapist never started the program: "I think it's a shame that the physiotherapist did not know how the program worked." For others, the physiotherapist had a positive influence by tailoring the exercise program to their needs, offering complementary therapy, monitoring progress and enhancing self-efficacy. Also, participants felt obliged to adhere because of the anticipated rewards for (non-)adherence by their physiotherapist. One participant explained: "This whole program just uses a carrot-and-stick approach. I think a lot of people – not just me – need that."

Table 3. P-values and β-coefficients of patient- and environment-related determinants of adherence to the online component

Determinant	β-coefficient	p-value
Patient-related factors		
Intercept	1.030	.008
Education		.064
Low education	- (indicator)	- (indicator)
Middle education	-.397	.264
High education	.316	.352
Osteoarthritis symptoms duration		.049
Less than one year	- (indicator)	- (indicator)
One to five years	-.873	.023
More than five years	-.340	.373
Environment-related factors		
Recruitment strategy		.032
Physiotherapist	- (indicator)	- (indicator)
Advertisement	.627	.032

Because inversed outcome data were used, negative β-coefficients indicate higher adherence, while positive β-coefficients indicate lower adherence.

Environment-related determinants

Several participants were extra motivated to adhere because they participated in a study. All themes describing determinants of adherence are summarized in Table 4.

Table 4. Themes describing determinants of adherence to e-Exercise

Patient-related factors	Intervention-related factors	Environment-related factors
Internet skills	Website usability	Participating in research
Self-discipline	Persuasive design	
Execution of the exercise plan	Flexibility of exercise schedule	
	Added value	
	Time required	
	The physiotherapist	

Discussion

This study found that 81.1% of the analyzed participants adhered to the online component of e-Exercise. Whereas fully web-based interventions oftentimes struggle with low adherence [16, 30], this study confirms e-Exercise is applicable for patients with hip and/or knee osteoarthritis [12]. In a future study we will investigate the relationship between adherence to the online component and effectiveness in terms of clinical outcomes [17]. Several nuances can be made regarding patient-, intervention- and environmental factors related to adherence to the online component.

The current results are in concordance with the Technology Acceptance Model (TAM) [31]. They illustrate that perceived ease of use and perceived usefulness can determine the attitude and behavioral intention towards use, influencing adherence. Nonetheless, the current results also offer insight in the specific factors influencing adherence to e-Exercise. For instance, adherence to the online component of e-Exercise was highest for middle-educated participants, while adherence to web-based interventions is typically highest for high-educated participants [32]. A possible explanation might be that participants with different educational levels might have different needs regarding the form and extent of given information, and the addition of videos to communicate information and exercises worked well for this sub-population. Furthermore, participants that had osteoarthritis for less than one year were less likely to adhere to the online component. It is possible that participants with a shorter osteoarthritis duration perceived less necessity and were therefore less motivated to adhere. This might also explain the finding that participants that were

recruited by advertisement were less adherent than patients recruited at a physiotherapy practice, since the latter group actively sought therapy for their experienced problems. Another influential aspect is the intervention's persuasive design [16]. For e-Exercise, two behavior change techniques of the CALO-RE taxonomy were found influential: monitoring of outcomes of behavior and prompts/cues [33]. Finally, some participants described to adhere because they participated in a study, which is a well-known environment-related factor [34], particularly in trials [16].

Little research is available about the adherence of patients with osteoarthritis to online interventions. The online component of e-Exercise was based on Join2Move. This study reported, based on intention-to-treat, that 46% adhered to the online intervention. According to the intention-to-treat principles the adherence of e-Exercise was 67.0% (73 out of 109 participants) [10]. This difference in adherence can be declared by improvements in the design and the addition of 3 extra week-modules. However, the most important difference between Join2Move and the online component of e-Exercise is the integration within the physiotherapy setting. Physiotherapists enticed participants to adhere because of perceived rewards or judgement. The physiotherapist could also adjust the treatment plan and stimulate the participant to keep executing it. The differences between both interventions and design characteristics of e-Exercise are described in more detail elsewhere [12, 17].

Several limitations of this study need to be addressed. First, it is unknown whether participants that adhered to the online component of e-Exercise also adhered to the intended exercise behavior. It is possible that participants evaluated activities and exercises that they did not perform, but also that participants exercised while not evaluating the module online. Second, the interview with one participant illustrated that her physiotherapist did not start her program, what she attributed to him being uninformed. It is unknown to what extent the physiotherapists of the other eighteen participants without an account or program start were accountable or whether these participants dropped out themselves. Finally, a sequential explanatory mixed methods design would have been more appropriate for the current study, since the quantitative findings could then potentially be explained during qualitative analysis. However, was not possible due to practical and time bound reasons.

Both the current findings and prior literature [8] underline the importance of the therapeutic role in blended care and that optimal integration is essential for patient adherence. Therefore, implementation of e-Exercise should focus on implementing the online component in the physiotherapists' routines. Although all physiotherapists underwent a half day of training [17], some physiotherapists still appeared unaware how to correctly use the intervention. To facilitate patient adherence, the online component should have added value, be flexible and easy to use. More persuasive design features can also be expected to influence adherence. Physiotherapists can consider offering patients with insufficient internet-skills or increased physical disabilities more extensive face-to-face treatment next to the online component.

Conclusions

The majority of participants adhered to the online component of e-Exercise, confirming that e-Exercise is applicable for patients with hip and/or knee osteoarthritis. The physiotherapist has influence on patient adherence due to his role in recruitment, program personalization and motivating the patient. The online components' usability, flexibility, time required, persuasive design and added value were linked to adherence.

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References

1. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clinics in geriatric medicine*. 2010;26:355-369.
2. Salaffi F, Carotti M, Stancati A, Grassi W. Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. *Aging clinical and experimental research*. 2005;17:255-263.
3. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. *The Journal of rheumatology*. 2009;36:1109-1117.
4. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *The Cochrane database of systematic reviews*. 2014:Cd007912.
5. Wicks P, Stamford J, Grootenhuis MA, et al. Innovations in e-health. *Qual Life Res*. 2014;23:195-203.
6. Elbert NJ, van Os-Medendorp H, van Renselaar W, et al. Effectiveness and cost-effectiveness of ehealth interventions in somatic diseases: a systematic review of systematic reviews and meta-analyses. *J Med Internet Res*. 2014;16:e110.
7. de la Torre-Diez I, Lopez-Coronado M, Vaca C, et al. Cost-utility and cost-effectiveness studies of telemedicine, electronic, and mobile health systems in the literature: a systematic review. *Telemed J E Health*. 2015;21:81-85.
8. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JE. Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. *JMIR mental health*. 2016;3:e9.
9. Pietrzak E, Cotea C, Pullman S, Nasveld P. Self-management and rehabilitation in osteoarthritis: is there a place for internet-based interventions? *Telemed J E Health*. 2013;19:800-805.
10. Bossen D, Buskermolen M, Veenhof C, et al. Adherence to a web-based physical activity intervention for patients with knee and/or hip osteoarthritis: a mixed method study. *J Med Internet Res*. 2013;15:e223.
11. Bossen D, Veenhof C, Van Beek KE, et al. Effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis: randomized controlled trial. *J Med Internet Res*. 2013;15:e257.
12. Bossen D, Kloek C, Snippe HW, et al. A Blended Intervention for Patients With Knee and Hip Osteoarthritis in the Physical Therapy Practice: Development and a Pilot Study. *JMIR Res Protoc*. 2016;5:e32.
13. Cugelman B, Thelwall M, Dawes P. Online interventions for social marketing health behavior change campaigns: a meta-analysis of psychological architectures and adherence factors. *J Med Internet Res*. 2011;13:e17.
14. Huis in 't Veld RM, Kosterink SM, Barbe T, et al. Relation between patient satisfaction, compliance and the clinical benefit of a teletreatment application for chronic pain. *J Telemed Telecare*. 2010;16:322-328.

15. Brouwer W, Kroeze W, Crutzen R, et al. Which intervention characteristics are related to more exposure to internet-delivered healthy lifestyle promotion interventions? A systematic review. *J Med Internet Res.* 2011;13:e2.
16. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE. Persuasive system design does matter: a systematic review of adherence to web-based interventions. *J Med Internet Res.* 2012;14:e152.
17. Kloek CJ, Bossen D, Veenhof C, et al. Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: study protocol of a randomized controlled trial. *BMC Musculoskelet Disord.* 2014;15:269.
18. Medicine ACoS. *ACSM's guidelines for exercise testing and prescription*: Lippincott Williams & Wilkins, 2013.
19. Peter W, Jansen M, Bloo H, et al. KNGF-richtlijn Artrose heup-knie. 2010.
20. Martina R, Kay R, van Maanen R, Ridder A. The analysis of incontinence episodes and other count data in patients with overactive bladder by Poisson and negative binomial regression. *Pharmaceutical statistics.* 2015;14:151-160.
21. Harrell F. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*: Springer, 2015.
22. Maxwell SE. Sample size and multiple regression analysis. *Psychol Methods.* 2000;5:434-458.
23. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* 1996;49:1373-1379.
24. Narsky I. Goodness of fit: what do we really want to know. *Proceedings of the PHYSTAT 2003.* 2003:70-74.
25. Ma Y, Hart JD, Janicki R, Carroll RJ. Local and omnibus goodness-of-fit tests in classical measurement error models. *Journal of the Royal Statistical Society. Series B, Statistical methodology.* 2011;73:81-98.
26. Rogers Everett M. *Diffusion of innovations*1995.
27. Carter N, Bryant-Lukosius D, DiCenso A, et al. The use of triangulation in qualitative research. *Oncol Nurs Forum.* 2014;41:545-547.
28. Maso I, Smaling A. Kwalitatief Onderzoek: Theorie en Praktijk [Qualitative Research: Theory and Practice]. *Amsterdam, Boom.* 1998.
29. Vries Hd, Kloek C, Bossen D, Veenhof C. Waarom wordt e-health (niet) gebruikt? Fysiotherapeutisch gebruik van een blended e-health-interventie. *FysioPraxis.* 2016:35-37.
30. Eysenbach G. The law of attrition. *J Med Internet Res.* 2005;7:e11.
31. Davis FD, Bagozzi RP, Warshaw PR. User acceptance of computer technology: a comparison of two theoretical models. *Management science.* 1989;35:982-1003.
32. Van 't Riet J, Crutzen R, De Vries H. Investigating predictors of visiting, using, and revisiting an online health-communication program: a longitudinal study. *J Med Internet Res.* 2010;12:e37.

33. Michie S, Ashford S, Sniehotta FF, et al. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. *Psychology & health*. 2011;26:1479-1498.
34. Wanner M, Martin-Diener E, Bauer G, et al. Comparison of trial participants and open access users of a web-based physical activity intervention regarding adherence, attrition, and repeated participation. *J Med Internet Res*. 2010;12:e3.
35. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*. 1991;39:142-148.
36. de Groot IB, Reijman M, Terwee CB, et al. Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthritis Cartilage*. 2007;15:104-109.
37. Klassbo M, Larsson E, Mannevik E. Hip disability and osteoarthritis outcome score. An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. *Scand J Rheumatol*. 2003;32:46-51.
38. de Groot IB, Favejee MM, Reijman M, et al. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health Qual Life Outcomes*. 2008;6:16.
39. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
40. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208.
41. Lorig K, Chastain RL, Ung E, et al. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis Rheum*. 1989;32:37-44.
42. Taal E, Rasker JJ, Wiegman O. Group education for rheumatoid arthritis patients. *Semin Arthritis Rheum*. 1997;26:805-816.
43. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Medicine and science in sports and exercise*. 1998;30:777-781.

8

Physiotherapists' experiences with a blended osteoarthritis intervention: a mixed methods study

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Abstract

Objectives: Identify the determinants that promote or hinder physiotherapists in the use of a blended intervention.

Design: An explanatory sequential mixed methods design embedded in a randomized controlled trial (RCT), comparing the blended intervention e-Exercise with usual physiotherapy in patients with hip and knee osteoarthritis.

Setting: Physiotherapists working in Dutch primary care setting, participating in the RCT and allocated to e-Exercise.

Participants: Recruitment rates and intervention usage of all 123 physiotherapists allocated to e-Exercise was used, 49 of them filled out a questionnaire and 9 participated in an interview.

Intervention: e-Exercise is a 12-week intervention consisting of around 5 face-to-face physiotherapy sessions and an online program for patients with hip/knee osteoarthritis.

Main outcome measures: Usage of e-Exercise was based on recruitment rates and objective website usage data. Determinants related to e-Exercise usage were investigated with a questionnaire and clarified with semi-structured interviews which were both based on the Measurement Instrument for Determinants of Innovations.

Results: Of the 123 physiotherapists allocated to e-Exercise, 54 recruited one or more eligible patients, 10 physiotherapists used e-Exercise after the study period. Determinants related to intervention usage were appropriateness, added value, time, workload, professional autonomy, environmental factors and financial consequences. Therapists recommended to improve the ability to tailor e-Exercise to patients' individual needs.

Conclusion: Overall, many therapists were interested in blended physiotherapy. Before implementation in physiotherapy practice, we need to integrate more flexibility into the online program and provide education about how to integrate an online program within physiotherapy to obtain maximal benefit from both delivery modes.

Introduction

In the last decade, a wide variety of digital technologies have been developed to improve and facilitate physiotherapy and rehabilitation [1]. Activity monitors, medical apps and websites provide physiotherapists' the ability to support patients' in managing their health within their everyday life. Supporting patients in coping with their (chronic) condition and adaptation to a healthy lifestyle is one of physiotherapists' responsibilities and also reflected within the new definition of health by Huber and others i.e. 'the ability to adapt and to self-manage, in the face of social, physical and emotional challenges' [2,3].

In order to complement face-to-face physiotherapy for patients with hip and knee osteoarthritis with the advantages of digital technology, we developed e-Exercise, a blended intervention that combines around five physiotherapeutic sessions with a web-based application [4]. A recent randomized controlled trial showed that e-Exercise and standard physiotherapy were comparable effective, with a substantial reduction of face-to-face sessions in the e-Exercise group [5]. Patients' adherence to the online part of e-Exercise was high and interviews revealed that the web-based application stimulated patients to take an active role within their treatment [6]. In order to benefit of e-Exercise' proven effectiveness, we aim to broadly implement the intervention within the physiotherapy.

Implementation of a blended physiotherapy intervention might be challenging, since physiotherapists' current use of e-Health is minimal. A survey in the Netherlands revealed that in 2014 only 1% of physiotherapy patients was supported with online interventions in the physiotherapy practice [7]. Reasons for non-usage of e-Health among healthcare professionals are multifactorial and include cost and liability issues, unwillingness to use technology and lack of trust in privacy and confidentiality [8,9]. Which specific determinants contribute to physiotherapists' usage or non-usage of a blended intervention such as e-Exercise is unknown.

Users and non-users can provide valuable insights and explanations for the usage of e-Exercise. To ensure effective implementation, physiotherapists' perspectives need to be considered in creating an environment that enables the adoption of e-Exercise in the physiotherapy setting. Therefore, the aim of this mixed methods study was to

explore the experiences of physiotherapist and identify determinants that facilitate and hinder the usage of e-Exercise in order to identify recommendations for future implementation.

Methods

Design

We used an explanatory sequential mixed methods design in order to clarify quantitative data with qualitative research [10]. For the quantitative part, data of a cluster-randomized controlled trial on the (cost-)effectiveness of e-Exercise were used [11]. For qualitative analysis, semi-structured interviews were performed. A detailed description of the study procedure [11] and the development study [4] have been published elsewhere. The study was approved by the Medical Ethical Committee of the St. Elisabeth hospital Tilburg, the Netherlands (Dutch Trial Register NTR4224).

Procedure and participants

For the recruitment of at least 200 physiotherapists, a random sample of 800 physiotherapists were invited by letter to participate in the study. In addition to this letter, a recruitment advertisement was placed in the magazine and online newsletter of the Dutch professional association for physiotherapists. Physiotherapists were eligible for participation if they (i) worked in a primary care practice and (ii) in one year provided services to at least six patients with knee and/or hip osteoarthritis. Physiotherapy practices could participate with either one or two therapists. After screening on in- and exclusion, cluster randomization was performed at the level of the physiotherapy practices. After all, 143 physiotherapy practices with in total 248 physiotherapists were randomly assigned either to the e-Exercise intervention or usual physiotherapy. This study focused on the 123 physiotherapists assigned to the e-Exercise intervention. All physiotherapists received an e-Exercise account (which had to be confirmed by clicking on a link) and followed a half-day instruction course to get familiar with the e-Exercise intervention.

The intervention

E-Exercise is a blended intervention for patients with hip and/or knee osteoarthritis,

developed together with patients and physiotherapists' [4]. A distinctive characteristic of e-Exercise is the aim to substitute part of usual physiotherapy sessions by online modules with the aim to create a cost-effective intervention for patients with osteoarthritis. The interventions consists of about five physiotherapy sessions in combination with a web-based application, whereas usual physiotherapy consists of on average twelve sessions. The web-based application contains a tailored 12-week behavioural graded activity program, videos with strength & mobility exercises and videos and texts with information about osteoarthritis related topics. The therapist can also login to the web-based application, for example to change the type of exercises. The therapist only needed to log in during the face-to-face physiotherapy sessions, in order to avoid extra workload. See Multimedia Appendix 1 for a video of the intervention e-Exercise (English subtitles can be switched on).

Quantitative data collection

Demographic characteristics of the included physiotherapists were gathered at the start of the study. Objective usage data from the backend of the e-Exercise application were used to evaluate the number of therapists that confirmed their account after receiving a signup confirmation email. Confirmation of the account was necessary to get access to the web-based application and to generate patient accounts. The number of recruited patients were monitored throughout the study period. Physiotherapists could include patients for the trial from September 2014 until April 2015. In October 2015, an anonymous questionnaire was sent to all physiotherapists in the intervention group to measure experiences with e-Exercise. This questionnaire was based on the Measurement Instrument for Determinants of Innovations (MIDI) [12]. As recommended by Fleuren et al. [12], a selection of relevant determinants was made and subsequently included in the final questionnaire that covered 1) characteristics of the innovation; 2) characteristics of the physiotherapist; 3) characteristics of the organization; 4) characteristics of the socio-political context. Two researchers [DB and CV] and two therapists pre-tested the questionnaire. Minor modifications were made after this expert-review. See Appendix 2 for the final version of the questionnaire. The questionnaire consisted of 17 questions, both multiple choice and open ended, as well as statements. Time to fill out the questionnaire was about 10 minutes. A reminder was sent after 2 weeks and after 6 weeks in order to enhance the number of responders. Demographic characteristics were compared using t-tests and Chi-square test to investigate whether characteristics of physiotherapists who used e-Exercise differed from physiotherapists who did not

recruit any patient. Results of the questionnaire were described per item. All analyses were performed using SPSS version 23.0.

Qualitative data collection

Respondents of the questionnaire were asked if they were willing to participate in an interview and, if so, to provide their name. To increase external validity, purposeful sampling was performed to obtain heterogeneity in age, specialisation, geographic location, number of patients included and survey answers. New therapists were approached based on theoretical sampling until data saturation appeared. One researcher (HdV), who was not involved in the development and evaluation of e-Exercise, conducted all individual semi-structured interviews in the physiotherapists' work environment. During the interviews, he used a topic list which was based on the answers from the questionnaire, on Fleurens' MIDI [12] and on Li et al. [13] (Appendix 3). All interviews were audiotaped and transcribed using NVivo for Mac version 10.2.1. Two researchers (HdV and CK) independently deconstructed the interviews. Assigned codes were compared (both within and between interviews) and axial and selective coding were performed in cooperation between HdV and CK. Codes expressing related concepts were grouped together to create broader categories. Data saturation was reached when the last two interviews revealed no new concepts and/or categories. A model was conducted through constant comparison of the emerging theory with data of deviant or negative cases. Finally, respondent validation was applied by verifying the validity of the model with all participating therapists.

Results

Within two months, a number of 248 eligible physiotherapists were recruited and randomized. The 123 e-Exercise therapists were on average 42 (SD 13) years of age and 65 (53%) were male. The demographics of the included therapists are shown in table 1. Of the 123 physiotherapists who were assigned to e-Exercise, 35 (29%) never activated their account. Of the 88 (71%) physiotherapists with an activated account, 54 physiotherapists (44%) recruited one or more eligible patients (in total 109 patients) and 33 therapists (27%) did not include any patients during the 7 months' inclusion period. Only 10 physiotherapists (8%) used the web-based application after the study period. We found no significant differences in demographics between users

and non-users. The usual physiotherapy group consisted of 125 physiotherapists, of whom 50 (40%) recruited one or more eligible patients.

Table 1. demographics physiotherapists (n=123)

Gender	
Male; % (n)	65 (53%)
Female; % (n)	57 (47%)
Age, mean ± sd (n)	42.2 (13)
Master specialization	42 (34%)

Quantitative results

A total of 49 therapists completed the questionnaire. Answers to the multiple choice questions are presented in table 2. Of the 49 therapists, 11 (22%) included no patients, 31 (63%) therapists used e-Exercise in 1 to 3 osteoarthritis patients and 7 (14%) physiotherapists recruited more than 4 patients for the e-Exercise treatment. Of the 49 respondents, 34 (69%) indicated that the user instructions were clear and easy to understand which facilitated the use of the web-based application. A total of 20 (41%) therapists reported that the content of the web-based application suited with their opinion about treating patients with osteoarthritis. With respect to the flexibility of the intervention, 14 (29%) therapists suggested in the open fields of the questionnaire to provide more flexibility in the web-based application in terms of intervention duration and the number of sets, repetitions and type of exercises. According to a minority of the physiotherapists (n=11, 24%) it was as a major disadvantage that e-Exercise results in a decrease in income, since the protocol recommends to minimalize the number of face-to-face sessions to five. Less than half of the physiotherapists (n=18, 43%) intended to use e-Exercise in the future. Most of the therapists (n=33, 67%) reported that they would recommend e-Exercise to their colleagues.

Table 2. Physiotherapists' evaluation of e-Exercise. Results of multiple choice questions (N=49)

Question	Totally disagree, N(%)	Disagree, N(%)	Neutral, N(%)	Agree, N(%)	Totally agree, N(%)
The instruction course and manual made that I knew how to work with e-Exercise	1 (2.0)	4 (8.2)	10 (20.4)	26 (53.1)	8 (16.3)
e-Exercise contains all essential elements for the treatment of hip/knee osteoarthritis	4 (8.2)	19 (38.8)	15 (30.6)	10 (20.4)	1 (2.0)
I do experience enough influence on the content of patients' individuals e-Exercise program	-	10 (20.4)	22 (44.9)	14 (28.6)	3 (6.1)
The content of e-Exercise suits with my opinion about treating patients with osteoarthritis	2 (4.1)	11 (22.4)	16 (32.7)	18 (36.7)	2 (4.1)
The intervention e-Exercise suits with the average profile of an osteoarthritis patient	5 (10.2)	13 (26.5)	16 (32.7)	15 (30.6)	-
I experience that e-Exercise supports patients in their home exercises	1 (4.1)	7 (14.3)	25 (51.0)	16 (32.7)	-
A major disadvantage of e-Exercise is that it results in less income	10 (20.4)	14 (28.6)	14 (28.6)	10 (20.4)	1 (4.1)
Patients who were treated with e-Exercise were generally positive about the intervention	2 (4.1)	9 (18.4)	23 (46.9)	13 (26.5)	2 (4.1)
Our physiotherapy practice has the intention to use e-Health innovations	2 (4.1)	2 (4.1)	12 (24.5)	28 (57.1)	5 (10.2)
I have not enough time available to get familiar with e-Exercise and to use the online program	7 (14.3)	13 (26.5)	10 (20.4)	17 (34.7)	2 (4.1)
I believe that patient data gathered at the e-Exercise website is stored safely	-	3 (6.1)	19 (38.8)	22 (44.9)	5 (10.2)

Qualitative results

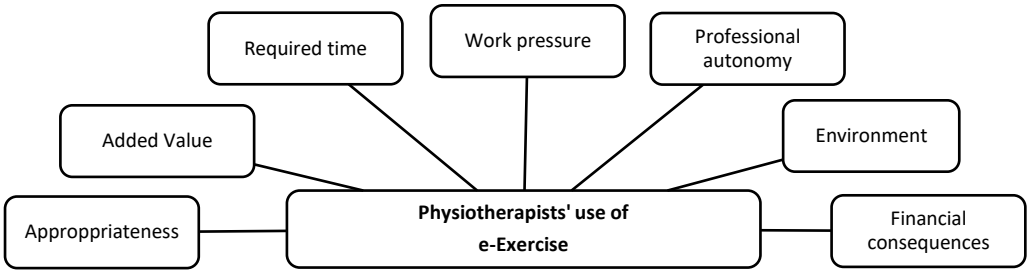
After nine interviews data saturation was reached. The physiotherapists' age ranged from 24-59 with a median of 52 years, six were male and three were female. Four of the therapists were self-employed, two had a master-specialization. The median of recruitment was one patient (0-3). After the data-analyses, seven main themes emerged which influenced the extent to which physiotherapists used the e-Exercise

intervention. These themes are displayed in Figure 1. All nine therapists confirmed the model's validity.

- *Appropriateness*

Physiotherapists' experienced appropriateness of e-Exercise for the individual patient was one of the determinants for usage of the intervention. As one therapist reported: *"The intervention is highly appropriate. To be honest, for me it was an eye-opener that so many patients can benefit from an intervention with less face-to-face guidance"*. On the other hand, physiotherapists explained that not all eligible patients were willing to participate. Reasons for patients' non-willingness were a lack of technology affinity or because they preferred regular face-to-face contact.

Figure 1. Determinants for the use of e-Exercise among physiotherapists



- *Added value*

Physiotherapists' perceived added value in terms of exercise adherence and treatment effect appeared to be an important determinant of web-based application usage: *"Patients need guidance in changing their behavior, also in their home-environment. E-Exercise is a valuable tool to support patients in doing their exercises."*

- *Required time*

Some therapists perceived the use of e-Exercise as an additional burden. A therapist explained: *"I did not have enough time to use the web-based application. It is an extra step in the treatment of patients"*. Closely linked aspects to these time-constraints were technical skills, clarity of online and offline instructions and the adaptive capacity to change treatment routines.

- *Work pressure*

Busy work schedules and administrative burden hindered therapists to test and use the e-Exercise in their practice. A therapist who perceived increased work-load due to an external audit said: *"We had to cancel everything that took extra work."*

- *Professional autonomy*

The reduced face-to-face contact due to the substitution of several face-to-face sessions interfered with the professional autonomy of some therapists. One therapist commented *"I prefer face-to-face guidance because of the ability of providing continuous feedback. You don't know how patients execute their exercises at home"*. As a solution, one therapist recommended to provide more flexibility in the intervention: *"I would prefer to have more possibilities to personalize the intervention to patients' individual needs."*

- *Environment*

Support from colleagues and the absence of a national eHealth guideline or standard influenced the use of e-Exercise. One therapist said *"It would be easier when there would be a national e-Health policy"*.

- *Financial consequences*

Although physiotherapists appeared to acknowledge the societal importance to limit healthcare costs, the loss of income due to the substitution of face-to-face session prohibited the implementation of e-Exercise. As one therapist commented: *"I believe this intervention is good for everyone, but especially for the insurers"*. On the other hand, some physiotherapists mentioned the advantage of reducing the number of treatments. Also, some therapists mentioned the benefit that offering an innovative intervention attracted new patients: *"We published an article about e-Exercise in the local newspaper and received about 80 phone calls of interested patients''*.

Discussion

Online tools and interventions provide huge opportunities for physiotherapists since they can act as an extension to face-to-face sessions. In this study, as much as 248 physiotherapists were willing to participate in the RCT on the (cost-)effectiveness of e-Exercise. The aim of this mixed methods study was to explore physiotherapists' experiences with e-Exercise and to identify determinants that facilitate and hinder the usage of a blended intervention in order to identify recommendations for future implementation. Qualitative data were used to explain quantitative data.

Generally, physiotherapists were positive about the content of e-Exercise. Results from the questionnaire and interviews revealed seven determinants for the usage of the blended intervention: 1) appropriateness; 2) added value; 3) required time; 4) work pressure; 5) professional autonomy; 6) environmental factors and 7) financial consequences. These determinants are in line with the results from Fleuren et al., which distinguish characteristics on the level of the innovation, the user, the organization and the socio-political context [12,14]. However, this study provides specific information about the use of a blended intervention within the physiotherapy setting. For example, physiotherapists' professional autonomy appeared to play an important role. Blended care is a new mode of delivering physiotherapy which required that therapists had to release their usual control.

Embedding blended care

Physiotherapists that participated in our trial were not only asked to use a web-based application, but also to reduce their number of billable face-to-face treatment sessions. In contrast to our expectation, most responders to the questionnaire reported no financial concerns. Yet, the interviews showed that some physiotherapists are seriously concerned about the financial consequences of e-Health. Cooperation with health insurance companies and the investigation of new eHealth business models should be the cornerstones for future implementation. Next, therapists reported difficulty in changing their treatment routines. Embedding blended care requires that physiotherapists admit online care as a substantial element of the physiotherapy treatment [15,16]. As for all new procedures and innovations, it takes time to get used to it [14]. Half of the physiotherapists used the intervention only once or twice during the study period, which also had to do with high workload and a

lack of time. Using the intervention only a couple times was probably not enough to make blended care part of their daily routine. Therefore, we recommend to expand the instruction course and complement this training with implementation lessons and optional refreshing meetups.

Non-usage

Less than half of the physiotherapists allocated to treat their patients with e-Exercise actually recruited patients. However, this recruitment rate was comparable with the group of physiotherapists allocated to treat their patients with usual physiotherapy [5] and shows that physiotherapists' actual involvement in research is challenging. More concerning was the fact only 10 physiotherapists used the web-based application after the study period. A frequently mentioned reason for non-usage was the inappropriateness of the intervention. First of all, online interventions are only suitable for patients with access to internet and adequate ICT skills. Next to this, e-Exercise was specifically developed for inactive patients with OA. The specificity of e-Exercise Osteoarthritis makes the intervention less for physiotherapists. However, the effectiveness of e-Exercise in this specific group underline the potential of blended care for the entire physiotherapy setting [17]. Physiotherapists' also suggested to complement the website with e-Exercise programs for other disorders. This recommendation has led to the development of interventions for patients with low back pain and medically unexplained physical symptoms, which are currently being studied for effectiveness by our research group. Therapists also recommended to provide more flexibility in the program, in terms of intervention duration and the number of sets, repetitions and type of exercises. The ability to tailor e-Exercise even more to patients' individual needs would probably increase the appropriateness and added value of the intervention. Moreover, more flexibility in composing individual programs for the individual patient is suspected to underline physiotherapists' professional autonomy.

Methodological considerations

This explanatory sequential mixed methods study is executed within the daily physiotherapy setting and is useful in helping to understand the complexity of integrating e-Health within physiotherapy. Since the questionnaire was anonymous, we were unable to perform an analysis to compare the characteristics of the

responders and non-responders. Only a minority of physiotherapists' allocated to e-Exercise filled out the questionnaire. Possibly, intervention interest of the responders was higher compared to non-responders. Although we expect that the model with determinants' for the use of a blended intervention can be used for other physiotherapeutic blended interventions as well, we recommend to validate the model in a bigger sample of physiotherapists.

Implications and conclusion

Previous studies already have shown the effectiveness of e-Exercise [5] and patients enthusiasm about e-Exercise and their high usage of the online application [6]. The seven determinants related to the usage of e-Exercise highlight the broad scope of factors that should be taken in account during broadly implementation of e-Exercise. Future steps in the implementation phase should comprise cooperation with health insurance companies, investigation of eHealth business models and providing education about optimally integrating online and face-to-face physiotherapy. Next to this, we need to extend the website with e-Exercise programs for other diseases and integrate more flexibility in order to tailor the intervention on patients' and physiotherapists' needs.

Ethical Approval, funding and conflict of interest

The study was approved by the Medical Ethical Committee of the St. Elisabeth hospital Tilburg, the Netherlands (Dutch Trial Register NTR4224). The study is funded by ZonMw, the Dutch Rheumatoid Arthritis Foundation and the Royal Dutch Society for Physiotherapy. All authors state that there are no conflicts of interest.

Contribution of the paper

-Physiotherapists' interest in a blended intervention like e-Exercise is high but actual usage is lagging behind.

-Determinants related to the use of e-Exercise are appropriateness, added value, time, workload, professional autonomy, environmental factors and financial consequences.

-Implementation strategies for e-Exercise should include education about how to integrate an online program within physiotherapy to obtain maximal benefit from both delivery modes.

Appendix 1. Video e-Exercise

https://www.youtube.com/watch?v=4l9GoQWWy58

Appendix 2. Questionnaire

1	How many patients did you treat with e-Exercise?
2	The instruction course and manual made that I knew how to work with e-Exercise (totally disagree-totally agree)
3	e-Exercise contains all essential elements for the treatment of hip/knee osteoarthritis (totally disagree-totally agree) If not, what kind of elements do you miss?
4	I do experience enough influence on the content of patients' individuals e-Exercise program (totally disagree-totally agree)
5	The content of e-Exercise suits with my opinion about treating patients with osteoarthritis (totally disagree-totally agree)
6	The intervention e-Exercise suits with the average profile of an osteoarthritis patient (totally disagree-totally agree)
7	I experience that e-Exercise supports patients in their home exercises (totally disagree-totally agree)
8	A major disadvantage of e-Exercise is that it results in less income (totally disagree-totally agree)
9	Patients who were treated with e-Exercise were generally positive about the intervention (totally disagree-totally agree)
10	Our physiotherapy practice has the intention to use e-Health innovations (totally disagree-totally agree)
11	I have not enough time available to get familiar with e-Exercise and to use the online program (totally disagree-totally agree)
12	I believe that patient data gathered at the e-Exercise website is stored safely (totally disagree-totally agree)
13	Would you recommend e-Exercise to a colleague?
14	Are there other reasons for being positive about e-Exercise?

15 Are there other reasons for being negative about e-Exercise?
16 Are you willing to use e-Exercise in the future?
17 Are you willing to participate in an interview about experiences with e-Exercise? If so, what is your mail address?

Appendix 3. Initial topic list

Physiotherapist - Motivation to participate - Outcome expectations and experiences - Attitude about e-Health in general - ICT skills	Patient - Recruitment - Patient satisfaction - Additional value
Organiation - Compatibility - Social support - Workload	Rules and financial topics - Income - Number of face-to-face contact - Ideas about physiotherapy in the future
e-Exercise - Complexity - Completeness - e-Exercise for other patient groups	Implementation - Procedural clarity - Time available - Study-load

References

1. Winstein C, Requejo P. Innovative technologies for rehabilitation and health promotion: what is the evidence? Physical therapy 2015 Mar;95(3):294-298.
2. Jambroes M, Nederland T, Kaljouw M, van Vliet K, Essink-Bot ML, Ruwaard D. Implications of health as 'the ability to adapt and self-manage' for public health policy: a qualitative study. Eur J Public Health 2016 June 01;26(3):412-416.
3. Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, et al. How should we define health? BMJ 2011 July 26;343:d4163.
4. Bossen D, Kloek CJJ, Snippe HW, Dekker J, de Bakker DH, Veenhof C. A blended intervention for patients with knee and hip osteoarthritis in the physical therapy practice: Development and a pilot study. JMIR Research Protocols 2016;5(1):e32.
5. Kloek CJ, Bossen D, de Bakker† DH, Dekker J, Veenhof C. Effectiveness of a blended physical therapy intervention in patients with hip and/or knee osteoarthritis: a randomized controlled trial. sumitted .
6. de Vries H, Kloek C, de Bakker† D, Dekker J, Bossen D, Veenhof C. Determinants of adherence to the online component of a blended intervention for patients with hip- and/or knee osteoarthritis: a mixed methods study embedded in the e-Exercise trial. Accepted for publication in Telemedicine and e-Health .
7. Krijgsman J, Peeters J, Burghouts A. Op naar meerwaarde – eHealth-monitor 2014. Tijdschrift voor gezondheidswetenschappen 2015 Feb;93(2):58-59.
8. de Grood C, Raissi A, Kwon Y, Santana MJ. Adoption of e-health technology by physicians: a scoping review. Journal of multidisciplinary healthcare 2016;9:335-344.
9. Peeters JM, Krijgsman JW, Brabers AE, Jong JDD, Friele RD. Use and uptake of ehealth in general practice: A cross-sectional survey and focus group study among health care users and general practitioners. JMIR Medical Informatics 2016;4(2):e11.
10. Creswell JW, Plano Clark VL. Designing and conducting mixed methods research. 2. ed. ed. Los Angeles [u.a.]: SAGE; 2011.
11. Kloek CJJ, Bossen D, Veenhof C, van Dongen JM, Dekker J, de Bakker DH. Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: Study protocol of a randomized controlled trial. BMC Musculoskeletal Disorders 2014;15(1):269.
12. Fleuren MAH, Paulussen, T G W M, van Dommelen P, van Buuren S. Towards a measurement instrument for determinants of innovations. International Journal for Quality in Health Care 2014;26(5):501-510.
13. Li J, Talaei-Khoei A, Seale H, Ray P, Macintyre CR. Health Care Provider Adoption of eHealth: Systematic Literature Review. Interactive journal of medical research 2013;2(1):e7.
14. de Veer AJ, Fleuren MA, Bekkema N, Francke AL. Successful implementation of new technologies in nursing care: a questionnaire survey of nurse-users. BMC Med Inform Decis Mak 2011 October 27;11:67.

15. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JE. Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. JMIR Ment Health 2016 February 09;3(1):e9.
16. Christensen CM, Bohmer R, Kenagy J. Will disruptive innovations cure health care? Harv Bus Rev 2000 October 01;78(5):12, 199.
17. Slater H, Dear BF, Merolli MA, Li LC, Briggs AM. Use of eHealth technologies to enable the implementation of musculoskeletal Models of Care: Evidence and practice. Best Pract Res Clin Rheumatol 2016 June 01;30(3):483-502.

9

General discussion

The integration of a web-application and therapeutic guidance suits to our latest ideas regarding chronic care management, in which patient-centeredness and the stimulation of self-management are emphasized. Blended care is a relatively new field since most web-based interventions from the "first generation" were unguided. However, high numbers of non-usage in unguided web-applications resulted in the recommendation to integrate online care and professional guidance [1, 2]. The main advantages of blended care are that 1) patients are offered a tool which can support self-management and trigger them 24/7 in changing their health behavior; 2) the healthcare provider can provide irreplaceable human support, tailored to patients' individual needs; and 3) part of the face-to-face care might be substituted by online guidance. This thesis focused on the case of patients with OA of hip and/or knee, which is the most common chronic joint disease. Part of the patients with OA tends to avoid physical activity in order to prevent pain or stiffness. However, avoidance of physical activity may lead to reduced levels of physical functioning in the long-term [3]. In order to support a physically active lifestyle within these patients, we developed the blended intervention e-Exercise. Within e-Exercise, a web-application consisting of a graded activity module, exercises and information themes, is integrated within 5 face-to-face physiotherapy sessions. The physiotherapist can tailor the content of the web-application to patients' individual needs. Next, remote monitoring of patients' usage of the application and insight in patients experienced difficulty in executing exercises provides valuable information to adapt the intervention and provide personalized care. The (cost-)effectiveness of e-Exercise compared to usual physiotherapy was assessed in a randomized controlled trial (RCT). In this general discussion section, the results from the previous seven chapters will be discussed, and implications for clinical practice as well as suggestions for future research will be provided.

Participatory development of e-Exercise

End-user involvement

In order to facilitate the long-term sustainability and successful uptake of e-Exercise, we used the Center for eHealth Research (CeHRes) Roadmap (*Chapter 1, Figure 2*) [4, 5]. This holistic research and development approach is not technology-driven, but takes in account the complexity of the healthcare setting, with interdependencies between healthcare givers, healthcare insurance companies, patients, environment and technology [5]. The 5-step CeHRes approach provided guidance during the

development, evaluation and implementation of e-Exercise. By involving end-users and stakeholders right from the beginning of the project, we aimed to create a technological solution that meets the values, needs and requirements of the end-users (patients and physiotherapists). Looking back at four years of e-Exercise, we can conclude that the CeHRes Roadmap truly stimulated our participatory design process (*Chapter 3*). For example, in the second month of the project (October 2013) we started to invite end-users (physiotherapists and patients) for participating in a focus group about their values and the design of the to be developed e-Exercise intervention. Right from the beginning of the project, physiotherapists were interested and willing to participate in the project. A focus group was used to discuss physiotherapists' preferences and needs regarding the web-application and the ratio between online care and face-to-face care.

We also aimed to involve patients with OA in this early stage of the project. However, the recruitment of patients in the first phase, when e-Exercise was no more than a set of ideas and concepts, appeared to be challenging. Possibly, our recruitment strategy (door by door flyer distribution and pamphlets in supermarkets) was too impersonal, or patients unfamiliarity with blended care hampered their interest in a focus group about an abstract idea and nonmaterial concept. In the next phase, when the first prototype of e-Exercise was developed and physiotherapists used the prototype in their daily practice, patient involvement appeared to be much easier. This probably had to do with the fact that these patients were recruited by their physiotherapist, who acted as an ambassador of the research project. Furthermore, providing an opinion about a concrete prototype, is less complex than providing an opinion about an abstract idea and nonmaterial concept. The third way of patient involvement was the participation of two OA patients in the stakeholder committee, which will be discussed in detail later. Recruitment of these two patients was facilitated by the Dutch rheumatic patient organization (ReumaZorg Nederland).

Overall, we underline the importance of involving patients as a research partner in the project and to engage patients before, during and after the study period [6]. Research has to be performed with patients, not only on patients. Within the e-Exercise project, insight in the needs and requirements of patients and physiotherapists right from the beginning of the project, resulted in a better understanding of the context and the development of a feasible intervention. For the successful recruitment of patients, we recommend others to collaborate with healthcare providers and patient organizations. Next, questions about needs and requirements regarding an

innovation need to be as concrete as possible, for example by showing drafts of prototypes.

Content of the blended intervention

The systematic development of e-Exercise consisted of multiple stages. We started this project with a systematic review in blended behavior change interventions in chronic somatic disorders (Chapter 2). It appeared that there is a huge heterogeneity in characteristics of blended interventions in terms of type of professional guidance, type of online application and the ratio between these delivery modes. To illustrate, in some interventions online care was combined with minimal therapeutic guidance, whereas other interventions mainly consisted of therapeutic contact.

Since the review (*Chapter 2*) showed that there is, up to now, no evidence about the most effective type of blended care, we discussed the most optimal ratio between face-to-face physiotherapy and online guidance, as well as the characteristics of e-Exercise, with the stakeholder committee and end-users (*Chapter 3*). As a result, e-Exercise became a twelve week intervention in which about five face-to-face sessions were integrated with a web-application. With respect to physiotherapists clinical competences, they were free to deviate from the protocol. The content and functionalities of the web-application were partly based on the previous developed and evaluated Join2Move intervention, an unguided web-based application for patients with OA of the hip and/or knee [7, 8].

When comparing the web-based part of e-Exercise with Join2Move, there are some differences and some similarities. The most important difference with Join2Move is that the web-based part e-Exercise consists of a log-in portal for both patient and physiotherapist. Within the therapist-portal, the physiotherapist can tailor assignments to patient's individual needs. Next, based on patient evaluations and website usage, the physiotherapist can adapt the intervention if necessary. Second difference between Join2Move and the web-based part of e-Exercise is that e-Exercise consists of extra persuasive features. New persuasive features in e-Exercise were: weekly e-mail reminders, weekly new video-supported information modules, visualization of baseline level, current status and personal goal, links to other websites with lifestyle related information and the professional face-to-face guidance of the physiotherapist. Persuasive features that were copied from Join2Move were the

goal setting feature for the graded activity module, automatically generated physical activity assignments, evaluations of these assignments and tailored feedback based on the principles of graded activity [7, 8].

The first prototype of e-Exercise was tested on feasibility in a one-group pilot study (*Chapter 3*). Pilot testing is also advocated by the CeHRes Roadmap, since it helps to uncover usability issues [4, 5]. Based on interviews with patients and physiotherapists that participated in the pilot study, adaptations related to e-Exercise' usability and content were made. The improved version of e-Exercise was evaluated in a multicenter RCT (*Chapter 4, 5 and Chapter 6*), with an investigation of end-user usage and -experiences (*Chapter 7 and Chapter 8*). Each step of the development phase, which started with Join2Move in 2010, contributed to the current version of e-Exercise. The version which was evaluated in the RCT differed substantially from the first prototype. Since RCT's are costly and the content of an eHealth intervention has to be "frozen" during a RCT, we strongly recommend other research teams to use systematic development processes as well, and start not too early with the execution of a RCT. Next to this, the development of eHealth is an iterative process which never finishes. Therefore, feedback from this summative evaluation can be given back to an earlier stage of the CeHRes Roadmap, in order to continuously keep improving e-Exercise based on end-user requirements and context [5].

Persuasive features of e-Exercise

E-Exercise aimed to facilitate all three necessary prerequisites for initiating and reaching behavior change, as described by Fogg et al. [9]: motivation, ability and trigger. Patient's motivation to perform physical activity was, for example, stimulated in the graded activity module which aimed to gradually increase levels of physical activity by means of a self-chosen activity, goal setting, time contingent assignments and positive reinforcement [10]. Next to this, the information modules of e-Exercise consisted of tips to make physical activity more attractive and to continue physical activity in the long-term. Other information modules payed attention to maladaptive behavior and -thoughts, as well as coping style. Also, the physiotherapists had a prominent role in listening to patients, showing empathy and motivating patients in using the web-application and changing their behavior. Ability, the second prerequisite for behavior change, was created by the personalization of the intervention. Since the graded activity assignments were based on patients' self-

chosen type of physical activity, on patients' individual baseline level and a short-term goal which was formulated together with the physiotherapist, the intervention matched the capacity of the individual patient. Next, the straightforwardness and easiness of the web-application, made that patients with less ICT skills were also able to follow e-Exercise. Finally, the third factor in Fogg's model, i.e. trigger, was created by automatically sending reminder-emails to visit the website and weekly new video-supported web-content. Next to this, patients were aware that physiotherapists could remotely monitor patients' usage of the web-application and follow their physical activity- and exercise assignments, which also aimed to trigger patients to use the web-application.

Results from a randomized controlled trial

Effectiveness

To evaluate the short- and long-term effectiveness of e-Exercise in patients with OA of the hip and/or knee, a multicenter cluster randomized controlled trial was conducted. Half of the 248 physiotherapists that were willing to participate received the instruction to treat their patients with e-Exercise and other half were instructed to provide physiotherapy as usual. Physiotherapists assessed patients' eligibility for participation in the study. A detailed description of the trial is provided in *Chapter 4*.

In total, 208 patients participated in the trial. Both on the short-term (3 months), as on the long-term (12 months), e-Exercise was not more effective compared to usual physiotherapy on primary and secondary outcome measures. However, within both groups, significant improvement was found on the primary outcome measure level of physical functioning, and on the secondary outcome measures level of pain, level of tiredness, quality of life and self-efficacy. Patients in the e-Exercise group visited the physiotherapist on average five times (which was in line with the e-Exercise protocol), whereas the usual physiotherapy group received on average twelve sessions.

Within both groups, no significant improvements were found in objectively measured physical activity. The results of the e-Exercise are in accordance with a recent systematic review in behavioral interventions for patients with lower limb OA, in which the authors neither found a long-term effect on physical activity [11]. Our results and this systematic review underline the complexity of changing physical activity behavior. Another explanation might be the difficulty of measuring free-living physical activity. This difficulty is illustrated by patients' overestimation of their self-

reported amount of physical activity, compared to objectively measured physical activity. Next to this, our single used parameter of physical activity ignores the multiple dimensions of physical activity, i.e. duration, frequency, intensity and type of activity. In the current study, all data generated by the accelerometer are summarized as minutes of moderate and/or vigorous activity per day. The downside of this approach is that, for example, it is unknown whether patients performed moderate to vigorous physical activity in bouts of at least 10 minutes. Insight in the length of physical activity bouts is important, since the World Health Organization (WHO) recommends a minimum of 150 minutes of moderate to vigorous physical activity per week, in bouts of at least 10 minutes [12]. To solve this problem, several recent studies recommend the investigation of physical activity profiles instead of analyzing a single parameter. These profiles (or phenotypes) should distinguish the amount of short or sustained episodes of moderate/vigorous physical activity, the amount of sedentary behavior and total energy expenditure [13, 14].

Overall, our hypothesis that e-Exercise would be more effective compared to usual physiotherapy has not been confirmed. When comparing the average change within e-Exercise and usual physiotherapy, minimal differences are seen in all primary and secondary outcome measures: between group effect sizes for subjective physical functioning was 0.01, for objective physical functioning 0.02, for subjective physical activity 0.04 and for objective physical activity 0.00. Since both interventions led to significant improvement on physical functioning and pain, and between group effect sizes are near zero, e-Exercise appeared to be an alternative treatment option for patients with hip and/or knee OA. The average improvements in physical functioning and pain in both interventions were in line with other exercise interventions in patients with knee and hip OA [15, 16].

Cost-effectiveness

The economic evaluation (*Chapter* 5) showed that intervention costs and medication costs of patients in the e-Exercise group were significantly lower compared to patients in the usual physiotherapy group. Total societal costs and total healthcare costs did not significantly differ between groups. Taking in account differences in effects and differences in costs, e-Exercise was not cost-effective compared to usual physiotherapy, from the societal- as well as the healthcare perspective.

The absence of a significant difference in total societal and total healthcare costs between e-Exercise and usual physiotherapy can be declared by the small share of

the physiotherapeutic costs within the entire costs related to OA, which also include expensive secondary healthcare costs. Next, a 12-month follow-up is too short to determine differences in for example the number of hip and/or knee replacements between both interventions. Therefore, we recommend to investigate the number of joint replacements five years after baseline.

Since no significant differences were seen in total costs and effects from both perspectives, the decision between e-Exercise or usual physiotherapy can be based on the preferences of the patient and the physiotherapist. In order to gain further insight in factors that facilitate or prohibited the usage of both patients and physiotherapists, two mixed-methods studies were conducted (Chapter 6 and Chapter 7).

End-user usage and experiences

Patients

Patients' adherence to the online part of e-Exercise appeared to be high, which illustrated the applicability of e-Exercise. Objective log-in data to the web-application of e-Exercise showed that 81% of patients treated with e-Exercise, followed at least 8 out of 12 online modules. Patients' high adherence to the web-application of e-Exercise is a strength of the intervention since adherence to eHealth interventions is often disappointing. To illustrate, from the people with OA who followed Join2Move, only 46% completed ≥6 out of 8 modules [2]. Since web-applications appeared to be more effective in patients that adhere, adherence to the online application is really important [17, 18]. A complete overview of which patient-, intervention- and environment related factors were related to patients' usage of the web-application as determined in our mixed-methods study was provided in *Chapter 6*. Remarkably, patients with a medium educational level showed highest levels of adherence. Generally, adherence to web-based interventions is highest for high-educated patients [19]. Other factors related to patients' usage of the web-application were patients' eHealth skills and their self-discipline. In relation to the web-application, patients evaluated the prompts and cues to log in as supporting in adhering to the web-application. Most patients described the role of the physiotherapist as facilitating. However, in some cases, optimal integration of physiotherapeutic guidance and the web-application appeared to be lacking. For example, some physiotherapists were not aware of the content in the information modules and did not connect patient education during the face-to-face sessions with the online

provided modules. In order to gain more insight in physiotherapists' experiences and reasons for (not) using e-Exercise, a second mixed methods study was conducted (*Chapter 7*).

Physiotherapists

At initiation of the e-Exercise project, a large number of physiotherapists showed interest and were willing to participate in the study (N=248). Part of the physiotherapists were positive about the appropriateness of e-Exercise, its user-friendliness, and its added value in stimulating patients to perform physical activity in their daily living. Alongside a group of enthusiastic physiotherapists, some physiotherapists were less convinced about the appropriateness of the web-application and recommended to integrate more flexibility in the web-application and to expand the intervention with modules for other (musculoskeletal) disorders. Physiotherapists reported blended care as a new way of delivering physiotherapy which requires that physiotherapists release their usual control. Physiotherapists' also reported that it takes time to get used to this new type of physiotherapy. Next, some physiotherapists reported concerns about the financial consequences of eHealth. Since physiotherapists in the Netherlands get paid per session, they have no financial incentive to apply an intervention with less face-to-face sessions. Unfortunately, only a minority of physiotherapists used e-Exercise after the study period. This minimally adoption is in line with nationwide usage of eHealth in primary care [20] and stresses the importance of incorporating all determinants that arose in *Chapter 7* within the implementation plan for e-Exercise.

E-Exercise: a successful intervention or not?

Based on this research, we cannot conclude that e-Exercise is more effective or cost-effective than usual physiotherapy in patients with OA of the hip and/or knee. However, patients in both intervention groups showed significant improvement on physical functioning and secondary outcome measures. Results of the (cost) effectiveness analyses showed that the decision between e-Exercise and usual physiotherapy can be based on the preferences of the physiotherapist and the patient.

It appeared that patients were generally enthusiastic about e-Exercise. Next, patients were highly adherent to the web-application. Taking in account the latest ideas about patient-centeredness and personalized care, we recommend to offer e-Exercise as a treatment option to patients with OA that are hypothesized to be suitable for blended care. To illustrate, e-Exercise perfectly suits to the needs of patients with busy schedules or less insurance coverage. Since blended care is no fixed formula, the ratio between online and face-to-face guidance should be based on patients' individual needs: some patients benefit from more face-to-face guidance, other patients can perform exercises and assignments more independently.

Implementation of e-Exercise

One of the biggest challenges within research is the implementation of innovations. A lot of innovations stay unused after the scientific research project has finished. In order to facilitate long-term sustainability and implementation of e-Exercise, a stakeholder committee was formed right in the beginning of the project. This committee consisted of two patients, a representative of the Royal Dutch Society for Physical Therapy, two rehabilitation centers, the Dutch arthritis foundation, an eHealth entrepreneur and a health insurer [21]. During 2-yearly meetings with interactive group activities, the stakeholders were encouraged to discuss about the development and implementation of e-Exercise (*Chapter 3*). For example, in one of the first meetings we created a matrix containing needs and perspectives regarding e-Exercise of all individual stakeholders. In another meeting, we organized a brainstorm session about potential facilitators and barriers in the implementation of e-Exercise, in order to take these factors in account during our project. In the third year of the project we presented five different implementation strategies, and discussed all different pros and cons per strategy. Based on our meetings with the stakeholder committee, we developed an implementation strategy for e-Exercise. This implementation strategy focused on 1) the hosting of e-Exercise; and 2) the stimulation of physiotherapists' usage of e-Exercise.

1) The hosting of e-Exercise

Most important issue within the implementation plan was the hosting of e-Exercise after the funding period. During the funding period, the web-application was hosted by the Netherlands Institute for Health Services Research (NIVEL). Several different

hosting parties were discussed with the stakeholder committee. Discussed hosting options were for example setting up an own e-Exercise enterprise, or to host and maintain the website together with students from the University of Applied Sciences Utrecht. For all scenarios we investigated the pros and cons. Based on this investigation, a commercial eHealth entrepreneur was hypothesized to be the most suitable and realistic option. Advantages of a commercial eHealth entrepreneur are that they have the knowledge and network to distribute an intervention like e-Exercise on a broader scale and to continuously maintain and improve technologic functionalities of e-Exercise. Therefore, we collaborated in 2017 with HWO-AA (in Dutch: Huiswerkoefeningen-Afsprakenapp). This company offers a physiotherapeutic digital application with therapeutic exercises and appointment reminders, which is available on a mobile phone app and website and meets the privacy regulations and safety records. The HWO-AA application is connected to the most frequently used physiotherapeutic electronic patient record, but will also be available as a stand-alone version for physiotherapists which use another type of electronic patient dossier. Physiotherapists can buy a license to use HWO-AA and use this application for all different kind of patients. The applicability of this system for all kind of patients is hypothesized to facilitate physiotherapists' familiarity with integrating technology within their daily practicing. For patients with OA specifically, physiotherapists can select the e-Exercise program within this HWO-AA application.

2) Stimulation of physiotherapists' usage of e-Exercise

Physiotherapists' usage of e-Exercise appeared to be minimal. In order to improve this usage, several steps need to be taken. For example, the e-Exercise intervention needs to be improved based on physiotherapists' feedback (connection with electronic patient record, availability of an e-Exercise app for mobile phone and applicability for other diagnoses). Next, education is required to inform physiotherapists how to integrate web-applications within daily physiotherapy practice in order to benefit from the best of both worlds. Furthermore, new physiotherapeutic business models need to be investigated which foster the use of innovations and leave room for personalized medicine. In the next paragraphs, current implementation activities will be discussed in more detail.

- *E-Exercise for other diagnoses*

With the aim to make e-Exercise more attractive and appropriate for physiotherapists', several new e-Exercise programs are currently being developed and studied. In 2016, we started with the development and evaluation of e-Exercise for patients with non-specific low back pain [22] and an e-Exercise intervention for patients with medical unexplained physical symptoms (PARASOL study).

- *The dissemination of e-Exercise (and related competences)*

In order to reach a broader group of physiotherapists, several activities are undertaken to widespread the e-Exercise programs and our knowledge and experiences in blended physiotherapy. First, we provided e-Exercise workshops at different physiotherapeutic symposia. Next, we organized a course for physiotherapists about eHealth within physiotherapy. This one-day course was organized on four different locations in The Netherlands. We also collaborated with the University of Applied Sciences in Utrecht and Amsterdam. We provided lectures about e-Exercise and necessary steps to integrate e-Exercise within daily healthcare setting. Next, we are collaborating in working groups to integrate technology within the curriculum of the physiotherapy bachelor. Over the years, we experienced some distrust regarding the integration of web-applications within physiotherapeutic guidance and noticed that these workshop should be more than providing an instruction about how the technology works. Instead, an important message should be that the integration of online care within face-to-face care is not supposed as a primary goal, rather as a tool to support self-management and self-care [20]. Supporting physiotherapists in the formulation of a general eHealth mission and vision will help them to see the added value of blended care and how blended care fits within modern healthcare. We recommend other lecturers on (applied science) universities to focus on the latest ideas about chronic care management, physiotherapeutic implications of the new proposed definition of health, and how blended care fits in physiotherapists' task to support patients' self-management.

- *The investigation of new business models*

In order to stimulate the use of innovations and leave room personalized medicine, our research group is currently working on a project to investigate the feasibility of a

"bundled payment system" within physiotherapy. In collaboration with healthcare insurance companies a living lab will be organized. Within this lab, physiotherapists will receive a fixed amount of money per patient with OA, instead of getting paid per session. Per patient, physiotherapists are stimulated to select the type of intervention that suits to the individual characteristics of the patient: some patients will benefit from an unguided intervention, other patients will benefit from e-Exercise and a third group will benefit from (extensive) face-to-face guidance. After one year, it will be evaluated to how many and which patients e-Exercise has been offered. Based on our finding that financial concerns are related to physiotherapists' usage of e-Exercise (*Chapter 7*), we hypothesize that such a business model might stimulate the use of innovations and leave room for personalized medicine.

An important merit of our investment in the implementation of e-Exercise right from the beginning of the project, is that the hosting of e-Exercise after the research project is arranged successfully. Hosting of the web-application is an essential precondition for the continuation of e-Exercise, since the web-application needs frequently technical maintenance. In order to facilitate long-term sustainability of eHealth, we recommend other research groups within this field to develop innovations in collaboration with a commercial entrepreneur. We also recommend collaboration with a wide range of other stakeholders, i.e. patients, healthcare providers, policy makers and healthcare insurance companies as well. Within this collaboration, stakeholders must be aware that the implementation of an innovation requires more than just being enthusiastic. All stakeholders need to invest time and effort in an innovation which has not been proven effective yet. It might seem ambiguous to work on an implementation plan, while the study results are not yet available. However, starting too late with implementation has the risk that research findings may go unused when the project funding expires.

In this project, we might have underestimated the amount of new knowledge, skills and attitude which physiotherapists require while adopting blended physiotherapy. Despite the collaboration with a stakeholder committee and a wide range of implementation activities, we admit that there is probably still a long way to go before blended physiotherapy has become part of physiotherapists' daily routines.

Methodological considerations

Several research designs were used during the e-Exercise project. For the design-phase of e-Exercise we used a participatory method and a single-group pilot study, in which we used qualitative and quantitative methods to investigate needs, requirements and experiences of patients and physiotherapists. For the evaluation of e-Exercise we used a single-blinded, multicenter, cluster randomized controlled trial. Finally, for the investigation of patients' and physiotherapists' usage and experiences with e-Exercise, we used mixed-methods designs.

Traditionally, an RCT is seen as the gold standard within the evaluation of an intervention. A strength of our RCT study is that it was conducted in the real-life clinical setting, which made it possible to investigate contextual factors related to the experiences of end-users with e-Exercise. Next, our study design, in which e-Exercise was compared with usual physiotherapy, allowed us to investigate the additional value of blended physiotherapy compared to face-to-face physiotherapy. However, based on the non-significant results of our superiority trial, we cannot claim that e-Exercise is as good as or not worse than usual physiotherapy. For this claim, it would have been better if we would have conducted an equivalence or a non-inferiority trial. If we would have used a non-inferiority design, we probably would have specified a non-inferiority margin of 0.5x 3=0.15 [15, 16, 23, 24]. Since all our between group effect sizes were below this value, e-Exercise is likely to be non-inferior to usual physiotherapy.

The challenge of this multicenter design was to cooperate with numerous physiotherapists (N=248). Although we have provided a half-day instruction course about the study procedure and (for the e-Exercise group) how to work with e-Exercise, discrepancies were seen between the provided instruction-protocol and physiotherapists execution in clinical practice. For example, physiotherapist' integration of the web-application within their face-to-face guidance differed per physiotherapists. For instance, *Chapter 7* showed that some physiotherapists forgot to press the start-button, or to integrate the online program during the face-to-face sessions. Second example is physiotherapists screening of patients' eligibility to participate in the study. A discrepancy was seen between our intended study population and the actual study population. Inclusion of patients was done by the physiotherapists at baseline and clinical diagnosis of OA was not confirmed by an independent caregiver. Next, physiotherapists assessed patients' level of physical

activity during anamneses with one single question. Baseline data showed that patients were sufficient physical active at initiation of the study and, as a result, had less room for improvement on this outcome measure. On the other hand, this screenings method has the advantage that it reflects physiotherapists' clinical reasoning process. After implementation of e-Exercise on broader scale, physiotherapists will select patients for e-Exercise in the same way.

Another limitation of our study was the high number of dropouts: 15% after 3 months and 35% after 12 months. Percentages of missing data in our accelerometer data and economic evaluation were even higher. Possibly, we may have overloaded the participants with too many measurements. Although we did not find clinical relevant differences in baseline demographics between responders and non-responders, results should be interpreted with caution. It is known that drop-out rates in eHealth studies are accompanied with non-usage attrition [25]. For future studies, we recommend to use in-person survey visits since this might increase response-rates and would also provide the possibility to measure objective physical functioning by an independent researcher [26]. Missing data within our economic evaluation were multiple imputed, which is considered as highly appropriate since this allow to account for the uncertainty about missing data [27].

Implications for clinical practice

To our opinion, e-Exercise perfectly suits in a stepped care OA strategy. A stepped care strategy promotes to start with relatively simple treatment modalities and expand therapeutic guidance in case of unsatisfying results [28]. Often, the general practitioner (GP) is the first healthcare provider to evaluate OA related symptoms. According to the stepped care OA strategy, the GP provides education and lifestyle advice. In order to support GPs in the provision of lifestyle advice, we recommend GPs to refer to an unguided internet-delivered intervention like Join2Move [7]. Nowadays, many patient seek online for healthcare information. Since Join2Move is freely accessible, patients with OA can also start with the intervention independently from their GP. If this unguided intervention modality appears to be inadequate, dietary guidance or physiotherapeutic guidance (e-Exercise) can be added. In case of deterioration of symptoms or unsatisfying results, the frequency of face-to-face sessions can be increased, or referral to/collaboration with secondary healthcare [28]. Since not every patient is suitable and/or motivated for receiving part of therapy online, physiotherapists' need to determine patients' willingness and suitability at

baseline (described in the next paragraph). An overview of a proposed stepped-care OA strategy with integration of Join2Move and e-Exercise is provided in Figure 1.

Figure 1. Join2Move and e-Exercise integrated in a stepped-care OA strategy

Suggestions for future research

Based on the e-Exercise project, several suggestions for future research can be made. First, we recommend to investigate which new knowledge, skills and attitude physiotherapists require while adopting blended physiotherapy in daily practice. Insight in these eHealth competences can, for example, be generated by observations in physiotherapy practices which start to work with e-Exercise. In order to integrate e-Exercise and blended physiotherapy in general, we suggest to develop an instrument, or checklist, which can be used by physiotherapists to determine patients' suitability for blended care, and to determine which amount of face-to-face guidance is needed in order to create an optimal integration between offline and online guidance (i.e. the ratio between offline and online guidance). An example of such an instrument is the "Fit for Blended Care Instrument" which is developed for patients in mental healthcare [29]. Our systematic review illustrated that generally, patients receive the same blended treatment, with the same ratio between therapeutic and online guidance. However, we believe that this ratio is independent from diagnosis, but is related to other factors like individuals' ICT access and skills, but also to patients motivation for blended care, self-management skills, cognition and environmental factors. In a new research project, we will develop such an instrument for the physiotherapeutic setting.

The previous described instrument can support physiotherapists in determining the most suitable delivery mode of physiotherapy. However, personalization of

physiotherapy in OA can also be based on the content of the therapy. Since OA is a heterogenous population, effectiveness of physiotherapy may improve by tailoring the content to specific subgroups of patients [30-32]. For example, Knoop et al. distinguished 5 different phenotypes within OA, which are hypothesized to benefit from 5 different interventions [32]. The current e-Exercise intervention was specifically developed for patients with an inactive lifestyle. In order to improve the applicability of e-Exercise, we recommend to integrate more flexibility within e-Exercise. By developing separate building blocks within e-Exercise, the physiotherapists can create an individual intervention which suit to the specific needs of the individual patient. Final recommendation for future research is the investigation of new business models that suits to blended care which aims to substitute part of the face-to-face sessions. Although we have planned a pilot study in investigating the possibilities of a "bundled payment system", we recommend to investigate other business models as well.

To end up with, this general discussion can be seen as the summative evaluation (step 5 of the CeHRes Roadmap) of e-Exercise in patients with OA. However, since the development of eHealth can be seen as an iterative process with ongoing formative evaluations, we recommend to conduct a future summative evaluation in about two or three years. Whereas the current summative evaluations focuses on e-Exercise as operationalized in the RCT, the next summative evaluation should include the operationalization of e-Exercise in the daily physiotherapeutic setting.

This thesis described the case of patients with OA of the hip and/or knee. For this common chronic joint condition we described how blended care can support healthcare providers to be a coach in learning patients to self-manage their chronic condition. Next, we described the importance of human support in patients' adherence to web-applications, and how part of the face-to-face care can be substituted by online guidance. Our lessons learned regarding participatory development, (cost-) effectiveness of blended care, the needs, requirements and experiences of patients and physiotherapists, as well as implementation, are supposed to be useful for other chronic conditions as well. Regardless from the specific type (or combination) of condition(s), chronic care management is not about treating a specific disease, it is about helping people to cope, adapt and self-manage in the face of the challenges related to their condition. In certain patients with a chronic disease, blended care might be a suitable treatment mode to reach this goal.

References

1. Baumeister H, Reichler L, Munzinger M, Lin J: The impact of guidance on Internet-based mental health interventions — A systematic review. *Internet Interventions* 2014, 1(4):205-215.
2. Bossen D, Buskermolen M, Veenhof C, de Bakker D, Dekker J: Adherence to a web-based physical activity intervention for patients with knee and/or hip osteoarthritis: a mixed method study. *J Med Internet Res* 2013, 15(10):e223.
3. Pisters MF, Veenhof C, van Dijk GM, Heymans MW, Twisk JW, Dekker J: The course of limitations in activities over 5 years in patients with knee and hip osteoarthritis with moderate functional limitations: risk factors for future functional decline. *Osteoarthritis Cartilage* 2012, 20(6):503-510.
4. Kensing F BJ: Participatory design: Issues and concerns. Computer Supported Cooperative Work (CSCW) 1998 Sep;, 7(3-4):167–85.
5. van Gemert-Pijnen JE, Nijland N, van Limburg M, Ossebaard HC, Kelders SM, Eysenbach G, Seydel ER: A holistic framework to improve the uptake and impact of eHealth technologies. *J Med Internet Res* 2011, 13(4):e111.
6. Sacristan JA, Aguaron A, Avendano-Sola C, Garrido P, Carrion J, Gutierrez A, Kroes R, Flores A: Patient involvement in clinical research: why, when, and how. *Patient Prefer Adherence* 2016, 10:631-640.
7. Bossen D, Veenhof C, Van Beek KE, Spreeuwenberg PM, Dekker J, De Bakker DH: Effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis: randomized controlled trial. *J Med Internet Res* 2013, 15(11):e257.
8. Bossen D, Veenhof C, Dekker J, de Bakker D: The usability and preliminary effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis. *BMC Med Inform Decis Mak* 2013, 13:61.
9. Fogg BJ: A behavior model for persuasive design. In: *Proceedings of the 4th international Conference on Persuasive Technology: 2009*: ACM; 2009: 40.
10. Veenhof C, Koke AJ, Dekker J, Oostendorp RA, Bijlsma JW, van Tulder MW, van den Ende CH: Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial. *Arthritis Rheum* 2006, 55(6):925-934.
11. Williamson W, Kluzek S, Roberts N, Richards J, Arden N, Leeson P, Newton J, Foster C: Behavioural physical activity interventions in participants with lower-limb osteoarthritis: a systematic review with meta-analysis. *BMJ Open* 2015, 5(8):e007642.
12. (WHO) WHO: Global Strategy on Diet, Physical Activity and Health. 2011, Geneva. 2011.
13. Kelly P, Fitzsimons C, Baker G: Should we reframe how we think about physical activity and sedentary behaviour measurement? Validity and reliability reconsidered. *The international journal of behavioral nutrition and physical activity* 2016, 13:32.
14. Thompson D, Peacock O, Western M, Batterham AM: Multidimensional physical activity: an opportunity, not a problem. *Exerc Sport Sci Rev* 2015, 43(2):67-74.
15. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL: Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2015, 1:CD004376.
16. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S: Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev* 2014(4):CD007912.

17. Cugelman B, Thelwall M, Dawes P: Online interventions for social marketing health behavior change campaigns: a meta-analysis of psychological architectures and adherence factors. *J Med Internet Res* 2011, 13(1):e17.
18. Huis in 't Veld RM, Kosterink SM, Barbe T, Lindegard A, Marecek T, Vollenbroek-Hutten MM: Relation between patient satisfaction, compliance and the clinical benefit of a teletreatment application for chronic pain. *J Telemed Telecare* 2010, 16(6):322-328.
19. Van 't Riet J, Crutzen R, De Vries H: Investigating predictors of visiting, using, and revisiting an online health-communication program: a longitudinal study. *J Med Internet Res* 2010, 12(3):e37.
20. Krijgsman J, Swinkels I, van Lettow B, de Jong J, Out K, Friele R, al. e: Meer dan techniek. eHealth-monitor 2016. [*More than technology. eHealth monitor 2016*]. . *De Haag/Utrecht: Nictiz/NIVEL* 2016.
21. Bossen D, Kloek C, Snippe HW, Dekker J, de Bakker D, Veenhof C: A Blended Intervention for Patients With Knee and Hip Osteoarthritis in the Physical Therapy Practice: Development and a Pilot Study. *JMIR research protocols* 2016, 5(1):e32.
22. Kloek C, van Tilburg M, Staal J, Veenhof C, Bossen D: Development and pilot testing of a blended physiotherapy intervention for patients with non-specific low back pain. *[Submitted]* 2017.
23. Greene CJ, Morland LA, Durkalski VL, Frueh BC: Noninferiority and equivalence designs: issues and implications for mental health research. *J Trauma Stress* 2008, 21(5):433-439.
24. Lesaffre E: Superiority, equivalence, and non-inferiority trials. *Bull NYU Hosp Jt Dis* 2008, 66(2):150-154.
25. Eysenbach G: The law of attrition. *Journal of medical Internet research* 2005, 7(1):e11.
26. Christensen AI, Ekholm O, Glumer C, Juel K: Effect of survey mode on response patterns: comparison of face-to-face and self-administered modes in health surveys. *Eur J Public Health* 2014, 24(2):327-332.
27. White IR, Royston P, Wood AM: Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011, 30(4):377-399.
28. Smink AJ, van den Ende CH, Vliet Vlieland TP, Swierstra BA, Kortland JH, Bijlsma JW, Voorn TB, Schers HJ, Bierma-Zeinstra SM, Dekker J: "Beating osteoARThritis": development of a stepped care strategy to optimize utilization and timing of non-surgical treatment modalities for patients with hip or knee osteoarthritis. *Clin Rheumatol* 2011, 30(12):1623-1629.
29. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JE: Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. *JMIR mental health* 2016, 3(1):e9.
30. Driban JB, Sitler MR, Barbe MF, Balasubramanian E: Is osteoarthritis a heterogeneous disease that can be stratified into subsets? *Clin Rheumatol* 2010, 29(2):123-131.
31. Felson DT: Identifying different osteoarthritis phenotypes through epidemiology. *Osteoarthritis Cartilage* 2010, 18(5):601-604.
32. Knoop J, van der Leeden M, Thorstensson CA, Roorda LD, Lems WF, Knol DL, Steultjens MP, Dekker J: Identification of phenotypes with different clinical outcomes in knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2011, 63(11):1535-1542.

Summary

The integration of a web-application and therapeutic guidance suits to our latest ideas regarding chronic care management, in which patient-centeredness and the stimulation of self-management are emphasized. As described in **Chapter 1**, the main advantages of blended care are that 1) patients are offered a tool which can support self-management and trigger them 24/7 in changing their health behavior; 2) the health care provider can provide irreplaceable human support, tailored to patients' individual needs; and 3) part of the face-to-face care might be substituted and extended by online guidance.

This thesis focused on the case of patients with OA of hip and/or knee, which is the most common chronic joint disease. In order to support a physically active lifestyle within these patients, we developed the blended intervention e-Exercise. Within e-Exercise, a web-application consisting of a graded activity module, exercises and information themes, is integrated within 5 face-to-face physiotherapy sessions. The physiotherapist can tailor the content of the web-application to patients' individual needs. Next, remote monitoring of patients' usage of the application and insight in patients experienced difficulty in executing exercises and other assignments, provides valuable information to adapt the intervention and provide personalized care.

In order to facilitate the long-term sustainability and successful uptake of e-Exercise, we used the Center for eHealth Research (CeHRes) Roadmap during the development, evaluation and implementation of e-Exercise. This holistic approach is not technology-driven, but takes in account the complexity of the health care setting, with interdependencies between a variety of stakeholders.

Chapter 2 presents the results of a systematic review in blended behavior change interventions in chronic somatic disorders. In four different databases was searched for randomized controlled trials published from 2000 till April 2017. Most of the 29 included studies compared blended care with no intervention. Blended behavior change interventions for patients with chronic somatic disorders show variety in type of therapeutic guidance, type of online care and how these two delivery modes are integrated. To illustrate, in some interventions online care was combined with minimal therapeutic guidance, whereas other interventions mainly consisted of therapeutic contact. In most studies, therapeutic guidance was non face-to-face by using email, phone or videoconferencing. The evidence of the effectiveness of blended interventions is inconsistent and non-significant for most outcome measures.

Chapter 3 outlines the development and feasibility of e-Exercise. Interviews, a focus group and discussions with a stakeholder-committee were conducted to explore the needs, values and requirements with respect to our to-be-developed blended intervention. The first version of e-Exercise was tested in a pre- and post-test pilot study. Feasibility outcomes, including recruitment rates within each practice, website usage (assignments completed and website visits), health related outcomes (physical activity, physical functioning pain and fatigue) and user satisfaction, were measured. In addition, therapists and patients from the pilot study were interviewed to investigate users' experiences. This study showed the feasibility of e-Exercise and provided valuable information to improve the intervention and to conduct a further trial to evaluate the (cost) effectiveness of e-Exercise compared to usual physiotherapy.

Chapter 4 presents the protocol of a prospective, single-blinded, multicenter cluster randomized controlled trial in the (cost)-effectiveness (3 and 12 months) of e-Exercise compared to usual physiotherapy in patients with OA of the hip and/or knee. Our hypothesis was that e-Exercise would be more effective and cost-effective compared to usual physiotherapy, since patients are offered a tool which can support self-management and trigger them 24/7 in changing their health behavior. The aim was to include 200 patients with OA of the hip and/or knee. Primary outcomes were physical activity and physical functioning. Secondary outcomes are health related quality of life, self-perceived effect, pain, tiredness and self-efficacy. All measurements were performed at baseline, 3 and 12 months after inclusion. Retrospective cost questionnaires were sent at 3, 6, 9 and 12 months and used for the cost-effectiveness and cost-utility analysis.

Chapter 5 describes the short- and long-term effectiveness of e-Exercise compared to usual physiotherapy in patients with OA of the hip and/or knee. The e-Exercise group (N=109) received (in accordance to the study protocol) on average 5 face-to face sessions, the usual physiotherapy group (N=99) received on average 12 sessions. No significant differences in primary outcomes between e-Exercise and usual physiotherapy were found. Within group analyses showed for both groups a significant improvement in physical functioning. After 3 months, the e-Exercise group reported an increase in physical activity, however, no objectively measured physical activity differences were found. With respect to the secondary outcomes, after 12 months sedentary behavior significantly increased in the e-Exercise group compared

to usual physiotherapy. Within both groups there were significant improvements for pain, tiredness, quality of life and self-efficacy, both in the short- as in the long term. Overall, the blended intervention e-Exercise was not more effective than usual physiotherapy in patients with hip/knee osteoarthritis.

Chapter 6 reports the findings of the economic evaluation which was conducted alongside the 12-month cluster randomized controlled trial. Costs were measured using self-reported questionnaires. Missing data were multiply imputed and bootstrapping was used to estimate statistical uncertainty. Intervention and medication costs were significantly lower in e-Exercise compared to usual physiotherapy. Total societal- and health care costs did not significantly differ between groups. No significant differences in effectiveness were found between groups. E-Exercise itself was significantly cheaper compared to usual physiotherapy in patients with hip and/or knee osteoarthritis, but not cost-effective from the societal- as well as health care perspective. The decision between both interventions can be based on the preferences of the patient and the physiotherapist.

Chapter 7 shows the results of a mixed-methods study which aimed to explore which patient-, intervention- and environment-related factors are determinants of adherence to the online component of e-Exercise. The majority (81.1%) of the patients that participated in the randomized controlled trial, followed at least 8 out of 12 online modules and adhered to the online component. Adherence was highest for participants with middle education, 1-5 year osteoarthritis duration and participants that were physiotherapist-recruited. The 10 analyzed interviews revealed that sufficient internet-skills, self-discipline, execution of the exercise plan, the intervention's usability, flexibility, persuasive design, added value, acceptable required time and research participation were linked to favorable adherence. Overall, patients high adherence to the online component illustrated the feasibility of e-Exercise.

Chapter 8 describes the results of a mixed-methods study which aimed to identify the determinants that promote or hinder physiotherapists in the use of a blended intervention. Prior to the study, many therapists were interested in blended physiotherapy. Of the 123 physiotherapists allocated to e-Exercise, 54 recruited one or more eligible patients, 10 physiotherapists used e-Exercise after the study period. Determinants related to intervention usage were appropriateness, added value, time,

workload, professional autonomy, environmental factors and financial consequences. Therapists recommended to improve the ability to tailor e-Exercise to patients' individual needs. Before implementation in physiotherapy practice, we need to integrate more flexibility into the online program and provide education about how to integrate an online program within physiotherapy to obtain maximal benefit from both delivery modes.

Chapter 9 discusses the results, conclusions and implications of this thesis. Next, suggestions for clinical practice and future research are provided. The research conducted in this thesis showed that e-Exercise was not more effective, neither cost-effective, compared to usual physiotherapy in patients with OA of the hip and/or knee. Since within group effectiveness and total (healthcare) costs were somewhat comparable between groups, the decision between e-Exercise and usual physiotherapy can be based on the preferences of the physiotherapist and the patient. In order to improve physiotherapists' integration of the web-application within their treatment, several important steps need to be taken. Most important steps are improving the e-Exercise application and integrating more flexibility within the online program, providing education about blended care and the investigation of new business models. With regard to patients' perspectives, this project showed that patients were generally enthusiastic about e-Exercise. Taking in account the latest ideas about patient-centeredness, we recommend to offer e-Exercise as a treatment option to patients with OA that are hypothesized to be motivated and suitable for blended care.

Future research should focus on which new knowledge, skills and attitude physiotherapists require while adopting blended physiotherapy in daily practice. Insight in these eHealth competences can, for example, be generated by observations in physiotherapy practices which start to work with e-Exercise. In order to integrate e-Exercise and blended physiotherapy in general, we suggest to develop an instrument, or checklist, which can be used by physiotherapists to determine patients' suitability for blended care, and to determine which amount of face-to-face guidance is needed in order to create an optimal integration between offline and online guidance (i.e. the ratio between offline and online guidance).

Our lessons learned regarding participatory development, (cost-) effectiveness of blended care, the needs, requirements and experiences of patients and physiotherapists, as well as implementation, are supposed to be useful for other chronic conditions as well. Regardless from the specific type (or combination) of

condition(s), chronic care management is not about treating a specific disease, it is about helping people to cope, adapt and self-manage in the face of the challenges related to their condition.

Samenvatting

De Nederlandse gezondheidszorg heeft, net zoals de zorg in andere westerse landen, de afgelopen eeuw grote veranderingen doorgemaakt. In het begin van de 20e eeuw was de gezondheidzorg vooral gericht op het bestrijden van infectieziekten als cholera en tuberculose. Door de komst van onder andere schoon drinkwater en antibiotica zijn veel van deze infectieziekten verdwenen. Hierdoor, in combinatie met onder andere ontwikkelingen op medisch technologisch gebied, is onze levensverwachting met meer dan 30 jaar gestegen. Deze extra levensjaren brengen echter ook nieuwe uitdagingen met zich mee. Vergrijzing is een risicofactor voor het krijgen van chronische aandoeningen als Alzheimer, hartfalen en artrose. Onze toegenomen levensverwachting, en de daarmee gepaarde stijging in het aantal mensen met één of meerdere chronische aandoeningen, maakt dat de gezondheidszorg momenteel meer en meer gericht is op het bevorderen van gezond gedrag en het leren omgaan met chronische aandoeningen. De patiënt neemt hierbij een centrale rol in en wordt gestimuleerd om de manager van zijn of haar aandoening te worden.

Het integreren van web-applicaties binnen het behandeltraject dat de patiënt krijgt aangeboden van zijn of haar zorgprofessional, ook wel blended zorg genoemd, past binnen de hierboven beschreven ontwikkelingen in de gezondheidszorg. Het kan hierbij gaan om bijvoorbeeld apps of websites waarop informatie over een bepaalde aandoening te vinden is, waarop opdrachten van de zorgverlener worden aangeboden, gecommuniceerd kan worden met de zorgprofessional, of die het mogelijk maken om ziekteverschijnselen of gezondheidsgedrag te monitoren. **Hoofdstuk 1** van dit proefschrift beschrijft onder andere de belangrijkste voordelen van blended zorg, namelijk: 1) door blended zorg hebben patiënten een digitaal hulpmiddel dat hen 24/7 kan ondersteunen in het managen van een ziekte, en kan motiveren tot gezond gedrag; 2) de patiënt hoeft niet alles alleen te doen, maar wordt begeleid door een zorgprofessional die ervoor zorgt dat de behandeling is afgestemd op de individuele behoeftes van de patiënt; 3) een deel van de face-to-face begeleiding door een zorgprofessional kan mogelijk vervangen worden door het online aanbieden van zorg.

In dit proefschrift stond de casus van patiënten met artrose aan de heup en/of knie centraal. Artrose is de meest voorkomende chronische gewrichtsaandoening. Bij artrose gaat de kwaliteit van het kraakbeen achteruit en kunnen mensen pijn en stijfheid ervaren. Als gevolg van deze klachten zijn mensen met artrose geneigd om minder te gaan bewegen, wat er voor zorgt dat de spierkracht en conditie achteruit gaan. De fysiotherapeut kan mensen met artrose begeleiden bij het hervatten of

continueren van een actieve leefstijl, ondanks de klachten die met artrose gepaard gaan. Eén van de grote uitdagingen hierbij is het stimuleren van de patiënt tot adequaat artrose-gedrag in de thuissituatie. Diverse studies hebben laten zien dat de helft van de patiënten hun fysiotherapeutische (beweeg)adviezen thuis niet opvolgen.

Met als doel de huidige fysiotherapeutische zorg voor patiënten met artrose aan de heup en/of knie te verbeteren en efficiënter te maken, is het idee ontstaan om de blended interventie e-Exercise te ontwikkelen. Het doel van dit onderzoek was om 1) een blended interventie (e-Exercise) voor patiënten met artrose aan de heup en/of knie te ontwikkelen die voldoet aan de behoeftes en voorkeuren van patiënten, fysiotherapeuten en andere stakeholders; 2) het inventariseren van de effectiviteit en kosteneffectiviteit van e-Exercise ten opzichte van reguliere fysiotherapie bij patiënten met artrose aan de heup en/of knie.

Hoofdstuk 2 presenteert een systematische literatuurstudie over blended interventies voor mensen met een chronische aandoening. Er is een overzicht gegeven van de beschikbare blended interventies, de karakteristieken van deze interventies en de effectiviteit. Het bleek dat de interventies erg van elkaar verschillen wat betreft type web-applicatie, type begeleiding van een zorgprofessional, maar ook hoe deze twee met elkaar geïntegreerd waren. Een voorbeeld hiervan is dat ene blended interventie intensieve begeleiding door een therapeut bevatte, waar in andere interventies mensen voornamelijk thuis met een web-applicatie aan de slag gingen. De therapeutische begeleiding was soms face-to-face, maar in de meeste gevallen op afstand via mail, telefoon of video-bellen. Door de grote diversiteit in interventie karakteristieken en studie-designs, was het lastig om conclusies te trekken met betrekking tot de effectiviteit van blended interventies voor mensen met een chronische aandoening. Over het algemeen blijken blended interventies voor mensen met een chronische aandoening niet effectief.

Hoofdstuk 3 beschrijft de ontwikkeling en haalbaarheidsstudie van e-Exercise. Interviews en focusgroepen met patiënten, fysiotherapeuten en stakeholders zijn gebruikt om de behoeftes en voorkeuren ten aanzien van e-Exercise in kaart te brengen. Het eerste prototype van e-Exercise is getest in een pilotstudie waar acht fysiotherapeut en acht patiënten aan mee hebben gedaan. Er is tijdens deze pilotstudie onder andere gekeken naar het gebruikersgemak van e-Exercise volgens patiënten en fysiotherapeuten. Ook is er gekeken naar de haalbaarheid van het onderzoek. Aangezien er gemiddeld gezien één patiënt per therapeut werd aangemeld, is er voor gekozen om extra veel fysiotherapeuten te werven voor het

vervolg onderzoek. De ervaringen van patiënten en fysiotherapeuten zijn gebruikt om e-Exercise te verbeteren (Box 1).

Box 1. E-Exercise voor patiënten met artrose aan de heup en/of knie

Binnen de twaalf weken durende e-Exercise interventie worden vijf fysiotherapiebehandelingen geïntegreerd aangeboden met een web-applicatie. Op deze web-applicatie konden zowel patiënten als fysiotherapeuten inloggen. De drie hoofdelementen van de web-applicatie zijn: 1) een graded activity module waarin een zelfgekozen activiteit, zoals fietsen of lopen, stapsgewijs wordt opgebouwd naar een zelfgekozen einddoel; 2) kracht- en stabiliteit oefeningen die geselecteerd zijn door de fysiotherapeut en worden aangeboden in de vorm van tekst en video; 3) een wekelijks nieuwe informatie-module, aangeboden in tekst en video, over een artrose gerelateerd onderwerp zoals pijnmanagement, het belang van bewegen of het duurzaam veranderen van beweeg- en pijngedrag. Patiënten werden wekelijks gevraagd om hun beweegopdrachten te evalueren en kregen hierop automatisch feedback via de web-applicatie. Fysiotherapeuten hadden eveneens inzicht in de voortgang van de patiënten konden op basis hiervan de behandeling aanpassen op de behoeftes van de individuele patiënt.

Hoofdstuk 4 beschrijft het protocol van de multicenter cluster gerandomiseerde trial naar de (kosten) effectiviteit van e-Exercise in vergelijking met reguliere fysiotherapie bij patiënten met knie- en heup artrose beschreven. Vooraf aan de studie is de hypothese gesteld dat e-Exercise effectiever en kosteneffectiever zou zijn dan reguliere fysiotherapie, aangezien patiënten toegang kregen tot een web-applicatie die mensen 24/7 kan motiveren bij het managen van hun aandoening en het veranderen van gedrag, daar waar reguliere zorg beperkt is tot een aantal contactmomenten. Het doel was om 200 patiënten aan het onderzoek mee te laten doen. Primaire uitkomsten waren fysiek functioneren en fysieke activiteit. Secundaire uitkomstmaten waren gezondheid gerelateerde kwaliteit van leven, zelf-ervaren herstel, pijn, vermoeidheid en zelfeffectiviteit. Metingen zijn uitgevoerd op baseline, na 3 maanden en na 12 maanden. Daarnaast zijn er nog kostenvragenlijsten verstuurd waarin patiënten na 3, 6, 9 en 12 maanden gevraagd werd naar hun uitgaven, ziekteverzuim en productiviteitsverlies gerelateerd aan hun artrose.

Hoofdstuk 5 beschrijft de korte- en lange termijn effectiviteit van e-Exercise in vergelijking met reguliere fysiotherapie bij patiënten met artrose van de heup en/of knie. De e-Exercise groep (N=109) ontving (zoals beschreven in ons protocol)

gemiddeld 5 face-to-face behandelingen. De reguliere fysiotherapie groep (N=99) ontving gemiddeld 12 behandelingen. Zowel na 3 als na 12 maanden waren er geen significante verschillen te zien op wat betreft fysiek functioneren en fysieke activiteit tussen de groep die heeft deelgenomen aan e-Exercise en de reguliere fysiotherapie groep. Kijkend binnen de groepen, gingen beide groepen significant vooruit in fysiek functioneren, zoals bijvoorbeeld het traplopen, opstaan uit bed of huishoudelijke activiteiten. Na 3 maanden rapporteerden de patiënten in de e-Exercise groep een toename in fysieke activiteit, maar objectieve accelerometer data bevestigde dit niet. Wat betreft de secundaire uitkomstmaten zagen we na 12 maanden een significante toename van zittend gedrag in de e-Exercise groep ten opzichte van de reguliere fysiotherapiegroep. Binnen e-Exercise was geen module over de gezondheidsrisico's van zittend gedrag opgenomen, wij adviseren om dit in een volgende versie van e-Exercise toe te voegen. Kijkend binnen de groepen, gingen beide groepen significant vooruit qua pijn, vermoeidheid, kwaliteit van leven en zelfeffectiviteit. Over het geheel gezien was e-Exercise niet effectiever dan reguliere fysiotherapie bij patiënten met artrose van de heup en/of knie.

Hoofdstuk 6 beschrijft de bevindingen van de economische evaluatie die is uitgevoerd naast de cluster gerandomiseerde trial waarin e-Exercise werd vergeleken met reguliere fysiotherapie voor patiënten met artrose aan de heup en/of knie. Kosten zijn gemeten met behulp van zelf-gerapporteerde vragenlijsten. Voor deze analyse zijn missende gegevens geïmputeerd. De interventiekosten van e-Exercise en de medicatiekosten die patiënten in de e-Exercise groep maakten, waren significant lager dan die van de reguliere fysiotherapiegroep. Het totaal aan maatschappelijke kosten en gezondheidszorgkosten was niet significant verschillend tussen beide interventies. Ook de effecten tussen beide groepen waren niet significant verschillend. Na het afwegen van de kosten ten opzichte van de baten bleek e-Exercise niet kosteneffectief vanuit zowel het maatschappelijk- als het gezondheidszorg perspectief. De keuze tussen beide interventies in de fysiotherapiepraktijk kan gebaseerd worden op de voorkeuren van de patiënt en de fysiotherapeut.

Hoofdstuk 7 toont de resultaten van een mixed-methods studie waarin is gekeken welke patiënt-, interventie- en omgevingsfactoren gerelateerd waren aan het gebruik van de e-Exercise web-applicatie door patiënten. De meerderheid (81,1%) van de patiënten die deelnam aan het e-Exercise onderzoek, volgden 8 of meer van de 12 online modules en waren daarmee gekwalificeerd als "gebruiker". Het gebruik van de web-applicatie bleek het hoogst bij patiënten met een mbo (of vergelijkbaar)

opleidingsniveau en met 1-5 jaar artrose klachten. Interviews lieten zien dat het beschikken over internet-vaardigheden, motivatie voor bewegen en therapietrouwheid aan de beweegopdrachten geassocieerd waren met het aantal keer dat mensen gebruik maakten van de web-applicatie. Daarnaast gebruikten mensen die de web-applicatie als gebruiksvriendelijk, flexibel en als meerwaarde ervoeren, vaker. De motiverende kenmerken van het programma, zoals het krijgen van herinnerings mailtjes en feedback, waren ook redenen om de web-applicatie vaker te gebruiken. Over het geheel gezien illustreert het hoge percentage van gebruikers (81,1%), de toepasbaarheid van e-Exercise.

Hoofdstuk 8 beschrijft de resultaten van een mixed-methods studie waarin is gekeken naar factoren die het gebruik van e-Exercise door fysiotherapeuten bevorderen of belemmeren. In aanloop op de e-Exercise trial was een groot aantal therapeuten geïnteresseerd in deelname. Van de 123 fysiotherapeuten die werden toegewezen tot de e-Exercise groep, waren er 54 fysiotherapeuten die één of meer patiënten hebben geincludeerd. Van deze groep zijn er 10 fysiotherapeuten die e-Exercise na afloop van de studie zijn blijven gebruiken. Determinanten gerelateerd aan het gebruik waren de ervaren mate van toepasbaarheid van e-Exercise, de ervaren meerwaarde ten opzichte van reguliere therapie, de beschikbare tijd van fysiotherapeuten, de ervaren werkdruk, de professionele autonomie (de voorkeur van fysiotherapeuten om volledige controle en zicht op het behandeltraject van de patiënt te hebben), omgevingsfactoren (zoals het enthousiasme van collega's voor eHealth) en financiële consequenties gerelateerd aan het gebruik van e-Exercise. Fysiotherapeuten gaven de aanbeveling om e-Exercise zo aan te passen dat het nog meer op de individuele behoeftes van de patiënt is aan te passen. Voordat e-Exercise op brede schaal geïmplementeerd kan worden, is het nodig om meer flexibiliteit te integreren in de web-applicatie. Daarnaast is het nodig om fysiotherapeuten te scholen in het integreren van digitale applicaties binnen de fysiotherapie op een manier waarmee maximaal voordeel behaald kan worden uit beide aanbiedingsvormen van therapie.

In **hoofdstuk 9** worden de resultaten, conclusies en implicaties van dit proefschrift bediscussieerd. Dit onderzoek heeft laten zien dat e-Exercise niet effectiever, noch kosteneffectiever, is dan reguliere fysiotherapie bij patiënten met artrose aan de heup en/of knie. Aangezien de progressie die patiënten maakten binnen beide interventiegroepen vergelijkbaar is, evenals de maatschappelijk- en gezondheidszorg gerelateerde kosten, kan de keuze om voor e-Exercise of reguliere fysiotherapie te kiezen overgelaten worden aan de patiënt en de fysiotherapeut. Om de integratie van

de web-applicatie binnen de fysiotherapeutische zorg te verbeteren zijn er een aantal stappen nodig. Het belangrijkste is dat er binnen het programma meer flexibiliteit wordt ingebouwd, dat er scholing over blended zorg wordt aangeboden en dat er onderzoek wordt gedaan naar nieuwe business modellen die aansluiten bij blended zorg. Patiënten die mee hebben gedaan aan het onderzoek waren over het algemeen erg enthousiast over e-Exercise. In een tijdperk waarin de patiënt centraal staat, zou e-Exercise daarom altijd als behandel-optie aan patiënten, die hier geschikt en gemotiveerd voor zijn, aangeboden moeten worden.

De geleerde lessen uit dit proefschrift op het gebied van eHealth ontwikkeling, co-creatie, effectiviteit en kosteneffectiviteit van blended zorg, de behoeften en voorkeuren van patiënten en fysiotherapeuten en implementatie van blended zorg binnen de fysiotherapie, kunnen ook gebruikt worden voor andere chronische aandoeningen dan artrose. Bij de aanpak van chronische aandoeningen ligt de focus niet op het genezen van een ziekte in specifieke zin, maar spelen generieke problemen en daarmee uitdagingen. De gemeenschappelijke deler van deze aandoening is de uitdaging om mensen te coachen zich aan te passen en eigen regie te voeren, in het licht van de uitdagingen die gerelateerd zijn aan hun conditie.

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De finish van deze proefschrift-marathon is bijna in zicht. Een finish die ik niet had kunnen bereiken zonder de hulp van zo'n 250 fysiotherapeuten die mee hebben gedaan aan het e-Exercise project. Dank aan al deze fysiotherapeuten. Maar bovenal wil ik ook alle patiënten die mee hebben gedaan bedanken. Zij hebben met elkaar in totaal zo'n 1400 vragenlijsten ingevuld.

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About the author

Corelien Kloek was born on March 24th 1987 in Marknesse, Noordoostpolder, the Netherlands. In 2005, after completing secondary school (VWO) at the Emelwerda College in Emmeloord, she moved to Utrecht to study Physiotherapy at the HU University of Applied Sciences Utrecht. After graduating in 2009, she started her career as a physiotherapist in a primary care practice in Utrecht. In 2010, she started to combine this work with her pre-master and master Health Sciences at the VU University Amsterdam. During her internship at the Netherlands Institute for Health Services Research (Nivel) she investigated general practitioners' policies in people with overweight and obesity. After achieving her master degree in 2013, she started her e-Exercise PhD project at Nivel and the Scientific Center for Care and Welfare (Tranzo) at Tilburg University, that resulted in the present thesis. Next to this, she worked from 2013-2015 as a part-time physiotherapist/junior-researcher at the department of Cognitive Neuropsychology at Tilburg University, on a project about home-based exercise with remote guidance for patients with gliomas. In 2016 and 2017, she combined her PhD project with a parttime junior-research function at the Department of Rehabilitation, Physiotherapy Science and Sport, Brain Center Rudolf Magnus, University Medical Center Utrecht, on the development and feasibility of e-Exercise in patients with low back pain.

Since 2016, Corelien is working as a parttime researcher at the research group Innovation of Human Movement Care at the HU University of Applied Sciences Utrecht, where she focuses on the development, evaluation and implementation of blended physiotherapy, including e-Exercise interventions for several other diagnoses. Next, she is working as a parttime researcher at Nivel, where she focuses on communication between patients and health care providers within primary care.

List of publications

Kloek, C.J.J., Bossen, de Bakker, D.H., Veenhof, C., Dekker, J. (2017). Blended interventions to change behavior in patients with chronic somatic disorders: systematic review. Journal of Medical Internet Research 19(12):e418

Kloek, C.J.J., Bossen, D., Spreeuwenberg, P., Dekker, J. de Bakker, D.H., Veenhof, C. (2017). Effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: a randomized controlled trial. (Physical Therapy, in press)

Gehring, K., Kloek, C.J.J., Aaronson, N.K., Janssen, K.W., Jones, L.W., Sitskoorn, M.M., Stuiver, M.M. (2017) Feasibility of a home-based exercise intervention with remote guidance for patients with stable grade II and III gliomas: a pilot randomized controlled trial. Clinical Rehabilitation Sep 1 (epub ahead of print)

De Vries, H.J., Kloek, C.J.J., de Bakker, D.H., Dekker, J., Bossen, D., Veenhof, C. (2017). Determinants of Adherence to the Online Component of a Blended Intervention for Patients with Hip and/or Knee Osteoarthritis: A Mixed Methods Study Embedded in the e-Exercise Trial. Telemedicine & eHealth; 23(12):1002-1010.

De Vries, H., Kloek, C.J.J., Bossen, D., Veenhof, C. (2016). Waarom gebruiken fysiotherapeuten e-Health (niet)? Fysiopraxis (3):35-37

Bossen, D., Kloek, C.J.J., Snippe, H.W., Dekker, J., de Bakker, D.H., Veenhof, C (2016). A blended intervention for patients with knee and hip osteoarthritis in the physical therapy practice: development and a pilot study. JMIR Research Protocols 5(1)

Heins, M., Kloek, C.J.J., Francke, A., Sinnige, J., Swinkels, I., Korevaar, J., de Jong, J. (2016). Naar een toekomstbestendige nazorg bij kanker: is er ruimte voor een grotere rol van de eerste lijn? Nivel rapport. ISBN 978-94-6122-392-0

Kloek, C.J.J., Tol, J., Veenhof, C., van der Wulp, I, Swinkels, I.C.S. (2015). Huisartsenzorg bij overgewicht en obesitas. Huisarts & Wetenschap 58(2):66-69

Kloek, C.J.J., Bossen, D., Veenhof, C., van Dongen, J.M., Dekker, J. de Bakker, D.H. (2014). Effectiveness and cost-effectiveness of a blended exercise intervention for patients with hip and/or knee osteoarthritis: study protocol of a randomized controlled trial. BMC Musculoskeletal Disorder 8(15):269.

Kloek, C.J.J., Tol, J., Veenhof, C., van der Wulp, I, Swinkels, I.C.S. (2014). Dutch General Practitioners' weight management policy for overweight and obese patients. BMC Obesity 1(2).