Beating osteoarthritis by e-self management in knee or hip osteoarthritis

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Colofon

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Beating osteoarthritis by e-self management in knee or hip osteoarthritis

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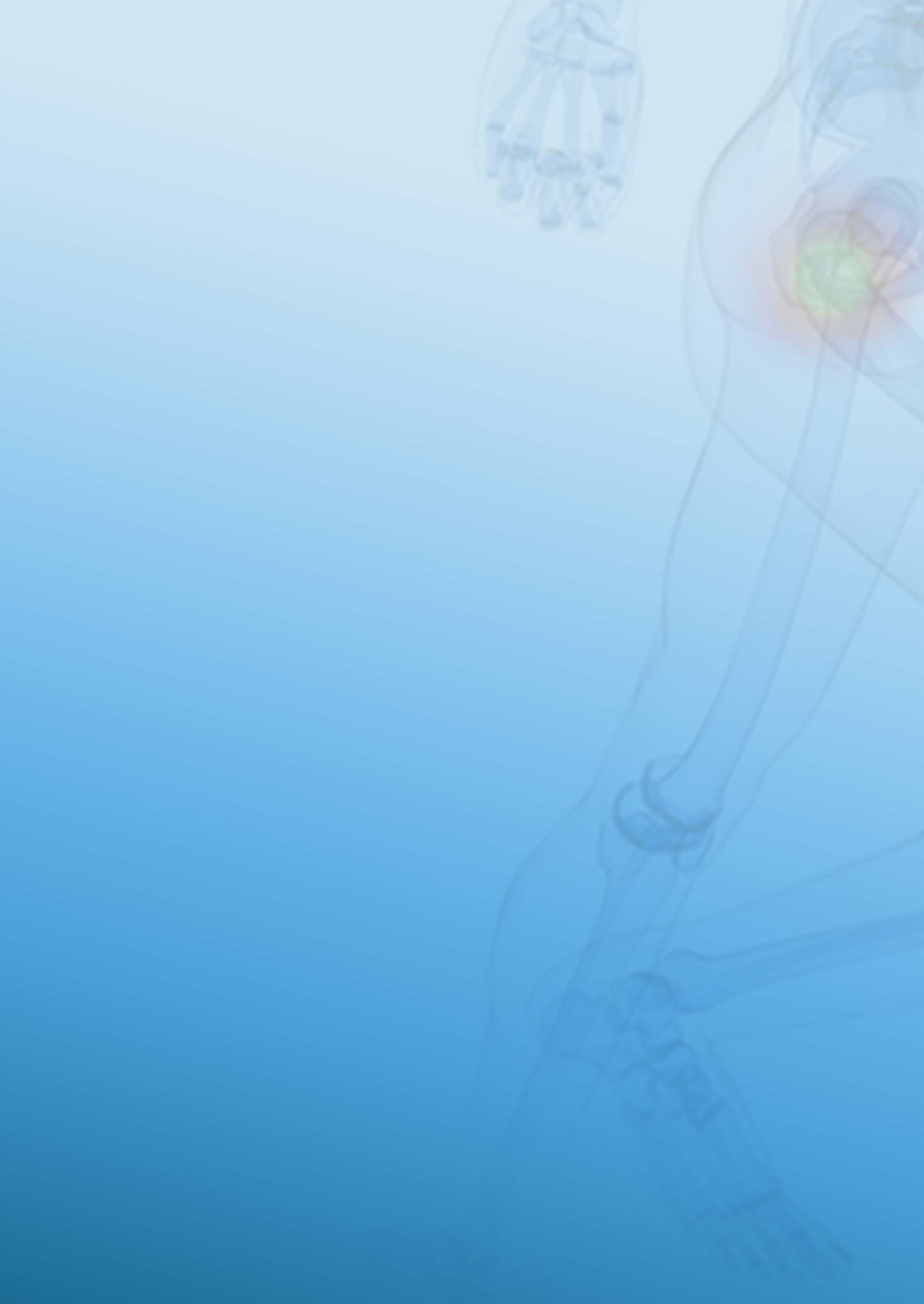
Chapter 1

General introduction



General introduction

Self-management is considered to be a cornerstone in the non-surgical management of osteoarthritis (OA). However, in clinical practice it is a challenge to actively involve patients in the management of their disease. Ehealth offers the possibility to effectively deliver self-management tools at any given time and place. This thesis focuses on the development and evaluation of a digital self-management application for patients with knee/hip OA: the dr. Bart app.

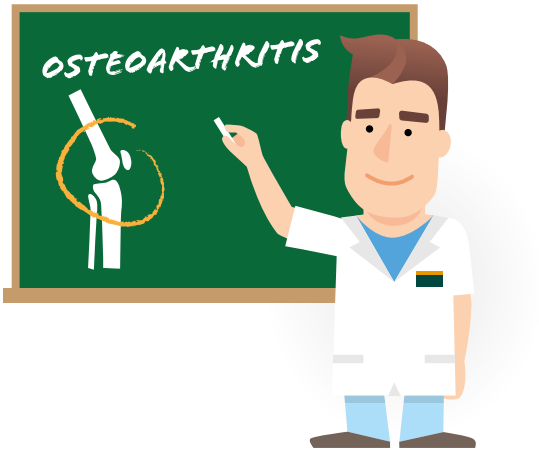


Figure 1. Cartoon of dr. Bart

What is osteoarthritis?

Epidemiology

Osteoarthritis is the most common chronic joint disease worldwide, affecting approximately 10-18% of the population aged 60 years and over[1–3]. Osteoarthritis mostly affects the knee(s) and hip(s) and is more common in females than in males. In the Netherlands, almost 1.5 million individuals suffered from OA in 2018. Annually, the societal burden of OA in the Netherlands is €1.2 billion, which is 1.4% of the total health care costs. Costs spent in secondary care are eight times higher than those spent in primary care[4]. It is expected that by 2040 OA is the most common noncommunicable chronic disease in the world, due to the ageing of the population and the obesity epidemic, resulting in a major challenge for health care systems. This demonstrates the need for effective strategies to manage chronic diseases like OA[5].

Pathogenesis

Contrary to historical theories, OA is not only a failure of the repair process of damaged cartilage due to biomechanical changes, but is a degenerative joint disease as well that develops progressively over several years and affects all structures throughout the joint: cartilage, menisci, synovium, ligaments, capsule, subchondral bone, and muscles (Figure 2)[6]. The structural destruction of the joint in OA is characterised as an active dynamic disbalance between the repair and destruction process of the joint structures, and not as a passive degenerative disease (i.e. wear-and-tear)[7].

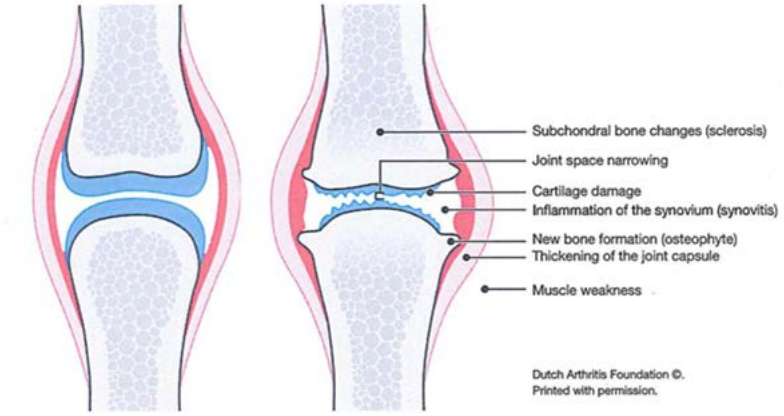


Figure 2. A normal joint and an osteoarthritic joint

Risk factors

Identified risk factors for developing OA are: increased age, obesity, female sex, previous knee injury, joint deformity, joint trauma, muscle weakness, heavy working activities (e.g. kneeling and heavy lifting), intense/high-impact sports activities, and genetic predispositions. Though age is the most evident risk factor for OA, ageing and OA should be considered as independent processes[8,9].

In general, OA is a joint disease that develops progressively over time. Prognostic factors for the progression of OA comprise biomechanical, psychological and clinical factors[10]. Potential modifiable factors for progression of OA are: weight, pain coping, proprioceptive inaccuracy, muscle strength, and physical activity. As a result, these are targeted for in conservative treatment[10–13].

Clinical consequences

Osteoarthritis is clinically characterised by pain, stiffness, crepitation, reduced range of motion, and sometimes inflammation of the affected joint(s), which in turn results in loss of function and quality of life[7]. For example, walking and other daily activities can become impaired. Specific (i.e. passive) coping styles are associated with higher levels of pain and disability in OA patients. Patients fear that activity induces pain, and as a consequence they avoid activities[14]. However, avoidance of activity results in a negative spiral towards worse symptoms resulting in even more limitations of daily activities[14,15]. As OA progresses over time, additional physical consequences can arise like loss of joint mobility, decreased muscle strength, instability and, in the end, postural deformities. End-stage OA is characterised by more joint pain compared to earlier stages, which disrupts normal sleep patterns, results in severe reduction of walking distance, and restrictions in daily activities[7,16,17].

Diagnosis of knee/hip OA

Pain and limitation of day-to-day activities among other symptoms are the main reason to consult a general practitioner. The diagnosis of knee/hip OA relies on patient's history, physical examination and/or radiographic features. Physical examination is necessary to confirm and characterise joint involvement. Clinical diagnostic features include joint effusion, bony

swelling, restricted passive movements, crepitus, joint deformities in advanced stages, and joint locking due to cartilage fragments (or menisci) in the joint space. Radiographic imaging is widely used, while radiographic knee OA is at most moderately associated with the level of pain; half of the patients without symptoms show radiological abnormalities indicating OA, and vice versa[18]. Thus, radiographic imaging has no additional value for diagnostic purposes in patients with typical presentation of OA[7,19]. In addition, laboratory tests are only performed to preclude other diseases[7]. Therefore, patient's history together with clinical features confirm an OA diagnosis.

Box 1. ACR clinical classification criteria for OA of the knee and hip[20,21]

Knee (95% sensitive, 69% specific)	**Hip** (86% sensitive, 75% specific)
Knee pain on most days of the month **and** in addition **three of the following**	Hip pain on most days of the month
AND/OR ≥ 50 years of age	**AND** ≥50 years of age
AND/OR Crepitus on active motion	**AND** Hip internal rotation ≥ 15°
AND/OR Morning stiffness ≤ 30 minutes	**AND** Pain on internal hip rotation
AND/OR Bony enlargement of knee on examination	**AND** Morning stiffness ≤ 60 minutes
AND/OR Bony tenderness of knee on examination	
AND/OR No palpable warmth of synovium	

The American College of Rheumatology (ACR) developed clinical classification criteria to differentiate knee/hip OA from other painful rheumatologically conditions (Box 1). These clinical classification criteria comprise age, pain, stiffness, range of motion, crepitus, bony tenderness, bony enlargement, and absence of palpable warmth of synovium[20,21]. These clinical classification criteria are, however, not feasible in large-scale epidemiological studies. For that reason, large-scale epidemiological studies commonly include participants based on self-reported OA. Self-reported OA is defined differently, comprising at least two of the following criteria: ≥50 years of age, pain, pain while being active, swelling, range of motion limitation, confirmation by a doctor[22–26]. A meta-analysis on diagnostic properties of self-reported OA showed a sensitivity of 0.75 (95% CI: 0.56; 0.88), and a specificity of 0.89 (95% CI: 0.77; 0.95). Such numbers are not acceptable in clinical practice, but for (large-scale) epidemiological studies these numbers and error margins are acceptable. Thus, for scientific purposes, pragmatic inclusion of participants based on self-reported OA is reliable for large-scale studies in the general population when reference standard rheumatologist examination is not feasible[22,23,26]. In this thesis self-reported OA is defined as:

Having a painful knee and/or hip

- **AND** knee and/or hip pain > 15 days of the past month
- **AND** morning stiffness ≤ 30 minutes (knee) and/or ≤ 60 minutes (hip)
- **AND** ≥ 50 years of age
- **AND NOT** having diagnosis of (other) inflammatory joint disease

1

Conservative non-pharmacological management

So far, OA is not curable and there are no disease modifying drugs. Current treatment is therefore predominantly symptomatic and focusses on controlling pain, improving function and health-related quality of life. International treatment guidelines emphasise the combined use of available evidence-based non-pharmacological and pharmacological treatment modalities, Table 1. In clinical practice a stepped care approach is adopted in which less advanced options, like education regarding OA and its treatment options, promotion of lifestyle changes (pacing of physical activity and exercise, weight loss), and self-management should be applied as a primary approach. Once these options have been adequately tried and failed, other treatment options (e.g. total joint arthroplasty (TJA)) should be considered. Total joint arthroplasty is considered a cost-effective treatment option in patients with OA when other less advanced options have failed[27,28]. However, a considerable proportion of OA patients has poor outcomes following TJA, especially in younger age groups[17,29]. Thus, a stepped care approach presents the optimal order of treatment modalities. Treatment modalities like self-management should be offered to all patients as early as possible as a first approach, which can be coordinated in primary care in the Netherlands.

Table 1. Treatment modalities for knee/hip OA

Non-surgical, non-pharmacological treatment	Pharmacological treatment	Surgical treatment options
Education about OA and its treatment modalities	Acetaminophen	Joint arthroplasty - Total - Unicompartimental (knee) - Patellofemoral arthroplasty
Improvement of self-management skills	(Topical) NSAIDs	Osteotomy - Tibia-wedge - Femoral
Lifestyle advice (weight management, physical activity)	Tramadol	
Exercise therapy	Intra-articular corticosteroids injections	
Dietary therapy	Hyaluronic acid injections	
Provision of walking aids and assistive technology		

Abbreviations: *OA*, osteoarthritis; *NSAIDS*, Non-steroidal anti-inflammatory drugs

Self-management of OA

As OA is a prevalent chronic disease, a cornerstone in non-surgical care is self-management. Self-management is defined as: "an individual's ability to manage symptoms, treatments, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition". Over the past years, the management of chronic diseases has changed; a shift towards a more patient-centred healthcare is apparent, aiming to actively involve patients in managing their disease. Effective elements of self-management include health education and goal setting. Self-management interventions often target on education and lifestyle modification in patients with chronic conditions[30]. We developed the dr. Bart app, that focuses on the following elements of effective self-management interventions: health education and goal setting to promote lifestyle changes (i.e. physical activity, and weight reduction in case of overweight). Reminders, rewards and self-monitoring are elements

that can enhance motivation to change behaviour and to reinforce app engagement[31,32]. The following paragraphs elaborate on effective elements of self-management in more detail.

Health education

Health education comprises information about OA and its treatment options, promoting lifestyle changes (pacing physical activity and exercise, weight loss), and informing about how to find and utilise resources[12,33,34]. Health education should start at the time of diagnosis. This educational information should be tailored to the person's illness perceptions, current knowledge, and educational capability. For patients it is important to adequately understand their OA to overcome misconceptions (e.g. that OA is an inevitable progress and cannot be treated)[35]. Thus, patient education is a cornerstone of disease management in OA.

Lifestyle advice

There is undisputed evidence for the effectiveness of physical activity and exercise on pain and physical function for patients with knee/hip OA[12,36,37]. In addition, physical activity is undoubtedly an important element of a healthy lifestyle and can have preventive effects on other chronic diseases like cardiovascular disease and cancers[36,38,39]. Following this, international guidelines recommend exercise and/or physical activity for patients with chronic diseases, but for the general population as well. International guidelines define physical activity as "any bodily movement produced by skeletal muscles that requires energy expenditure above resting (basal) levels"[40–42]. Whereas exercise is defined as "a subcategory of physical activity that is planned, structured, repetitive, and purposeful (in the sense that the improvement or maintenance of one or more components of physical fitness is the objective)"[42]. Thus, physical activity comprises exercise, sports, and physical activity as any domain of daily living (e.g. commuting, occupation and gardening)[43]. None of the abovementioned international guidelines specifies the minimum and optimal amount, type and nature of performed activities to most benefit in patients with knee/hip OA.

Additionally, weight is considered an important modifiable risk factor for knee/hip OA, as obesity is likely to have a negative mechanic as well as metabolic effect on the joint[44]. For overweight and obese patients with knee/hip OA weight loss is strongly recommended, as it positively influences pain and functioning. Dietary advice complementary to exercise and/or patient education and/or self-management has shown additional improvements of pain and function in knee/hip OA[12]. Therefore, information regarding nutrition and its positive influences on health and OA symptoms is important to enhance a healthy lifestyle in patients with knee/hip OA, especially in overweight patients.

Goal setting

Next to patient education, goal setting is considered as a fundamental element of self-management interventions, since setting goals helps patients to change behaviour and improve health outcomes[45,46]. Goals are defined as "objects or aims of an action", usually within a specified time limit[47], and goal setting is the process by which a goal can be achieved. The aim of goal setting is to change behaviour. The goal setting theory mentions five core principles that are essential to attain successful goal achievement: 1) Commitment; attachment to a goal, 2) Clarity; goal can be measured, no room for misunderstanding, 3) Challenge; goal is sufficiently difficult, 4) Complexity; goals should not be too difficult, and 5) Feedback; presence of progress reporting. Next to this, the goal setting theory makes a distinction between goals

that focus on outcomes (i.e. performance goals) and goals that focus on behaviour. An example of a performance goal is: "I would like to lose 5 kg within a month", whereas a behavioural goal states: "Today I eat an apple rather than an unhealthy snack between meals"[45,47,48]. The accumulation of such behavioural goals results in an overarching target outcome, for example weight reduction, and subsequently better health. The Fogg Behaviour Model, also known as "tiny habits"[49] utilises the concept of accumulating small goals to change health behaviour and, ultimately, health outcome. This model states that behaviour is the product of three elements that must be present for changing or maintaining the target behaviour: People must 1) be (sufficiently) motivated, 2) have the ability and, 3) be triggered or reminded to perform the target behaviour. These three factors must be present and balanced for changing or maintaining a target behaviour. Thus, people with low motivation need an easy objective (e.g. perform 5 squats) and a simple trigger (e.g. after brushing my teeth) to incorporate the target behaviour in daily life[49,50]. The dr. Bart focuses on changing health behaviour by using the "tiny habits" method for behaviour change, augmented with reminders, rewards and self-monitoring to reinforce app engagement.

Evidence of self-management interventions

International treatment guidelines uniformly recommend self-management in the treatment of knee/hip OA[12,13,33]. Self-management interventions in OA can be described as behavioural interventions that aim to increase the patients' coping with symptoms rather than controlling symptoms. Considerable variation exists in self-management interventions considering the variety of combinations with other interventions (e.g. exercise programs), mode of delivery (telephone, booklets or internet), difference in mode (group or individual), and intensity (duration and frequency). Thus, there is large heterogeneity between self-management interventions in OA. In general, traditional self-management interventions for OA show small benefits on self-management skills, pain, function and symptoms compared to usual care[30,51]. Moreover, there is evidence that self-management interventions change health care utilisation[51–57].

Modern persuasive technologies offer new possibilities for self-management programs with major advantages; providing tailored information 24/7, supporting patients in managing their disease at any given place, promoting proactive health behaviours, and offering remote monitoring of disease[58]. Another important advantage of applying modern technologies is its potential to be cost and time saving. Besides the major advantages of modern technologies, its use can also have downsides; user rates, adherence, and usability of digital interventions can be unsatisfactory[59,60]. So, the use of modern technologies seems promising, but the majority of digital interventions have not proven their effectiveness in clinical trials[61,62]. A recent review including applications on symptom monitoring, activity monitoring, and joint function measurement by means of wearables showed promising results for the use of mobile eHealth technologies in OA management[63]. Applications of studies included in this review, lacked important elements of self-management such as education, goal setting and exercise.

Table 2 shows an overview of six studies regarding digital self-management interventions in OA. Two studies evaluated fully automated web-based (i.e. without therapeutic guidance) interventions, two evaluated web-based interventions in combination with face-to-face sessions with a physical therapist, and two evaluated web-based interventions with digital guidance of either physical therapist or peers. The interventions included in the overview

showed variation with regard to content (education, exercise), intensity of intended use, duration, and follow-up time. The presented studies showed inconsistent effects over 3 and 12 months of follow-up; three studies on digital self-management interventions, of which one was a stand-alone web-based intervention and two were web-based in combination with either 7 skype meetings with a physical therapist or peer interaction, resulted in effects on physical activity, functioning, self-efficacy, health distress, activity limitation, global health and pain[64–66]. Three studies, of which one was a stand-alone web-based intervention and two were web-based in combination with face-to-face sessions with a physical therapist, reported no effect of the studied digital self-management interventions on clinical outcomes[67–69]. Thus, the heterogeneity among digital self-management interventions in OA is high with the current evidence being inconclusive. Interestingly, none of the digital self-management interventions comprised an application. In contrast to web-based interventions, an application offers the possibility to induce behavioural changes using reminders and real-time feedback and provide tailored information at any given time and place. Moreover, applications can monitor health behaviour and provide real-time feedback, which are considered important elements of self-management.

Given the potential of applications to support patients in taking an active role to manage their chronic condition in daily life, we iteratively and systematically developed a stand-alone self-management application: the dr. Bart app. The dr. Bart app is based on a solid theoretical framework and focuses on multiple aspects of healthy behaviours that can be incorporated in daily life. The applied behavioural change techniques are chosen by specialists from different fields, including patient representatives. We assume that machine learning techniques can provide tailored guidance and therefore better adherence to the application, which might substitute part of therapeutic guidance.

Measurement of outcome

The marginal benefits of self-management interventions could be explained by the lack of consensus in the literature regarding primary outcomes of self-management interventions; numerous (primary) outcomes are assessed that are not aimed at in the interventions. Commonly used primary outcome measures to assess effectiveness of self-management interventions are pain, self-efficacy, and physical functioning[30,51]. These measures, however, do not reflect the ultimate goal of effective self-management; changing behaviour (e.g. changes in health care utilisation, ability to take care of one's own health)[34,46]. Hence, there seems to be a mismatch between primary outcomes assessed in studies and the goal of the investigated interventions, which in turn might dilute the overall effectiveness of self-management interventions[70].

In line with the aim of self-management interventions it has been observed that self-management changes health care utilisation[51–57], reflecting behaviour change and thus serves as an appropriate measure to assess self-management. Following this, changing health care utilisation patterns (i.e. make optimal use of primary care services and less use of secondary health care services) could reduce health care costs, which in turn makes self-management cost-effective. However, evidence regarding cost-effectiveness of non-pharmacological, non-surgical treatment modalities is scarce in patients with knee/hip OA[71]. The rapidly increasing prevalence and rising economic burden on health care costs related to OA urge the need to achieve (novel) (cost-)effective strategies to manage OA. In this thesis, we evaluated the (cost-) effectiveness of a digital self-management tool (dr. Bart app).

Outline of this thesis

This thesis has multiple aims. The first is to deepen the insight of physical activity in terms of amount and nature of physical activity in patients with different subsets of knee and/or hip OA (including total joint arthroplasty) and the general population and to compare the amount of physical activity among these subsets and the general population (**chapter 2**).

Self-management is of paramount importance in the non-surgical treatment of knee/hip OA, and modern technologies offer the possibility to support self-management 24/7 at any given place.

The second aim is to develop a stand-alone e-self management intervention: the dr. Bart app for patients with knee and/or hip osteoarthritis (**chapter 3**). This chapter also describes the design of a study that aims 1) to evaluate the short-term effects (over 3 and 6 months) of using the dr. Bart app in terms of (self-reported) number of consultations in secondary health care due to knee and/or hip OA in the Netherlands 2) To explore differences in use, usability and clinical outcomes between the Netherlands and Germany.

The third aim is to evaluate the short-term effectiveness of this stand-alone e-self management intervention compared to usual care in the Netherlands (**chapter 4**).

The fourth aim is to describe use and usability of this stand-alone e-self management intervention and investigate its relation with health care utilisation and clinical outcomes (**chapter 5**).

The fifth aim is to study the cost-effectiveness, from a health care payer perspective, of the dr. Bart app (**Chapter 6**).

Finally, **Chapter 7** summarizes the results of this thesis and discusses main findings. Furthermore, methodological considerations, implications for clinical practice and further research are presented.

Table 2. Overview of studies regarding digital self-management interventions in OA

Author, year of publication	Study population	Mode of delivery	Intervention description and comparator	Treatment effect
Lorig et al. 2008[65]	OA, RA, fibromyalgia, N=855 OA N=546, IG: Age: 52.2 (10.9); 90% females CG, Age: 52.5(12.2); 91% females	Web-based, combined with workshop taught by peers.	Web-based learning centre; pain management, goal setting, exercises, medication diaries during 6 weeks. In addition, web-based workshop taught by peers. Interaction with peers. **Comparator:** usual care	Significant improvement in 4 out of 6 health measures and self-efficacy. No significant improvement in health behaviour or HCU.
Bossen et al. 2013[66]	Knee and/or hip OA, N= 199, Age: 62(5.7); 64.8% females	Stand-alone, web-based	PA intervention (Join2Move): behavioural graded activity program, goal setting, time-contingent PA objectives, text messages, positive reinforcement, without human support during 9 weeks **Comparator**: wait list.	Sign. Effect on physical function and self-perceived effect at 3 months, not on PA. Sign. Effect on subjective and objective PA, not for physical function over 12 months.
Bennell et al. 2017[64]	Chronic knee pain, N=148, IG IG, Age: 60.8 (7.5); 58% females CG Age: 61.5 (7.6); 54% females	Web-based in combination with 7 skype meetings with a physical therapist.	Web-based pain coping skills training (PainCoach), web-based education material, and 7 skype meetings with physical therapist for home-based exercises for 12 weeks **Comparator**: web-based education material	Clinically meaningful improvements in pain and function, sustained for 6 months.
Bennell et al. 2018[67]	Hip OA, N=144 Age IG: 61.2(7.2); 62% females Age CG: 61.3(7.1); 52% females	Web-based with 5 face-to-face meetings with a physical therapist	Automated web-based pain coping skills training (PainCoach) for 8 weeks, in addition to comparator. **Comparator**: web-based education material during 8 weeks, home-based exercise for 16 weeks (guided with 5 face-to-face meetings with physical therapist).	No additional benefit of automated web-based pain coping skills training program compared to comparator.
Kloek et al. 2018[69]	Knee and/or hip OA, N=208, Age IG: 63.8(8.5); 67.9% females Age CG: 62.3(8.9); 67.7% females	Web-based in combination with 5 face to face session with a physical therapist	E-exercise for 12 weeks: graded activity, strength and stability exercise, and information + 5 face-to-face sessions. **Comparator**: usual physical therapy	No significant differences on physical functioning and PA over 3 and 12 months. Possible reduction in physical therapy sessions.
Allen et al. 2018[68]	Knee OA, N=350, Age: 65.3 (11.1); 71.7% females	Stand-alone, web-based	Automated IBET-program for 12 months: Tailored exercises, Exercise progression, Video Display of exercises, Reminders, Progress tracking. Option to contact researchers for technical support. **Comparator**: physical therapy arm and waiting list arm	No statistically or clinically meaningful differences between intervention groups and waiting list. IBET was non-inferior to physical therapy at both 4 and 12 months for the primary outcome.

Abbreviations: *OA*, osteoarthritis; *RA*, Rheumatoid arthritis; *IG*, intervention group; *CG*, control group; *PA*, physical activity; *Sign*, significant.

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Chapter 2

Comparison of physical activity among different subsets of patients with knee or hip osteoarthritis and the general population

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Abstract

Objective

To compare the amount of physical activity (PA) among patients with different subsets of knee or hip osteoarthritis (OA) and the general population.

Methods

Secondary analyses of data of subjects ≥ 50 years from four studies: a study on the effectiveness of an educational program for OA patients in primary care (n = 110), a RCT on the effectiveness of a multidisciplinary self-management program for patients with generalised OA in secondary care (n = 131), a survey among patients who underwent total joint arthroplasty (TJA) for end-stage OA (n = 510), and a survey among the general population in the Netherlands (n = 3,374). The Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) was used to assess PA in all 4 studies. Differences in PA were analysed by multivariable linear regression analyses, adjusted for age, body mass index, and sex.

Results

In all groups, at least one-third of total time spent on PA was of at least moderate intensity. Unadjusted mean duration (hours/week) of at least moderate intensity PA was 15.3, 12.3, 18.1, and 17.8 for patients in primary, secondary care, post TJA, and the general population, respectively. Adjusted analyses showed that patients post TJA spent 5.6 hours (95% CI: 1.5; 9.7) more time on PA of at least moderate intensity than patients in secondary care.

Conclusion

The reported amount of PA of at least moderate intensity was high in different subsets of OA and the general population. Regarding the amount of PA in patients with different subsets of OA, there was a substantial difference between patients in secondary care and post TJA patients.

Background

Hip and knee osteoarthritis (OA) are among the most common joint conditions, with treatment being predominantly symptomatic and focusses on controlling pain, improving function, and health-related quality of life. In all stages of knee or hip OA, promotion of general physical activity (PA) is, in parallel with joint-specific exercises, considered to be a key component in the conservative management, including the trajectory after total joint arthroplasty (TJA)[1–6]. PA is defined by the World Health Organisation as "any bodily movement produced by skeletal muscles that requires energy expenditure"[7,8]. According to this definition, PA is not only restricted to exercise but also comprises any activity in any domain of daily life, e.g. commuting, work activities, cycling, gardening, household activities and sports[9].

PA has multiple potential benefits in patients with knee or hip OA as it has proven to play a role in improvement of pain, physical function, mobility, and weight management[1,6,10–13]. In addition, PA is considered an important preventive measure for other chronic diseases (e.g. cardiovascular disease) associated with OA[11,14–16].

The proportion of OA patients meeting public health recommendations for health enhancing PA varies largely in the literature, from 13 to 60%[14,17–19]. This variation could probably be due to heterogeneity in participants, settings, monitoring devices and methods across studies[17]. Currently, studies that compare the amount of PA between early and advanced stages of knee and or hip OA, including TJA, and the general population are scarce[17,19,20]. Regarding the comparison of PA in patients before and after TJA, a recent systematic review and meta-analysis concluded that PA does not change 6 months post TJA compared with preoperative levels[20,21]. Moreover, these studies concluded that PA after TJA was less compared to that of healthy controls[20–22]. On the other hand, Meessen et al. found that patients following TJA were more physically active compared to the general population[23]. In none of the aforementioned studies the nature of performed activities in different stages of the disease were presented.

It is conceivable that pain is a barrier for performing PA, and pain increases in more advanced stages of OA. Therefore, one would expect that PA decreases over the course of knee or hip OA[24,25] and that the amount of PA of patients with OA is lower than that of the general population. On the other hand, we expect that patients after TJA perform more PA than patients with advanced OA but without indication for surgery, since TJA results in less pain and improved function[14,17].

Therefore, the aim of the present study was to deepen the insight in terms of amount and nature of self-reported PA levels in different stages of the disease (i.e. patients in primary and secondary care and post TJA) and to compare PA characteristics of patients with knee or hip OA with those of the general Dutch population.

Methods

Study design

This study has an observational cross-sectional design; research questions were answered by secondary analyses of data from four studies performed in the Netherlands in four different populations: (1) patients with knee or hip OA in primary care[26], (2) patients with generalised OA in secondary care[27], (3) patients with knee or hip OA who underwent TJA[23,28], and (4) the general population[29]. Only data of subjects ≥ 50 years was included in this study.

Participants

Patients in primary care

Baseline data of an observational study to determine (preliminary) effects of an OA educational, community based program on healthcare utilisation and clinical outcomes was used[26]. This educational program consisted of two 1.5-h meetings, led by a physiotherapist and a GP, with information on OA and its disease course, conservative treatment modalities using a stepped-care approach, and surgical treatment options. Patients were recruited through searching GP electronic patient records and advertisements in local newspapers. In total, 148 patients with a clinical diagnosis of knee or hip OA were included from the region of Nijmegen between October 2015 and March 2016[26]. Main inclusion and exclusion criteria are presented in the supplementary material.

Patients in secondary care

We used baseline data of a randomised controlled trial (RCT) on the effectiveness of two non-pharmacological multidisciplinary self-management programmes for generalised OA in secondary care (i.e. face-to-face versus a telephone-based). Patients who visited the outpatient department of the Sint Maartenskliniek at Nijmegen in 2010 were included if they were clinically diagnosed with generalised OA and referred by their rheumatologist for multidisciplinary treatment. A total of 147 patients completed baseline assessments[27].

Total Joint Arthroplasty (total knee and hip arthroplasty)

For the post TJA stage we used data from a cross-sectional study on patients who underwent total knee or hip joint arthroplasty due to end-stage OA. The original study was conducted to make an inventory of the use of physical therapy and the presence of comorbidities after TJA. Orthopaedic surgeons of four different hospitals invited by mail all patients who underwent TJA in the preceding 7-22 months to participate in this study. In total, 522 patients responded[23,28]. Results on the comparison of the amount of PA between TJA patients and the general population were previously published[23], and will thus not be highlighted in this study.

General population

Data from the general Dutch population were obtained from a nationwide survey on general health (Gezondheidsmonitor 2012). Annually this survey is distributed (randomly) amongst more than 14,000 residents in the Netherlands, collected by the Dutch National Bureau of Statistics[29]. First, the survey on basic characteristics was sent to people living in private households, with a response rate of 60-65%. Subsequently, responders aged ≥ 12 years received a questionnaire regarding PA among other health-related subjects. Response rate of the health-related questionnaire was 55%[29]. This survey yielded individual participant data and was obtained from the CBS[29].

Ethical approval for this study was asked for and waived by the local Medical Research Ethics Committee of the University Medical Centre, Leiden (Protocol Number: G17.113, Date: 2 November 2017). The study fell outside the remit of the law for Medical Research Involving Human Subjects Act, and was approved by the local ethical committee.

Assessments

Sociodemographic characteristics

All databases included the following demographic characteristics: sex (male / female), age, body mass index (BMI) (kg/m^2), and included information about marital status.

Physical activity

In all databases, PA was assessed with the validated Short Questionnaire to ASses Health-enhancing physical activity (SQUASH)[9,30]. The SQUASH is a structured questionnaire consisting of activities at work, commuting, household activities, leisure time, and sport activities. Additionally, persons who filled out the SQUASH were asked to report the nature of (up to) four sports activities they actually perform. From this questionnaire, we calculated the mean duration of PA at light intensity (< 4 metabolic equivalent of task (MET) for persons < 55 years and < 3 for persons ≥ 55 years), mean duration of PA at moderate intensity (≥ 4 and < 6.5 MET for persons < 55 years and activities ≥ 3 and < 5.0 MET for persons ≥ 55 years) and mean duration of PA at vigorous-intensity (≥ 6.5 MET for people < 55 years and ≥ 5 MET for ≥ 55 years). We combined the latter two categories into PA of at least moderate intensity. The MET for an activity was derived from the Ainsworth compendium[31].

Statistical analysis

Baseline descriptive statistics for each group were provided as mean and standard deviation (SD) for continuous variables and numbers (N) with percentages (%) for nominal variables. We performed a mean centring operation for the variables age and BMI.

To compare mean amount (hours/week) of total PA and PA of at least moderate intensity between three stages of OA and the general population, we performed multivariable linear regression analyses. All regression analyses were performed on complete cases adjusted for (mean centred) age, (mean centred) BMI and sex. Subsequently the residuals of the linear regression analyses were plotted to inspect normality assumptions. On the basis of the residual plots we concluded that transformation of the continuous data would not improve the accuracy of the models.

The seven most frequently reported sport activities are presented per subgroup separately. We refrained from statistical testing because a type I error could occur due to multiple testing.

Sensitivity analyses

As OA is a prevalent disease, we performed a sensitivity analysis excluding patients with a possible diagnosis of OA from the general population. Therefore, we repeated all analyses excluding participants from the general population with a positive answer on the question whether they suffered from "wear and tear of the joints" (yes/no) in the preceding 12 months. A p-value of ≤ 0.05 was considered significant. All analyses were performed using Stata 13.1[32].

Results

Participants

In total, the present study used data of 4,125 patients with knee or hip OA or from the general population aged ≥ 50 years who completed the SQUASH questionnaire. Datasets representing the primary and secondary care patients comprised 110 and 131 participants, respectively. The dataset representing patients post TJA consisted of 510 participants. The database from the general (Dutch) population of 14,374 persons contained 3,374 persons who filled out the SQUASH and were ≥ 50 years of age and thus met inclusion criteria for the present study. Of these latter 3,374 persons, 853 (25.3%) reported that they suffered from "wear and tear of the joints" in the previous 12 months.

Patients' demographics and characteristics

Table 1 shows the demographic characteristics of the patients selected for the present analysis in all four study populations. The mean age was highest in patients post TJA (70.5 years (SD 8.5)) and lowest (61.1 (SD 6.7)) in the secondary care group. The proportion of males was lowest in the secondary care subgroup (15.3%) and highest in the general population (50.5%). The lowest mean BMI was found in the general population (26.1 kg/m^2 (SD 4.1)) and the highest (27.8 kg/m^2 (SD 4.5)) was found in both secondary care patients and in patients post TJA.

Symptoms in both knee(s) and hip(s) were perceived by almost 25% in primary care patients and 50% in secondary care patients. In the TJA group, 273 (53.5%) patients received TKP and 237 (46.5%) THP, Table 1.

Table 1. Demographics and characteristics of patients in different subsets of OA and the general (Dutch) population

Patient characteristics		Primary care *N* = 110	Secondary care *N* = 131	Post TJA *N* = 510	General population *N* = 3,374	*P*-value†
Male, *N* (%)		46 (41.8)	20 (15.3)	172 (34.1)	1,705 (50.5)	0.0001
Age (years), mean (SD)		69.8 (9.1)	61.1 (6.7)	70.5 (8.5)	63.8 (9.1)	0.0001
BMI (kg/m^2 (SD))		26.9 (4.3)	27.8 (4.5)	27.8 (4.6)	26.1 (4.1)	0.0001
Localisation of symptoms	Knee, *N* (%)	77 (70.0)	104 (79.4)	273 (53.5)	N/A	N/A
	Hip, *N* (%)	55 (50.0)	79 (60.3)	237 (46.5)	N/A	
	Both, *N* (%)	27 (24.5)	63 (48.1)	N/A	N/A	
Level of education, *N* (%)						0.0001
Low		10 (9.2)	4 (3.1)	157 (40.1)	1,383 (41.6)	
Medium		67 (61.5)	85 (65.4)	149 (38.0)	1,628 (49.0)	
High		32 (29.4)	41 (31.5)	86 (21.9)	314 (9.4)	
Marital status, *N* (%)						
Married		78 (71.6)	98 (74.8)	271 (66.3)	2,476 (73.4)	0.024
Work Status, *N* (%)						
Paid work		22 (20.2)	47 (36.2)	N/A	2,013 (59.7)	0.0001

† *P*-value is given for ANOVA or Chi-square test between groups.
Abbreviations: *OA*, osteoarthritis; *SD*, Standard Deviation; *N*, number; *TJA*, Total Joint Arthroplasty; *N/A*, not applicable.

Physical activity

The percentage of missing data on the primary outcomes was approximately 3% for total duration. Table 2 shows the mean duration of PA (unadjusted for age, BMI and sex) for the different subgroups.

Regarding the total amount of PA (light, moderate, and vigorous intensity), the mean duration (unadjusted for age, BMI and sex) in the different subgroups ranged from 36.0 (19.5) hours/week for primary care patients to 40.1 (26.9) hours/week for the general population. Results of multiple linear regression analyses, adjusted for (mean centred) age, (mean centred) BMI and sex, shows that patients post TJA were on average 10.9 (95% CI: 5.7; 16.1 (p = 0.000)) hours/week more active than secondary care patients and 6.1 (95% CI: 3.5; 8.7 (p = 0.000) hours/week more active than the general population (Table 3). Adjusted analyses also showed that patients in secondary care were on average 4.7 (95% CI: -9.4; -0.1 (p = 0.046)) hours/week less active than the general population.

The mean duration of PA of at least moderate intensity (unadjusted) ranged from 12.3 (12.0) hours/week for secondary care patients to 18.1 (17.8) hours/week for patients post TJA, Table 2. Adjusted analyses revealed that patients post TJA were on average 5.6 (95% CI: 1.5; 9.7 (p = 0.007)) hours/week more active on PA of at least moderate intensity than patients in secondary care and 2.4 (95% CI: 0.3; 4.5 (p = 0.022)) hours/week more active than the general population (Table 4).

We found comparable patterns in differences between groups in PA of light, moderate or vigorous intensity (see Supplement 2, 3 and 4).

The proportions of people spending a certain amount of time on total PA and PA of at least moderate intensity for each subgroup are displayed in Figure 1. The proportion of people at least spending 150 minutes per week on PA of at least moderate intensity ranged from 84.7% to 92.1%. The proportion of people at least spending 300 minutes per week on PA of at least moderate intensity ranged from 73.7% to 81.5% (Table 2).

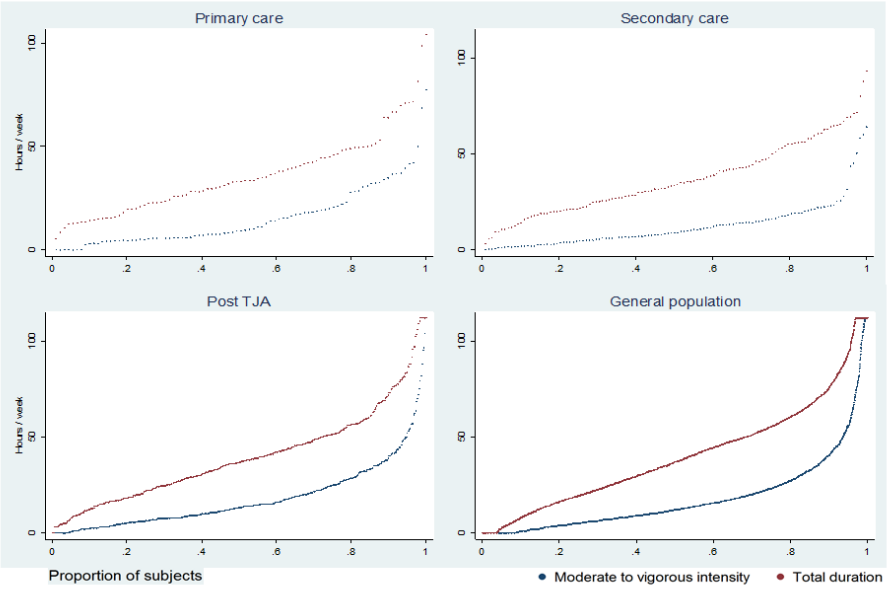
Table 2. Unadjusted duration of physical activity of patients in different stages of OA and the general (Dutch) population.

Physical activity	Primary care *N* = 110	Secondary care *N* = 131	Post TJA *N* = 510	General population *N* = 3,374	*P*-value[†]
Total mean duration of PA (hours/week) (SD)	36.0 (19.5)	36.8 (18.7)	39.6 (23.9)	40.1 (26.9)	0.2893
Mean PA duration of at least moderate intensity (hours/week) (SD)	15.3 (14.9)	12.3 (12.0)	18.1 (17.8)	17.8 (19.9)	0.0135
Adhering to 150 min./ week of at least moderate intensity, yes (*N* (%))	82 (92.1)	102 (86.4)	355 (89.9)	2,858 (84.7)	0.0 12
Adhering to 300 min./ week of at least moderate intensity PA, yes (*N* (%))	69 (77.5)	87 (73.7)	322 (81.5)	2,578 (76.4)	0.118

[†] *P*-value is given for ANOVA or Chi-square test between groups.
Abbreviations: *PA*, physical activity; *OA*, osteoarthritis; *SD*, Standard Deviation; *N*, number; *TJA*, Total Joint Arthroplasty; *min*, minutes.

2

Figure 1. Proportion of subjects with hours per week spent on at least moderate intensity physical activity and total duration of physical activity for each subject. Presented in hierarchical order for each group separately. Only non-missing values are presented



Abbreviations: *TJA*; Total Joint Arthroplasty.

Table 3. Difference in total mean (95% confidence interval) duration (hours/week) of PA between groups for people with average age and BMI, adjusted for sex

	General population 39.4 (38.3; 40.6)	Primary care 40.0(34.6; 45.4)	Secondary care 34.7 (29.9; 39.4)
Primary care	0.6		
	(- 4.8; 6.0)		
Secondary care	**- 4.7***	-5.3	
	(- 9.4; -0.1)	(-12.4; 1.7)	
Post TJA	**6.1***	5.5	**10.9***
	(3.5; 8.8)	(-0.3; 11.4)	**(5.7; 16.1)**

*Indicates *p*-value ≤ 0.05.

Abbreviations: *PA*; physical activity, *BMI*; Body Mass Index, *TJA*; Total Joint Arthroplasty

Table 4. Difference in mean (95% confidence interval) duration (hours/week) of PA of at least moderate intensity between groups for people with average age and BMI, adjusted for sex

	General population 20.6 (19.7; 21.4)	Primary care 20.5 (16.3; 24.8)	Secondary care 17.4 (13.6; 21.1)
Primary care	0.0		
	(-4.3; 4.2)		
Secondary care	-3.2	-3.2	
	(-6.9; 0.5)	(-8.7; 2.4)	
Post TJA	**2.4***	2.5	**5.6***
	(0.3; 4.5)	(-2.2; 7.1)	**(1.5; 9.7)**

*Indicates *p*-value ≤ 0.05.

Abbreviations: *PA*; physical activity, *BMI*; Body Mass Index, *TJA*; Total Joint Arthroplasty

Sensitivity analyses, excluding persons reporting "wear and tear" of the joints in the general population yielded similar results for all performed analyses. Additional sensitivity analyses, separating the TJA group in TKP and THP, showed that the mean duration of PA in patients with TKP was 3.0 (95% CI: 0.1; 6.0) hours/week higher than the general population, whereas no significant difference was found between patients after THP and the general population (2.0 (95% CI: -0.8; 4.7)).

Nature of physical activities

Table 5 shows the seven most frequently reported sports activities, presented per subgroup. Patients post TJA least frequently reported fitness as performed activity, whereas they reported cycling most often. General exercise at moderate intensity is reported more often by OA patients than the general population. Yoga is more often reported by primary and secondary care patients. Patients in secondary care reported swimming most often. We visually inspected differences in proportions between groups, thus no statistical testing was performed.

Table 5. Main sports activities reported by the four different groups with accompanying MET value, presented in hierarchical order for primary care patients.

	Primary care *N* (%)	Secondary care *N* (%)	Post TJA *N* (%)	General population *N* (%)
Fitness at the gym	27	29	69	684
5.5 MET	(24.5)	(22.1)	(13.5)	(20.3)
General exercises at moderate intensity	17 (15.4)	20 (15.3)	112 (22.0)	100 (3.0)
4.0 MET				
Tennis	10	4	15	202
7.0 MET	(9.1)	(3.1)	(2.9)	(6.0)
Cycling	10	9	52	250
7.0 MET	(9.1)	(7.7)	(10.2)	(7.4)
Swimming	9	20	37	217
6.0 MET	(8.2)	(15.3)	(7.3)	(6.4)
Yoga	8	10	5	57
2.5 MET	(7.3)	(7.6)	(1.0)	(1.7)
(Nordic) Walking	8	8	25	254
3.5 MET	(7.3)	(6.8)	(4.9)	(7.5)

Abbreviations: *MET*; Metabolic Equivalent of Task, *N*; Number, *TJA*; Total Joint Arthroplasty.

Discussion

The aim of this study was to document the amount and nature of PA among patients with OA in different stages of their disease and to compare PA characteristics of patients with knee or hip OA with those of the general population. On average patients reported to be physically active for at least 5.1 hours per day, and to spend about one-third of PA in at least moderate intensity PA. We found that OA patients post TJA are on average more physically active than patients in secondary care. No other relevant differences across different stages of OA and the general population were found.

We found differences in the nature of PA that patients perform in different stages of OA and the general population: patients post TJA report more often low-impact activities (e.g. aerobic exercise (general exercises at moderate-intensity) and cycling) than other OA patients and the general population. On the other hand, swimming, also considered a low-impact activity, is most often reported by patients in secondary care. A possible explanation for the differences in the nature of PA is that high-impact sports such as running and contact sports are discouraged for patients after TJA[33–35]. Our findings are in line with a meta-analysis concluding that patients after TJA return more often to low-impact activities than high impact activities[36]. This may indicate that patients after TJA follow rehabilitation advice.

International guidelines recommend to perform at least 150 minutes per week of PA on at least moderate intensity for general health benefits[8,37]. The WHO states that there is evidence for additional health benefits up to 300 minutes per week[8]. However, recommendations about the optimal amount and intensity of PA for OA patients are lacking. Apart from general health

benefits, it is well known that increasing PA has positive effects on pain in OA patients[1,10], suggesting a dose-response relationship. Currently, there is debate about the exact shape of the dose-response relationship between performed PA and health benefits[38–40]. Some research groups assume a (curvi)linear relationship implying the more PA the better[37,41,42], whereas other research groups assume an optimal range beyond which health benefits may be partially lost[38–40]. Epidemiologic studies on the optimal dose of PA are, however, mainly performed in cardiovascular patients and physically active volunteers rather than in OA patients. Therefore, future studies should assess the exact relation between PA and actual health benefits in OA patients in order to determine the optimal dose of PA.

We could not confirm our first hypothesis that the duration of PA decreases over the course of OA. Subgroups in the present study were based on the assumption that primary care patients (recruited trough searching GP electronic patients records and advertisements in local newspapers) and secondary care patients (recruited after referral by a rheumatologist to self-management program of a hospital) reflect increasing rates of severity, rather than upon well-accepted criteria (i.e. Kellgren and Lawrence classification or joint space width). Our results are in line with a meta-analysis, showing no clear differences in PA between mild or moderate and severe OA[17]. A possible explanation could be that patients with more severe knee or hip OA substitute activities so that PA can be performed despite their complaints. However, our findings are contradictory with results of a longitudinal study in over 1,200 OA patients showing that the amount of PA decreases with 11% over the course of 4 years[24]. The observed decrease in PA over time in the latter study could be explained by the influence of ageing; higher age is associated with lower PA levels[20,43]. Future studies should focus on unravelling the influence of ageing and severity of the disease on PA in OA patients.

Additionally, we could not confirm our hypothesis that patients in primary and secondary care were less active than the general population. Our results are in line with a recent study showing comparable levels of objectively measured activity of at least moderate intensity for patients with knee OA and the general population[44]. On the other hand, our findings are inconsistent with a study concluding that patients with end-stage OA were less active than controls[45]. However, it is likely that in the latter study more severely affected patients were included. Our findings suggest that having OA in the early and more advanced stages does not impact PA levels, and that patients with OA manage to stay as active as the general population. However, prospective longitudinal research is needed to study the impact of symptoms related to OA on actual PA levels.

This study confirms our second hypothesis that patients who underwent TJA are more physically active than patients in secondary care. Regarding the effect of TJA on PA, recent studies showed no differences in preoperative PA levels compared to 6, 12 and 24 months post TJA, as well as compared to matched controls[20,21,46]. There are several possible explanations that patients following TJA spent more time on PA in our study. First, TJA results in less pain and improved function[14,17]. Second, in our sample 50% of patients received physical therapy for more than 3 months post TJA[28]. Therefore, these patients could be better instructed and motivated to perform PA. Another explanation could be that relatively active patients with end-stage OA receive TJA, and will therefore resume their old PA level easily.

This is the first study that compares the amount of PA in different stages of OA and the general population. This study also reports activities that are actually performed in different stages of OA and in the general population. However, data must be interpreted with caution, since this study has some potential limitations. Compared to the literature, we studied a relatively physically active cohort of patients[17,43,47], however, comparison with studies utilising objective measures of PA (e.g.. accelerometers) should be done with caution. Despite the regular use of self-administered measures, questionnaires tend to overestimate PA[30]. The SQUASH takes walking and cycling into account in three different modules; commuting, recreational and as a sports activity, and overlap in reporting these activities cannot be excluded. In particular, overestimation of the amount of PA spent on cycling, a common daily activity in the Netherlands, is likely. On the other hand, all datasets in this study used the same questionnaire assessing PA, i.e. the SQUASH, and, in our view, our results regarding differences between groups are valid. A note of caution is due here since we compared baseline data of four separate, previously published studies of different clinical settings in different time periods. Due to the heterogeneity of the subjects included in the separate studies, it is possible that there is some overlap in patients' characteristics among different subsets of OA patients. The subgroups comprising OA patients in different stages of disease were relatively small, and this could result in lack of power. Although we adjusted for age, sex and BMI we cannot rule out possible confounding of other factors such as education, profession, and comorbidities not included in our analysis. However, sample sizes were appropriate to detect differences of 10% or higher.

In conclusion, this study showed that patients with different subsets of OA and the general population spend on average considerable time on PA and that at least one-third of time active was spent on PA of at least moderate intensity. On the one hand we found no major differences in the amount of PA among OA patients in primary, secondary care and the general population, on the other hand we found substantial differences in the amount of PA between patients in secondary care and post TJA patients. Although we found that PA levels for patients in different stages of OA and the general population were comparable, it is well known that PA has beneficial effects on OA symptoms. Thus, continued efforts are needed to enhance PA in patients in different stages of OA. More research is needed to assess the exact relation between PA (in terms of duration and intensity) and actual health benefits in patients with OA over time.

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Supplementary material

Supplementary Table 1. Main in- and exclusion criteria of the four studies

	Primary care	Secondary care	Post TJA	General population
Inclusion	• ≥ 18 years • Clinical diagnosis of OA (knee or hip). • Recruited between October 2015 – March 2016	• ≥ 18 years • Two objective signs indicating GOA in ≥ 2 joints areas. • Complaints in ≥ 3 joint areas. • Limited in daily activities. • Motivated to alter lifestyle and willing to participate in a group. • Recruited between January 2010 – March 2013	• ≥ 18 years • Primary TJA due to end-stage OA (knee/ hip) • Recruited between January – December 2011 in one of the four participating hospitals	• Private household • ≥ 12 years
Exclusion	• Inability to read or understand Dutch language • Previous joint replacement surgery.	• Diagnosed with another rheumatic disease. • Awaiting surgery. • Already participated unsuccessfully in self-management program. • Psychosocial problems. • Incapable of coming to the hospital. • Unable to write or understand Dutch language.	• Revision surgery • Other diagnosis than end-stage OA	• Institutionalized

Abbreviations: *OA*, osteoarthritis; *GOA*, generalised osteoarthritis; *TJA*, Total Joint Arthroplasty

Supplementary Table 2. Difference in mean (95% confidence interval) duration (hours/week) of PA at light-intensity between groups for people with average age and BMI, adjusted for sex

	General population 19.9 (19.1; 20.8)	Primary care 19.4 (15.3; 23.4)	Secondary care 17.3 (13.7; 20.8)
Primary care	-0.5		
	(-4.6; 3.5)		
Secondary care	-2.6	-2.1	
	(-6.1; 0.9)	(-7.3; 3.2)	
Post TJA	**2.8***	3.4	**5.4***
	(0.8; 4.8)	(-1.0; 7.7)	**(1.5; 9.3)**

*Indicates *p*-value ≤ 0.05.
Abbreviations: *PA*; physical activity, *BMI*; Body Mass Index, *TJA*; Total Joint Arthroplasty

Supplementary Table 3. Difference in mean (95 % confidence interval) duration (hours/week) of PA at moderate-intensity between groups for people with average age and BMI, adjusted for sex

	General population 15.2 (14.4; 16.0)	Primary care 13.8 (10.1; 17.5)	Secondary care 12.8 (9.6; 16.0)
Primary care	-1.4		
	(-5.0; 2.3)		
Secondary care	-2.4	-1.0	
	(-5.5; 0.7)	(-5.8; 3.7)	
Post TJA	1.0	2.3	3.4
	(-0.8; 2.8)	(-1.6; 6.3)	(-0.1; 6.9)

*Indicates *p*-value ≤ 0.05.
Abbreviations: *PA*; physical activity, *BMI*; Body Mass Index, *TJA*; Total Joint Arthroplasty

Supplementary Table 4. Difference in mean (95 % confidence interval) duration (hours/week) of PA at vigorous-intensity between groups for people with average age and BMI, adjusted for sex

	General population 5.5 (5.1; 5.9)	Primary care 6.8 (5.0; 8.6)	Secondary care 4.6 (3.0; 6.3)
Primary care	1.3		
	(-0.5; 3.1)		
Secondary care	-0.8	-2.2	
	(-2.4; 0.7)	(-4.5; 0.2)	
Post TJA	**1.4***	0.1	**2.3***
	(0.5; 2.3)	(-1.9; 2.1)	**(0.5; 4.0)**

*Indicates *p*-value ≤ 0.05.
Abbreviations: *PA*; physical activity, *BMI*; Body Mass Index, *TJA*; Total Joint Arthroplasty

2

Chapter 3

Development and evaluation of a tailored e-self management intervention (dr. Bart app) for knee and/or hip osteoarthritis: study protocol

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Abstract

Background

This paper describes (the development of) an eHealth tool (dr. Bart app) to enhance self-management and to optimize non-surgical health care utilisation in patients with knee and/or hip osteoarthritis (OA) and presents a study aiming 1) to study the effectiveness of the dr. Bart app on health care use 2) to explore differences in use, usability and the clinical outcomes of the dr. Bart app between the Netherlands and Germany.

Methods

The dr. Bart app is a fully automated eHealth application and is based on the Fogg model for behavioural change, augmented with reminders, rewards and self-monitoring to reinforce app engagement and health behaviour. The dr. Bart app propose goals to a healthier lifestyle based on machine learning techniques fed by data collected in a personal profile and choosing behaviour of the app user. Patients ≥50 years with self-reported knee and/or hip OA will be eligible to participate. Participants will be recruited in the community through advertisements in local newspapers and campaigns on social media. This protocol presents a study with three arms, aiming to include 161 patients in each arm. In the Netherlands, patients are randomly allocated to usual care or dr. Bart app and in Germany all patients receive the dr. Bart app. The primary outcome of the first research question is the number of self-reported consultations in secondary health care. The primary outcome of the second research question (comparison between the Netherlands and Germany) is self-management behaviour assessed by the patient activation measure (PAM-13) questionnaire. Secondary outcomes are costs, health-related quality of life, physical functioning and activity, pain, use and usability of the dr. Bart app. Data will be collected through three online questionnaires (at baseline and after 3 and 6 months after inclusion).

Discussion

This study will gain insight into the effectiveness of the dr. Bart app in the (conservative) treatment of patients with knee and/or hip OA and differences in the use and usability of the dr. Bart app between the Netherlands and Germany.

Background

Osteoarthritis (OA) is the most common joint disease in the world[1], affecting approximately 10-18% of the population aged 60 years and over. Most often hip and knee joints are affected by OA[2]. Osteoarthritis causes functional disability as a consequence of major structural changes of the joint (i.e. progressive loss of articular cartilage) and has a major impact on the quality of life[2–5]. As a result, the societal burden of OA is high; the annual burden of OA is 1.6 % of the total health care expenditure in the Netherlands[6]. In the Netherlands, health care costs attributable to OA spent in secondary care are eight times higher than costs spent in primary care[6]. As the prevalence of OA increases with age[2,7], it is expected that the burden of OA will increase dramatically in the near future.

Although OA is not curable, a variety of treatment options is available to reduce symptoms[8,9]. Core elements comprise education, promotion of lifestyle changes (physical activity (PA)), pain management, exercise therapy, and weight reduction in case of overweight. Although total joint arthroplasty (TJA) is considered a (cost-)effective treatment for people with OA, TJA should only be considered after conservative treatments have failed[10–12]. Since OA is a chronic disease, a key element in the non-surgical management of knee and/or hip OA is self-management[5,10,11,13]. Self-management interventions offer patients guidance in improving their skills to take care of themselves and to improve skills to navigate the health care system[14,15].

Despite recommendations about the content of non-surgical treatment options in OA, quality of care in OA in primary care is suboptimal[12,16,17]. Lack of time and detailed guidance in clinical practice result in underutilisation of non-surgical treatment options and (unnecessary) referrals to secondary health care in people with OA[10,12]. Therefore, it is of importance to promote self-management in people with OA to optimise the use of non-surgical care and to prevent unnecessary referrals to secondary care.

Health education and goal setting should be considered as fundamental elements of (effective) self-management interventions[18–21]. Health education should include education about OA and its treatment options, pacing of PA and exercise, weight loss (if applicable) and how to find and utilise resources[10,11,15]. This information should be tailored to the person's illness perception and educational capability[10]. Additionally, goal setting is a widely used behavioural change technique in many fields, especially in health care[21]. Goal setting is associated with positive effects on behaviour at both short and long term[21,22]. Monitoring of behaviour or outcome (e.g. amount of PA, weight and achievement of goals), providing direct feedback and getting rewards may augment the effects of goal setting[21]. Traditional self-management programmes for OA show small benefits on self-management skills, pain, function and symptoms compared to usual care[23]. Ultimately, effective self-management implies that patients are able to take better care of their illness and, consequently, make optimal use of primary and secondary health care options.

Quality of care for people with OA is suboptimal and varies among (European) countries[17]. It is conceivable that differences in health care policies and cultural differences in health behaviour related to self-management account for differences in quality of care and clinical outcomes[24]. For example, in the Netherlands, the general practitioner (GP) functions as a gatekeeper while in Germany secondary care (e.g. rheumatologist and orthopaedic surgeon)

is directly and more easily accessible to patients[25]. Dutch GPs tend to give more information and advice about a disease than their German colleagues in a consultation[26]. In addition, variations in culture could influence internet use and thus information seeking behaviour[24,27]. These differences among countries may affect the way people with OA navigate the health care system[15,28–30]. To our knowledge, there is limited insight in the differences in use and effects of e-self management interventions among countries.

Modern persuasive technologies (e.g. applications) offer the possibility to enhance goal setting and provide tailored information to people with OA that suits individual preferences and to enhance self-management at all times[31,32]. Moreover, modern technologies can monitor health behaviour and provide real-time feedback, which are considered important elements of self-management[15,33]. Although the use of modern technologies seems promising, the majority of eHealth applications have not proven their effectiveness in clinical trials[34–38], especially in the field of OA. Therefore, we iteratively and systematically developed a standalone e-self management application (dr. Bart app) in both Dutch and German language, incorporating education, setting achievable health behaviour goals and provision of feedback.

This paper describes the design of a study that aims 1) To evaluate the short term effects (after 3 and 6 months) of use of the dr. Bart app in terms of (self-reported) number of consultations in secondary health care due to OA of the knee and/or hip in the Netherlands. We hypothesize that the app is (cost-)effective compared to usual care. 2) To explore differences in use, usability and clinical outcomes between the Netherlands and Germany. This paper also describes the systematical and iterative development of the dr. Bart app.

Methods

Development of the dr. Bart app

We developed the dr. Bart app to enhance self-management and to actively involve people with OA in managing their disease. Prior to the development of the app, a project group of experts consisting of (medical) researchers, physicians, physical therapists, patient representatives and app developers (including a user experience expert) was installed. This project group decided upon the theoretical framework (Figure 1), starting points and elements to be incorporated in the app. A model of behavioural change for the dr. Bart application was proposed based on the Fogg's behaviour model (FBM)[39] and augmented with other motivation enhancing techniques (i.e. reminders, rewards and self-monitoring), that will help users to achieve goals and in the long run result in better lifestyle behaviour and ultimately health (Figure 1)[22,39,40].

The steps followed during the different development phases of the dr. Bart app are elaborated upon in detail below. First, the applied theoretical framework of this standalone e-self-management intervention and its components are described and justified. Secondly, the iterative process of the development of the dr. Bart app is described.

Theoretical framework of the dr. Bart app

Considering the fact that behavioural change is difficult to achieve, the project group decided to base the application on the widely used Fogg model for behavioural change, also known as the 'tiny habits method'[39]. It states that three elements must be present for the target behaviour to happen: People must 1) be (sufficiently) motivated. 2) have the ability and 3) be triggered, or reminded to perform the behaviour[39]. The FBM states that there is a trade-off between these 3 factors; motivation and ability must occur at the same moment at a given trigger, otherwise, the behaviour will not happen. A trigger is referred to as an event in daily life that elicits the behaviour. According to FBM, people with low motivation need an easy objective and a simple trigger to be motivated to perform a target behaviour. Rather than stating "I want to lose five kilograms within one month", FBM suggest to establish tiny healthy habits. Thus, an objective could be "I eat one apple instead of unhealthy snack during my lunch break". The accumulation of such small behavioural lifestyle changes results in the achievement of an overarching target behaviour (e.g. weight reduction) and ultimately better health.

Goal setting

The project group decided after review of the literature and consensus meetings that users should have the option to choose goals related to four main themes that are core elements in the (non-surgical) management of OA; 1. education regarding OA, its treatment modalities and the benefits of a healthy lifestyle 2. Physical activity (both generic and OA specific information), 3. Vitality, and 4. Nutrition. To facilitate goal setting by the user, a library of pre-formulated goals with suggestions for triggers was incorporated in the dr. Bart app. Moreover, the project group agreed that machine learning techniques should be used to propose goals tailored to the personal situation and needs of users and taking into account the user's history of already achieved and discarded goals.

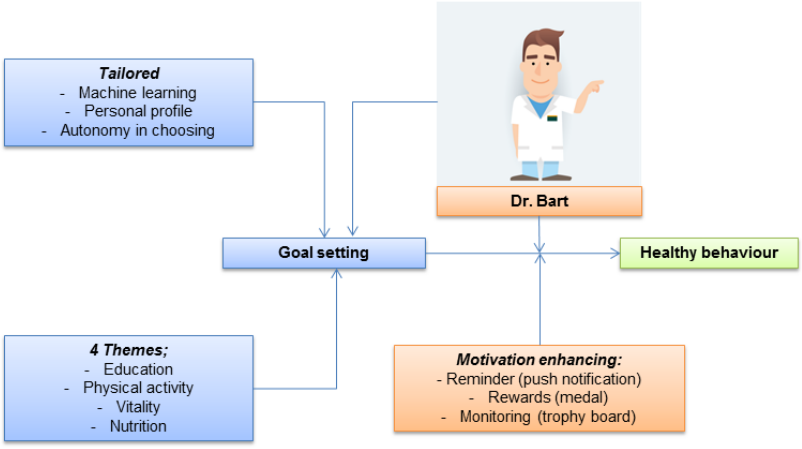

Figure 1. Theoretical framework of the dr. Bart app

Tailoring goal setting

As motivation and ability are dynamic processes and vary among individuals in real life, dr. Bart uses machine learning techniques based on a recommender system to propose (tailored) pre-formulated goals to users that suits the motivation and ability of each user. A recommender system is a general term for algorithms concerned with providing recommendations to users[41]. One of the most well-known examples is found in web shops like Amazon. These web shops provide suggestions of products to buy based on earlier purchases and contextual information about their users. For the dr. Bart app the machine learning comprises a dynamic model (Contextual Multi-armed Bandit approach) proposing goals that will be challenging, achievable and tailored for that specific user. The machine learning will be fed with contextual and personal information collected in a personal profile[42].

To generate a personal profile, dr. Bart asks some relevant questions the first time users log in; name, gender, year of birth, length, weight, localisation of symptoms, maximum walking distance and quality of sleep. Moreover, during the intake a user can select a preference of categories of goals he/she would like to work on. This preference is taken into account when making the initial recommendations for goals.

In order to give users autonomy in choosing goals, two techniques are incorporated in the dr. Bart app. First, users will be provided with the ability to tailor goals to their preferences by adapting both the level and trigger of a given pre-formulated goal. Second, the recommender system of the dr. Bart app proposes five pre-formulated goals to the user. Subsequently, the user can select or discard a goal to work on the next 24 hours. Users can work on up to three goals simultaneously in the app.

Motivation enhancing techniques

The project group agreed to incorporate a combination of techniques in the dr. Bart app (i.e. reminders[43,44], rewards[43,44] and self-monitoring of behaviour[40]) to enhance motivation and to reinforce app engagement and, thus, augment the potential intervention effect. In addition, the project group embraced the idea to incorporate an authoritative and approachable character (dr. Bart cartoon) to address the needs of users for reliable information and advice[45–47] and to mimic personal interaction. Positive feedback by dr. Bart is provided by positive gestures and positive expressions (e.g. "well done!)".

Reminders

After installing the app, users will receive a daily push notification from dr. Bart. This push notification is twofold; first, it reminds the user of the chosen goals for that day: "do you think of your goals today" and second, the push notification contains an interesting fact or a frequently asked question with an answer, or "Did you know that" about OA[48]. Additionally, the app automatically sends a push notification stating: "we have not seen you in a while, do you think of your goals?" when a user has not opened the app for more than 7 days.

Rewards

The dr. Bart app provides different types of rewards to users. By means of performance feedback, dr. Bart compliments the user: "Well done, 2 more goals to go for today". Additionally, after a user checks the box that he/she achieved a goal, confetti appears on the screen and dr. Bart says for example "Well done, you achieved all of your goals today". In a predetermined

sequence, users can earn achievements. For instance, an individual can earn a bronze medal after achieving the same goal five times. Subsequently, a gold medal can be earned after 21 times of achieving a goal.

Monitoring

An overview of achieved goals and how often these goals are achieved is presented in the "my goal page". A trophy cupboard in the app is used to illustrate the individual progress, i.e. earned achievements.

The development process of the app

Prior to the actual development of the dr. Bart app, a list of starting points was formulated by the project group to establish stakeholders' most important needs and functionalities in the use of the app based on the described theoretical framework.

Iterative design process

Both the (graphical) design and the content of the dr. Bart app were developed in an iterative design process with sprints of 3 weeks. Each sprint consisted of development, (user-)testing, adaptation, re-testing and final design[44,49]. Applications that are developed according to the methodology of persuasive design result in better treatment adherence compared to other techniques[50].

Development of the (graphical) design of the dr. Bart app

First, user stories regarding user requirements were developed by the app developer based on the list of starting points and input of the project group for the different components of the app (e.g. personal profile, library of goals, education library). First step in the development was the delivery of mock-ups (graphical design) for the different components of the app. In each mock-up round for the graphical design, 5-10 participants (including members of the project group) gave suggestions for improvements and alterations were made. This process was repeated until no further adaptations were deemed necessary for the graphical design. Subsequently, the actual screens were developed and a blueprint for navigation was created (wire-frame). This wire-frame was iteratively tested until no further adaptations were deemed necessary resulting in a beta version of the dr. Bart app.

Development of content

Parallel with the (graphical) design process the content of the dr. Bart app was iteratively developed.

Formulation of goals

The pre-formulated goals used in the dr. Bart app were formulated in co-creation with physical therapists, physicians and patient representatives. First, 4 members of the project group each delivered a list of 30 goals relevant for the treatment of OA and fulfilling the SMART criteria (Specific, Measurable, Achievable, Relevant and Time-bound)[18]. These 4 lists were merged and duplicates were removed by the first author (TP), resulting in a list of 72 goals. Subsequently, the goals of this new list were rephrased by the first author (TP) so that the goals require low motivation and ability (tiny habits)[39].

Education of OA

In the educational library of the dr. Bart app specific information regarding OA, and generic lifestyle advice can be found. Moreover, Frequently Asked Questions (FAQs) are part of the educational library of the dr. Bart app. The answers to these FAQs are thoroughly considered by an expert group[48]. In addition, information about the themes (i.e. physical activity, vitality and nutrition) is given in the educational library.

Physical activity and exercise library

To facilitate exercise and PA the dr. Bart app contains generic information on PA and its positive influences on health. In addition, an exercise library is incorporated in the dr. Bart app. Four physical therapist specialised in the treatment of OA each delivered a list of ten exercises which they considered important and were easy to execute without supervision. These lists were combined by the first author (TP) and duplicates were removed resulting in a list of 21 different exercises. After a consensus meeting with all involved physical therapists and the project group, a list of 14 exercises remained, focusing on both strengthening and flexibility of the lower extremity. These 14 exercises are illustrated in an exercise library by means of animated Graphics Interchange Format (GIF). These GIFs are accompanied with textual information on how to perform the specific exercise.

Vitality

For people with OA it is important to learn to pace their activities. Therefore, the dr. Bart app contains generic information regarding pacing of activities and vitality (e.g. sleep quality) and its positive influences on health and OA symptoms.

Nutrition

To enhance a healthy lifestyle, the dr. Bart app contains generic information regarding nutrition and its positive influences on health and OA symptoms. Goals regarding nutrition will target on weight management and healthy behaviour (e.g. “today I eat an apple rather than an unhealthy snack” or “today I do not drink alcoholic beverages”).

Pilot test of the dr. Bart app combined with training of the machine learning

The beta version of the dr. Bart app was pilot tested on usability in a sample of the target population. Machine learning has a “cold start”: at the beginning the recommender system does not know anything about the relation between the goals because it has no history of users picking goals. To reduce this issue and to make sure that the first users get recommendations that are sensible, the system is bootstrapped by providing it domain knowledge about the goals.

In order to “train” the machine learning, 25 persons with knee and/or hip OA with the same characteristics as the target population consented to pilot test the dr. Bart app for one month. Simultaneously, the feasibility and usability of the dr. Bart app were evaluated in the same pilot group. Moreover, we invited 5 participants from the pilot group for a user experience session with a semi-structured group interview, led by a user experience expert. In addition, we invited 5 people with equal sociographic characteristics as the target population to use the app for the very first time, including downloading the app, while making use of the “thinking-aloud” principle[49]. Based on the usability test, final alterations were made (version number 1.3.7, end of 2017).

Translation process of the dr. Bart app

The second aim of the described study is to explore potential (cultural) differences in use of the dr. Bart app and its effect on clinical outcomes between the Netherlands (arm B) and Germany (arm C). Therefore, the final version of the app and its content was translated to the German language by an independent native non-medical German speaker. All German texts were reviewed by an independent German communication adviser, one non-medical involved person, a medical doctor and a physical therapist. Consequently, small alterations to the German texts were made.

Study design

This manuscript was reported according to the SPIRIT statement[51]. This is a three-armed study comprising a two-armed unblinded randomised controlled trial (RCT) in the Netherlands and a controlled clinical trial (CCT) in Germany and the Netherlands in patients with OA (Figure 2). The RCT comprises a usual care group (group A) and a group receiving the dr. Bart app (group B). In addition, a third arm consisting of only German participants will all receive the dr. Bart app (group C).

Participants

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Self-reported OA of the knee and/or hip, defined as:
  - Having a painful knee and/or hip
  - **AND** - Knee and/or hip pain > 15 days of the past month
  - **AND** - Morning stiffness < 30 minutes (knee) and/or < 60 minutes (hip)
- ≥ 50 years
- Having an email address
- Possession of smartphone or tablet and willing to download the dr. Bart app on one or more devices.
- Able to read, write and sufficiently communicate in Dutch or German language, where appropriate.

Exclusion criteria

Potential participants will be excluded from participation in this study if they meet any of the following criteria:

- Being wheelchair-bound
- Total joint arthroplasty of the knee and/or hip in the past
- Scheduled for knee and/or hip total joint arthroplasty in the next 6 months
- Diagnosis of (other) inflammatory rheumatic disease

Study procedure

Recruitment and screening procedure

This study will be conducted by two hospitals, i.e. Sint Maartenskliniek Nijmegen (the Netherlands) and Sankt Elisabeth-Hospital Meerbusch (Germany). All participants for the described study will be recruited in the community through advertisements in local newspapers

(i.e. region Nijmegen in the Netherlands and Meerbusch in Germany) and in campaigns on social media of the involved hospitals (i.e. Facebook, LinkedIn, Twitter). Individuals with OA in the community willing to participate will be invited to visit the website www.drbart.eu and to complete a number of questions to check their eligibility for participation in this study. Eligible individuals are asked to sign in for the study by providing their e-mail address on the website. Hardcopy Information regarding the described study and generally on scientific research will be sent to their home address on demand. Potential participants will receive online baseline assessment via CastorEDC (https://www.castoredc.com/). CastorEDC is an electronic software application for data collection and management. CastorEDC is approved with ISO 27001 and ISO 9001, and is in line with the EU Data Protection Directive.

Randomisation, allocation concealment and blinding

Dutch consenting participants will be randomly allocated by the researcher to usual care (A) or dr. Bart (B) (allocation ratio 1:1) after completing baseline assessment performed with CastorEDC. CastorEDC uses a validated variable block randomisation method (with randomly varying block sizes of 2, 4, and 6) and is stratified on the individual level by hip or knee OA. The researcher who will ascertain randomisation will be concealed for treatment allocation. Due to the design of this study, blinding of participants and researchers is not possible. Data collectors will be blinded as data will be collected with validated questionnaires via CastorEDC. All German participants receive the dr. Bart app during the study (C), see Figure 2.

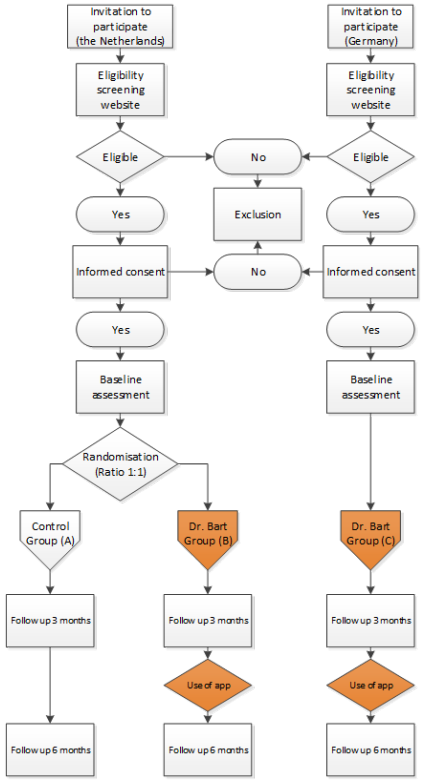

Figure 2. Flowchart of the study design with two arms in the Netherlands (A + B) and one arm (C) in Germany

Intervention (dr. Bart app)
Participants allocated to the Dutch dr. Bart group (B) and all German participants (C) will receive the dr. Bart app during the study.

Experimental intervention groups (arms B and C)
Participants allocated to the Dutch intervention group (B) and all German participants (C) will receive the dr. Bart app (version number 1.3.7) for 6 months. They can use the dr. Bart app "ad libitum". The app is only accessible for users after the researcher has provided access for the app. Throughout the study, participants are able to call and send e-mails to the researcher when they have questions regarding the dr. Bart app or the study.

Usual care control group (arm A)
Half of the participants in the Netherlands will be allocated to the usual care group (arm A) and will receive no active treatment, but care as usual. Usual care is defined as de facto clinical care and will not interfere with usual care.

Measurements

Three self-assessed sets of online questionnaires (at baseline and, 3 and 6 months after inclusion) will be collected with CastorEDC, (Table 1) and, where applicable, a reminder will be sent after one week. Participants will not receive (financial) incentives or other compensation for completion of the questionnaires or the study.

Study parameters

Main study parameter
The main study parameter for the RCT in the Netherlands (arm A vs. B) is the number of self-reported consultations in secondary healthcare (i.e. orthopaedic surgeon, rheumatologist, physician assistant) due to OA in the knee and/or hip in the past six months, collected every three months. The primary endpoint in the Netherlands is the difference in mean consultations in secondary health care at 6 months between the usual care group (A) and the dr. Bart app group (B).

The primary endpoint for the comparison between the Dutch dr. Bart app group and the German dr. Bart app group (arm B vs. C) is self-management behaviour, as collected with the Patient Activation Measure (PAM-13) questionnaire[52,53] at six months.

Secondary study parameters
Secondary study parameters include direct medical costs, self-management behaviour, health-related quality of life, physical function (in daily living, sport and recreation), physical activity, treatment beliefs in OA, illness perception, perceived quality of care, and use and usability of the dr. Bart app.

Assessments

Direct medical costs
By means of an OA specific questionnaire direct medical costs (i.e. healthcare-related) due to OA in the 6 months of follow-up will be collected, in both secondary and primary healthcare.

Standard cost prices of the Dutch costing guideline will be used[54]. Direct medical costs will be computed by multiplying the cost prices with the usage frequency as reported by participants.

Self-management behaviour

The PAM-13 questionnaire measures knowledge, skills and confidence to cope with one owns health[55]. The PAM-13 questionnaire is scored on a 13 to 52 scale. A higher score indicates higher level of patient activation. The PAM-13 shows good psychometric capabilities for measuring patient activation[53].

Health-Related Quality of Life

EQ-5D-3L will be used to measure health-related quality of life. This instrument contains questions about; mobility, self-care, usual activities, pain/discomfort and anxiety/depression, scored on a 3-point Likert scale. Moreover, the EQ-5D-VAS (visual analogue scale) will be used to indicate health-related quality of life on a vertical line, ranging from 0 (worst imaginable health) to 100 (best imaginable health)[56,57].

Physical function in daily living, sport and recreation

Pain, symptoms, function in daily living, function in sport and recreation and knee or hip related quality of life in the previous week will be assessed with the Knee or Hip Osteoarthritis Outcome Score (KOOS or HOOS), depending on the affected joint[58,59]. We will report subscales, since the total score is not validated. A higher score on the subscale indicates less complaints on that domain.

Table 1. Assessments in the Netherlands (arm A + B) and in Germany (arm C) at baseline and at follow-up of 3 and 6 months

	Baseline assessment (To)	Follow-up 3 months (T3)	Follow-up 6 months (T6)
Patient characteristics (A+B+C)	X		
Cost questionnaire (A+B)	X	X	X
PAM-13 (A+B+C)	X	X	X
EQ-5D-3L (A+B+C)	X	X	X
HOOS/KOOS (A+B+C)	X	X	X
SQUASH (A+B+C)	X	X	X
TOA (A+B+C)	X	X	X
IPQ-K (A+B+C)	X	X	X
OA-QI (A+B+C)	X	X	X
SUS (B + C)		X	X
Use of app (B + C)		X	X

Abbreviations: *PAM-13*; Patient activation measure, *EQ-5D-3L*; Euro Quality of Life – 5 Dimensions - 3 Level, *HOOS/KOOS*; Hip/Knee Osteoarthritis Outcome Score, *SQUASH*; Short Questionnaire to assess health-enhancing physical activity, *TOA*: Treatment beliefs in knee and hip osteoarthritis, *IPQ-K*; Illness Perception Questionnaire, *OA-QI*; Osteoarthritis Quality Indicators, *SUS*; System Usability Scale.

Physical activity

Physical activity will be assessed with the Short Questionnaire to ASses Health-enhancing physical activity (SQUASH). The SQUASH is a structured questionnaire consisting of activities at work, commuting, household activities, leisure-time and sports activities[60]. From this questionnaire time spent in light, moderate and vigorous physical activity can be calculated. The SQUASH is considered a reasonably valid tool to assess PA[60,61].

Treatment beliefs in OA

The Treatment beliefs in osteoarthritis (TOA) questionnaire will be used to assess participants beliefs about various treatment modalities in hip and knee OA and is based on the theory of planned behaviour. Both positive and negative beliefs regarding five treatment modalities in OA are assessed; 1) Physical activities, 2) Pain medication, 3) Physical therapy, 4) Injections, 5) Joint replacement surgery. For each subscale items are measured on a 5-point Likert scale (1 'disagree to 5 'agree'). Psychometric properties are satisfactory to good[62]. The TOA is not yet available in German language. Therefore, we will translate and culturally adapt the TOA to the German language according to the forward and back translation principle[63].

Illness perception

Illness perception will be assessed with the brief illness perception questionnaire[64]. This is a short questionnaire consisting of eight dimensions of illness perceptions which can be scored on a 10 point scale. From these eight dimensions a total score can be calculated, where a higher score reflects more threatening views regarding OA than a lower score. An additional open question asks the three perceived most causative factors for an individual's hip and/or knee OA.

Quality of care

A questionnaire regarding quality indicators for OA care is used to assess quality of care[65]. This questionnaire is available in Dutch, but not yet validated. For the German variant, we will translate and culturally adapt the English OA quality indicators questionnaire to the German language according to the forward and back translation principle[63].

Usability of the app

The usability of the app will be assessed with the System Usability Scale (SUS)[66,67]. This questionnaire contains 10 questions regarding usability of the app. A total score ranging from 0 to 100 is calculated, where a higher score indicates better usability. Additionally, we provided a free-text opportunity after each question so that participants could elaborate on their given answers.

Adherence to the dr. Bart app

Adherence to the dr. Bart app will be quantitatively measured in the back-end of the app. Parameters of use will be logged and extracted automatically for each user:

- *The proportion of active users (e.g. who completed minimal one goal) over time*
- *Number of average logins per active user per week*
- *Number of recommended goals, not chosen*
- *Number of chosen goals*
- *Number of achieved goals*
- *Number of goals set to non-active (i.e. choose to not do goal anymore)*

- *Number of goals set to active (i.e. choose to do goal again)*
- *Ranking of goals on the basis of times chosen*

Other assessments

Socio-demographic characteristics (i.e. age, gender, length, weight, localisation and duration of OA symptoms, marital status, living situation, education, ethnicity, and (paid) work) will be collected at baseline.

3

Sample size

The primary outcome measure for the RCT is number of consultations in secondary health care due to OA of the knee and/or hip in the past six months. We performed a sample size calculation for an unpaired t-test to compare two independent means. Based on previous research a mean difference of 0.35 consultations between two independent groups was considered credible, with a standard deviation (SD) of 1.00[68]. With a power of 0.80 and an alpha (α) of 0.05 (two-sided) a sample size of 129 participants per arm is needed. Accounting for loss to follow-up of 20%, 161 participants per arm will be included. Sample size was calculated with Stata version 13.1.

The second aim of the presented study is to explore cultural differences in use and usability of the app and its effect on clinical outcomes. For pragmatic reasons, we decided to include 161 participants (including 20% loss to follow-up) as well in the German arm of the study (C). A total of 129 participants is sufficient to detect a minimal difference of 4.6 (SD = 13.2) on a 52 point scale in the PAM-13 questionnaire between the Dutch (B) and German (C) groups (all using the dr. Bart app) with a power of 0.80 and an alpha of 0.05 (two-sided). The target sample will be able to detect a small to medium effect size (0.2-0.4) in primary outcomes (i.e. number of consultations in secondary health care and self-management behaviour) between groups.

(Planned) Statistical analyses

All statistical analyses will be performed using Stata 13.1 (www.stata.com). For each questionnaire separately, (missing) data will be managed according to recommendations of the specific questionnaire. Descriptive statistics will be used to present group characteristics. Normality will be assessed for continuous data by checking histograms. Continuous variables will be reported as mean and SD or median and inter-quartile ranges, as appropriate. For nominal variables, number (N) and percentage (%) will be presented. The primary analysis will be performed according to the intention-to-treat principle. In addition, a per-protocol analysis, including adherent participants of the dr. Bart group and the entire usual care group will serve as sensitivity analyses. In order to check for selective attrition, baseline characteristics of completers and non-completers of the study will be compared. In all analyses, a two-tailed significance level of $p < 0.05$ is regarded as statistically significant. Differences between treatment arms at baseline will not be statistically tested.

Efficacy

Differences in the primary and secondary outcomes between the two arms of the RCT in the Netherlands (A vs. B) after 3 and 6 months will be assessed by either linear mixed models or Poisson regression, as appropriate, with a random intercept, including treatment group (i.e. usual care (A) or dr. Bart (B)), baseline value and interaction between treatment group and time as covariates. The primary outcome in the Netherlands will be reported as an incidence

rate ratio in case of Poisson regression, or negative binomial regression, as appropriate.

The Netherlands vs. Germany

Differences in means, at 3 and 6 months of follow-up, between the Dutch dr. Bart group (B) versus the German dr. Bart group (C) will be explored by mixed model repeated measures analyses with a random intercept, including country (i.e. the Netherlands or Germany), accompanying baseline value and interaction between country and time. Analyses will be corrected for relevant confounders; age, gender and BMI among others.

Use of the app and its relation with clinical outcomes

The relation between clinical outcomes and use of the app will be studied using multivariable regression analyses with clinical outcome (e.g. physical functioning, PA) as the dependent variable, whereas quantitative data about use of the app will serve as independent variable(s). We hypothesize that participants who more frequently use the dr. Bart app will improve more on clinical outcomes (e.g. physical functioning) compared to less frequent and non-users. Additionally, a Kaplan-Meier curve will be constructed to illustrate the proportion of persons who start using the app (i.e. who have chosen at least one goal) over time.

Economic evaluation from the health care perspective

The economic evaluation is based on the general principles of cost-utility analysis (CUA) and cost-effectiveness analysis (CEA), applying a health care perspective. Direct medical cost in the Netherlands due to OA in the 6 months of follow-up will be analysed, in both primary and secondary care and will be measured retrospectively by online questionnaires on a three month recall basis. Standard cost prices of the Dutch costing guideline will be used[54]. To determine the incremental cost-effectiveness ratio (ICER) for the CUA, differences in costs between the usual care group (A) and the dr. Bart group (B) will be divided by differences in QALYs. For the CEA, differences in costs between the groups (A vs. B) will be divided by the differences in secondary outcomes (e.g. physical functioning, physical activity). Uncertainty (95% CI (confidence interval)) around the ICERs will be stochastically determined by the bootstrap method.

Timeline

The development of the dr. Bart app was finished at the end of 2017. Recruitment of participants in the Netherlands is ongoing as of January 2018. Participants will be included until the required sample size is acquired. For the German part of the study, we will start recruiting participants as of June 2019.

Discussion

As the prevalence of OA is expanding and costs related to OA care will increase, effective treatment modalities need to be developed for people with OA. The presented study will investigate the effect of an e-self management intervention, equipped with machine learning techniques, on changing behaviour to improve health behaviour in people with knee and/or hip OA. This study comprises three arms; a usual care arm (A) and a dr. Bart app arm (B) in the Netherlands and one arm, all receiving the app, in Germany (C).

Our choice for the primary outcome in the Dutch part of the study (i.e. number of self-reported consultations in secondary health care) needs further explanation. Self-management interventions aim to increase the capacity of patients to cope with symptoms rather than controlling symptoms. Optimal self-management requires that the person understands the illness and manages their care, including skills navigating the health care system and apply these to take better care of themselves[15,69]. In the literature there is no mutual agreement on the primary outcome assessing e-self management interventions[23,70]. Commonly used primary outcome measures for assessing effectiveness of self-management interventions are measures for pain, self-efficacy and physical functioning, but these measures do not reflect the ultimate aim of self-management; take care of one's own health and improve skills to navigate the health care system and thus change health behaviour[70,71]. In our view, change in health care utilisation patterns reflects indeed a change in behaviour and is a valid proxy for self-management[48,72].

As to the design of the study there are potential issues that need to be addressed. First, we include participants on the basis of self-reported knee and/or hip OA and this could result in a selective study population, and as a consequence reduce generalisability to the wider population. However, a meta-analysis showed that the self-reporting of OA results in acceptable diagnostic properties; sensitivity of 0.75 (95% CI: 0.56-0.88) specificity of 0.89 (95% CI: 0.77-0.95)[73]. Therefore, we assume that the inclusion on the basis of self-reported OA is appropriate.

Second, (non)adherence to eHealth applications is considered a problem and as a consequence the effectiveness of these interventions possibly diminishes. In the dr. Bart app, a variety of elements (e.g. reminders) is incorporated to reinforce app engagement and in turn augment intervention effects[43,50]. Moreover, the dr. Bart app is a standalone software application without human interaction, while it has been shown that blended options have more impact on health outcomes[50]. We assume, however, that the machine learning will provide tailored guidance and therefor better adherence to the treatment of OA.

Several strengths need to be underlined. The theoretical framework of the dr. Bart app is based on a solid rationale and the incorporated behavioural change techniques are chosen by specialists from different fields. In addition, all elements of the dr. Bart app are developed in co-creation with patient representatives and specialists. The design process of the dr. Bart app was based on an iterative design process resulting in a beta version which was pilot tested during a month in 21 people with OA. This is the first study that examines potential differences in use, usability and clinical outcomes of an e-self management application for people with OA between the Netherlands and Germany.

In conclusion, this study will gain insight in the effectiveness of a standalone software application (dr. Bart app) equipped with machine learning techniques in the (conservative) treatment of people with knee and/or hip OA. Additionally, this study provides information regarding (cultural) differences in the (conservative) treatment of OA between the Netherlands and Germany.

Patient involvement

Patient representatives from the Netherlands actively collaborated with researchers in a project group during the entire iterative design process of the dr. Bart app, as presented in our methods section. They were involved in the choice for the theoretical framework, formulation of goals, choice of the applied behaviour change techniques, iterative development of the (graphical) design, content, user experience session and pilot test among others.

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Chapter 4

Effect of the dr. Bart application on health care use and clinical outcomes in people with osteoarthritis of the knee and/or hip in the Netherlands; a randomised controlled trial

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Abstract

Objective

To evaluate the short-term effects of use of the dr. Bart app, compared to usual care, on the number of secondary health care consultations and clinical outcomes in people with knee/hip OA in the Netherlands.

Methods

A randomised controlled design involving participants ≥50 years with self-reported knee and/or hip OA recruited from the community. The number of secondary health care consultations (primary outcome) and secondary outcomes were assessed at baseline, 3 and 6 months via online questionnaires. Data were analysed using longitudinal mixed models, corrected for baseline values. Due to the design of this study, blinding of participants and researchers was not possible.

Results

In total, 427 eligible participants were allocated to either the dr. Bart group (n = 214) or usual care (n = 213). We found no difference between groups in the number of secondary (i.e. orthopaedic surgeon, rheumatologist, or physician assistant) health care consultations (incidence rate ratio (IRR) 1.20 (95% CI: 0.67; 2.19)). We found positive treatment effects of the dr. Bart app on symptoms (2.6 (95% CI: 0.4; 4.9)), pain (3.5 (95% CI: 0.9; 6.0)), and activities of daily living (2.9 (95% CI: 0.2; 5.6)) on a 0-100 scale, higher score indicating less complaints, but not in any other secondary outcome.

Conclusion

The dr. Bart app did not change the number of secondary health care consultations compared to usual care. However, we found small positive effects (not clinically relevant) on pain, symptoms, and activities of daily living in people with knee/hip OA.

Background

Knee and hip osteoarthritis (OA) are among the most prevalent forms of disability worldwide[1,2]. Knee and/or hip OA cause pain and functional disability and have a major impact on quality of life[2–5]. As a result, the personal and societal burden of OA is high[6,7]. In the Netherlands health care costs attributable to OA spent in secondary care (i.e. orthopaedic surgeon, rheumatologist, or physician assistant) are eight times higher than costs spent in primary care (e.g. general practitioner or physical therapist)[8]. As the prevalence of OA increases with age[2,9], it is expected that the burden of OA will increase dramatically in the near future due to the increase in life expectancy, with an extra demand on health services as a consequence[2].

Current treatment of OA is predominantly symptomatic and focuses on controlling pain and improving function and health-related quality of life[10–13]. Although total joint arthroplasty is considered a (cost-)effective treatment for people with OA, it should be considered only after conservative treatment (i.e. education, promotion of lifestyle changes, pain management, exercise therapy, and weight reduction in case of overweight) has failed[12,14–16]. Despite recommendations about the content of non-surgical treatment options in OA, quality of care in OA in primary care is suboptimal[15,17,18], resulting in underutilisation of non-surgical treatment options and untimely referrals to secondary health care in people with OA[12,15]. This suboptimal use of care could be improved by promoting self-management in people with OA[5,12,14,19]. Self-management interventions offer patients guidance in improving their skills regarding management of symptoms, treatment, and physical and psychological consequences, as well as to improve skills to navigate the health care system[20,21].

Health education and goal setting are considered fundamental elements of effective self-management interventions[22–25]. Goal setting is a widely used behavioural change technique[25] that is associated with positive effects on behaviour in both the short and long term[25,26]. Monitoring of behaviour or outcomes, providing direct feedback, and getting rewards may augment the effects of goal setting[25]. Thus, self-management interventions augmented with providing feedback and getting rewards may help patients to take better care of their illness and make optimal use of health care options.

Modern persuasive technologies (e.g. applications) offer the possibility to enhance goal setting and provide tailored information to people with OA that suits individual preferences. This enhances self-management at all times[27,28]. Moreover, modern technologies can monitor health behaviour and provide real-time feedback, which are considered important elements of self-management[21,29]. The use of modern technologies seems promising and can support patients in taking an active role in the management of their chronic condition in daily life. However, most eHealth applications have not been evaluated in clinical trials[30–34], especially in the field of OA.

Given the high potential of modern technologies to enhance self-management 24/7, we developed an e-self-management application that promotes self-management and supports people with OA to optimise the use of non-surgical treatment options: dr. Bart app. The dr. Bart app is a fully automated eHealth application based on the Fogg model for behavioural change[35], also known as the “tiny habits method”, and augmented with reminders, rewards, and self-monitoring to reinforce app engagement and health behaviour. According to the

tiny habits method, people with low motivation need an easy objective and a simple trigger to incorporate the target behaviour in daily life. The central feature of the app is a library of predefined "tiny habit" goals and triggers to a healthier lifestyle, for instance, "I will perform two squats after brushing my teeth" or "During my lunchbreak I eat an apple rather than an unhealthy snack". The dr. Bart app proposes a list of five pre-formulated goals to a healthier lifestyle, based on machine learning techniques fed by data collected in a personal profile and previous choosing behaviour of the app user; i.e. previously selected and discarded goals. We assumed that use of the app promotes health behaviours, better self-management, and optimal use of non-surgical treatment options, ultimately resulting in better coping with symptoms and fewer secondary health care consultations. The primary objective of this randomised controlled trial (RCT) was to evaluate the short-term effects (after 3 and 6 months) of use of the dr. Bart app (ad libitum), compared to usual care, on secondary health care in people with knee/hip OA in the Netherlands. Secondary objectives were to examine the short term effects on clinical outcomes (e.g. pain, physical functioning) attributable to the dr. Bart app in people with knee and/or hip OA.

Methods

Trial design and setting

This was a monocentre, stratified (main OA location; i.e. knee or hip), prospective, unblinded, RCT comprising one intervention group (dr. Bart app) and one control group (usual care) with an allocation ratio of 1:1, conducted in the Netherlands. We examined the effectiveness of the dr. Bart app on the number of self-reported consultations in secondary health care over half a year. Details of the development of the intervention and trial design have been published elsewhere[36]. This study was conducted alongside a controlled clinical trial in Germany. The results of this controlled clinical trial will be reported separately. Moreover, we will report the results regarding use, usability of the dr. Bart app and its relation with clinical outcomes as well as on the cost-effectiveness analysis in two other manuscripts. There were no changes to methods/design after the trial commenced. Ethical approval for this study was asked for and waived by the local Medical Research Ethics Committee of the Radboud University Medical Centre, Nijmegen (CMO Arnhem-Nijmegen, Protocol Number: 2017-3625). The study fell outside the remit of the law for Medical Research Involving Human Subjects Act and was approved by the local ethical committee. This study is registered in the Dutch trial register (Trial NL 6505 (NTR6693)). This trial is reported according to the CONSORT-EHEALTH checklist.

Recruitment and screening procedure

This study was conducted at the Department of Rheumatology of the Sint Maartenskliniek Nijmegen (the Netherlands) from January 2018 to January 2019. All participants in this RCT were recruited in the community through advertisements in local newspapers (i.e. region Nijmegen, the Netherlands) and in campaigns on social media of the Sint Maartenskliniek (i.e. Facebook, Twitter, LinkedIn). Individuals with OA in the community willing to participate, were invited to the website (www.drbart.eu) to complete several questions to check their eligibility for this RCT. Eligible individuals were asked to sign in for the study by providing their e-mail address on the website. Potential participants received online baseline assessment via CastorEDC (www.castoredc.com). CastorEDC is an electronic software application for data collection and management. CastorEDC is approved with ISO 27001 and ISO 9001 and is in line with the EU Data Protection Directive.

Participants

Participants were included under the following circumstances: 1) having self-reported OA of the knee and/or hip (i.e. having a painful knee and/or hip, knee and/or hip pain > 15 days of the past month, morning stiffness < 30 minutes (knee) and/or < 60 minutes (hip)); 2) being ≥ 50 years age; 3) having an e-mail address; 4) possessing a smartphone or tablet and willing to download the dr. Bart application on one or more devices; and 5) being able to read, write, and sufficiently communicate in Dutch.

Exclusion criteria were as follows: 1) being wheelchair bound, 2) having a diagnosis of (other) inflammatory rheumatic disease, 3) having knee and/or hip replacements and 4) having scheduled for knee and/or hip joint arthroplasty in the next six months.

Randomisation and blinding

Patients were allocated to the intervention group or control group (allocation ratio 1:1) by the researcher (TP) with CastorEDC after completing baseline assessment. CastorEDC is an electronic software application for data collection and management. Randomisation on the individual level was stratified by main OA location (knee or hip) with randomly varying block sizes of two, four, and six, performed with CastorEDC. The researcher who ascertained randomisation was concealed for treatment allocation. After allocation, participants in the intervention group received an e-mail from the researcher (TP) with information to access the dr. Bart app. Participants allocated to the control group received an e-mail that they were assigned to the control group. Due to the design of this RCT, blinding of participants and researchers was not possible. Throughout the study participants were able to call and send mails to the researcher when they had questions regarding the dr. Bart app or the study.

Intervention (dr. Bart app)

The theoretical framework and development process of the dr. Bart app and its pilot test are published elsewhere[36]. The overall goal of the dr. Bart app is to enhance self-management and to actively involve people with OA in managing their own disease. The dr. Bart app is a standalone eHealth application which invites users to select pre-formulated goals (i.e. “tiny habits”) and triggers to a healthier lifestyle. The pre-formulated goals are based on four themes that are core elements in the (non-surgical) management of OA: education regarding OA and its treatment modalities and the benefits of a healthy lifestyle, physical activity (both generic and OA specific information), vitality, and nutrition[12–14]. In the education library users can find specific information regarding OA and its treatments modalities, as well as generic lifestyle advice. Moreover, an exercise library is incorporated in the app, containing 14 exercises that are important for the treatment of OA. Users can select or discard goals; the app will continue with proposing goals until three goals are selected by the user. Once one or more goals are completed, the app will propose new goals. Proposed goals are based on machine learning techniques fed by data collected in a personal profile and previous choosing behaviour of the app user, i.e. previously selected and discarded goals. In this way, the proposed goals are tailored to the user and suit their personal preferences. To reinforce app engagement and health behaviour, the dr. Bart app is augmented with motivation enhancing techniques; reminders, rewards, and self-monitoring, Figure 1. Users receive a daily push notification to remind them of their chosen goal, combined with an interesting fact or answer to frequently asked question[36].

Participants allocated to the intervention group had the ability to use the dr. Bart app (version 1.3.7.) "ad libitum". The app was only accessible for users after the researcher (TP) provided access to the app. The content and functionalities of the dr. Bart app were frozen during the RCT. However, bug fixes (e.g. failure to log in) and system failures were resolved.

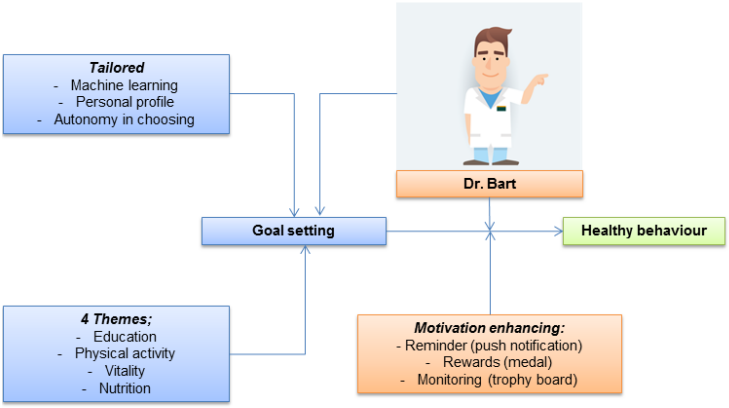

Figure 1. Theoretical framework of the dr. Bart app

Usual care

Half of the participants were allocated to the usual care group and received no active treatment. Usual care is defined as non-standardised care initiated by the participant (self-medication, self-referral) to non-medical professionals or initiated by the general practitioner (after consultation initiated by the participant). Health care providers of participants of neither study group were not informed about the study. Participants in the control group were also offered the dr. Bart app after they fulfilled the last follow-up questionnaire.

Outcomes

Participants received validated online questionnaires at baseline, after 3 and 6 months of follow-up, and, a reminder was sent after a week, where applicable. Participants did not receive (financial) incentives or other compensation for completion of the questionnaires or the study. In cases of missing data on the primary outcome participants were asked to record the number of visits to a secondary health care provider (i.e. orthopaedic surgeon, rheumatologist, or physician assistant) via an additional e-mail. Demographic data was collected at baseline. A detailed description of outcome measures is given in a design article[36].

Primary outcome measure

The primary outcome was the difference in the number of self-reported consultations in secondary healthcare (i.e. orthopaedic surgeon, rheumatologist, physician assistant) due to OA in the knee/hip over the previous 6 months (assessed with a 3-month recall period) between groups, reported as an incidence rate ratio (IRR).

Secondary outcome measures

To evaluate the effectiveness of the dr. Bart app, several self-administered questionnaires were used. We assessed health care utilisation with a self-developed questionnaire with a three month recall period. Participants were asked to record the number of visits to predefined primary (e.g. general practitioner and physical therapist) and secondary (i.e. orthopaedic surgeon, rheumatologist, or physician assistant) health care providers in the preceding 3-month period because of their knee or hip symptoms. Pain, symptoms, and functional limitations were assessed with either knee/hip OA outcome Score (KOOS or HOOS), where appropriate, with a standardized score being presented per sub scale (0-100; higher scores reflecting better health status)[37,38]. Health-related quality of life was assessed with the Euro Quality of Life (EQ-5D-3L) (0-1; higher score reflects better health)[39]. From the Short Questionnaire to ASsess Health-enhancing physical activity (SQUASH), we calculated the time spent in light, moderate, and, vigorous intensity per week[40]. Knowledge, skills, and confidence to cope with one's own health were assessed with the Patient Activation Measure (PAM-13) questionnaire[41]. We used the brief Illness Perception Questionnaire (IPQ) to measure patient's cognitive and emotional perceptions with respect to their OA (0-80); higher scores indicate more threatening views of OA[42]. Moreover, quantitative data about the use of the app was automatically extracted from the back-end of the dr. Bart app to determine which participants to be included in our per-protocol analysis. As described in our protocol paper, we measured costs, treatment beliefs in OA, system usability scale and quality indicators of OA care as well. These outcomes will be reported in separate manuscripts on costs and the comparison between the Netherlands and Germany.

Sample size

Based on previous research[43], an a priori sample size of 322 participants (161 per group) would provide 80% power at 5% level of significance (two-sided unpaired t-test) to detect a mean difference of 0.35 (standard deviation 1.00) in the number of consultations in secondary health care between groups, anticipating a maximum loss to follow-up of 20%, assuming a normal distribution.

Statistical analysis

All statistical analyses were performed using Stata 13.1 (www.stata.com). Missing data was managed according to the recommendations of the specific questionnaire. For the PAM, we also calculated a total score when a maximum of two items of the questionnaire were missing, though the PAM recommend to only calculate a total score if no single item is missing. For this, we calculated the mean score of the answered questions in the PAM questionnaire and multiplied this by 13. We assessed the percentage of missing data only in participants who were not lost to follow up. Baseline differences between groups were not statistically tested. Primary analyses were performed according to the intention-to-treat principle (ITT). Secondary analyses included per-protocol analysis, including adherent participants of the dr. Bart app group (i.e. who chose at least one goal) and the entire usual care group. Descriptive statistics were used to present group characteristics. Selective attrition was checked by comparing baseline characteristics of respondents to baseline characteristics of dropouts at both follow-up points.

According to the recommendations of Twisk et al. about missing data in longitudinal mixed-model analyses, no imputation techniques were used[44]. Differences in the primary and secondary outcomes between the dr. Bart app group and usual care group after 3 and 6 months were assessed with either negative binominal regression (number of visits to health care professional) or linear mixed models (measures of self-management behaviour, physical activity, quality of life, illness perceptions, and subscales of KOOS/HOOS), with random intercept, treatment group (dr. Bart app or usual care), baseline value, and interaction between treatment group and time as covariates, without random slope. In the mixed models analyses regarding the KOOS and HOOS, main OA location (knee or hip) was added as covariate. To evaluate whether the proportion of secondary health care health visits (yes/no) was different between groups, we performed a generalised estimating equation using binomial distribution, reporting an odds ratio. Per-protocol analyses were adjusted in the same manner. The primary outcome measure is reported as an IRR with 95% confidence interval (CI).

Results

Participants

In total 692 people were assessed for eligibility in this trial (Figure 2). A total of 427 participants were allocated to either the intervention group (dr. Bart) (n = 214) or the control group (usual care) (n = 213). The response rates for the follow-up questionnaires were 75.4% (intervention group, n = 150; control group, n = 172) and 69.3% (intervention group, n = 130; control group, n = 166) at 3 and 6 months, respectively. We did not find relevant differences on baseline characteristics between those who filled out the follow-up questionnaires and those who did not fill out questionnaires at follow-up (see Supplementary Table 1a + b). We defined adherence as choosing at least one goal in the dr. Bart app. Subsequently, we considered 151 (70.6%) participants adherent with the dr. Bart app and 63 (29.4%) participants non-adherent. The percentage of missing data on the primary outcome was 0.7%, 3.7% and 5.4% at baseline, and at 3 and 6 months of follow-up, respectively.

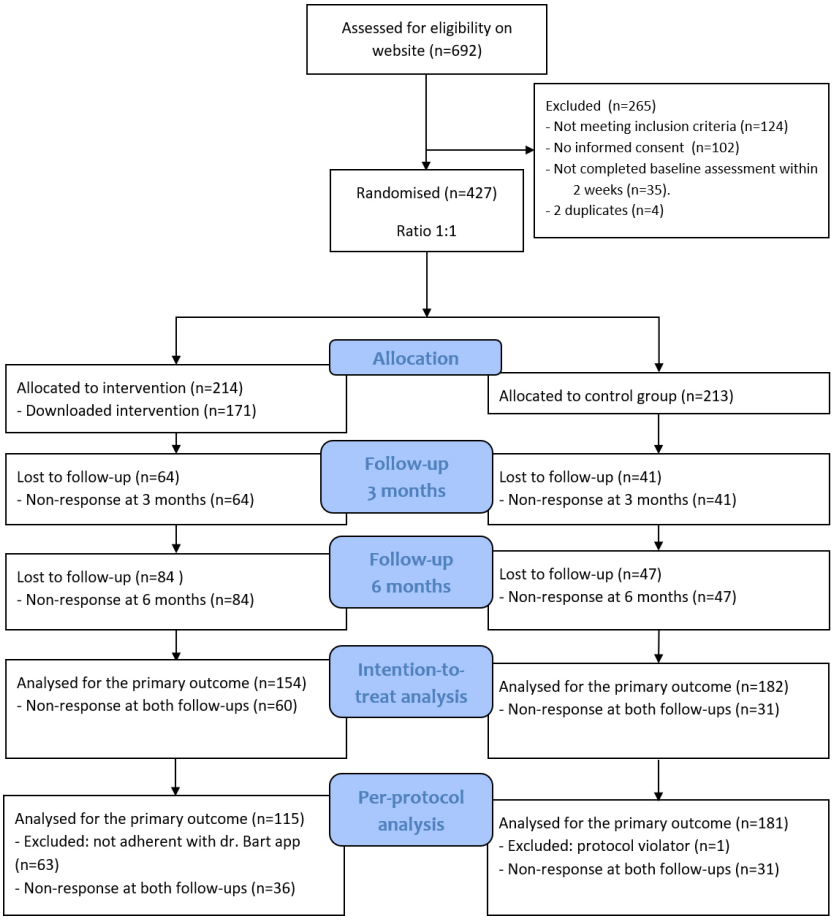

Figure 2. Flow diagram of participant inclusion in the trial

The mean age of participants was 62.1 years (SD 7.3), with the majority being female (71.7%) and having symptoms predominantly in the knee(s) (73.3%). Among the participants, 58% experienced their OA symptoms for less than five years (Table 1).

Table 1. Baseline characteristics of participants allocated to the intervention and control group (n=427)

	Dr. Bart app group (*N* = 214)	Control group (*N* = 213)
Age, years; mean (SD)	62.1 (7.7)	62.1 (7.0)
Female, *n*(%)	147 (68.7)	159 (74.7)
Body Mass Index, kg/m²; mean (SD)	27.8 (5.1)	27.3 (4.8)
Living together with partner and/or family, *n* (%)	161 (78.9)	168 (84.2)
Years of education (≤ 12 years), *n* (%)	56 (28.0)	36 (18.6)
OA diagnosed by health care professional		
Yes, *n* (%)	206 (96.3)	198 (93.0)
Main OA-location		
Knee, *n*(%)	157 (73.4)	156 (73.2)
Duration of symptoms, *n* (%)		
< 1 year	25 (11.7)	15 (7.0)
1 – 5 years	104 (48.6)	102 (47.9)
6 – 10 years	49 (22.9)	53 (24.9)
> 10 years	36 (16.8)	43 (20.2)

Abbreviations: *SD*, Standard Deviation; *n*, number; *OA*, osteoarthritis.

Primary outcome

Table 2 depicts health care use of the intervention and control group. We did not find a difference in the primary outcome measure, i.e. the number of secondary health care consultations over 6 months (incidence rate ratio: 1.20 (95% CI: 0.67; 2.16), intervention group compared to control group).

Secondary outcomes

We did not find a difference in the proportion of participants (yes/no) that consulted a secondary health care provider over 6 months (OR (1.24 (95% CI: 0.74; 2.06), intervention group compared to control group)). In both groups, consultations with a physical therapist were most common. We did not find differences in the number of consultations with other health care providers between groups over 6 months (Table 2).

Table 2. Health care use and proportion of patients who visited a health care provider at baseline, at 3 and 6 months per group, and mean treatment effect (95% CI) between groups over 6 months

Measures	Dr. Bart group *(N = 214)*				Control group *(N = 213)*				Treatment effect of dr. Bart app
	Baseline N = 214	*3 months N = 150*	*6 months N = 130*	*Mean number of consultations during follow-up (SD)*[∞]	*Baseline N = 213*	*3 months N = 172*	*6 months N = 166*	*Mean number of consultations during follow-up (SD)*[∞]	*Δ overall (95% CI)*
Consultations in secondary health care, total number (%[¥])	116 (29.6)	54 (20.4)	59 (23.3)	0.73 (1.60)	137 (32.7)	83 (23.8)	72 (19.4)	0.84 (1.82)	1.20[†] (0.67; 2.16)
Consultation in secondary care? Yes (%[¥])	63 (29.6)	29 (20.4)	28 (23.3)	N/A	69 (32.7)	40 (23.8)	31 (19.4)	N/A	1.24[§] (0.74; 2.06)
Consultations with GP, total number (%[¥])	116 (37.5)	63 (28.8)	45 (24.6)	0.91 (1.67)	105 (43.0)	65 (28.1)	59 (24.2)	0.81 (1.49)	1.24[†] (0.82; 1.89)
Physical therapist, total number (%[¥])	575 (56.3)	360 (46.6)	329 (46.5)	5.00 (7.56)	611 (49.4)	545 (45.3)	538 (38.2)	6.70 (10.71)	1.05[†] (0.58; 1.90)

Abbreviations; *GP*, General Practitioner; *ITT*, Intention-to-treat; n, number; *CI*, confidence interval; *N/A*, not applicable
[†] Incidence rate ratio (Negative binomial regression) corrected for baseline values, [§] Odds ratio (generalised estimating equation) corrected for baseline values, [¥] denotes the percentage of (non-missing) participants having at least one consultation, [∞] denotes the mean number of consultations per (non-missing) participant during follow-up.

Table 3 shows the results of secondary outcomes at baseline and 3 and 6 months of follow-up. We found a difference in positive changes in symptoms (2.6 (95% CI: 0.4; 4.9)) over 6 months in favour of the intervention group. Moreover, we found differences in positive changes for pain (3.5 (95% CI: 0.9; 6.0)) and activities of daily living (2.9 (95% CI: 0.2; 5.6)) in favour of the intervention group over 6 months. We did not find differences between groups in other secondary outcome measures. Treatment effects between groups at 3 and 6 months are reported in Supplementary Table 2a + b.

Per-protocol analysis

One participant in the control group reported in the follow-up questionnaire to have rheumatoid arthritis. Therefore, this participant was considered a protocol violator and was excluded from the per-protocol analysis. In the intervention group, we considered 63 participants non-adherent and 151 participants adherent (i.e. who chose at least one goal) with the dr. Bart app and these 63 participants were excluded in the per-protocol analysis, Figure 2.

We found comparable results in the per-protocol analyses regarding our primary and secondary outcome measures (Supplementary Table 3a + b +c).

Use of the app

Of the 214 participants allocated to the intervention group, 171 (80%) opened the app at least once. Of all participants, 151 (71%) chose at least one goal. A total of 113 (53%) participants achieved at least one goal. Altogether, more than 9,000 goals were achieved over half a year. For people active with completing goals (N=113), the median length of use was 144 (interquartile range (IQR: 63; 173)) days, with a median of 33 (IQR: 16; 89) logins per user. A total of 56 (26%) of all participants allocated to the intervention still used the app (i.e. logged in) after 26 weeks.

Table 3. Mean scores of secondary outcomes at baseline, at 3 and 6 months per group, and mean differences (95% CI) between groups over 6 months

Measures	Dr. Bart group (N=214)			Control group (N=213)			Treatment effect of dr. Bart app[§]
	Baseline mean (SD) N=214	*3 months mean (SD) N=150*	*6 months mean (SD) N=130*	*Baseline mean (SD) N=213*	*3 months (SD) N=172*	*6 months (SD) N=166*	*Δ overall[§] (95% CI)*
Self-management behaviour (range 13-52)	40.8 (5.3)	41.2 (5.2)	40.7 (5.4)	40.2 (5.7)	40.6 (6.1)	39.8 (5.5)	0.7 (-0.2; 1.6)
PA, total hours/week	31.6 (21.2)	33.1 (22.4)	26.5 (17.6)	26.6 (18.3)	29.0 (20.7)	26.3 (18.1)	1.1 (-2.2; 4.4)
MVI, hours/week	18.2 (18.7)	18.2 (15.3)	14.6 (11.6)	14.8 (14.3)	17.2 (16.5)	26.3 (14.3)	0.2 (-2.1; 2.6)
Health related quality of life (0-1)	0.72 (0.19)	0.73 (0.18)	0.71 (0.20)	0.71 (0.21)	0.73 (0.19)	0.70 (0.23)	0.00 (-0.03;0.03)
Health related quality of life (slider) (0-100)	70.9 (15.5)	69.2 (17.5)	70.6 (18.1)	69.8 (16.9)	71.2 (15.5)	68.7 (17.6)	-1.7 (-4.5; 1.0)
Illness Perceptions (range 0-80)	43.1 (8.9)	41.6 (10.5)	40.8 (10.3)	42.2 (10.4)	41.3 (9.7)	41.0 (9.2)	-0.7 (-2.3; 0.8)
Symptoms[†]	57.7 (16.3)	57.3 (18.2)	57.3 (17.7)	57.0 (18.9)	56.2 (19.2)	55.2 (19.4)	**2.6 (0.4; 4.9)***
Pain[†]	57.5 (15.5)	59.5 (16.5)	59.4 (17.7)	58.2 (17.8)	57.4 (18.0)	57.5 (18.0)	**3.5 (0.9; 6.0)***
Activities of daily living[†]	58.5 (19.7)	61.4 (19.3)	62.1 (20.8)	59.4 (20.2)	58.5 (19.6)	58.6 (19.3)	**2.9 (0.2; 5.6)***
Activities[†]	32.6 (23.9)	31.9 (22.3)	33.4 (25.0)	32.5 (23.1)	33.2 (25.0)	33.2 (23.4)	1.9 (-2.0; 5.9)
Quality of life[†]	38.0 (17.5)	39.2 (17.0)	39.1 (18.3)	38.3 (17.1)	38.3 (17.1)	40.5 (15.8)	0.3 (-2.5; 3.1)

* Indicates *p*-value ≤ 0.05. [§]Linear mixed models analyses corrected for baseline values. [†]Assessed with either KOOS or HOOS.
Abbreviations; *ITT*, Intention to treat; *n*, number; *PA*, physical activity; *MVI*, moderate-vigorous-intensity.

Discussion

The aim of this RCT was to study the short term effectiveness of the dr. Bart app, compared to usual secondary health care, in people with knee/hip OA in the Netherlands. The results of this RCT show that use of the dr. Bart app, based on the "tiny habits" method, does not change the number of consultations for OA in secondary health care compared to usual care. Moreover, we found no significant differences in healthcare utilisation (HCU), health-related quality of life, physical activity, self-management behaviour or illness perceptions between the intervention and control group over half a year. However, the dr. Bart app is effective with respect to symptoms, pain, and activities of daily living, although these benefits were small.

We found that the dr. Bart app did not have an impact on HCU in patients with knee/hip OA after 6 months. A possible explanation could be that the impact of our eHealth intervention on HCU might take longer than 6 months; it is conceivable that the "tiny habits"[35] will be further incorporated in daily life by participants in following months, and the accumulation of these tiny habits will result in larger health benefits and changes in HCU patterns over time. Self-management aims to increase the capacity of patients to cope with symptoms and managing their care, including skills navigating the health care system. The dr. Bart app stimulates the use of conservative treatment options. We assumed that better self-management will result in change in health care utilisation patterns (i.e. optimal use of primary care services and less use of secondary health care services). Previous studies show that the self-management programs did influence HCU, i.e. postpone total joint replacement surgery in OA patients[45,46]. We chose, however, for a shorter follow-up because of the rapidly evolving nature of eHealth. Future research is needed to assess long-term effects of use of the dr. Bart app.

We found small but significant positive effects on symptoms, pain, and activities of daily living attributable to the dr. Bart app. Although the importance of self-management programs is underlined by international recommendations, there is no consensus on the size of a clinically meaningful effect of e-self management programs. Effects of the dr. Bart app on pain, function, and symptoms are comparable with more intensive (traditional) self-management programs in OA[47]. Thus, considering the non-invasive character of the intervention and the unlikeness of harmful effects, we think the positive effects found in this RCT could be worthwhile for patients with knee/hip OA.

We found that 20% of participants allocated to the intervention group did not download the app, while they were willing to participate in eHealth research. Moreover, we considered 30% to be non-adherent with the app. This could indicate a lack of engagement of participants or user-friendliness for the app itself. However, these rates are in line with studies on standalone eHealth applications assisting patients with OA in their preparation for the first consult with an orthopaedic surgeon, which could be used one or two weeks prior to consultation[48,49]. So, compared to other standalone eHealth interventions, our rates are comparable[50]. Nevertheless, we found mean (SD) usability scores of the app at 3 and 6 months of follow-up of 68.6 (16.5) and 69.2 (16.9), meaning that it does not reach an acceptable score (i.e. 70); thus, there is room for improvement of the app, which in turn might improve usage.

Currently, RCTs are considered the gold standard for evaluating interventions. It is well known that executing a RCT is time and money consuming. This in contrast to the rapidly evolving nature of eHealth interventions. Logically, the design to evaluate these eHealth interventions should reflect this iterative process. Recently, several frameworks have been proposed in the evaluation of eHealth interventions, but these novel frameworks are not commonly applied in practice by researchers[51]. It could be valuable to explore the possibilities of the use of these novel frameworks in the continuous evaluation of eHealth interventions.

To the best of our knowledge, this is the first RCT examining the effectiveness of a standalone (self-management) eHealth application in people with knee/hip OA. Studies on stand-alone eHealth in other chronic diseases (e.g. chronic pulmonary disease, heart failure, and diabetes) showed positive results on disease management, clinical outcomes, and health behaviour changes among others (e.g. reduction of hospitalisation and improving quality of life)[30,34]. Nevertheless, these reviews concluded that methodological quality of included studies is low, and thus the evidence of efficacy of standalone eHealth is very limited.

The current study has several limitations that should be taken into account when interpreting the results. First, an unavoidable issue in this respect is the lack of blinding of participants. Moreover, loss to follow-up was high at 3 and 6 months in both groups, even though we sent newsletters just before participants received follow-up questionnaires to stimulate response rates. It is conceivable, that the lack of face-to-face contact could have resulted in the relatively high loss to follow-up[52]. In addition, our study might have been underpowered. We assumed a normal distribution of the number of consultations in secondary care in our sample size calculation, because to the best of our knowledge, there is no generally accepted method to calculate the sample size for negative binomial regression analysis. However, as our analyses were based on considerably more participants than anticipated, it is unlikely that we failed to detect an effect that was present (Type II error). Interestingly, loss to follow-up was higher in the intervention group than in the control group. A possible explanation could be that in the control group the participants were offered the dr. Bart app after completing the last questionnaire. However, we found no differences in baseline characteristics between respondents and dropouts. Finally, the association between intensity of use of the intervention and clinical outcomes is not taken into account in this study[53], this will be further investigated in a future in-depth analysis.

Although effects of the intervention were not clinically relevant, but considering the non-invasive nature of the intervention, the low costs and the safety of the intervention, we think that implementation and further development of the dr. Bart app is worthwhile. The dr. Bart app incorporates treatments of first choice in knee/hip OA; education, lifestyle advice, and healthy behaviors[12,15,19,54]. Our baseline characteristics are similar to participants included in previous OA research. Moreover, we used a mixture of recruitment strategies, resulting in a heterogeneous group of people with OA and guaranteeing the external generalisability of this study. Taking this in mind, the app could be applied as primary approach for the treatment of OA in clinical practice as it has the potential to serve as a trustworthy tool to provide education and goal setting regarding OA and its treatment options.

We showed that use of an e-self management intervention did not impact HCU compared to usual care over 6 months, but did result in small, albeit not clinically relevant positive effects on pain, symptoms, and activities of daily living in people with knee/hip OA. Additional research is needed to identify possible subgroups of patients who benefit most. Future research is necessary to replicate these results and to determine whether the dr. Bart app is more effective in the long term.

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Supplementary material

Supplementary Table 1a. Baseline characteristics of participants who filled out the questionnaire and who did not at 3 months

	Respondents at T3 (*n* = 322)	Dropouts at T3 (*n* = 105)
Age, years; mean (SD)	62.2 (7.6)	61.7 (6.5)
Female, *n*(%)	231 (71.7 %)	75 (71.4%)
Body Mass Index, kg/m²; mean (SD)	27.5 (5.0)	27.6 (4.7)
OA diagnosed by health care professional		
Yes, *n* (%)	309 (96.0%)	95 (90.5%)
Main OA-location		
Knee, *n*(%)	241 (74.8 %)	72 (68.6%)

Abbreviations: *SD*, Standard Deviation; *n*, number; *OA*, osteoarthritis.

Supplementary Table 1b. Baseline characteristics of participants who filled out the questionnaire and who did not at 6 months

	Respondents at T6 (*n* = 296)	Dropouts at T6 (*n* = 131)
Age, years; mean (SD)	62.5 (7.5)	61.2 (6.8)
Female, *n*(%)	214 (72.3%)	92 (70.2)
Body Mass Index, kg/m²; mean (SD)	27.3 (4.9)	28.1 (5.0)
OA diagnosed by health care professional		
Yes, *n* (%)	282 (95.3%)	122 (93.1%)
Main OA-location		
Knee, *n*(%)	214 (72.3%)	99 (75.6%)

Abbreviations: *SD*, Standard Deviation; *n*, number; *OA*, osteoarthritis.

Supplementary Table 2a. Treatment effects between groups at 3 and 6 months (intention-to-treat)

	Treatment effects of dr. Bart app		
	Δ 3 months (95 % CI)	*Δ6 months (95 % CI)*	*Δ overall (95 % CI)*
Consultations in secondary health care	1.06† (0.55; 2.02)	1.32† (073; 2.40)	1.20† (0.67; 2.16)
Consultation in secondary care (yes/no)	0.99§ (0.55; 1.78)	1.64§ (0.84; 3.21)	1.24§ (0.74; 2.06)
Consultations with GP	1.12† (0.69; 1.81)	1.26† (0.74; 2.13)	1.24† (0.82; 1.89)
Physical therapist	1.02† (0.53; 1.96)	1.06† (0.57; 1.96)	1.05† (0.58; 1.90)

Abbreviations; *GP*, General Practitioner; *ITT*, Intention-to-treat; *n*, number; *CI*, confidence interval.
†Incidence rate ratio (negative binomial regression) corrected for baseline values, §Odds ratio (generalised estimating equation) corrected for baseline values.

Supplementary Table 2b. Mean differences (95% CI) between groups at 3 & 6 months (intention-to-treat)

Measures	Treatment effect of dr. Bart app§		
	Δ3 months (95 % CI)	*Δ6 months (95 % CI)*	*Δ overall (95 % CI)*
Self-management behaviour (13-52)	0.68 (-0.37; 1.73)	-0.02 (-1.20; 1.16)	0.68 (-0.21; 1.58)
PA, total hours/week	3.0 (-1.1; 7.1)	-4.2 (-9.4; 1.0)	1.1 (-2.2; 4.4)
MVI, hours/week	0.9 (-2.0; 3.7)	-1.5 (-5.2; 2.1)	0.2 (-2.1; 2.6)
Health related quality of life (0-1)	-0.00 (-0.04; 0.04)	0.00 (-0.04; 0.04)	0.00 (-0.03; 0.03)
Health related quality of life (slider) (0-100)	**-4.0 (-7.5; -0.6)***	**4.9 (0.6; 9.2)***	-1.7 (-4.5; 1.0)
Illness Perceptions (range 0-80)	-0.5 (-2.3; 1.3)	-0.4 (-2.3; 1.4)	-0.7 (-2.3; 0.8)
Symptoms†	1.5 (-1.2; 4.1)	2.5 (-0.4; 5.5)	**2.6 (0.4; 4.9)***
Pain†	**3.1 (0.2; 5.9)***	0.9 (-2.0; 3.8)	**3.5 (0.9; 6.0)***
Activities of daily living†	2.5 (-0.7; 5.7)	0.9 (-2.6; 4.4)	**2.9 (0.2; 5.6)***
Activities†	-1.7 (-6.4; 2.9)	**7.7 (2.7; 12.7)***	1.9 (-2.0; 5.9)
Quality of life†	0.1 (-3.1; 3.2)	0.6 (-2.6; 3.7)	0.3 (-2.5; 3.1)

Abbreviations; *ITT*, Intention-to-treat; *n*, number; *PA*, physical activity; *MVI*, moderate-vigorous-intensity.
§Linear mixed models analyses corrected for baseline values. †Assessed with either KOOS or HOOS.
*Indicates *p*-value ≤ 0.05.

Supplementary Table 3a. Baseline characteristics of participants in the dr. Bart app group or control group for the per-protocol analysis

	Dr. Bart app group (*n* = 151)	Control group (*n* = 212)
Age, years; mean (SD)	61.8 (8.0)	62.0 (6.9)
Female, *n*(%)	104 (68.9)	159 (75.0)
Body Mass Index, kg/m²; mean (SD)	27.3 (4.7)	27.3 (4.8)
Low (≤ 12 years) level of education, *n*(%)	38 (26.4)	36 (18.7)
OA diagnosed by health care professional		
Yes, *n* (%)	146 (96.7)	197 (92.9)
Main OA-location		
Knee, *n*(%)	110 (72.9)	156 (73.6)
Duration of symptoms, n(%)		
< 1 year	18 (11.9)	15 (7.1)
1 – 5 years	72 (47.7)	102 (48.1)
6 – 10 years	38 (25.2)	52 (24.5)
> 10 years	23 (15.2)	43 (20.3)

Abbreviations: *SD*, Standard Deviation; *n*, number; *OA*, osteoarthritis.

Supplementary Table 3b. Treatment effects between groups at 3 and 6 months (per-protocol)

Per-protocol	Treatment effects of dr. Bart app		
	Δ 3 months (95 % CI)	*Δ6 months (95 % CI)*	*Δ overall (95 % CI)*
Number of consultations in secondary health care	1.15† (0.58; 2.29)	1.39† (0.74; 2.59)	1.29† (0.68; 2.42)
Consultation in secondary care (yes/no)	1.22§ (0.65; 2.30)	1.64§ (0.80; 3.35)	1.53§ (0.88; 2.65)
Consultations with GP	1.14† (0.67; 1.93)	1.19† (0.66; 2.14)	1.23† (0.78; 1.94)
Physical therapist	1.00† (0.49; 2.07)	1.09† (0.54; 2.18)	1.04† (0.54; 2.00)

Abbreviations; *GP*, General Practitioner.
†Incidence rate ratio (Negative binomial regression) corrected for baseline values, §Odds ratio (generalised estimating equation) corrected for baseline values.

Supplementary Table 3c. Treatment effects between groups at 3 and 6 months (per-protocol)

Per-protocol	Treatment effect of dr. Bart app[§]		
	Δ3 months (95 % CI)	*Δ6 months (95 % CI)*	*Δ overall (95 % CI)*
Self-management behaviour (13-52)	0.5 (-0.6; 1.6)	0.3 (-1.0; 1.6)	0.7 (-0.3; 1.6)
PA, total hours/week	3.0 (-1.4; 7.4)	-4.3 (-9.8; 1.2)	1.0 (-2.6; 4.6)
MVI, hours/week	1.5 (-1.6; 4.7)	-2.1 (-6.0; 1.9)	0.6 (-1.9; 3.2)
Health related quality of life (0-1)	-0.01 (-0.04; 0.03)	0.01 (-0.04; 0.05)	-0.00 (-0.03;0.03)
Health related quality of life (slider) (0-100)	**-4.3 (-8.0; -0.6)***	3.9 (-0.8; 8.5)	-2.5 (-5.4; 0.5)
Illness Perceptions (range 0-80)	-0.7 (-2.6; 1.2)	-0.4 (-2.4; 1.6)	-0.9 (-2.5; 0.8)
Symptoms[†]	2.2 (-0.6; 5.0)	1.7 (-1.5; 4.9)	**3.0 (0.6; 5.4)***
Pain[†]	2.7 (-0.3; 5.7)	0.9 (-2.3; 3.8)	**3.1 (0.4; 5.7)***
Activities of daily living[†]	2.9 (-0.3; 6.2)	1.2 (-2.5; 4.9)	**3.5 (0.7; 6.2)***
Activities[†]	-0.0 (-4.9; 4.8)	**8.4 (3.0; 13.8)***	4.0 (-0.1;8.0)
Quality of life[†]	1.4 (-2.0; 4.8)	-0.1 (-3.4; 3.2)	1.3 (-1.7; 4.3)

Abbreviations; *n*, number; *PA*, physical activity; *MVI*, moderate-vigorous-intensity.
[§]Linear mixed models analyses corrected for baseline values. [†]Assessed with either KOOS or HOOS.
*Indicates *p*-value ≤ 0.05.

Chapter 5

Use and usability of the dr. Bart app and its relation with health care utilisation and clinical outcomes in patients with knee and/or hip osteoarthritis: back-end data of the intervention group of a randomised controlled trial

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Submitted

Abstract

Background

Self-management is of paramount importance in non-surgical treatment of knee/hip osteoarthritis (OA). Modern technologies offer the possibility to support self-management 24/7. We developed an e-self management application (dr. Bart app) for patients with knee/hip OA.

Objective

To document the use and usability of the dr. Bart app and its relation with health care utilisation and clinical outcomes in patients with knee/hip OA.

Methods

For this study we used back-end data of the first 26 weeks of the intervention group (N = 214) of an RCT examining the effectiveness of the dr. Bart app. Participants were included based on self-reported knee/hip OA. A central element of the dr. Bart app is that the app proposes a selection of 72 pre-formulated goals for health behaviours based on the 'tiny habits method' (e.g. After lunch I rise 12 times from my chair to train my leg muscles). The proposals are tailored to user characteristics and related to four themes that are core elements in the non-surgical management of OA. Usability of the app was measured using the System Usability Scale questionnaire (SUS, 0-100). To assess the association between intensity of use of the app and health care utilisation (i.e. consultations in primary or secondary health care) and clinical outcomes (i.e. self-management behaviour, physical activity, health-related quality of life, illness perceptions, symptoms, pain, activities of daily living) we calculated Spearman rank correlation coefficients.

Results

171 / 214 participants (80%) logged in at least once whilst 151 (71%) chose at least one goal and 114 (53%) completed at least one goal during the 26 weeks. Of those who chose at least one goal, 56 participants (37%) continued to log in up to 26 weeks, 12 (8%) continued to select new goals from the offered goals and 37 (25 %) continued to complete goals. Pre-formulated goals regarding the themes activity (e.g. performing an exercise from the exercises library of the app) and nutrition (e.g. eat 2 pieces of fruit today) were found to be most popular by users. Mean usability scores (standard deviation) at 3 and 6 months of follow-up were 65.9 (16.9) and 64.5 (17.5), respectively. The vast majority of associations between intensity of use of the dr. Bart app and target outcomes were weak at $\rho < (-) 0.25$.

Conclusions

More than one-third of patients with knee/hip OA who started using the app, persistently used the app up to 26 weeks, though usability could be improved. Patients appear to have preferences for goals related to activity and nutrition, rather than for goals related to vitality and education. We found weak/no associations between intensity of use of the dr. Bart app and health care utilisation and clinical outcomes.

Background

Osteoarthritis (OA) of the knee/hip is the most common form of disability of movement and is characterised by pain, stiffness and a decline in daily functioning. The primary approach for non-surgical treatment in early stages of knee/hip OA is lifestyle education, exercise therapy, weight management and pain medication[1–4]. As OA is a chronic disease, a cornerstone in the non-surgical treatment is self-management. Self-management interventions offer patients guidance in improving their skills to take better care of themselves and take an active role in their disease management[5,6], including skills navigating the health care system (i.e. making optimal use of primary and secondary health care options).

Compared to usual care, traditional self-management interventions show small benefits on self-management skills, pain, and function in patients with knee/hip OA[7]. EHealth applications have the potential to enhance self-management 24/7. The growing and emerging popularity of eHealth applications have resulted in a proliferation of applications in the health domain. However, the majority of eHealth applications have not proven their effectiveness in clinical trials[8–12].

Given the high potential of these modern technologies, we developed a fully automated stand-alone eHealth application (dr. Bart app) to enhance self-management. The content of the dr. Bart app is based on the Fogg model for behavioural change, augmented with reminders, rewards and self-monitoring to reinforce app engagement[13]. In a randomised evaluation, we found that the dr. Bart app did not impact health care utilisation, but resulted in small positive effects on pain, symptoms and activities of daily living[14]. However, a fundamental issue in eHealth research is non-usage attrition; a proportion of participants do not use the intervention at all, or use it sparsely[15].

Although the issue regarding non-usage attrition is well known, most eHealth studies do not provide information regarding use, while possible effects of the intervention may be diminished by low exposure rates[16–18]. Studies on stand-alone eHealth in other chronic diseases (e.g. diabetes and chronic pulmonary disease) showed that after a month the applications were used by less than 50% of participants[19]. Two studies evaluating stand-alone eHealth intervention assisting patients in their preparation for the first consultation with an orthopaedic surgeon, which could be used either one or two weeks prior to consultation, found relatively high user-rates (i.e. 70%) in patients with OA[20,21]. So far, there is little insight in actual usage of stand-alone eHealth applications in patients with OA to enhance self-management. Besides actual usage of an application, it is likely that there is a dose-response relationship between the (intensity of) use of an eHealth intervention and clinical outcomes[22]. However, there is little insight in the association between extent of use of (different components of) an app and its effects on target outcomes. Therefore, the aim of this study was to quantify use, identify patterns of use and to assess usability of the dr. Bart app over half a year. Furthermore, we explored the association between intensity of use of the dr. Bart app and its relation with health care utilisation and clinical outcomes in patients with knee/hip OA over half a year. Finally, we aimed to gain insight in the demographic and clinical characteristics of various types of users.

Methods

Design and setting

Data in the present study were collected as part of a randomised controlled trial (RCT), evaluating the effectiveness of the dr. Bart app on health care use and clinical outcomes, which was conducted by the Sint Maartenskliniek Nijmegen (the Netherlands) from 24 January 2018 to 7 January 2019. The original study is registered in the Dutch Trial Register (Trial Number NTR6693/NL6505) (https://www.trialregister.nl/trial/6505). Baseline and follow-up data at 3 and 6 months from the intervention group together with back-end data of the app were used for the present analysis.

All participants provided digital informed consent for participation. Ethical approval for this study was asked for and waived by the Medical Research Ethics Committee of the Radboud University Medical Centre, Nijmegen (CMO Arnhem-Nijmegen, Protocol Number: 2017-3625) as the study was considered to be outside the remit of the law for Medical Research Involving Human Subjects Act. This study is registered in the Dutch trial register (Trial NL 6505 (NTR6693)).

Participants and procedure

Participants were recruited from the community via campaigns on social media (i.e. Facebook, Twitter, LinkedIn) and through local newspapers. Participants willing to participate were invited to the website (www.drbart.eu) to check their eligibility. Inclusion criteria were: 1) having self-reported OA of the knee and/or hip (i.e. having a painful knee and/or hip, knee and/or hip pain > 15 days of the past month, morning stiffness < 30 minutes (knee) and/or < 60 minutes (hip)), 2) ≥ 50 years, 3) Having an e-mail address, 4) Possession of smartphone or tablet and willing to download the dr. Bart application on one or more devices and 5) Able to read, write and sufficiently communicate in Dutch. Exclusion criteria were as follows: 1) Being wheelchair bound, 2) Diagnosis of (other) inflammatory rheumatic disease, 3) Knee and/or hip replacements and 4) Scheduled for knee and/or hip joint arthroplasty in the next 6 months. Eligible participants were asked to provide their e-mail address and subsequently received a baseline assessment via CastorEDC, an electronic software application for data collection and management (https://www.castoredc.com/). Baseline and follow-up data at 3 and 6 months from the intervention group (N=214) of an RCT examining the effectiveness of the dr. Bart app, together with back-end data of the app during 26 weeks were used for the present analysis[13].

Intervention

The dr. Bart app is a stand-alone eHealth application which aims to enhance self-management and actively involve patients with knee/hip OA in managing their disease. This eHealth application is based on the Fogg model for behavioural change[23], augmented with other motivation enhancing techniques such as reminders, rewards and self-monitoring, to reinforce app engagement and health behaviour. The Fogg model, also known as the 'tiny habits method', utilises the concept of accumulating small goals to structurally change health behaviour, and in the long run health outcome. Machine learning techniques are used to propose tailored goals based on data collected in a personal profile and choosing behaviour of the user. For the dr. Bart app the machine learning comprised a dynamic model (Contextual Multi-armed Bandit approach) proposing goals that are challenging, achievable and tailored for that specific user[24]. The machine learning is fed with contextual and personal information

collected in a personal profile. The content and functionalities of the dr. Bart app were frozen during the study period, although bug fixes (e.g. failure to log in) and system failures were resolved. Further details on the theoretical framework, development and functionalities of the dr. Bart app are published elsewhere[13]. Screenshots of the dr. Bart app are presented in the Supplementary Material.

Assessments

Use of the dr. Bart app

Prior to start of the study we chose which actions of a user reflect the main feature of the app and should be logged. We quantitatively measured use in the back-end of the dr. Bart app during the study period (i.e. 26 weeks). Parameters of use were automatically logged and extracted for each participant. 'Non-users' were those participants who never logged in. To elaborate on the nature and extent of use of the app, we further classified use of the app as:

1) active with logins, but no further activity
2) active with choosing goals, but without completing goals
3) active with completing ≥ 1 goals

Users can choose more than one of the proposed goals simultaneously and goals can be completed more than once by the same user. The following indicators of use were extracted from the back-end of the app: number of logins, number of (unique) chosen goals, number of (unique) goals completed, and total number of completed goals. Moreover, we quantified use of information as the number of read paragraphs in the educational library (range 0 – 108).
For participants who chose at least one goal, we constructed Kaplan-Meier curves to illustrate the percentage of persons who used the app over time, based on the aforementioned indicators of use.

Usability

We assessed the usability of the dr. Bart app with the System Usability Scale (SUS) at 3 and 6 months[25,26]. The SUS is a 10-item questionnaire scored on a five-point Likert scale ("Strongly agree" to "Strongly disagree". We calculated a total score ranging from 0 to 100, with a higher score indicating better usability. Additionally, we provided a free-text option after each question, so participants could elaborate on their given answers.

Demographic and clinical characteristics

Demographic data were collected at baseline. We assessed pain, symptoms, activities of daily living, quality of life and physical functioning in sports and recreation with sub scales of either Knee/Hip Osteoarthritis Outcome Score (KOOS or HOOS), ranging from 0 to 100, where a higher score indicates less problems in that domain[27,28]. We assessed health-related quality of life with the EQ-5D-3L (0-1; higher score reflecting better health)[29]. Physical activity was assessed with the Short Questionnaire to ASsess Health-enhancing physical activity (SQUASH)[30]. Knowledge, skills and confidence to cope with one's health were assessed with the Patient Activation Measure (PAM-13) questionnaire[31,32]. We used the Illness Perception Questionnaire (IPQ) to assess patient's cognitive and emotional perception regarding their OA (0-80; higher score indicating more threatening views of OA)[33]. Moreover, we assessed both positive and negative treatment beliefs regarding various treatment modalities in knee and

hip OA with the treatment beliefs in osteoarthritis (TOA) questionnaire[34]. We calculated mean sub scale scores ranging from 1 to 5 for the TOA.

Statistical analysis

Data analysis

All statistical analyses were performed using Stata 13.1 (www.stata.com). For each questionnaire separately, (missing) data was handled according to the recommendations of the specific questionnaire. For the PAM, we also calculated a total score when a maximum of two items of the questionnaire were missing, though the PAM recommends to only calculate a total score if no single item is missing. Descriptive statistics were used to describe participant characteristics and parameters of use. In all analyses, we considered $p < 0.05$ as statistically significant. Since this is an explorative study, we refrained from correction for multiple testing.

Subgroup characteristics

In order to determine whether baseline characteristics could identify subgroups of participants with regard to use of the app, parameters of use functioned as the dependent variable in univariate regression analyses, with baseline characteristic as the independent variable.

Association between use and clinical outcomes

To assess the association between intensity of (different indicators of) use of the app and changes in health care utilisation (HCU) and clinical outcomes over six months of follow-up we calculated Spearman rank correlation coefficients. Additionally, we classified users into six groups for the four separate indicators of use (i.e. number of logins, number of chosen goals, number of completed goals and number of read paragraphs) based on back-end data; non-users and a population split into five equal groups (i.e. quintiles). Subsequently, boxplots of relative differences in clinical outcomes were created for those six groups for the four different indicators of use separately.

Results

In total 214 participants with knee/hip OA were included in this study. The mean age of participants was 62.1 years (SD 7.7), with the majority being female (68.7%) and having symptoms predominantly in their knee(s) (73.4%). Sixty percent experienced their OA symptoms for less than 5 years (Table 1).

Table 1. Baseline and clinical characteristics of participants in the study (N = 214)

	Dr. Bart app group (*n* = 214)
Age, years; mean (SD)	62.1 (7.7)
Female, *n* (%)	147 (68.7)
Body Mass Index, kg/m²; mean (SD)	27.8 (5.1)
Level of education (≤ 12 years, *n* (%)	56 (28.0)
Main OA location	
Knee, *n* (%)	157 (73.4)
Duration of symptoms, *n* (%)	
< 1 year	25 (11.7)
1 – 5 years	104 (48.6)
6 – 10 years	49 (22.9)
> 10 years	36 (16.8)
Clinical characteristics	
Symptoms† (0-100)	57.7 (16.3)
Pain† (0-100)	57.5 (15.5)
Activities of daily living† (0-100)	58.5 (19.7)
Activities† (0-100)	32.6 (23.9)
Quality of life† (0-100)	38.0 (17.5)
Self-management behaviourᵝ (13-52)	40.8 (5.3)
PA, total hours/week	31.6 (21.2)
Health-related quality of life (0-1)	0.72 (0.19)
Health-related quality of life (slider) (0-100)	70.9 (15.5)
Illness Perceptions (range 0-80)	43.1 (8.9)

Abbreviations: *SD*, Standard Deviation; *n*, number; *OA*, osteoarthritis; *PA*, physical activity. †Measured with either KOOS or HOOS. ᵝ Measured with the Patient Activation Measure Short Form (PAM-13)

Use of the dr. Bart app

Among the participants, 171 (79.9%) were active with logins, 151 (70.6%) were active with choosing goals and 113 (52.8%) were active with completing goals. We did not find relevant differences in baseline characteristics between those who were active with the dr. Bart app and who were less or not active (Supplementary Table 1).

In total, participants logged in 7,006 times, chose 1,062 goals, completed 884 unique goals and completed 9,229 goals during 26 weeks (Table 2). The median number (IQR) of read paragraphs in the educational library was 42 (18-84) for persons active with completing goals (Table 2). Fifty percent of participants active with choosing goals, read more than 30 paragraphs in the educational library. Paragraphs about OA and its complaints, progression, conservative treatment options, and the exercise library were read more often than paragraphs related to pathogenesis of OA, pharmacological care, assistive technologies and surgical treatments (Supplementary Table 3c).

Table 2. Indicators of use over 26 weeks, presented for three pre-specified groups of users based on their activity

	Logged in, but no further activity (*n* = 20)	Chose ≥ 1 goal, but did not complete goals (*n* = 38)	Completed ≥ 1 goal (*n* = 113)
Number of logins, median [IQR]	2.5 [1.5; 4.5]	4 [3; 11]	33 [16; 89]
Length of use, mean days	26.1	66.0	115.9
median days [IQR]	4.5 [1; 29.5]	60.5 [6;102]	144 [63; 173]
SUS score at 3 month follow-up, mean (SD)	65.2 (17.7)	55.0 (15.1)	68.6 (16.5)
SUS score at 6 month follow-up, mean (SD)	51.3 (15.5)	52.0 (16.2)	69.2 (16.9)
Number of paragraphs read (0-108 range), median [IQR]	0 [0; 11.5]	5.5 [1; 21]	42 [18; 84]
Number of unique chosen goals, median [IQR]	N/A	2 [1; 3]	6 [3; 11]
Number of unique completed goals, median [IQR]	N/A	N/A	5 [3; 10]
Number of total completed goals median [IQR]	N/A	N/A	35 [11; 117]

Abbreviations: *IQR*, interquartile range; *SD*, Standard Deviation; *n*, number; *OA*, osteoarthritis. † Measured with either KOOS or HOOS

Figure 1 shows the proportion of participants active with the dr. Bart app over time during half a year, with separate lines for three indicators of use. Of the participants who chose at least one goal, 38% was active with logins, 8% was active with choosing goals and 25% was active with completing goals after 26 weeks. Supplementary Figure 1a and 1b show the median and interquartile range of the number of cumulative logins and completed goals over time of users who chose at least one goal, respectively.

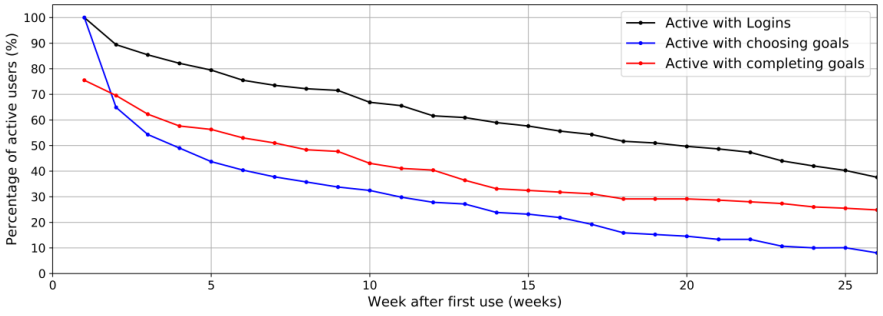

Figure 1. Percentage of active users (n=151) over time, based on different classifications

Goals related to physical activity were relatively most often chosen (times chosen divided by times proposed) and completed (times completed divided by times chosen), whereas goals related to nutrition were more popular than goals related to vitality or education.

Supplementary Table 3 shows the five relatively most and least often chosen (times chosen divided by times proposed) and completed (times completed divided by times chosen) goals.

Usability

After 3 and 6 months of follow-up, mean usability scores were 65.9 (16.9) and 64.5 (17.5), respectively. Participants who more intensively used the app, had higher usability scores (Table 2). Participants rated the main features (i.e. education and exercise library) of the app positively in the additional free-text option of the SUS. Moreover, the ability to access this information at any given time and place was considered important, as well as to incorporate the 'tiny habits' easily in daily life. On the other hand, 14 participants stated that the app did not provide any new information or exercises and did they not always carry their mobile phone. Moreover, some participants did not see the benefits of using such an application.

Subgroup characteristics

We could not (clearly) distinguish between non-users and different intensities of users, based on age, gender, BMI, living situation, level of education, main OA location (Supplementary Table 2).

Association between use and clinical outcomes

We found Spearman's rank correlation coefficients ranging from -0.20 to 0.30 between different indicators of use and HCU and clinical outcomes (Table 3). We found a statistically significant correlation between visiting a general practitioner (yes/no) and the number of unique chosen goals (ρ = 0.25) and unique goals completed (ρ = 0.28).

Negative beliefs about PA, medication and physical therapy were associated with lower app use (Table 4).

Visual inspection of boxplots showed absence of dose-response relation (data not shown).

Table 3. Spearman rank correlation coefficients between different indicators of use and health care utilisation and clinical outcomes (relative difference between baseline and 6 month follow-up)

	Logins	Unique goals chosen	Unique goals completed	Total goals completed	Paragraphs
Visited a secondary health care provider? (yes/no)	0.02	0.05	0.08	0.06	0.09
Visited a general practitioner? (yes/no)	0.07	**0.25* (p=0.0139)**	**0.2824* (p=0.0106)**	0.09	0.03
Self-management behaviour	0.05	0.02	-0.04	0.08	-0.11
PA, total hours	-0.03	0.11	0.05	-0.00	0.08
Health-related quality of life	-0.02	-0.07	-0.12	-0.06	-0.13
Illness Perceptions	0.04	0.07	0.02	0.04	0.06
Symptoms†	-0.07	-0.11	-0.15	-0.21	-0.19
Pain†	-0.17	-0.18	-0.22	-0.16	-0.07
Activities of daily living†	0.08	-0.03	-0.09	0.06	0.02
Activities†	0.09	-0.19	0.01	0.22	-0.08
Quality of life†	-0.01	-0.07	-0.11	-0.01	-0.07

†Measured with either KOOS or HOOS.

Table 4. Spearman rank correlation coefficients between different indicators of use and beliefs regarding 5 treatment modalities in knee/hip OA as measured with the treatment beliefs in osteoarthritis questionnaire (TOA) (relative difference between baseline and 6 month follow-up)

TOA (1-5)	Logins	Unique Goals Chosen	Unique Goals Completed	Total goals completed	Paragraphs
PA Pos.	-0.01	-0.18	-0.22	-0.11	-0.17
PA Neg.	**-0.38* (p=.0002)**	-0.18	-0.11	-0.22	-0.20
Med. Pos.	0.08	0.05	0.14	0.19	0.11
Med. Neg.	-0.19	**-0.30* (p=.0059)**	**-0.31* (p=.0071)**	**-0.27* (p=.0224)**	**-0.24* (p=.0222)**
PT Pos.	0.01	0.03	0.05	-0.13	-0.09
PT Neg.	-0.12	**-0.23* (p=.0463)**	**-0.32* (p=.0001)**	-0.09	0.01
Inj. Pos.	-0.01	0.09	0.11	-0.03	0.09
Inj. Neg.	0.06	-0.05	0.01	0.14	0.07
TJR Pos.	0.02	-0.01	0.05	0.02	-0.14
TJR Neg.	-0.04	-0.06	-0.17	-0.02	-0.05

Abbreviations: *PA*, physical activity; *Med*., medication; *PT*, physical therapy; *Inj*, injections; *TJR*, total joint arthroplasty; *Pos*., positive; *Neg*., Negative.
* Indicates *p*-value ≤ 0.05.

Discussion

The aim of this study was to document the use and usability of the dr. Bart app and to examine intensity of use of the app and its relation with HCU and clinical outcomes. The results of this study show that more than one-third of participants who were offered the dr. Bart app persistently used the app during the first six months after accessing the app. The two main features of the app were extensively used; goal setting and the educational library (including the exercise library). More than half of the participants completed at least one goal, of which goals related to physical activity and nutrition were most popular. In the educational library, participants were predominantly interested in general information regarding OA, complaints (specifically on fatigue), treatment options, prognosis, and the exercise library. After half a year, a quarter of users still used the app to set and complete goals and two-fifth of users still opened the app. We could not identify differences in characteristics between non-users and users of the dr. Bart app. Moreover, we were not able to demonstrate a dose-response relation between different indicators of use and HCU and clinical outcomes.

To our knowledge little is known about the use of stand-alone eHealth applications in OA. Our user rates are in line with two studies evaluating stand-alone eHealth applications assisting patients with OA in their preparation for their first consult with an orthopaedic surgeon. These applications, however, had relatively short time frames (i.e. one or two weeks prior to consultation) and a different focus, which might have resulted in higher user rates in these studies[20,21]. Stand-alone applications in other chronic diseases (chronic pulmonary disease or diabetes) are not directly comparable, as the use of these applications is more likely to result in

short term benefits (e.g. fewer exacerbations and betters glucose levels), and are consequently more likely to be used than the dr. Bart app. Nevertheless, the user rates over time observed in our study were even higher than those observed in stand-alone eHealth applications on self-management in other chronic diseases[35–38]. Additionally, the use of the dr. Bart application is comparable with the use of a self-management application embedded in clinical practice (blended intervention in patients with OA)[39], though the use of blended interventions is likely to result in higher user rates compared to stand-alone applications[16]. Taken together, we conclude that the use of the stand-alone dr. Bart application is relatively high. Our relatively high user rates could possibly be explained by applying different techniques (i.e. rewards, reminders and self-monitoring) to reinforce engagement with the dr. Bart app[13].

Users consulted the educational library on a regular basis and were particularly interested in general information regarding OA, complaints, progression and, (non-pharmacological) conservative treatment options. Moreover, the majority of users consulted the exercise library. These results support the idea that patients with OA have educational needs with regard to conservative non-pharmacological treatment options[40–42]. This is also underlined by international guidelines; self-management is considered a key element in the non-surgical treatment of OA[1–4]. Interestingly, information about services of health care professionals was consulted to a lesser extent, though navigating the health care system is an important aspect of self-management. A possible explanation is that the majority of our sample is highly educated, which is known to be associated with better skills navigating the health care system[43]. Also, information with respect to the pathogenesis of OA, pharmacological care, walking aids, assistive technology, and surgical treatments were found to be less popular. This is an interesting finding, as these treatments are also considered important in the treatment of OA. However, topics to be considered important in guidelines, does not necessarily reflect the educational needs of patients. In addition, previous research showed that a considerable proportion of patients has interests in the newest developments and experimental treatments regarding their chronic disease[40]. We were not able to confirm these needs, as we did not address these topics in our educational library. Nevertheless, our study provides insights in the educational needs for patients with knee/hip OA and offer starting points for optimising patient education.

Contrary to expectations, we did not find associations between (intensity of) use of the dr. Bart app and HCU and clinical outcomes. Studies on web-based interventions in patients with mental disorders suggest that certain amounts of use result in therapy saturation, and that patients are most likely to obtain benefits of the intervention early on[22]. The lack of any strong relationship between use and HCU and clinical outcomes might be explained by this model; users might have reached a plateau in which they did not benefit from additional use, with most benefits of the intervention early on. Given the nature of the collected data (we only have clinical outcomes after 3 and 6 months of follow-up), we were not able to assess this relationship between early use of use of the app and its relation with HCU and clinical outcomes. Future studies should assess the exact relation between use and HCU and clinical outcomes.

Strength and limitations

The current study has several limitations that should be taken into account when interpreting the results. First, sample selection is likely to be apparent, as participants were willing to participate in research on eHealth, which in turn might induce the Hawthorne effect (i.e. a change in behaviour of participants due to awareness of being observed). Moreover, it is unknown why twenty percent did not open the app. So, it is conceivable that user rates are lower and non-use is higher when the application is applied in clinical practice. Furthermore, results in this exploratory study were based on four different indicators of use, since consensus on a definition of use and how to measure use is lacking. Nevertheless, we think that applying four different indicators of use, resulted in a thorough understanding of the use of the app. In addition, the usability of the app (assessed with the SUS) could be improved, as it does not reach an acceptable score (i.e. 70), which in turn might result in higher user rates. However, a study with satisfactory to good usability score regarding an application for post-operative self-report after colorectal surgery showed that participants did not use the app or used it only once[44]; thus, high usability alone is not sufficient to motivate patients to use eHealth applications. This is in line with the Technology Acceptance Model (TAM), which states that actual system use is not only dependent of the perceived ease-of-use (i.e. usability), but is also dependent of the perceived usefulness. Perceived usefulness is described as: "the degree to which a person believes that using a particular technology would enhance his/her performance". So, it is important that participants see the necessity and benefits of using an application, besides usability alone. Qualitative information about the usability of the app, not covered by the SUS, could help to identify aspects to improve the usability[45].

This is the first study that actually deepens the insight in use and usability of a stand-alone eHealth application in patients with knee/hip OA. A considerable proportion of participants persistently used the dr. Bart app up to half a year, confirming that a stand-alone eHealth application has the potential to reach patients with knee/hip OA. However, we were not able to demonstrate a dose-response relationship between use of the app and HCU and clinical outcomes. Additionally, this study provides insights in the educational needs for patients with knee/hip OA. In conclusion, we think that the dr. Bart app has the potential to serve as a trustworthy tool to provide education and goal setting in patients with knee/hip OA.

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Supplementary material

Supplementary Table 1. Baseline characteristics of participants in the study per indicator of use and non-users

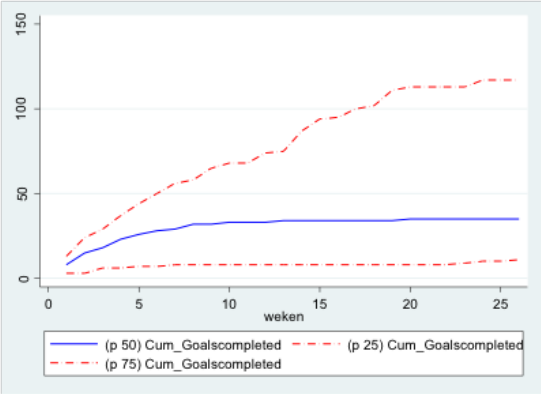
	Non-user (*N* = 43)	Logged in, but no further activity (*N* = 20)	Chose ≥ 1 goal, but did not complete goals (*N* = 38)	Completed ≥ 1 goal (*N* = 113)
Age, years; mean (SD)	62.2 (7.1)	63.9 (6.4)	64.7 (10.5)	60.8 (6.8)
Female, *n* (%)	31 (72.1)	12 (60.0)	23 (60.5)	81 (71.7)
Body Mass Index, kg/m²; mean (SD)	29.0 (6.0)	28.9 (5.6)	27.5 (4.8)	27.2 (4.7)
Level of education (≤ 12 years, *n* (%)	13 (33.3)	5 (29.4)	12 (33.3)	26 (24.1)
Main OA-location				
Knee, *n* (%)	31 (72.1)	16 (80.0)	28 (73.7)	82 (72.6)
Duration of symptoms, *n* (%)				
< 1 year	5 (11.6)	2 (10.0)	7 (18.4)	11 (9.7)
1 – 5 years	23 (53.5)	9 (45.0)	18 (47.4)	54 (47.8)
6 – 10 years	9 (20.9)	2 (10.0)	11 (29.0)	27 (23.9)
> 10 years	6 (14.0)	7 (35.0)	2 (5.3)	21 (18.6)

Abbreviations: *SD*, Standard Deviation; *n*, number; *OA*, osteoarthritis.

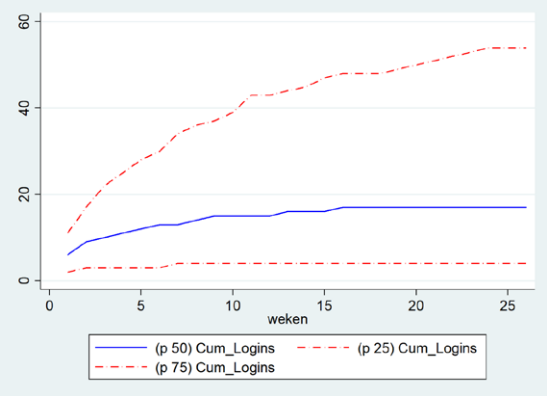
Supplementary Table 2. Regression coefficient and 95% CI of the relation between baseline characteristics and different parameters of use

	Age	Gender[a]	BMI	Main OA location[b]	Level of education[c]	Duration of symptoms[d]
Logins	0.0 (-1.1; 1.1)	9.9 (-8.3; 28.2)	-1.5 (-3.2; 0.3)	8.9 (-10.5; 28.3)	-10.1 (-29.3; 9.1)	-8.8 (-35.3; 17.8)
Unique Goals Chosen	0.0 (-0.1; 0.2)	0.8 (-1.9; 3.4)	-0.8 (-0.3; 0.2)	0.4 (-3.1; 2.4)	-0.9 (-3.6; 1.9)	-1.5 (-5.3; 2.2)
Unique Goals Completed	0.1 (-0.1; 0.3)	0.1 (-2.9; 3.1)	-0.1 (-0.3; 0.2)	-0.5 (-3.6; 2.6)	-1.2 (-4.4; 1.9)	-2.9 (-7.5; 1.7)
Total goals completed	2.7 (-0.1; 5.5)	9.1 (-34.2; 52.4)	-3.2 (-7.3; 0.9)	14.1 (-29.6; 57.8)	-34.7 (-81.5; 12.1)	-30.0 (-95.6; 35.6)
Paragraphs	-0.8 (-1.5; -0.2)	10.2 (-0.9; 21.4)	-1.0 (-2.1; 0.1)	3.2 (-8.7; 15.1)	12.9 (0.8; 24.9)	19.0 (3.0; 35.1)

[a] Male as reference category
[b] Knee as reference category
[c] Less than 12 years as reference category
[d] duration of symptoms > 10 years as reference category



Supplementary Figure 1a. Median and interquartile range of the number of cumulative completed goals over time of the active users (*n* = 151)



Supplementary Figure 1b. Median and interquartile range of the number of cumulative logins over time of the active users (*n* = 151)

Supplementary Table 3a. The 5 relatively most and least often completed goals (i.e. times completed/ times chosen)

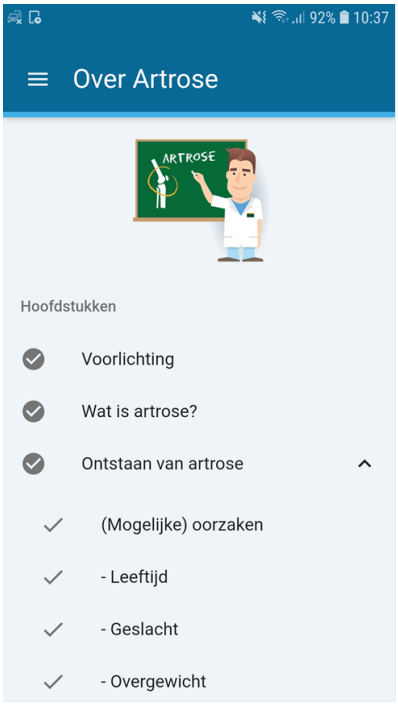
The 5 relatively most often completed goals	The 5 relative least often completed goals
1. Today I participate in Netherlands on the move {trigger] on the television.	**1.** Today I'm telling to {spouse/neighbour} what osteoarthritis comprises.
2. Today I walk [number of] steps.	**2.** Today I'm telling {spouse/neighbour} about the dr. Bart app.
3. Today I won't spoon more than once with dinner.	**3.** Today I read a chapter about osteoarthritis from the education library.
4. I'm going to perform [number of exercises] from the exercise library {trigger}.	**4.** I'm going to swim [number of laps] {trigger}.
5. {Trigger} I 'm going to get up [number of times] from my chair to train my leg muscles.	**5.** Today I put a sweetener in the coffee or tea instead of sugar.

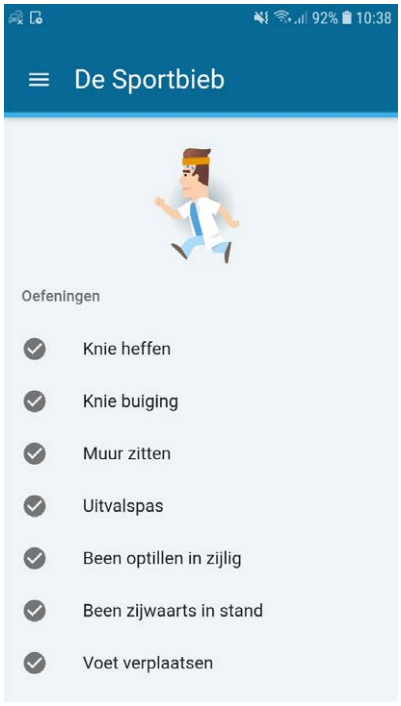
Supplementary Table 3b. The 5 relatively most and least often chosen goals (i.e. times chosen / times proposed).

The 5 relatively most often chosen goals	The 5 relatively least often chosen goals
1. During {trigger} I drink a glass of water.	**1.** Today I participate in Netherlands on the move {trigger] on the television.
2. Today I won't spoon more than once during dinner.	**2.** Today I'm telling to {spouse/neighbour} what osteoarthritis comprises.
3. I'm going to improve the stability of my legs by doing an exercise from the exercise library during {trigger}	**3.** Today I get out of the bus one stop earlier than usual and walk the rest.
4. Today I don't drink any sweetened drinks (such as soda or fruit juice).	**4.** Today I divide my household activities over the day.
5. During {trigger} I'm going to stand on my toes and slowly lower myself again and repeat this [number] times.	**5.** {Trigger} I'm going to walk for [number] minutes.

Supplementary Table 3c. The 5 most and least often read paragraphs

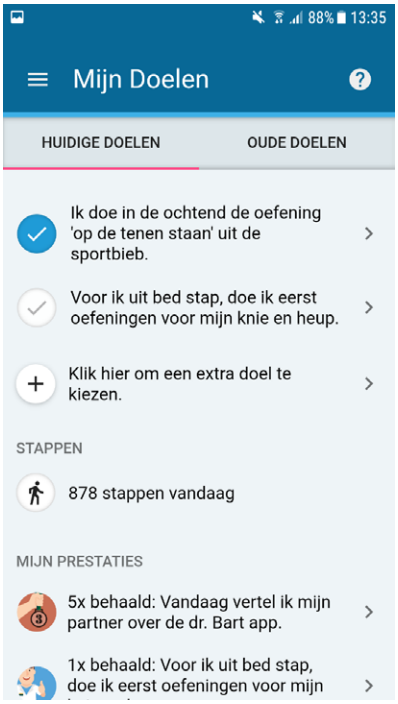
Most popular paragraphs	Least popular paragraphs (<20%)
1. General information regarding osteoarthritis.	**1.** Information about the four themes in the dr. Bart app.
2. What is osteoarthritis?	**2.** If drugs do not help enough, what other treatment are available?
3. Complaints (especially fatigue)	**3.** With what frequency and intensity should I exercise?
4. Prognosis of OA	**4.** Are there any specific points I need to consider with regard to my job activities?
5. Treatment of osteoarthritis	**5.** How long does an artificial joint (joint replacement) last?


92% 10:37
Over Artrose
ARTROSE
Hoofdstukken
Voorlichting
Wat is artrose?
Ontstaan van artrose
(Mogelijke) oorzaken
- Leeftijd
- Geslacht
- Overgewicht


92% 10:38
De Sportbieb
Oefeningen
Knie heffen
Knie buiging
Muur zitten
Uitvalspas
Been optillen in zijlig
Been zijwaarts in stand
Voet verplaatsen


92% 10:37
Ontstaan van artrose
(Mogelijke) oorzaken
Over het ontstaan van artrose bestaat nog veel onduidelijkheid. Wel is bekend dat het ontstaan van artrose een combinatie is van meerdere factoren.
De exacte ontstaanswijze van artrose is onderwerp van wetenschappelijk onderzoek en men hoopt hier in de nabije toekomst een antwoord op te kunnen geven.
Er is wel bekend dat de volgende factoren de kans op artrose vergroten: - Hogere leeftijd - Vrouwelijk geslacht - Overgewicht, - Regelmatige overbelasting - Erfelijkheid - Gewrichtsschade / Gewrichtsproblemen
Ontstaan van artrose: 1 / 7


88% 13:34
Sportbieb
Mobiliseren heup
(kijk onder de video voor meer uitleg)
Ga op uw rug liggen. Buig uw knie en pak de achterkant van het bovenbeen vast, net onder de knieholte en breng vervolgens uw knie richting de borst. Laat uw andere been liggen. Ga weer terug naar de startpositie. Herhaal deze oefening ook voor uw andere been. Doe voor ieder been 10 tot 15
Sportbieb: 13 / 14



Supplementary Figure 2. Screenshots of the dr. Bart app

Chapter 6

Economic evaluation of the dr. Bart app in people with knee and/or hip osteoarthritis

Tim Pelle
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Submitted

Abstract

Objective

To evaluate the cost-utility and cost-effectiveness of the dr. Bart app compared to usual care in people with knee/hip OA, applying a health care payer perspective.

Methods

This economic evaluation was conducted alongside a 6-month randomised controlled trial, involving 427 participants. Self-reported outcome measures were health care costs, quality-adjusted life years (QALYs) according to the EuroQol (EQ-5D-3L), the EuroQol rating scale (QALY-TRS), patient activation measure (PAM-13) and five subscales of KOOS/HOOS. Cost and effect differences were estimated using longitudinal linear mixed models and cost-effectiveness acceptability curves. Bootstrapping was applied to estimate statistical uncertainty.

Results

Mean age of participants was 62.1 (SD 7.3) years, with the majority being female (72%). Health care costs were non-significantly lower for the intervention group (€-31 (95% CI: -66; 3)). For QALY and QALY-TRS, the probability of the dr. Bart app being cost-effective compared to usual care was 0.80 and 0.60 at a willingness to pay (WTP) of €10.000 and 0.72 and 0.44 at WTP €80.000, respectively. For self-management behaviour, symptoms, pain and ADL, the probability that dr. Bart app was cost-effective was >82% and for activities and quality of life <40%, regardless of WTPs.

Conclusion

This economic evaluation showed that costs were (non-significantly) lower for the dr. Bart app group compared to usual care. Given the non-invasive character of the intervention and the moderate probability of being cost-effective for the majority of outcomes, the dr. Bart app has the potential to serve as a tool to provide education and goal setting regarding OA and its treatment options.

Significance and innovation

- This is the first study that performed an economic evaluation of a stand-alone (e-)self-management tool for people with knee/hip OA.
- This economic evaluation shows, from a health care payer perspective, that an (e-)self-management tool for knee/hip OA has moderate probabilities of being cost-effective.

Background

OA is a chronic disease mainly affecting the knee(s) and hip(s) resulting in pain, stiffness, and functional disability[1,2]. Apart from this health burden, the financial annual burden of OA was 1.6% of the total health care expenditure in the Netherlands in 2015; € 1.3 billion. Costs attributable to OA spent in secondary care are 8 times higher than costs spent in primary care[3]. Due to the ageing population – and OA prevalence increases with age – the economic burden of OA is expected to increase, resulting in an extra demand on OA health care services in the future[1,4].

First choice non-surgical treatments in knee/hip OA are education, lifestyle advice and healthy behaviours[5,6]. Since OA is a chronic disease, a key element in non-surgical management is self-management[7,8]. Compared to usual care, traditional self-management programs show small benefits on self-management skills, pain, function and symptoms[9]. Despite recommendations about the content of non-surgical treatment options in OA, the quality of care is suboptimal; lack of time and detailed guidance results in underutilisation of non-surgical treatment options and unnecessary referrals to secondary health care in people with knee/hip OA[10].

Due to the considerable costs related to OA, there is need for cost-effective interventions in the treatment for people with knee/hip OA. EHealth technologies (e.g. applications) offer the possibility to provide self-management 24/7 at lower costs compared to traditional interventions. EHealth interventions can be divided in blended interventions which combine face-to-face consultations with eHealth, while it is also possible to offer eHealth applications without therapeutic guidance. By using interventions without therapeutic guidance, the burden of OA on health care will be less for providers, but for patients as well, as they do not need to travel and can apply it at their own pace[11]. Despite the high potential of these applications, the majority of applications have not proven their (cost-)effectiveness in trials in people with OA[12]. Within mental healthcare and cardiac rehabilitation, blended interventions have been found to be cost-effective[13,14], but not for people with knee/hip OA[15]. Yet, high quality evidence regarding economic evaluations in standalone applications without therapeutic guidance for people with knee/hip OA is lacking.

Given the huge potential of eHealth technologies, we developed the dr. Bart app to enhance self-management in people with knee/hip OA. The dr. Bart app is based on the Fogg model for behavioural change, augmented with reminders, rewards and self-monitoring to reinforce app engagement[16]. We hypothesized that use of dr. Bart would result in better self-management (and thus reduction of secondary health care consumption) and improvement of pain and functioning. However, in our evaluation regarding the dr. Bart app we did not find changes in health care utilisation over six months between the control and intervention group. On the other hand, the dr. Bart app has small but positive effects on pain, symptoms and activities of daily living in people with knee/hip OA[17]. To be implemented on a larger scale, insight in the cost-effectiveness is warranted. Therefore, this study presents the (incremental) cost-utility analysis and cost-effectiveness analyses of the dr. Bart app compared to usual care in people with knee/hip OA, from a health care payer perspective.

Methods

Design overview

We conducted this economic evaluation alongside a randomised controlled trial (RCT) evaluating the effectiveness of the dr. Bart app on health care use (HCU) and clinical outcomes over half a year, performed by the Sint Maartenskliniek Nijmegen (the Netherlands) from January 2018 to January 2019. This economic evaluation was based on the general principles of cost-utility analysis and cost-effectiveness analysis, from a health care payer perspective, comparing a fully automated eHealth application with care as usual. Details of the trial design and development of the dr. Bart app have been published elsewhere[16]. Ethical approval for this study was asked for and waived by the local Medical Research Ethics Committee of the Radboud University Medical Centre, Nijmegen (CMO Arnhem-Nijmegen; Protocol Number: 2017-3625 / Dutch Trial Register NTR6693). This study is reported according the CHEERS statement.

Participants

Participants were recruited via newspapers and campaigns on social media (e.g. Facebook and LinkedIn). Potential participants were invited to visit the website (www.drbart.eu) to check for eligibility. Participants were included when: 1) Having self-reported OA of the knee and/or hip (i.e. having a painful knee and/or hip, knee and/or hip pain > 15 days of the past month, morning stiffness < 30 minutes (knee) and/or < 60 minutes (hip)), 2) ≥ 50 years, 3) Having an e-mail address, 4) Possession of smartphone or tablet and willing to download the dr. Bart application on one or more devices and 5) Able to read, write and sufficiently communicate in Dutch. Participants were excluded when: 1) being wheelchair bound, 2) having diagnosis of (other) inflammatory rheumatic disease, 3) having knee and/or hip replacements and 4) scheduled for knee and/or hip joint arthroplasty in the next 6 months[16].

Participants who fulfilled baseline assessment were allocated to either intervention group (dr. Bart app) or control group (usual care) in a 1:1 ratio performed with CastorEDC by the researcher (TP). Further details regarding the study population can be found in our papers[16,17].

Intervention: dr. Bart app

We developed the dr. Bart app to enhance self-management and to actively involve people with OA in managing their disease. The dr. Bart app is a fully automated eHealth application and its main function is to set goals for a healthier lifestyle based on the Fogg model for behavioural change[18]. The dr. Bart app is augmented with reminders, rewards and self-monitoring to reinforce app engagement and health behaviour. The dr. Bart app proposes goals to a healthier lifestyle on the basis of machine learning techniques fed by data collected in a personal profile and previous choosing behaviour of the user. Further details regarding the applied theoretical framework and development of the dr. Bart app are published elsewhere[16]. Participants allocated to the intervention group received an e-mail with information to access the dr. Bart app.

Control group: usual care

Half of the participants were allocated to the usual care group and received no active treatment. Participants allocated to the control group received an e-mail that they were assigned to the control group. After fulfilling the last follow-up questionnaire, participants in the control group were offered the dr. Bart app as well.

Outcome measures
Participants were assessed at baseline, and after 3 and 6 months. Demographic data were collected at baseline.

Utility measures
We measured health-related quality with the EQ-5D-3L[19]. We calculated utility scores on a scale anchored at 0 ("worst imaginable health") to 1 ("full health"). Moreover, the EuroQol rating scale (RS) was used to indicate health-related quality of life on a vertical line ranging from 0 ("worst imaginable health") to 100 ("full health"). We transformed the RS score into a utility score (TRS) using the formula: TRS = ((1-(1-RS)/100)^1.61)[20] We determined quality adjusted life years (QALYs) for each participant with the trapezoid method to obtain area under the EQ-5D and TRS curves (AUCs).

Clinical outcome measures
Knowledge, skills and confidence to cope with one's health were assessed with the Patient Activation Measure (PAM-13) questionnaire[21,22]. We used the KOOS or HOOS where applicable to assess pain, symptoms, activities of daily living, quality of life and physical functioning in sport and recreation (0-100), with higher scores indicating fewer complaints[23,24].

Cost outcome measures
Costs included health care costs related to knee/hip OA during the study. Cost outcome measures were assessed at baseline, and at 3 and 6 months of follow-up.

Health care costs
Participants reported their total number of visits to primary and secondary health care providers in the preceding 6 months (assessed with a three-month recall period) related to knee/hip OA. Health care utilisation was valued by Dutch standard cost prices of 2014[25]. In order to account for cumulative inflation, costs were multiplied with a factor 1.041 to obtain cost prices for 2018[25,26]. To determine health care costs, we multiplied the number of visits with the accompanying price per resource. To estimate costs of knee/hip OA related surgery, we obtained prices of surgical operations from the Dutch Health Authority (www.nza.nl).

Intervention costs
We did not take development costs of the eHealth intervention into account in this economic evaluation.

Statistical analysis
All statistical analyses were performed using Stata 13.1 (www.stata.com). Statistical analyses were performed according to the intention-to-treat principle. Descriptive statistics were used to present group characteristics.

Missing data was managed according to the recommendations of the specific questionnaire. Missing data on health care utilisation were imputed using a zero, when not being loss to follow-up. For the PAM, we also calculated a total score when a maximum of two items of the questionnaire were missing, though the PAM recommends to only calculate a total score if no single item is missing. For this, we calculated the mean score of the answered questions in the PAM questionnaire and multiplied this by 13. Missing data for utility measures were imputed according to the last observation carried forward principle.

We used longitudinal linear mixed models to evaluate the effectiveness of the dr. Bart app on utility scores and clinical outcomes, adjusted for baseline values. Our primary analysis focused on the costs and effects over 6 months of follow-up. Differences in mean fitted predicted values were used to indicate group differences.

For the cost utility analysis and cost-effectiveness analysis, we reported incremental net monetary benefit (iNMB), because this measure is easier to interpret than the ICER when differences are small and around zero. The iNMB was calculated with the formula: iNMB = Willingness to Pay (WTP) * (incremental effect) – incremental costs[27]. Uncertainty (95% CI (confidence interval)) around costs and effects were estimated by bootstrap intervals with 2500 replications. Bootstrapped incremental cost-effect pairs were plotted on cost-effectiveness planes[28]. Moreover, we plotted cost-effectiveness acceptability curves to indicate the probability of the dr. Bart app being cost-effective compared to usual care at different willingness-to-pay values (€ 0 to € 80,000)[29]. Results presented in Tables and Figures are based on society's WTP of €10,000.

Sensitivity analyses

We performed two sensitivity analyses. First, we performed a per-protocol analyses excluding one participant from the control group (protocol violator), whereas in the intervention group 63 participants were considered non-adherent with the dr. Bart app and therefore excluded. For the second sensitivity analysis, we performed multiple imputation by chained equations to estimate missing cost data to preserve power and reduce bias. In total 20 imputed data sets were predicted based on available data.

Results

Participants

In total, 427 participants were included in this economic evaluation; 214 allocated to the dr. Bart app group and 213 to the usual care group (Figure 1). Baseline characteristics were similar for both groups; mean age was 62.1 years (SD 7.3), with the majority being female (71.7%) and having symptoms predominantly in their knee(s) (73.3%). Almost 60% experienced symptoms due to OA less than five years (Table 1). The response rate for the follow-up questionnaires were 75.4% (intervention group, n = 150; control group, n = 172) and 69.3% (intervention group, n = 130; control group, n = 166) at 3 and 6 months, respectively.

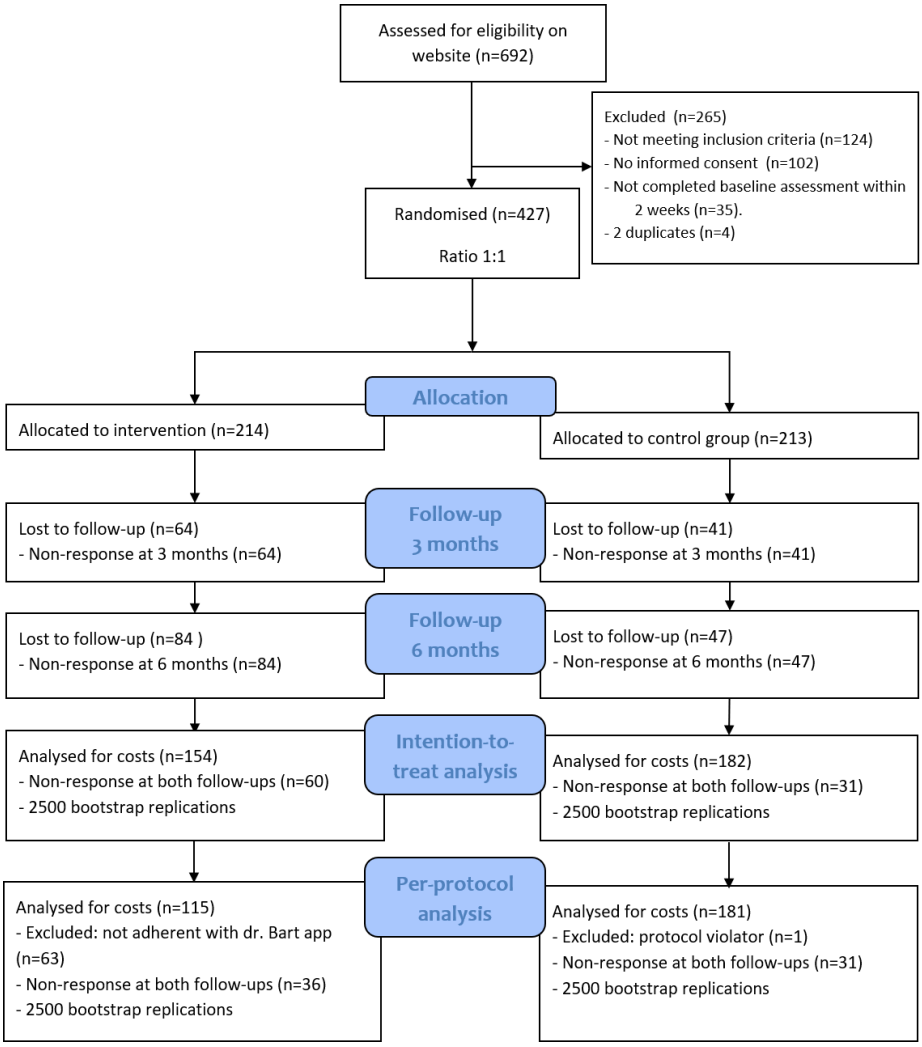

Figure 1. Flow chart of the study

Table 1. Baseline characteristics of participants allocated to the intervention (dr. Bart app) and control group (*n* = 427)

	Dr. Bart app group (n = 214)	Control group (n = 213)
Age, years; mean (SD)	62.1 (7.7)	62.1 (7.0)
Female, *n* (%)	147 (68.7)	159 (74.7)
Body Mass Index, kg/m²; mean (SD)	27.8 (5.1)	27.3 (4.8)
Level of education (≤ 12 years, *n* (%)	56 (28.0)	36 (18.6)
Main OA-location		
Knee, *n* (%)	157 (73.4)	156 (73.2)
Duration of symptoms, n (%)		
< 5 years	129 (60.3)	117 (54.9)
≥ 5 years	85 (39.7)	96 (45.1)
Self-management behaviour	40.8 (5.3)	40.2 (5.7)
Symptoms†	57.7 (16.3)	57.0 (18.9)
Pain†	57.5 (15.5)	58.2 (17.8)
Activities of daily living†	58.5 (19.7)	59.4 (20.2)
Activities†	32.6 (23.9)	32.5 (23.1)
Quality of life†	38.0 (17.5)	38.3 (17.1)

Abbreviations; *SD*, standard deviation; *n*, number; *OA*, osteoarthritis. †Assessed with either KOOS or HOOS.

Utilities

We found no differences in utility measures for the usual care group and the dr. Bart app group (mean group difference QALY 0.0045 (95%CI: -0.01; 0.02) and QALY TRS -0.0015 (95%CI: -0.01; 0.01)), Table 2.

Effects

After 6 months, no significant differences were seen in clinical outcomes between the dr. Bart app group and usual care group after bootstrapping (2500 replications), except for self-management behaviour (Table 3).

Health care costs

Primary and secondary health care costs did not differ significantly between groups. The estimated mean health care costs during follow-up were €496 (SD 1240) and €439 (SD 1294) for the control group and dr. Bart app group, respectively (Table 2). Over the period of six months the estimated difference between groups was non-significantly lower for the dr. Bart app group (€-31 (95% CI: -66; 3)).

Table 2. Utility scores and average health care costs per patient during follow-up for the intervention and control group separately

	Dr. Bart app group¥ (*N* = 214)	Control group¥ (*N* = 213)	Group difference*
QALY / Utility score (0.0 - 0.5)	0.36 (0.08)	0.36 (0.09)	0.0045 (-0.01; 0.02)
QALY / Utility score TRS (0.0 - 0.5)	0.42 (0.07)	0.42 (0.06)	-0.0015 (-0.01; 0.01)
Total health care costs during follow-up, € mean (SD)[a]	439 (1294)	496 (1240)	-31 (-66; 3)
Total health care costs during follow-up, € mean (SD)[b]	468 (1425)	499 (1243)	-16 (-57; 29)

¥Raw estimates *Mixed models, adjusted for baseline value, with 95% confidence interval obtained from bootstrapping with 2500 replications. [a] When not loss to follow-up, missing data were imputed with zero cost [b] Per-protocol analysis

Cost-utility analysis

The primary economic evaluation of the current study was the cost-utility analysis comparing the difference between the dr. Bart app and control group in healthcare costs to the difference in QALY and QALY TRS, obtained with the EQ-5D. Since both costs and QALYs were in favour of the dr. Bart app group (i.e. dr. Bart app dominates control group) the iNMB was also in favour of the dr. Bart, regardless of society's WTP (Table 3). We found an iNMB of €77 (95% CI: -99; 253) at a WTP of € 10,000. Accordingly, the cost-effectiveness acceptability curve (CEAC) for QALYs showed a probability of the dr. Bart being cost-effective of 0.80 and 0.72, for a WTP of €10,000 and €80,000, respectively (Figure 2).

For QALYs, estimated using the TRS, we found an iNMB of €17 (-128; 155). At a WTP of €10,000, we found a probability of the dr. Bart app being cost-effective of 0.60. At higher WTPs, this probability decreased (not shown). The net benefit between groups did not reach statistical significance.

Cost-effectiveness analysis

Since both costs and self-management behaviour were in favour of the dr. Bart app group, the iNMBs were also in favour of the dr. Bart app, regardless of society's WTP (Table 3). The CEAC showed a probability of 0.99 of the dr. Bart app being cost-effective, regardless of society's WTP.

For symptoms, pain and activities of daily living we found iNMBS of €20,000 to €30,000 at a WTP of €10,000, none statistically significant (Table 3). Accordingly, the CEAC showed that the probability of dr. Bart app being cost-effective compared to usual care was 0.93, 0.97, and 0.82 at different WTPs for symptoms, pain, and activities of daily living, respectively.

For activities and quality of life, assessed with either KOOS or HOOS, we found iNMBS of €7,000 in favour of the control group. The CEAC showed that the probability of dr. Bart being cost-effective was 0.37 and 0.36 for activities of daily life and quality of life. At higher WTPs, this probability remained about the same.

Sensitivity analyses

Our first sensitivity analysis (per-protocol analysis) gave similar results (Table 2 and Supplementary Table 1) as our main analysis. In addition, we performed a second sensitivity analyses (multiple imputation of cost data), and found comparable results (€ -22 (-58; 14) (data not shown) as our main analysis.

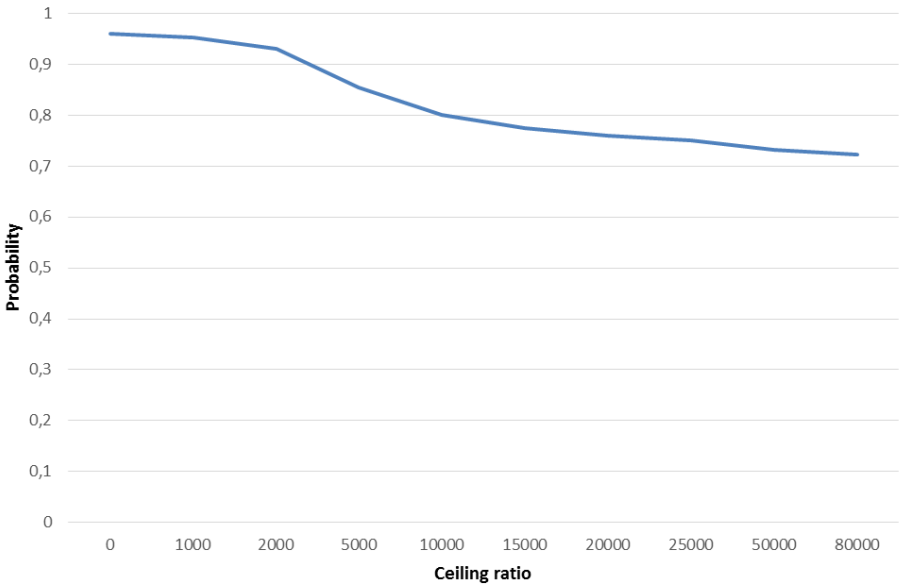

Figure 2. Cost-effectiveness acceptability curve showing the probability that the dr. Bart app is cost-effective compared to usual care for different willingness to pay thresholds for an additional QALY

Table 3. Differences in predicted mean costs and effects between the dr. Bart app group and control group

Outcome	ΔC^∞ In euros	ΔE^∞ In points	iNMB *^∞ (€ 10,00)	iNMB *^∞ (€ 80,00)	Distribution CE plane %			
					SE[a]	NE[b]	SW[c]	NW[d]
QALY (0-1)	-31 (-66; 3)	0.0045 (-0.01; 0.02)	77 (-99; 253)	394 (-929; 1701)	68.84	1.88	27.24	2.04
TRS (0-1)	-31 (-66; 3)	-0.0015 (-0.01; 0.01)	17 (-128; 155)	-85 (-1169; 916)	40.84	1.24	55.24	2.68
PAM	-31 (-66; 3)	**1.2 (0.3; 2.2)**	**12495 (3053; 22193)**	**99738 (24474; 177333)**	95.52	3.88	0.56	0.04
Symptoms	-31 (-66; 3)	2.6(-0.8; 5.8)	25865 (-8010; 58344)	206704 (-64218; 466591)	89.64	3.56	6.44	0.36
Pain	-31 (-66; 3)	3.0 (-0.2; 6.1)	30431 (-2013;60745)	243234 (-16223; 485581)	93.16	3.76	2.92	0.16
ADL	-31 (-66; 3)	1.9 (-2.3; 6.1)	19026 (-22770; 61213)	151993 (-182487; 489500)	78.96	2.72	17.12	1.20
Activities	-31 (-66; 3)	-0.7 (-5.1; 3.8)	-7334 (-50553; 37964)	-58889 (-404768; 303401)	35.68	0.96	60.40	2.96
QoL	-31 (-66; 3)	-0.7 (-4.8; 3.2)	-7185 (-47915; 32015)	-57696 (-383493; 255873)	34.84	0.88	61.24	3.04

*Positive sign indicates that the intervention is cost-effective compared to usual care at a given willingness-to-pay threshold (€10,000), after 2500 bootstrap replications.
^∞Control group as reference.

Costs are expressed in 2018 Euros. **Abbreviations:** *CE-plane*: Cost-Effectiveness plane, *iNMB*: increment Net Monetary Benefit

[a] SE: Southeast quadrant: indicating that dr. Bart is more effective and less costly than usual care.
[b] NE: Northeast quadrant: indicating that dr. Bart is more effective and more costly than usual care.
[c] SW: Southwest quadrant: indicating that dr. Bart is less effective and less costly than usual care.
[d] NW: Northwest quadrant: indicating that dr. Bart is less effective and more costly than usual care.

Discussion

We performed an economic evaluation of the dr. Bart app versus usual care in patients with knee/hip OA, from a health care payer perspective. We found small (non-significant) differences in health care costs in favour of the dr. Bart app group. Our analyses showed that half of the utility measures resulted in dominance for the dr. Bart app group, regardless of threshold for WTP. Furthermore, 4 out of 6 clinical outcomes showed a chance of > 80% that the dr. Bart app was cost-effective at WTP thresholds between €10,000 and €80,000.

Regardless of the limited clinical outcomes[17], we considered it important to conduct an economic evaluation as these analyses are necessary to implement interventions on a larger scale. In addition, an important aim of self-management interventions is to actively involve people with OA to manage their disease, including skills navigating the health care system (i.e. making optimal use of primary and secondary health care options)[30]. In the current economic evaluation we found no differences in utility measures between both study groups over six months, which is in line with two systematic reviews on traditional self-management interventions in OA[9,31], indicating that these interventions are not cost-effective, when

measured with quality-adjusted life-years[31]. On the other hand, we found that the dr. Bart has high chances of being cost-effective (>80%) in four out of six clinical outcomes. This might suggest that for non-pharmacological conservative treatments in OA, clinical outcomes are more responsive to change over time than utility measures. Taken together, there seem to be some inconsistencies over a range of utility measures and clinical outcomes. Overall, our findings seem to be indicative for moderate to high chances of dr. Bart app being cost-effective, albeit modest.

Although we a found moderate to high probability of the dr. Bart app being cost-effective for the majority of outcomes, differences in costs were small and did not reach statistical significance. The small differences in costs might be explained by the fact that our six month follow-up is too short to appropriately investigate whether the dr. Bart app reduces secondary health care costs in the long term. It is conceivable that the "tiny habits"[18] will be incorporated in daily life by participants, resulting in larger health benefits and changes in HCU patterns over time. In addition, one could hypothesize that differences in costs over time will rise because orthopaedic surgery might be necessary or patients will become impaired and have loss of productivity, leading to higher net cost savings. This is underlined by two studies showing that non-pharmacologic conservative treatment programs can postpone and thus reduce the number of total joint replacements after 5 years[32,33]. The relatively small net saving found in the present study could be of importance given the high prevalence of OA and its burden on society. Further research should be undertaken to investigate the long term (cost-) effectiveness of non-pharmacologic conservative treatment (including self-management) interventions.

The growing prevalence of OA will result in an additional demand on health care services. Therefore, there is a need for cost-effective interventions in the non-pharmacological conservative treatment of OA. At present evidence about the cost-effectiveness of stand-alone eHealth applications to enhance self-management in people with OA is absent. As a consequence, no proper comparison of our economic evaluation with other studies is possible. Currently there is limited evidence for cost-effectiveness of a blended web-based option in OA[15], as well as for telemedicine in in other chronic conditions (e.g. diabetes). Nevertheless, these studies remark that telemedicine has the potential to be cost-saving when appropriately executed[34,35]. Therefore, more high quality or intensive self-management interventions accompanied with economic evaluations are necessary to enlarge our understanding on the cost-effectiveness of eHealth applications that enhance self-management in chronic conditions, especially in OA.

This is the first study that performed an economic evaluation of a stand-alone e-self management application for people with knee/hip OA. A potential limitation of this study is the self-reported nature of HCU; self-reports are susceptible to underreporting and recall bias. However, we used the same cost questionnaire for the intervention and control group, i.e. underreporting would be similar in both groups. To minimize recall bias, we have chosen a recall period of three months. In our opinion, there is no better alternative to assess HCU as OA does not require continuous supervision of a physician, like in other chronic conditions (e.g. diabetes and COPD) and thus verifying data from other sources is not possible[36,37]. A second potential limitation is the missing data on health care costs. We performed multiple imputations, which is considered highly appropriate to account for missing data. Third, this

economic evaluation was conducted alongside a clinical trial and the required sample size was based upon the primary outcome of the RCT. Since costs have a larger variation and skewness than clinical outcome measures, the current study might be underpowered[38,39]. Fourth, one should bear in mind that we applied a health care payer perspective in this economic evaluation. Thus, productivity losses were not taken into account. Last, it should be mentioned that we recruited participants for participation in a study on eHealth. This might have resulted in a selection of participants. Thus, generalisability is restricted to people with knee/hip OA who have an interest in using modern technologies to manage their disease. A strength of the performed study is that we performed not only a cost-utility analysis based on two different utility measures, but also used six different clinical outcomes to estimate cost-effectiveness, enabling trade-off between a range of benefits.

Considering the abovementioned results and limitations, this economic evaluation from a health care payer perspective, shows moderate probability that an eHealth application to enhance self-management (dr. Bart app) in people with knee/hip can be considered cost-effective. In view of the prevalence of OA and the fact that inducing difficult lifestyle changes is the cornerstone of management of OA and therefore a potentially long term investment, we think the magnitude of effects attributable to the dr. Bart app are worthwhile. Thus, the app could be applied as primary approach to deliver useful information and support self-management in people with knee/hip OA, specifically for patients who are interested in eHealth.

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Supplementary material

Supplementary Table 1. Differences in predicted mean costs and effects between the dr. Bart app group and control group of the per-protocol analysis

Outcome	ΔC∞ In euros	ΔE∞ In points	iNMB * (€ 10,00)	Distribution CE plane %			
				SE[a]	NE[b]	SW[c]	NW[d]
QALY (0-1)	-16 (-57; 29)	0.0054 (-0.01; 0.02)	71 (-121; 271)	57.76	13.96	19.64	8.64
TRS (0-1)	-16 (-57; 29)	-0.0004 (-0.01; 0.01)	12 (-137; 168)	40.00	9.60	37.40	13.00
PAM	-16 (-57; 29)	1.5 (0.5; 2.5)	14914 (4892; 24824)	77.28	22.52	0.12	0.08
Symptoms	-16 (-57; 29)	3.0 (-0.6; 6.7)	29815 (-6175; 66883)	74.20	20.60	3.20	2.00
Pain	-16 (-57; 29)	2.7 (-0.7; 6.2)	26979 (-6708; 61622)	74.08	20.80	3.32	1.80
ADL	-16 (-57; 29)	2.2 (-1.9; 6.6)	22422 (-19022; 65960)	67.12	18.24	10.28	4.36
Activities	-16 (-57; 29)	-0.7 (-4.1; 5.7)	7085 (-41430; 57120)	50.08	13.28	27.32	9.32
QoL	-16 (-57; 29)	0.0 (-4.0; 4.1)	130 (-39809; 41756)	41.20	9.72	36.20	12.88

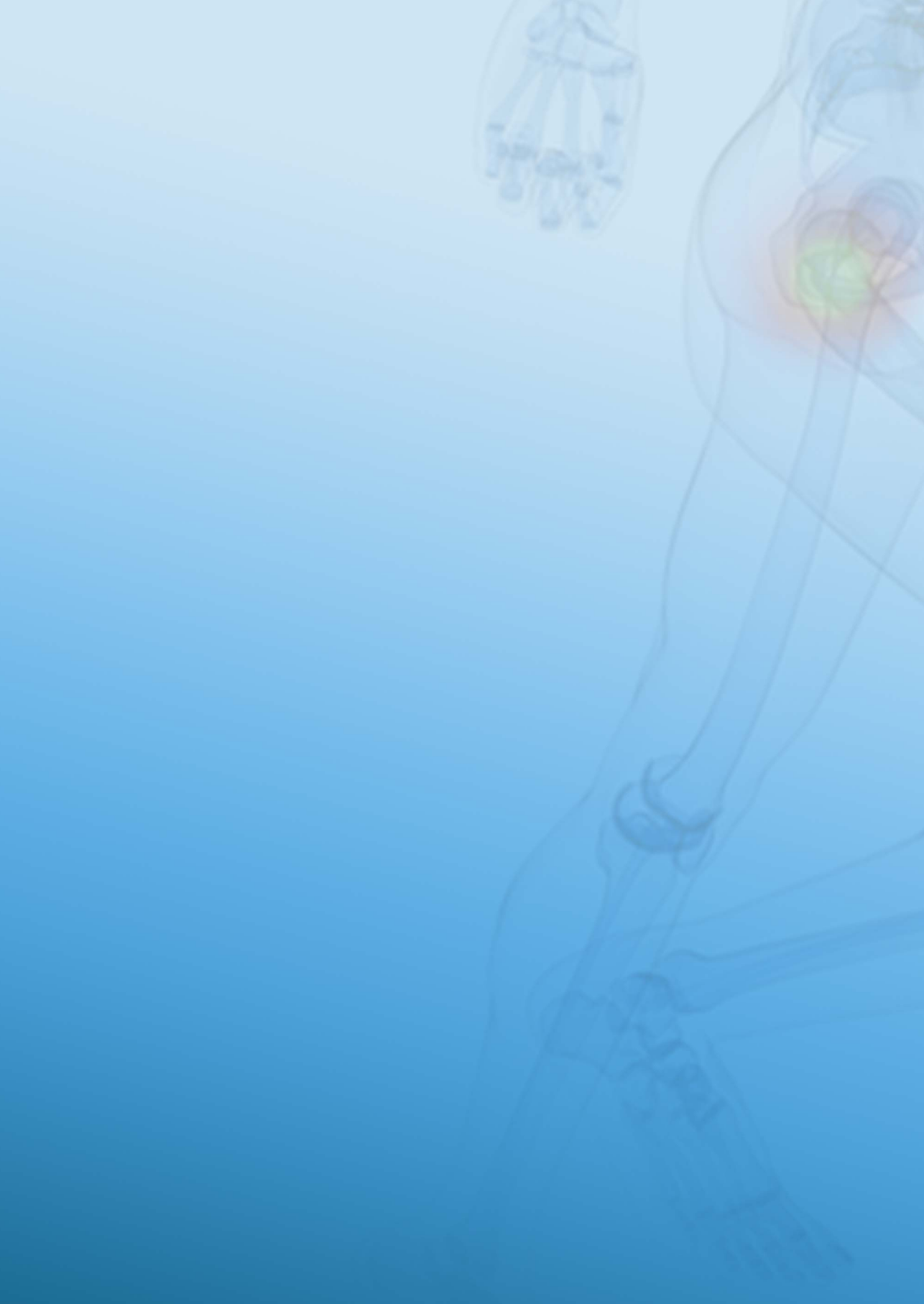
*Positive sign indicates that the intervention is cost-effective compared to usual care at a given willingness-to-pay threshold (€10,000), after 2500 bootstrap replications.
∞Control group as reference.

Costs are expressed in 2018 Euros. **Abbreviations:** *CE-plane*: Cost-Effectiveness plane, *iNMB*: increment Net Monetary Benefit

[a] SE: Southeast quadrant: indicating that dr. Bart is more effective and less costly than usual care.
[b] NE: Northeast quadrant: indicating that dr. Bart is more effective and more costly than usual care.
[c] SW: Southwest quadrant: indicating that dr. Bart is less effective and less costly than usual care.
[d] NW: Northwest quadrant: indicating that dr. Bart is less effective and more costly than usual care.

Chapter 7

General discussion



General discussion

In this chapter I describe the four main findings that are derived from this thesis.

Main finding I: Patients with different stages of osteoarthritis (OA) spend considerable time on physical activity, of which one-third is of at least moderate intensity (*Chapter 2*). Patients who underwent total joint arthroplasty spend more time on physical activity of at least moderate intensity than patients in secondary care (*Chapter 2*). Patients after total joint arthroplasty perform more often low-impact activities (e.g. aerobic exercise and cycling) compared to patients in other stages of OA and the general population (*Chapter 2*).

Main finding II: The dr. Bart intervention, an eHealth application that aims to enhance self-management and optimize non-surgical health care utilisation, has small positive effects on symptoms, pain, and activities of daily living in patients with knee/hip OA, but does not have an impact on health care utilisation patterns (*Chapter 4*).

Main finding III: The dr. Bart app intervention reduces health care spending, albeit modest. This eHealth intervention for patients with knee/hip OA has a moderate probability of being cost-effective, from a health care payer perspective (*Chapter 6*).

Main finding IV: The dr. Bart app intervention is persistently used to a considerable extent for half a year. More intensive use of the eHealth intervention does not result in additional health benefits. Furthermore, this study identified educational needs with regard to general information about OA, complaints, progression, and (non-pharmacological) conservative treatment options for patients with knee/hip OA (*Chapter 5*).

Discussion

In this chapter, I shall elaborate on the main findings from the previous chapters, put these into perspective, and discuss several questions that occurred during the process of doing my research. I will end with conclusions regarding physical activity in patients with OA, eHealth in the conservative treatment of OA, implications for clinical practice and suggestions for future work.

Is there a role for eHealth in the non-pharmacological conservative treatment of patients with knee/hip OA?

Given the marginal benefits of the investigated eHealth intervention, it is important to critically reflect on the question: "Is there value for digital self-management programs in patients with knee/hip OA?". At present, there are no disease modifying treatments available for patients with knee/hip OA. Total joint replacement is a (cost-)effective treatment in end-stage OA. However, current guidelines recommend a stepped care approach in which an operation should only be considered after less invasive conservative treatment (i.e. education about OA and its treatment options, promotion of lifestyle changes, physical therapy and weight loss) has been adequately tried and failed. Moreover, total joint replacement is unattractive in relative young patients, considering the need for revision after 10-15 years.

Self-management is of paramount importance in conservative OA treatment. Modern persuasive technologies offer new possibilities for self-management programs with major advantages; providing tailored information 24/7, supporting patients in managing their disease at any given place, promoting proactive health behaviours, and offering remote monitoring of disease. Given the high potential of applications to support patients in taking an active role to manage their chronic condition in daily life, we developed a stand-alone self-management application: the dr. Bart app. The dr. Bart app, an eHealth application that aims to enhance self-management and optimise non-surgical health care utilisation, had small beneficial effects on pain, symptoms, and activities of daily living. These benefits were comparable to the benefits of traditional self-management programs[1]. Despite unsatisfactory appreciation, the dr. Bart app intervention is persistently used to a considerable extent for half a year. More intensive use of the dr. Bart app does not result in additional health benefits. Users consulted the educational and exercise library on a regular basis, which are considered cornerstones in the disease management of chronic diseases like OA. In addition, educational needs for patients with knee/hip OA were identified; this offers starting points for optimising patient education.

Evidence regarding cost-effectiveness of (traditional) self-management interventions in OA is scarce. Nevertheless, the use of such interventions fits the idea of current recommendations that less complex interventions should be offered first. Logically, self-managing a disease will result in fewer consultations with health care professionals. In contrast to our hypothesis, use of the dr. Bart app did not reduce the number of secondary health care consultations. On the other hand, use of the dr. Bart app did result in less health care spending, with moderate probability to be cost-effective at the short term. Previous studies have shown that the use of self-management programs could postpone total joint replacement on the long term, which has a significant impact on costs[2,3]. Given the scarce health resources, I advocate to invest in secondary prevention of OA or lifestyle changes as these might prolong the time in low disease severity, which is relatively inexpensive. Considering the high prevalence of OA and its burden on society, and the accessibility of the dr. Bart app at any given time and place, the dr. Bart could be beneficial for both patients with OA but for society as well. Thus, the dr. Bart app fits perfectly in a stepped care strategy for the treatment of OA in clinical practice, because the dr. Bart app incorporates treatments of first choice recommended by international guidelines for knee/hip OA[4–7]. Nevertheless, the use of modern technologies does not suit the preferences of each patient. Offering different ways of delivering self-management programs, such as stand-alone applications, blended options, or group or individual treatments, suits the current thoughts of tailored treatment.

In this paragraph I discuss some methodological considerations that need to be taken into account when interpreting the results of this thesis.

Study design

In clinical research, the randomised controlled trial (RCT) is considered the gold standard for evaluating the effectiveness of interventions (e.g. treatments or drugs), because an RCT is generally considered to have the highest strength of evidence. On the other hand, it is well-known that RCTs are time- and money-consuming[8,9]. Currently, there is no consensus about the appropriate evaluation methodology of eHealth interventions[10], but there are more and more signs that RCTs are not the appropriate evaluation methodology of eHealth

interventions. The rigid nature of RCTs differs from the rapidly evolving nature of eHealth interventions, which follows an iterative design process with sprints of several weeks (or more); after each sprint a new, improved version of the intervention is finished. The design to evaluate such novel eHealth interventions should reflect this design process so it reflects the real-world setting[8,10–13]. In my opinion, a paradigm shift from commonly applied study designs, i.e. RCTs, to novel evaluation methodologies for eHealth applications that follow the continuously iterative development process, is necessary.

In this thesis we evaluated the dr. Bart app by applying an RCT, allowing us to study the additional benefits of an e-self management intervention. In hindsight, I recommend to explore the use of novel evaluation methodologies that follow the iterative development process of eHealth technologies, such as the CEEBIT framework (Continuous Evaluation of Evolving Behavioural Intervention Technologies)[11]. By applying the CEEBIT framework, we could have evaluated different versions of the dr. Bart app while continuously evaluating the app among its users with a control arm in clinical practice without freezing functionalities and content. After (significant) improvements to the app are made, a newer version is deployed alongside the older version, and evaluated in the same manner, according to this framework. Since evaluation between deployed versions is consistent, comparison is possible. This process is continuously applied for following versions until evaluation shows that one version is inferior. Subsequently, this inferior version is eliminated from the experiment. Applying this novel framework makes analysis more complex, but Bayesian methods could be a solution.

Another novel methodology that has been introduced to evaluate technological interventions is the "Trials within Cohorts (TWICS)" design, also known as the cohort multiple randomised controlled trial design, see Figure 1. Following this methodology, a large observational cohort of eligible patients with the condition of interest is recruited and their outcomes are regularly measured. Then for each new version, eligible patients are randomly selected from the cohort and offered the trial intervention. The outcomes of these randomly selected patients are then compared with the outcomes of patients not randomly selected; that is, those receiving usual care. This process can be repeated for newer versions[14].

To the best of our knowledge such novel methodologies are not commonly applied by researchers who evaluate eHealth interventions, while both described novel methodologies take into account advantages of a traditional RCT (e.g. randomisation and inclusion and exclusion criteria) and are powered to evaluate efficacy of interventions throughout study duration while accounting for deploying different interventions[8]. Moreover, in the trial within cohorts design, patients are randomly selected before they are informed about the newly offered intervention, maximizing the applicability of the results to clinical practice. Thus, exploring novel evaluation methodologies will result in more suitable, highly rigorous, cost-effective and timely evaluation of eHealth interventions[10], that follow the real-life setting. Besides evaluation of effectiveness, contextual themes like end-user's experience, end-user technological ability among others should be taken into account[10]. In this thesis we performed semi-structured interviews in the development phase of the dr. Bart app (*Chapter 3*). For future studies I propose to perform qualitative studies in parallel with the evaluation of a new intervention as this is essential to derive rich insights from end-users and to elicit suggestions for improvement to be incorporated in newer versions and to identify facilitators and barriers for use of the intervention.

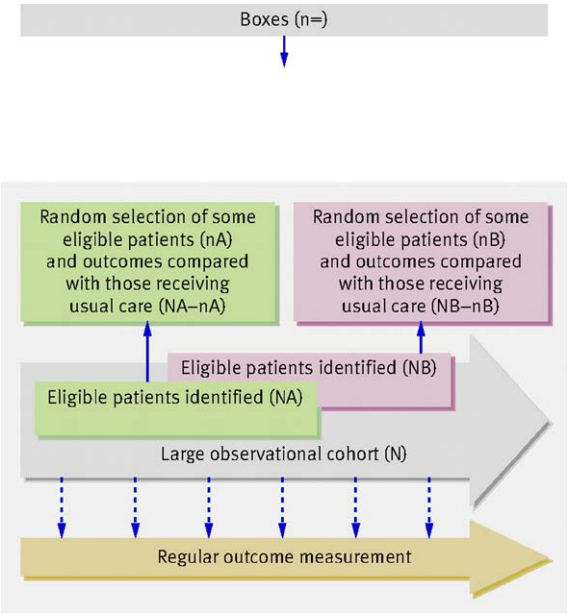


Figure 1. The "cohort multiple randomised controlled trial" design[14]

QALY; love to debate

Due to the considerable costs related to OA, there is need for cost-effective interventions in the treatment for patients with knee/hip OA. The majority of economic evaluations uses generic quality of life measures to assess quality adjusted life years (QALYs)[15]. Quality adjusted life years do not differentiate between being in a health state of 0.5 for 10 years or being in perfect health for 5 years; both result in 5 QALYs. In essence, QALY makes objective policy possible as the QALY is blinded for disease severity and personal characteristics. This is also reflected in a quote of Weinstein in 1988: "a QALY is a QALY is a QALY"[16]. However, the National Health Care Institute allows higher cost for a QALY when disease burden is high or concerns sick children, which is also supported by society. Thus, this makes the QALY context specific. This latter issue makes the QALY controversial. In the Netherlands a range of context specific QALYs are defined; the minimum threshold is €20,000 for low disease severity and a maximum of €80,000 per QALY for high disease severity. The severity weighing factor for OA (relative disability value of a particular disease) compared to other diseases is low (ranging from 0.023 for mild OA to 0.171 for severe OA). So, our study population should be regarded as patients with low burden of disease, and thus the minimum threshold of €20,000 applies.

Since self-management interventions in OA in general do result in minor QALY gain compared to the usual care group, it could be questioned whether QALYs are appropriate to guide policy making for self-management interventions in OA. First, QALYs in our study were fairly stable over time and consistent between groups (i.e. group difference was 0.01 (95% CI: -0.01; 0.02) and -0.00 (95% CI: -0.01; 0.01) for both QALY measures. This minor QALY difference is mainly driven by the insignificant change in both length of life and quality of life in both groups. Moreover, the generic EQ-5D-3L may not be sensitive to change to evaluate a self-management intervention in patients with knee/hip OA[17]. Clinical outcomes are more direct measures of

effect and might thus be more suitable to evaluate self-management interventions in knee/hip OA than QALYs. In my opinion, a trade-off between costs and clinical outcomes could also be worthwhile. Therefore, we performed not only a cost-utility analysis based on QALYs, but also used six different clinical outcomes. Results in this thesis showed that effects were larger for clinical outcomes than for QALYs, which seems logical, as these clinical outcomes are more related to the aim of the studied eHealth intervention than QALYs. This might suggest that for non-pharmacological conservative treatments in OA, clinical outcomes are more responsive to change over time than utility measures. For future economic evaluations, I recommend to perform both cost-utility analyses (to allow for broader comparisons across condition, treatments, and clinical settings) and cost-effectiveness analyses (enabling a trade-off between a range of benefits). Overall, the results in this thesis suggest that the dr. Bart app is cost-effective, albeit modest. Hence, from an economical perspective it would be reasonable to implement the dr. Bart app in clinical practice.

Implementation of cost-effective interventions

A considerable proportion of (cost-)effective interventions are not implemented in clinical practice after finishing a scientific research project. The overarching problem is who is responsible for implementing the new intervention, and thus, who takes the lead. There are several possibilities to apply the dr. Bart app in clinical practice. Health care professionals (e.g. GP and physical therapist) could offer each OA patient the dr. Bart app to stimulate healthy lifestyle behaviours right at the time of diagnosis. However, this is unattractive for both the GP and physical therapist as they feel not responsible for the integrated care of OA and are unable to perform integrated maintenance of such applications. The dr. Bart app could also be applied as a blended option within physical therapy, rather than as a stand-alone application. This, however, might substitute a part of the physical therapy consultations, which affects the revenues of practices. Even when the app would be freely available, health care providers might be reluctant to use such technologies, as this might substitute a part of their care delivery. Thus, for health care providers this is not a reasonable solution. Nevertheless, in an ideal situation, primary care should be responsible for all facets (e.g. transmural agreements and alignment) of OA care, which could be supported by eHealth. Another option might be to exploit the dr. Bart app with a commercial entrepreneur. Advantages of a commercial entrepreneur are that they have the knowledge and network to distribute an intervention on a broader scale and to maintain and improve technologic functionalities[18]. A disadvantage is that a commercial entrepreneur does not necessarily have the knowhow to provide reliable and up-to-date information regarding chronic diseases and its treatment options. For single stakeholders it seems unattractive to exploit the dr. Bart app, however a combination of a commercial entrepreneur with a thought leader on OA would be a reasonable option. To the best of our knowledge, business models for eHealth technologies are currently lacking, since none of the mentioned parties has incentives that outweigh the disadvantages to implement eHealth technologies. Therefore, new business models for eHealth technologies should be investigated as these are of importance for actual implementation of such technologies in clinical practice.

In hindsight, I do realize that I have focused on the content and evaluation of the dr. Bart app rather than on the actual implementation. Implementation of an intervention requires more than eagerness to get the app implemented. Therefore, I recommend to develop an implementation strategy together with a commercial entrepreneur and relevant

stakeholders (e.g. patients, health care professionals, policy makers, and health insurance companies) in parallel with the actual evaluation of an intervention to stimulate the use and uptake of eHealth technologies in clinical practice. This, however, requires commitment of all relevant stakeholders, as (cost-)effectiveness of an intervention is still to be determined while developing the implementation strategy.

Minimal clinical important difference (MCID)

The term clinical relevance is used to determine whether the observed change is perceived as beneficial or detrimental from the patients' or clinicians' perspective[19]. Although the MCID is a standard approach to assess change in health by means of patient reported outcomes, there is still discussion whether the MCID for a specific patient reported outcome should be a fixed value or not[20–25]. MCIDs for interventions in OA are predominantly based on surgical interventions[23,26,27]. Contextual factors such as costs, risk, and inconveniences of the intervention are not taken into account to determine whether the magnitude of treatment effects are clinically relevant, while different authors in epidemiologic research concluded that the MCID is context specific[20,21,23,28–30]. In my opinion, there is an important difference in the impact on patients of for example total joint replacement with months of rehabilitation versus the use of an eHealth application, like the dr. Bart app. Thresholds for beneficial effects should justify the use of the intervention in clinical practice with respect to costs and risks[28]. Results of our study regarding the dr. Bart app did not exceed the clinically relevant range (8-10) suggested in the literature for sub scales of either KOOS or HOOS[26]. As said, this range is based on surgical interventions, rather than on non-invasive interventions[23,26,27]. Currently, there is a lack of estimation of MCID thresholds for non-surgical interventions. Considering that the dr. Bart app can be easily incorporated in daily life, is non-invasive, relatively inexpensive, and safe, the magnitude of MCID should be (considerably) lower than for invasive, costly and relatively hazardous total joint replacement in my opinion. Moreover, traditional self-management interventions are uniformly recommended by international treatment guidelines[6,31,32], and show comparable small benefits as the dr. Bart app, while traditional interventions are more invasive than the use of a simple application. Thus, when taking into account contextual factors, implementation of the dr. Bart app is worthwhile. Since there is no such thing as a fixed value for beneficial effect of patient reported outcomes, I propose to establish separate MCID thresholds for non-invasive, non-pharmacological interventions, so that a range of context specific MCIDs are available.

Unforeseen hick ups in cross cultural science

In the scientific field we have shared values for the responsible conduct of research; honesty, accuracy, efficiency, and objectivity. Efficiency implies that resources are used wisely and research waste is avoided[33]. While executing my PhD project several (unforeseen) obstacles were encountered, so that a part of the study project suffered from loss of efficiency.

As described in *chapter 3*, we aimed to explore potential cultural differences in use, usability, and clinical outcomes of the dr. Bart app between the Netherlands and Germany. As variations in culture could influence provision of information in consultations with a health care professional, internet use and information seeking behaviour[34,35], we hypothesized that these cultural differences affect use, usability and clinical outcomes of the dr. Bart app. For that reason the study regarding the dr. Bart app originally comprised three arms (of which one arm in Germany), aiming to include 161 participants in each arm. In the Netherlands, patients

were randomly allocated to usual care or dr. Bart app and in Germany all participants were to receive the dr. Bart app. In order to tailor the research project to the German situation, German colleagues participated in the project group; a communication adviser, a non-medical involved person, a medical doctor, and a physical therapist contributed to the theoretical framework of the app, (graphical) design, and translation process of the app, as well as recruitment strategies.

Despite extensive efforts, we were not able to recruit sufficient patients in Germany (i.e. 28 signed informed consent after 8 months of recruiting). Therefore, the project group had to decide to terminate the German study arm before the aimed number of participants was included. Consequently, we were not able to explore potential cultural differences regarding use, usability, and clinical outcomes between the Netherlands and Germany. It is therefore important to critically reflect on the question: was this avoidable? And what are the lessons learned from this disillusionment?

While executing the study, two unforeseen obstacles were identified. First, ethical approval for the conducted study was asked and waived by the local Medical Research Ethics Committee of the Radboud University Medical Centre within two weeks after submission. In Germany, ethical approval took more than one and a half year. The ethical board in Germany seems to be more reluctant with regard to novel eHealth technologies and privacy regulations than the Netherlands, though both are members of the European Union. As the study in the Netherlands fell outside the remit of the law for Medical Research Involving Human Subjects, only a liability insurance was necessary, while according the German ethical board we needed full insurance for all participants. Due to delayed ethical approval, the timeframe to include German participants was short. Second, the inclusion rate in Germany was disappointing. Despite extensive recruitment strategies from May 2019 till January 2020 in Germany, we were not able to include the aimed number of 161 participants. Altogether, 97 participants were considered eligible, 28 gave informed consent, of whom 23 participants completed baseline assessment in Germany. It would have taken us approximately another three extra years in order to include 161 participants with such an inclusion rate. We are not able to make a proper comparison with the Dutch inclusion rate, as we do not exactly know how many people we reached with our Dutch recruitment strategy. Nevertheless, in the Netherlands we were able to include 427 participants within 6 months of recruitment. Thus, it seems that German patients were more reluctant to participate in this study than Dutch patients. There are several possible explanations for the reduced willingness to participate; first, German ethical board considered it necessary that informed consent consisted of detailed information regarding privacy regulations, whereas in the Netherlands it suffices to give this information in the information letter regarding the study. Paying attention to privacy regulations may have caused unjustified anxiety or detrimental attitudes towards privacy of the app and the electronic data capture system (CastorEDC). Moreover, the German ethical board deemed it necessary that the insurance for participants was also mentioned in the information letters and informed consent. Again, this might have caused unjustified anxiety to participate.

Lessons learned

Considering the fact that ethical approval took long, we should have planned the study preparation more rigorously. Moreover, we should have identified whether German patients are willing to endorse online self-management programs by using an eHealth application

rather than a group self-management program or face-to-face sessions with a health care professional. In hindsight, we should have included German patient representatives in our project group right from the start to guide development of the study and the app. So, in the Netherlands we performed research with patients rather than research on patients, whereas in Germany the opposite was true. In future studies I advocate to cooperate with patients from across borders as soon as possible in the research process to avoid research waste. In addition, I propose to conduct a pilot study in situations where researchers are less familiar with.

In summary, we were not able to include sufficient participants in Germany to explore potential cultural differences in use, usability, and clinical outcomes of the dr. Bart app between the Netherlands and Germany. Besides unused data, we spent considerable time, effort and money which could have been used in other projects, and this all could thus be regarded as research waste, see Table 1. However, in my opinion this research waste was unforeseen and thus unavoidable. It was a difficult decision to terminate the German part of the study, but I think the project group made a thoughtful decision as more research waste was lurking and thus prevented. Although this international collaboration did not answer part of our research questions, hopefully our knowledge, experiences, and lessons learned will help avoid future research waste. In order to prevent others facing the same problems, we shared our "lessons learned" with the funding agency of this project (INTERREG-programme, receiving financial support by the European Union), whose main goal is supporting cross-border cooperation between countries.

Table 1. Research waste in German part of the study

	Activity	Resources spent by research team	Resources spent by others
Making German version of the dr. Bart app	Technical adaptation to make app bilingual	Time, money	Time
	Translation of the app	Time, money	Time
	Extend maintenance period	Money	Time
Research protocol	Writing	Time, money	
	Ethical approval	Time, money	Time
Preparing data collection	Translation of questionnaires	Time, money	Time
	Preparation of electronic data capture system	Time, money	
	Tailor recruitment to German situation	Time, money	
Recruiting participants	Advertisements in local newspapers	Time, money	Time
	Social media campaigns	Time, money	Time
	Brochures in the physiotherapy practice (hospital and practices) and over the counter pharmacist	Time, money	Time
	Google Adwords	Time, money	Time
Collected data	Data collection	Time, money	Time and effort of participants

Personal deliberation

As I am writing the final parts of this thesis (i.e. general introduction and discussion), I am in a partial lock down because of the COVID-19 pandemic. Before the outbreak, clinical practice was that health care professionals gave face-to-face consultations in the outpatient department of hospitals, and in the physical therapy setting as well. However, quite fast after patient zero in the Netherlands, most hospitals decided that elective care should go to the background for a while, in order to provide backup for the COVID-19 units. A shift in working activities was considered necessary to deliver appropriate care for the masses of COVID-patients to be expected. In my residence hospital (Sint Maartenskliniek, Nijmegen) for example, we normally deliver care for patients with rheumatologic, orthopaedic and rehabilitation disorders. However, due to the pandemic, we scaled up to care for COVID-19-patients. It is really interesting to see how creative people are in times of great despair; health care professionals – not directly occupied with virus – were able to deliver (remote) care without physical contact within one week either by phone or digital solutions. At the moment it is still uncertain how long we will be gripped by this novel virus. As a result, digital consultations may become more common practice. So, I hope that this outbreak, despite its horrific consequences on health, economy, and health care sector among others, gives eHealth a kick-start, as this is the time to embrace and change attitudes regarding eHealth by both patients and health care professionals. In addition, the partial lock down because of the COVID-19 pandemic affects everyone's physical and mental well-being. Therefore, this period might be an excellent opportunity to encourage healthy behaviours by applying the tiny habits methods.

Future research and implementation

The research described in this thesis highlights several topics that need to be explored further:

- New evaluation methodologies which comply with the iterative design process of digital interventions are warranted.
- The magnitude of minimal clinically important differences for non-invasive, non-pharmacological interventions should be determined.
- Both long term effectiveness and cost-effectiveness of (stand-alone) eHealth interventions should be investigated.
- New business models for eHealth technologies should be investigated as these are of importance for actual implementation of such technologies in clinical practice.

To conclude

Findings in this thesis contribute to the evidence that effects of self-management programs for patients with knee/hip OA are small, also when delivered via novel eHealth pathways without human support, but probably cost-effective. In view of the prevalence of OA, the non-invasive character, low cost and adoption of this eHealth intervention, the dr. Bart app can be applied as primary approach for patients with knee/hip OA, which should be embedded in the continuum of prevention, care, and cure.

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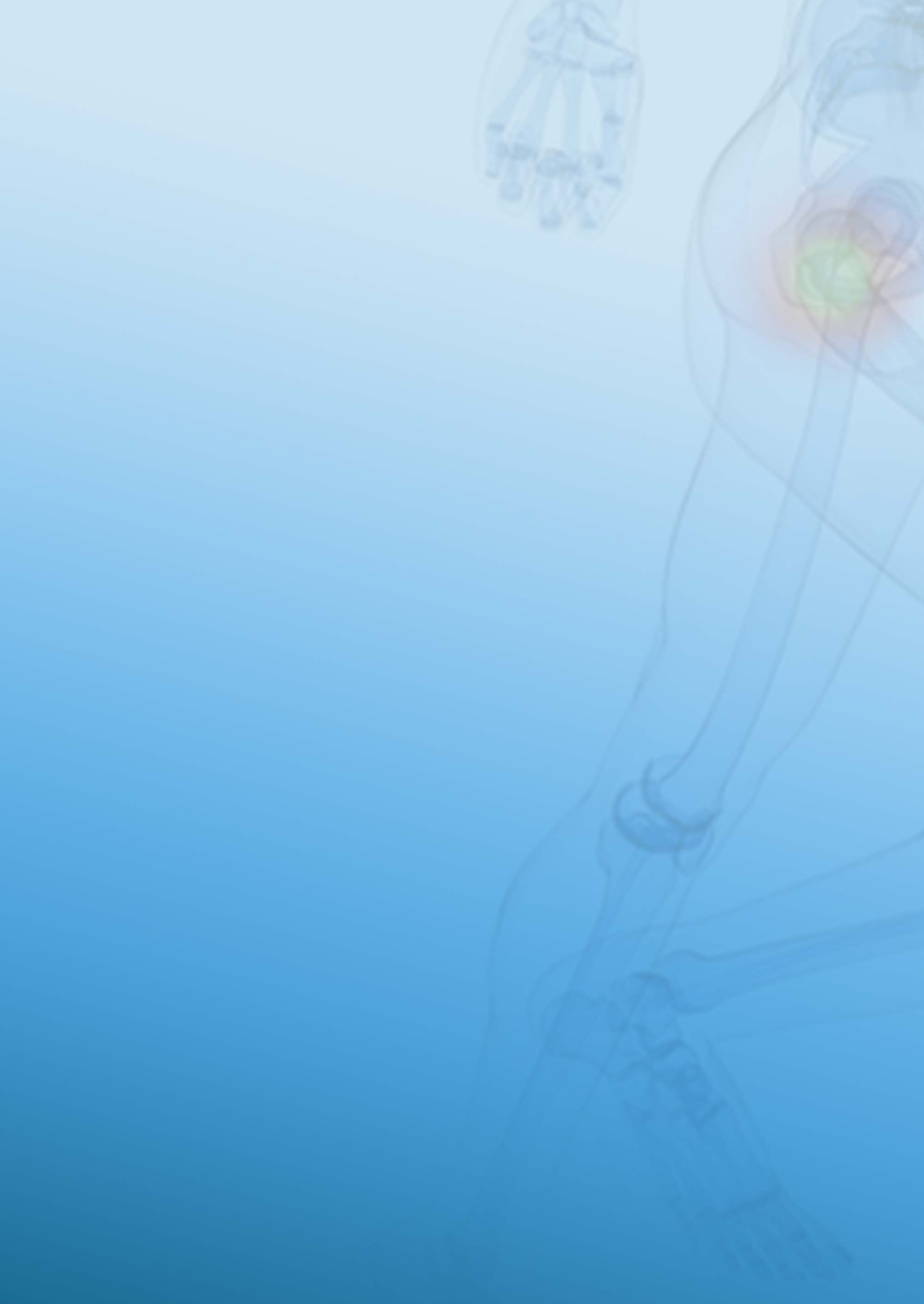
Chapter 8

Summary



Summary

As described in **Chapter 1**, osteoarthritis (OA) is the most prevalent form of disability of movement and posture. As a consequence, OA has a significant impact on both patients and society as a whole. So far there are no curative treatment options for OA, and therefore therapy focuses on reducing symptoms. In clinical practice a stepped care approach is adopted in which conservative treatment options, like education regarding OA, use of analgesics, and promotion of lifestyle changes (pacing of physical activity and exercise, weight loss) should be applied as primary approach. As OA is not curable, self-management is of major importance for patients with knee/hip OA. Modern technologies offer the possibility to support self-management at any time at any given place. Given the high potential of applications to support patients in taking an active role to manage their chronic condition in daily life, we iteratively and systematically developed a stand-alone self-management application: the dr. Bart app.

The main objectives of this thesis were:
- To provide insight in physical activity levels in different subsets of patients with OA and the general population and to compare the amount of physical activity among these subsets (**Chapter 2**)
- To describe the development and evaluation of a stand-alone e-self management intervention: the dr. Bart application (**Chapter 3**)
- To evaluate the effectiveness of the dr. Bart app compared to usual care (**Chapter 4**)
- To explore use and usability of this application and its relation with health care utilisation and clinical outcomes (**Chapter 5**)
- To study the cost-effectiveness of the dr. Bart app (**Chapter 6**)

There is undisputed evidence for the effectiveness of physical activity and exercise on pain and physical function for patients with knee/hip OA regardless of disease stage. Therefore, we described and compared in **chapter 2** the amount and nature of physical activity in different subsets of OA patients (i.e. primary care, secondary care, and after total joint arthroplasty) and the general population. By means of a secondary analysis of data of subjects aged 50 years and over from four studies: 1) a study on the effectiveness of an educational program for OA patients in primary care (n = 110), 2) an RCT on the effectiveness of a multidisciplinary self-management program for patients with generalised OA in secondary care (n = 131), 3) a survey among patients who underwent total joint arthroplasty for end-stage OA (n = 510), and 4) a survey among the general population in the Netherlands (n = 3,374). The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) was used to assess physical activity in all four studies. Differences in physical activity were analysed by multivariable linear regression analyses, adjusted for age, body mass index and sex. In all groups, at least one-third of total time spent on physical activity was of at least moderate intensity. Unadjusted mean duration (hours/week) of at least moderate-intensity physical activity was 15.3, 12.3, 18.1 and 17.8 for patients in primary, secondary care, post total joint arthroplasty, and the general population, respectively. Adjusted analyses showed that patients post total joint arthroplasty (TJA) spent 5.6 hours (95% CI: 1.5; 9.7) more on physical activity of at least moderate intensity than patients in secondary care. Moreover, the nature of activities was different among subsets: patients post TJA reported more often low-impact activities (e.g. aerobic exercise and cycling) than other OA patients and the general population. The self-reported amount of physical activity,

regardless of intensity, was high in all subsets of OA and the general population, with a substantial difference between patients in secondary care and post TJA patients. Although physical activity levels were high and comparable with the general population, it is well-known that physical activity has beneficial effects on OA symptoms. Thus, continued efforts are needed to enhance physical activity in patients with different stages of OA.

Chapter 3 describes the development of an eHealth intervention (dr. Bart app) that aims to enhance self-management and to optimise non-surgical health care utilisation in patients with knee/hip OA. The dr. Bart app was developed in close collaboration with (medical) researchers, physicians, physical therapists, patient representatives, and app developers (including user experience expert). The dr. Bart app is a fully automated stand-alone eHealth application that is based on the Fogg model for behavioural change (i.e. the "tiny habits" method). The Fogg model utilises the concept of accumulating small goals to change behaviour and, ultimately, health outcome. The dr. Bart app invites users to select pre-formulated behavioural goals (i.e. "tiny habits") and triggers to a healthier lifestyle. These goals are related to four core elements in the non-surgical management of OA: education about OA and its treatment modalities, physical activity (both generic and OA specific information), vitality and nutrition. Users can select or discard goals; the app will propose goals until three goals are selected by the user. Once a goal is achieved, the app will propose new goals. The app proposes goals on the basis of machine learning techniques fed by data collected in a personal profile and previous choosing behaviour of the user, i.e. previous selection and discarding of goals. To reinforce app engagement and health behaviour, the dr. Bart app is augmented with motivation enhancing techniques; reminders, rewards, and self-monitoring. Both the (graphical) design and content of the dr. Bart app were developed in an iterative design process with sprints of three weeks, resulting in a beta version. Twenty-five persons from the target population were invited to pilot test this beta version. Simultaneously, feasibility and usability of the beta version were evaluated. Moreover, a user experience session was performed. After the pilot test and user experience session, further development took place, resulting in the final version of the dr. Bart app (version 1.3.7).

Chapter 3 also presents the protocol of a study with three arms comprising an unblinded randomised controlled trial on the (cost-)effectiveness of the dr. Bart app over six month compared to usual care in patients with knee/hip OA in the Netherlands and a controlled clinical trial in Germany. The aim was to include 161 participants per arm with self-reported knee/hip OA, who were recruited in the community. Eligible participants were randomly allocated to either control group (usual care) or the intervention group (dr. Bart app). Primary (number of secondary health care consultations) and secondary outcomes were assessed at baseline, after 3 and 6 months through online questionnaires. Data were analysed using negative binomial regression (number of visits to health care professional) and linear mixed models (measures of self-management, physical activity, quality of life, illness perceptions, and sub scales of KOOS/HOOS) corrected for baseline value.

Results from a randomised controlled trial

Chapter 4 presents the results of the randomised controlled trial that evaluated the effectiveness of the dr. Bart app over six months involving 427 patients with knee/hip OA in the Netherlands. We found no difference between groups in the number of secondary (i.e. orthopaedic surgeon, rheumatologist, or physician assistant) health care consultations

(incidence rate ratio (IRR) 1.20 (95% CI: 0.67; 2.19)). We found positive treatment effects of the dr. Bart app on symptoms (2.6 (95% CI: 0.4; 4.9)), pain (3.5 (95% CI: 0.9; 6.0)), and activities of daily living (2.9 (95% CI: 0.2; 5.6)) on a 0-100 scale, with higher score indicating fewer complaints, but not in any other secondary outcome. Improvements attributable to the dr. Bart app were relatively small and it is unknown whether these differences are clinically relevant, since thresholds for minimally clinical important difference for non-surgical interventions are lacking.

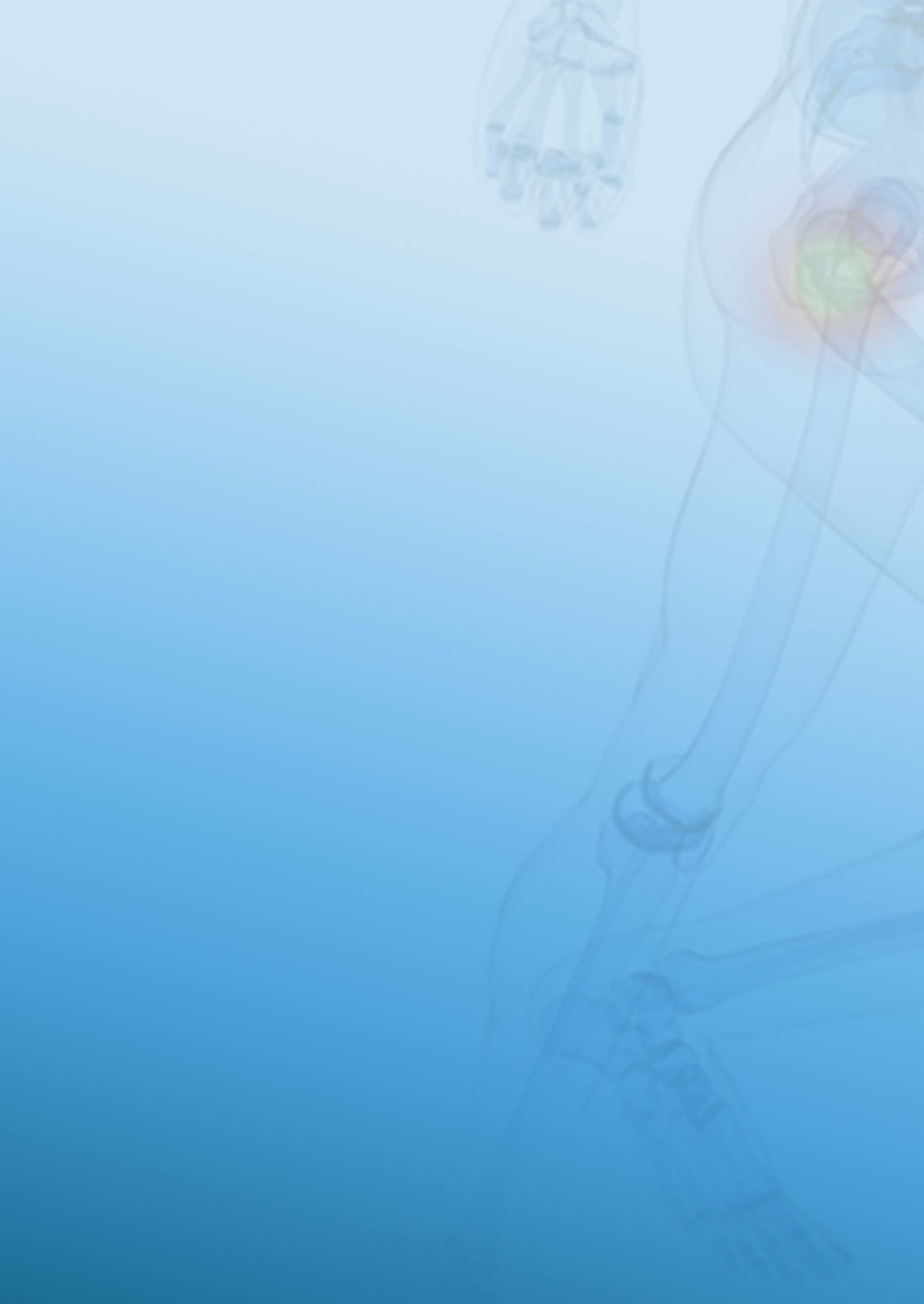
Chapter 5 deepens the insight in actual use and usability of the eHealth intervention and its relation with clinical outcomes. We used back-end data from the dr. Bart app group described in **Chapter 4** (n = 214). A central element of the dr. Bart app is that it proposes a selection from 72 pre-formulated health behaviour goals based on the "tiny habits" method. Goals can be completed more than once by the same user. To elaborate on the nature and extent of the eHealth intervention use, we classified use as follows 1) active with logins, but no further activity, 2) active with choosing goals, but did not complete goals, 3) active with completing ≥ 1 goals, and 4) the number of read paragraphs in the educational library (0-108). We used the System Usability Scale (SUS, 0-100) to assess usability of the eHealth intervention. Back-end data showed that 80%, 71%, and 53% opened the app, chose at least one goal and completed at least one goal, respectively. The two main features of the app were extensively used: goal setting and the educational library (including the exercise library). More than half of the participants completed at least one goal, of which goals related to physical activity and nutrition were most popular. This study also showed that users had specific interest in general information about OA, complaints, progression, and (non-pharmacological) conservative treatment options. This might offer a starting point for optimising patient education. After half a year, a quarter of users still used the app to set and complete goals and two-fifths of users still opened the app. Usability scores at both 3 (68.6 (SD 16.5)) and 6 (69.2 (SD 16.9)) months of follow-up did just not reach the acceptable score of 70. Contrary to expectations, no dose-response relationship between intensity of use and clinical outcomes was evident. Moreover, we were not able to find differences in baseline characteristics between those who were active with the eHealth intervention and who were less or inactive. In sum, the dr. Bart app is persistently used up to half a year by a considerable proportion of participants, but we were not able to find subgroups of those who were active with the app and those who were less or inactive. This confirms that a stand-alone eHealth intervention has the potential to reach a substantial amount of patients with knee/hip OA.

Besides the individual disease burden of OA, there is a substantial economic burden for individuals, health care, and society. Therefore, it is important to perform an economic evaluation alongside clinical evaluation, which might guide policy makers about uptake of novel treatments in routine care. In **chapter 6**, the cost-utility and cost-effectiveness of the dr. Bart app from a health care payer perspective is described, which was conducted alongside the RCT described in **chapter 4**. Participants were asked to report all OA related health care costs using self-reported health care utilisation questionnaires at baseline and at 3 and 6 months of follow-up. Quality adjusted life years (QALYs) were estimated using two utility measures, i.e. the EuroQol-5D-3L and EuroQol Rating (VAS) scale. Clinical outcome measures were: patient activation measure (PAM-13) and five sub scales of KOOS/HOOS. Cost and effect differences were estimated using longitudinal linear mixed models and cost-effectiveness acceptability curves. Total health care costs for the dr. Bart app group and control group were €439 and

€496 per patient, respectively. The estimated difference in total health care costs was non-significantly in favour of the dr. Bart app group (difference €-31 (95% CI: €-66; 3). QALYs were similar for both groups according to both EQ-5D and rating scale. The probability of the dr. Bart app being cost-effective compared to usual care according utility measures was 0.44 to 0.80 at WTPs of €10,000 to €80,000. The majority of clinical outcomes resulted in moderate to high chances (>80%) of dr. Bart app being cost-effective. This economic evaluation from a health care payer perspective shows that an eHealth intervention has moderate probability of being cost-effective. Since there was no significant difference in costs between groups, the decision whether or not to use the dr. Bart app can be based on the preferences of both the patient and health care provider.

Given the prevalence of OA, the non-invasive character of the application, adoption of the intervention, possible beneficial effects, and low costs, we concluded that the dr. Bart app can be applied as a primary approach for patients with knee/hip OA.

Lekensamenvatting



Lekensamenvatting

Artrose is een van de meest voorkomende gewrichtsaandoeningen die veelal voorkomt bij ouderen en vaker bij vrouwen dan bij mannen. Artrose kan in ieder gewricht voorkomen, maar de knie en heup zijn het vaakst aangedaan. In tegenstelling tot wat eerder werd gedacht is artrose een degeneratieve aandoening van het hele gewricht en alle omliggende structuren. De aandoening wordt gekarakteriseerd door pijn en stijfheid wat op termijn beperkingen geeft bij dagelijkse activiteiten en leidt tot een verminderde kwaliteit van leven. Artrose heeft daarom een aanzienlijke impact op zowel patiënten als de maatschappij. Tot nu toe is artrose niet te genezen, daarom richten behandelingen zich op het verminderen van symptomen. Beschikbare behandelingen met bewezen effectiviteit zijn informatievoorziening, leefstijlverandering, oefeningen, afvallen (bij overgewicht), pijnmedicatie of een operatie. Omdat artrose nog niet te genezen is en daarmee behoort tot de chronische aandoeningen, is het van wezenlijk belang dat patiënten zelf leren om te gaan met de consequenties van hun aandoening in het dagelijks leven en hun weg vinden in het gezondheidszorgsysteem, kortweg wordt dit zelfmanagement genoemd. De zorg voor patiënten met knie- en/of heupartrose vindt veelal plaats in de eerste lijn (bijvoorbeeld bij de huisarts, fysiotherapeut of diëtist). Hier hanteert men een zogenoemde getrapte zorgaanpak, dit betekent dat conservatieve behandelingen zoals informatie over artrose, gebruik van pijnstillers en het bevorderen van leefstijlveranderingen worden toegepast als eerste benadering. Mochten deze conservatieve behandelingen onvoldoende werken, dan worden patiënten doorverwezen naar het ziekenhuis, ook wel de tweede lijn genoemd (orthopeed of reumatoloog).

Nationale en internationale richtlijnen adviseren om patiënten te begeleiden naar een actieve rol in hun behandeling, bijvoorbeeld door middel van zelfmanagementprogramma's. Middels deze programma's worden patiënten ondersteund bij een betere omgang met hun symptomen. In de literatuur zien we dat bestaande zelfmanagementprogramma's kleine positieve effecten laten zien op pijn en functioneren in vergelijking met de reguliere zorg. Daarnaast zijn er aanwijzingen dat zelfmanagementprogramma's invloed hebben op zorggebruik. Digitale technologieën zoals mobiele applicaties maken het mogelijk toegang te hebben tot zelfmanagementprogramma's op ieder moment van de dag, 7 dagen per week, ongeacht locatie. Een ander belangrijk voordeel van deze technologieën is de potentie om kosten en tijd te besparen. Naast deze voordelen zijn er ook een aantal nadelen bij de inzet van digitale middelen: het gebruik en de bruikbaarheid ervan kunnen onbevredigend zijn. Hoewel digitale interventies dus veelbelovend lijken, hebben de meeste hun effectiviteit nog niet bewezen middels wetenschappelijk onderzoek. Gezien de grote mogelijkheden van zulke innovatieve technologieën om patiënten te ondersteunen bij het nemen van een actieve rol in het omgaan met de gevolgen van hun aandoening in het dagelijks leven, hebben we op systematische wijze een zelfmanagementapplicatie ontwikkeld: de dr. Bart app. De naam dr. Bart is gekozen omdat dit staat (acroniem) voor Behandelstrategie ARTrose.

De hoofddoelen van dit proefschrift waren:
- Inzicht geven in de hoeveelheid en aard van lichaamsbeweging in verschillende stadia van artrose in vergelijking met de algemene bevolking (**Hoofdstuk 2**).
- Het beschrijven van de ontwikkeling van de dr. Bart app en de studieopzet om deze app te evalueren (**Hoofdstuk 3**).
- Evalueren van de effectiviteit en kosteneffectiviteit van de dr. Bart app ten opzichte van de reguliere zorg bij patiënten met knie- en/of heupartrose (**Hoofdstuk 4** en **6**).
- Inzichtelijk maken van de relatie tussen het daadwerkelijke gebruik en bruikbaarheid van de dr. Bart app en klinische uitkomsten (**Hoofdstuk 5**).

Hoofdstuk 2

Er is onomstotelijk bewijs voor de effectiviteit van lichaamsbeweging en oefeningen op pijn en fysiek functioneren voor patiënten met knie- en/of heupartrose ongeacht het ziektestadium. Momenteel is er weinig bekend over de hoeveelheid en aard van lichaamsbeweging die artrosepatiënten daadwerkelijk uitvoeren. Daarom hebben we dit in **hoofdstuk 2** in kaart gebracht bij verschillende stadia van artrose (patiënten in de eerste lijn, patiënten in de tweede lijn en patiënten die een gewrichtsvervangende operatie ondergingen) en bij de algemene Nederlandse bevolking. Dit hebben we gedaan door gegevens over de mate van lichaamsbeweging van mensen met artrose van vier verschillende bestaande databases met deelnemers van 50 jaar en ouder opnieuw te analyseren:
- Database 1) bevatte gegevens over een onderzoek naar de effecten van voorlichting voor artrosepatiënten in de eerste lijn (110 patiënten)
- Database 2) bevatte gegevens over een onderzoek dat een multidisciplinaire groepsbehandeling met een telefonische behandeling voor patiënten met artrose in de tweede lijn vergeleek (131 patiënten)
- Database 3) bevatte gegevens over patiënten die een gewrichtsvervangende operatie ondergingen ten gevolge van eindstadium knie- en/of heupartrose (510 patiënten)
- Database 4) bevatte gegevens uit een enquête onder de algemene Nederlandse bevolking (3374 deelnemers).

Alle databases bevatten de zogenoemde 'Short Questionnaire to Assess Health-enhancing physical activity (SQUASH)' vragenlijst om lichaamsbeweging in kaart te brengen. In alle groepen vonden we dat tenminste een derde van de totale tijd die aan lichaamsbeweging werd besteed, minimaal matig intensief van aard was. De tijd die besteed werd aan lichaamsbeweging van minimaal matig intensieve aard lag tussen de 15 en 18 uur per week voor de verschillende groepen. Onze analyses toonden aan dat mensen die een gewrichtsvervangende operatie hadden ondergaan, substantieel meer tijd besteedden aan lichaamsbeweging dan patiënten die een dagbehandeling volgden in de tweede lijn. Daarnaast vonden we dat mensen na zo'n operatie vaker lichamelijke activiteiten ondernamen met minder impact op de gewrichten (fitness, fietsen) dan andere artrosepatiënten of de algemene bevolking. Hoewel de hoeveelheid lichaamsbeweging in alle groepen hoog was en vergelijkbaar met de algemene bevolking, is het alom bekend dat lichaamsbeweging bij artrose een gunstig effect heeft op symptomen. Daarom is het extra belangrijk om lichaamsbeweging te blijven adviseren bij patiënten met artrose, ongeacht het ziektestadium.

Hoofdstuk 3

In **hoofdstuk 3** beschrijven we de ontwikkeling van een zelfmanagementapplicatie (de dr. Bart app). Deze app heeft als doel het zelfmanagement te ondersteunen en het gebruik van niet-operatieve behandelingen bij patiënten met knie- en/of heupartrose te optimaliseren. De dr. Bart app is ontwikkeld in nauwe samenwerking met (medische) onderzoekers, artsen, fysiotherapeuten, patiënten en app-ontwikkelaars. De dr. Bart app is een volledig geautomatiseerde eHealth applicatie die gebaseerd is op het Fogg model voor gedragsverandering. Het Fogg model maakt gebruik van het concept dat het behalen van meerdere kleine doelen (zogenoemde 'tiny habits') resulteert in gedragsverandering wat uiteindelijk leidt tot gezondheidsverbetering. De dr. Bart app nodigt gebruikers uit vooraf geformuleerde gedragsdoelen, kleine gewoontes die in te passen zijn in het dagelijks leven, te selecteren en te behalen. Deze vooraf geformuleerde doelen zijn gerelateerd aan vier pijlers in de niet-operatieve behandeling van artrose: voorlichting over artrose en behandelmogelijkheden, fysieke activiteit (zowel algemene informatie als artrosespecifieke oefeningen), vitaliteit en voeding. Gebruikers kunnen uit de voorgestelde doelen kiezen. Zodra een doel behaald is, stelt de app nieuwe doelen voor. De doelen worden voorgesteld op basis van gegevens die zijn verzameld in een persoonlijk profiel en door de eerdere keuzes van de gebruiker. Om het gebruik van de app te stimuleren gebruikt de app verschillende motivatieverhogende technieken: herinneringen aan het behalen van de gekozen doelen, beloning in de app als men een doel behaald en een bijbehorende trofeeënkast in de app. Zowel de (grafische) vormgeving als de inhoud van de app zijn ontwikkeld in een iteratief ontwikkelproces. Dit resulteerde in een proefversie. Vijfentwintig personen uit de doelgroep werden uitgenodigd om deze proefversie gedurende een maand te testen. Naar aanleiding van het gebruik en feedback van deze groep hebben we laatste aanpassingen gedaan wat resulteerde in de definitieve versie van de dr. Bart app. Deze laatste versie is gebruikt in het hierna beschreven wetenschappelijk onderzoek.

Daarnaast beschrijven we in **hoofdstuk 3** uitgebreid het protocol dat uitlegt hoe we de wetenschappelijke studie hebben opgezet om de (kosten)effectiviteit van de dr. Bart app te bepalen. Om de (kosten)effectiviteit van de dr. Bart app aan te tonen hebben we gekozen om mensen met zelf-gerapporteerde artrose (op basis van een aantal vragen) een half jaar te volgen. Door middel van online vragenlijsten keken we of er na 3 en 6 maanden verschillen waren in het gebruik van zorg, zelfmanagementvaardigheden, lichaamsbeweging, kwaliteit van leven, functioneren in het dagelijks leven en symptomen.

Hoofdstuk 4

In **hoofdstuk 4** beschrijven en presenteren we de resultaten van het gerandomiseerde onderzoek onder 427 deelnemers met zelf-gerapporteerde knie- en/of heupartrose. Zij werden, voor een periode van zes maanden, willekeurig toegewezen aan:

- een groep die de dr. Bart applicatie ontving om zelf met hun ziekte aan de slag te gaan
- een groep die geen aanvulling op de reguliere zorg kreeg.

Onze aanname was dat het gebruik van de dr. Bart zou leiden tot minder tweedelijns zorggebruik ten gevolge van artrose (zoals een bezoek aan de reumatoloog of orthopedisch chirurg). Verder was onze aanname dat we verwachtten dat de klachten verminderden waardoor onder andere (dagelijkse) activiteiten beter uitgevoerd konden worden. We vonden geen verschil in het aantal consulten (in zowel eerste- als tweedelijns zorg) tussen patiënten

die de dr. Bart app hadden gekregen en de patiënten die de app niet ontvingen. Wel vonden we positieve effecten op symptomen, pijn en activiteiten in het dagelijks leven bij mensen die de app hadden gekregen. Deze verschillen waren echter klein, maar omdat het gebruik van een app niet-invasief is, kan de app toegepast worden als primaire benadering voor mensen met knie- en/of heupartrose.

Hoofdstuk 5

In **hoofdstuk 5** hebben we het daadwerkelijke gebruik van de dr. Bart app en de gebruiksvriendelijkheid van de app verder uitgediept. In **hoofdstuk 5** hebben we ook gekeken of er een verband was tussen de intensiteit van gebruik en het effect op klinische uitkomsten. Aanvullend hebben we gekeken of er factoren waren die voorspelden of iemand de app gebruikt. Om deze vragen te beantwoorden analyseerden we de gegevens van 214 app-gebruikers. Eén van de belangrijkste elementen van de dr. Bart app is dat deze steeds een selectie van 72 verschillende doelen voorstelt op basis van de 'tiny habits' methode. De gekozen doelen kunnen vaker dan 1 keer behaald worden door een gebruiker. Om het gebruik en de aard van het gebruik verder te beschrijven hebben we gebruikers van de app op 3 manieren geclassificeerd: 1) deelnemers die actief met logins zijn, informatie lezen, maar verder niet actief zijn in de app, 2) deelnemers die actief doelen kiezen, maar geen doelen behalen en 3) deelnemers die minimaal 1 doel behaald hebben. Daarnaast hebben we gekeken naar het aantal gelezen paragrafen uit de bibliotheek (0-108). De data toonde aan dat 80% de app opende, 71% tenminste één doel heeft gekozen en dat 53% minimaal één doel heeft behaald. Verder vonden we dat de twee belangrijkste elementen van de app intensief gebruikt werden: doelen stellen naar een gezondere leefstijl en de informatiebibliotheek (inclusief oefeningen). Meer dan de helft van de deelnemers behaalde minimaal één doel, waarvan doelen gerelateerd aan fysieke activiteit en voeding het meest populair waren. Daarnaast toonde deze studie aan dat patiënten met knie- en/of heupartrose vooral geïnteresseerd waren in algemene informatie over artrose, klachten, progressie en (niet-farmacologische) conservatieve behandelmogelijkheden. Dit zijn startpunten in het optimaliseren van patiëntenvoorlichting. Van de mensen die de app tenminste één keer gebruikten, is na een half jaar nog ruim een kwart actief in het kiezen en behalen van doelen. De gebruiksvriendelijkheid van de app scoorde niet heel hoog (68.6 na 3 maanden en 69.2 na 6 maanden, op een schaal van 0 tot 100). In tegenstelling tot onze verwachting, konden we geen relatie vinden tussen (intensiteit) van gebruik van de app en de invloed hiervan op uitkomstmaten. Daarnaast konden we geen karakteristieken van gebruikers aanwijzen die bepalend waren voor het wel of niet gebruiken van de app. Samenvattend: een aanzienlijk deel van de deelnemers gebruikt de dr. Bart app tot een half jaar na start van het onderzoek, maar we konden niet identificeren wie de dr. Bart app veel of minder gebruikte. Wel toont dit onderzoek aan dat een innovatieve applicatie de potentie heeft om een grote groep patiënten met knie- en/of heupartrose te bereiken.

Hoofdstuk 6

Voor beleidsmakers is het van belang dat klinische evaluaties van nieuwe therapieën of technologieën gepaard gaan met een economische evaluatie. Om deze reden beschrijft **hoofdstuk 6** de bevindingen van de economische evaluatie die is uitgevoerd naast de in **hoofdstuk 4** beschreven gerandomiseerde trial waarin we de dr. Bart app vergeleken met reguliere zorg voor patiënten met knie- en/of heupartrose. Zorgkosten direct gerelateerd aan de zorg voor artrose zijn gemeten met behulp van zelf-gerapporteerde vragenlijsten. Men

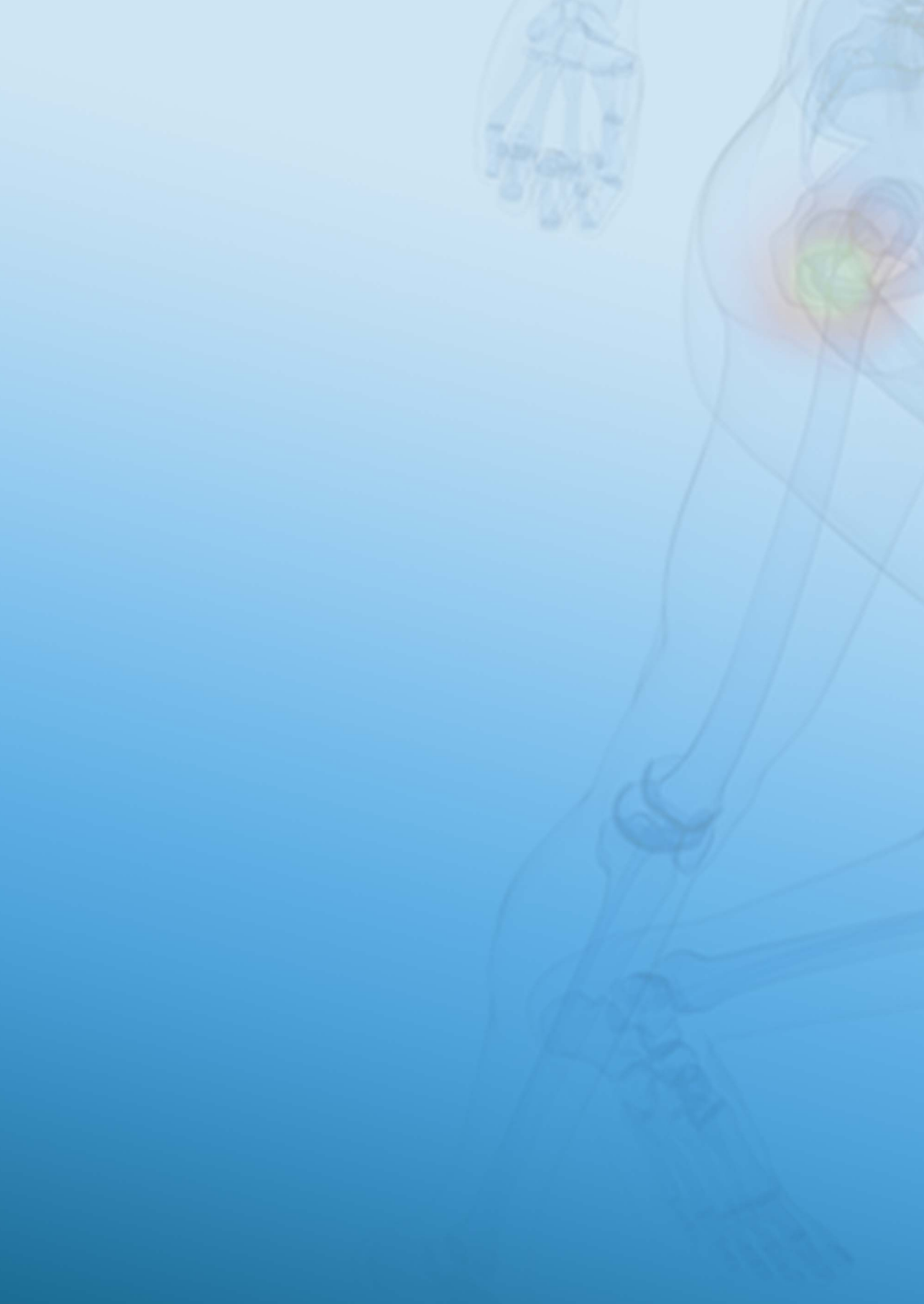
ontving deze online vragenlijsten bij aanvang van de studie en na 3 en 6 maanden. Hieruit bleek dat de artrose-gerelateerde zorgkosten gedurende een half jaar gemiddeld iets lager waren in de dr. Bart app groep dan in de reguliere zorg groep. Zoals beschreven in **hoofdstuk 4** vonden we kleine positieve effecten op symptomen, pijn en activiteiten in het dagelijks leven bij mensen die de app hadden gekregen. Als we dit combineren met de zorgkosten zien we dat de dr. Bart app een relatief grote kans heeft om kosteneffectief te zijn. Gezien de positieve effecten van de app kan de dr. Bart app worden toegepast als primaire benadering in de dagelijkse praktijk.

In **hoofdstuk 7** worden de belangrijkste bevindingen en voor de liefhebber de methodologische overwegingen besproken en bediscussieerd. Ook worden er een aantal implicaties voor de klinische praktijk en suggesties voor verder onderzoek gedaan.

De studies in dit proefschrift laten zien dat de dr. Bart app iets beter scoort op het gebied van symptoombestrijding dan de reguliere zorg. Deze verschillen waren klein en men kan zich afvragen of deze daadwerkelijk relevant zijn voor de patiënt. Met betrekking tot de kosten zijn de verschillen ook klein. Omdat er veel mensen met artrose zijn (in Nederland al meer dan een miljoen), is dit wel degelijk van maatschappelijk belang, ook met het oog op de alsmaar toenemende zorgkosten. Daarnaast liet ons onderzoek zien dat de app de mogelijkheid heeft om een groot publiek te bereiken en dat men de app dan ook relatief intensief gebruikt.

Concluderend, gezien het grote aantal patiënten, het niet-invasieve karakter van de dr. Bart applicatie, het draagvlak voor de applicatie, lage kosten en de kleine positieve effecten kan de dr. Bart app worden toegepast als primaire benadering in de dagelijkse praktijk voor patiënten met knie- en/of heupartrose.

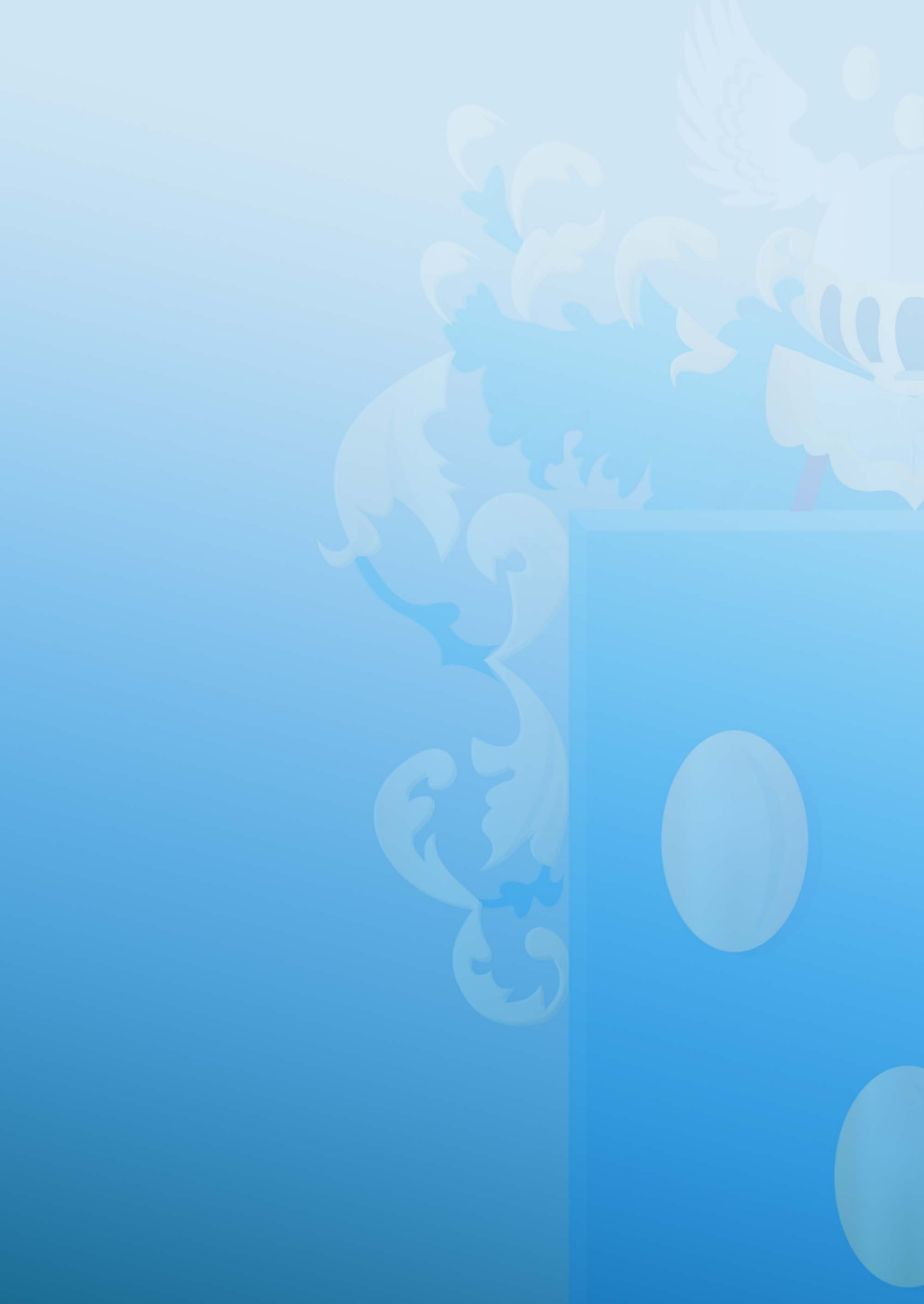
Dankwoord



Dankwoord

Een woord van dank aan eenieder die mij op enigerlei wijze - direct of indirect - van raad of daad heeft voorzien bij de totstandkoming van dit proefschrift: Bedankt!

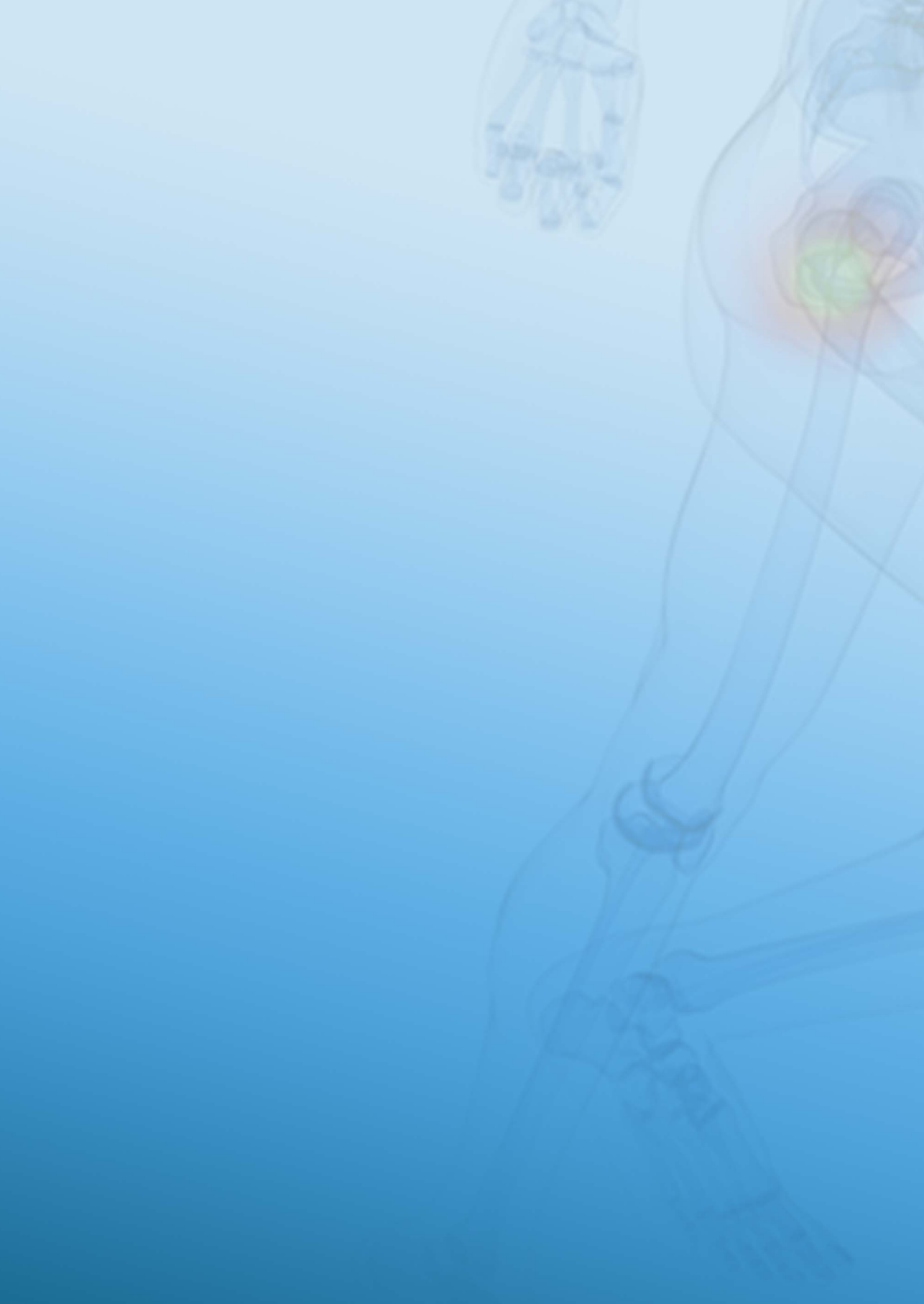
Curriculum vitae



Curriculum Vitae

Tim Pelle werd geboren op 23 juli 1991 te Eibergen. Hij groeide op in Eibergen met zijn ouders en zijn broer. In 2009 behaalde hij zijn middelbare school diploma aan het Assink Lyceum in Eibergen en Haaksbergen. In datzelfde jaar begon hij aan zijn studie Fysiotherapie aan Hogeschool Saxion te Enschede, met differentiatierichting musculoskeletale indicaties, waar hij ook zijn eerste wetenschapsvaardigen onderwezen kreeg. Na voltooiing van de studie Fysiotherapie in 2013 begon hij aan zijn pre-master voor de studie Biomedische wetenschappen aan de Radboud Universiteit Nijmegen, alwaar hij in 2014 zijn pre-master behaalde. Vervolgens startte hij in 2014 met de master 'Biomedical Sciences' met als hoofdvakken 'Clinical Human Movement Sciences' en 'Epidemiology' gecombineerd met een onderzoeksprofiel. Zijn masterstage voor het hoofdvak 'Clinical Human Movement Sciences' met de titel 'The SOFIE bicycle enhances comfort and balance in older cyclists' werd voltooid bij het Roessingh Research and Development in Enschede, onder begeleiding van dr. Rosemary Dubbeldam. Zijn masterstage voor het hoofdvak 'Epidemiology' met de titel 'Do sputum biomarkers provide a viable means of detecting (bacterial) pneumonia in mechanically ventilated patients in the ICU?' werd voltooid bij de Intensive Care afdeling van het Medisch Spectrum Twente onder begeleiding van prof. dr. Job van der Palen, dr. Bert Beishuizen en dr. Alexender Cornet. Gedurende zijn universitaire studie heeft Tim in verschillende eerstelijns fysiotherapiepraktijken in Nederland en Duitsland gewerkt. Na het behalen van zijn Master of Science graad in 2016 aan dezelfde universiteit, startte hij in 2017 met zijn promotieonderzoek bij de afdeling Reumatologie van de Sint Maartenskliniek Nijmegen, waar dit proefschrift het resultaat van is. Gedurende zijn promotietraject werd hij begeleid door dr. Els van den Ende, dr. Karen Bevers, prof. dr. Frank van den Hoogen en prof. dr. Job van der Palen. Na het behalen van zijn doctorsbul is Tim ook geregistreerd als 'Epidemioloog B'.

List of publications



List of publications

This thesis

Pelle T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Development and evaluation of a tailored e-self-management intervention (dr. Bart app) for knee and/or hip osteoarthritis: study protocol. BMC Musculoskeletal Disorders. 2019;20(1):398

Pelle T, Claassen A, Meessen J, Peter W, Vliet Vlieland T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Comparison of physical activity among different subsets of patients with knee or hip osteoarthritis and the general population. Rheumatology International. 2020 Jan;40(3):383-392.

Pelle T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Effect of the dr. Bart application on healthcare use and clinical outcomes in people with osteoarthritis of the knee and/or hip in the Netherlands; a randomized controlled trial. Osteoarthritis and Cartilage. 2020 Apr;28(4):418-427.

Pelle T, Bevers K, van den Hoogen F, van der Palen J, van den Ende C. Economic evaluation of the dr. Bart app in people with knee and/or hip osteoarthritis. *Manuscript submitted.*

Pelle T, van der Palen J, de Graaf F, van den Hoogen F, Bevers K, van den Ende C. Use and usability of the dr. Bart app and its relation with health care utilization and clinical outcomes in people with knee and/or hip osteoarthritis: back-end data of the intervention group of a randomized controlled trial. *Manuscript submitted.*

Other publications

Pelle T. Dossier knie- en heupartrose – Dr. Bart (app). Fysiopraxis. 2017 Okt;28-29.

Krikhaar N, **Pelle T**. Hulpmidel voor mensen met knie- en/of heupartrose – Praktische richtlijnen vanuit een app. ReumaMagazine. 2018 Apr;(3): 10-11.

Krikhaar N, **Pelle T**. Test en techniek in beeld – Praktische richtlijnen voor mensen met knie- en/of heupartrose. Fysiopraxis. 2018 Mei;24-25.

Pelle T. Education material BROK course for clinical investigators. 2020 *(Video)*

Pelle T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Reply to letter to the editor: 'effect of the dr. Bart application on healthcare use and clinical outcomes in people with osteoarthritis of the knee and/or hip in the Netherlands - a randomized controlled trial'. Osteoarthritis and Cartilage. 2020 Nov;28(11):1494-1496.

Conference abstracts

Pelle T, Claassen A, Meessen J, Peter W, Vliet Vlieland T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Comparison of physical activity between patients with different stages of osteoarthritis and the general population: a cross-sectional study. EULAR Amsterdam, 2018 *(poster presentation)* & NVR Najaarsdagen Arnhem, 2018 *(oral presentation)*

Pelle T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Study protocol of a randomized controlled trial and a controlled clinical trial. NVR Najaarsdagen Arnhem, 2019 *(Poster)*

Pelle T, van der Palen J, de Graaf F, van den Hoogen F, Bevers K, van den Ende C. Use of a self-management app (dr. Bart app) in people with knee and/or hip OA. NVR Najaarsdagen Arnhem, 2019 *(poster presentation)*

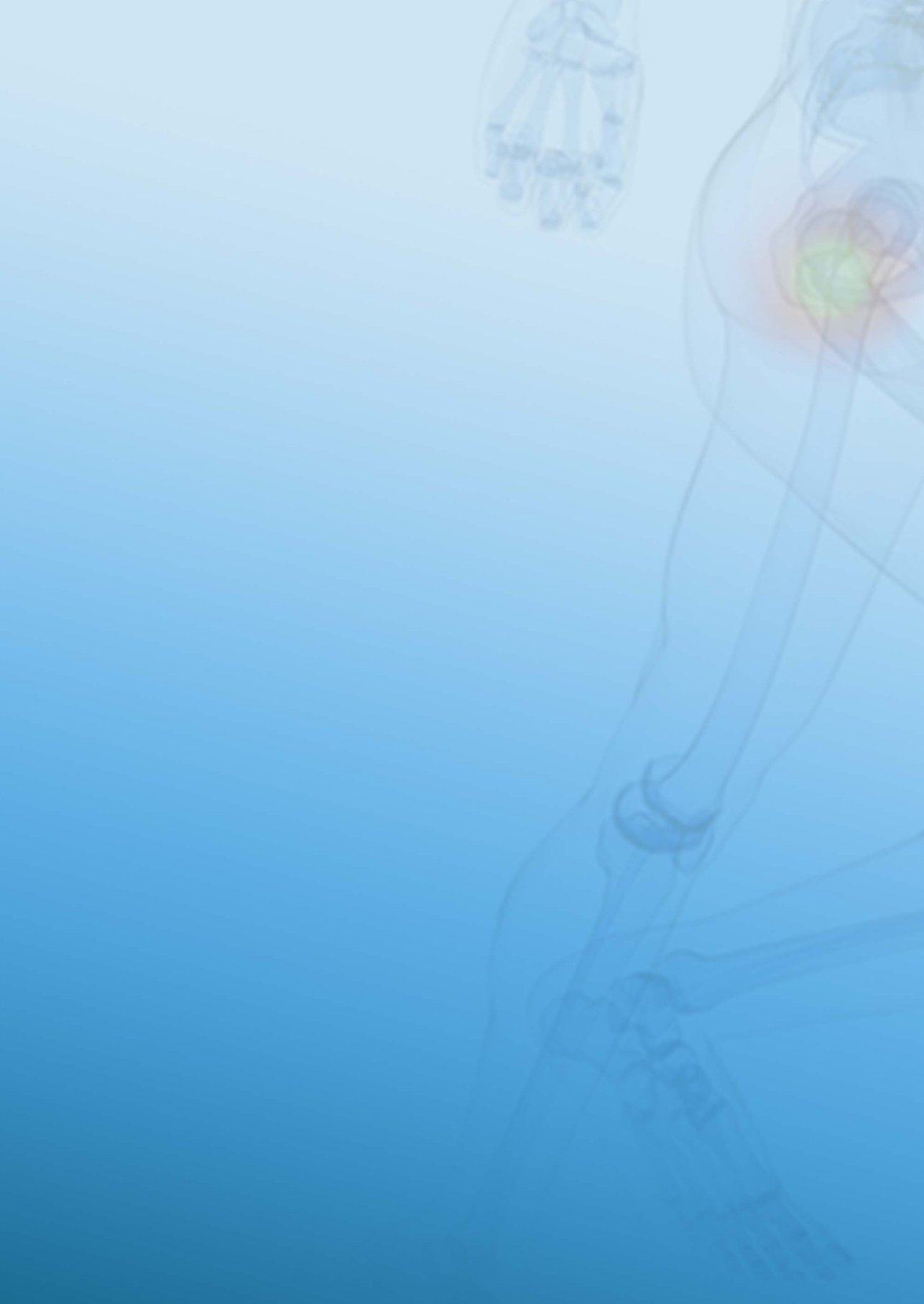
Pelle T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Effect of the Dr. Bart Application on Healthcare Use and Clinical Outcomes in People with Osteoarthritis of the Knee And/or Hip in the Netherlands; A Randomized Controlled Trial. American College of Rheumatology Annual Meeting, Atlanta, USA, 2019 *(oral presentation)*

Pelle T, Bevers K, van den Hoogen F, van der Palen J, van den Ende C. Economic evaluation of the dr. Bart app in people with knee and/or hip osteoarthritis. EULAR Frankfurt, digital, 2020 *(abstract book)*

Pelle T, van der Palen J, de Graaf F, van den Hoogen F, Bevers K, van den Ende C. Use and usability of the dr. Bart app and its relation with clinical outcomes in people with knee and/or hip osteoarthritis. EULAR Frankfurt, digital, 2020 *(poster presentation)*

Pelle T, Bevers K, van der Palen J, van den Hoogen F, van den Ende C. Effect of the dr. Bart application on healthcare use and clinical outcomes in people with osteoarthritis of the knee and / or hip in the Netherlands; a Randomized Controlled Trial. EULAR Frankfurt, digital, 2020 *(oral presentation)* **(Best abstract award)**

Research data management



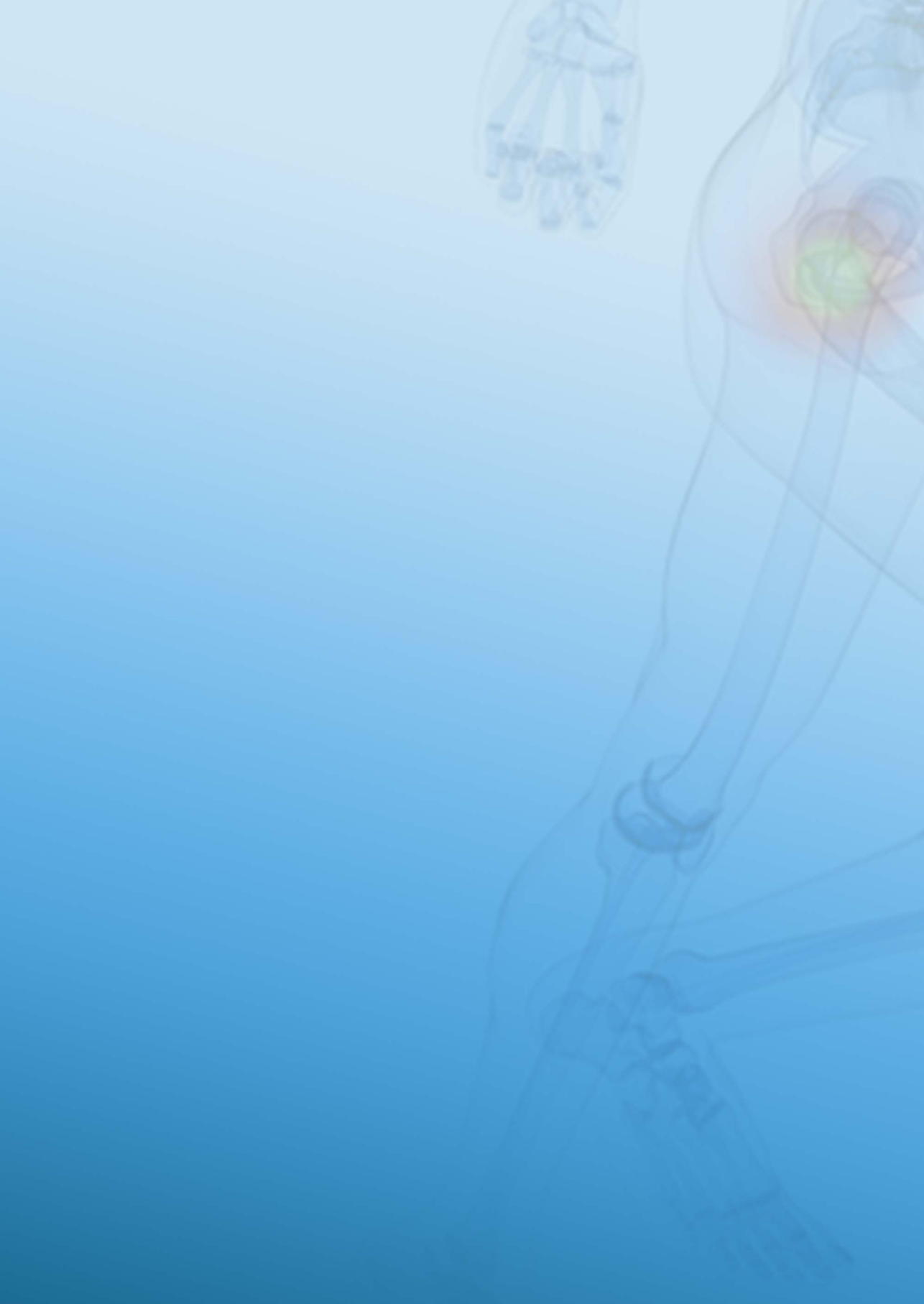
Research Data Management

All studies in this thesis were presented to the medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem-Nijmegen, the Netherlands. For all studies the review board provided a waiver as all studies fell outside the remit of the law for Medical Research Involving Human Subjects Act and were approved by the local ethical committees. Additionally, for the study in chapter 2, the local Medical Research Ethics Committee of the University Medical Centre, Leiden, the Netherlands, provided a waiver. In addition, the independent Deutsches Institut für Medizinische Dokumentation und Information (DIMDI) judged that the dr. Bart app is not a medical device (number 94.1.10–5660-11283). The German part of the study was approved by the Medical Research Committee of the 'Ethik-Kommission Ärztekammer Nordrhein' (protocol number: 2018-281). The study regarding the dr. Bart app is registered in the Dutch trial register (trial number: NTR 6693).

All subjects were well informed about the study and provided digital informed consent prior to participation, as collected with CastorEDC. The raw and processed data are stored on the Sint Maartenskliniek department server: (V:\) under reuma_research_studies and research_archief.

The privacy of the participants in all studies of this thesis is warranted by use of encrypted and unique individual subject codes. All data were converged to Stata (StataCorp LLC, College Station, Texas, USA) for analyses.

PhD portfolio



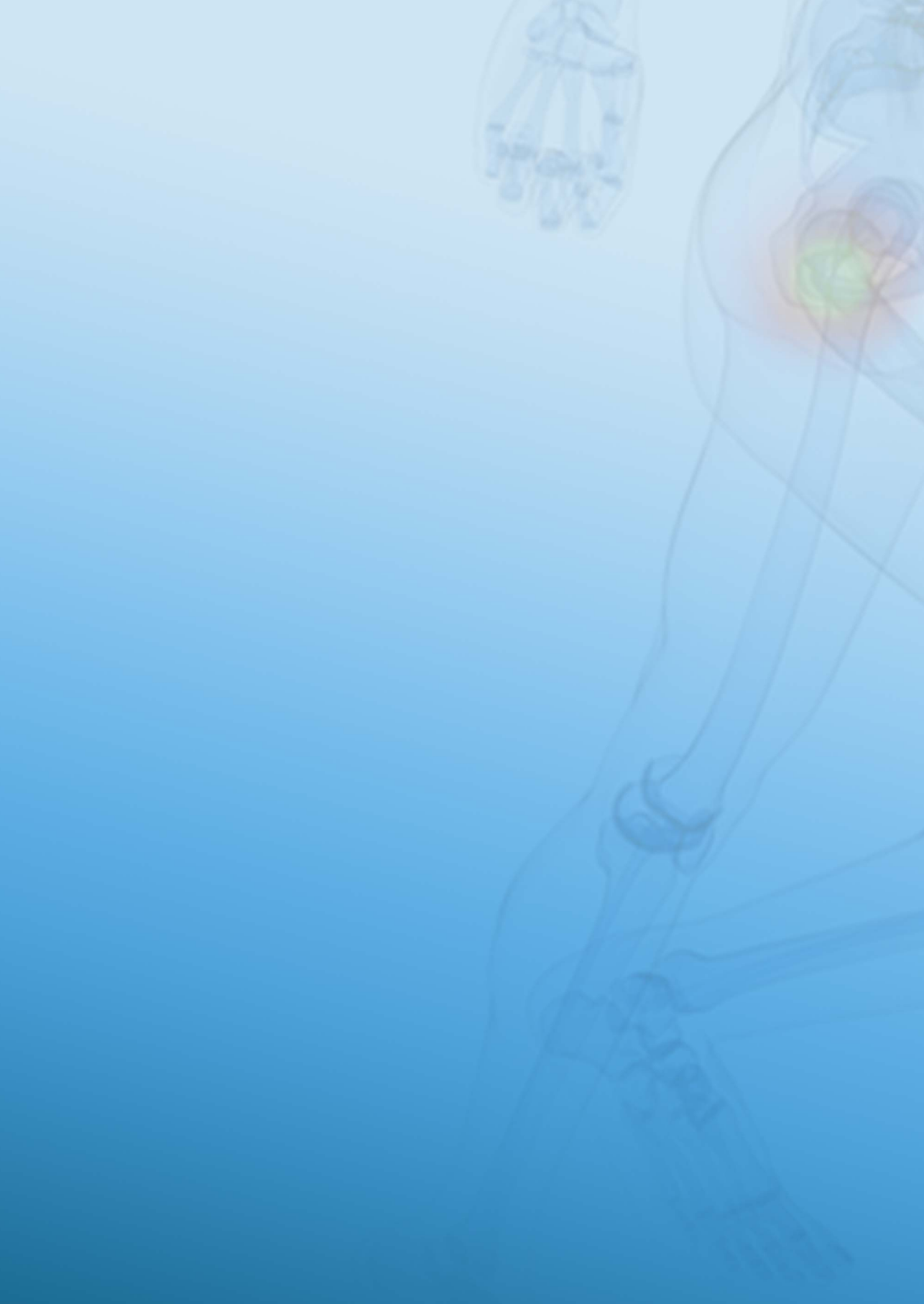
PhD portfolio

Name PhD candidate: T. Pelle	**PhD period:** 09-01-2017 – 07-01-2021
Department: Rheumatic diseases, Sint Maartenskliniek	**Promotor(s):** Prof. dr. F.H.J. van den Hoogen, Prof. dr. J. van der Palen
Graduate school: Radboud Institute for Health Sciences	**Co-promotor(s):** Dr. C.H.M. van den Ende, Dr. K. Bevers

		Year(s)	ECTS
	TRAINING ACTIVITIES		
a)	**Courses & Workshops**		
	• Graduate School specific introductory course (RIHS)	2017	0.5
	• BROK course	2017	1.5
	• Topics in Meta-analysis (Erasmus Summer Programme)	2017	0.7
	• Clinical trials (Erasmus Summer Programme)	2017	0.7
	• CiEP-cursus – Time/Project management	2018	2.5
	• Presentation skills	2018	1.5
	• Scientific writing for PhD-candidates	2018	3.0
	• Longitudinal data-analysis (EpidM)	2018	3.0
	• 'How to write a medical scientific paper?'	2019	0.1
	• Perfecting your academic writing skills	2020	1.5
	• Loopbaanmanagement voor promovendi	2020	0.6
	• Scientific integrity course	2020	1.0
b)	**Seminars & lectures^**		
	• Discussion & Drinks: 'Forensic epidemiology'	2017	0.1
	• Masterclass patient participatie	2017	0.1
	• Work visit from Sarah Hewlett / Emma Dures (UWE Bristol)	2017	0.25
	• Work visit from Krysia Dziedzic (Keele Univeristy)	2017	0.25
	• Seminar Discrete Choice Experiments	2017	0.1
	• CastorEDC workshop	2018	0.1
	• Scientific integrity (Lex Bouter)	2018	0.1
	• Work visit from George Peat (Keele University) (2019)	2019	0.25
	• Deutschland-Nederland Stakeholder Konferenz	2019	0.25
	• 'Carrièreperspectieven voor junior epidemiologen'	2019	0.1
	• Workshop statistiek	2019	0.1
	• 'Weten & Eten'	2017-2019	0.3
	• Various grand rounds (Radboudumc)	2017-2020	0.5
	• Radboud research Rounds	2017-2020	0.5
	• Various patient representatives symposia	2017-2020	0.5
	• Various 'Round Table conversations' EURegional forum– Grensoverschrijdende gezondheidszorg	2017-2020	0.5

c)	**Symposia & congresses^**		
	• Spine Symposium	2017	0.25
	• FEDERA-dag 2017	2017	0.25
	• Hacking health ('Hackathon')	2017	0.75
	• NVR conference	2017	0.25
	• EULAR Conference (Poster presentation)	2018	1.5
	• PhD Retreat	2018	0.5
	• NVR conference (Oral presentation)	2018	0.5
	• Health valley event (Presentation)	2019	0.5
	• WEON (Dutch Epidemiology Conference)	2019	0.5
	• ACR Annual Meeting (Presentation) Atlanta, USA	2019	1.75
	• NVR Conference (Poster presentation + poster)	2019	0.75
	• Treatment of rheumatic diseases: developments and opportunities symposium	2019	0.1
	• EULAR Conference (Oral presentation + poster)	2020	1.5
	• 'Verder in beweging' conference	2017-2020	1.0
	• Health valley event	2017-2018	0.5
	• Wetenschapsdag fysiotherapie	2018-2019	0.5
	• Digitalisierung Sorg (Oral presentation)	2017-2020	0.5
d)	**Other**		
	• **Abstract award** EULAR conference	2020	N/A
	• EULAR task force on RMD and remote care	2020	N/A
	• Schrijfdagen (3-day writing retreat)	2017-2020	1.5
	• Reumaclub – 'Kunst van het schrijven' (journal club)	2017-2020	1.0
	• Researchlunch (journal club)	2017-2020	1.0
	• 'Junior refereren epidemiologie' and Epidemiology journal club	2017-2020	7.0
	• Review scientific publications	2017-2020	0.5
	TEACHING ACTIVITIES		
e)	**Lecturing**		
	• 'PhD experience' – Master Biomedical Sciences (Epidemiology)	2020	0.1
	• Education material BROK course (Video)	2020	N/A
f)	**Supervision of internships/other**		
	• Supervision assignment 14 students – Master communication sciences	2017	0.25
	• Supervision assignment 16 students – Master communication sciences	2018	0.25
	TOTAL		**43.80**

Theses Sint Maartenskliniek



Theses Sint Maartenskliniek

Van Heuckelum, M. (2020). *Novel approaches to improve medication adherence in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Mathijssen, E. (2020). *The voice of patients with rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bakker, S. (2019). *Regional anesthesia and total knee arthroplasty. Anesthetic and pharmacological considerations.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Claassen, A. (2019). *Strategies for patient education in rheumatic diseases.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Fenten, M. (2019). *Optimizing locoregional anesthesia in fast track orthopaedic surgery.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Verhoef, L. (2019). *Effective and efficient use of bDMARDs in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Minten, M. (2019). *On the role of inflammation and the value of low dose radiation therapy in osteoarthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bekker, C. (2018). *Sustainable use of medication. Medication waste and feasibility of redispensing.* Utrecht University, Utrecht. The Netherlands.

Bikker, I.(2018). *Organizing timely treatment in multi-disciplinary care.* University of Twente, The Netherlands.

Bouman, C. (2018). *Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors.* Radboud University Nijmegen, The Netherlands.

Mahler, E. (2018). *Contributors to the management of osteoarthritis.* Utrecht University, The Netherlands.

Tweehuysen, L. (2018). *Optimising biological treatment in inflammatory rheumatic diseases. Predicting, tapering and transitioning.* Radboud University Nijmegen, Nijmegen, The Netherlands.

Geerdink, Y. (2017). *Getting a grip on hand use in unilateral cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

Remijn, L. (2017). *Mastication in children with cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

Selten, E. (2017). *Beliefs underlying treatment choices in osteoarthritis.* Radboud University, Nijmegen, The Netherlands.

Van Hooff, M. (2017). *Towards a paradigm shift in chronic low back pain? Identification of patient profiles to guide treatment.* VU University Amsterdam, Amsterdam, The Netherlands.

Lesuis, N. (2016). *Quality of care in rheumatology. Translating evidence into practice.* Radboud University, Nijmegen, The Netherlands.

Luites, J. (2016). *Innovations in femoral tunnel positioning for anatomical ACL reconstruction.* Radboud University, Nijmegen, The Netherlands.

Pakvis, D. (2016). *Survival, primary stability and bone remodeling assessment of cementless sockets. An appraisal of Wolff's law in the acetabulum*. Radboud University, Nijmegen, The Netherlands.

Schoenmakers, K. (2016). *Prolongation of regional anesthesia. Determinants of peripheral nerve block duration.* Radboud University, Nijmegen, The Netherlands.

Altmann, V. (2015). *Impact of trunk impairment on activity limitation with a focus on wheelchair rugby.* Leuven University, Leuven, Belgium.

Bevers, K. (2015). *Pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis.* Utrecht University, Utrecht, The Netherlands.

Cuperus, N. (2015). *Strategies to improve non-pharmacological care in generalized osteoarthritis.* Radboud University, Nijmegen, The Netherlands.

Kilkens, A. (2015). *De ontwikkeling en evaluatie van het Communicatie Assessment & Interventie Systeem (CAIS) voor het aanleren van (proto-)imperatief gedrag aan kinderen met complexe ontwikkelingsproblemen.* Radboud University, Nijmegen, The Netherlands.

Penning, L. (2015). *The effectiveness of injections in cuffdisorders and improvement of diagnostics.* Maastricht University, Maastricht, The Netherlands.

Stegeman, M. (2015). *Fusion of the tarsal joints: outcome, diagnostics and management of patient expectations.* Utrecht University, Utrecht, The Netherlands.

Van Herwaarden, N. (2015). *Individualised biological treatment in rheumatoid arthritis.* Utrecht University, Utrecht, The Netherlands.

Wiegant, K. (2015). *Uitstel kunstknie door kniedistractie.* Utrecht University, Utrecht, The Netherlands.

Willems, L. (2015). *Non-pharmacological care for patients with systemic sclerosis.* Radboud University, Nijmegen, The Netherlands.

Witteveen, A. (2015). *The conservative treatment of ankle osteoarthritis.* University of Amsterdam, Amsterdam, The Netherlands.

Zwikker, H. (2015). *All about beliefs. Exploring and intervening on beliefs about medication to improve adherence in patients with rheumatoid arthritis.* Radboud University, Nijmegen, The Netherlands.

Koenraadt, K. (2014). *Shedding light on cortical control of movement.* Radboud University, Nijmegen, The Netherlands.

Smink, A. (2014). *Beating Osteoarthritis. Implementation of a stepped care strategy to manage hip or knee osteoarthritis in clinical practice.* VU University Amsterdam, Amsterdam, The Netherlands.

Stolwijk, N. (2014). *Feet 4 feet. Plantar pressure and kinematics of the healthy and painful foot.* Radboud University, Nijmegen, The Netherlands.

Van Kessel, M. (2014). *Nothing left? How to keep on the right track. Spatial and non-spatial attention processes in neglect after stroke.* Radboud University, Nijmegen, The Netherlands.

Brinkman, M. (2013). *Fixation stability and new surgical concepts of osteotomies around the knee.* Utrecht University, Utrecht, The Netherlands.

Kwakkenbos, L. (2013). *Psychological well-being in systemic sclerosis: Moving forward in assessment and treatment.* Radboud University, Nijmegen, The Netherlands.

Severens, M. (2013). *Towards clinical BCI applications: assistive technology and gait rehabilitation.* Radboud University, Nijmegen, The Netherlands.

Stukstette, M. (2013). *Understanding and treating hand osteoarthritis: a challenge.* Utrecht University, Utrecht, The Netherlands.

Van der Maas, A. (2013). *Dose reduction of TNF blockers in Rheumatoid Arthritis: clinical and pharmacological aspects.* Radboud University, Nijmegen, The Netherlands.

Zedlitz, A. (2013). *Brittle brain power. Post-stroke fatigue, explorations into assessment and treatment.* Radboud University, Nijmegen, The Netherlands.

Beijer, L. (2012). *E-learning based speech therapy (EST). Exploring the potentials of E-health for dysarthric speakers.* Radboud University, Nijmegen, The Netherlands.

Hoogeboom, T. (2012). *Tailoring conservative care in osteoarthritis.* Maastricht University, Maastricht, The Netherlands.

Boelen, D. (2011). *Order out of chaos? Assessment and treatment of executive disorders in brain-injured patients.* Radboud University, Nijmegen, The Netherlands.

Heesterbeek, P. (2011). *Mind the gaps! Clinical and technical aspects of PCL-retaining total knee replacement with the balanced gap technique.* Radboud University, Nijmegen, The Netherlands.

Hegeman, J. (2011). *Fall risk and medication. New methods for the assessment of risk factors in commonly used medicines.* Radboud University, Nijmegen, The Netherlands.

Smulders, E. (2011). *Falls in rheumatic diseases. Risk factors and preventive strategies in osteoporosis and rheumatoid arthritis.* Radboud University, Nijmegen, The Netherlands.

Snijders, G. (2011). *Improving conservative treatment of knee and hip osteoarthritis.* Radboud University, Nijmegen, The Netherlands.

Vriezekolk, J. (2011). *Targeting distress in rheumatic diseases.* Utrecht University, Utrecht, The Netherlands.

Willems, P. (2011). *Decision making in surgical treatment of chronic low back pain. The performance of prognostic tests to select patients for lumbar spinal fusion.* Maastricht University, Maastricht, The Netherlands.

Aarts, P. (2010). *Modified constraint-induced movement therapy for children with unilateral spastic cerebral palsy: the Pirate group intervention.* Radboud University, Nijmegen, The Netherlands.

Groen, B. (2010). *Martial arts techniques to reduce fall severity.* Radboud University, Nijmegen, The Netherlands.

Van Koulil, S. (2010). *Tailored cognitive behavioral therapy in fibromyalgia.* Radboud University, Nijmegen, The Netherlands.

Van den Bemt, B. (2009). *Optimizing pharmacotherapy in patients with rheumatoid arthritis: an individualized approach.* Radboud University, Nijmegen, The Netherlands.

Van Nes, I. (2009). *Balance recovery after supratentorial stroke. Influence of hemineglect and the effects of somatosensory stimulation.* Radboud University, Nijmegen, The Netherlands.

Ruiter, M. (2008). *Speaking in ellipses. The effect of a compensatory style of speech on functional communication in chronic agrammatism.* Radboud University, Nijmegen, The Netherlands.

Baken, B. (2007). *Reflexion on reflexes. Modulation during gait.* Radboud University, Nijmegen, The Netherlands.

Gaasbeek, R. (2007). *High tibial osteotomy. Treatment of varus osteoarthritis of the knee.* Radboud University, Nijmegen, The Netherlands.

Koëter, S. (2007). *Patellar instability. Diagnosis and treatment.* Radboud University, Nijmegen, The Netherlands.

Langeloo, D. (2007). *Monitoring the spinal cord during corrective spinal surgery: a clinical study of TES-MEP.* Radboud University, Nijmegen, The Netherlands.

De Haart, M. (2005). *Recovery of standing balance in patients with a supratentorial stroke.* Radboud University, Nijmegen, The Netherlands.

Den Otter, R. (2005). *The control of gait after stroke: an electromyographic approach to functional recovery.* Groningen University, Groningen, The Netherlands.

Spruit, M. (2005). *Surgical treatment of degenerative disc conditions of the lumbar spine. Biomechanical, clinical and radiological aspects.* University Utrecht, Utrecht, The Netherlands.

Weerdesteyn, V. (2005). *From the mechanisms of obstacle avoidance towards the prevention of falls.* Radboud University, Nijmegen, The Netherlands.

Jongerius, P. (2004). *Botulinum toxin type-A to treat drooling. A study in children with cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

Van de Crommert, H. (2004). *Sensory control of gait and its relation to locomotion after a spinal cord injury.* Radboud University, Nijmegen, The Netherlands.

Van der Linde, H. (2004). *Prosthetic prescription in lower limb amputation. Development of a clinical guideline in the Netherlands.* Groningen University, Groningen, The Netherlands.

Hendricks, H. (2003). *Motor evoked potentials in predicting motor and functional outcome after stroke.* University of Nijmegen, Nijmegen, The Netherlands.

Hosman, A. J. F. (2003). *Idiopathic thoracic spinal deformities and compensatory mechanisms*. University of Nijmegen, Nijmegen, The Netherlands.

Donker, S. (2002). F*lexibility of human walking: a study on interlimb coordination.* Groningen University, Groningen, The Netherlands.

Hochstenbach, J. (1999). *The cognitive, emotional, and behavioural consequences of stroke.* University of Nijmegen, The Netherlands.

De Kleuver, M. (1998). *Triple osteotomy of the pelvis. An anatomical, biomechanical and clinical study.* University of Nijmegen, Nijmegen, The Netherlands.

Van Balen, H. (1997). *A disability-oriented approach to long-term sequelae following traumatic brain injury. Neuropsychological assessment for post-acute rehabilitation*. University of Nijmegen, Nijmegen, The Netherlands.

Tromp, E. (1995). *Neglect in action: a neuropsychological exploration of some behavioural aspects of neglect.* University of Nijmegen, Nijmegen, The Netherlands.

Van Lankveld, W. (1993). *Coping with chronic stressors of rheumatoid arthritis.* University of Nijmegen, Nijmegen, The Netherlands.

Geurts, A. (1992). *Central adaptation of postural organization to peripheral sensorimotor impairments.* University of Nijmegen, Nijmegen, The Netherlands.

De Rooij, D. (1988). *Clinical and serological studies in the connective tissue diseases.* University of Nijmegen, Nijmegen, The Netherlands.

Sint Maartenskliniek