Self-directed m-health exercise interventions for patients with knee osteoarthritis: Insights from a mixed methods evaluation

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„Wege entstehen dadurch, dass man sie geht."
(Franz Kafka)

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List of abbreviations

1 RM	One-Repetition Maximum
ACSM	American College of Sports Medicine
App	Application
BCT	Behavioral Change Technique
BfArM	Bundesministerium für Arzneimittel und Medizinprodukte, Federal Institute for Drugs and Medical Devices
CI	Confidence Interval
DiGA	Digitale Gesundheitsanwendung, digital health application
DiGA directory	Directory of reimbursable digital health applications (DiGAs)
DVG	Digitale-Versorgung-Gesetz, Digital Healthcare Law
e-health	Electronic health
FITT	Frequency, Intensity, Time, and Type
HrQoL	Health-related Quality of Life
ICT	Information and Communication Technologies
IPD	Individual Participant Data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Institute for Quality and Efficiency in Health Care
KOOS	Knee Injury and Osteoarthritis Outcome Score
KOOS-PS	Shortened version of the Knee Injury and Osteoarthritis Outcome Score exclusively designed for the evaluation of knee function

MCID	Minimal Clinically Important Difference
m-health	Mobile health
MIC	Minimal Important Change
MID	Minimal Important Difference
NNT	Numbers Needed to Treat
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OR	Odds Ratio
PDA	Personal Digital Assistant
PROM	Patient-Reported Outcome Measure
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristics
RPE	Rating of Perceived Exertion
RR	Risk Ratio
SEM	Standard Error of Measurement
SMD	Standardized Mean Difference
SWE	Smallest Worthwhile Effect
VAS	Visual Analog Scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Arthritis Index

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1 Introduction

1.1 Problem statement

Osteoarthritis (OA) is a highly prevalent, degenerative joint disease and one of the leading causes of global disability (Cross et al., 2014). Almost 18% of German adults suffer from OA (Fuchs et al., 2017), with a higher incidence observed in individuals with female sex, higher age, and higher body mass index (Fuchs et al., 2017; Steinmetz et al., 2023). In particular, the knee joint is the most frequently affected (Steinmetz et al., 2023). Alongside the progression of the disease, patients experience increased pain, limitations in physical function, and a reduction in quality of life (Fuchs et al., 2017; Zhang et al., 2010). Nevertheless, patients' disease progression can still exhibit considerable variation. In the management of knee OA, clinical guidelines worldwide outline exercise and education as first-line treatment (Conley et al., 2023). Thereby, different exercise types (e.g. strengthening, balance, aerobic, mind-body activities) and delivery modes (e.g. non-digital supervised training, home training, digital-based training) have been demonstrated to be effective in reducing pain and improving physical function (Fransen et al., 2015). However, despite the consensus on the importance of exercise in the treatment of patients with knee OA, considerable discrepancies exist regarding the implementation and accessibility of exercise programs within healthcare settings. To date, less than 40% of patients with hip, knee, or polyarticular OA receive prescriptions for therapeutic exercise (Hagen et al., 2016; Jacobs et al., 2021). Consequently, the implementation of alternative care models, such as the use of digital health technologies, offers a promising pathway to address these deficiencies in the future. A key benefit of this approach can be observed in their simple accessibility and high flexibility, allowing individuals to exercise at any location and time (Chen et al., 2021; Cronström et al., 2019). Furthermore, various features of digital programs can facilitate exercise conduction without supervision, including prompts to support adherence to exercise programs, exercise videos and instructions for in-depth guidance on how to exercise correctly, and feedback mechanisms (e.g. biofeedback via motion sensors) (Nelligan et al., 2020). The findings from recent meta-analyses indicated that digital-based exercise interventions for patients with knee OA have demonstrated comparable beneficial effects on pain to those of non-digital, face-to-face interventions, and were even superior to usual care (Chen et al., 2021; Yang et al., 2023). Divergent findings were reported in terms of improvements in physical function (Chen et al., 2021; Yang et al., 2023). However, there is no one-size-fits-all solution. Individuals prefer varying levels of human support and have different prerequisites and needs (Nelligan et al., 2020). Accordingly, it is imperative to distinguish between various digital-based exercise delivery modes, including supervised

blended care models (a hybrid format of in-person and electronic health (e-health) or mobile health (m-health) intervention), supervised synchronous or asynchronous e-health or m-health interventions, and self-directed e-health or m-health interventions. Thereby, m-health (e.g. applications [apps]) can be classified as a subgroup of e-health (e.g. web-based platforms, videoconferencing tools, telephone), with a specific focus on mobile communication tools (Nacinovich, 2011). To date, in meta-analyses and systematic reviews evaluating the effectiveness of digital-based exercise programs, distinctions between the various delivery modes have been reported only in subgroup analyses involving a small number of studies. Thereby, differences in intervention duration and the type of intervention lead to high heterogeneity between studies and low quality of evidence (Chen et al., 2021; Yang et al., 2023). To account for the small subgroups, more studies with large sample sizes are needed to improve the certainty of evidence and acceptability of the various exercise delivery modes. Another challenge for digital health technologies can be seen in their successful implementation into clinical routine. In this regard, appropriate reimbursement strategies are needed. In Germany, the so-called fast-track process for digital health applications (Digitale Gesundheitsanwendung, DiGA) allows physicians to prescribe approved DiGAs that are listed in a DiGA directory. However, a prerequisite for approval is the demonstration of a positive care effect (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023).

Consequently, the project presented in this dissertation aimed to address parts of the research gap by providing additional data on the subgroup of self-directed m-health exercise interventions. In this context, a mixed-methods design was employed to examine the effects on clinical outcomes, adherence, usability, satisfaction, and safety, and to evaluate patients' experiences when using the self-directed m-health exercise intervention re.flex in patients with knee OA. For this purpose, three studies were conducted. The first was a pilot randomized controlled trial (RCT) for the evaluation of the efficacy and the acquisition of early insights into the research question, study design, and intervention. The second was a qualitative study for the evaluation of patients' experiences, usability, and acceptability, and the third was a confirmatory RCT with a larger sample size to evaluate the effectiveness. Simultaneously, these studies were designed to evaluate whether re.flex can demonstrate a clinically relevant positive care effect in the context of an application for approval in the DiGA directory.

1.2 Structure of the dissertation

The formal structure of this cumulative, publication-based dissertation is divided into three main parts. The first part of the work provides the theoretical background, the context, and the research questions (see chapter 2 and 3). The second part of the thesis includes the scientific

program, which consists of three studies and a study protocol. All of these refer to the evaluation of a self-directed m-health exercise intervention in patients with knee OA and were conducted in the context of a research project in the Department of Sports Medicine at the University Hospital Tübingen. The scientific program is presented in four research articles that have been published in international peer-reviewed journals (see chapter 4). Finally, the third part of the present work provides a comprehensive discussion on the results of the scientific program, contextualizing the findings within the current state of research in the literature (see chapter 5).

2 Theoretical background and state of research

2.1 Knee osteoarthritis

OA is a degenerative joint disease and a leading cause of global disability (Cross et al., 2014). By definition, OA is characterized by the progressive destruction of joint cartilage, accompanied by the simultaneous impact on almost all joint structures (e.g. ligaments, synovium, joint capsule, bones) and the surrounding musculature (Deutsche Gesellschaft für Orthopädie und Unfallchirurgie e. V., 2024). The global burden of OA increases continuously and by 2020 already 7.6% of the global population (equivalent to 595 million individuals) were affected (Steinmetz et al., 2023). In Germany, 17.9% of German adults suffer from OA (Fuchs et al., 2017). Overall, the prevalence rate of OA increases with female sex, higher age and higher body mass index (overweight and obesity) (Fuchs et al., 2017; Steinmetz et al., 2023). Consequently, almost half of the female (48.1%) and one third (31.2%) of the male German population within the age group >65 years are affected. Further risk factors associated with OA include biomechanical stress caused by overload or malalignment, previous injuries, inactivity, and genetic predisposition (Fuchs et al., 2017). Although, OA may occur in various joints (e.g. knee, hip, hand), the knee joint is the most commonly affected (Steinmetz et al., 2023). With disease progression, knee OA is accompanied by an increase in pain, and limitations in physical function and daily activities (e.g. stair climbing, walking), leading to a subsequent reduction in quality of life (Fuchs et al., 2017; Zhang et al., 2010). Other symptoms experienced by patients may include stiffness in the affected joint, particularly in the morning or after prolonged sitting (Katz et al., 2021), and limitations in the range of movement (Dieppe & Lohmander, 2005). The nature of pain experienced by individuals coping with knee OA can vary depending on the severity of the disease. In the early stage of OA, the onset of pain is usually triggered by specific activities (e.g. high-impact activities). However, in the mid-stage of OA, pain becomes more constant over time and gradually begins to affect daily activities. Eventually, in the advanced stage of OA, the pain is described as constant and dull with short episodes of intense pain, leading to avoidance of social and recreational activities (Hawker et al., 2008). Yet, patients' disease progression exhibits considerable variation and is highly individualized. While some patients experience a slow and gradual deterioration of symptoms over time, others remain quite stable, show non-linear patterns of change over time, reveal a fast and progressive decline, or suffer unstable patterns on a daily basis (Previtali et al., 2020; White et al., 2016).

The preferred treatment options for OA are best described by a stepped care model (see Figure 1) (Dieppe & Lohmander, 2005; Lohmander & Roos, 2007). In general, treatment

options can be divided into three categories: non-pharmacological, pharmacological, and surgical treatments (Conley et al., 2023). As no cure for OA is currently known, the main focus of OA treatment should be directed to the reduction of symptoms, the improvement of physical function (Bijlsma et al., 2011), and a delayed need for joint replacement (Svege et al., 2015). The basic and general OA treatments should be patient-centered and involve patient empowerment and self-management. Thereby, it is imperative to ensure the accessibility of these basic treatments for all patients (Dieppe & Lohmander, 2005; Lohmander & Roos, 2007). This is in accordance with clinical guidelines worldwide, which recommend exercise and education as first-line treatment for knee OA (Bannuru et al., 2019; Conley et al., 2023; Deutsche Gesellschaft für Orthopädie und Unfallchirurgie e. V., 2024; Fernandes et al., 2013). In this context, education may encompass information on understanding OA (e.g. associated causes, disease process), effective treatment options, options for self-help, the importance of continuing physical activity, the benefits and different types of exercise therapy, and knowledge of how to adapt exercises in the event of increased pain (Conley et al., 2023; Skou et al., 2018). Additionally, patients should be instructed and advised on lifestyle alterations, weight loss (if appropriate), and, if required, the supplementation of simple analgesics and topical agents (Lohmander & Roos, 2007). Exercise can be provided using different types, dosage principles, and delivery modes, depending on the patient's treatment response, preferences, and needs. A comprehensive overview of exercise therapy, addressing its effectiveness, safety, and adherence can be found in chapter 2.4. In cases where a patient's response to basic treatment options is either non-existent or insufficient, second- and third-line pharmacological treatment options (e.g. non-steroidal anti-inflammatory drugs (NSAID) or other pain-relieving drugs) and surgical treatment options (e.g. joint replacement) can be considered. However, despite the large effect sizes demonstrated by the surgical intervention, it should be applied only in advanced cases where other treatment options have failed and symptoms such as severe pain and disability are present (Conley et al., 2023; Deutsche Gesellschaft für Orthopädie und Unfallchirurgie e. V., 2024; Dieppe & Lohmander, 2005; Lohmander & Roos, 2007). The national S3 guideline of Germany on the prevention and treatment of knee OA, issued by the German Society for Orthopedics and Trauma Surgery, similarly emphasizes the importance of active interventions (Deutsche Gesellschaft für Orthopädie und Unfallchirurgie e. V., 2024). The report recommends aquatic and land-based exercise therapy that is tailored to individual needs and administered under supervision. The provision of education or strategies to modify behavior (e.g. maintaining regular and consistent exercise) is also indicated. Pharmacological therapy (e.g. topical and oral NSAIDs) is only recommended when necessary and in conjunction with non-pharmacological treatment or in support of exercise therapy. In cases of severe knee OA, surgical interventions such as joint replacement therapies may be

considered. However, this decision should be made only after a detailed consultation and confirmation through clinical and radiological assessments (Deutsche Gesellschaft für Orthopädie und Unfallchirurgie e. V., 2024).

To evaluate the effectiveness of these recommended treatment options in clinical practice and research, standardized outcome measures are crucial. In this context, an international consensus group defined a standard set of outcome measures (Rolfson et al., 2016). Thereby, the assessment of knee pain and physical function, health-related quality of life (HrQoL), and work status were identified as the core outcome domains, reflecting the prevailing limitations associated with knee OA. A variety of patient-reported outcome measures (PROMs) exist to assess knee pain and physical function, including subscales of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) (Bellamy et al., 1988; McConnell et al., 2001) and the related Knee Injury and Osteoarthritis Outcome Score (KOOS) (Kessler et al., 2003; Roos & Lohmander, 2003). In addition, given the licensing fee associated with the WOMAC and length of the KOOS (42 items), a shortened version (KOOS-PS) has been developed (Perruccio et al., 2008). The KOOS-PS is a tool designed exclusively for the evaluation of knee function, lacking measures of pain. Consequently, when using the KOOS-PS, it is further recommended to apply a visual analog scale (VAS) or a numeric rating scale (NRS) to evaluate knee pain.

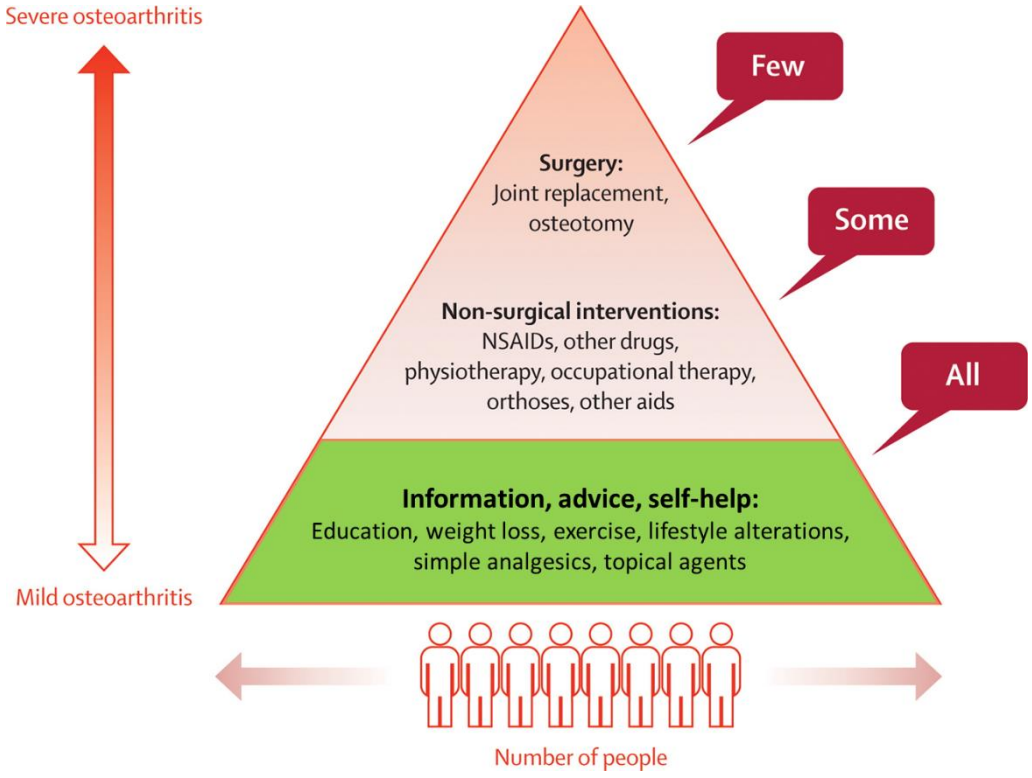

Figure 1: Treatment options for knee osteoarthritis. Modified according to Lohmander and Roos (2007).

While symptoms, disease progression, treatment strategies, and standardized outcome measures have primarily emphasized the clinical impact of OA on patients, the disease also bears a significant economic burden on healthcare systems and society. Within the domain of healthcare economics, it is imperative to distinguish between two categories of expenditure: direct and indirect healthcare costs. Direct healthcare expenditures encompass visits to physicians, diagnostic procedures, and treatment costs for medications, surgeries, and physical therapy. Conversely, indirect healthcare expenditures are associated with loss of workplace productivity, early retirement, and disability (Leifer et al., 2022; Salmon et al., 2016). It is imperative to note that direct healthcare expenditures can vary substantially depending on the consideration of surgical interventions (Salmon et al., 2016). In Europe, the annual economic burden for patients suffering from knee and hip OA was found to be €1.000 per patient for direct costs and €3.800 per patient for indirect costs (Salmon et al., 2016). On a global scale, the mean total expenditure per patient and year can even rise up to €11.100 (Salmon et al., 2016).

Summary chapter 2.1

OA is a degenerative joint disease and a leading cause of global disability. It most commonly affects the knee joint. Its prevalence increases with age, female sex, and higher body mass index. Symptoms associated with knee OA include increased pain, reduced physical function, and decreased quality of life. Treatment options follow a stepped-care approach, focusing on patient-centered non-pharmacological interventions such as exercise and education as first-line treatments. Second- and third-line treatment options encompass pharmacological and surgical interventions. To evaluate the effectiveness of these treatments, PROMs focusing on pain and physical function are recommended as core domains. Moreover, OA induces a substantial economic burden, with annual healthcare expenditures ranging up to €11,100 per patient.

2.2 Current care situation

The current care situation in the treatment of knee OA demonstrates deficiencies in the utilization of recommended first-line non-pharmacological and non-surgical treatment options. According to a meta-analysis encompassing studies from Europe, United States, Canada, Mexico, and Australia, the recommendation rate for non-pharmacological approaches (exercise and education) in OA care is less than 40% (Hagen et al., 2016). These findings were corroborated by a second systematic review with similar study characteristics, which revealed a referral rate of only 36% for non-drug treatment and 38% for drug treatment (Basedow & Esterman, 2015). In this context, a German study analyzing health insurance data

from participants with hip, knee, or polyarticular OA demonstrated that 50% of German patients received recommendations for physical therapy at least once in the previous 12 months, but only 36% were treated with therapeutic exercise (Jacobs et al., 2021). In particular, men, individuals with a low household income, patients with less impairments in functional status or pain severity, and patients of higher age were found to utilize physical therapy less frequently (Jacobs et al., 2021; Postler et al., 2018). Conversely, in the age group >60 years, 63% of German patients with hip or knee OA received analgesics. Thereby, increasing utilization was observed with higher age and higher number of comorbidities (Postler et al., 2018). Total joint replacement surgery was performed in 5.3% of the OA-affected population, whereas the number of knee replacement surgeries was 3.5% (Postler et al., 2018). In general, there appears to be considerable room for improvement in the utilization of conservative, first-line clinical treatment in German patients suffering from OA, particularly within the older population (Postler et al., 2018). The aforementioned findings and trends appear to be present in a variety of regions worldwide, including Europe, Canada, Australia, and the United States (Hagen et al., 2016). In particular, the latter country has observed a trend of decreasing adherence to non-pharmacological treatments, while concurrently reporting an increase in prescriptions for NSAIDs and narcotics over the past several years, with no prospect of improvement over time. During the triennial period from 2013 to 2015, the recommendation rate for managing knee OA in the US was found to be 9.2% for physical therapy, 15.2% for lifestyle alterations, 30.0% for NSAIDs, and 24.8% for narcotics. This represented an increase of 30-50% in NSAID prescriptions and 10-15% in narcotics prescriptions in comparison with the triennial period of 2007-2009 (Khoja et al., 2020). The authors of this study concluded that the prevailing management of knee OA primarily emphasizes the control of symptoms rather than enhancing physical function, or overall fitness and well-being (Khoja et al., 2020). To further examine current clinical practice in the management of knee OA in Germany, a nationwide online survey was conducted among physical therapists. The findings revealed that only 8.6% of physical therapists fully adhered to guideline recommendations. The majority of survey respondents lacked awareness of all recommended interventions, and even more than half (50.7%) were not at all familiar with the OA guidelines. However, the results of the study indicated that, in accordance with first-line guideline recommendations, the most commonly used physical therapy interventions in the management of patients with knee OA were exercise therapy (96.4%), self-management advice (89.4%), and education (74.9%). Regrettably, interventions with low or conflicting evidence were also still frequently utilized (e.g. manual therapy [70.4%] and joint traction [45%]) (Bahns & Kopkow, 2023). In this context, a qualitative study revealed that physical therapists identified time constraints, concerns that treatment could lose individuality, and differing patient expectations as key barriers to the implementation of the

guidelines in clinical practice. They criticized the low frequency of prescriptions and the lack of time during therapy sessions (<20min), and suggested that apps could be useful in order to generate home exercise programs for their patients (Bahns et al., 2024). Consequently, there is a growing potential that digital health technologies will be utilized with greater frequency in the future to address the deficiencies in current healthcare. This could facilitate the widespread provision of and access to education and exercise programs for patients suffering from knee OA.

Summary chapter 2.2

The current care situation in the treatment of knee OA is characterized by deficiencies in the utilization of non-pharmacological first-line treatments (e.g. less than 40% of German OA patients were treated with therapeutic exercise) and frequent use of medications. Consequently, there is substantial room for improvement in conservative treatment options for knee OA. In this context, digital health technologies have the potential to address existing gaps in healthcare.

2.3 Definition and classification of digital health technologies

Digital health is an umbrella term for the field of e-health, m-health, and telehealth. They enable the delivery of health services directly to people's homes or underserved regions, integrating digital devices and tools that improve the accessibility and efficiency of health care (World Health Organization, 2022). The term e-health comprises a variety of concepts, including telehealth, telemedicine, and the management of electronic health data. According to the World Health Organization (WHO), e-health is defined as "the cost-effective and secure use of information and communication technologies (ICT) in support of health and health-related fields" (World Health Organization, n. d.). The German Federal Ministry of Health has further stated that e-health applications in particular have the potential to support the treatment and care of patients by using digital ICTs (Bundesministerium für Gesundheit, n. d.). Another definition describes e-health as "an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies" (Eysenbach, 2001). Moreover, e-health can be utilized "to improve health care locally, regionally, and worldwide by using information and communication technology" (Eysenbach, 2001). M-health technologies are a subgroup of e-health with the focus on "mobile communications for health information and services" (Nacinovich, 2011) and the goal to improve health outcomes. The WHO Global Observatory for e-health further defines m-health as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants

(PDAs), and other wireless devices" (Kay et al., 2011). The functionality of these devices can be utilized to support care delivery, patient communication, data collection, monitoring, and therapy adherence (Tomlinson et al., 2013).

In general, healthcare interventions delivered by digital health technologies can be classified into three main categories:

(1) Self-directed e-health and m-health interventions (e.g. web or mobile apps) (Allen et al., 2018; Mecklenburg et al., 2018; Nelligan et al., 2021)
(2) Synchronous (Bennell et al., 2017; Hinman et al., 2020) or asynchronous (Dahlberg et al., 2016) supervised e-health and m-health interventions (e.g. videoconferencing, chat messages in combination with mobile apps, phone calls)
(3) Blended care approaches (Kloek et al., 2018; Weber et al., 2023): a hybrid format combining an in-person supervised intervention guided by a health professional in individual treatment or group sessions blended with a self-directed or remotely supervised e-health or m-health intervention.

At this point, it should be briefly mentioned that the author of this dissertation, together with the research group of the Department of Sports Medicine at the University Hospital Tübingen, is involved in several studies on the digital provision of exercise for patients with OA. In addition to the self-directed m-health exercise intervention re.flex presented in this dissertation, there is a collaboration within the SmArt-E project (Weber et al., 2023) – a multicenter RCT on a blended care exercise and education program for patients with hip and/or knee OA.

Summary chapter 2.3

Digital health is an umbrella term encompassing e-health, m-health, and telehealth. It describes the remote delivery of health services to patients' homes using digital tools that enhance accessibility and efficiency of healthcare. Healthcare interventions delivered by digital health technologies can be classified into three main categories: (1) self-directed e-health and m-health interventions (e.g. web or mobile apps), (2) synchronous or asynchronous supervised e-health and m-health interventions (e.g. videoconferencing), and (3) hybrid formats such as blended care.

2.4 Exercise therapy in knee osteoarthritis

Exercise therapy is defined as a specific type of physical activity that is intended to pursue therapeutic goals and to improve impairments caused by injuries or diseases (Caspersen et al., 1985; National Center for Biotechnology Information, n. d.). Thereby, exercise is characterized as "planned, structured, and repetitive" (Caspersen et al., 1985). In Germany,

exercise therapy is usually indicated based on a medical diagnosis. Thereby, the interventions are designed and carried out by qualified therapists (Deutscher Verband für Gesundheitssport und Sporttherapie e. V., n. d.). In general, evidence supports the effectiveness of land-based therapeutic exercise interventions in reducing pain and improving physical function among patients with knee OA (Fransen et al., 2015). However, latest work has reported new uncertainty, questioning the clinical relevance of exercise in terms of symptoms improvement and are calling for a better understanding of its mechanisms as well as the identification of responder characteristics for the different exercise types and delivery modes (Holden et al., 2023; Lawford et al., 2024). Therefore, the aim of this chapter is to provide a comprehensive overview of the general modalities of exercise therapy in knee OA based on the FITT principle (frequency, intensity, time, and type). In addition, it will summarize the current state of research in terms of effectiveness, safety, and adherence. Furthermore, particular emphasis will be placed on the group of digital health technologies, with a focus on the functionalities, facilitators, and barriers of digital health technologies in exercise intervention delivery.

2.4.1 FITT (frequency, intensity, type, time) criteria and delivery modes

Achieving beneficial outcomes requires the implementation of an effective exercise program that is tailored to the individual patient. In this regard, the FITT principle can be employed to structure the exercise regimen. Therefore, the subsequent section delineates the various types of exercise, recommendations concerning frequency, intensity, and time, as well as the ability to utilize different modes of delivery in exercise therapy for patients with knee OA. In this regard, a variety of exercise types can be considered effective and safe for all patients suffering from knee OA, including strengthening exercises, neuromuscular exercises, balance training, aerobic training, and mind-body activities such as tai chi or yoga (Bannuru et al., 2019; Fernandes et al., 2013; Kolasinski et al., 2020; McAlindon et al., 2014). The prevailing consensus on the recommendation of aquatic exercises is also strong, yet they do not belong to the core treatments (Bannuru et al., 2019). Aquatic exercises are particularly recommended for overweight patients or individuals with a high pain level during full-weight-bearing exercises, as the buoyancy of the water can reduce joint load (Bartels et al., 2016; Krauß & Janßen, 2015). Aerobic training may encompass low-impact activities such as cycling, walking, or swimming (Krauß, 2016), whereas strengthening exercises should primarily address lower extremity muscle strength with a focus on the quadriceps and the surrounding musculature of the hip joint (Fernandes et al., 2013; Krauß, 2016). In addition, exercises for core stability can be implemented (Ageberg et al., 2010). Individuals can perform these exercises with their own body weight, with the option of utilizing additional equipment such as resistance bands or weights, or by using exercise machines (Krauß, 2016). Thereby, studies have identified

comparable benefits for individuals engaging in different types of strength training (e.g. isotonic, isometric, or isokinetic) (Pelland et al., 2004), or performing exercises in non-weight-bearing and weight-bearing positions (Jan et al., 2009). Moreover, neuromuscular exercises combine the muscle strength training with the improvement of sensorimotor control and the ability to achieve functional stability of the joint during physical activities (Ageberg et al., 2010).

The provision of explicit recommendations concerning the optimal exercise dosage (frequency, intensity, time) remains challenging, as dosage principles vary considerably between studies. Thereby, a variety of exercise modalities have been shown to demonstrate beneficial effects to improve OA symptoms (Moseng et al., 2024). The participation in a minimum of three exercise therapy sessions per week has been demonstrated to be more efficacious in reducing symptoms when compared to a frequency of fewer than two sessions per week (Juhl et al., 2014) and no or only a small difference exists between high- and low-intensity (Juhl et al., 2014; Regnaux et al., 2015) or high- and low-dose (in terms of time duration or number of exercises per session) (Torstensen et al., 2023) exercise interventions. In the absence of an alternative guideline concerning dosage principles specific to patients diagnosed with knee OA, recommendations from the American College of Sports Medicine (ACSM) for healthy adults are frequently employed as reference (Garber et al., 2011). The implementation of this guideline in the context of chronic diseases, such as OA, is feasible, assuming it is advised and modified by a health professional in accordance with patients' prerequisites (American College of Sports Medicine, n. d.). In this context, Moseng and colleagues (2017) demonstrated in their meta-analysis on patients with hip OA that land-based supervised exercise interventions with high adherence to the ACSM recommendations led to larger improvements in pain and physical function than those interventions with uncertain adherence. According to this guideline, aerobic training should be performed on three (vigorous intensity) to five (moderate intensity) days per week. Thereby, 30-60 minutes per day (150 minutes per week) of moderate-intensity exercise or 20-60 minutes per day (75 minutes per week) of vigorous-intensity exercise is recommended for most adults. Strengthening exercises for the major muscle groups should be conducted on two to three days per week with an intensity of 40-50% of the individual's one-repetition maximum (1 RM, very light to light intensity) for older adults beginning with strength training, 60-70% of the 1 RM (moderate to hard intensity) in the case of novice to intermediate experience in strength training, and ≥80% of the 1 RM (hard to very hard intensity) with regard to experienced individuals in strength training. Furthermore, there have been no specific recommendations for the duration of the training; however, 2-4 sets of 10-15 repetitions for an exercise are advised. In addition, it is recommended to perform exercises that focus on improving balance and flexibility on two to three days per week (Garber

et al., 2011). Further support for specifying and adjusting the appropriate exercise dosage could be provided by the utilization of the patient's individual pain and exertion data. Signs that the intensity of an exercise may be excessively high or that the dosage requires modification may include the presence of severe pain during exercise or the following day, pain that does not return to its usual level within a few hours after exercise, or increased swelling in the hours after exercise or the next day (K.L. Bennell et al., 2014). However, it is imperative to educate individuals that experiencing slight discomfort or pain during exercise is to be expected and does not necessarily cause joint damage (K.L. Bennell et al., 2014). Moreover, it is recommended that the duration, frequency, and intensity of the exercise program should be increased gradually over time (Holden et al., 2021). In this context, the utilization of a rating of perceived exertion (RPE) scale is a proposed method of facilitating progression, particularly during strength training. Consequently, the last repetitions of an exercise set should be rated as strenuous to very strenuous (7-9 on a scale of 0-10, with 0=no exertion and 10=maximum exertion) (Garber et al., 2011).

Finally, a variety of delivery modes can be utilized to facilitate the implementation of exercise therapy among patients diagnosed with knee OA. In general, exercise therapy can be delivered under the supervision of a qualified healthcare professional (e.g. physical therapist, sports scientist) in group training or an individual one-to-one setting, or unsupervised at home. In addition, especially since the COVID-19 pandemic, digital health technologies have gained popularity and enable remote exercise delivery via self-directed e-health and m-health interventions (e.g. web or mobile apps) (Allen et al., 2018; Mecklenburg et al., 2018; Nelligan et al., 2021), synchronous (Bennell et al., 2017; Hinman et al., 2020) or asynchronous (Dahlberg et al., 2016) supervised e-health and m-health interventions (e.g. videoconferencing, chat messages in combination with mobile apps, phone calls), or hybrid formats such as blended care (Kloek et al., 2018; Weber et al., 2023). In this context, irrespective of whether exercise is delivered non-digitally or digitally, supervision can be of particular importance for individual adjustments in exercise intensity and type based on the patient’s response (e.g. perceived pain or effectiveness), to ensure the quality of performance and avoid unphysiological stress, to provide education and enhance self-efficacy, and to answer any questions that arise concerning the conduction of exercise or perceived pain during exercise (Durst et al., 2020; Krauß, 2016; Skou et al., 2018). However, the level of human support preferred by patients varies according to their individual healthcare needs, preferences, and context factors (Nelligan et al., 2020). Ultimately, although initial instruction is recommended, patients should be guided toward self-directed exercise (Fernandes et al., 2013).

Summary chapter 2.4.1

The modalities of exercise therapy for knee OA can be structured based on the FITT principle (frequency, intensity, type, and time). Various exercise types have been demonstrated to be effective and safe, including strengthening, aerobic, neuromuscular, mind-body, balance, and aquatic exercises. In the absence of OA-specific guidelines concerning dosage principles, recommendations from the American College of Sports Medicine (ACSM) for healthy adults are frequently used as a reference. Strengthening exercises for the major muscle groups should be performed on two to three days per week. The intensity and duration of the program should be adapted to the patient's experience and pain level, and gradually increased over time. Thereby, the delivery of exercise therapy for patients diagnosed with knee OA can involve a variety of modes, ranging from non-digital to digital supervised or self-directed interventions.

2.4.2 Effectiveness and safety of exercise therapy in knee osteoarthritis

2.4.2.1 Non-digital exercise therapy

The established status of exercise therapy as first-line treatment for patients with knee OA can be primarily attributed to its proven effectiveness in reducing pain and enhancing physical function, concurrent with a low incidence of side effects. In 2015, Fransen and colleagues (2015) demonstrated in a Cochrane meta-analysis involving 54 studies that land-based exercise programs have a moderate short-term treatment effect in reducing knee pain (= between-group difference of 12 points on a scale 0-100, best to worst) and improving physical function (= between-group difference of 10 points on a scale 0-100, best to worst) in patients with knee OA when compared to no or minimal treatment (see Table 1). The reported benefits on patient outcomes were even comparable to those resulting from the intake of oral NSAID and paracetamol (Weng et al., 2023). However, given the adverse events associated with analgesics intake (e.g. gastrointestinal, cardiovascular), particularly in people with comorbidities or in the elderly, exercise, with its excellent safety profile, can justify its status as a core treatment (Weng et al., 2023). In addition, increased physical activity has been shown to have a number of positive health-promoting effects (e.g. on cardiovascular health status and metabolism) and to decrease the risk of comorbidities (Skou et al., 2018). Nevertheless, analogous to the diminishing effect of discontinued medication intake, the beneficial effects of exercise therapy are known to disappear if the prescribed exercise program is not continued at a sufficient level (Skou et al., 2018). Indeed, two to six months after the cessation of exercise, the pain-relieving effect becomes small, and after six months, has fully disappeared (Fransen et al., 2015). Consequently, this emphasizes the importance of patient education to ensure the continuity of exercise. With regard to the different types of exercise, various meta-analyses

provide evidence that they offer similar beneficial effects in reducing pain and improving physical function among patients with knee OA (see Table 1). In general, greater benefits have been demonstrated for land-based exercise types (e.g. strengthening exercise, aerobic exercise, mind-body activities) compared to aquatic exercises, whereas mixed programs do not appear to demonstrate any additional benefits. Moreover, despite the growing interest in neuromuscular exercise, research in this area is still somewhat underrepresented in current meta-analyses, thereby limiting the evidence for this type of exercise. Comparable low-quality evidence can be observed for balance exercises (Kolasinski et al., 2020). In addition, no statistically significant differences in effectiveness were identified between the various non-digital delivery modes in terms of reducing pain and improving physical function (see Table 2). The most beneficial effects were found for individual treatments, with moderate effect sizes. Comparatively, class-based and home-based programs yielded slightly smaller effects (Fransen et al., 2015). Overall, all types of therapeutic exercise are considered to be safe, irrespective of the presence of comorbidities, and with minimal risk of side effects (Bannuru et al., 2019; K.L. Bennell et al., 2014; Fransen et al., 2015). There is no evidence to suggest that serious adverse events occur at the group level (Holden et al., 2021). If adverse events were reported, they were related to increased knee, hip, or back pain (Bannuru et al., 2019; Fransen et al., 2015). Additionally, a comparison of the various delivery modes revealed no significant differences between group- and home-based programs, with a comparable low number of adverse events reported in both settings (K.L. Bennell et al., 2014). Nevertheless, the implementation of supervision, at least during the initial stage of exercise programs, could ensure the safe execution of exercise (Holden et al., 2021).

2.4.2.2 Digital exercise therapy

Alongside the traditional non-digital modes of exercise delivery, an increasing number of digital-based exercise programs have been developed and evaluated in recent years to enable remote exercise provision. Concerning the effectiveness of digital-based exercise programs, findings from two meta-analyses indicate that such programs have demonstrated a similar, small short-term beneficial treatment effect in terms of pain reduction when compared to non-digital treatments, usual care, or no care (see Table 2) (Chen et al., 2021; Yang et al., 2023). However, the findings on the effectiveness of improving physical function were observed to be inconsistent. Notable improvements concerning this patient outcome were found only in a subgroup analysis comparing digital-based exercise interventions with usual care alone (Yang et al., 2023). A further meta-analysis did not distinguish between control conditions, and thus, was not able to find a positive treatment effect on improvements in physical function (Chen et al., 2021). Nevertheless, it has been demonstrated that digital-based exercise programs are

at least as effective as traditional, non-digital, in-person treatments for both patient outcomes (pain and physical function) (Hinman et al., 2024; Yang et al., 2023). The digital health technologies included in the trials varied in their design and functionality, encompassing telephone-based systems, web-based platforms, mobile apps, and virtual reality systems. With regard to the type of technology utilized, the findings of the meta-analyses (Chen et al., 2021; Yang et al., 2023) suggested that the delivery of exercise interventions via mobile apps and web-based platforms may result in greater pain relief and improvements in physical function, while telephone interventions did not show significant improvements in either pain or physical function (Yang et al., 2023). The potential benefits of web- and app-based programs may be related to special features that could improve patient understanding and performance of exercise. For instance, the integration of video-based exercise demonstrations, automated reminders to perform exercises, incorporation of educational material, sensor-based motion and physical activity tracking, and individualized exercise recommendations have been associated with greater improvements in patient outcomes compared to programs that did not include these features (Chen et al., 2021). For a more thorough understanding of the potential benefits, facilitators, and barriers of digital delivered exercise, as well as a comprehensive overview of associated features, refer to chapter 2.4.4. Overall, it is important to note that the evidence presented in the analyses of digitally delivered exercise programs (pooled analyses and subgroup analyses) is only of low to moderate quality. This is primarily attributable to the fact that the majority of the studies included in the analyses were characterized by small sample sizes and high heterogeneity. Furthermore, the absence of blinding of the participants resulted in a high risk of bias and the subgroup analyses only included a small number of studies (Chen et al., 2021; Yang et al., 2023). To the best of my knowledge, to date, no meta-analysis or systematic review has distinguished between self-directed or supervised digitally delivered exercise programs, and none of them have reported data on safety or adverse events. However, the findings of certain RCTs have indicated that the safety profile of digitally delivered exercise interventions is comparable to that of traditional, non-digital in-person or home-based exercise programs (Bennell et al., 2022; Gohir et al., 2021; Nelligan et al., 2021).

Table 1: Overview of the effect sizes and safety profile of exercise therapy in patients with knee osteoarthritis, differentiated by exercise type.

Exercise type	Effect size for pain	Effect size for physical function	Safety
Land-based exercise	0.49 (Fransen et al., 2015)[1] to 0.52 (Bannuru et al., 2019)[1]	0.45 (Bannuru et al., 2019)[1] to 0.52 (Fransen et al., 2015)[1]	Therapeutic exercises of all types are considered safe, irrespective of comorbidities and with minimal risk of side effects (Bannuru et al., 2019; K.L. Bennell et al., 2014; Fransen et al., 2015). There is no evidence of serious adverse events at the group level (Holden et al., 2021). If adverse events were reported, they were related to increased knee, hip or back pain (Bannuru et al., 2019; Fransen et al., 2015).
Strengthening exercise	0.53 (Fransen et al., 2015) to 0.62 (Juhl et al., 2014)[1] 0.52 (Katz et al., 2021)[2]	0.54 (Fransen et al., 2015) to 0.60 (Juhl et al., 2014)[1]	
Aerobic exercise	0.48 (Fransen et al., 2015) to 0.67 (Juhl et al., 2014)[1]	0.35 (Fransen et al., 2015) to 0.56 (Juhl et al., 2014)[1]	
Neuromuscular exercise/Balance training	0.48 (Juhl et al., 2014)[1] to 0.56 (Jeong et al., 2019)[3], 0.15 (Villadsen et al., 2014)[1,4] 1.04 (Kim L Bennell et al., 2014)[3,4]	0.40 (Jeong et al., 2019)[3] to 0.56 (Juhl et al., 2014)[1] 0.23 (Villadsen et al., 2014)[1,4] 0.80 (Kim L Bennell et al., 2014)[3,4]	
Mind-body activities	0.63 (Bannuru et al., 2019)[1] 0.63 (Katz et al., 2021)[2]	0.65 (Bannuru et al., 2019)[1]	
Aquatic exercise	0.31 (Bartels et al., 2016)[1] to 0.52 (Bannuru et al., 2019)[1]	0.32 (Bartels et al., 2016)[1] to 0.37 (Bannuru et al., 2019)[1]	
Mixed program (strengthening and aerobic)	0.50 (Fransen et al., 2015)[1]	0.52 (Fransen et al., 2015)[1]	

Effect sizes were calculated by meta-analyses, with exception of those marked separately.

[1]Control condition: Non-exercise control, usual care, or no intervention.

[2]Control condition: Placebo-controlled.

[3]Control condition: Other exercise.

[4]Only RCT data, no meta-analysis. Data from RCTs with explicit inclusion of neuromuscular exercises.

Table 2: Overview of the effect sizes and safety profile of exercise therapy in patients with knee osteoarthritis, differentiated by exercise delivery mode.

Exercise delivery mode	Effect size for pain	Effect size for physical function	Safety
Individual treatment (1:1)	0.76 (Fransen et al., 2015)[1]	0.76 (Fransen et al., 2015)[1]	The risk for adverse events during group- and home-based exercise programs is low (K.L. Bennell et al., 2014). Supervision, at least in the initial stage of exercise programs, may increase safe execution of exercises (Holden et al., 2021). The safety profile of digital-supported exercise programs seems to be similar to that of traditional non-digital in-person or home-based exercise programs (Bennell et al., 2022; Nelligan et al., 2021).
Class-based (group)	0.42 (Fransen et al., 2015)[1]	0.38 (Fransen et al., 2015)[1]	
Home-based	0.38 (Fransen et al., 2015)[1]	0.37 (Fransen et al., 2015)[1]	
Digital-supported[2]	0.28 (Yang et al., 2023)[3,4] to 0.29 (Chen et al., 2021)[3,4]	0.17 (Yang et al., 2023)[3,4] to 0.22 (Chen et al., 2021)[3,4]	
Digital-supported supervised	No data available[5]	No data available[5]	
Digital-supported self-directed	No data available[5]	No data available[5]	

Effect sizes were calculated by meta-analyses, without differentiation between exercise types.

[1]Control condition: Non-exercise control, usual care, or no intervention.

[2]Included digital exercise delivery types comprise telephone, web-based, and app programs.

[3]Control condition: non-digital treatments, usual care, or no care

[4]Subgroup analyses by delivery type demonstrated that exercise delivery via app (pain: 0.45 (Chen et al., 2021) - 0.80 (Yang et al., 2023), physical function: 0.23 (Chen et al., 2021) - 0.79 (Yang et al., 2023)) or web (pain: 0.24 (Yang et al., 2023) - 0.48 (Chen et al., 2021), physical function: 0.12 (Yang et al., 2023) - 0.50 (Chen et al., 2021)) might show larger effect sizes compared to the delivery type telephone (pain: 0.03 (Yang et al., 2023) - 0.12 (Chen et al., 2021), physical function: 0.08 (Chen et al., 2021) - 0.10 (Yang et al., 2023)). However, as only a few studies could be included in the subgroup samples, there is high heterogeneity between studies and only low-quality evidence.

[5]This refers to review articles; individual studies are available.

2.4.2.3 Recent findings and the question of clinical relevance

Over the years, numerous studies have evaluated non-digital and digital delivered exercise programs in the treatment of knee OA. Consequently, in 2018, Verhagen and colleagues (2019) concluded that findings demonstrating the short-term effectiveness and clinical relevance of exercise compared to no or minimal treatment in reducing pain for patients with knee OA are robust. Accordingly, the consensus was reached that further research in this domain would not yield any new evidence (Lawford et al., 2024; Verhagen et al., 2019). However, latest research, including the 2024 update of the Cochrane meta-analysis on exercise for knee OA (Lawford et al., 2024) and an individual participant data (IPD) meta-analysis on therapeutic exercise for knee and hip OA (Holden et al., 2023), has started to question the clinical relevance of the beneficial effects on pain and physical function. The 2024 updated Cochrane meta-analysis (Lawford et al., 2024), which included 60 studies, found low-certainty evidence for short-term pain reduction (mean difference of 13.1 points, 95% CI 10.4 to 15.9 points, scale 0-100) and moderate-certainty evidence for short-term improvements in physical function (mean difference of 12.5 points, 95% CI 9.7 to 15.3 points, scale 0-100) when comparing land-based exercise with no treatment, usual care, or limited education. To assess the clinical relevance of the findings, the results were compared with minimal clinically important difference (MCID) scores that have been established in the literature (12 points for pain and 13 point for physical function, each on a scale 0-100) (Devji et al., 2017). In contrast to the conclusion reached in 2015, the observed benefits were of uncertain clinical relevance, as the confidence intervals of the mean differences included both clinically important and unimportant improvements. Notably, despite the rising interest in the MCID approach in recent years, its implementation is accompanied by a number of challenges. These issues will be addressed in greater detail in chapter 5.2. Moreover, the confidence in the findings of the meta-analysis was diminished by the lack of blinding of participants, which resulted in the treatment arm being known and could potentially have influenced the reported improvements. For this reason, in a second analysis exercise was compared to attention control and placebo, resulting in slightly smaller benefits for the exercise group than when compared to no intervention, usual care, or limited education. Currently, there is an absence of clear evidence as to whether apparently exercise-induced clinical improvements are rather a result of contextual factors or a placebo response (Henriksen et al., 2024). The IPD analysis of 31 RCTs in patients with hip and knee OA reached the same conclusion regarding the discussion of clinical relevance. The findings revealed only small beneficial effects (mean difference of 6.4 points [95% CI 4.3 to 8.5] in pain reduction and 4.5 points [95% CI 3.0 to 6.0] in physical function improvement, both on a scale 0-100) of exercise in comparison to non-exercise controls, which diminished over

time (Holden et al., 2023). Accordingly, the findings are even smaller than those of the aforementioned meta-analyses (Fransen et al., 2015; Lawford et al., 2024) in this area. However, the observed discrepancies may be partly explained by different inclusion and exclusion criteria (e.g. incorporation of knee and hip OA, inclusion of aquatic exercise types), as well as lack of access to data from potentially eligible RCTs.

2.4.2.4 Moderators and individual response

On an individual level, research has demonstrated that patients' responses to exercise therapy can vary and that not all patients will experience significant improvements. Accordingly, there is an increasing need to identify the characteristics of responders within different subgroups, including the distinction between different types of exercise and different modes of delivery. Previous assumptions concerning the response to exercise were based on a variety of factors, including the different characteristics of the exercise regimen, environmental conditions, and individual factors (e.g. physical activity, fitness level, social and psychological factors), which were associated with different effects among individuals (Garber et al., 2011). However, recent evaluations on moderators of treatment effect embedded in the IPD meta-analysis (Holden et al., 2023) only revealed that participants with more severe pain and disability at baseline may benefit to a greater extent than those with less symptoms at baseline. The investigation did not identify any influence on outcomes from other moderators, including age, body mass index, physical activity, comorbidity, quadriceps strength, education level, self-efficacy, mental well-being, pain duration, or radiographic severity. Yet, the moderator analysis was biased by limited access to data from eligible RCTs and showed some differences in the characteristics of exercise interventions and participants (Holden et al., 2023). A further explorative study using a machine learning approach was utilized to identify optimal exercise therapies for individual patients with knee OA, depending on their characteristics. The analysis revealed that lower age and low fear of movement were identified as moderating factors for an effective digital-based exercise program. Conversely, in patients with older age, higher body mass index (between 26 and 37 kg/m²), and high fear of movement, in-person physical therapy appears to have a more favorable impact on symptom improvements (Kim et al., 2023). However, these findings must be further investigated. In this context, there is a necessity for consistent reporting of participant characteristics or intervention variables and data sharing for future studies. This will facilitate a more profound understanding of the dose-response relationship and the subgroups that respond best to a particular type of exercise therapy (Holden et al., 2023). To date, the greatest benefits have probably been achieved when exercise programs were tailored to the individual's preferences and enjoyment, allowing for appropriate adherence

to exercise, incorporating behavior change techniques (BCT, e.g. goal setting), or considering individual responses to exercise (Garber et al., 2011).

Summary chapter 2.4.2

Non-digital exercise therapy in patients with knee OA has been shown to provide moderate short-term improvements in pain and physical function. The benefits are comparable to those of oral NSAIDs and paracetamol, yet exercise has a better safety profile. While a variety of exercise types and delivery modes are effective and safe, land-based programs and individual treatments yield the greatest benefits. Long-term adherence is essential to sustain these effects. Moreover, supervision of the exercise program can be important, particularly during the initial phase. Digital-based exercise programs have demonstrated a similar, small short-term beneficial effect in terms of pain reduction and are comparable in effectiveness to traditional, non-digital programs. The findings concerning the effectiveness of improving physical function were observed to be inconsistent. App- and web-based programs, with their special features, may result in greater benefits than telephone interventions and the safety appear to be comparable to that of non-digital exercise programs. However, the evidence for digital-based exercise interventions is only of low to moderate quality. In general, recent findings have questioned the clinical relevance of the benefits of exercise in knee and hip OA. An updated Cochrane meta-analysis and an IPD meta-analysis have shown only small, short-term improvements in pain and physical function, which fall below the MCID thresholds. However, in the aforementioned analyses, methodological quality was criticized due to a lack of blinding and the potential for placebo effects. Individual responses to exercise therapy in OA vary considerably, with evidence suggesting that patients with more severe baseline symptoms may benefit to a greater extent. In this regard, tailoring exercise programs to patients' preferences and needs appears to be a crucial factor in maximizing outcomes. In summary, the effectiveness of exercise therapy can still be considered proven, although the beneficial improvements may be smaller and of questionable clinical relevance than previously assumed. Given the lack of other low-cost, safe, and equally beneficial non-surgical alternatives, exercise should be maintained as a first-line treatment option in the management of knee OA.

2.4.3 Adherence to exercise

As the beneficial effects of exercise in the treatment of knee OA have been shown to persist only as long as patients continue to exercise, patient adherence to exercise appears to be of particular importance (Fransen et al., 2015; Holden et al., 2023). Thereby, several factors can influence exercise adherence, either by facilitating or inhibiting participation. Intrinsic factors

may encompass motivational level, individual personality, health and exercise attitudes, knowledge regarding OA, exercise history, or personal experiences. External factors, on the other hand, include the support of the social environment, but also other environmental factors such as the availability of and access to exercise facilities or further exercise offers (Petursdottir et al., 2010). In this context, potential barriers to exercise participation may include time constraints, the perception that exercise will exacerbate OA or induce pain, the perception that exercise is ineffective, lack of motivation or enjoyment, forgetfulness, lack of energy, or limited confidence in exercise ability (K.L. Bennell et al., 2014). Conversely, regular supervision and monitoring by a health professional may facilitate adherence to exercise and increase self-efficacy and positive experiences with exercise. In this regard, the supervision and monitoring can enable modification and progression of the exercise program according to the patient's changing needs and disease status, thus fostering ongoing motivation and interest (Hurley et al., 2010). Additionally, education is a key component in providing patients with relevant knowledge and advice, for instance on the benefits of exercise and the low risk of side effects. Other facilitators of exercise participation include self-monitoring strategies (e.g. logbooks, accelerometers, activity trackers) and support from family, friends, or other individuals (Roddy et al., 2005). In general, strategies incorporating BCTs (e.g. goal setting, development of exercise plans), booster sessions, reminders, or new technologies seem to improve patient adherence to exercise (Geidl et al., 2012; Meade et al., 2019; Pérez-Maletzki et al., 2024; Pisters et al., 2010). In this context, the term “new technologies” is primarily related to digital health technologies (e.g. e-health, m-health, telehealth, motion sensors) that can be used to provide remote support and monitoring (Schafer et al., 2018). Accordingly, they could facilitate interaction with a healthcare professional, even for individuals residing in rural and remote areas (Holden et al., 2021). Moreover, digital health technologies already incorporate various features and strategies to overcome barriers to exercise participation and support behavior change (see chapter 2.4.4).

A review of the extant literature revealed that patients with knee OA completed between 62-75% of the prescribed exercise sessions in non-digital home exercise programs (Ay et al., 2016; Pisters et al., 2010). In comparison to this, the adherence to digital-based home exercise programs for patients with knee OA or chronic knee pain ranged from 68-88% (for sources of digital exercise delivery that include apps, web-based platforms, or videoconferencing tools) (Alasfour & Almarwani, 2020; Bennell et al., 2017; Doiron-Cadrin et al., 2020; Gohir et al., 2021; Mecklenburg et al., 2018). Adherence rates appear to be higher when remote exercise guidance and monitoring is more extensive (e.g. via in-app exercise demonstration videos, synchronous videoconferencing exercise sessions, or by support of wearable devices). This

phenomenon can be substantiated by the findings of a study in which patients with chronic knee pain used an app with narrated videos to demonstrate exercises, along with motion sensors that tracked exercise performance and provided real-time feedback. The study reported an adherence rate of 76% for the participants who started the exercise program and 95% for those who completed it (Mecklenburg et al., 2018). Notably, only a single meta-analysis has been identified that has examined the impact of digital health technologies on exercise adherence in comparison to non-digital exercise delivery in patients with knee disease. The analysis encompassed 13 trials, whose findings suggested that digital health technologies improved adherence in the short term. Yet, they performed no better than non-digital exercise delivery modes in the medium and long term. However, the findings were characterized by very low certainty of evidence and predominantly comprised interventions subsequent to total knee replacement (Liu et al., 2025). Overall, meta-analyses and systematic reviews of adherence rates in exercise programs for patients with knee OA are scarce. High heterogeneity between delivery modes and intervention types, as well as the use of varying measurement tools to assess adherence, are primary contributing factors to this observation. To date, there is no standardized, objective measurement tool to accurately assess adherence (Hall et al., 2015). The majority of the studies utilize self-reported adherence rates, which are known to be biased by adequate recall and the social desirability of overreporting. Given the increasing use of digital-based exercise delivery, an alternative approach for the assessment of adherence involves the use of objective data derived from apps and wearable devices (e.g. accelerometers). Accordingly, in future research, adequate adherence to exercise reporting should include information on exercise frequency, intensity, duration and correct exercise performance (Liu et al., 2025).

Summary chapter 2.4.3

Adherence to exercise is crucial for sustaining its benefits in knee OA. Thereby, several factors influence adherence to exercise, including supervision, monitoring, education, social support, and the incorporation of BCTs. Digital health technologies have demonstrated their potential to enhance exercise adherence in the short term, with rates frequently exceeding those of non-digital programs. This is particularly evident when remote exercise guidance, monitoring, or feedback features are incorporated. To date, there is no standardized, objective instrument for accurately assessing adherence.

2.4.4 Digital health technologies in exercise therapy: features, facilitators and barriers

In the management of knee OA, digital health technologies offer a (cost)-effective, flexible, and widely accessible treatment option for exercise therapy (Chen et al., 2021; Cronström et al., 2019; Shah et al., 2022). Thereby, digital exercise programs are designed with the objective of decreasing pain, improving physical function, promoting self-management, and increasing adherence to exercise. In order to achieve the aforementioned goals, a variety of features were implemented in the design of digital-based exercise technologies. This also encompasses the implementation of various BCTs (Michie et al., 2013). In this context, a systematic review of 36 studies was conducted to provide an overview of existing digital health technologies that incorporate behavioral change in patients with knee OA (Zhu et al., 2024). The most frequently utilized BCTs were attributable to the domains “goals and planning” (e.g. goal setting, action planning, problem solving) and “repetition and substitution” (e.g. behavioral practice, graded tasks). Additional techniques pertain to the domain “feedback and monitoring” (e.g. feedback on behavior, biofeedback, self-monitoring), include prompts that remind users for upcoming exercise sessions, or provide instructions on how to perform the behavior. In contrast to in-person exercise sessions guided by a health professional, digitally delivered exercise programs require patients to possess the necessary knowledge for appropriate exercise selection, ensuring correct exercise execution, adhering to appropriate dosage principles, recognizing incorrect or potentially harmful exercise execution, and understanding how they should feel during and after exercise (Pearson et al., 2016). Consequently, the provision of video and written exercise instructions, as well as educational videos, are crucial components to support patients in doing so (Allen et al., 2018; Bennell et al., 2017; Mecklenburg et al., 2018; Pearson et al., 2016). Furthermore, self-monitoring of patient progress can be accomplished by using online diaries or motion sensors, which can enable tracking the successful completion of exercises, physical activity status, or pain and exertion levels. This method has been demonstrated to be an effective strategy for enhancing or sustaining engagement with the conducted exercise program (Pearson et al., 2016). Additionally, the knowledge that a health professional can remotely monitor the exercise program and provide feedback or guidance for progression has been demonstrated to increase patients’ self-efficacy and motivation. Consequently, these components are key features of digital health technologies (Liu et al., 2025; Pearson et al., 2016). A comparable effect can be achieved by integrating movement sensors to the exercise program, which, in addition to monitoring exercise behavior, can also provide real-time biofeedback on exercise movements (Mecklenburg et al., 2018). Moreover, the utilization of automated reminder functions via e-

mail, text message, or push notification has been shown to effectively enhance adherence in exercise programs (Bennell et al., 2017; Mecklenburg et al., 2018). The incorporation of exercise goal setting and subsequent monitoring of progress against achievement is a feature that is predominantly observed in supervised digital health technologies (Kloek et al., 2018).

In the context of qualitative evaluations exploring the utilization of digital health technologies for exercise interventions, patients diagnosed with knee OA valued the increased accessibility, simple and easy-to-use technology, and comprehensive content and information, irrespective of the level of support provided (Cronström et al., 2019; Fernandes et al., 2022; Hinman et al., 2017; Nelligan et al., 2020). Moreover, time efficiency and the flexibility to perform exercise at any time and in any location without travel times or waiting were highly appreciated (Cronström et al., 2019; De Vries et al., 2017; Fernandes et al., 2022; Hinman et al., 2017). However, some kind of human connection associated with the digital health intervention appears to be important and could facilitate regular exercise participation. For instance, patients have reported feelings of motivation and support when they receive regular SMS messages or have the opportunity to communicate with the physical therapist via chat, videoconferencing, or telephone (Cronström et al., 2019; Hinman et al., 2017; Lawford et al., 2018). Particularly in the context of supervised digital exercise programs, patients found the undivided attention they received from the corresponding health professional to be highly valuable. It has been demonstrated that this approach can foster a patient-centered and personalized treatment with a focus on the most effective elements (e.g. exercise, education, self-management) rather than on the utilization of hands-on methods. As a result, physical therapists were forced to allocate a greater proportion of their time to listening to and talking with patients (Fernandes et al., 2022; Hinman et al., 2017; Lawford et al., 2018). Consequently, the implementation of supervised digital exercise programs has the potential to positively influence individualized tailoring and progression of exercise programs to patients' needs (De Vries et al., 2017). In this context, blended care approaches have also demonstrated to be a suitable option (Lawford et al., 2018; Nelligan et al., 2020). Additionally, the majority of digital health interventions include educational information or are designed to promote self-efficacy and enhance self-management. Accordingly, these factors appear to be associated with the successful implementation of exercise programs, contributing to enhanced adherence to exercise recommendations and potentially empowering individuals to perform exercises in a correct and safe manner without the need for supervision (Fernandes et al., 2022; Hinman et al., 2017). Further factors that facilitate motivation, confidence, and acceptability for the utilization of digital exercise delivery include a credible source behind the digital health intervention, an acceptable time requirement, and the support by family and friends in the home environment

(Cronström et al., 2019; Fernandes et al., 2022; Nelligan et al., 2020). However, for a subset of patients, digital exercise delivery may be perceived as impersonal, evoke feelings of unindividualized interventions, is accompanied by technological challenges and privacy concerns, and can contain content that does not align with patient characteristics or expectations. Consequently, this may result in demotivation, bad mood, and difficulties in concentrating on the exercise intervention (Fernandes et al., 2022).

Summary chapter 2.4.4

A variety of features have been incorporated into the design of digital-based exercise technologies to offer accessible and cost-effective exercise therapy for patients with knee OA. These include BCTs (e.g. goal setting, feedback, self-monitoring, reminders) and further supportive functionalities (e.g. video and written exercise instructions, educational videos). Patients suffering from knee OA generally value increased accessibility, simple and easy-to-use technology, comprehensive content and information, flexibility, and some degree of human support when using digital health technologies for exercise delivery. However, a small subset of patients also reports negative associations with digital-based exercise programs.

2.5 Reimbursement strategies for digital health technologies based on the example of the German DiGA program

The sustainable implementation of digital health solutions within the health system is highly dependent on reimbursement and pricing policies (Robin van Kessel et al., 2023). Consequently, worldwide appropriate strategies for the integration of these innovations in healthcare were explored (R. van Kessel et al., 2023). In Germany, the Digital Healthcare Law (Digitale-Versorgung-Gesetz, DVG) was introduced in 2019 (Bundesministerium der Justiz, 2019), enabling patients to receive approved DiGAs on prescription. The DVG has established the DiGA as a fourth pillar of healthcare within the statutory health insurance system, alongside drugs, therapeutic remedies, and assistive devices. However, in order to be eligible for prescription, DiGAs must successfully complete an evaluation process (the so-called “fast-track” process at the Federal Institute for Drugs and Medical Devices (Bundesministerium für Arzneimittel und Medizinprodukte, BfArM, see Figure 2) and be listed in a directory of reimbursable digital health applications (DiGA directory). Overall, this reimbursement approach enables up to 73 million individuals insured in the German statutory health insurance system to access DiGAs as part of routine care. A DiGA can be prescribed by physicians, psychotherapists, or directly by the health insurance company with the proof of a corresponding medical indication (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023). In general, a DiGA is a medical device (class I or IIa, will be expanded in future to class IIb)

that supports the “detection, monitoring, treatment, and alleviation of diseases or the detection, treatment, alleviation or compensation of injuries and disabilities” (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023). Therefore, a DiGA must be directed to patients and primarily be utilized by them individually, or in conjunction with the attending physician or psychotherapist. The DiGA fast-track process aims to evaluate the manufacturer's information on the required product characteristics (e.g. functionality, quality, user-friendliness, safety, data protection, information security) and whether evidence of a positive care effect could be provided. By definition, positive care effects comprise either a medical benefit for the patient (e.g. improvement in health status, reduction in illness duration, prolongation of survival, improvement in quality of life) or patient-relevant structural and procedural improvements in healthcare delivery (e.g. alignment of treatment with guidelines, improved treatment adherence, facilitation of access to care, patient sovereignty, health literacy). To be considered for inclusion in the DiGA directory, at least one positive care effect must be demonstrated. The majority of DiGAs (83%) already listed in the directory predominantly focused on the proof of medical benefits during the inclusion process (vfa, 2025). Thereby, evidence of positive care effects must be provided by the results of a comparative study, demonstrating that the use of the DiGA is superior to its non-use. In instances where the manufacturer cannot apply directly for inclusion, it is possible to apply for provisional inclusion and demonstrate the positive care effect within a one-year follow-up probationary period (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023). During this time, the DiGA can already be prescribed and reimbursed according to the manufacturers’ own prize conditions (within a maximum price limit). In the event that a positive care effect is demonstrated following the initial 12-month period, the manufacturer must negotiate the price of the DiGA with the Central Federal Association of Health Insurance Funds (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023). Notably, starting on January 1, 2026, a performance-based reimbursement component will be implemented. In this context, performance can be measured by adherence, patient satisfaction and patient-reported health status (Bundesgesetzblatt, 2024). As of September 16, 2025, the directory listed 57 DiGAs, including 12 provisional and 45 permanent listings. Moreover, 15 formerly provisionally listed DiGAs were removed from the directory due to the absence of a positive care effect or at the request of the manufacturer. Of the listed DiGAs, 7 DiGAs belong to the category ‘treatment of muscles, bones, and joints’, and treat diseases or injuries of the back (3x), patella (2x), general chronic pain (1x), and shoulder (1x). However, none of them were found to treat patients with knee or hip OA. Overall, the majority of listed DiGAs are affiliated with the field of psychology (29 of 57). Currently, DiGAs are available as mobile apps or web applications (Bundesinstitut für Arzneimittel und Medizinprodukte, n. d.), and they contain elements of lifestyle or disease-specific advice, behavioral therapy, education,

physiotherapy programs, and tracking capabilities. Although the integration of external sensors is permitted, this feature is only utilized by a limited number of DiGAs (Schmidt et al., 2024). In the period from the establishment of the DiGA program (September 2020) to December 31, 2024, a total of 861.000 DiGA prescriptions have been accessed by insurers. This corresponds to cost expenditures of 234 million euros for the statutory health insurance system. The utilization of DiGAs has been observed to grow steadily, with an 85% increase in prescriptions in 2024 compared to 2023. It has been demonstrated that DiGAs were most frequently used to treat psychological disorders (30%), followed by metabolic disorders (28%) and musculoskeletal disorders (16%). Overall, sociodemographic data from the year 2024 indicate a mean age of 47 years among all users, in addition to a higher frequency of DiGA use among females (73%) (GKV Spitzenverband, 2025).

A review of reimbursement approaches for digital health technologies in other countries reveals a divergence in the methods applied. The first approach involves the reimbursement of the digital health technology itself (as implemented in Germany, France, Sweden, and the United Kingdom). The second approach pertains to the reimbursement of the clinical pathways within which the digital health solution is integrated (as evidenced by policies in Belgium and Israel). In the countries of Germany, France, Sweden, and the United Kingdom, digital health technologies are defined as self-directed healthcare products. Conversely, in Belgium and Israel, these technologies are developed for the purpose of delivering traditional healthcare. Presently, specific policy frameworks for the concept of digital health technologies are only available in Germany, France, Belgium, Italy, and the United Kingdom (R. van Kessel et al., 2023). In Belgium, a platform has been established that is accessible to patients, healthcare professionals, and healthcare institutions, with the objective to inform users about mobile apps that are classified as medical devices. In this context, mobile apps are assigned to a validation pyramid with three different levels, whereas only apps of level three are reimbursable. Another framework approach can be observed in the United Kingdom, where high-quality evidence of effectiveness is linked to mandatory health economic analysis and, in the case of cost-intensive digital health technologies, a cost-utility analysis. In France, they attempt to mimic the German fast-track approach (Schliess et al., 2022). Overall, in the majority of countries a cost-based pricing model is used, wherein prizes are negotiated between manufacturers and national or regional committees. To date, Belgium and, at least partly Germany, have been the only countries to implement a value-based pricing system, utilizing performance variables to demonstrate the beneficial value of digital health technologies (R. van Kessel et al., 2023).

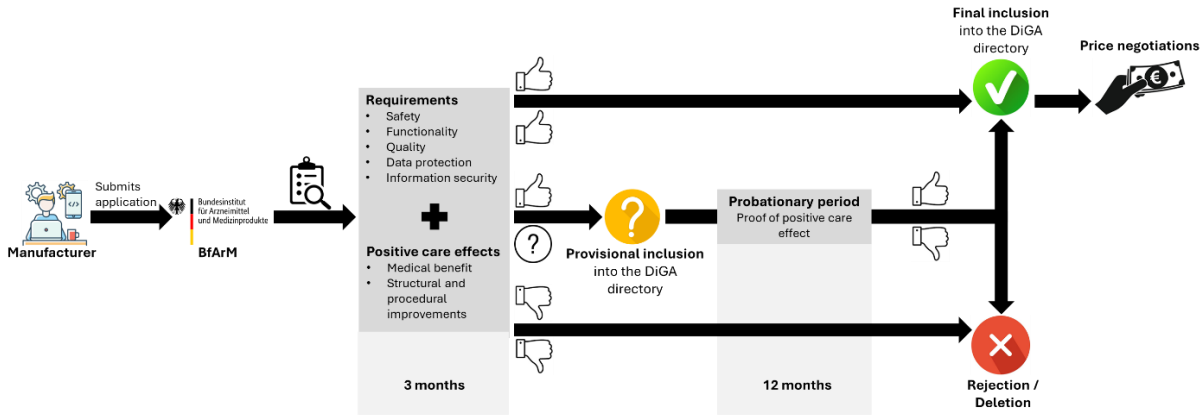

Figure 2: Fast-track process of digital health applications (DiGA), modified according to Bundesinstitut für Arzneimittel und Medizinprodukte (2023).

Summary chapter 2.5

The sustainable implementation of digital health solutions is highly dependent on appropriate reimbursement strategies. Germany's DiGA program, which was introduced by the 2019 Digital Healthcare Law, established a reimbursement framework that allows patients to receive approved DiGAs on prescription. In order to be included in the official directory of reimbursable applications (DiGA directory), a DiGA must demonstrate a positive care effect during the evaluation process conducted by the Federal Institute for Drugs and Medical Devices. As of September 2025, 57 DiGAs are listed, but none specifically target knee or hip OA. Internationally, reimbursement strategies vary, with some countries reimbursing the technology itself (e.g. Germany, France, Sweden, United Kingdom) and others reimbursing the clinical pathways within which the digital health solution is integrated (e.g. Belgium, Israel).

3 Context and research questions of the dissertation

3.1 Summary of research gaps

The research gaps can be derived from the problem statement presented in chapter 1.1 and the theoretical background and state of research described in chapter 2. A key aspect that should be considered include that, despite the established efficacy of exercise as a core treatment for knee OA, the care situation demonstrates that less than 40% of patients receive these interventions. Consequently, a promising pathway to address these deficiencies in the future may be the implementation of alternative care models, such as the use of digital health technologies for exercise delivery. In this context, findings from recent meta-analyses indicated that digital-based exercise interventions for patients with knee OA have demonstrated comparable beneficial effects on reducing pain to those of non-digital, face-to-face interventions, and were even superior to usual care. Findings concerning the effectiveness of improving physical function were observed to be inconsistent. In general, app- and web-based programs, with their special features, may result in greater benefits than telephone-based interventions. Moreover, individuals prefer varying levels of human support and have different prerequisites and needs. Nevertheless, to date, in meta-analyses and systematic reviews evaluating the effectiveness of digital-based exercise programs, distinctions between the various delivery modes (supervised vs. self-directed) have been reported only in subgroup analyses involving a small number of studies. Thereby, considerable heterogeneity among studies and a low quality of evidence were observed. To account for the small subgroups, further studies with large sample sizes are needed to improve the certainty of the evidence and the acceptability of the various exercise delivery modes. Consequently, the project presented in this dissertation aimed to address parts of the research gap by providing additional data on the subgroup of self-directed m-health exercise interventions and to examine the feasibility, effectiveness, and safety of such an intervention for achieving effects in terms of pain reduction and improvement of physical function. Furthermore, the implementation of digital health technologies in clinical routine is contingent upon the implementation of appropriate reimbursement strategies. To this end, Germany has enacted a specific law that allows for the prescription of approved DiGAs, which are listed in a DiGA directory. Thereby, a prerequisite for approval is the demonstration of a positive care effect. However, to date, none of the listed DiGAs have been specifically developed for the treatment of patients with knee or hip OA. Consequently, an additional objective of the present project was to assess whether re.flex can demonstrate a clinically relevant positive care effect in the

context of an application for approval in the DiGA directory, thereby enhancing the accessibility to an effective and safe first-line exercise treatment.

3.2 Research project re.flex

The sub-projects described in the present work were part of a comprehensive project that included the scientific evaluation of the app re.flex as part of the DiGA evaluation process in Germany. The overarching objective of this project was to demonstrate a positive care effect of the self-directed m-health exercise intervention re.flex for patients with knee OA. In this context, a mixed-methods design was employed to examine the effects on clinical outcomes, adherence, usability, satisfaction, and safety, and to evaluate patients' experiences when using the self-directed m-health exercise intervention re.flex in patients with knee OA.

The underlying software and hardware of the exercise app re.flex including features for visual and verbal feedback, monitoring, push-notifications, chat function for technical issues, and two motion sensors to allow biofeedback on knee joint motion via an avatar was developed by Kineto Tech Rehab SRL© (Romania). In October 2019, the research team from the Department of Sports Medicine of the University Hospital of Tübingen participated in a collaborative project in which the app was optimized to the requirements of patients with knee OA. In the initial phase of the project, this involved the implementation of a graduated 12-week exercise program. The program was developed based on disease-specific recommendations (Fernandes et al., 2013; Garber et al., 2011; McAlindon et al., 2014) and the study team's experience in planning and implementing exercise interventions for patients with hip and knee OA (Haupt et al., 2014; Krauss et al., 2014; Merk et al., 2005; Steinhilber et al., 2012). Furthermore, during the course of the project, new exercise videos were produced, written exercise instructions were drafted, dosage principles were specified, and the range of motion for each exercise was defined to allow proper biofeedback on movement control. Additionally, new app features such as monitoring of perceived exertion and pain have been integrated. Detailed information regarding the content and functions of the re.flex app, along with screenshots illustrating the most important features, can be found in the "methods" section of the research articles 1, 3, and 4, as well as in the appendix of research article 4. An iterative design approach was employed in two test phases of two and four weeks, to evaluate and improve parts of the exercise program, the app handling, and usability. This approach involved volunteers who reported knee concerns. In a second step, the efficacy of the 12-week digital exercise program for patients with knee OA conducted with the re.flex app was evaluated in a pilot RCT including 61 participants, which started on September 21, 2020 (study 1). Notably, a particular challenge that was encountered during the study was that the recruitment and

intervention period coincided with the peak of the COVD-19 pandemic. Finally, the study phase was completed with the final follow-up assessments conducted on January 27, 2021. After this period, the second study phase commenced (which was not part of the evaluation of study 1). During this phase, patients primarily allocated to the control group also received the intervention, as the study was conducted in a waitlist control design. Participants of this second study phase were subsequently included in the qualitative interview study, which was conducted with 14 participants between May 6, 2021 and May 19, 2021 (study 2). On March 22, 2021, the study sponsor applied for the inclusion of re.flex in the DiGA directory. Thereby, the research team of the Department of Sports Medicine contributed an evaluation concept (including the study protocol of the pilot study), a systematic literature review on the effectiveness of digital apps to guide exercise interventions in patients with knee and hip OA, and study results of the pilot RCT. However, the approval application had to be withdrawn by the submitter in September 2021 due to the lack of pre-specification. In a second approach, re.flex was re-submitted for provisional inclusion in the DiGA directory in April 2022. Again, the research team of the Department of Sports Medicine contributed an evaluation concept that included study results from the pilot RCT, an updated systematic literature review, and a new study protocol of the intended confirmatory RCT (study 3) for proofing the postulated positive care effects. Ultimately, the one-year probationary period commenced with the decision for provisional inclusion into the DiGA directory on September 26, 2022. The pre-specified confirmatory RCT (study 3, proof of effectiveness) was conducted between January 25, 2023 and August 11, 2023, and included 195 participants. On November 28, 2023, the study report with the results of the confirmatory RCT was submitted for final inclusion of re.flex in the DIGA directory. Following an initial rejection of the aforementioned application for approval for the final inclusion of re.flex in the DiGA directory on May 24, 2024 due to questionable clinical relevance of the reported effects, the BfArM proceeded to permanently remove re.flex from the DiGA directory on November 18, 2024, subsequent to an unsuccessful appeal process. The entire project workflow is summarized in Figure 3.

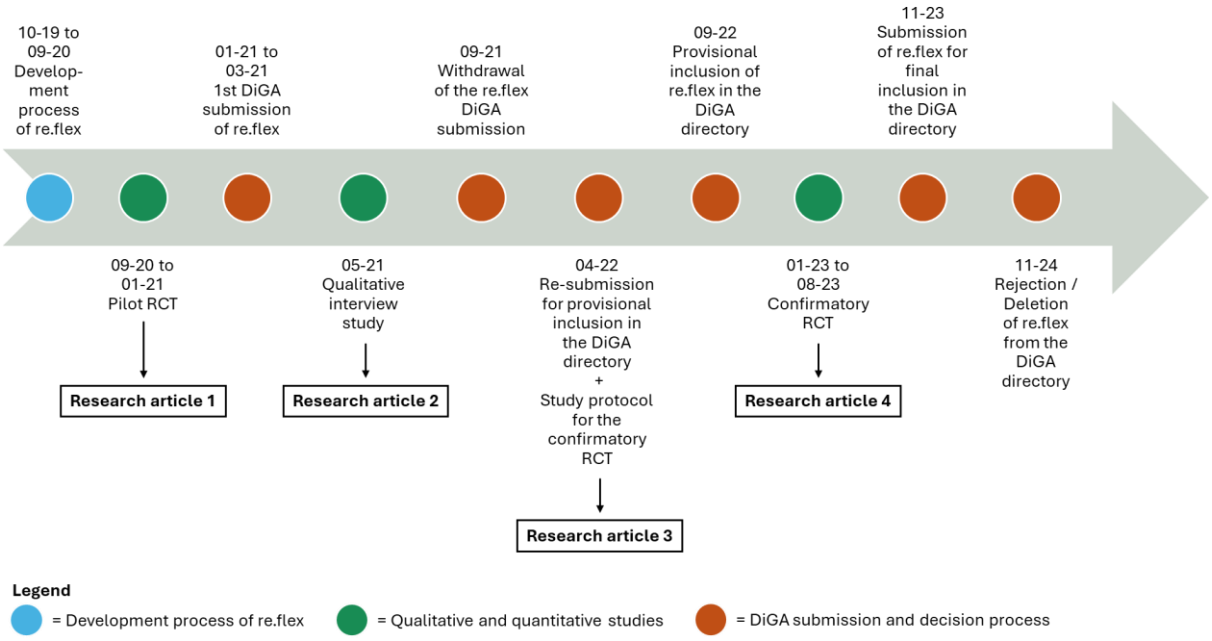

Figure 3: Workflow of the re.flex research project.

3.3 Research questions

The research articles that were included in this dissertation were drafted as part of the aforementioned project and addressed the following overarching research questions:

- Evaluation of the efficacy of a 12-week self-directed m-health exercise intervention (re.flex) on health-related outcomes, performance measures, and adherence in patients with knee OA (research article 1)
- A qualitative evaluation of patients' experiences, usability, and acceptability of a 12-week self-directed m-health exercise intervention (re.flex) for patients with knee OA (research article 2)
- Evaluation of the effectiveness of a 12-week self-directed m-health exercise intervention (re.flex) concerning the superiority of the intervention over usual care in reducing pain and improving physical function in patients with knee OA (research article 3 & 4).

4 Scientific research articles

The following chapter of this cumulative dissertation consists of the four included research articles. All four refer to the self-directed m-health exercise intervention re.flex for patients with knee OA that was evaluated in a mixed-methods approach. A general overview of the articles and the author's contribution is provided in Table 3.

Table 3: Research articles of the cumulative dissertation.

Authors	Year	Study design	Status	Journal	Author's Contribution
Dieter V, Janssen P, Krauss I (Dieter et al., 2024)	2024	Pilot RCT	Published	Journal of Medical Internet Research (mHealth and uHealth)	• Development of the study design[1] • Data acquisition • Data analysis • Drafting and revising[1] the manuscript
Dieter V, Schmidt J, Krauss I (Dieter, Schmidt, et al., 2025)	2025	Qualitative study	Published	BMJ Open	• Development of the study design[1] • Data acquisition • Data analysis[1] • Drafting and revising[1] the manuscript
Dieter V, Martus P, Janssen P, Krauss I (Dieter et al., 2023)	2023	Study protocol	Published	BMC Digital Health	• Development of the study design[1] • Drafting and revising[1] the manuscript
Dieter V, Martus P, Seissler D, Serna-Higuita LM, Janssen P, Krauss I (Dieter, Martus, et al., 2025)	2025	Confirmatory RCT	Published	Journal of Medical Internet Research	• Development of the study design[1] • Data acquisition • Data analysis[1] • Drafting and revising[1] the manuscript

RCT Randomized Controlled Trial

[1]in cooperation with co-authors

4.1 Research article 1: Efficacy of the mHealth-based exercise intervention re.flex for patients with knee osteoarthritis: Pilot randomized controlled trial

Dieter, V., Janssen, P., & Krauss, I. (2024). Efficacy of the mHealth-based exercise intervention re. Flex for patients with knee osteoarthritis: pilot randomized controlled trial. *JMIR mHealth and uHealth*, *12*(1), e54356.

Published online on September 9, 2024. Page numbers have been added for this dissertation.

Original Paper

Efficacy of the mHealth-Based Exercise Intervention re.flex for Patients With Knee Osteoarthritis: Pilot Randomized Controlled Trial

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Abstract

Background: Exercise therapy is recommended by international guidelines as a core treatment for patients with knee osteoarthritis. However, there is a significant gap between recommendations and practice in health care. Digital exercise apps are promising to help solve this undersupply.

Objective: This study aims to evaluate the efficacy of a 12-week fully automated app-based exercise intervention with and without a supporting knee brace on health-related outcomes, performance measures, and adherence in patients with knee osteoarthritis.

Methods: This closed user group trial included participants with moderate to severe unicondylar painful knee osteoarthritis. Randomization was 1:1:2 into an intervention group (IG) with 2 subgroups (app-based training [IG A] and app-based training and a supportive knee brace [IG AB]) and a control group (CG). The intervention included a 12-week home exercise program with 3 sessions per week. Instructions for the exercises were given via the app and monitored using 2 accelerometers placed below and above the affected knee joint. Participants in the CG did not receive any study intervention but were allowed to make use of usual care. Osteoarthritis-specific pain (Knee Injury and Osteoarthritis Outcome Score) was defined as the primary outcome, and secondary outcomes included all other Knee Injury and Osteoarthritis Outcome Score subscales, general health-related quality of life (Veterans RAND 12-item Health Survey), psychological measures (eg, exercise self-efficacy), performance measures (strength and postural control), and the monitoring of adherence and safety. Outcomes were assessed at baseline and after 12 weeks. Intervention effects were calculated using baseline-adjusted analysis of covariance for the joint comparison of IG A and IG AB versus the CG using a per-protocol approach. Subgroup analyses were conducted for each IG separately.

Results: A total of 61 participants were included (IG: n=30, 49%; CG: n=31, 51%; male: n=31, 51%; female: n=30, 49%; mean age 62.9, SD 8.5 years; mean BMI 27.7, SD 4.5 kg/m^2). Analysis revealed statistically significant effects in favor of the IG for pain reduction (P<.001; effect size [ES]=0.76), improvements in physical function (P<.001; ES=0.64), improvements in symptoms (P=.01; ES=0.53), improvements in sport and recreation activities (P=.02; ES=0.47), improvements in knee-related quality of life (P<.001; ES=0.76), and improvements in the physical component of general health-related quality of life (P<.001; ES=0.74). Mean differences ranged from 6.0 to 13.2 points (scale range 0-100). ESs indicated small to medium effects. No effects were found for psychological and performance measures. Participants adhered to 92.5% (899/972) of all scheduled exercise sessions.

Conclusions: Individuals with knee osteoarthritis undergoing a 12-week sensor-assisted app-based exercise intervention with or without an additional knee brace experienced clinically meaningful treatment effects regarding pain relief and improvements in physical function as well as other osteoarthritis-specific concerns compared to controls.

Trial Registration: German Clinical Trials Register (DRKS) DRKS00023269; https://drks.de/search/de/trial/DRKS00023269

(JMIR Mhealth Uhealth 2024;12:e54356) doi: 10.2196/54356

KEYWORDS

digital app; mobile health; mHealth; knee osteoarthritis; exercise; knee brace

Introduction

Background

Osteoarthritis is a degenerative joint disease and one of the major contributors to global disabilities [1]. The prevalence rate of osteoarthritis increases with age, with women being more frequently affected than men [1,2]. Almost 30% of the German population in the sixth decade of life have been diagnosed with osteoarthritis [3]. The knee joint is the most commonly affected joint of the lower extremities. With disease progression, knee osteoarthritis is more frequently associated with increasing pain, limitations in physical function [4], and decreased health-related quality of life (HRQoL). National and international guidelines recommend exercise therapy as a nonpharmacological core treatment for patients with knee osteoarthritis [5-8]. Exercise programs have shown to decrease pain and improve physical function [9]. They can include strengthening exercises but also aerobic training, neuromuscular training, balance training, mixed exercise programs, aquatic exercises, or mind-body activities such as tai chi or yoga [5,6,8,10]. Different training settings (individual, group based, and home based) have also shown to be effective, allowing patients to exercise according to their individual preferences [5]. However, it is suggested that most people with knee osteoarthritis need some form of ongoing monitoring or supervision to optimize the clinical benefits of exercise treatment [9,10]. Despite given consensus on the need to recommend exercise with some kind of supervision, there is a considerable discrepancy regarding its implementation in health care. In 2016, <40% of patients with hip, knee, or polyarticular osteoarthritis who were customers of a German statutory health insurance company received a prescription for therapeutic exercise [11], and similar numbers have been described in an international meta-analysis [12]. Therefore, it seems reasonable to explore alternative approaches for people with limited access to therapeutic services [13]. In this regard, digital apps for exercise instructions could be particularly suitable to support patients in doing exercises. A recently conducted questionnaire study with health care professionals revealed very high acceptance of mobile health (mHealth)–based intervention therapies in osteoarthritis treatment. This indicates that they would also recommend or prescribe m-Health exercise interventions [14]. The main advantages of apps are related to their use independent of time and location, making this kind of intervention available for many patients even in rural areas [15-17]. In addition, special app features such as information and advice for guidance, tracking and self-monitoring of health behavior, feedback mechanisms, and reminders via push notifications can be of particular value [18,19]. The integration of accelerometers can additionally support patients in conducting exercises in a correct and safe manner by imitating human supervision. In general, 2 main types of mHealth apps are differentiated: interactive and stand-alone apps. Interactive mHealth apps can be used for communication between patients and health care professionals such as physical therapists [20]. These kinds of apps are frequently used in the context of blended care [21]. In contrast, stand-alone apps do not involve interaction with a health care professional, and patients exercise autonomously [22,23].

Both kinds of apps can provide an added value for patients by supporting them in implementing and maintaining exercise in their life and profiting from associated health benefits. A recent meta-analysis reported short-term improvements in pain relief and quality of life (QoL) in patients with knee osteoarthritis or chronic knee pain following the use of technology-based exercise and physical activity programs [19]. However, only 2 of 12 included randomized controlled trials explicitly used an mHealth app [23,24], and only one of these examined a structured exercise program [23]. Therefore, it seems reasonable to conduct further research specifically to evaluate mHealth-based structured exercise programs for patients with knee osteoarthritis. Consideration should also be given to the type of interaction between patients and health care providers in the app.

In addition to exercise, unloading knee braces for patients with tibiofemoral unicondylar medial knee osteoarthritis can be used with the aim to reduce pain, joint stiffness, and medial compartment loading and enhance joint proprioception and functional stability [6,10,25,26]. These effects may also support the conduction of exercises, and in that case, unloader braces have the potential to serve as a treatment-supporting device. Despite limited evidence of the effectiveness of knee braces [6,8], the German guideline for the treatment of knee osteoarthritis recommends unloader knee braces as a “can do” option [7].

Objectives

Considering that exercise is one of the core treatment options for knee osteoarthritis, as well as the fact that mHealth provides new opportunities to guide home-based exercise, and the potential benefit of unloader braces to support exercise conduction, this study aimed to investigate the efficacy of a 12-week mHealth app–supported exercise intervention (re.flex) with (intervention group [IG] AB) and without (IG A) a corrective knee brace in comparison to a control group (CG) on health-related outcomes in patients with moderate to severe unicondylar knee osteoarthritis. The primary outcome was the joint comparison of the 2 app-based study arms (IG A and IG AB) regarding osteoarthritis-specific pain (Knee Injury and Osteoarthritis Outcome Score [KOOS], pain subscale) versus the CG immediately after the 12-week intervention phase.

Methods

Study Design

This study was conducted as a randomized controlled superiority trial. Study participants were randomly assigned in a 1:1:2 ratio to an IG with 2 subgroup arms (app-based exercise training [IG

A] and app-based exercise training in combination with a supportive knee brace [IG AB]) and a CG. The study is reported following the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [27] and the Consensus on Exercise Reporting Template checklist for reporting exercise interventions [28].

Ethical Considerations

Ethics approval was obtained from the ethics committee of the University Hospital Tübingen (550/2020BO). The participants signed a written informed consent and were given a study ID number. Identifiable information was stored on password-protected servers. There was no compensation for participation in the study. Study materials were provided to participants for free. The study was registered in the German Clinical Trials Register (DRKS00023269).

Participants

Participants with knee osteoarthritis were recruited via advertisements in regional newspapers as well as emails sent to the employees of the University Hospital Tübingen and the University of Tübingen. Interested persons were screened for eligibility via phone call. Final inclusion or exclusion took place at the University Hospital Tübingen in the context of the medical examination at baseline. Inclusion and exclusion criteria are described in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for study participants.

Inclusion criteria

- Age of ≥18 years
- Knee osteoarthritis (self-reported according to the wording of the study questionnaire Gesundheit in Deutschland aktuell [29] and verified by the study physician at t0)
- Unicondylar tibiofemoral concerns
- Moderate to severe knee osteoarthritis assessed using the Knee Injury and Osteoarthritis Outcome Score, pain subscale (≤60 points at the time of screening)
- Knee osteoarthritis as the primary location of symptoms
- Access to a tablet or mobile phone with iOS operating system
- Willingness to use the app to exercise
- Willingness to wear a brace while exercising
- Informed consent for study participation

Exclusion criteria

- Scheduled or implanted knee joint replacement
- Osteoarthritis primarily located in the hip joint or a joint other than the knee
- Diffuse knee pain or retro-patellar pain only
- Concerns affecting physical performance in everyday life (measured using the Physical Activity Readiness Questionnaire [30,31] and verified by the study physician at t0)
- Concerns located at the back or lower extremities currently treated by a physician or health professional and other previous surgeries, injuries, or concerns that may impair measures of strength and balance or the exercise intervention itself
- Insufficient German language skills for self-administered questionnaires and app instructions during training

Development of the Intervention

The re.flex intervention (Kineto Tech Rehab SRL) served as the underlying software and hardware for the intervention, including the basic app structure and the biofeedback via an avatar of the moving body part that is regulated by 2 accelerometers to guide and control training exercises. On the basis of this, a 12-week exercise program specifically designed for patients with knee osteoarthritis was developed by a team of experts of the Department of Sports Medicine at the University Hospital Tübingen. This program was then implemented into the app by the software manufacturer. Exercises were selected based on current knee osteoarthritis–specific recommendations from international guidelines [5,6,32] and years of experience by the study team in planning and conducting exercise interventions for patients with hip and knee osteoarthritis [33-38]. To test, analyze, and improve the re.flex knee osteoarthritis intervention during the development process, an iterative design approach [39] was used. In 2 test phases of 2 and 4 weeks, parts of the exercise program, as well as the app handling and usability, were tested by volunteers with knee concerns (data not published). Volunteers involved in the test phases were not included in the randomized controlled trial. In this study, the iOS app version 1.1.38 at the time of intervention completion of the IG was evaluated. During the intervention phase, minor technical bugs were fixed.

App-Guided Exercise Intervention

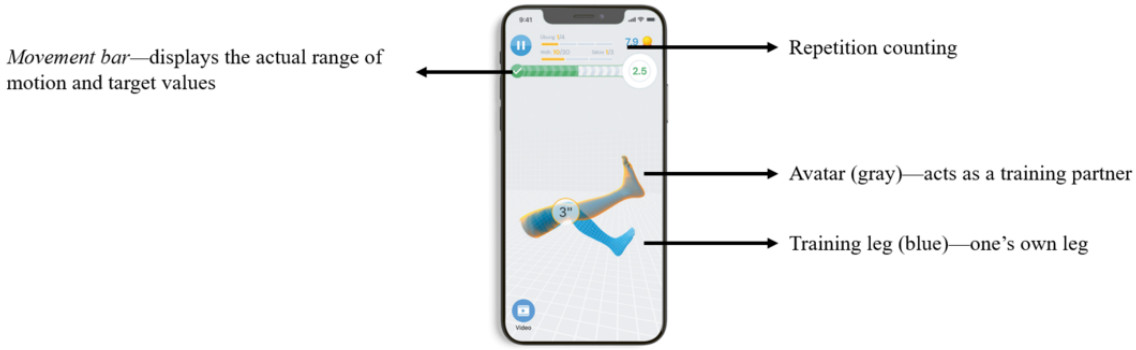
The exercise intervention was a 12-week app-guided home training program specifically designed for patients with knee osteoarthritis.

App Features

The re.flex app can be classified as a fully automated, digital health app including a training app and 2 accelerometers to monitor joint movement. It was used to guide and monitor the 12-week exercise intervention of this study. Sensors were attached proximally and distally to the affected knee joint or to the more affected joint (ie, signal joint) in case of bilateral knee osteoarthritis. They were directly attached to the skin using a hook-and-loop tape (IG A; Figure 1, left) or integrated into the brace (IG AB; Figure 1, right). Before each training session, sensors had to be calibrated by performing a movement task. The app acted as a virtual training partner, providing exercise descriptions and videos as well as setting the number of repetitions and sets of the exercises. Movement execution was monitored by the sensors and visualized via a blue avatar leg in the app interface. The blue avatar had to be aligned with another displayed gray avatar leg that moved according to the recommended movement velocity. A movement bar further visualized the current range of motion of the training leg. This bar served as an orientation on how far the leg should be moved in each direction relative to the starting position. If an exercise was not performed correctly, verbal instructions were given (eg, “extend your knee more”). After each set of exercises with the sensor-equipped leg, patients were called to conduct the set with the other leg as well. However, sets and repetitions of the other leg were performed autonomously and were not monitored in the log files of the app. Another feature of the app was to remind users of upcoming training sessions via push notifications. Figure 2 and the app manual (Multimedia Appendix 1) illustrate the structures and features of the re.flex app. The use of the app and sensors for IG A and IG AB was introduced after randomization at baseline by the pretrained study staff. Patients further received a user manual for software and hardware and log-in data for their personal anonymous and free app user account. The login data did not contain any personal data of the participants but used a fake email address with the patient’s pseudonym and an individual password. Only the authors of this study were able to reidentify them with their personal data.

Figure 1. Re.flex technology directly attached to the lower limb (left) and Sporlastic GmbH GENUDYN OA SMART with re.flex technology (right).

Figure 2. Screenshot with features of the re.flex app.

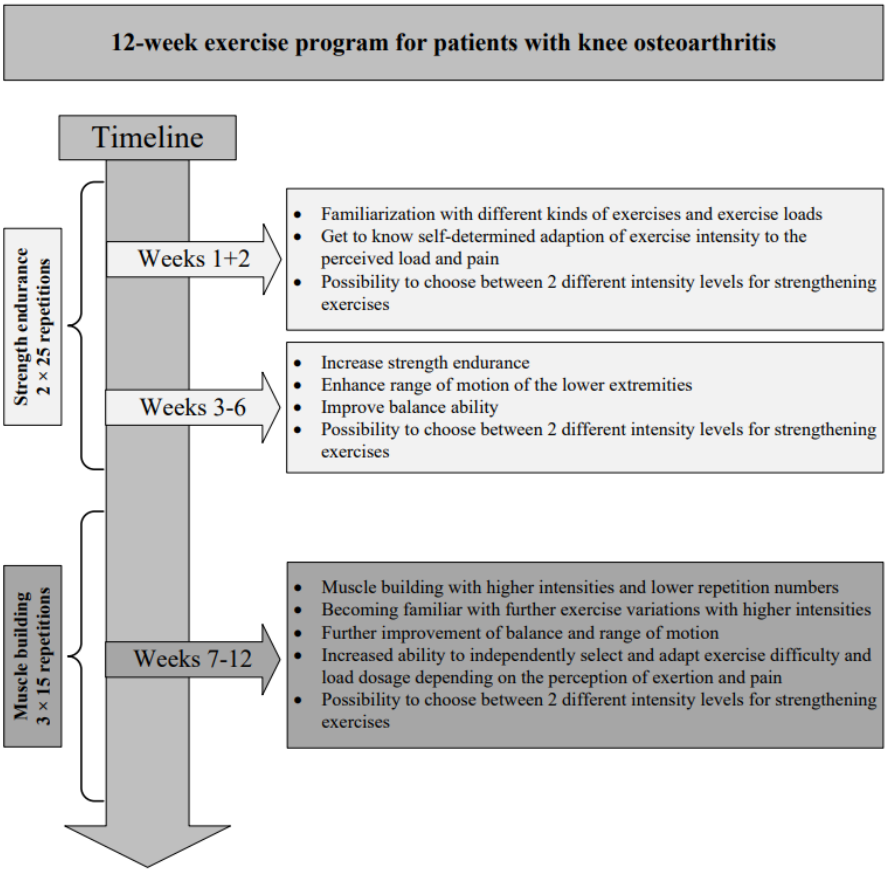


Exercise Program

The progressively designed 12-week program included 3 sessions per week with 5 different exercises and a duration of 25 to 30 minutes each. The exercise poses differed between supine, sitting, and standing. The primary focus of the intervention was to strengthen knee extensors, knee flexors, and hip abductors. Furthermore, exercises aimed for mobilization, muscle stretching, and balance training. The required training material included a chair, a ball or a pillow, and the provided training bands with different resistance levels.

The first 2 weeks focused on familiarization with different kinds of exercises and exercise loads. In this regard, patients were able to adapt exercise intensity self-determinately according to perceived strain and pain, which were assessed after each set of exercises as well as before and after each training session using in-app scales. After the period of familiarization, the exercise sessions of the following 4 weeks were designed to increase strength endurance, enhance the range of motion of the lower extremities, and improve balance ability. From week 7 on, the intervention mainly focused on muscle building. Concurrently, the complexity of the balance tasks was increased accordingly by reducing the sensory input (eg, eyes closed) or modifying the supporting surface (eg, tandem stance). The exercises provided in 2 intensity levels were predefined for each session. An overview of the different phases and objectives within the 12-week exercise program is given in Figure 3. Throughout the intervention phase, users could contact the provider for technical and medical issues using the app messenger service. In the context of the study, this function was supervised by the study personnel.

Figure 3. Objectives of the 12-week exercise program.



Individual Exercise Dosing

At baseline, participants were instructed by the study staff to perform the last 2 to 3 repetitions of each set within a strenuous to very strenuous exertion level. During balance tasks, participants were instructed to perform the task properly at all times while still maintaining the challenge. To ease the fitting of the optimal intensity level, patients could always choose between 2 different intensity levels via an in-app button feature and could further vary the resistance of elastic exercise bands, if applicable. In addition to the intensity specifications, exercises should be performed in a pain-free to low-level pain range. The following instructions were given to the patients if they experienced increased pain during exercising: (1) check exercise performance and correct if necessary, (2) reduce training intensity by selecting an easier exercise variation or reducing the number of repetitions or sets, or (3) skip the exercise. Exercise adaptations in case of increased pain were prioritized versus intensity specifications. The information and guidance for training were provided both orally and written on a fact sheet.

Knee Brace Intervention (Additional to Exercise)

The 2 exercise groups (IG A and IG AB) only differed with respect to the additional use of a corrective knee brace (GENUDYN OA SMART; Sporlastic GmbH) in IG AB. The brace works according to the 3-point principle and exerts pressure onto the unaffected condyle to correct the leg axis.

Thus, it is indicated for patients with unicondylar concerns only. The use of the brace while exercising was mandatory. However, patients were free to use the brace in everyday life as well. Participants were asked to document the wear time of the brace in a paper-and-pencil study diary. The brace was worn at the knee joint affected by osteoarthritis or at the signal joint in case of bilateral knee osteoarthritis. It was fitted by an orthopedic technician during the baseline examination.

CG Arm

Participants on the waiting list did not receive any study intervention or instruction for any change to their normal habits—"Just keep on like before." They were allowed to make use of usual care provided by the treating physician, if applicable. Usual care was defined as any kind of prescribed pharmacological or physical interventions a patient with knee osteoarthritis usually receives when consulting a medical doctor because of knee osteoarthritis. These may include physical therapies such as regular physiotherapy, manual therapy, electrotherapy as well as orthotic devices, and medical prescriptions for pharmacological agents such as nonsteroidal anti-inflammatory drugs (NSAIDs). These reflect the relevant treatment options according to the current national guidelines in Germany [7]. Moreover, participants in this group were informed about the opportunity to make use of the app after the follow-up assessment.

Outcomes

Data collection was conducted at baseline (t0) and at the 3-month follow-up (t3). Medical examinations and the outcome assessments of performance measures before and after the intervention (t3) took place on-site at the University Hospital Tübingen. Patient-reported outcome measures (PROMs) were assessed using web-based questionnaires (Questback GmbH). Questionnaires were activated on the days of assessment (t0 and t3), and study participants were asked to answer promptly. In case of delayed response, participants received a reminder via email.

Patient Characteristics

Age, gender, BMI, medical history (eg, relevant diagnoses and previous injuries or surgeries at the lower extremities or lower back), previous experiences with strengthening exercises or hip or knee exercise groups, and technical affinity were determined at baseline (t0).

Primary Outcome

The primary outcome measure was the joint comparison of the 2 app-based study arms (IG A and IG AB) versus the CG with regard to osteoarthritis-specific pain immediately after the 12-week intervention phase (t3). Pain was determined using the 10-item pain subscale of the KOOS [40,41]. The KOOS is a patient-reported outcome measurement instrument developed to assess the patient's opinion on their knee and associated problems and uses a 5-point Likert scale. It evaluates short-term and long-term consequences of knee injuries and primary osteoarthritis in 5 separately scored subscales. Each subscale is transformed to a scale of 0 to 100 points, with a higher score reflecting a better health status.

Secondary Outcomes

Overview of PROMs

Osteoarthritis-specific symptoms, physical function (activities of daily living), sport and recreation, and knee-related QoL were assessed using the other KOOS subscales. Patient-reported HRQoL was evaluated using the Veterans RAND 12-item Health Survey [42,43]. The Mental Component Score (MCS) and Physical Component Score (PCS) were calculated and used for further analysis. They both can adopt values in the range of 0 to 100 points. Higher scores indicate a better overall HRQoL. Patients' fear of movement was determined using the 11-item German version of the Tampa Scale of Kinesiophobia [44], with a scoring range of 6 to 24 whereby a higher score indicates a greater fear of movement. Physical and sports activity of a typical week, including frequency and time spent on transportation-related cycling and sports, fitness, or recreational activities, were quantified using the European Health Interview Survey–Physical Activity Questionnaire [45]. Exercise-specific self-efficacy was examined using the 9-item multidimensional Self-Efficacy for Exercise Scale [46], which ranges from 0 (not safe at all) to 10 (absolutely safe). The scale was used as a total score and then further divided into 3 subscales: task, coping, and scheduling. Higher scores indicate a higher exercise-specific self-efficacy. Control competence for physical exercising is a subcompetency of the physical activity–related health competence model. It relates to the perceived competence to individually structure and control physical activity in a health-effective way. It is mainly based on action-related knowledge but also requires the ability to sense and interpret body signals (eg, to adjust intensities based on muscle soreness) [47]. Control competence for physical exercising was quantified using 6 items according to Sudeck and Pfeifer [47] and 4 self-constructed items specifically focusing on exercises for the lower limbs [15]. Each item was scored on a 4-point Likert scale ranging from 1 (totally disagree) to 4 (totally agree). The mean value of all items was used for analysis, with higher scores reflecting a higher level of control competence.

Performance Measures

Performance measures included isometric maximum strength measurement of the knee extensors and knee flexors using DAVID strength machines (F200 Leg Extension and F300 Leg Curl; Schupp GmbH & Co. KG). Knee extensor strength was measured at 60° knee flexion, and knee flexion strength was measured at 30° knee flexion. Before testing, participants were instructed to conduct 5 to 8 dynamic concentric repetitions of the target movement at 50% to 60% of maximum force and 2 isometric repetitions at submaximal force in the given test position. Participants were instructed not to provoke an increase in pain level during testing. All measures were taken twice for each leg, and the highest value was used for analysis. Relative values (Newton meters per kilogram of body weight) were reported.

The 30-second chair stand test [48] is an instrument to measure leg strength endurance. Participants were seated with a straight back in the middle of a chair (seat height: 17 inches; participants with a knee angle of <90° received a pad to increase chair height) with hands and arms crossed in front of the upper body.

The feet were completely positioned on the floor. Participants were asked to stand up to full knee extension and then sit back again as many times as possible within 30 seconds. The total number of times the patient did come to a full standing position within the 30 seconds were counted. One complete movement execution was allowed before measurement.

Postural control tests were performed using a plantar pressure mat (zebris GmbH) to evaluate the course of the center of pressure in four different conditions: (1) bipedaled parallel stance with eyes open and (2) eyes closed, (3) bipedaled tandem stance with eyes open and the leg with knee osteoarthritis or signal joint in front and behind, and (4) one-legged stance with eyes open standing on the leg with knee osteoarthritis or signal joint. All tests were conducted in an upright position looking forward with both hands fixed at the superior iliac crest. After one test trial to become familiar with the procedure, conditions 1 and 2 were taken once, and conditions 3 and 4 were performed twice. The lowest value of each condition was used for analysis. The test duration was 10 seconds for conditions 1, 2, and 3 and 6 seconds for condition 4.

Adherence

Sensor- and app-based log files were read out for each exercise session separately and were used to quantify exercise adherence. Intervention finishers were defined as individuals who participated with >50% of overall exercise session adherence and were still active at weeks 11 and 12 of the intervention phase. Overall exercise session adherence was quantified by calculating the percentage of conducted exercise sessions relative to the overall number of prescribed exercise sessions irrespective of the adherence to the prescribed exercise dosage (number of sets and repetitions). Exercise repetition adherence was determined using the number of valid repetitions of all exercises of a session related to the prescribed repetitions. Percentage data were averaged across all exercise sessions (mean and SD). The active training time of an exercise session was calculated by adding all intervals between the time stamps of successive repetitions of an exercise unless the differences were of >60 seconds. If so, these data were not considered to exclude resting times within the active training time. The active training time was averaged across all exercise sessions (mean and SD) and further differentiated for weeks 1 to 6 and 7 to 12. The daily training time was the gross training time. It was calculated as the difference between the first and last repetition on a training day including all breaks, recalibrations, reviewing the exercise instructions, and the training of the other leg. For analysis of the active training time and gross training time, only cases with an exercise repetition adherence of 100% were considered. In addition, cases were excluded for which the gross training time was of >180 minutes as these cases indicate long breaks during the training or split training sessions and, thus, also possibly falsify pain and intensity data. To monitor perceived exercise intensity, participants were asked to rate their perceived overall exertion at the end of each exercise session. Perceived exertion was measured using the rate of perceived exertion scale from 0 (no exertion at all) to 10 (maximum conceivable exertion). Perceived pain before and after each exercise session was measured using the Faces Pain Scale [49]. Instead of numbers, 6 faces with different facial expressions were used to comment on perceived pain. Each face was associated with a textual reference for the pain intensity, and the faces were scored as 0 (no pain), 2 (little pain), 4 (moderate pain), 6 (much pain), 8 (very much pain), and 10 (highest imaginable pain). In the app, the 6 faces of the original version were replaced by standardized emojis of the iOS platform. For perceived exertion and pain analysis, only cases in which the training session was at least started (exercise repetition adherence of >0) were considered.

Concomitant Care

Concomitant pharmacological care (NSAIDs and analgesics) during the study phase was assessed retrospectively at t3.

Safety

Participants included in the study were asked to document all adverse events (AEs) that occurred during the study period. Participants in the IGs were further instructed to interrupt the training program in case of any suspicious symptoms, fatigue, or severe pain during exercising or wearing the knee brace. Mild AEs had to be reported to the responsible study staff within 1 week (via email, phone, or in-app support chat). AEs that required referral to a physician or other health care professional had to be reported immediately. The decision on how to proceed was up to the study physician as well as the study director (sports scientist and physiotherapist) and referred to the options of complete or temporary discontinuation or modification of the training regime. During data analysis, the reports were classified into AEs and serious AEs (SAEs; events related to death, life-threatening illness or injury, or inpatient hospitalization). They were further classified into expected and unexpected events, and the link to the intervention was differentiated into *sure*, *likely*, *possible*, *unlikely*, or *none*. Actions taken were classified into need or no need for immediate medical care (eg, referral to orthopedist, physiotherapy, or medication) and change in intervention modalities (eg, modification, pausing, stopping, or none).

Sample Size

Sample size was calculated based on an a priori power analysis (PASS 2020; NCSS, LLC). The sample size estimation was related to the primary outcome regarding the comparison of the 2 app-guided IGs (independently of the possible supplementary use of a knee brace in IG AB) versus the CG. Furthermore, the sample size estimation was based on the following assumptions: α level of.05, power of β=.8, and a correlation of pretest-posttest values of r=0.5 [50]. Standardized effect sizes (ESs) were used due to a lack of studies with comparable interventions and measures of dispersion. In this regard, required sample sizes to prove ESs between f=0.2 (equal to Cohen d=0.4) and f=0.4 (equal to Cohen d=0.8) were calculated with n=14 for f=0.2 and n=51 for f=0.4. Under the aforementioned assumptions and an expected dropout rate of approximately 15%, 30 participants should be recruited into each group (IG and CG) to verify a medium ES of f=0.2.

Randomization

Before study start, a randomization list was created using computer-generated random numbers (0 and 1) in 7 blocks with 10 slots each. Subsequently, sealed envelopes were prepared containing sequential numbers corresponding to the group

assignment resulting from the randomization list. Randomization into the IG and CG in a 1:1 ratio took place after baseline testing (t0) in order of appointment (eg, the first patient received the envelope with the first lot and so on). Participants allocated to the IG were then again randomized in a 1:1 ratio to 1 of the 2 intervention subgroups, IG A or IG AB, using the aforementioned procedure, including the prestudy preparation of the randomization list and sealed envelopes as outlined previously. The sealed envelopes were handed over by the study personnel. The randomization list and the sealed envelopes were prepared by a person not involved in the conduction, assessment, or data analysis of the study. Participants were not randomized in case of exclusion before completion of the baseline examination at t0.

Blinding

Participants and study personnel responsible for data collection and data analysis were not blinded to the group assignment or type of study intervention.

Statistical Analysis

Baseline characteristics of the IG (IG A and IG AB) and CG study groups at t0 were described using descriptive statistics, with continuous data being presented as mean and SD or median and IQR and categorical variables being presented as absolute numbers and percentages. Unpaired Student 2-tailed *t* tests or Mann-Whitney *U* tests (in case the normal distribution of the data were violated) and Pearson chi-square tests for categorical data were used to compare baseline characteristics in the IG and CG. The primary outcome was evaluated using an analysis of covariance (ANCOVA) with the dependent variable at t3 (KOOS pain subscale at t3), the fixed-effect group (IG and CG), and the covariate (KOOS pain subscale at t0) to adjust for baseline values. Secondary outcomes for the comparison of the IG and CG were handled accordingly. Mann-Whitney *U* tests using the difference t3–t0 of the variable of interest were calculated as a nonparametric alternative. Imputation of missing data was not foreseen. The α level was set to .05. Adjustments for multiple testing were applied for the tandem stance to account for 2 test conditions using Bonferroni correction (α=.025). Data were analyzed as randomized (intention to treat) following the complete case analysis approach. Sensitivity analyses regarding the evaluations of the 5 KOOS subscales (primary analysis and additional explorative analysis) using the last observation carried forward method and the mean imputation method were conducted to replace missing data and, thus, control for any possible bias due to missing values. In case of no significant deviation compared to the complete case analyses, the analyses were continued as initially intended. Between-group ESs were calculated according to Olejnik and Algina [51], with the differences of the adjusted postintervention values divided by the pooled SD at t3 (original data) and interpreted according to Cohen. Thereby, ESs of 0.2 to <0.5 were interpreted as small, ESs of 0.5 to <0.8 were interpreted as medium, and ESs of ≥0.8 were interpreted as large. Data were analyzed using the software packages Microsoft Excel (Microsoft Corp) and SPSS Statistics (IBM Corp).

Subgroup Analysis

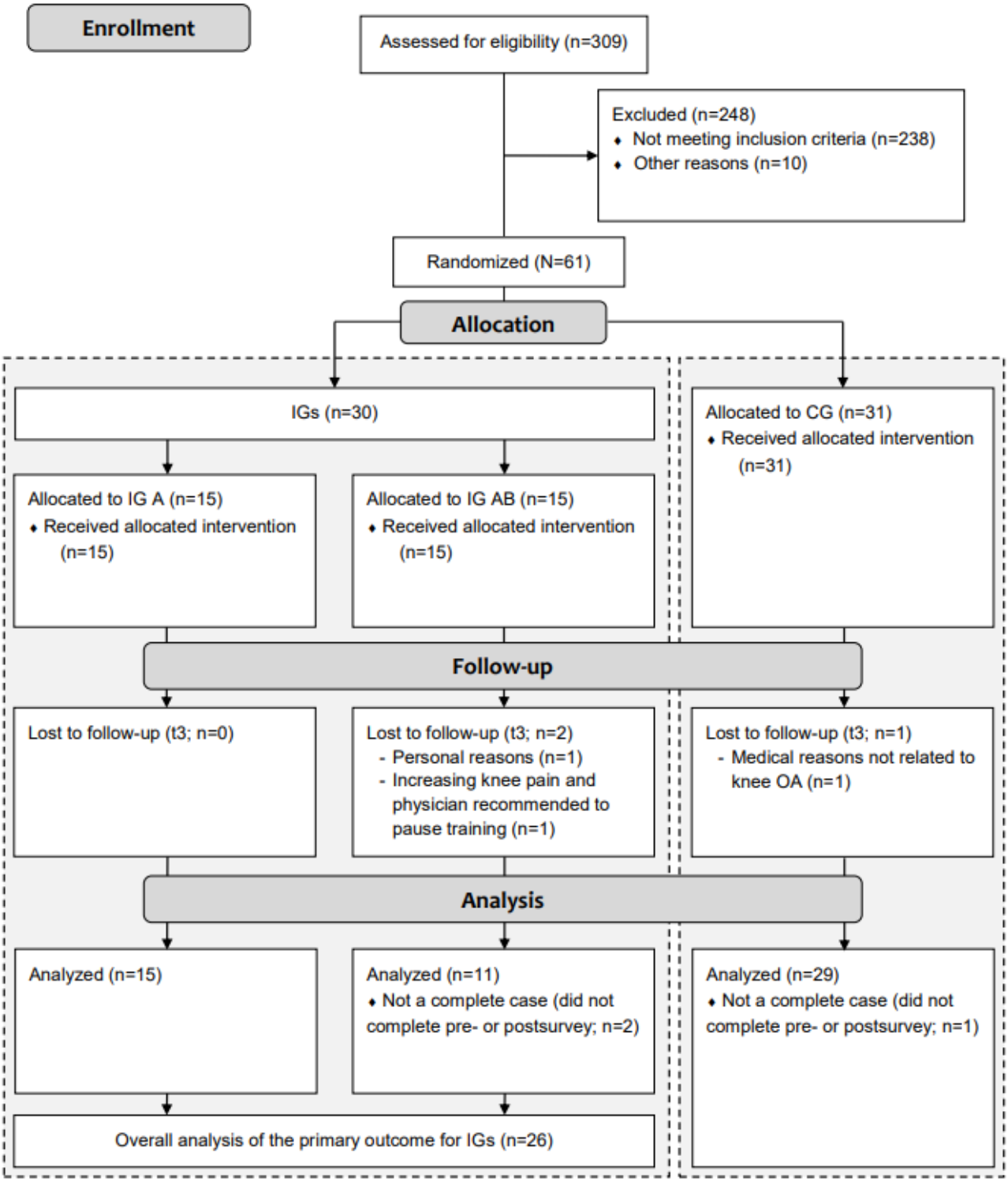
In addition to the aforementioned pooled comparison of the IG versus the CG, explorative separate subgroup comparisons of IG A and IG AB versus the CG as well as comparisons of IG A versus IG AB were conducted for the KOOS at t3. ANCOVA was used according to the procedure described previously.

Results

Participant Flow

Details on participant flow are outlined in Figure 4. Recruitment started on September 21, 2020. All patients were enrolled within 2 weeks, with the first patient included on October 12, 2020. The follow-up after the 12-week intervention period was completed on January 27, 2021. In total, 61 participants were randomized. Thereof, of the 61 participants, 30 (49%) were allocated to the IG (re.flex; n=15, 50% into IG A and IG AB each), and 31 (51%) were assigned to the CG (usual care). Loss to follow-up was 7% (2/30) for the IG and 3% (1/31) for the CG. In addition, 3 complete data sets were excluded from analysis (listwise case exclusion) due to surveys not completed at t0 or t3. Finally, 87% (26/30) of the participants from the IGs and 94% (29/31) of the participants from the CG were considered in the analysis of the primary outcome.

Figure 4. Participant flowchart. CG: control group; IG: intervention group; IG A: app-based training; IG AB: app-based training+brace; OA: osteoarthritis.



Baseline Data

Table 1 reports the sociodemographic and outcome-related baseline values of the participants. At t0, none of the variables showed a statistically significant difference between the IG and CG. Overall, the gender distribution of the participants was balanced (31/61, 51% male and 30/61, 49% female), mean age was 62.9 (SD 8.5) years, and mean BMI was 27.7 (SD 4.5) kg/m^2. However, it has to be noted that the number of male participants was higher in the IG and, on average, the participants in this group were also younger. Most of the participants (58/61, 95%) had never taken part in a hip or knee exercise group before. IG A and IG AB showed statistically significant differences at baseline for the one-legged stance of the signal joint (P=.02), with higher mean values for IG A.

Table 1. Baseline data for the complete case sample in total as well as differentiated according to group assignment (N=61).

Characteristic	Total (N=61)	IG[a] (n=30)	CG[b] (n=31)	*P* value[c]
Gender, n (%)				.16
Men	31 (51)	18 (60)	13 (42)	
Women	30 (49)	12 (40)	18 (58)	
Age (y), mean (SD)	62.9 (8.5)	61.5 (7.5)	64.2 (9.3)	.21
BMI (kg/m^2), mean (SD)	27.7 (4.5)	27.5 (5.0)	27.9 (4.2)	.75
Education, n (%)[d]				.34
Academic education	32 (53)	13 (45)	19 (61)	
Vocational education	27 (45)	15 (52)	12 (39)	
No vocational education	1 (2)	1 (3)	0 (0)	
Employment, n (%)[d]				.44
Employed	30 (50)	16 (55)	14 (45)	
Retired	30 (50)	13 (45)	17 (55)	
Previous experience with exercise therapy, n (%)				.51
Very high	5 (8)	2 (7)	3 (10)	
High	13 (21)	8 (27)	5 (16)	
Moderate	30 (49)	15 (50)	15 (48)	
Low	11 (18)	3 (10)	8 (26)	
Very low	2 (3)	2 (7)	0 (0)	
Previous participation in a hip or knee sports group, n (%)				.54
Yes	3 (5)	2 (7)	1 (3)	
No	58 (95)	28 (93)	30 (97)	
Technical affinity[e], mean (SD)	2.6 (0.6)	2.5 (0.7)	2.7 (0.6)	.25
KOOS[f], mean (SD)				
Pain	53.7 (15.9)	51.0 (15.8)	56.2 (15.8)	.22
Symptoms	56.7 (17.4)	54.3 (17.7)	58.9 (17.1)	.33
Physical function (ADLs[g])	70.4 (17.2)	68.9 (15.6)	71.8 (18.8)	.54
Sport and recreation	33.7 (21.2)	33.9 (21.5)	33.6 (21.3)	.97
QoL[h]	39.0 (15.2)	38.7 (15.7)	39.2 (15.0)	.90
Health-related QoL[i], mean (SD)				
PCS[j]	38.2 (9.3)	37.3 (9.0)	39.0 (9.7)	.51
MCS[k]	55.2 (9.3)	54.6 (10.9)	55.7 (7.9)	.67
Exercise-specific self-efficacy[l]				
Overall, median (IQR)[m]	8.4 (1.9)	8.7 (2.3)	8.3 (1.5)	.79
Task efficacy, median (IQR)[m]	8.3 (2.7)	8.5 (2.8)	8.3 (2.3)	.60
Coping efficacy, mean (SD)	7.7 (1.8)	7.7 (2.2)	7.7 (1.5)	.97
Scheduling efficacy, median (IQR)[m]	9.7 (1.7)	9.5 (2.1)	9.7 (1.2)	.20
Control competence[n], mean (SD)	3.0 (0.7)	3.1 (0.7)	3.0 (0.6)	.50
Fear of movement[o], mean (SD)	10.7 (3.7)	10.9 (3.9)	10.4 (3.5)	.62
Aerobic physical activity[m,p] (minutes per week), median (IQR)	300.0 (425.0)	275.0 (435.0)	345.0 (402.5)	.56

Characteristic	Total (N=61)	IG[a] (n=30)	CG[b] (n=31)	*P* value[c]
Isometric maximum force measurement[q]				
Knee extension (N m/kg), mean (SD)	1.2 (0.5)	1.3 (0.5)	1.1 (0.4)	.08
Knee flexion (N m/kg), median (IQR)[m]	1.02 (0.5)	1.1 (0.5)	1.0 (0.3)	.13
30-second chair stand (repetitions)[m,r], median (IQR)	10.0 (3.0)	10.0 (4.0)	10.0 (3.0)	.18
Postural control—COP[s] path (mm)				
Bipedaled parallel stance (eyes open), median (IQR)[m,t]	47.1 (29.1)	45.5 (31.4)	49.8 (39.5)	.10
Bipedaled parallel stance (eyes closed), median (IQR)[m,u]	86.3 (53.4)	88.5 (50.5)	83.5 (72.5)	.41
Bipedaled tandem stance with signal joint leg in front, mean (SD)[v]	245.6 (91.4)	235.7 (98.0)	256.2 (84.2)	.42
Bipedaled tandem stance with signal joint leg at the back, median (IQR)[m,w]	222.1 (120.1)	213.2 (110.4)	224.1 (128.4)	.64
One-legged stance of signal joint, mean (SD)[x]	184.4 (75.2)	182.5 (78.7)	186.4 (72.8)	.86

[a]IG: intervention group.
[b]CG: control group.
[c]The *P* value related to the comparison of the IG versus the CG.
[d]n=1 missing value.
[e]5-point Likert scale from 1 (*not true at all*) to 5 (*fully true*); n=6 missing values.
[f]KOOS: Knee Injury and Osteoarthritis Outcome Score. Scored from 0 to 100, with higher scores reflecting a better health status; n=6 missing values.
[g]ADL: activity of daily living.
[h]QoL: knee-related quality of life.
[i]Scored from 0 to 100, with higher scores reflecting a better health-related QoL; n=6 missing values.
[j]PCS: Physical Component Score.
[k]MCS: Mental Component Score.
[l]10-point scale from 0 (*not safe at all*) to 10 (*absolutely safe*); n=6 missing values.
[m]In case of nonparametric testing, median and IQR were reported.
[n]4-point Likert scale from 1 (*totally disagree*) to 4 (*totally agree*); n=6 missing values.
[o]Scored from 6 (*no fear*) to 24 (*extreme fear*); n=6 missing values.
[p]n=6 missing values.
[q]n=4 missing values.
[r]Number of counted repetitions; n=4 missing values.
[s]COP: center of pressure.
[t]n=5 missing values.
[u]n=4 missing values.
[v]n=7 missing values.
[w]n=8 missing values.
[x]n=11 missing values.

Primary Outcome

Table 2 and Figure 5 present the primary outcome, the KOOS pain subscale, at 3 months. ANCOVA showed a statistically significant between-group effect ($F_{1,\ 52}$=20.01; P<.001; ^{2}=0.278), with greater pain reduction for the IG compared to the CG. The baseline-adjusted mean difference was 13.2 points, demonstrating a medium effect in favor of the IG (ES=0.76).

Table 2. Primary and secondary outcome measures.

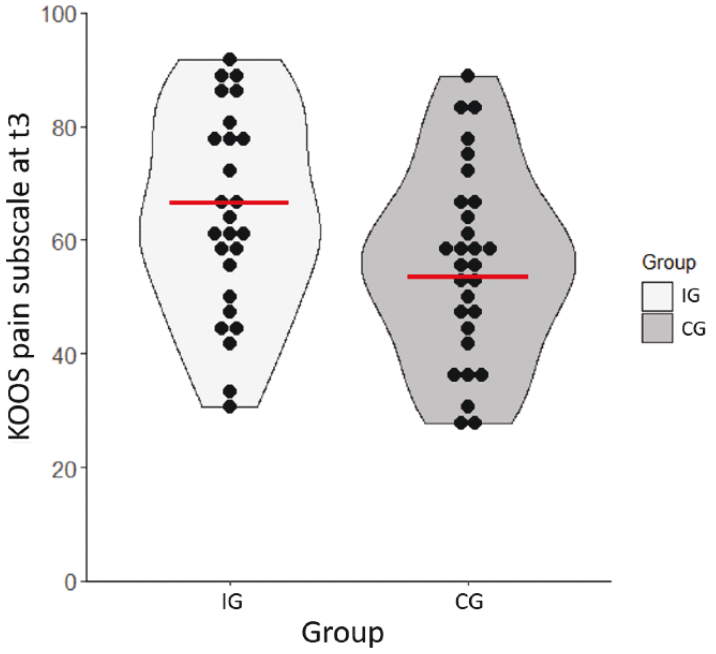
Outcome measure and group	Mean (SEM)		Mean difference (IG[a]–CG[b]; 95% CI)[c]	*P* value	ES[d]
	t0[e]	t3[f]			
Patient-reported outcome measures					
KOOS[g] (score of 0-100; worst to best)					
Pain subscale			13.2 (7.3 to 19.1)	<.001	0.76
IG (n=26)	51.0 (3.1)	66.7 (2.1)			
CG (n=29)	56.2 (2.9)	53.5 (2.0)			
Symptoms subscale			10.0 (2.4 to 17.5)	.01	0.53
IG (n=26)	54.3 (3.5)	65.1 (2.7)			
CG (n=29)	58.9 (3.2)	55.2 (2.6)			
Physical function (ADLs[h]) subscale			12.0 (5.9 to 18.1)	<.001	0.64
IG (n=26)	68.9 (3.1)	79.5 (2.2)			
CG (n=29)	71.8 (3.5)	67.5 (2.1)			
Sport and recreation subscale			10.7 (1.9 to 19.5)	.02	0.47
IG (n=26)	33.8 (4.2)	48.2 (3.2)			
CG (n=29)	33.6 (4.0)	37.5 (3.0)			
QoL[i] subscale			12.5 (6.8 to 18.1)	<.001	0.76
IG (n=26)	38.7 (3.1)	47.6 (2.0)			
CG (n=29)	39.2 (2.8)	35.1 (1.9)			
Health-related QoL (score of 0-100; worst to best)					
PCS[j]			6.0 (2.8 to 9.2)	<.001	0.74
IG (n=26)	37.3 (1.8)	44.0 (1.2)			
CG (n=29)	39.0 (1.8)	38.0 (1.1)			
MCS[k]			−2.6 (−6.2 to 1.0)	.15	—[l]
IG (n=26)	54.6 (2.1)	53.0 (1.3)			
CG (n=29)	55.7 (1.5)	55.6 (1.2)			
Exercise-specific self-efficacy (score of 0-10)					
Overall			0.1[m] (−0.8 to 1.0)	.44	—
IG (n=26)	8.1 (0.4)	7.7 (0.4)[n]			
CG (n=29)	8.2 (0.2)	7.6 (0.3)[n]			
Task efficacy			0.8[m] (−0.2 to 1.8)	.13	—
IG (n=26)	8.1 (0.4)	8.1 (0.4)[n]			
CG (n=29)	7.8 (0.3)	7.3 (0.3)[n]			
Coping efficacy			0.4 (−0.3 to 1.2)	.24	—
IG (n=26)	7.7 (0.4)	7.2 (0.3)			
CG (n=29)	7.7 (0.3)	6.7 (0.3)			
Scheduling efficacy			−0.9[m] (−1.8 to 0.0)	.42	—
IG (n=26)	8.6 (0.4)	7.8 (0.4)[n]			
CG (n=29)	9.2 (0.2)	8.7 (0.2)[n]			

Outcome measure and group	Mean (SEM)		Mean difference (IG[a]–CG[b]; 95% CI)[c]	*P* value	ES[d]
	t0[e]	t3[f]			
Control competence (score of 1-4)			0.2 (−0.0 to 0.3)	.09	—
IG (n=26)	3.1 (0.1)	3.1 (0.1)			
CG (n=29)	3.0 (0.1)	2.9 (0.1)			
Fear of movement (score of 6-24)			−1.6 (−3.3 to 0.1)	.06	—
IG (n=26)	10.9 (0.8)	9.9 (0.6)			
CG (n=29)	10.4 (0.7)	11.5 (0.6)			
Aerobic physical activity (min/wk)			150.5[m] (13.7 to 287.4)	.28	—
IG (n=26)	451.2 (97.6)	388.3 (62.9)[n]			
CG (n=29)	382.2 (66.2)	237.8 (31.6)[n]			
Performance measures					
Muscle strength					
Isometric maximum force—knee extension (N m/kg)			0.0 (−0.1 to 0.2)	.59	—
IG (n=28)	1.3 (0.1)	1.3 (0.1)			
CG (n=29)	1.1 (0.1)	1.3 (0.1)			
Isometric maximum force—knee flexion (N m/kg)			0.2[m] (−0.1 to 0.5)	.40	—
IG (n=28)	1.2 (0.1)	1.2 (0.1)[n]			
CG (n=29)	1.0 (0.1)	1.0 (0.1)[n]			
30-second chair stand test (repetitions)			1.8[m] (0.2 to 3.4)	.23	—
IG (n=28)	10.6 (0.6)	12.3 (0.5)[n]			
CG (n=29)	9.6 (0.5)	10.5 (0.6)[n]			
Postural control					
Bipedaled parallel stance (eyes open; COP[o] path in mm)			2.2[m] (−11.0 to 15.4)	.08	—
IG (n=28)	43.3 (3.3)	57.3 (4.9)[n]			
CG (n=28)	52.3 (4.3)	55.1 (4.4)[n]			
Bipedaled parallel stance (eyes closed; COP path in mm)			−23.2[m] (−53.4 to 7.0)	.22	—
IG (n=28)	89.4 (8.0)	92.2 (9.8)[n]			
CG (n=29)	101.9 (12.5)	115.4 (11.4)[n]			
Bipedaled tandem stance with signal joint in front (COP path in mm)			11.0 (−30.6 to 52.6)	.60[p]	—
IG (n=28)	235.7 (18.5)	263.4 (14.3)			
CG (n=26)	256.2 (16.5)	252.4 (14.9)			
Bipedaled tandem stance with signal joint at the back (COP path in mm)			49.8[m] (−100.9 to 1.3)	.048[p]	—
IG (n=27)	236.6 (18.1)	218.5 (14.1)[n]			
CG (n=26)	248.4 (16.9)	268.3 (21.4)[n]			
One-legged stance of signal joint (COP path in mm)			−6.5 (−30.1 to 17.1)	.58	—
IG (n=26)	182.5 (15.4)	177.1 (8.1)			

Outcome measure and group	Mean (SEM)		Mean difference (IG[a]–CG[b]; 95% CI)[c]	*P* value	ES[d]
	t0[e]	t3[f]			
CG (n=24)	186.4 (14.9)	183.6 (8.5)			

[a]IG: intervention group.
[b]CG: control group.
[c]Reporting the baseline-adjusted means.
[d]ES: effect size; only calculated for significant results.
[e]t0: baseline.
[f]t3: 12 weeks after baseline.
[g]KOOS: Knee Injury and Osteoarthritis Outcome Score.
[h]ADL: activity of daily living.
[i]QoL: quality of life.
[j]PCS: Physical Component Score.
[k]MCS: Mental Component Score.
[l]Not applicable.
[m]Mann-Whitney *U* test comparing the within-group differences t3–t0.
[n]Reporting unadjusted means; prerequisites for analysis of covariance not given.
[o]COP: center of pressure.
[p]Adjusted for multiple testing (*P*<.03).

Figure 5. Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscale at 3 months (t3) of the intervention group (IG) and control group (CG). Violin plots display data distribution (tails are trimmed to the range of the data) and baseline-adjusted means (red line).



Secondary Outcomes

PROMs and Performance Measures

Secondary outcome measures at 3 months are outlined in Table 2. At t3, statistically significant differences between the IG and the CG were observed for all additional KOOS subscales in favor of the IG (symptoms: $F_{1, 52}$=7.01, *P*=.01, and η^2=0.119; physical function [activities of daily living]: $F_{1, 52}$=15.56, *P*<.001, and η^2=0.230; sport and recreation: $F_{1, 52}$=5.98, *P*=.02, and η^2=0.103; QoL: $F_{1, 52}$=19.87, *P*<.001, and η^2=0.277), as well as for the HRQoL PCS ($F_{1, 52}$=13.94; *P*<.001; ^{2}=0.211). Baseline-adjusted mean differences between the IG and CG were between 10.0 and 12.5 points for the KOOS subscales and 6.0 points for the PCS. Interpreted according to the Cohen *d*, the intervention showed a medium treatment effect for improvements in patients' symptoms, physical function, knee-related QoL, and the physical component of the HRQoL and a small treatment effect for sport and recreation activities. No statistically significant differences between groups were observed for any other secondary patient-reported or performance-related outcome measures.

Subgroup Analyses

The exploratory subgroup analyses between IG A and IG AB demonstrated baseline-adjusted mean differences ranging from 4.7 to 12.1 points for the 5 KOOS subscales in favor of the IG AB group. However, between-group differences were not statistically significant. Subgroup analyses for IG A and IG AB separately versus the CG showed superiority of IG AB versus the CG in all KOOS subscales as well as superiority of the IG A versus the CG for pain, physical function, and QoL. Table S1 in Multimedia Appendix 2 provides more details.

Adherence

Of the 30 participants in the IG, 27 (90%) were defined as intervention finishers. During the intervention phase, one participant dropped out due to personal reasons, and another dropped out because of non–device-related increasing knee pain and a subsequent physician-recommended pausing of the training intervention. One participant ceased the intervention from week 8 onward for unknown reasons. Overall, exercise session adherence for intervention finishers was 92.5% (899/972), indicating the percentage of training sessions that were at least started. In total, 7.5% (73/972) of all training sessions were not performed (adherence=0%). The overall mean exercise repetition adherence was 86.8% (SD 28.9%). The average active training time and gross training time in weeks 1 to 12 (total) was 15.5 (SD 4.1) minutes and 31.7 (SD 17.1) minutes, respectively. On average, participants reported a perceived pain score of 0.9 (SD 1.4) points before and 1.1 (SD 1.5) points after the exercise sessions. This was according to the Faces Pain Scale, equivalent to a slight traction or mild pain. The mean difference from after to before exercise sessions was 0.2 points. After the exercise sessions, the participants reported an average intensity value of 3.5 (SD 1.4) points. According to the rate of perceived exertion scale, this indicates a slight to somewhat exhausting load. Further details on adherence, training time, exertion, and pain outcomes are outlined in Tables 3 and 4.

Table 3. Adherence and training time.

Outcome measure	Weeks 1-12	Weeks 1-6	Weeks 7-12
Overall exercise session adherence (%)[a]	92.5	93.0	92.0
Exercise repetition adherence (%), mean (SD)[a]	86.8 (28.9)	87.6 (28.0)	85.9 (29.8)
Active training time (min), mean (SD)	15.5 (4.1)	17.6 (3.3)[b]	13.3 (3.7)[c]
Gross training time (min), mean (SD)	31.7 (17.1)	36.2 (19.3)[b]	27.3 (13.2)[c]

[a]Data refer to 972 exercise sessions (12 weeks with 3 sessions per week; n=27 [n=3 no intervention finishers]).

[b]Data out of 360 exercise sessions.

[c]Data out of 364 exercise sessions.

Table 4. Perceived exertion and pain outcomes.

Outcome measure	Values, mean (SD)	Values, median (IQR)	Range
Perceived exercise intensity after exercise sessions, mean (SD)[a,b]	3.5 (1.4)	3.0 (1.0)	3.5-9.0
Perceived pain before exercise sessions, mean (SD)[b,c]	0.9 (1.4)	0.0 (2.0)	0.9-6.0
Perceived pain after exercise sessions, mean (SD)[b,c]	1.1 (1.5)	0.0 (2.0)	1.1-6.0

[a]10-point scale from 0 (*no exertion at all*) to 10 (*maximum conceivable exertion*).

[b]Data out of 888 exercise sessions.

[c]10-point scale from 0 (*no pain*) to 10 (*highest imaginable pain*).

Concomitant Care

Concomitant pharmacological care data during the study phase were available for 93% (28/30) of the IG participants and 97% (30/31) of the CG participants. Overall, at t3, a total of 14% (4/28) of the IG participants compared to 10% (3/30) of the CG participants reported a daily intake of NSAIDs or analgesics during the study phase, and 7% (2/28) of the IG participants compared to 7% (2/30) of the CG participants reported a weekly intake of NSAIDs or analgesics during the study phase.

Safety and Technical Issues

No SAEs were reported throughout the intervention phase to the study personnel. In summary, 7 AEs were reported. In total, 4 of the AEs were sure to be intervention related (AEs number 11, 21, 40, and 59), of which 3 (75%) required a modification of the training (AEs number 11, 40, and 59) and 1 (25%) required pausing the training intervention (AE number 21). Medical care was necessary in one case (AE number 40). The remaining 43% (3/7) of the AEs were not intervention related (AEs number 29, 44, and 49). Further details are outlined in Table 5.

Table 5. Adverse events (AEs) throughout the study period.

ID	Group	Harm	Type	Expectation	Link to intervention	MC[a]	CoI[b]
11	IG[c]	Increased pain due to device-initiated overload (repetition count failure and range of motion)	AE	UE[d]	Sure	No	Modification
21	IG	Increased pain and feeling of permanent muscle soreness in legs and arms	AE	EE[e]	Sure	No	Pausing
29	IG	Training interruption due to lumbago	AE	—[f]	No	No	Pausing
40	IG	Increased pain (especially for standing exercises on one leg) and activated OA[g]	AE	UE	Sure	Yes	Modification
44 (DO[h])	CG[i]	Dizziness and personal health problems	AE	—	No	Yes	None
49 (DO)	IG	Fall on knee and subsequently irritated and overloaded knee	AE	—	No	Yes	Stopping
59	IG	Increased pain and knee joint unusually warm	AE	UE	Sure	No	Modification

[a]MC: medical care; need for immediate medical care (yes) or no need for medical care (no).

[b]CoI: change of intervention.

[c]IG: intervention group.

[d]UE: unexpected event.

[e]EE: expected event.

[f]Not applicable or no link.

[g]OA: osteoarthritis.

[h]DO: dropout.

[i]CG: control group.

Technical issues reported by participants when using the app were used for minor technical bug fixes during the study period as well as for adjustments after the study period. In the following paragraph, only the summarized incident report of a participant on a specific topic is considered. On the one hand, bug fixes related to failures of the movement sensors, which, in some cases, did not adequately recognize patients' movements and, thus, led to incorrect counting of exercise repetitions. This was the case for the following exercises: wall slide (n=12), knee extension exercises (seated and supine position; n=7), and hip abduction exercises (seated and standing position; n=5). Other problems included the need for multiple recalibrations during an exercise session (n=17), an incorrect representation of the training leg on the app (twisted and no reaction; n=12), and initial problems connecting the sensors (n=7).

Discussion

Principal Findings

Overview

This pilot study aimed to evaluate the efficacy of a 12-week app-based exercise intervention with or without an additional knee brace on symptoms and function in participants with knee osteoarthritis. The results of the study demonstrated small to medium treatment effects with statistically significant reductions in self-reported osteoarthritis-related pain (primary outcome) and other osteoarthritis-specific concerns (KOOS symptoms, physical function, sports and recreation, and QoL subscales), as well as an increase in the PCS of the general HRQoL after the 12-week app training versus the CG. No intervention effects were found for any other of the secondary outcomes. The intervention showed an excellent adherence rate and no SAEs.

Overview of PROMs

Previous studies have shown superiority of exercise interventions guided by fully automated mobile apps versus control to reduce knee-related pain and improve physical function in patients with knee osteoarthritis [22,23,52]. However, in contrast to our results indicating medium ESs of >0.6 for pain and physical function, Bossen et al [52], who focused their intervention primarily on increasing general physical activity, demonstrated much smaller effects of 0.2 for pain and physical function. Regarding the absolute differences between the baseline-adjusted postmeasures of the IG and CG, substantially higher between-group differences (10.0 to 13.2 points) were reported in this study in comparison to other studies with digital interventions (2.9 to 7.7 points), of which only Mecklenburg et al [23] used a similar sensor-assisted and app-based exercise program [22,23,52]. Uesugi et al [53] did not find a significant between-group effect at all.

From a clinical perspective, within-group differences for pain in the IG of our study exceeded the minimal clinically important improvement (MCII) of 8.7 points/100 as reported for patients with knee osteoarthritis who underwent a 12-week rehabilitation intervention with active and passive therapeutic treatments. Reported cutoff values for physical function (13.4 points/100) could not be reached [54]. However, regarding minimal clinically important differences (MCIDs) between the IG and CG, the ESs of our study are within or above reported thresholds for MCIDs [55]. Nevertheless, there are many different calculation methods for determining MCII and MCID, and these values may also differ between population groups and

interventions, leading to a lack of consensus on which cutoff values should be used. Therefore, future studies should apply an own anchor-based approach to be able to define intervention-related MCID and MCII values for pain and physical function.

At present, nondigital interactions are the gold standard for exercise guidance, and novel interventions should not only be compared between each other but also in reference to the standards. Studies on nondigital interactions have reported small to medium effects in terms of pain reduction and improvement in physical function for delivery modes such as one-on-one treatments, class-based programs, and home-based exercises [9,56]. Verhagen et al [57] recently stated that the estimated effects regarding pain reduction of supervised exercising are very robust and no further intervention studies in this domain would change these findings. This is in contrast to cutting-edge results of an individual patient data meta-analysis on exercise therapy in knee and hip osteoarthritis questioning the clinical importance of reported effects versus those of a CG [58]. Accordingly, it seems reasonable to expand the field of application and investigate alternative, innovative ways of delivering exercise therapy that may further increase our knowledge of the effectiveness and mechanisms of action of new treatment delivery opportunities. Considering this, the app-based instruction appears to be a promising evolution of the currently proven standard therapy, especially as the results of this study indicate clinically important ESs. Another possible reason for the larger effects reported in our study may be related to the fact that we only included patients with at least moderate knee osteoarthritis symptoms. This reduced the potential risk of ceiling effects as the possible range of improvements for patients with early or mild disease-specific symptoms was much lower and baseline pain has been described as a moderator for treatment effectiveness [58].

The exploratory subgroup analyses for the KOOS subscales showed superiority of IG AB versus the CG in all KOOS subscales as well as superiority of IG A versus the CG for pain, physical function, and QoL. The direct comparison of both IGs provided a first indication of the superiority of IG AB versus IG A. However, these findings were not statistically significant. This potential trend of superiority of IG AB must be considered with caution due to the small subgroup sample size and should be verified in a subsequent data analysis with a larger sample.

Benefits of exercise therapy on mental and physical HRQoL in patients with knee osteoarthritis have also been reported in a recent meta-analysis with reported standardized mean differences of 0.52 for the PCS and 0.44 for the MCS [59]. Compared with these values, this study showed even greater improvements for the PCS with an ES of 0.74, yet no improvements in the MCS were observed. However, baseline scores for the MCS already exceeded the US population norm of 50 points [60].

When looking at health-psychological measures, participants in the IG had less fear of movement after the intervention in comparison to participants in the CG, although this finding failed to reach statistical significance. Mean values at baseline already indicated a low level of fear of movement in the population under study. As most participants were recruited via newspapers or newsletters, it seems reasonable that only patients who did not have fear of activity-induced worsening of symptoms would have applied to participate. We also investigated whether the self-efficacy and control competence subcompetencies of the physical activity–related health competence model improved after taking part in the stand-alone mHealth intervention. However, no differences between the IG and CG were observed. In the study population, both measures that included the subscales showed ceiling effects at baseline. Thus, the possibility of change after the intervention phase was limited.

Performance Measures

Strength endurance quantified using the 30-second chair stand test increased by 1.7 repetitions for the IG versus the CG. However, this finding was not statistically significant. Therefore, the results are in contrast to those of a study on the effectiveness of a 6-week internet-based exercise intervention against usual care in patients with knee osteoarthritis reporting a statistically significant between-group effect in favor of the intervention. The participants in the IG improved by an average of 4.5 repetitions. The between-group difference after the intervention was 3.4 repetitions [61].

Change in knee extension strength has been described as a mediator for clinical benefit in patients with knee and hip osteoarthritis [62]. Our results showed no improvement in maximum knee extension strength in the IG. This is in contrast to a meta-analysis including results of 10 studies in which low-intensity resistance training reported short-term ESs with a standardized mean difference of 0.5 when compared to the CG. However, there was also a small group of studies that failed to show significant benefits for strength outcomes. The authors of the meta-analysis [63] hypothesized that one reason for the absence of benefit may be related to the low intensity of these exercise programs as too low intensities cannot trigger sufficient muscle activity to promote neuromotor adaptations and hypertrophy to ultimately generate muscle gains [63]. This could also explain the lack of strength improvements in our study as the analysis of the sensor and app log files after the training sessions revealed only a perceived “slight” to “somewhat exhausting” intensity level, and thus, this tends to fall in the subthreshold exercise dose. In the future, patients should be better educated to enable them to independently adjust their training intensity (eg, by choosing a heavier or lighter exercise variation). At the end of an exercise set, a training-effective exercise load in the range of “strenuous” to “very strenuous” should be achieved.

We did not find consistent superiority of the IG versus the CG for postural control outcomes, and we refrain from discussing this further as measurement instruments, postures, and durations differ across trials and the measures used in our study are not part of the recommended set of performance-based measures to assess physical function in people diagnosed with knee and hip osteoarthritis [64].

Adherence

The success of exercise therapy and the associated improvements in pain, physical function, and QoL are highly dependent on the maximization of the adherence to exercise. Therefore, it is recommended to supervise exercise sessions at least in the initial exercise period to enhance adherence before continuing exercise independently [65]. Various factors (eg, motivational level, physical status, personal goals, self-regulation, and several extrinsic factors) can impact exercise adherence [47,66]. To overcome these barriers, especially for nonsupervised training, the field of digital-based exercising may offer a different approach for guidance and motivation as well as an independence from time and location. The particular group of sensor-based apps can additionally supervise the training execution and provide real-time feedback. The impact of supporting features for barrier management in eHealth and mHealth technologies may also be the reason for the high adherence rates of up to 82% to 91% for digital-based home exercise interventions (all sources, not only sensor based) in patients with knee osteoarthritis [67,68]. These numbers correspond to the adherence rate of 92.5% (899/972) in our study and exceed reported rates of 62% to 75% for nondigital home exercise interventions [69,70]. The results of our study only refer to the short term. As adherence to exercise is critical for the long-term benefit of lifestyle interventions [13], future studies may investigate whether better adherence to app-guided interventions can be sustained over a longer period as well.

Limitations

One limitation of our study is related to potential bias due to missing values of the complete case analyses. According to Jakobsen et al [71], a complete case analysis can be applied up to a threshold of approximately 5% missing values. They further report that missing data can be ignored in the analysis if the impact of missing data on the results is negligible. In our study 9.8% of data were missing but no significant differences were observed for the complete case analyses in comparison to the sensitivity analyses (data not shown) for the KOOS subscales. Another limitation is the lack of blinding of participants because of their obvious group assignment. This may have particularly influenced subjective outcome measures in the CG due to a lack of treatment expectations. A major limitation of the study is related to the sample size of the 2 subgroups, IG A and IG AB. Our study was powered for a joint comparison of IG A and IG AB versus the CG. Therefore, subgroup comparisons of IG A and IG AB versus the CG may lack statistical power and generalizability. Due to the relatively small subgroup sample size, additional data are needed to substantiate or revise the findings of a possible additional treatment effect of wearing a knee brace during exercising.

It should also be mentioned that the study design does not allow for clarification on whether the favorable study results of the IGs were the result of app use or just of the fact that participants exercised more than those in the CG. However, the aim of this trial was not to conduct a comparison of different delivery modes of exercise (eg, supervised in person vs stand-alone app) but to obtain first insights into the efficacy of a sensor-based mHealth intervention in comparison to usual care. Further comparative studies are needed to answer the question of which patients respond best to which type of delivery.

Conclusions

Individuals with knee osteoarthritis undergoing a 12-week sensor-assisted app-based exercise intervention program with or without an additional knee brace experienced positive treatment effects with medical benefits regarding pain relief and improvements in physical function as well as other osteoarthritis-specific concerns compared to those in the CG. Adherence to the exercise intervention was high, and the mobile app can be classified as a safe intervention, with no SAEs being reported. To overcome limitations in the generalizability of the results because of the rather small sample size and the joint comparison of IG A and IG AB, a well-powered trial on the effectiveness of re.flex versus a CG is currently being conducted.

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Authors' Contributions

All authors contributed to the conception and design of the study. IK and PJ were responsible for the acquisition of funding. VD and PJ contributed to the collection of data. PJ was the responsible orthopedist. VD and IK were responsible for data management, data analysis, and interpretation of the data and drafting and revising the paper. All authors read and approved the final manuscript.

Conflicts of Interest

This study was an investigator-initiated trial in cooperation with an industrial partner, the financial supporter of the study. The authors declare no further potential conflict of interest.

Multimedia Appendix 1

Re.flex manual.
[PDF File (Adobe PDF File), 48606 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Subgroup analyses for the Knee Injury and Osteoarthritis Outcome Score.
[PDF File (Adobe PDF File), 171 KB-Multimedia Appendix 2]

Multimedia Appendix 3

CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (V 1.6.1).
[PDF File (Adobe PDF File), 68132 KB-Multimedia Appendix 3]

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Abbreviations

AE: adverse event
ANCOVA: analysis of covariance
CG: control group
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
ES: effect size

HRQoL: health-related quality of life
IG A: intervention group with app-based exercise training
IG AB: intervention group with app-based exercise training in combination with a supportive knee brace
IG: intervention group
KOOS: Knee Injury and Osteoarthritis Outcome Score
MCID: minimal clinically important difference
MCII: minimal clinically important improvement
MCS: Mental Component Score
mHealth: mobile health
NSAID: nonsteroidal anti-inflammatory drug
PCS: Physical Component Score
PROM: patient-reported outcome measure
QoL: quality of life
SAE: serious adverse event

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Appendix 1: Subgroup analyes for the Knee Osteoarthritis Outcome Score

Table A1: Subgroup analyses for the Knee Osteoarthritis Outcome Score (KOOS).

Knee Osteoarthritis Outcome Score (KOOS, 0-100 worst to best)	**Group (n)**	**Mean (SE_{mean})**		**Mean difference (95 % CI)**		***P* value**	**ES**[a]
		t0	**t3**[b]				
Pain Subscale	IG-A (15)	49.8 (3.7)	61.1 (3.3)	IG-A – IG-AB	-7.7 (-18.1 to 2.7)	.139	
	IG-AB (11)	52.5 (5.5)	68.8 (3.8)				
	IG-A (15)	49.8 (3.7)	64.1 (2.4)	IG-A – C	10.5 (4.6 to 16.5)	< .001	0.62
	C (29)	56.2 (2.9)	53.6 (1.7)				
	IG-AB (11)	52.5 (5.5)	72.2 (3.2)	IG-AB – C	17.4 (9.7 to 25.1)	< .001	1.01
	C (29)	56.2 (2.9)	54.8 (2.0)				
Symptoms Subscale	IG-A (15)	51.2 (4.0)	60.5 (3.9)	IG-A – IG-AB	-6.6 (-19.1 to 5.9)	.286	
	IG-AB (11)	58.4 (6.2)	67.1 (4.6)				
	IG-A (15)	51.2 (4.0)	62.3 (3.8)	IG-A – C	7.5 (-2.0 to 16.9)	.117	
	C (29)	58.9 (3.2)	54.8 (2.7)				
	IG-AB (11)	58.4 (6.2)	70.0 (3.8)	IG-AB – C	13.4 (4.4 to 22.3)	.005	0.73
	C (29)	58.9 (3.2)	56.7 (2.3)				
Physical function (ADL) Subscale	IG-A (15)	69.4 (3.8)	76.3 (3.7)	IG-A – IG-AB	-4.7 (-16.3 to 7.0)	.418	
	IG-AB (11)	68.2 (5.2)	80.9 (4.3)				
	IG-A (15)	69.4 (3.8)	78.2 (2.6)	IG-A – C	10.3 (3.9 to 16.7)	.002	0.51
	C (29)	71.8 (3.5)	67.9 (1.8)				
	IG-AB (11)	68.2 (5.2)	82.4 (3.1)	IG-AB – C	14.5 (7.1 to 21.8)	< .001	0.82
	C (29)	71.8 (3.5)	67.9 (1.9)				
Sport/Recreation Subscale	IG-A (15)	35.7 (6.0)	43.2 (5.1)	IG-A – IG-AB	-12.1 (-28.4 to 4.3)	.140	
	IG-AB (11)	31.4 (5.9)	55.2 (6.0)				
	IG-A (15)	35.7 (6.0)	43.2 (3.3)	IG-A – C	5.2 (-3.0 to 13.4)	.210	
	C (29)	33.6 (4.0)	38.0 (2.4)				
	IG-AB (11)	31.4 (5.9)	54.8 (4.8)	IG-AB – C	17.8 (6.5 to 29.2)	.003	0.82
	C (29)	33.6 (4.0)	37.0 (2.9)				

Table A1: Subgroup analyses for the Knee Osteoarthritis Outcome Score (KOOS) (continued).

Quality of life (QoL) Subscale	IG-A (15) IG-AB (11)	38.3 (4.0) 39.2 (5.1)	43.7 (2.8) 52.4 (3.2)	IG-A – IG-AB	-8.7 (-17.5 to 0.2)	.054	
	IG-A (15) C (29)	38.3 (4.0) 39.2 (2.8)	43.8 (2.6) 35.1 (1.9)	IG-A – C	8.7 (2.2 to 15.1)	.009	0.56
	IG-AB (11) C (29)	39.2 (5.1) 39.2 (2.8)	52.9 (2.8) 35.3 (1.7)	IG-AB – C	17.5 (10.9 to 24.2)	< .001	1.15

t0: Baseline; t3: 12 weeks post baseline
SE_{mean}: standard error of mean; CI: confidence interval
IG-A: intervention group A (only app-assisted exercise training), IG-AB: intervention group AB (app-assisted exercise training in combination with an axis-correcting knee brace), C: control group
[a]ES: effect size, were only calculated for significant results.
[b] Reporting the baseline adjusted means.

4.2 Research article 2: Patients' experiences and usability of a self-directed m-health exercise intervention for knee osteoarthritis: A qualitative study

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Patients' experiences and usability of a self-directed m-health exercise intervention for knee osteoarthritis: a qualitative study

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ABSTRACT

Objectives The aim of the study was to analyse patients' experiences, usability and acceptability of a 12-week self-directed m-health exercise intervention for patients with knee osteoarthritis (OA).

Design and participants This qualitative study was included in a randomised controlled trial. After completion of a 12-week m-health exercise intervention, 14 structured telephone interviews were conducted in patients with knee OA. The interviews were audio recorded, transcribed and analysed using a combined deductive and inductive content analysis approach.

Setting The study was conducted at a university hospital in southern Germany.

Results Four themes were identified: (1) facilitators and (2) barriers for (correct) digital exercise participation, (3) ease of use and (4) outcomes. Participants valued ease of use, comprehensibility, flexibility and certain app features (eg, push notifications as reminders, instruction videos, real-time biofeedback) that facilitated guidance, control and motivation to complete exercises. However, some participants requested some kind of human support.

Conclusions The participants demonstrated predominantly positive experiences and acceptability with the self-directed m-health exercise intervention. As some participants lacked human support, we suggest that the optimal treatment option should be selected according to the preferences and needs of the individual patient.

Trial registration number DRKS00023269.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The interviews were conducted within a time window of 2–5 weeks following intervention completion, enabling adequate recall of the mobile app and the exercise programme.
⇒ The independent development of themes and subthemes by two researchers, and the subsequent review and discussion process with a third researcher, led to rigorous results.
⇒ No purposive sampling (eg, with age, sex, technical affinity, positive or negative outcomes) was included.

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent, degenerative joint disease that affects almost 18% of German adults.[1] The burden of OA increases with age, female sex and higher body mass index. The knee joint is most commonly affected.[2] In several clinical guidelines, exercise and education are recommended as first-line treatments for knee OA.[3] However, less than 50% of the German OA population received physical therapy at least once in the previous 12 months. In particular, men and individuals with a low household income were found to use physical therapy less frequently.[4] Overall, the recommendation for first-line non-pharmacological therapeutic exercise treatment is even less than 40%.[5] This is the case even though the beneficial effects of exercise are comparable to those of analgesics and oral non-steroidal anti-inflammatory drugs, and exercise therapy is known to have few side effects.[6 7] In order to address the current deficiencies in healthcare, the utilisation of digital health technologies in the delivery of exercise programmes could be increased in the future. It can be assumed that this could additionally facilitate patients' access and adherence to unsupervised home-based exercise. By definition, digital health technologies integrate information and communication tools that can be used to improve accessibility and efficiency of healthcare.[8 9] In this context, digital health is an umbrella term that encompasses electronic health (e-health), mobile health (m-health) and telehealth,[9] whereby m-health technologies specifically focus on mobile communication tools.[10] Overall, people with knee OA have already demonstrated positive experiences when using an e-Health exercise intervention. They valued the technical ease of use, simplicity and comprehensiveness of the information provided, regular prompts to support participation in self-directed exercise programmes and a credible content

source (eg, universities).[8] Additional features, including feedback mechanisms, exercise instructions, exercise images and videos, can further support correct exercise conduction without supervision[11] and thus constitute favourable determinants for the implementation of the intervention. Conversely, the absence of human presence could be perceived as a barrier by at least some patients.[11 12] The potential uncertainty regarding correct exercise performance is a reason for stopping training and can ultimately lead to non-adherence.[13] In this context, the special group of sensor-assisted digital exercise delivery represents a promising avenue for enhancing the support available to patients exercising at home. These technologies can provide additional guidance on the correct exercise execution (eg, verbal, visual and auditory) and appropriate training load, using real-time biofeedback. Consequently, they have the potential to replace supervision to a certain extent.

To date, most qualitative studies on patients with knee OA have investigated the feasibility and acceptability of web-based programmes[11 12] or supervised digital delivery modes (eg, Skype).[14] Consequently, there remains a limited understanding of patients' experiences, usability and acceptability when using a self-directed app-delivered and sensor-assisted exercise intervention for patients with knee OA. Ultimately, addressing this gap is crucial for the successful implementation of a programme.[15] In this context, existing studies on digital exercise interventions have largely overlooked the distinction between different types of digital health technologies. However, this is a critical oversight, as varying levels of technological support may present unique challenges for patients, potentially influencing their engagement and outcomes.

To investigate this, a randomised controlled pilot trial (RCT) was conducted involving a 12-week self-directed m-Health exercise intervention (re.flex). The efficacy of the intervention on knee pain and further patient-reported outcome measures was evaluated in 61 participants and published elsewhere.[16] This qualitative examination aimed to identify patients' perspectives on facilitators and barriers, usability and acceptability of a self-directed app-delivered and sensor-delivered exercise intervention. In this context, 'acceptability' was defined as a construct that reflects the evaluation of the m-health exercise app as a suitable method for delivering an exercise intervention, based on patients' experiences and needs.

METHODS

Design

The qualitative study design was integrated within an RCT (German clinical trial register: DRKS00023269)[16] (for the study protocol, see online supplemental appendix 3). The study is reported following the Consolidated criteria for Reporting Qualitative research checklist.[17]

Participants

Participants were a subsample of those allocated to the control arm of the pilot RCT, who had completed their 12-week intervention after the initial 12-week control period. Initial recruitment for the RCT was obtained via advertisements in regional newspapers and mailing lists. Eligibility criteria included a diagnosis of knee OA with unicondylar tibiofemoral complaints and at least a Knee Osteoarthritis Outcome Score (0–100, worst to best) of the subscale pain ≤60 points at the time of screening. In addition, participants were required to have access to a tablet or mobile phone with an iOS operating system. Details on full RCT eligibility criteria are reported elsewhere.[16] Participants were randomly selected. The sample size was specified a priori according to previous qualitative research studies examining digital exercise interventions for patients with knee OA.[11 12] No purposive sampling was included. After selection, the potential participants were contacted by telephone and asked for their consent to participate in the interview survey. Participation was based on voluntary consent and was independent of the previous RCT study. In case of participation, an extended consent form was signed.

Intervention

Details of the digital app-based exercise intervention conducted by the participants prior to the interview are described elsewhere.[16] The intervention included a 12-week self-directed home exercise programme with three sessions per week. Exercises were guided and monitored by use of the training app *re.flex* (figure 1) and two motion sensors that were attached proximally and distally to the affected knee joint. Thereby, the app provided exercise videos and exercise instructions. The utilisation of motion sensors enabled the visualisation of the patient's virtual limb in conjunction with an avatar reflecting the target condition. The goal was to align both avatars. Biofeedback allowed control over movement execution, predefined range of motion, movement velocity and repetition counting. Visual and auditive feedback were provided by a movement bar, a real-time rating of movement quality and an auditive signal whenever reaching the end position of a movement. Verbal instructions were given if an exercise was not performed correctly. Further app features allowed push notifications to remind for upcoming training sessions, rating of perceived pain and exertion, to pause or skip exercises and to monitor training progress with statistics. The programme comprised exercises for strengthening, balance, mobilisation and stretching with a special focus on musculature of knee extensors, knee flexors and hip abductors. The exercises were predefined for each session but could be individually tailored by choosing between two different intensity levels or varying the resistance of the bands. In case of technical and medical issues, participants could contact the provider using the app messenger service. In the context of the study, this function was supervised by the study personnel. The content of the

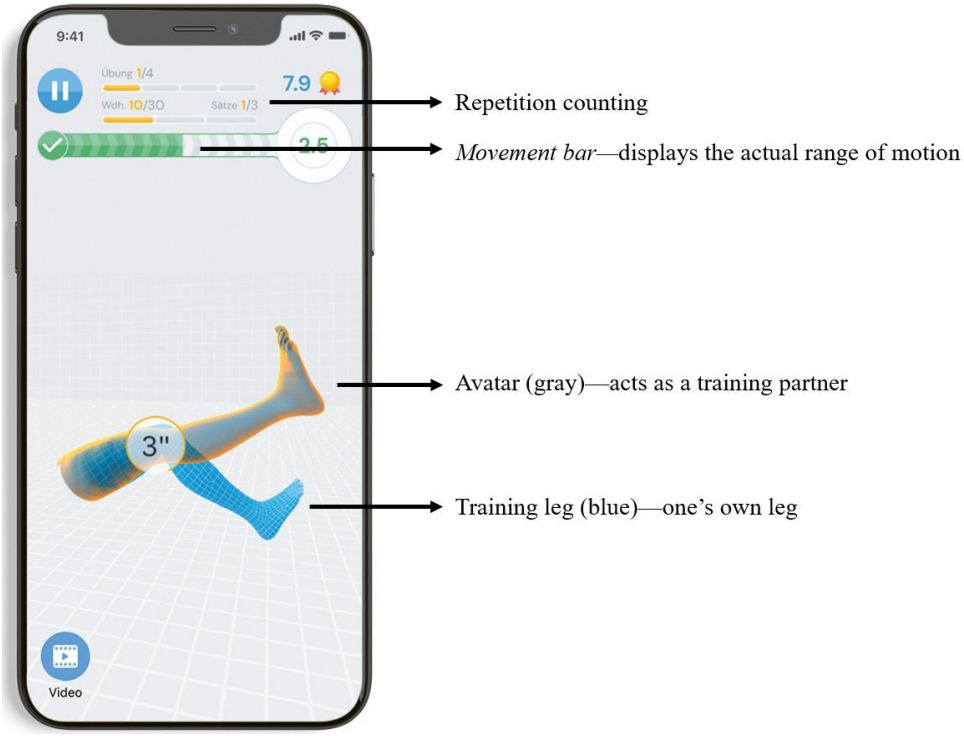

Figure 1 Screenshot with features of the re.flex app. This screenshot illustrates the key features of the re.flex app. In the upper section, repetition counting and a movement bar displaying the actual range of motion of the user are provided. The grey avatar leg acts as a training partner, demonstrating the target condition. The blue training leg represents the patient's virtual limb. The goal is to align both avatars in order to execute exercises with the correct technique, range of motion and movement velocity.

exercise programme was developed by researchers and physical therapists (eg, VD, IK) from the Department of Sports Medicine at the University Hospital of Tübingen and specifically designed for knee OA patients. The selection of exercises was based on disease-specific recommendations[18–20] and experiences of previous clinical trials in which similar exercise interventions for patients with hip and knee OA were employed.[21–24]

Interviews

Structured telephone interviews were conducted by two study staff members (IS and AM, student assistants during Health Management Studies/Sports Science Studies) who were not involved in intervention design, the recruitment for and the evaluation of the RCT. The interview guide was developed by the authors VD (sports scientist, RCT coordinator) and IK (sports scientist and physiotherapist) and addressed patients' (positive and negative) experiences with the app and its features during the course of the exercise intervention. In addition, the patients' needs and perspectives on usability, the design of the app, and suggestions for improvement to optimise app functionality were gathered (online supplemental appendix 1). Interviewers had no previous experience in guided interviews but were introduced and trained by the RCT coordinator. The participants had met one of the interviewers during the RCT assessment appointments. Interviews were audio recorded and transcribed verbatim by AM and JS. Audio records and transcripts have been pseudonymised and stored with restricted access to comply with data protection guidelines. Transcripts were not returned to participants for comment or correction, nor could participants provide feedback on the findings. No data saturation was discussed and no repeated interviews were conducted.

Data analysis

We used MAXQDA V.24 (VERBI, Berlin, Germany) for organising the pseudonymised transcripts. Data were analysed following the steps according to qualitative content analysis by Kuckartz and Rädiker.[25] A first category system was developed by one researcher (JS), combining a deductive (derivation of content of the interview guide) and inductive (elaboration of additional themes) approach. JS was not involved in interview data collection or design and evaluation of the RCT. The category system was discussed by all authors while creating new themes. In the next step, two researchers (JS and VD) independently grouped codes of all interviews into themes and subthemes. They compared and discussed results in order to seek agreement. A third researcher (IK) was included to refine subthemes and themes names and definitions. The analysis process was iterative and reflective with forward and backward movement within the different steps. After completing the analysis with data reduction, JS and VD translated all quotes from German into English language.

Patient and public involvement

None.

Table 1 Study population characteristics

	n=14
Gender (♂ / ♀), n (%)	7 (50)/7 (50)
Age in years, mean (SD)	63.9 (6.9)
Body mass index in kg/m², mean (SD)	28.0 (4.5)
Education, n (%)	
Academic education	10 (71)
Vocational education	4 (29)
Employment, n (%)	
Employed	7 (50)
Retired	7 (50)
Previous experience with exercise therapy, n (%)	
Very large	0 (0)
Large	2 (14)
Moderate	6 (43)
Low	6 (43)
Very low	0 (0)
Previous participation in a hip/knee sports group, n (%)	
Yes	0 (0)
No	14 (100)
Technical affinity*, mean (SD)	2.7 (0.6)
Baseline knee pain†, mean (SD)	57.7 (18.2)

*5-point Likert scale from 1 (not true at all) to 5 (fully true).
†Self-reported knee pain in the past week rated with the subscale pain of the Knee Osteoarthritis Outcome Score, 0–100, worse to best.

RESULTS

Participant characteristics

Out of 16 randomly selected participants, 14 gave consent and were interviewed between 6 May 2021 and 19 May 2021. All participants completed the interview within a time window of 2–5 weeks after intervention completion. Two other participants declined to participate—one for time reasons in combination with a rehabilitation stay and one due to lack of interest. The average duration of the interviews was 57 min. Table 1 reports the baseline characteristics of the interviewed participants.

Content analysis

Four main themes were identified during the data analysis. Additional details on themes, subthemes and supporting quotes can also be found in online supplemental appendix 2.

Theme 1: facilitators for (correct) digital exercise participation

App features for guidance, support and monitoring of correct exercise execution

An instruction of the exercises with a combination of videos from multiple perspectives and text descriptions was found to be useful by participants because of its ability to show even the smallest details. Additionally, an avatar acting as a training partner to demonstrate and control the exercises, auditory and visual signals when the preset target movement range was reached and verbal feedback were also rated as helpful and supportive, particularly insofar as they serve to mitigate uncertainty to conduct exercises without supervision, provide a control mechanism and offer real-time feedback on correct or incorrect movement execution.

> Yes, that [avatar acting as a training partner] helped me a lot with some exercises that I didn't understand straight away […], this highlighted color [avatar leg] and your own [patient's virtual limb], you could see, I have to stretch it [the leg] differently or I don't have to hold it that low […] that was simply a good support. [AT51]

> Yes, that [verbal feedback] was actually almost always helpful, for example when you were told 'stretch your leg a bit more' or 'your knee is too high' […], I would say that was true in most cases, it was then comprehensible, correctable, and you could also synchronize it to some extent with the avatar. [AT58]

Flexibility

The flexibility to conduct exercises at any time and in any location was seen as a key benefit of the app. The utilisation of m-health for the delivery of exercises was perceived as an optimal alternative for training at home, particularly for individuals with limited time availability or access to other training options.

> I think another big advantage is that you can simply integrate it into your day, that you are flexible, you don't have to be somewhere at a certain time and you don't lose any time […] getting from A to B to see a physiotherapist, you can just do it yourself at home. [AT38]

App features to increase motivation and regularity of the exercise programme

Participants emphasised that some of the app features, including the motion sensors that provide a control mechanism and objective monitoring of the frequency with which exercises were performed, the positive verbal feedback that was perceived as acknowledgement, the exercise overview and the reminder feature for the scheduled training days and times, were effective motivators for regular training. These features contribute to a sense of safety, control and enjoyment, which in turn increased the user's motivation to adhere to the exercise programme.

> I always felt so supported and guided, […]. I realized for myself that if I would not have had the reminder [push-notifications at training days] and the knowledge about the training days, I probably wouldn't have been so disciplined. [AT38]

Positive experiences with the exercise programme

Positive experiences with the exercise programme were linked to noticeable progress with recurring exercises

and increased difficulty level, enjoyment while exercising, alternation of demanding strength exercises and relaxed mobilisation or stretching exercises, and a manageable training volume that could be easily integrated into everyday life.

Theme 2: barriers for (correct) digital exercise participation

No on-site instruction by a health professional

Participants felt that in certain cases, for example, if pain occurred during exercise or if uncertainty was experienced during a presumably incorrect exercise execution, a health professional such as a physical therapist could have provided additional or more precise instructions or could have facilitated a more rapid correction of incorrect movements. In addition, the focus of a health professional would not have been limited to the knee; it could have also been extended to the entire body.

> I sometimes need someone to say 'your posture isn't quite okay or try this'. You do like to make evasive movements if it is painful somewhere […], so you want someone to tell you 'not like that'. […] a trained professional who looks at you and says 'now do the exercise like this'. That you simply have real control. Of course, you have control through the sensors and the app, but you can still cheat a bit. [AT10]

Technical issues

Due to technical issues, some participants encountered difficulties in conducting certain exercises. In certain instances, the calibration process required multiple attempts to accurately reproduce the correct position of the virtual training leg within the environment. A further issue was experienced with the sensor registration of performed exercise repetitions, which failed in some cases due to unreachable range of motion. This particularly concerned exercises involving resistance bands. The participants reported that technical issues had a detrimental effect on their motivation and training performance, as the affected exercise could not be completed.

> Always assuming that the thing [app with the technical features] really works. Then that would be a really great thing for me [pause]. However, if these technical issues occur and I can't solve them, then that's rather demotivating. [AT63]

Difficulties with the exercise programme

The participants identified barriers that were related to the exercise programme itself. One difficulty comprised individual exercises requiring high knee flexion in combination with high load on the affected leg (eg, one-sided exercises, wall squat) with the consequence that participants could have experienced pain. This finding seemed to be particularly pronounced among participants with a high body mass index.

Associated problems with app features

Not every incorrect exercise execution could be detected and admonished by the app. Participants reported accepting incorrect exercise execution in order to cheat the app in the absence of repetition counting due to failed sensor registration. In doing so, they sometimes did more repetitions than specified in order to register all repetitions as completed in the app. Moreover, if movements were repeatedly performed incorrectly, the verbal feedback with the error message was repeated again and again. This was sometimes perceived as annoying. Additionally, as only one leg was equipped with sensors, participants reported that the training with the non-sensor leg was done less accurately, faster and more carelessly.

Theme 3: ease of use

Usability, feasibility and comprehensibility

Most participants found the app easy to use, the navigation easy to follow and the practical implementation and information easy to understand and self-explanatory. It was reported that the technical procedures before and during the training sessions had become routine.

> I really didn't have had any difficulties, the handling is okay, it is clear, understandable, self-explanatory, and it's good. [AT10]

Handling and screen size

Several participants reported that the screen size of a smartphone was insufficient to view all available information and details, suggesting that a tablet would be a more suitable option. When exercising in the supine position, for some participants, it was a challenge to find an optimal position for the device in order to have a clear view and still be able to operate the app.

Theme 4: outcomes

Positive outcomes

Most of the participants reported that they had benefited in some way from the exercise intervention. Many of them felt less pain, required less pain medication, noticed an improvement in function or were able to do everyday activities (eg, walking, cycling, climbing and descending stairs) for a longer time and with less discomfort. Several participants also experienced a noticeable increase in muscle strength and stability around the knee, as well as improved self-efficacy.

> […] but the pain has now decreased considerably thanks to all the exercises, I am taking far fewer painkillers and when I go in with pain, it hasn't got any worse. [AT56]

> Well, I just wished or hoped that I would build up muscle in my knee and thus, become more pain-free, and that has actually turned out to be the case [pause]. So, it improved, I can walk the stairs much better, I can walk better at all. […] Overall, I was very happy with the app and also with the results. [AT53]

Not met outcome expectations

A few participants reported that their expectations of participating in the exercise study were not met, as they were unable to make any progress in terms of muscle building or pain relief. As a result, their motivation for participating in the study and weekly exercise sessions, which was to delay or avoid knee surgery, may not have been fulfilled. Moreover, one participant stated that the absence of training success resulted in a loss of enjoyment in continuing the exercises.

> As I said, the expectation that it will really improve to such an extent that surgery is no longer an option is not given, so that I will probably expect one in the next six or nine months. I didn't really have had any other expectations. [AT58]

DISCUSSION

Principal findings

This study investigated experiences, usability and acceptability of a 12-week self-directed m-health exercise intervention for patients with knee OA. Most participants reported positive outcomes, including reduced pain, an improvement in function and daily activities and an increase in muscle strength. Overall, the participants valued the ease of use, comprehensibility and self-explanatory nature of the m-health-supported exercise programme. The flexibility to conduct exercises at any time and in any location was seen as a key benefit. In addition, app features including videos, real-time biofeedback, verbal feedback and the reminder for upcoming exercise sessions via push notifications were found to be useful, supportive and motivating in order to guide and control regular exercising. However, some participants would have found some kind of human supervision in combination with the m-health intervention even more beneficial. In general, technical issues had a detrimental effect on motivation and adherence to exercise.

The participants in our study identified the ease of use, comprehensibility and self-explanatory nature of the m-health-supported exercise programme as being of significant importance. This is in accordance with findings from other qualitative studies examining experiences with self-directed or (partly) supervised e-health exercise interventions in patients with hip or knee OA. They also emphasised the importance of simplicity and comprehensibility in the use of e-health technologies and highlighted their potential impact on adherence and motivation.[11 13 26] Furthermore, push notifications as a reminder for regular exercise were valued by the participants. In other qualitative studies, email reminders and SMS messages were used in order to prompt or push participants to perform exercises.[11 27] Most participants found the reminders to be a positive facilitator and motivator.[27] Other app features that were described as facilitators and motivators for exercise participation were instructional videos,[27] the positive effect of monitoring when they knew someone was watching[13] and a feedback system.[27] These findings are consistent with the results of our study, in which participants identified videos, real-time biofeedback, verbal feedback and push notifications as supportive and motivating tools for regular exercise participation.

Flexibility to undertake exercises at any time and in any location was found to be a key benefit of the m-health exercise delivery in the current study. In particular, it was considered to be a highly appreciated alternative for training at home, which could be conducted without wasting time travelling to another location. This finding was corroborated by two further studies using e-health technologies to promote physical activity, exercise and education, either without human support or asynchronous chat support.[12 27] Overall, the combination of flexibility with appropriate exercise guidance using e-health technologies could facilitate greater access to conservative OA exercise treatment for a larger number of individuals. This also has a societal value, as exercise is classified as a first-line treatment in knee and hip OA care.[3]

However, despite the numerous benefits and facilitating factors associated with participating in m-health delivered exercise, the participants identified a significant barrier in the absence of human supervision and on-site instruction by a health professional. The participants indicated a lack of additional or more precise instructions, particularly if pain occurred during the exercise or if the exercises were performed incorrectly. Studies investigating self-directed e-health interventions have reported similar findings.[11 12] Participants suggested that e-health interventions could be improved by the provision of human support when needed, for example, in the context of clinical questions.[11] This appears to be of particular importance in patients with comorbidities,[12] who may require more tailored exercise programmes. In studies incorporating asynchronous chat support from a physical therapist or a blended intervention of e-health exercise, participants valued the daily contact compared with traditional care[27] and perceived the support to be important and motivating to continue exercising.[26 27] The ability of physical therapists to tailor exercise programmes according to patients' needs was described as a key benefit in a blended care intervention.[26] It appears that individuals seek support from a health professional, at least on a basic level, enabling that someone monitors their progress, guides progression and provides motivation and feedback.[28] In addition, the incorporation of human interaction with a health professional via telehealth or blended care in digital exercise delivery may address the importance of adequately preparing patients for upcoming digital exercise sessions by empowering them for correct and safe exercise technique, answering questions, providing reassurance or managing technological issues.[14 29] To summarise, some kind of human support could be useful even in e-health exercise delivery, but the necessary amount of support is dependent on patients' preferences and needs.

Strengths and limitations

One strength of our study includes that all participants completed the interview within a time window of 2–5 weeks after intervention completion. This enabled adequate recall of the mobile app and the exercise programme. A potential bias associated with the researcher (JS) who developed the coding system could be mitigated, as she did not interact with the participants nor was she involved in the design or conduction of the study. Using an investigator triangulation approach, themes and subthemes were independently developed by two researchers (JS and VD), and subsequently reviewed and discussed by a third researcher (IK). Furthermore, the utilisation of audio recording, the aforementioned triangulation, and reflexivity strategies (eg, documentation sheets for the analysis process) in the research design served to strengthen the reliability of the findings. However, there were some limitations. First, the interviews were conducted by telephone, which may have resulted in less in-depth information of the interviews and more superficial responses due to the absence of personal interaction. Furthermore, the sample size was determined a priori. However, despite this limitation, inductive thematic saturation, as well as a priori thematic saturation, could be confirmed in the data set.[30] Moreover, there was a potential selection bias, as no purposive sampling (eg, with age, sex, technical affinity, positive/negative outcomes) was included. This might have implications for the generalisability of the findings, as certain patient characteristics could be underrepresented in the study sample. In addition, the participants self-selected to participate in the related RCT. This suggests that they had already developed an interest in attending an exercise programme with digital guidance and may, therefore, have had a more positive attitude on the use of digital technologies in exercise delivery. Lastly, the involvement of the researchers (VD and IK) in the development of the exercise programme and the conduction of the RCT could have affected findings.

Conclusion and implications for clinical practice

Participants demonstrated positive experiences and acceptability of the self-directed m-health exercise intervention for knee OA. The majority of participants reported positive outcomes and valued ease of use, comprehensibility, flexibility and certain app features (eg, push notifications as reminders, instruction videos, real-time biofeedback) to facilitate guidance, control and motivation of the self-directed digital exercise participation. Nevertheless, some participants requested some kind of human support in combination with the digital intervention. For clinical practice, this study demonstrates that self-directed digital exercise interventions are not a 'one-size-fits-all' solution. Instead, potential advantages and disadvantages should be discussed with the individual patient, as personal and environmental context factors (eg, level of support, previous experience in physical exercise, technical affinity, access to healthcare providers) need to be considered when selecting the appropriate treatment option. In the future, further modifications, for example, the implementation of an automated feedback system reacting on exertion and pain levels from previous exercise sessions, could lead to a more individualised and tailored exercise intervention. Moreover, future research should focus on the comparison between supervised and self-directed digital exercise delivery in knee OA. In this context, it is crucial to identify the responder characteristics for the different delivery modes, thus enabling the recommendation of a best-fit solution for each patient, tailored to their individual characteristics.

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Contributors VD and IK contributed to the conception and design of the study. VD contributed to the collection of data. VD, JS and IK were responsible for data analysis and interpretation of data, drafting and revising the article. All authors read and approved the final manuscript. IK acted as the guarantor.

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Competing interests The RCT was an investigator-initiated trial in cooperation with an industrial partner, the financial supporter of the study. The exercise intervention that is implemented into the re.flex app was designed by employees of the University Hospital (ie, VD and IK) in the context of the cooperation project between the trial sponsor Sporlastic GmbH and the University Hospital Tübingen. The University Hospital will be compensated for the granting of rights of use to the results generated by employees of the University Hospital (intellectual property) in the event of successful commercialisation of the app. The University Hospital will compensate the employees (ie, VD and IK) who were involved in the previous collaboration and are authors of the intellectual property from these revenues. All other authors have no competing interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ethics committee of Tübingen, approval number: 550/2020B01. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data that support the results of this study will be made available on reasonable request to the corresponding author.

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Appendix 1: Interview guide

Interviewleitfaden

Studie App-gestützte Trainingsintervention (re.flex)

Forschungsfrage

Wie wurde die Interaktion mit der App erlebt und bewertet?

Wie sind die Usability und das Design der re.flex-App zu bewerten?

Welche Hinweise zur Optimierung lassen sich hieraus erarbeiten?

Informationen zum Interview

Danke, dass Sie sich die nächsten circa 45-60 Minuten Zeit nehmen, um Ihre bisherigen Erfahrungen während der Studie „App-gestützte Trainingsintervention“ zu teilen. Die beantworteten Fragen dienen einem wissenschaftlichen Zweck und werden für die Weiterentwicklung und Optimierung der App genutzt.

Da wir Ihre Aussagen gerne auswerten und für diesen Zweck nutzen möchten, würden wir das Gespräch gerne aufzeichnen. Sind Sie damit einverstanden, dass wir das Interview für diesen Zweck aufnehmen?

Alle Audiodateien werden pseudonymisiert gekennzeichnet und nicht an Dritte weitergegeben. Die Aufnahmen werden nach dem Interview von dem Aufnahmegerät gelöscht und in einen Ordner geladen, auf den nur Studienbetreuer Zugriff haben.

Das Beenden des Interviews ist zu jeder Zeit und ohne Begründung möglich.

[AUFNAHME STARTEN]

Uns interessiert vor allem wie Sie die Interaktion mit der App erlebt sowie Benutzerfreundlichkeit und Design der App wahrgenommen haben. Zudem möchten wir erfahren, ob sich im Rahmen des Trainings mit der App Schwierigkeiten oder Sicherheitsbedenken aufgetan haben oder Sie Verbesserungsvorschläge zur Optimierung der Durchführbarkeit des app-gestützten Trainings haben.

Gibt es an dieser Stelle von Ihnen noch Fragen? Ansonsten möchte ich Sie noch bitten die Fragen offen und ehrlich zu beantworten.

Einstieg

Freude und Abneigung

„Ice breaker“

1. Haben Sie das erste Mal mit einer App trainiert?
2. Wie haben Sie sich gefühlt (beim Nutzen/Trainieren mit der App)?
3. Welche Erfahrungen konnten Sie bisher während der Studie beim Training mit der App sammeln?

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Formalia

4. Mit welchem Endgerät haben Sie das Training durchgeführt (Bei Nachfrage: Hinweis auf Smartphone, Tablet, ggf. Größe, wenn bekannt).
5. Wie lange nutzen Sie das Endgerät oder ein vergleichbares Vorgängermodell schon?

Allgemein

6. Welche Vorteile sehen Sie im Nutzen einer solchen App?
7. Was hat Ihnen an der App gefallen?
8. Welche Nachteile sehen Sie im Nutzen einer solchen App?
9. Was hat Ihnen an der App nicht gefallen?
10. Welche Schwierigkeiten hatten Sie beim Nutzen der App?

Layout und Darstellung/Design

11. War die Farbauswahl und Größe der Schaltflächen (Buttons) ausreichend an Ihre Bedürfnisse angepasst?
    a. War die Schrift gut zu lesen (beispielsweise in Hinblick auf Größe der Schrift, Schrifttyp oder sonstiges)?
12. Waren alle Schaltflächen (Buttons) gut ersichtlich?
13. Wussten Sie immer, für welchen Zweck diese eingesetzt werden sollten?
14. Ist die Menge an Informationen, die zeitgleich auf dem Bildschirm präsentiert werden, angemessen? (Stichwort: Übersichtlichkeit?)
15. Wie bewerten Sie die Wahl der Sprache, in der die Anweisungen in der App gestaltet sind? (Stichwort: leichte und verständliche Sprache)
16. Was fällt Ihnen positiv an dem Design der App auf?
17. Was würden Sie am Design der App gerne verbessern?
18. Können Sie uns bitte hierzu mitteilen, ob Sie Einschränkungen der Sehfähigkeit haben, die Sie bei der Nutzung der App beeinträchtigt haben (ggf. kommentieren)
19. Können Sie uns bitte hierzu mitteilen, ob Sie Einschränkungen der Hörfähigkeit haben, die Sie bei der Nutzung der App beeinträchtigt haben (ggf. kommentieren)

Technische Aspekte

<u>Umgang mit den technischen Instrumenten (App und Orthese)</u>

20. Wie empfanden Sie die Handhabung mit den Sensoren vor und während des Trainings (Gruppe A und AB)?
    a. Sensoren laden
    b. Sensoren/Orthese anlegen
    c. Sensoren verbinden
    d. Sensoren kalibrieren
    e. Handhabung während des Training
21. Wie empfanden Sie die Handhabung der Orthese vor und während des Trainings (nur Gruppe AB)?
    a. Orthese anlegen
    b. Handhabung während des Training

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22. Wie empfanden Sie den Vorbereitungsprozess mit der technischen Ausrüstung im Vorfeld des Trainings?

Trainingsdurchführung mit der App

Anleitung des Trainings

23. Wie empfanden Sie die Anleitung des Trainings durch die App?
    a. Wie bewerten Sie die Video- und Übungsbeschreibung?
        i. Wie verständlich waren für Sie die Instruktionen der Übungen 1.) durch die Videos und II.) durch die schriftlichen Beschreibungen?
        ii. Wie beurteilen Sie die gewählten Bildausschnitte und Perspektiven der Videos?
        iii. Was hat Ihnen an den Instruktionsvideos/ -beschreibungen gefehlt?
    b. Wie empfanden Sie die Übungsdurchführung gemeinsam mit dem Avatar (das graue Vormachbein)?
    c. Wie empfanden Sie insgesamt die Handhabung eines Smartphones/Tablets während des Trainings?

Fehlfunktionen während der Nutzung

24. Haben Sie irgendwelche „Fehler/Bugs“ in Ihrer App gefunden?
    a. Wenn die App nicht reagierte oder abstürzte war es leicht sie neu zu starten und wieder in Gang zu bringen?
    b. Mussten Sie jemals eine Trainingseinheit aufgrund von technischen Schwierigkeiten abbrechen?
    c. Mussten Sie sich jemals aufgrund technischer Schwierigkeiten an den Support wenden? Wenn ja, waren die Informationen hilfreich um Ihre Probleme zu lösen oder hätten Sie sich mehr Hilfestellung gewünscht (wenn mehr Hilfestellung, welcher Art könnte/sollte diese aussehen?)

Allgemeine Menüführung

25. Bitte bewerten Sie die Verständlichkeit der Menüführung während der Trainingsdurchführung.
    a. Haben Sie bei der Bedienung der App etwas vermisst?
26. Welche Schwierigkeiten sind während des Trainings beim Navigieren durch die App aufgetreten?

Bewertung einzelner Menüpunkte/Features/Funktionen

27. Wie bewerten Sie die folgenden Menüpunkte/Funktionen?
    d. Balken mit Blase am Ende zur Orientierung der Bewegungsweite
    e. Verbales Feedback bei fehlerhafter Übungsdurchführung
    f. Avatar + Ihr dargestelltes Trainingsbein zur Orientierung
    g. Übung wechseln
        i. Haben Sie diese Funktion verwendet?
    h. Übung überspringen

   i. Haben Sie diese Funktion verwendet? Wenn ja, welche Gründe gab es für ein Überspringen?
  i. Angabe des Schmerz- und Anstrengungsempfindens nach jedem Durchgang einer Übung? Wren diese hilfreich für Sie?
28. Würden Sie sich weitere Funktionen wünschen? Wenn ja, welche?

Orthese (nur Gruppe AB)

29. Wie empfanden Sie das zusätzliche Tragen der Orthese während des Trainings?
    a. Was war positiv? / Was war negativ?
30. Veränderte das zusätzliche Tragen der Orthese Ihr Gefühl z.B. bezüglich der Kniestabilität, des Sicherheitsempfinden während des Übens, der Belastbarkeit des Kniegelenks oder weiteren Faktoren? Wenn ja, welche?

Akzeptanz der Intervention mit der App / Erfahrung durch die Videos und das Erleben des Trainings

Nützlichkeit einer solchen Intervention

31. Wie beurteilen Sie die gesellschaftliche Relevanz/Notwendigkeit einer solchen App?
32. Glauben Sie, dass Sie ein regelmäßiges Training mit der App in Ihren Lebensalltag in Zukunft integrieren könnten? Warum ja/nein?

Sicherheit

33. Wie sicher sind Sie sich, dass Sie die Übungen mit Hilfe der Instruktionsvideos sowie der Kontrolle durch die Sensoren korrekt durchführen konnten (bzgl. der richtigen Bewegungsausführung)?
34. Hatten Sie Sicherheitsbedenken beim Üben mit der App? Wenn ja welcher Art?
35. Was verstärkte dieses Sicherheitsgefühl? / Was schwächte dieses Sicherheitsgefühl ab?
36. In welchen Bereichen hätten Sie sich eine zusätzliche Hilfestellung gewünscht?

Motivation

37. Wie motiviert waren Sie, die Übungen alleine mit der App zu Hause durchzuführen?
38. Hat Ihnen die App geholfen Ihre Trainingsmotivation zu steigern? Wenn ja, inwiefern?

Programm

Umfang/Zeit

39. Wie beurteilen Sie den Umfang der Trainingseinheiten?
40. Wie beurteilen Sie den zeitlichen Aufwand, den Sie für die Ausführung des Trainings mit der App benötigt haben inklusive Anlegen und Kalibrieren der Sensoren?

Inhalte

41. Wie beurteilen Sie die Auswahl der Übungen?
    a. Hinsichtlich der Schwierigkeit der Übungen (ggf. Hilfe: zu einfach / genau richtig / zu schwer)?
    b. Gab es Übungen die Sie nicht durchführen konnten? Aus welchem Grund?

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   c. Waren alle Übungen mit den Materialien, die Ihnen zu Hause zur Verfügung standen, durchführbar?
42. Denken Sie an die Trainingsvorgaben (Häufigkeit: 3x/Woche, Wiederholungszahl: bei Kräftigungsübungen 2x25 Wiederholungen in den Wochen 1-6 und 3x15 Wiederholungen in den Wochen 7-12, im Verlauf der 12 Wochen intensiver werdende Übungen). Wie beurteilen Sie die Belastungsdosierung?
   a. Wie beurteilen Sie die an Sie gestellten Trainingsanforderungen in Bezug zu Ihrem Leistungsniveau (ggf. über- unterfordert, genau richtig)?
43. Haben Sie auch die Anweisung für das Training mit dem anderen Bein befolgt und die Übungen dort ebenfalls durchgeführt?

Umsetzung und Machbarkeit

44. Welche Erwartungen hatten Sie an die Teilnahme im Vorfeld Studie?
   a. Welche Erwartungen konnten nach den 12 Wochen Training erreicht werden?
   b. Welche Erwartungen wurden nicht erfüllt?

Vorkommnisse während der Studienzeit

Adverse Events (unerwünschtes Ereignis)

45. Können Sie sich an eine Situation während des Trainings erinnern, in der Sie sich gesundheitlich nicht wohl gefühlt haben (ggf. Hilfe Beschwerden/Schmerzen sich verstärkt haben)?
   a. Wann und in welcher Situation (z.B. in Zusammenhang mit einer bestimmten Übung) trat das Ereignis auf?
46. Können Sie sich an eine Situation während des Trainings erinnern, in der Sie sich gesundheitlich besonders wohl gefühlt haben (ggf. Hilfe Beschwerden/Schmerzen die sich verbessert haben)?
   a. Wann und in welcher Situation (z.B. in Zusammenhang mit einer bestimmten Übung) trat das Ereignis auf?

Fazit und Praktikabilität für spätere Umsetzung

47. Würden Sie die App in Zukunft gerne nutzen?
48. Was wären Sie bereit für ein solches 12-wöchiges Trainingsprogramm inklusive Sensortechnik zu zahlen?
49. Würden Sie die App weiterempfehlen?
50. Wenn Sie etwas an der App verbessern könnten, damit Sie sie weiterhin nutzen, was wäre das?
51. Gibt es noch etwas, das Sie hinzufügen möchten?

Dank und Verabschiedung

Vielen Dank für Ihre Zeit und Ihre Teilnahme am Interview! Damit ist Ihre Teilnahme an der Studie jetzt beendet. Wir werden Sie über die Studienergebnisse informieren, sobald diese

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vorliegen. Wir hoffen das Training hat Ihnen Spaß gemacht und die gewünschten körperlichen Erfolge gezeigt und wünschen Ihnen für die Zukunft alles Gute!

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Appendix 2: Themes, sub-themes, and exemplary quotes.

(Sub)theme	Exemplary quote
Theme 1: Facilitators for (correct) digital exercise participation	
App features for guidance, support and monitoring of correct exercise execution	AT58: "[…] I thought that was good. The videos were very clear, even from different perspectives, from the side, from the front and so on, you could actually grasp the position, how to stand, how to hold your arms and so on, very well. Additionally, the text description was certainly helpful, as it simply explained a few more details of what to look out for." AT38: "That's [the movement bar to display range of motion] good, because of course you have good control over whether you're doing it correctly. You are happy when you hear that clicking sound. And vice versa, you also notice when it is missing. You know, okay, what I'm doing right now isn't perfect and then you can actually make a bit of an effort to do it better and more correctly next time." AT51: "[…] the app also corrected you, so that if you didn't do it correctly, you were told to 'please stretch' [laughs], so from that point of view, you were corrected. […] I like that feedback, […], you don't want to be criticized, but it shows you that you are not doing it in the correct way, […]. I thought that was good.
Flexibility	AT51: "[…] the advantage is that you don't have to leave the house, you don't have to get changed [your clothes], so I've always dressed sporty of course [laughs], shorts. […], you can do it from home. […]. And you can do it at any time of day." AT66: "You could use the app all day, you could get out again, you could get back in again and you simply weren't as time-bound as when you say, okay, I have a fixed appointment at a fixed location."
App features to increase motivation and regularity of the exercise program	AT01: "In doubt, you become more motivated, I would say. And the fact that you also feel a bit monitored by the app certainly increases your level of ambition compared to doing it for yourself or turning pages or something like that. That's how I felt. A certain ambition comes with it." AT10: "And it was also fun doing it. I say yes, of course you don't necessarily feel like doing it every day or every second day [laughs], I would rather sit down or do something else. […]. The app reminds you, so you really do have the urge, the compulsion to say 'okay, you have to do sport today or at least a little bit'." AT63: "I find it much easier to do this regular training simply because of the support from the app or the knowledge that the app is there and it records it [the training], than it would be without the app." AT10: "No, I mean in principle I had a very secure feeling. In principle, the avatar made me feel very confident. You can actually see quite well whether you are doing the exercises correctly."
Positive experiences with the	AT27: "Yes, overall the second half of the training phase was very positive. When I was doing new exercises, I realized that they really

exercise program	weren't that difficult anymore and once I knew the exercises, I noticed how much better they worked and when the update fixed the calibration problem, it was really fun." AT56: "You don't need weights to exercise in order to make progress. I would never have thought that, if it is only to hold the exercise accordingly, i.e. some exercises require you to hold the position for three seconds, three, two, one, you would not believe how long three seconds are. Yes, it was really good." AT04: "I mean, I thought it was good that you had two exercises that were relatively easy most of the time and two exercises that were a bit difficult [in every exercise session]. That's how I felt, and then one exercise was for stretching or relaxation. […] that's very good, that's fine, you can do it, you can manage it." AT58: "The amount. Yes, the individual sessions, as I said, that's good, it can be integrated, it's achievable, even if you are not really motivated, you know it will be over in half an hour [laughs] and the 12 weeks, yes, that's a reasonable length. I don't think I have ever done any exercises so consistently for 12 weeks."
Theme 2: Barriers for (correct) digital exercise participation	
No on-site instructions by a health professional	AT27: "Obviously, a physiotherapist can see even more. The sensors have controlled my leg and when I do the exercises with a physiotherapist, they can of course also see the rest of my body and whether something is going wrong in other parts of the musculoskeletal system, e.g. that you assume a bad posture elsewhere in order to do the knee exercise. Of course, the app can't see that, it can only see the movement of the knee." AT07: "So that I couldn't show someone on site how I do it [the exercises], and then they say to me, 'you overlooked the fact that you should have done this or that'. Then it might have been easier for me to accept that the app was right."
Technical issues	AT56: "Sometimes it was annoying because the nice female voice always pointed out 'bend your knee more' or when you had the exercise band in a hip extension movement, in which direction should I […] I have to say it differently the advice came 'stretch more, a bigger lunge', sometimes more [range of motion] was not possible at all. I couldn't get rid of the error." AT58: "I have to say that the correction factor was very difficult to implement for certain exercises. These include exercises with the band, for example, where you move your leg sideways, outwards, abduction I think it's called. […] I just couldn't complete the exercise, because something was always wrong, even though I couldn't go any further [regarding the range of motion]. […] So, it was always 'keep going outwards', but it just didn't go any further and at some point, you give up. I think I stopped the exercise once or twice. AT27: "Yes, I skipped certain exercises as I was always asked to recalibrate because the device didn't recognize what my leg was doing and the avatar looked really dangerous and my virtual knee bent sideways. Then there were no useful hints and then I stopped some exercises, in total I stopped four exercises or something like that. Not the whole workout, but certain exercises."

Difficulties with the exercise program	AT63: "Well, I mean, of course there are certain exercises that you like to do and other exercises you tend to say no to. So, for me, for example, all those squat exercises that involved doing knee flexion were always rather disliked because they simply caused pain in my knee." AT38: "I actually only had, I think, one flexion exercise where I actually thought 'I don't like this right now or my knee doesn't like this right now'. Usually, that are always exercises that require a lot of flexion and load on the affected leg. A lot of standing on the affected leg, that is actually something where I just have some problems." AT58: "That was this downward stair exercise and a weight-bearing exercise on the damaged knee where you had to shift to the front. It was always difficult when a load was combined with a downward movement." AT56: "That was the exercise on the wall. That was the pushing up and down, exactly. Because it was very demanding for my knees." AT07: "[…], what was very difficult for me personally, at that time I had relatively severe pain in my knees, was the fact that exercises on the floor were prescribed. So, for me, these exercises meant that I first had to get down on the floor and then come up again afterwards. […] that was uncomfortable for me."
Associated problems with app features	AT38: "So then I just, I just kept trying until something happened and then I don't think the exercise was done exactly the way it was supposed to be. It was a bit bizarre, because then it was obvious that I wasn't doing it the way I was supposed to, but then I kind of wanted to, I wanted to make it count." AT56: "Good, good. As I said, it was annoying when the error occurred several times. Sometimes I would have preferred to switch off the voice or whatever, but apart from that it was easy to understand. The error was there, you try to fix it and I got to deal with it quite quick, if that is what happened." AT53: "Yes, I did it, but sloppily. Because I just didn't have had the motivation, as I said, the sensor on the other leg would be very useful. You do it faster there, you don't hold the time as long, because you have to count it down yourself, and it's just, yes, you just don't do it. So, I don't."
Theme 3: Ease of use	
Usability, feasibility and comprehensibility	AT27: "Putting on these sensors, starting the app and things like that, you get into a routine rather fast, so I actually found it to be very smooth and good." AT58: " […] that was easy to understand, most of it was easy to understand and to implement." AT56: "In general, the performance when using the software, for me it was easy to understand, I got to grips with it quite fast and that counts for me when I get to grips with an IT device or software rather fast."

	AT38: “Of course you have to find your way around it, you have to see what the individual menu items offer and where to go. But it's so good and self-explanatory that I think you can work with it without any major problems.” AT10: “It is quick and easy. It is very quick, very easy. So, I found that it was no problem at all for me. You put on the straps, put on the sensors, open the app and then get started [laughs].”
Handling and screen size	AT10: “Sometimes it [smartphone] was just too small for me. But of course, as soon as you have either a computer in front of you, a monitor or a tablet, then of course it is better.” AT57: “Well, of course, the handling of the iPad was sometimes difficult, because when you're lying on the floor, where do I put it, where do I hang it up? [laughs] Well, it was good at the table, I could, my wife gave me a reading stand, a book stand, it was quite good, you could do it there, but if you're lying on the floor, it's difficult of course.”
Theme 4: Outcomes	
Positive Outcomes	AT51: “[…] the muscles around the knee were definitely strengthened, which I probably wouldn’t have done in that time without this app.” AT27: “[...] in my case it relieved the symptoms, and increased flexibility [...]” AT53: “But I think I can walk down the stairs very quickly with both legs, I only walked down the stairs with one foot step-by-step, the other foot following, that's how I walked down the stairs. Now I can walk down the stairs with both legs at a brisk pace, which is a huge success.” AT53: “The pain has also improved a lot, a lot, it is not gone. But, I didn’t expect that either.” AT56: “There has been a significant increase in strength of my thigh muscles, because now I can also feel it on the bike. It is at least one gear easier.” AT27: “That was actually what I expected - better flexibility, better stability and being able to do more things without pain - and they [the expectations] were fulfilled. For example, I rode my bike up to the health center for the final consultation, which is something I couldn't have imagined in October or even in January that it would be possible, in terms of the strain on my knee, and it was easy to do. As an example of how much this has made my knee usable again.” AT38: “I have the feeling that it's up to me what I do with it. It puts me in a position where I can just keep at it [doing exercises].”
Not met outcome expectations	AT10: “I don't have the feeling that I really have more strength in my legs because of it, so I haven't noticed any difference.” AT58: “As I said, the expectation that it will really improve to such an extent that surgery is no longer an option is not given, so that I will

	probably expect one in the next six or nine months. I didn't really have had any other expectations." AT07: "No. For the simple reason that at some point I stopped enjoying it. So, I didn't have had any medical, I didn't have had the feeling that I was somehow [pause] building up I don't know what skills, I didn't have had any experience of success, that it had improved or that I was better at it or whatever."

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4.3 Research article 3: Evaluation of a 12-week app-guided exercise intervention in patients with knee osteoarthritis (re.flex): a study protocol for a randomized controlled trial

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BMC Digital Health

STUDY PROTOCOL

Open Access

Evaluation of a 12-week app-guided exercise intervention in patients with knee osteoarthritis (re.flex): a study protocol for a randomized controlled trial

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Abstract

Background Current health care demonstrates an insufficient provision and utilization of physical exercises despite their recommendation as a first-line treatment in clinical guidelines for patients with knee osteoarthritis (OA). Mobile health (m-health) technologies offer new opportunities to guide and monitor home-based exercise programs by using mobile devices and inertial sensors in combination with a digital application (app). This study will evaluate patient benefits resulting from the use of the specific digital health application re.flex for patients with knee OA.

Methods This monocentric, two-arm, randomized controlled parallel-group trial will evaluate the effectiveness of the app- and sensor-guided exercise program re.flex for patients with moderate-to-severe knee OA. We aim to recruit 200 participants via newspapers, newsletters and information events. Participants will be randomly allocated to the intervention group and the control group in a 1:1 ratio. Participants in the control group will not receive any study intervention or instruction for any change to their previous health care utilization. Despite this, they are allowed to make use of usual care provided by their treating physician. The intervention group comprises a 12-week home training program with three sessions per week in addition to usual care. Exercises will be guided and monitored by use of the training app (re.flex) and two accelerometers that are attached proximally and distally to the affected knee joint. Pre- and postmeasurements will take place at baseline (t0) and after 12 weeks (t1). Primary outcomes will be osteoarthritis-specific pain and physical function measured with the Knee Osteoarthritis Outcome Score (KOOS) subscales Pain and Function in daily living (ADL). Second, further self-reported health outcomes, a performance measurement, app logfiles and safety will be assessed. Intervention effects will be calculated by baseline-adjusted analysis of covariance (ANCOVA) using an intention-to-treat approach. Multiple imputation will be applied.

Discussion Re.flex can bridge part of the gap between recommendations for strengthening exercises in patients with knee OA and the insufficient actual care situation. This randomized controlled trial is designed to provide conclusions on the effectiveness of the health application re.flex for the population under study and will provide further insight into adherence rates and the safety of its use.

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Trial registration The trial was registered on 20/01/2023 at www.drks.de (ID: DRKS00030932).
Keywords Digital application, m-health, Knee osteoarthritis, Exercise

Background

Osteoarthritis (OA) is the most common degenerative joint disorder in Germany and worldwide [1]. According to the GEDA 2014/2015-EH Interview Survey of the Robert Koch Institute, the 12-month prevalence of OA in adults in Germany is assessed at 17.9% [2]. It is estimated that more than half of those affected suffer from knee OA [3]. Older age, female sex and biomechanical stress induced by overuse or malalignment as well as previous injuries or overweight are potential risk factors for OA [2].

Disease progression is frequently associated with increasing pain and growing limitations in physical functioning and health-related quality of life. Due to its progressive degenerative character, interventions primarily aim for a reduction in disease symptoms and improvements in physical functioning. They further intend to foster disease self-management and patient education. Medical guidelines worldwide recommend physical exercises and patient education as nonpharmacological core treatments for patients with knee OA [4, 5]. However, there is an insufficient provision and utilization of these first-line treatments in current health care. A recent meta-analysis of 15 studies evaluating the quality of OA care in the community concluded that less than 40% of eligible OA patients received recommendations to exercise [6]. Furthermore, only 35% of the German people with OA reported that they engage in strength training at least twice a week [7]. Data from a German health insurance company show that more than 60% of the insurance holders aged 60 years and above and diagnosed with OA received medication compared with only 41% receiving a prescription for physiotherapy [8]. The latter does not necessarily include exercise instructions [9].

From a mechanical perspective, strengthening exercises aim to stabilize the affected joint and decrease abnormal joint loads by improving muscle strength and neuromuscular control [10, 11]. To date, many studies on exercise therapy in knee OA have shown increased strength in the short and mid-term [12, 13]. In this regard, adherence to exercise seems to be crucial, as exercise interventions are categorized as lifestyle interventions. Initial instructions are given, after which the exercises should be continued in a self-dependent manner [14]. An ongoing need for the development of highly stimulating exercise programs designed for long-term adherence can therefore be postulated [13]. In this regard, home-based exercise programs seem to be of particular relevance, as they can be conducted independently [10]. Digital health applications have great potential to support patients in performing exercises correctly and safely. The outstanding advantages of digital health applications are related to their extensive availability, allowing users to be instructed in exercises independent of time and location. They further appeal to a wide range of possible users [15–17] and have the possibility of closer monitoring, such as an objective method of measuring adherence to exercise by use of additional motion sensors [18]. In a randomized controlled trial, Bennell and colleagues [19] compared home exercise prescribed by therapists' usual methods with home exercise prescribed using a web-based exercise programming system for people with musculoskeletal conditions. Conclusively, web-based home exercise resulted in improved adherence and self-confidence in the ability to perform exercises independently.

The digital transformation in health care is advancing rapidly. One example of this ongoing process is the Digital Care Law in Germany, which came into force in 2019 [20]. This law aims for better care using digitalization and innovation. Among others, it allows patients to gain access to specific health apps that are listed in a register for disease-specific digital health applications (DiGA). Costs for DiGAs are reimbursed from the statutory health insurance companies. However, evidence of a positive care effect, such as patient benefit, is a prerequisite for the final inclusion of a DiGA into the reimbursable DiGA register [21]. To create incentives using digital interventions, such or similar reimbursement models are needed from a clinician's perspective [22].

This randomized controlled trial will investigate the patient benefits associated with the preliminary listed DiGA re.flex that is used to instruct and guide exercises for patients with knee OA.

Objectives

The main objective of this study is to investigate the effectiveness of a 12-week sensor-assisted and app-supported exercise intervention in addition to usual care (intervention group) in comparison to a control group with usual care only (control group).

The two primary endpoints are the comparison of baseline-adjusted scores between the intervention and control group regarding osteoarthritis-specific pain (subscale Pain of the Knee Osteoarthritis Outcome Score, KOOS) and physical function (subscale Function in daily

living (ADL) of the Knee Osteoarthritis Outcome Score, KOOS) directly after the 12-week intervention phase. Other study endpoints include further self-reported health outcomes, a performance measurement, app log-files and safety aspects (Table 2).

Methods

Study design

The study is designed as a monocentric pragmatic two-armed randomized controlled superiority trial and will be conducted in an academic hospital with an outpatient clinic for Sports Medicine located in Tübingen, Germany. Subjects are randomly allocated to the intervention group and control group in a 1:1 ratio with $n=100$ in each group.

Pre- and postmeasurements will take place at baseline (t0) and after 12 weeks (t1). The study was prospectively registered in the German Clinical Trial Register (DRKS00030932) on 20/01/2023 and will be reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [23] (Supplement 1).

Eligibility criteria

Eligible patients are those of any sex ≥ 18 years suffering from knee OA (International Classification of Disease, ICD codes M17.0–17.5 and 17.9). The knee must be the primary location of OA symptoms. Knee OA is first diagnosed via self-reported previous OA diagnosis by a physician according to the wording of the GEDA questionnaire [2]. Patients are further asked to rate their OA severity via the Subscale Pain of the KOOS [24, 25]. Only patients with at least moderate self-reported symptoms at the time of screening are eligible for the study (KOOS pain ≤ 60 points, where 100 points indicate no complaints at all). To address that criterion, the KOOS pain subscale will be administered by phone and based on possible symptoms that typically occurred during the last week. OA diagnosis is verified in the context of the physical examination at t0 by a physician (orthopaedist). If available, the diagnosis is confirmed using X-ray or MRI images provided by the patient. Further inclusion and exclusion criteria are outlined in Table 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- ≥ 18 years	
- Mobile electronic device with an iOS or Android operating system	- No mobile electronic device or device with an operating system other than iOS or Android
- Willingness to participate in the study - Willingness to use the app to exercise - Informed consent of the participant	
- Self-reported previous knee OA diagnosis by a physician according to the wording of the GEDA questionnaire [2] - Tibiofemoral OA (uni- or bicompartmental or in combination with retro-patellar OA) - Verification of knee OA diagnosis in the context of the physical examination at t0 by a physician (orthopaedist) - Self-reported KOOS Subscale Pain Score ≤ 60 during the screening process - The knee joint is the index joint[a]	- OA primarily located in the hip joint or others than the knee (the knee joint is not the index joint[a]) - Diffuse knee pain or retro-patellar pain only - History of knee joint replacement or osteotomy on the index joint
	- Any medical or physical impairment precluding safe participation in exercise, measured by use of the Physical Activity Readiness Questionnaire (PAR-Q) [26, 27] and verified by the physician at t0 - Any complaints of the lower extremity or lower back other than knee OA that are currently treated by a physician and/or physiotherapist - Any previous surgeries, injuries or complaints that are a contraindication to exercise without supervision (e.g. injuries or complaints that are associated with restricted motor skills and an increased risk of falling) - Any scheduled elective orthopaedic surgery in the lower limb or lower back in the next 4 months - Inability to walk unaided
	- (Digital) exercise interventions that are similar to the intervention under study, i.e., other physiotherapy applications for OA or regular structured strengthening exercise for the lower extremities more than once a week during the past 6 months
	- Insufficient German language skills to understand the study documents and the instructions of the app

[a] The index joint is the joint that is most affected by self-reported symptoms of OA in cases of multisite OA

Intervention

Control group

Participants in the control group will not receive any study intervention or instruction for any change to their previous health care utilization. They are allowed to make use of usual health care provided by their treating physician, if applicable.

Usual care is defined as any kind of prescribed pharmacological or physical intervention a patient with knee OA usually receives when consulting a medical doctor because of knee OA. These may include physical therapies such as regular physiotherapy, manual therapy, electrotherapy, orthotic devices and medical prescriptions for pharmacological agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) [28]. These reflect the relevant treatment options according to the current national guidelines in Germany [4].

App-guided exercise intervention for knee osteoarthritis (intervention group)

The exercise intervention comprises a 12-week app-guided home training program that was specifically designed for patients with knee osteoarthritis. Exercises are guided by use of the training app and two accelerometers (re.flex, © 2019, KINETO TECH REHAB SRL) that are attached proximally and distally to the affected knee joint (Fig. 1).

The primary focus of the intervention is to strengthen knee extensors, knee flexors and hip abductors. Further exercises aim for joint mobilization, muscle flexibility and balance training.

The first two weeks focuses on familiarization with different kinds of exercises and exercise loads. In this regard, patients should be enabled to adapt exercise intensity self-determinately according to perceived strain and pain. Therefore, patients can choose between two different intensity grades. They further have to comment about their strain and pain levels after each set of exercises (see outcome measures). The following four weeks are designed to increase strength endurance, enhance the range of motion of the lower extremities and improve balance ability. In this phase, strengthening exercises should be performed with 2 sets of 25 repetitions (Fig. 2).

The last six weeks of the intervention mainly focus on muscle hypertrophy with higher intensities and lower repetition numbers. Strength training should be performed with 3 sets of 15 repetitions in this phase. Moreover, balance and range of motion should be further improved (Fig. 2). From week 5 onwards, the training program can partly be modified by the users by choosing their preferred exercises for some of the strength, mobility, flexibility or balance exercises out of the exercise pool that they became familiar with during previous sessions. Alternative exercises relate to the same musculature and task, yet they may differ regarding the exercise position or an open versus closed kinetic chain.

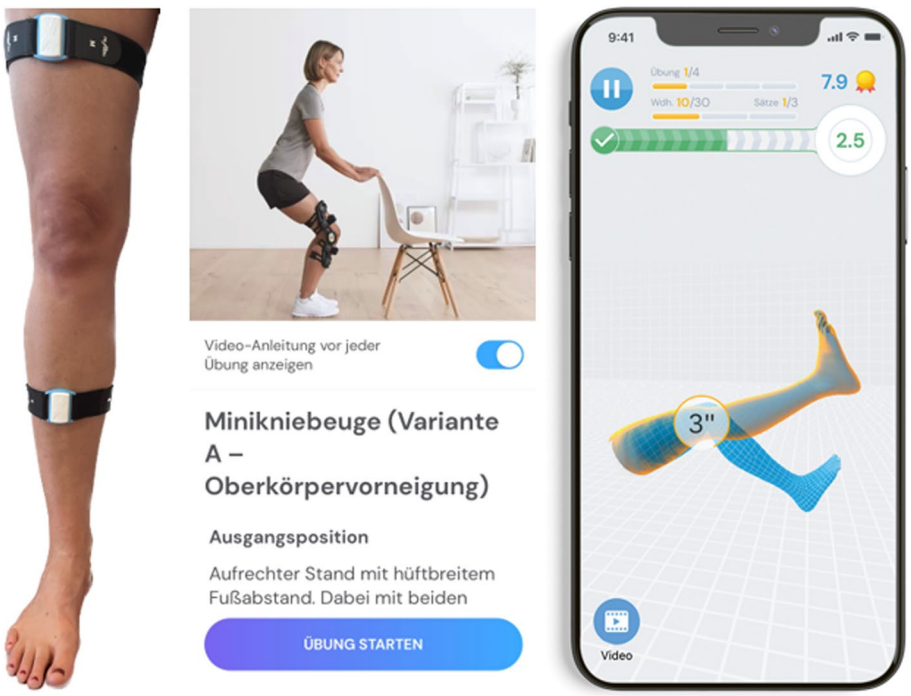

Fig. 1 Re.flex technology (left picture) and examples for app-guided exercise instructions (middle and right pictures)

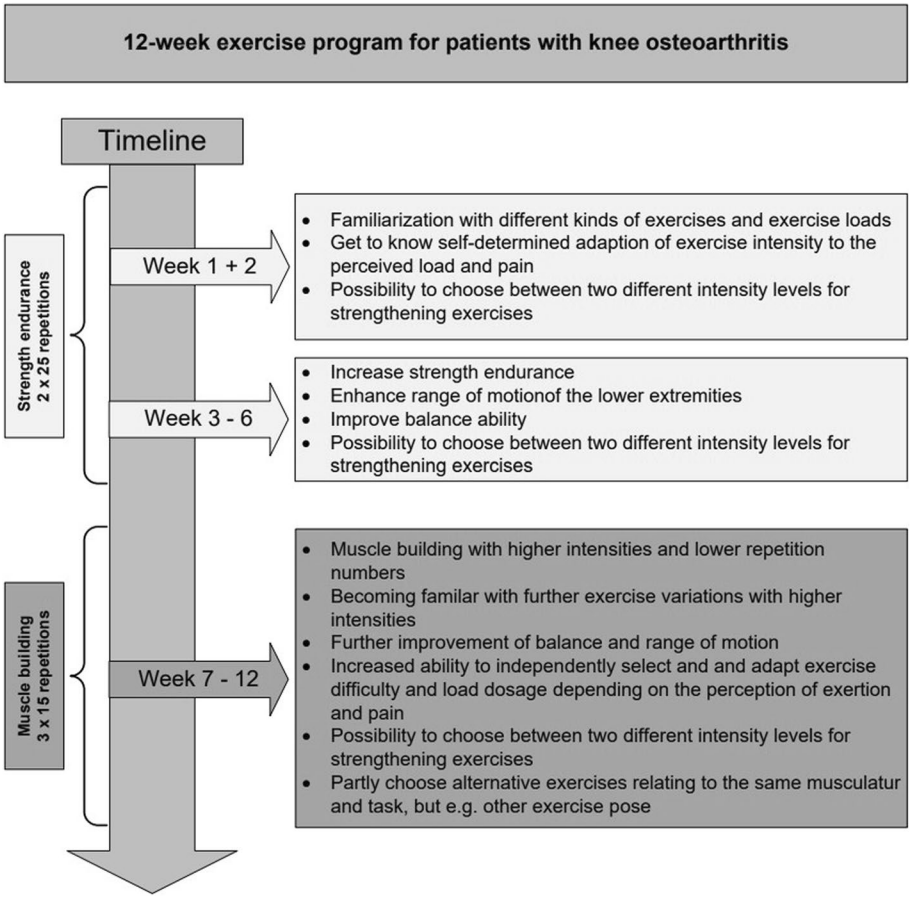

Fig. 2 Objectives within the different phases of the 12-week exercise program for patients with knee osteoarthritis

The use of the app and sensors will be introduced in the context of the baseline examination on site by the pretrained study staff, and patients will further receive a manual for using the software and hardware.

The app acts as a virtual training partner, providing exercise descriptions and videos (Fig. 1), setting the number of repetitions and sets, predefining joint angles and the related range of motion for the exercises and defining the movement velocity of the exercises.

Each of the 12 weeks foresees 3 exercise sessions with a respective duration of 25–30 min each, which can be performed independently of location and time. Different types and variations of exercise (i.e., the use of long or short lever arms or different starting positions: supine, seated, standing) as well as elastic exercise bands are used to allow progression of training loads. All one-sided exercises are conducted alternately with each leg to avoid muscular imbalances. Furthermore, subjects will be instructed prior to the start of the intervention that strength exercises are effective when the final two to three repetitions are perceived as strenuous to very strenuous [7, 8] on the RPE (rating of perceived exertion) scale 0–10. If at the end of the exercise it is realized that the exercise was too easy or too difficult, the exercise intensity can be adjusted the next time the exercise is performed by choosing a more difficult or easier variation of the exercise.

The app further reminds the user to conduct upcoming training sessions via push notifications. All training sessions, including the number of repetitions actually performed compared to the given number of repetitions of an exercise, are tracked by the two accelerometers and thus can help to evaluate training adherence in the future. Throughout the intervention phase, users can contact the provider via the app messenger. The provider is responsible for clarification of technical issues. Participants are instructed to interrupt the training program in case of any suspicious symptoms, fatigue or excessive pain during the exercise intervention with the re.flex system. They are asked to inform the study personnel about any adverse event to allow judgement on how to proceed. This decision is up to the study physician as well as the

study personnel (sports scientist/physiotherapist) and will refer to the options of modification of the training regime or its temporary or complete discontinuation.

In correspondence to the control group, participants of the intervention group are allowed to make use of usual health care provided by their treating physician, if applicable.

Outcome measures

The following Table 2 gives an overview of all outcome measures, their study instruments with references and their time points of assessment. Details on each measure are provided in the subsequent sections. Patient-reported outcome measures (PROMs) will be assessed using an online questionnaire (Questback GmbH, Köln, Germany) during the examinations at the study site (t0, t1) and at home (only applicable for concomitant care at 4 and 8 weeks). The physical performance measure will be assessed on-site at t0 and t1. Sociodemographic data, clinical status (e.g., relevant previous injuries or surgeries, comorbid conditions) [29], outcome expectations [30], previous experiences with strengthening exercises and physical activity as well as technical affinity [31] and fear of movement [32] are assessed in addition to the primary and secondary outcomes. The participants will receive an e-mail prior to the data collection, reminding them of the upcoming data collection. All used survey instruments are license-free or, in the case of the Veterans RAND 12-Item Health Survey (VR-12), permission was obtained from the authors.

The selection of outcome measures aligns with the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) core domain set for trials of people with hip and knee osteoarthritis [40]. The selection also aligns with the Consensus of the International Consortium for Health Outcomes Measurement Hip and Knee Osteoarthritis Working Group (ICHOM) on Standard Outcome Measures for hip and knee OA released in 2016 [29]. The mandatory set of outcome measures is supplemented by further relevant outcome measures in the context of exercise therapy and m-Health.

Primary outcomes

The KOOS is a widely accepted and comprehensive outcome measure for several domains, including pain and physical function. It was developed as a nonproprietary comprehensive extension to the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and has been proven to be valid, reliable, and responsive to OA outcomes [25, 29]. The test–retest reliability of the German version was in the range of $r_s = 0.65–0.78$, which corresponds to a sufficiently high reliability for all subscales. The validity was determined by comparing the subscales with the patient's self-assessment of health status and the results of the SF-12 (quality of life questionnaire). A sufficiently high convergence validity was shown [24]. The Knee Injury and Osteoarthritis Outcome Score (KOOS) [24, 25] was developed to assess the patient's opinion about their knee and associated problems. The KOOS evaluates both short-term and long-term consequences of knee injury and consequences of primary OA. It contains 42 items in five separately scored subscales: KOOS Pain, KOOS Symptoms, Function in daily living (KOOS ADL), Function in Sport and Recreation (KOOS Sport/Rec), and knee-related Quality of Life (KOOS QoL). All scores will be included; however, the KOOS Pain score and the KOOS ADL score are the primary outcomes of the study.

Secondary and other outcomes

Patient-reported outcome measures (PROMs)

(1) Further OA-specific complaints

Further subscales from the KOOS, such as the subscales Symptoms, Function in Sport and Recreation (Sport/Rec) and knee-related Quality of Life (QoL), will be analysed to consider a wide range of OA-specific complaints.

(2) Patient global assessment

The patient's global assessment of knee osteoarthritis will be used as a one-item scale "Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?" using a 5-point Likert scale (1-very good: asymptomatic and no limitation of normal activities; 2-good: mild symptoms and no limitation of normal activities; 3-fair: moderate symptoms and limitation of some normal activities; 4-poor: severe symptoms and inability to carry out most normal activities; 5-very poor: very severe symptoms that are intolerable and inability to carry out all normal activities). The description for each answer category refers to Schnitzer and colleagues and will be translated into the German language [33].

(3) Health-related quality of life

The Veterans RAND 12-Item Health Survey (VR-12) [34] is a generic questionnaire to assess the patient's opinion about their health-related quality of life. The VR-12 allows the calculation of a mental as well as a physical component scale and includes a 1-item scale for general health.

Table 2 Outcome measures and study instruments

Outcome Description	Instrument [ref]	Sample	Collection points
Patient characteristics			
Sociodemographic data, anthropometric data, other baseline data	Variables and definitions according to the International Standard Set of Outcome measures for patients with hip or knee OA [29]	IG, C	t0
Technical affinity towards electronic devices	Self-report questionnaire on subjective technical affinity (Technical Affinity – Electronic Devices (TA-EG)) [31]	IG, C	t0
Outcome expectations	Expectation for Treatment Scale (ETS, German version) [30]	IG, C	t0
Fear of Movement	Tampa Scale for Kinesiophobia (German Version, TSK-GV) [32]	IG, C	t0
Health outcome measures			
Patient reported outcome measures (PROMS)			
Subscale knee pain (Co1° outcome)	Knee Osteoarthritis Outcome Score KOOS [24, 25]: A disease related questionnaire asking for patient's opinion about their complaints	IG, C	t0, t1
Subscale function in daily living (ADL) (Co1° outcome)	Knee Osteoarthritis Outcome Score KOOS [24, 25]: A disease related questionnaire asking for patient's opinion about their complaints	IG, C	t0, t1
Subscales symptoms, function in sport and recreation (Sport/Rec), knee-related quality of life (QoL)	Knee Osteoarthritis Outcome Score KOOS [24, 25]: A disease related questionnaire asking for patient's opinion about their complaints	IG, C	t0, t1
Patient's global assessment	Patient Global Assessment of osteoarthritis – Knee [33]	IG, C	t0, t1
Health related quality of life	VR-12 Questionnaire [34]	IG, C	t0, t1
Subjective assessment of overall change, change in pain and function	Transition question according to Angst, Benz [35]	IG, C	t1
Objective outcome measures			
Functional strength measure for the lower extremities	30-s Chair Stand Test [36]	IG, C	t0, t1
Concomitant care			
Treatment progression	Variables and definitions according to the International Standard Set of Outcome measures for patients with hip or knee OA [29]	IG, C	t0, t1
Care utilization		IG, C	t0, t1 + after 4 and 8 weeks
Perceived human-digital interaction, patient satisfaction			
Usability of the app	- mHealth App Usability Questionnaire (MAUQ) [37] - 1 item from Harder, Holroyd [38] (Item B1)	IG	t1
Patient satisfaction with the app	Patient satisfaction questionnaire (ZUF-8) [39]	IG	t1
Patient satisfaction with the results of the treatment	Satisfaction with the results [29]	IG, C	t1
Logfiles			
Adherence to exercise	Logfiles relate to adherence to overall training sessions and each exercise	IG	continuously during intervention phase
Rating of perceived exertion (RPE) during exercising	Entry into the app after each exercise and after the training using an adapted RPE-Scale (NRS 0–10)	IG	continuously during intervention phase
Rating of perceived pain before, during and after exercising	Entry into the app before/after the training and after each exercise using a faces pain scale referring to the numbers 0, 2, 4, 6, 8, 10	IG	continuously during intervention phase
Safety aspects			
Exercise related pain	Frequency, duration, intensity	IG, C	t1
Adverse event report	Direct contact to study personal	IG, C	if reported

t0 Baseline, t1 directly after the 12- week intervention phase, IG Intervention group, C Control group

(4) Subjective assessment of overall change, change in pain and function

The following transition questions will be used to assess the subjective change in health status at t1: "Please imagine how your health status was 3 months ago. How do you feel about your osteoarthritis in the index knee joint today compared to 3 months ago? Please mark the answers that are applicable: (1) in general; (2) in the area of pain; (3) in the area of walking." The questions are each answered with a 5-point Likert scale with the response options "much better", "somewhat better", "unchanged", "somewhat worse" and "much worse". The questions and answers refer to Angst and colleagues and were translated into German by the author [35].

Objective measures The 30-s chair stand test [36] aims to test leg strength as well as leg strength endurance. The participant is seated in the middle of a chair with the hands and arms crossed in front of the upper body. Feet are completely positioned on the floor, and the back is straight. Out of this initial position, the participant is asked to stand up until an upright position and to sit again as often as possible within a 30-s time window. The results can be related to sex- and age-matched norm values.

Concomitant care Utilization of previous care and treatment will be assessed at t0 with a retrospective time window of 12 months. Utilization of concomitant care (yes vs. no entry) during the study period will be assessed 4 and 8 weeks after baseline and at t1 (twelve weeks after baseline) with a retrospective time window of 4 weeks. Assessments will include the type of care utilization (i.e., physical therapist, general practitioner, dietician, etc.) and the type of received treatment referring to different kinds of information/advice, self-managed care, non-surgical care, clinical care and surgery [29]. Within the categories self-managed care/clinical care, medication intake (regularly, sporadic, no), the type of medication taken, and its dose and frequency of intake will explicitly be asked for.

Perceived human-digital interaction, patient satisfaction The perceived usability of the digital health application will be assessed with the m-Health App Usability Questionnaire (MAUQ) [37] in addition to 1 item from Harder et al. [38] (Item B1). The MAUQ is not available in a validated German language version and is used in a self-translated version. The assessment of this questionnaire takes place after the exercise intervention period.
The modified version of the 8-item scale ZUF-8 will be used to assess patient satisfaction with the received care [39]. The modifications relate to changes according to the kind of care (stand-alone app here versus hospital setting in the original version).

Patient perspective on the satisfaction with the results of their treatment in general will be asked with the one-item question "How satisfied are you with the results of your treatment?" using a 5-point Likert scale (very satisfied; satisfied; neither satisfied nor dissatisfied; unsatisfied; very unsatisfied) [29].

Logfiles Logfiles of the re.flex digital application for the evaluation of adherence to exercise, rating of perceived exertion during exercising and perceived pain before, during and after exercising will be read out for each training session separately.

(1) Adherence to exercise

Overall adherence will be quantified using the percentage of conducted exercise sessions relative to the overall number of prescribed exercise sessions, irrespective of compliance with the prescribed exercise dosage. In addition, logfiles of the app provide detailed information on the number of valid repetitions and sets of each exercise within a given training session as well as overall data for each training session during the 12-week intervention phase for the sensor-equipped leg. Training adherence is therefore further quantified by calculating the percentage of all valid repetitions conducted with the affected leg during the training related to the number of requested repetitions. The overall exercise repetition adherence is the mean value of the adherence of all training sessions of the 12-week program considering the calculation procedure as mentioned before. Further data include the time in action as well as the total training time (including calibration, instruction, training of the other leg, etc.).

(2) Rating of perceived exertion (RPE) during exercising

Participants are asked to rate their exertion using the entry field of the app after each set of exercises as well as overall exertion at the end of the training session. RPE is measured using a numerical rating scale (NRS) with 0 indicating no exertion at all and 10 indicating the maximal conceivable exertion. Values are read out for each set of an exercise separately. Average values are calculated.

(3) Perceived pain before, during and after exercising

Pain ratings are requested before and after each training as well as after each exercise set. Values are read out for

each exercise separately. Patients are asked to rate their pain using the entry field of the app. Perceived pain is measured using the Faces Pain Scale (FPS-R) [41]. Face emojis are scored 0 (no pain), 2 (little pain), 4 (moderate pain), 6 (much pain), 8 (very much pain) or 10 (highest imaginable pain). In case of an entry with a pain index of more than 8, the user gets a recommendation to pause training and to contact the physician in charge.

The In-app pain report is not aimed at replacing the comprehensive KOOS. Rather, it is intended to be used to monitor pain levels throughout the course of the exercise intervention.

Safety aspects Exercise-related pain and adverse events will be assessed retrospectively at t1, including frequency, duration, intensity, and potential causes. Exercise-related pain will only be assessed in participants in the intervention group, and adverse events (AEs) will be assessed in both study arms.

Participants are informed at t0 to contact the study personal in case of AEs during the study period. Minor AEs must be reported to the responsible study personnel within one week (postal letter, email, telephone, in-app support chat). Adverse events causing the need for referral to a physician or hospital have to be reported to the responsible study personnel immediately. Judgement on whether the AE is related to the intervention is carried out by an orthopaedist or physician for internal medicine of the Dept. of Sports Medicine. In case of an unclear connection between an AE and the intervention or in case of a serious AE, representatives of the study sponsor Sporlastic and other study independent physicians of the University Hospital will report the situation to a safety board. This safety board will then decide on the continuation or premature termination of the trial for safety reasons.

Participant timeline and recruitment

The first patient was recruited in January 2023. Continued inclusion of patients is planned until the

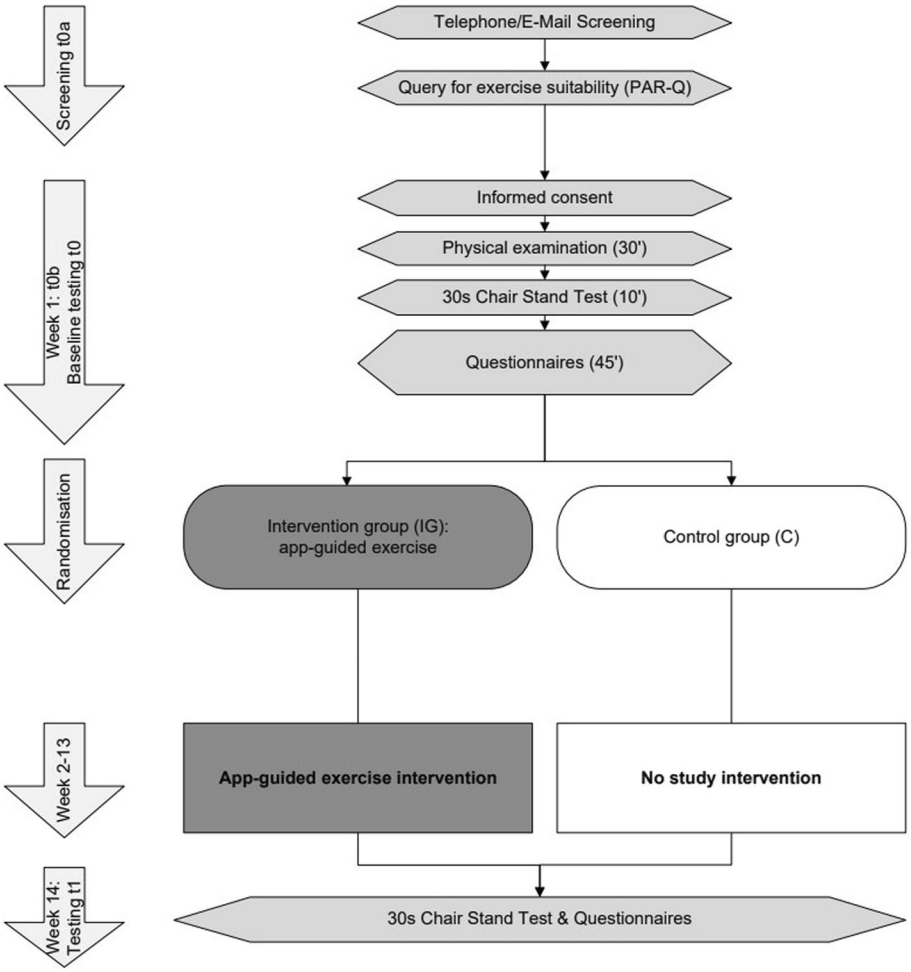

Fig. 3 Study flow chart

end of April 2023. Assessments at baseline (t0) and immediately after the 12-week intervention/control phase (t1) will be conducted on-site at the University Hospital, Tübingen, Germany, and data will be collected as outlined in Fig. 3 and Table 2. Assessors for the performance outcome measure are thoroughly instructed by the study personnel who are responsible for the use of the measurement instrument as well as for all other assessments, including the randomization process prior to the start of the study. Prior to the independent execution of the tests, all assessors performed up to three supervised assessments until these were carried out correctly. Additionally, an online questionnaire asking for concomitant care will be sent at weeks 4 and 8. All participants are expected to have completed the study by the end of July 2023.

A detailed timeline for the individual patients can be seen in the study flow chart in Fig. 3.

Potential study participants will be recruited via newspaper, newsletter for employees of the University Hospital and the University and people who were interested in participating in a previous study (DRKS00023269) but could not be included because of bicondylar symptoms (eligibility criteria have been changed for this trial).

Recruiting will take place in a two-step procedure. The first contact will be held by telephone or email. The purpose of this contact is to inform the interested person about the content and aims of the study as well as its timeline. The first screening for eligibility by querying the inclusion and exclusion criteria is also part of this contact. In this regard, the Physical Activity Readiness-Questionnaire PAR-Q is used to screen for exercise suitability. If one or more questions related to restrictions other than musculoskeletal are answered with "yes", the interested person must provide a confirmation for cardiopulmonal exercise suitability from his personal doctor in case of further interest in study participation. This step takes place before study inclusion and must be done on the patient's initiative.

In the context of the second step, the eligible patient is invited to a face-to-face meeting. This meeting includes comprehensive oral and written study information and the option for the patient to ask and respond to open study-related questions. After providing written consent, the patient is included on a provisional basis and referred to the study physician (orthopaedist) for medical examination (anamnesis and physical examination). The patient is finally included in case of alignment to inclusion criteria and absence of exclusion criteria. Otherwise, the subject is definitely excluded before randomization takes place.

The examination is followed by the outcome assessments. Finally, patients will be randomized to the intervention or control group. This first baseline examination will take approximately two hours. The first examination (t0) is followed by the 12-week intervention or control phase. Follow-up measures (t1) will be conducted directly after the 12-week intervention or control phase. The complete study duration for each participant will be approximately 14 weeks, including two assessments as well as the 12-week intervention or control phase.

Sample size

The two primary endpoints of the study are the KOOS subscales of pain and ADL. The results of a pilot study comparing the KOOS pain subscale and KOOS ADL subscale of 29 patients in the control group (usual care) with 15 patients in the intervention group (re.flex) using baseline adjusted analysis of covariance revealed effect sizes of 1.16 (Pain subscale) and 1.03 (ADL subscale). A recent meta-analysis on exercise interventions in patients with knee OA reported a standardized mean difference of 0.5 (95% CI 0.37 to 0.63) for pain reduction immediately posttreatment in comparison to usual care or minimal treatment [42]. Additionally, minimal clinically important differences (MCIDs) were reported between 5.5 and 8.7 points on the WOMAC pain subscale (score 0–100) for nonsurgical treatment strategies in patients with knee OA [35, 43]. These correspond to standardized mean differences between 0.59 and 0.94. Based on the preceding, rather heterogeneous results with effect sizes between 0.5 and 1.2 from the results of the pilot study and findings and recommendations of other sources, the planned study is powered to demonstrate a MCID of 5 points (0–100) on the KOOS Pain Subscale between the intervention and control group with a standard deviation of 10. This leads to an effect size of 0.5 and to a sample size of evaluable participants of $2*78=156$. For adjustment of baseline, aetiology, medication and laterality, 4 additional degrees of freedom are spent, and the sample size is increased to 160. Considering a drop-out rate of ~ 20%, 200 patients will be recruited to achieve a power of 80% with a type 1 error of 0.025 (two-sided Bonferroni correction for two confirmatory outcomes) by baseline adjusted comparison of outcome values at t1 between study arms (analysis of covariance, ANCOVA).

Randomization

Before the study start, randomization lists will be created for each of the eight combinations of the strata aetiology (primary, secondary), medication (regularly/no or sporadic) and laterality of the disease (one-sided, two-sided) using computer-generated random numbers (0;1) with

varying block lengths and 50 subjects per stratum combination. The randomization list will be transferred to the data management system SecuTrial (Interactive Systems Berlin). Online randomization will be performed after confirmation that the respective subject fulfils all selection criteria, after baseline assessments take place and after entry of the stratification criteria. Randomization will be performed on site using the randomization tool SecuTrial and will be conducted in the order of patient appearance by the assessors.

Participants will not be randomized in case of exclusion before completion of the examination and tests at t0.

Blinding

The study intervention is obvious, and therefore, an adequate comparable placebo intervention is not possible. As such, this trial is nonblinded for participants. Blinding of health care providers is not applicable, as the intervention of interest is a stand-alone app without human interaction. Baseline assessments will take place before randomization, and data collectors for the performance test will be blinded to the group allocation of the participants for follow-up assessment. All other outcomes are self-reported, and blinding is not possible, as they include outcomes that are only assessed in the intervention group (e.g., logfiles, patient satisfaction with the app); thus, group allocation is obvious. The creation of the computer-generated randomization list using the software nQuery will be done by an employee of the IKEAB who is not involved in the conduction and assessment of the study. Statisticians will be blinded for the analyses of the primary endpoints and all other health outcome measures. For further analyses, statisticians will be unblinded, as treatment allocation is obvious (i.e., perceived human-digital interaction, logfiles, etc.).

Statistical methods

The two primary endpoints of the statistical analyses are the KOOS subscales pain and KOOS ADL. They will be analysed at t1 immediately after the termination of the intervention using a baseline adjusted analysis of covariance (ANCOVA) with the primary factor "study arm". The level of significance will be 0.025 (two-sided Bonferroni correction for two confirmatory outcomes). We hypothesize that the exercise intervention will be superior to the control. Additionally, the stratification factors aetiology (primary, secondary), medication (regularly/no or sporadic) and laterality of the disease (one-sided, two-sided) will be coded by binary variables. The model equation is:

$$Y = \beta 0 + \beta 1 * BL + \beta 2 * Arm + \beta 3 * aetiology + \beta 4 * medication + \beta 5 * laterality + \varepsilon.$$

Y: KOOS (Pain resp. ADL) at t1, BL: baseline KOOS (Pain resp. ADL), Arm: study arm coded as 0 (control) and 1 (exercise intervention), ε random error (normally distributed, equal variance, independent). Reference categories "primary", "no or sporadic medication", and "one-sided disease", H0: $\beta 2 = 0$, H1: $\beta 2 \neq 0$ (two-sided test, scientific hypothesis: superiority of exercise intervention, i.e., $\beta 2 < 0$).

Continuous secondary endpoints will be analysed using the same statistical methods (analysis of covariance (ANCOVA) if baseline values are available; otherwise, analysis of variance else). For the main results, two-sided 95% confidence limits will be given in addition to significance tests.

The success of randomization will be assessed using baseline comparisons between both study arms. The primary analysis population will be the intent-to-treat population. This population includes all patients who contribute at least baseline values of the primary outcomes. Multiple imputation will be applied to subjects who drop out or do not contribute measurements of the primary outcome for other reasons. Five hundred imputation samples will be drawn. Baseline measurements will be included as predictors (c.f. definition of intent-to-treat population). The "jump to reference" method will be used for the primary analysis, i.e., patients who drop out will be assigned to the control arm in the imputation model but not in the analysis model. Sensitivity analyses will be performed with "complete case analysis", "baseline observation carried forward" (single imputation) and with inclusion of the correct study arm in the imputation model (multiple imputation). A per protocol analysis will be conducted with all participants of the intervention group complying with the study criteria and still using the app until the last two weeks of the intervention phase with an overall adherence rate of 80% of the scheduled sessions. The same procedure will be performed for all other secondary health outcome measures for which baseline values are complete.

Exploratory subgroup analyses will be performed for the stratification factors and patient age (18–40 years, 40–55 years, 55–65 years, older than 65 years). Additionally, in the case of frequent or differential occurrence of concomitant care (medication, physical therapy – active treatment) between the study groups, an exploratory subgroup analysis will be performed. P values for interaction of study arm with stratification factors and patient age as well as p values of study arms within strata will be reported but should not be interpreted as confirmatory.

An additional analysis is planned for subjective ratings of overall change (general, pain, function). Response scales will be first dichotomized into improved (somewhat/much better) and not improved (unchanged or worse). Between-group comparisons will be expressed as relative risks of improvement [44]. Exploratory, prognostic factors, including baseline pain, age, BMI, sex, technical affinity and fear of movement, will be analysed using multiple regression models (linear regression) to identify potential responders to the training. Binary outcomes will be analysed using similar logistic regression models.

Data management

Data from all participants with informed written consent will be pseudonymized. On-site data will be captured with paper and pencil case report forms (CRFs) and using an online questionnaire (Questback GmbH, Köln, Germany) for PROMS. Log-Data of app usage will be captured by the software and transferred to the study team (*.csv-file). Paper and pencil CRFs will be double entered into an electronic data sheet (Excel). Doubly entry will be checked for errors. The data bank will be closed after the last patient out and after all queries are processed. Study data are then exported via *.csv-File to the statistical programs in use.

Data monitoring

There is no external data monitoring committee for this study.

Discussion

M-health interventions such as the sensor-guided digital-based exercise intervention re.flex can be used independently from time and location and allow most patients to gain access to this kind of exercise guidance. Re.flex was specifically developed to support home training in patients with knee OA. If effective, it can bridge part of the gap between recommendations for strengthening exercises in patients with knee OA and the insufficient actual care situation. However, to be classified as a digital health application reimbursed by German health insurance companies, the intervention must prove patient benefit. There are several ways to define appropriate controls for digital therapeutic clinical trials, e.g., using a sham control intervention such as a low-functional digital health tool lacking the elements to be reasonably effective [45]. The selection of the control group in this trial agreed with the responsible authority (Federal Institute for Drugs and Medical Devices in Germany, BfArM).

Limitations

The following limitations must be addressed for the outlined study. All participants are allowed to make use of usual health care provided by their treating physician during the study period. This concerns the intervention and control group, and cannot be prohibited, as all persons with German health insurance have a right to receive physician-recommended usual care treatments. Exclusive participation in re.flex (intervention) or doing nothing (control) cannot be ensured. To address this issue, all concomitant care will be queried retrospectively for one year and every 4 weeks until the end of the study.

Considering the intervention duration of 12 weeks, only short-term effects can be assessed. Long-term effects will not be determined.

Conclusion

This randomized controlled trial is designed to provide conclusions on the effectiveness of re.flex for the population under study. Patient benefit is primarily related to OA-specific pain reduction and improvement of physical function. Superiority of re.flex versus control for pain and function is a prerequisite for the permanent listing of the app into the DiGA register.

In addition, this study will add important knowledge to the scientific community on the short-term effectiveness of exercise-related digital health interventions on health outcomes in general, and it will further provide evidence on its usability, patient acceptance and safety. Regarding this, sensor-based technology allows objective measures of exercise performance and may therefore help to control and analyse exercise training at home.

Abbreviations

ADL	Function in daily living
AE	Adverse event
ANCOVA	Analysis of covariance
App	Application
CRF	Case report form
DiGA	Digital health application – Digitale Gesundheitsanwendung
DRKS	German clinical trials register - Deutsches Register Klinischer Studien
ETS	Expectation for Treatment Scale
FPS-R	Faces Pain Scale
ICD	International Classification of Disease
ICHOM	International Consortium for Health Outcomes Measurement
IKEAB	Institute for Clinical Epidemiology and Applied Biometrics
KOOS	Knee Osteoarthritis Outcome Score
MAUQ	M-Health App Usability Questionnaire
MCID	Minimal clinically important difference
m-health	Mobile health
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PAR-Q	Physical Activity Readiness Questionnaire
PROM	Patient-reported outcome measure
QoL	Quality of life
RPE	Rating of perceived exertion
Sport/Rec	Sport and recreation
t0	Timepoint 0, collection point at baseline

t1	Timepoint 1, collection point after 12-week study phase
TA-EG	Questionnaire to assess technical affinity regarding electronic devices
TSK-GV	Tampa Scale for Kinesiophobia, German Version
VR-12	Veterans Rand 12: 12-item questionnaire assessing Health related quality of life
WOMAC	Western Ontario and McMaster Universities Arthritis Index
ZUF-8	Patient satisfaction questionnaire

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s44247-023-00040-1.

Additional file 1. Reporting checklist for protocol of a clinical trial (SPIRIT guidelines).

Additional file 2. The TIDieR (Template for Intervention Description and Replication) Checklist.

Additional file 3. Consent form.

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Dissemination policy
The University Hospital Tübingen has a basic right of publication of study data. The study protocol and results will be communicated at scientific congresses and/or in peer-reviewed scientific journals. The sponsor Sporlastic GmbH has the right to make the study results public as a part of corporate communications.

Authors' contributions
IK, VD, PM and PJ contributed to the conception and design of the study. VD drafted the manuscript. IK, PM and PJ critically revised the manuscript. All the authors have read and approved the final manuscript.

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Availability of data and materials
Data and material will be made available upon reasonable request after the conclusion of the study.

Declarations

Ethics approval and consent to participate
The complete final trial dataset will only be assessed by employees of the University Hospital Tübingen. Any information provided in the context of the interaction with the digital application (technical queries, log files, information given within the scope of the software use) can be assessed by the app producer and the study sponsor. However, these data are pseudonymized and cannot be reidentified by any party other than the University Hospital.
This study is approved by the Ethics Committee of the Medical Faculty of the University of Tübingen (688/2022BO2). The trial was registered on 20/01/2023 at www.drks.de (ID: DRKS00030932). Participants will be informed about the potential harms and benefits of the study and the voluntariness of study participation. Written informed consent will be obtained from all participants prior to study inclusion. In case of modifications of the protocol, an amendment will be sent to the local ethics committee prior to the implementation.

Consent for publication
The person in Fig. 1 gave written informed consent for the image to be included in this manuscript.

Competing interests
The exercise intervention that is implemented in the re.flex app was designed by employees of the University Hospital (i.e., VD, IK) in the context of a previous cooperation project between the trial sponsor Sporlastic GmbH and the University Hospital Tübingen. The pilot study of this trial protocol was conducted during this cooperation project as well. The University Hospital will be appropriately compensated for granting rights of use to the results generated by employees of the University Hospital (intellectual property) in the event of successful commercialization of the app. University Hospital will compensate the employees (i.e., VD, IK) who were involved in the previous collaboration and are authors of the intellectual property from these revenues. Contract negotiations are currently underway. However, the PI (PJ) of the study outlined in this study protocol and the biomedical statisticians (PM) do not have any conflicts of interest.

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Publisher's Note

4.4 Research article 4: Effectiveness of the self-directed m-health exercise intervention re.flex in patients with knee osteoarthritis: A randomized controlled trial

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Original Paper

Effectiveness of the Self-Directed mHealth Exercise Intervention re.flex in Patients With Knee Osteoarthritis: Randomized Controlled Trial

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Abstract

Background: About 1 in 2 patients with knee osteoarthritis (OA) receives a referral or recommendation for exercise. Digital health applications could counteract this undersupply.

Objective: We aimed to investigate the effectiveness of a 12-week self-directed mobile health exercise intervention (re.flex) when used in addition to usual care compared to a control group receiving usual care only on pain reduction and improvement in physical function in patients with knee OA.

Methods: This monocentric, 2-arm, randomized controlled parallel-group trial included patients from Germany with moderate to severe knee OA. Participants were mainly recruited via newspapers. Randomization was 1:1 into an intervention group (re.flex+usual care) and a control group (usual care) using computer-generated blocks. Participants were unmasked to group assignment. The re.flex group conducted a 12-week self-directed app-based and sensor-assisted exercise program with 3 sessions per week in addition to usual care. Primary outcomes were OA-specific knee pain and physical function (using the subscales pain and activities in daily living of the Knee Osteoarthritis Outcome Score, 0-100) at 3 months. Secondary outcomes included adherence and safety. Multiple imputation was used to account for missing data. Intervention effects were calculated using a baseline-adjusted analyses of covariance (ANCOVA). Bonferroni correction with an alpha level of .025 was applied.

Results: Between January 25, 2023, and August 11, 2023, a total of 195 participants were enrolled. Of them, 98 participants were allocated to re.flex, and 97 participants to usual care. The primary analysis included 194 participants. The mean age was 61.9 (SD 7.7) years, and the majority were female (132/194, 68%). Pain reduction was significantly larger in re.flex than in usual care, with an adjusted mean difference between study groups of 4.8 (95% CI 0.7-8.9; *P*=.02; Cohen *d*=0.35) points. Improvement in physical function was not statistically significant (beta coefficient [β]=3.9 points, 95% CI 0.0-7.9, *P*=.049). A total of 12 adverse events were linked to re.flex, none of which were serious. Participants adhered to 77% (2705/3528) of all scheduled exercise sessions.

Conclusions: The self-directed sensor-based mobile health exercise intervention re.flex demonstrates superiority over usual care for pain reduction and justifies this kind of intervention as an alternative exercise delivery mode for patients with knee OA.

Trial Registration: German Clinical Trial Register (DRKS) DRKS00030932; https://drks.de/search/de/trial/DRKS00030932

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Keywords: digital health; mHealth; exercise intervention; knee osteoarthritis; knee pain; physical function

Introduction

Osteoarthritis (OA) is a degenerative joint disease and a leading cause of adult chronic pain and long-term disability. It most commonly affects the knee, hip, and hand joints [1,2]. Higher prevalence rates are reported for higher age, female sex, and number of comorbidities, for example, obesity [3]. According to the German Gesundheit in Deutschland aktuell (GEDA) 2014/2015-European Health Interview Survey (EHIS), 17.9% of German adults have been diagnosed with OA. Among the age group of >65 years, almost half of the female and one-third of the male German population are affected [4].

Clinical guidelines worldwide outline exercise as a first-line treatment in patients with knee OA [5]. However, only 50% of patients receive recommendations for physiotherapy and only 36% for therapeutic exercise [6,7]. There is an urgent need to investigate additional ways for guiding exercise in these patients. To this end, digital health technologies seem promising, as they are widely available and allow users to exercise independent of location and time. Digital health is an umbrella term for the field of eHealth, mobile health (mHealth), and telehealth. They enable the delivery of health services by integrating digital devices and tools that improve the accessibility and efficiency of health care [8]. In general, health care interventions delivered by digital health technologies can be classified into three main categories: (1) self-directed eHealth and mHealth interventions (eg, web or mobile apps [9-11]), (2) synchronous [12,13] or asynchronous [14] supervised eHealth and mHealth interventions (eg, videoconferencing, chat messages in combination with mobile apps, and phone calls), and (3) blended care approaches [15,16] (hybrid format combining an in-person supervised intervention guided by a health care professional in individual treatment or group sessions blended with a self-directed or remotely supervised eHealth or mHealth intervention).

The results of a qualitative study indicate that patients with knee OA mostly seem to have positive experiences with and attitudes toward the use of self-directed eHealth exercise interventions [17]. However, people prefer different levels of human support, illustrating that there is no one-size-fits-all solution for implementing eHealth exercise interventions in OA care [17]. Thus, a variety of delivery modes could be offered, depending on the patient's individual health care needs, preferences, and individual context factors. To better ensure tailoring an appropriate level of input, the implementation of digital interventions could be integrated into a stepped care model [18]. This would entail the initial provision of self-directed offers, with the possibility of progressing to a more supervised option in case no meaningful improvements were achieved in previous steps [17,19]. The results of recent meta-analyses demonstrated that eHealth exercise interventions have a beneficial effect on pain and physical function in patients with knee OA. The effects are comparable to those of nondigital, face-to-face interventions and superior to usual care [20,21].

To our knowledge, no systematic review or meta-analysis has directly compared treatment effects between supervised and self-directed eHealth exercise interventions for knee OA. However, the possibility of human supervision and interaction in digitally delivered exercise interventions is considered to positively influence motivation for and adherence to exercise and may improve clinical outcomes [22,23]. The effectiveness of supervised exercise interventions can be attributed to specific factors, including the high quality with which exercise programs are performed (eg, instructional guidance, technical execution of exercises, higher intensity, more comprehensive introduction of individualization and progression principles, and direct feedback) and giving patients the confidence to perform the exercises correctly [24-26]. Thus, incorporating health care professional input may foster acceptance and engagement [17]. Nevertheless, this does not fully address the issue of limited health care accessibility. In the absence of human interaction, the use of app features, such as biofeedback (eg, movement sensors) or self-monitoring, in-depth guidance on how to exercise correctly (eg, exercise videos, instructions, repetition, and set numbers), and SMS text messages or push notifications to remind users of upcoming exercise sessions may provide a similar level of assistance [17,27,28].

As previously stated, self-directed digital care solutions have the potential to address the insufficient provision of exercise as a first-line treatment in knee OA. However, patient benefit and reimbursement strategies are prerequisites for a successful implementation into clinical routine. In Germany, the Digital-Care-Law (Digitale-Versorgung-Gesetz, DVG) allows physicians to prescribe digital health applications (Digitale Gesundheitsanwendung, DiGA) registered in the "DiGA directory" [29].

This randomized controlled trial aimed to examine the effectiveness of the sensor-assisted mHealth exercise intervention (re.flex). The confirmatory study aims to test the primary hypotheses concerning the superiority of the intervention (re.flex+usual care) over usual care in reducing pain and improving physical function.

Methods

Study Design and Participants

The study was conducted as a monocentric randomized controlled superiority trial as outlined in the study protocol [30]. The study report follows the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [31]. Participants were recruited via advertisements in newspapers, digital media, referrals from physicians, and 2

information events about OA. Individuals aged 18 years or older with (1) a self-reported tibiofemoral knee OA diagnosed by a physician, (2) a self-reported Knee Osteoarthritis Outcome Score (KOOS) of the subscale pain ≤60 points during the screening process, and (3) a mobile electronic device with an iOS or Android operating system were eligible for inclusion. Participants were excluded (1) if they had a history of knee joint replacement or osteotomy on the signal joint, (2) if contraindications were present that precluded the safe execution of exercise without supervision, (3) if they were currently treated by a physician or physiotherapist for any complaints of the lower extremity or lower back other than knee OA, (4) if they had been conducting regular structured strengthening exercises for the lower extremities more than once a week during the past 6 months, or (5) if they had insufficient German language proficiency. Computer or internet literacy was not an eligibility criterion. Interested persons were screened by phone. Final inclusion or exclusion took place at the University Hospital Tübingen in the context of the medical examination at baseline.

Randomization and Masking

Participants were randomly assigned (1:1) to re.flex (see intervention section) in addition to usual care (intervention group) or usual care (control group). Randomization lists were created for each of the 8 combinations of the stratification factors etiology (primary and secondary OA), medication (regularly, none, or sporadic), and laterality of the disease (one-sided, both-sided) using computer-generated random numbers (0, 1) with varying block lengths. The randomization lists were transferred to the data management system SecuTrial (Interactive Systems). Sequence generation and concealment were done by an employee (RB) who was not involved in the conduction and assessment of the study. By using randomization via the software SecuTrial (Interactive Systems), allocation concealment was ensured. Participants were not randomized in case of exclusion before completion of the examination and assessments at baseline. This trial was not blinded for participants. Baseline assessments took place before randomization, and assessors for the 30-Second Chair Stand Test were blinded toward group allocation for follow-up assessments. However, the assessment of patient-reported outcome measures (PROMs) was at risk for reporting bias. The statistician was blinded toward the primary outcomes (except for the jump to reference imputation, where the blinding was not possible). For further analyses, the statistician was unblinded, as treatment allocation was obvious (eg, usability, logfiles).

Intervention

The intervention group received re.flex (2019, Kineto Tech Rehab SRL, Romania), a 3-month training program with exercises guided by use of an app and 2 wearable motion sensors (3-axis gyroscope, L 43 mm x W 24 mm x H 12 mm, weight 16 grams, Bluetooth Low Energy) attached proximally and distally to the OA-affected knee joint (refer to Multimedia Appendix 1). The primary focus of the intervention was to strengthen knee extensors, knee flexors, and hip abductors. Further exercises were aimed at joint mobilization, muscle stretching, and balance training. Different types (eg, open and closed kinetic chain), exercise variations (eg, short or long lever arms, elastic resistance bands), and poses (supine, sitting, and standing) were used to allow progression of training loads. In addition, the user could choose one of two difficulty levels for strengthening exercises, with the lower one set as default. Details on the progressively designed program with dosage principles and objectives are described in the Multimedia Appendix 1. All training sessions were self-directed and conducted at home. At baseline, the patient was introduced into downloading, logging into the free user account, and usage of the app, sensors, and dosage principles by the study staff. The app provided the exercises with text descriptions and videos. Using biofeedback provided by the motion sensors, the patient was asked to align his virtual limb to the target condition displayed with another avatar in order to control movement execution, predefined range of motion, movement velocity, and number of repetitions. Visual and auditory feedback was further provided by a movement bar, a real-time rating of movement quality, and an auditory signal whenever reaching the end position of a movement. If an exercise was not performed correctly, verbal instructions were given. Further app features allowed users to pause or skip exercises, rate pain and perceived exertion during exercise sessions, remind users of upcoming training sessions via push notification, monitor training progress with statistics, and allow users to contact the app provider in case of technical issues via an app messenger service. A recommendation to pause training and to contact the physician in charge was provided if the maximum pain level was entered. In the context of the study, medical issues (adverse events [AEs]) were reported to the study personnel via email or phone call. In addition, patients did receive information on how to deal with increasing pain during or after exercising, if applicable. All information given at baseline was provided orally and written on a fact sheet and an instruction manual. Details and screenshots of the app features are displayed in Figure 1 and the Multimedia Appendix 1. Participants in the control group did not receive any study intervention but were allowed to use usual care (for details of how usual care was defined, refer to the study protocol [30]), in correspondence to the re.flex group. Furthermore, participants were given the opportunity to use re.flex after study completion.

Figure 1. Screenshot with features of the re.flex app.

Outcomes

Data were collected at baseline (t_0) and 3 months (t_1). PROMs were assessed web-based (Questback GmbH, Germany), and the 30-Second Chair Stand Test was conducted on-site. Concomitant care was additionally assessed web-based 4 and 8 weeks after baseline. App log files were read out after 3 months. Primary outcomes were baseline-adjusted follow-up scores (t_1) of pain and physical function, measured with the KOOS subscales pain and activities in daily living, each on a scale of 0-100, worst to best.

Secondary outcomes included: (1) KOOS subscales, such as symptoms, function in Sport and Recreation, and knee-related quality of life (QoL); (2) patient global assessment (PGA) of knee OA; (3) Health-related quality of life (HrQoL; Veterans RAND 12-Item Health Survey [VR-12]) with the mental component scores (MCS) and physical component scores (PCSs); (4) subjective change in health status along the study period in general, for pain, and walking; (5) the mHealth App Usability Questionnaire (MAUQ, self-translated into German language); (6) patient satisfaction with the app and results of the treatment; and (7) the 30-Second Chair Stand Test. Additional outcomes included the evaluation of log files (adherence, active time, rating of perceived exertion, and pain), AEs occurring during the study period, and any concomitant care as a potential confounder. Full details on descriptive and outcome measures are in the study protocol [30] and the Multimedia Appendix 1.

Statistical Analysis

The extant literature has reported minimal clinically important differences (MCIDs) between 5.5 and 8.7 points for nonsurgical treatment strategies in patients with knee OA [32,33]. Accordingly, this study was powered on an MCID of 5 points (0-100) between the intervention and control group for the first primary outcome "KOOS subscale pain," assuming the pooled SD of differences to baseline according to the pilot study [34]. This led to an effect size of 0.5. Therefore, an estimated sample size of 156 participants was required to detect a MCID of 5 points between groups for the primary outcomes, with a type I error of 0.025 (2-sided, Bonferroni correction for 2 confirmatory outcomes and success of the study if at least 1 outcome was significant in favor of the intervention) and a power of 80%. For adjustment of baseline, etiology, medication, and laterality, 4 additional df are spent, and the sample size was increased to 160. Considering a dropout rate of ~20%, we aimed to recruit 200 participants (100 per group) into the study. The sample size was determined using the software nQuery+ nTerim (Statistical Solutions Ltd) release 4.0. For additional information regarding the sample size, refer to the published study protocol [30] or Multimedia Appendix 1.

All statistical analyses have been done using the software SPSS (version 27.0; IBM Corp) and R (version 4.1.2; R Foundation for Statistical Computing). No interim analysis was performed. There was no external data monitoring committee for this study.

The primary analysis population was the intent-to-treat (ITT) population. This population includes all patients who contributed at least baseline values of the primary outcomes. Multiple imputation (MI) on score level was applied under the assumption of data missing at random to participants who dropped out or did not contribute measurements of the primary outcomes for other reasons. Baseline measurements were included as predictors. The "jump to reference" method was used for the primary analysis, that is, patients who dropped out were assigned to the control arm in the imputation model but not in the analysis model (ITT). This leads to a shrinkage of the intervention effect and is thus a conservative approach. The 2 primary outcomes (KOOS subscale pain and KOOS subscale activities in daily living at 3 months) were evaluated using a baseline-adjusted analyses of covariance (ANCOVA) with the primary factor "intervention" (study arm). The 3 stratification variables (etiology, medication, and laterality) were included as additional fixed factors (binary coding). For the main results, parameter estimates (beta coefficients, unstandardized differences), *P* values, 2-sided 95% CIs, and effect measures (Cohen *d* calculated as mean difference divided by SD of differences) were calculated.

Sensitivity analyses included an analysis with the ITT using MI without jump to reference, a complete case analysis, a per-protocol analysis (all participants using the app until the last 2 weeks of the intervention phase with an overall adherence rate of at least 80% of the scheduled exercise sessions, applicable only in the intervention group), and last

observation carried forward (LOCF) in the ITT. Continuous secondary outcomes were analyzed using the same statistical methods as used for the primary outcomes. However, these were secondary analyses, which may not be interpreted as confirmatory.

Exploratory subgroup analyses for the 2 primary outcomes were performed for the stratification factors (etiology, medication, and laterality), patient age (40-55 years, 55-64 years, and ≥65 years), and patient sex. Additional subgroup analyses were performed in the case of frequent or differential occurrence of concomitant care between study groups. In this context, nonsteroidal anti-inflammatory drugs, physiotherapy, and insoles qualified for subgroup analysis, with medication only being considered if taken on a regular basis (weekly or daily). Subgroup analyses were considered if interaction terms of the study arm and the respective subgroup variable were statistically significant.

A responder analysis was conducted using transition scales for subjective ratings of overall change, change in pain, and change in function with a 5-point Likert scale (much worse, somewhat worse, unchanged, somewhat better, and much better). In this analysis, the categorical values of response scales were dichotomized into the 2 groups "improved" (somewhat better or much better) and "not improved" (unchanged, somewhat worse, or much worse). Missing values of dichotomized data were imputed with jump to reference and analyzed using logistic regression models with linear predictors identical to the model of the primary analysis. Odds ratio obtained from logistic regression analysis, success ratio (SR) according to the calculation of "risk ratio," and numbers needed to treat (NNT) obtained from descriptive analyses were used as effect measures for each scale separately.

Ethical Considerations

All participants provided written informed consent. Ethical approval was obtained from the ethics committee of the University Hospital Tübingen (688/2022BO2). The participants were given a study ID number. Identifiable information was stored on password-protected servers. There was no compensation for participation in the study. Study materials were provided to participants for free. The study was registered in the German clinical trial register (DRKS00030932).

Results

Participant Flow and Baseline Data

Between January 25, 2023, and August 11, 2023, 195 participants were enrolled. Thereof, 98 participants were allocated to the re.flex group and 97 participants to usual care. Loss to follow-up was 9.2% (9/98) in the re.flex group and 6.2% (6/97) in usual care. One participant had to be excluded from the analyses due to the participant's request to delete all his data. Details on participant flow are displayed in Figure 2.

The trial recruitment was stopped once the planned number of evaluable participants was reached, as the dropout rate was lower than assumed (<20%). Baseline characteristics and baseline values of primary and secondary outcomes of participants did show comparable distributions between study groups (Table 1 and Multimedia Appendix 1).

Figure 2. Participant flowchart. KOOS: Knee Osteoarthritis Outcome Score; OA: osteoarthritis.

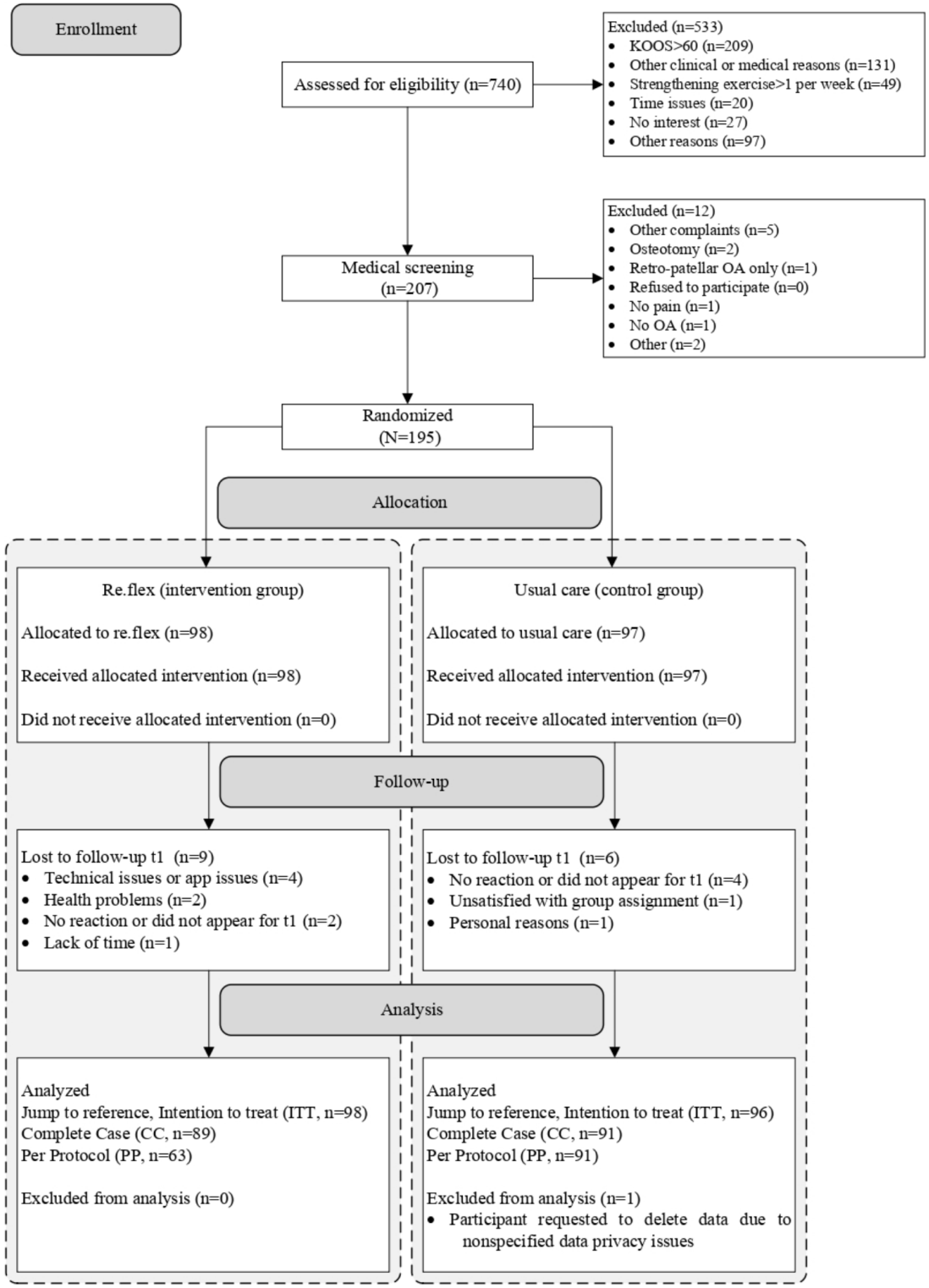


Table 1. Baseline characteristics of participants by study group[a].

Baseline characteristics	re.flex group (n=98)	Usual care group (n=96)
Demographics, anthropometry, and socioeconomics		
Age (years), mean (SD)	61.6 (8.0)	62.1 (7.5)
Sex, n (%)		
Female	70 (71)	62 (65)
Male	28 (29)	34 (35)

Baseline characteristics	re.flex group (n=98)	Usual care group (n=96)
BMI (kg/m²), median (IQR)	28.4 (26.8-32.2)	27.8 (25.0-31.4)
German nationality, n (%)	95 (97)	93 (97)
Life situation, n (%)		
Working	61 (62)	48 (50)
Retired	34 (35)	43 (45)
Others	3 (3)	5 (5)
Education, n (%)		
Low (<10 years)	8 (8)	9 (9)
Middle (≥10 years)	36 (37)	34 (35)
High (university entrance qualification)	49 (50)	48 (50)
Others	5 (5)	5 (5)
Housing, n (%)		
Together with partner	83 (85)	82 (85)
Alone	14 (14)	13 (14)
Others	1 (1)	1 (1)
Stratification factors		
Laterality, n (%)		
One-sided knee OA[b]	37 (38)	36 (38)
Both-sided knee OA[b]	61 (62)	60 (62)
Etiology, n (%)		
Primary knee OA[b]	84 (86)	83 (87)
Secondary knee OA[b]	14 (14)	13 (13)
Medication (knee OA–related)[b], n (%)		
No or sporadic	91 (93)	90 (94)
Regularly	7 (7)	6 (6)
Anamnesis		
Time since diagnosis of knee osteoarthritis (months), median (IQR)	65 (24-120)	61 (24-120)
Signal joint – Knee, n (%)		
Right	52 (53)	57 (59)
Left	46 (47)	39 (41)
History of injury, n (%)		
Ligament injury	22 (22)	21 (22)
Meniscus damage	50 (51)	57 (59)
No previous history	31 (32)	25 (26)
Comorbidities, n (%)		
Heart disease	6 (6)	8 (8)
Hypertension	35 (37)	33 (34)
Stroke	0 (0)	0 (0)
Circulatory disorder	2 (2)	1 (1)
Lung disease	7 (7)	5 (5)
Diabetes	3 (3)	3 (3)
Kidney disease	1 (1)	0 (0)
Neurological disease	0 (0)	1 (1)
Liver disease	1 (1)	2 (2)
Cancer	6 (6)	3 (3)
Depression	4 (4)	4 (4)
Back injury	14 (15)	8 (8)

Baseline characteristics	re.flex group (n=98)	Usual care group (n=96)
Activity and training variables		
Physical activity (per week), n (%)		
No	3 (3)	2 (2)
30 minutes	9 (9)	5 (5)
1 hour	20 (20)	20 (21)
2 hours	20 (20)	19 (20)
More than 2 hours	46 (47)	50 (52)
Previous experience with strength training, n (%)		
Very high	2 (2)	11 (11)
High	22 (22)	16 (17)
Medium	49 (50)	43 (45)
Low	22 (22)	17 (18)
Very low	3 (3)	9 (9)
Previous experience with hip or knee group training, n (%)		
Yes	6 (6)	9 (9)
No	92 (94)	87 (91)
Primary outcomes, mean (SD)		
Pain (0-100[c])	53.9 (14.4)	54.9 (12.8)
Physical function (0-100[d])	66.7 (15.1)	67.7 (15.2)
Others, mean (SD)		
Technical affinity (–2 to 14[e])	7.4 (2.1)	7.7 (1.9)
Outcome expectation (5-20[f])	14.4 (3.3)	14.3 (2.9)
Fear of Movement (6-24)[g]	9.8 (3.3)	9.5 (2.6)

[a]Data are mean (SD), n (%), or median (IQR). Some percentages might not add to 100% due to rounding.
[b]OA: osteoarthritis.
[c]Pain was assessed with the Knee Osteoarthritis Outcome Score (KOOS) subscale pain (0-100, worst to best) using a 5-point Likert scale.
[d]Physical function was assessed with the Knee Osteoarthritis Outcome Score (KOOS) subscale Activities in Daily Living (ADL) (0-100, worst to best) using a 5-point Likert scale.
[e]Technical affinity was assessed with the Technical Affinity – Electronic Devices (TA-EG) questionnaire using a 5-point Likert scale with options of "completely applicable," "rather applicable," "partly," "rather not applicable," and "not applicable at all." Higher scores reflect a better technical affinity.
[f]Outcome expectation was assessed with the Expectation for Treatment Scale (ETS, German version) using a 4-point Likert scale with options of "partially disagree," "partially agree," "agree," and "definitely agree." Higher scores reflect a higher outcome expectation.
[g]Fear of Movement was assessed with the Tampa Scale for Kinesiophobia (TSK-GV, German version) using a 4-point Likert scale with options of "strongly disagree," "disagree," "agree," and "strongly agree." Higher scores reflect greater fear of movement.

Primary Outcomes

The difference between study groups at 3 months was statistically significant for the primary outcome pain (β=4.8 points, 95% CI 0.7-8.9; *P*=.02), with re.flex being superior to usual care. Cohen *d* was 0.35, demonstrating a small effect. After Bonferroni correction, no statistically significant difference was observed for physical function (β=3.9 points, 95% CI 0.0-7.9; *P*=.049; Table 2, Figure 3, and Multimedia Appendix 1). The findings of the sensitivity analyses for the primary outcome pain confirmed the superiority of re.flex, with the exception of the conservative approach LOCF, which achieved a *P* value that was slightly above the significance level (Multimedia Appendix 1).

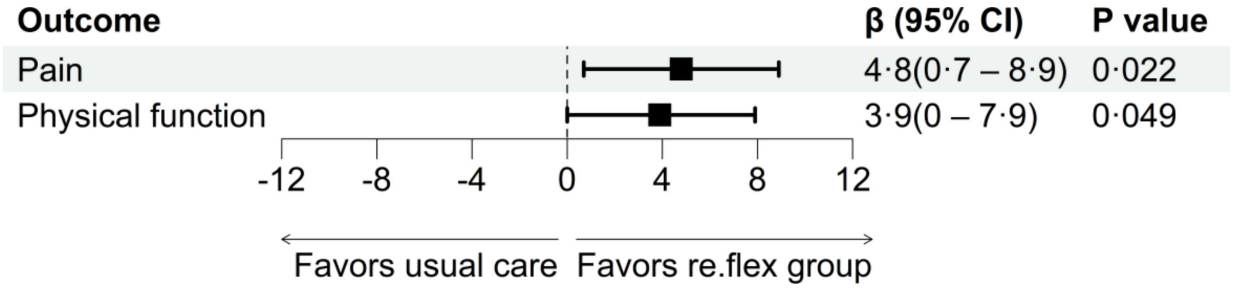
Table 2. Primary and secondary outcomes (primary analysis)[a].

	Change within group (3 months minus baseline)		Difference in change between groups (3 months)		
Outcomes	re.flex group (n=98), mean (SD)	Usual care group (n=96), mean (SD)	β (95% CI)	*P* value	Cohen *d*
Primary outcomes					
Pain (KOOS Pain)[b,e]	9.7 (15.9)	4.5 (14.0)	4.8 (0.7-8.9)	.02	0.35
Physical function (KOOS ADL)[c,e]	9.0 (16.2)	4.7 (11.5)	3.9 (0-7.9)	.049	0.31

Outcomes	Change within group (3 months minus baseline)		Difference in change between groups (3 months)		
	re.flex group (n=98), mean (SD)	Usual care group (n=96), mean (SD)	β (95% CI)	*P* value	Cohen *d*
Secondary outcomes					
Symptoms (KOOS Symptoms)[e]	9.6 (17.9)	5.0 (14.4)	4.1 (–0.2 to 8.5)	.06	0.28
Function in sport and recreation (KOOS Sport and Recreation)[e]	9.5 (18.7)	5.2 (16.9)	4.5 (–0.8 to 9.7)	.09	0.24
Knee-related quality of life (KOOS QoL)[e,d]	4.1 (15.6)	1.6 (13.5)	2.4 (–1.6 to 6.5)	.24	0.18
Patients Global Assessment[f,g]	–0.1 (0.8)	–0.1 (0.7)	–0.1 (–0.3 to 0.1)	.36	0.10
VR-12 PCS[e,h]	1.7 (8.6)	–0.4 (6.6)	2.4 (0.3-4.5)	.03	0.28
VR-12 MCS[e,h]	–0.6 (10.2)	–0.3 (7.8)	–0.1 (–2.6 to 2.5)	.96	0.03
30s Chair Stand Test[e]	1.7 (1.9)	1.4 (1.9)	0.3 (–0.3 to 0.9)	.35	0.15

[a]Data are mean (SD). Differences in change between groups are adjusted for baseline and stratification variables.
[b]KOOS: Knee Osteoarthritis Outcome Score (0-100, worse to best).
[c]ADL: activities of daily living.
[d]QoL: quality of life.
[e]For change within groups, positive changes indicate improvement. For differences in change between groups, positive differences favor intervention group (re.flex).
[f]Patients' Global Assessment is scored 1-5 (best to worse).
[g]For change within groups, negative changes indicate improvement. For differences in change between groups, negative differences favor intervention group (re.flex).
[h]VR-12: Veterans RAND 12-Item Health Survey; PCS: Physical Component Score; MCS: Mental Component Score; Health-related quality of life (0-100, worse to best, normalized to a mean value of 50 (SD 10).

Figure 3. Primary outcomes pain and physical function.



Secondary Outcomes

For secondary outcomes, a statistically significant effect between study arms with superiority of re.flex was only observed for the PCS (β=2.4 points, 95% CI 0.3-4.5; *P*=.03; Cohen *d*=0.28; Table 2 and Multimedia Appendix 1). Again, findings were confirmed by the sensitivity analyses (Multimedia Appendix 1).

Subgroup Analyses

Regarding the subgroup analyses, the only significant interaction with the study arm (*P*=.03) was found for physical function in patients undergoing concomitant physiotherapy compared to patients not undergoing physiotherapy. Patients in the usual care group who received concomitant physiotherapy showed greater improvements than those with physiotherapy in the re.flex group. Conversely, patients in the re.flex group who did not receive concomitant physiotherapy demonstrated greater improvements than those of the usual care group. For all other subgroup variables, no significant interaction was found. Details on the number of patients receiving concomitant care and forest plots of subgroup analyses for the primary outcomes of pain and physical function can be found in the Multimedia Appendix 1.

Responder Analyses

Details of the responder analyses can be found in Table 3. For each of the 3 transition scales (overall, pain, and function), positive effects (odds ratios and SRs >1) with significant benefits for the re.flex group could be found in the primary analysis (*P*<.001). The NNTs were between 2.6 and 3.4, and the SRs were between 2.1 and 2.7.

Table 3. Responder analyses for primary analysis.

Transition scales	re.flex group (3 months)[a], n (%)	Usual care group (3 months)[a], n (%)	OR (95% CI)[b]	*P* value	SR[c]	NNT[d]
Overall[e]	60 (61.2)	22 (22.9)	5.7 (2.9-11.0)	<.001	2.7	2.6
Pain[e]	56 (57.1)	26 (27.1)	3.8 (2.0-7.2)	<.001	2.1	3.3
Function[e]	53 (54.1)	24 (25)	3.8 (2.0-7.1)	<.001	2.2	3.4

[a]Only numbers for the category improved (somewhat better or much better).
[b]OR: odds ratio.
[c]SR: success ratio; quotient percentage of success in the re.flex group divided by percentage in the usual care group ("relative risk").
[d]NNT: Number needed to treat.
[e]Subjective change in health status along the study period overall, for pain and walking (reflecting function) compared to 3 months ago was assessed using a 5-point Likert scale with options "much better," "somewhat better," "unchanged," "somewhat worse," "much worse". Response scales were dichotomized into improved (somewhat better or much better) and not improved (unchanged, somewhat worse, or much worse).

Safety, Adherence, Usability, and Satisfaction

AEs in the re.flex group were minor and mainly of a musculoskeletal nature. Overall, 12 AEs were sure (n=5), likely (n=5), or possibly (n=2) linked to the re.flex intervention. Thereof, 7 AEs led to the discontinuation of the training, and 4 AEs were needed to seek medical care (Multimedia Appendix 1). No intervention-related serious adverse events were reported. A more detailed analysis of exercise-related pain can be found in the Multimedia Appendix 1. The objectively measured overall exercise session adherence was 77% (2705/3528), indicating that 23% (823/3528) of all exercise sessions were not performed. This also includes sessions of participants who stopped the intervention before the end of the study. The attrition rate in the re.flex group increased during the study period from 2% (2/98) at week 1 to 28% (27/98) at week 12. Participants of the re.flex group reported a high level of usability and satisfaction with the re.flex app and a high treatment satisfaction. More details can be found in Table 4 and the Multimedia Appendix 1.

Table 4. Log files and usability of the re.flex app[a].

Outcomes	re.flex group (n=98)	re.flex group (n=86)
Exercise session adherence (%)[b,c]	77	—[d]
Exercise repetition adherence (%), mean (SD)[c,e]	74 (43)	—
Active time (minutes), mean (SD)[f,g]	18 (6)	—
Usability (MAUQ)[h] mean (SD)	—	5.4 (1.0)

[a]Missing data were not replaced with multiple imputation.
[b]Exercise session adherence is the percentage of conducted exercise sessions relative to the overall number of prescribed exercise sessions during the study period.
[c]Data refer to all patients of the re.flex group (n=98); 12 weeks with 3 exercise sessions per week.
[d]Not applicable.
[e]Exercise repetition adherence is the percentage of all valid repetitions in percent with a maximum value of 100%.
[f]Active time is the crude time for exercising with the sensor-equipped leg without login, calibration, video watching, and feedback on pain and exertion.
[g]Data refer to 2706 exercise sessions.
[h]MAUQ: mHealth App Usability Questionnaire (1-7, higher values indicating higher usability of the app).

Discussion

Principal Findings

This randomized controlled trial was designed to investigate patient benefit of the digital health app re.flex, which was designed as a self-directed intervention to instruct and guide exercises for patients with knee OA. Compared with usual care, re.flex showed superior findings with a small treatment effect in the primary outcome of pain at 3 months. No statistically significant difference was found for the primary outcome of physical function after adjustment for multiple testing. Except for the PCS score in the VR-12 instrument, no other secondary study outcomes did reveal significant treatment effects in favor of re.flex at 3 months. Overall, the study intervention showed a high adherence rate, high usability, and satisfaction with the re.flex app, and no intervention-related serious adverse events.

The findings and superiority of re.flex over usual care for the primary outcome of pain are in accordance with recent meta-analyses on the effectiveness of technology-based exercise interventions in patients with knee OA [20,21]. The meta-analyses revealed beneficial effects of using smartphone apps or web-based programs in reducing pain intensity [20,21]. In terms of improvements in physical function, the evidence is divergent, with studies reporting either no significant effect or only significant improvements when using the delivery-type app [20,21]. As only 5 [20] and 4 [21] studies with the delivery type app or web-based

could be included, the quality of evidence is still low [35]. In addition, a direct comparison of study results is made difficult by the heterogeneity of study interventions, the presence or absence of human interaction, and sample characteristics. At present, nondigital interactions are the gold standard for exercise guidance, and the effectiveness of mHealth interventions should be comparable to this. Nondigital exercise interventions, delivered via one-to-one supervision, class-based programs, or home-based exercises, reveal small to medium effects for pain reduction and improvement in physical function [2,36]. Looking at the latest results of an individual participant data (IPD) meta-analysis on exercise therapy in knee and hip OA (short-term treatment effects of −6.4 points for pain and −4.5 for physical function; scale: 0-100, best to worst) [37], the between-group differences of our study are quite comparable. However, the clinical relevance of the between-group differences in terms of pain and physical function has previously been questioned in the IPD meta-analysis. Thus, we would now like to situate our results according to these findings. In this context, we refer to our responder analysis, in which we assessed the subjective changes in OA-related health status of the participants and calculated the SR ("relative risk") for treatment response. It was shown (see Table 3) that the risk for subjective improvement is between 2.1- and 2.7-fold higher in the re.flex group than in usual care. NNTs between 2.6 and 3.4 revealed smaller numbers than those reported in the latest Cochrane Review on land-based exercise therapy in knee OA derived from continuous variables (self-reported pain and physical function score on a scale of 0-100, best to worst) [2], indicating a clinically relevant effect of the re.flex intervention. This is of particular importance as it also bears a societal value. Exercise is recommended as a first-line treatment in patients with knee OA [38,39], and digital health apps could address the undersupply of current health care treatment options. Moreover, the sensitivity analyses "MI ITT," "complete case," and "per protocol" showed similar results as the primary analysis for pain and physical function, indicating that the findings are robust (data are shown in the Multimedia Appendix 1). Despite the aforementioned findings, re.flex was not permanently listed in the DiGA directory in Germany, as the clinical relevance was questioned by the decision-making committee. As this is a recurring issue, for example, also addressed in the IPD meta-analysis by Holden and colleagues [37], we propose the development of precise criteria for clinical relevance in conservative OA therapy in the future.

The objective measure of the 30-Second Chair Stand Test failed to demonstrate any significant between-group differences. The within-group differences for both groups were found to be below the previously described improvements of clinical relevance of 2.5 repetitions in a population with knee OA receiving physiotherapeutic treatment [40]. Two reasons can explain the lack of improvement. One possibility is that the exercise intensity was insufficient to elicit adaptations in muscle gains. The values for perceived exertion recorded during the exercise sessions indicated a fairly moderate to somewhat strenuous intensity level. An efficacious training load would be considered to be within a strenuous to very strenuous range. In the future, it must be ensured that patients are well educated and supported in independently adjusting their exercise intensity. Another reason may be related to the construct validity and responsiveness of the 30-Second Chair Stand Test, as well as the correlations between the 30-Second Chair Stand Test and the PROMs pain and physical function that are considered to be low in the population of knee OA receiving conservative treatment. Therefore, improvements in pain and physical function may not be reflected in comparable improvements in the performance test, and the test should be used with caution to assess changes in functionality over time [41].

Adherence to exercise therapy is known to be essential for the success of treatment and the associated improvements in pain and physical function. Although supervised interventions are considered favorable for adherence to exercise [42], the use of digital apps for exercise guidance can also increase adherence level, as they enhance motivation and offer the opportunity to exercise independent of time and location. The special group of sensor-based apps can further increase adherence rates, as they give additional information and instruction on training execution and training load (eg, frequency and duration) and provide real-time biofeedback in order to prevent incorrect movement execution and teach correct movement patterns. So far, most digital-based exercise interventions were not supported by sensor technology. To our knowledge, only Mecklenburg and colleagues [11] also used a sensor-guided exercise approach and reported an adherence rate of 76% among those who started the program, which is on the same level as in our study (adherence to exercise 77%). Moreover, the adherence rate exceeds reported rates of 62%-75% for nondigital home exercise interventions [43,44]. Ultimately, the occurrence of AEs and the dissatisfaction with treatment results observed in some patients also suggest that self-directed mHealth-based exercise training may not be the optimal choice for all individuals. This finding strengthens the conclusions of qualitative studies on digital exercise interventions for patients with knee OA, which have previously demonstrated that some patients require at least a certain degree of human supervision [22,45,46]. In this context, hybrid formats could be used to a greater extent.

Strengths and Limitations

In general, the usage of usual care as the control group offers certain advantages and disadvantages. It enables the evaluation of an intervention's effectiveness in relation to real-world conditions that are accessible to a wide patient population, thereby enhancing the generalizability of the results. Conversely, usual care can vary extensively across patients and health care systems and may induce bias due to its lack of standardization and replicability. According to the results of the subgroup analysis, we assume that concomitant physiotherapy did not positively influence the effectiveness of the study intervention. Further strengths of the trial are the large sample size, few missing outcome data (<10%), and a rigorous statistical analysis, including jump to reference for MI, as well as different sensitivity analyses that underpin the findings of the primary analysis.

The risk of randomization bias was minimized, resulting in well-balanced baseline characteristics between study groups. The concomitant treatments during the interventional period were comparable for the most part, resulting in a low risk of bias related to deviations from intended interventions. A risk of bias in selection of the reported results can be ruled out, as the analysis was conducted according to the prespecified published study protocol. Another strength of the study is the use of motion sensors to collect accurate data on adherence to exercise. We can further assume a good external validity of the trial findings, as baseline characteristics (age, sex, and BMI) and baseline outcome measures for pain and physical function are in line with those reported in a recently published IPD meta-analysis on 31 studies [37] with more than 4240 participants affected by knee or hip OA. Therefore, findings should be generalizable to other patients with OA with similar disease severity in predominantly industrialized countries.

The trial has some limitations. As eligibility required a pain score of <60 (out of 0-100, worst to best), findings may not be generalizable to individuals with milder symptoms. In addition, a selection bias toward sociodemographic characteristics cannot be ruled out, as baseline data demonstrate higher educational levels and only a small proportion of foreigners in comparison to the age-equal German population. Moreover, we have to state a risk of reporting bias as participants were not blinded and primary outcomes were self-reported. We must further acknowledge that using an MCID derived from minimal important improvements of within-group changes to evaluate between-group differences was inadequate. However, the between-group differences of a large IPD meta-analysis were of a similar size (3.8-6.4 for short-term improvements in physical function and pain) and can therefore serve as a benchmark [37]. Finally, a potential source of error for the training by an incorrect use of the sensors and technical features could not be ruled out. However, this risk is rather low, as the system has been designed to alert users to malfunctions.

Conclusions

In summary, the findings of this randomized controlled trial provide evidence for the superiority of a self-directed sensor-based mHealth exercise intervention in comparison to usual care. The usage of the digitally delivered exercise program is associated with clinically meaningful improvements in knee-related pain in patients with knee OA. The high adherence rate, positive usability ratings, and high satisfaction levels with the app demonstrate that the implementation of a digital, self-directed exercise program is well accepted by the majority of users. However, minor exercise- and app-related AEs and dissatisfaction in some patients also illustrate that self-directed interventions are useful in many but not all patients with knee OA, and personal context factors should be considered when choosing the best delivery mode for exercises. In summary, a low-threshold and widely accessible treatment option, such as re.flex, can improve treatment access and effectiveness among patients with OA.

In the future, further research should evaluate supervised versus self-directed digital exercise delivery in knee OA and examine if the inclusion of sensors has an additional effect on movement quality or effectiveness. In addition, it would be important to focus on the development of selection criteria that allow accurate allocation of patients who may benefit from digital, self-directed exercise interventions and those who require more human support or are even better suited to traditional treatment.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the conceptualization and validation process of the study. IK, VD, PM, and DS developed the methodology. IK and PJ were responsible for the acquisition of funding. VD and IK were responsible for project administration and supervision. VD and PJ contributed to the investigation. VD, IK, and PM were responsible for data curation, formal analysis, resources and writing the original draft. LS supported VD, IK, and PM in the visualization of the data. All authors reviewed and edited the article.

Conflicts of Interest

The exercise intervention that is implemented into the re.flex app was designed by employees of the University Hospital (ie, VD, IK) in the context of a previous cooperation project between the trial sponsor Sporlastic GmbH and the University Hospital Tübingen. The pilot study of this trial was conducted during this cooperation as well. The University Hospital will

be compensated for the granting of rights of use to the results generated by employees of the University Hospital (intellectual property) in the event of successful commercialization of the app. University Hospital will compensate the employees (ie,VD, IK) who were involved in the previous collaboration and are authors of the intellectual property from these revenues. However, the PrincipaI Investigator (PJ) of the study as well as the biomedical statisticians (PM) do not have any conflict of interest.

Multimedia Appendix 1

Additional information.
[DOCX File (Microsoft Word File), 4349 KB-Multimedia Appendix 1]

Checklist 1

CONSORT-EHEALTH (V 1.6.1) checklist.
[PDF File (Adobe File), 70319 KB-Checklist 1]

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Abbreviations

AE: adverse event
ANCOVA: analyses of covariance
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DiGA: Digitale Gesundheitsanwendung
DVG: Digitale-Versorgung-Gesetz
EHIS: European Health Interview Survey
GEDA: Gesundheit in Deutschland aktuell
HrQoL: health-related quality of life
IPD: individual participant data
ITT: intention-to-treat
KOOS: Knee Osteoarthritis Outcome Score
LOCF: last observation carried forward
MAUQ: mHealth App Usability Questionnaire
MCID: minimal clinically important difference
MCS: mental component score

mHealth: mobile health
MI: multiple imputation
NNT: numbers needed to treat
OA: osteoarthritis
PCS: physical component score
PGA: patient global assessment
PROM: patient-reported outcome measure
QoL: quality of life
SR: success ratio
VR-12: Veterans RAND 12-Item Health Survey

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Appendix 1 to „Effectiveness of the self-directed m-Health exercise intervention re.flex in patients with knee osteoarthritis: A randomized controlled trial."

This appendix has been provided by the authors to give readers additional information about the work.

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Development process of the intervention

Kineto Tech Rehab SRL© (Romania) developed the exercise app including features for visual and verbal feedback, monitoring, push-notifications, chat function for technical issues and two sensors to allow biofeedback on knee joint motion. The app was then optimized by implementing a graded 12-week exercise program specifically designed for the patient target group according to disease-specific recommendations (1-3) and the experience of the study team in planning and conducting exercise interventions for patients with hip and knee OA (4-7). In addition, exercise videos were optimized, the range of motion for each exercise defined to allow proper biofeedback on movement control, and app features such as monitoring of perceived exertion and pain have been added.

Re.flex underwent repeated usability testing and was further evaluated in a pilot study (8). At the beginning of the evaluation period, the software was only available for iOS devices. Starting on Mar 06, 2023, it was expanded for use on Android operating systems. This study evaluated the latest version of re.flex (iOS 1.1.81 and Android 1.0.10) at time of intervention completion of the intervention group. Minor bug fixes were made concerning app design and technical issues, e.g. device crashes. No new features were implemented and functional components of the app (e.g. the exercise program) were not changed during the study phase.

Table A1: 12-week exercise program (re.flex) for patients with knee osteoarthritis – phases, dosage principles and objectives.

Phase	Week	General information	Sets and repetitions/seconds by training method	Objectives
1	1-2	• 3 sessions à 5 exercises per week • Each session lasting 25-30 minutes • Training material: chair, ball or pillow, elastic resistance bands	• Strengthening exercises: 2x25 repetitions • Balance tasks: 6x15 seconds (bilateral exercises), 3x15 seconds on each leg (unilateral exercises) • Mobilization exercises: 1x30 repetitions • Stretching exercises: 2x20 seconds ➔ All one-sided exercises were conducted alternately	• Familiarization with different kinds of exercises and exercise loads • Get to know self-determined adaption of exercise intensity to the perceived load and pain • Possibility to choose between two different intensity levels for strengthening exercises
2	3-6			• Increase strength endurance • Enhance range of motion of the lower extremities • Improve balance ability • Possibility to choose between two different intensity levels for strengthening exercises
3	7-12		• Strengthening exercises: 3x15 repetitions • Balance tasks: 6x15 seconds (bilateral exercises), 3x15 seconds on each leg (unilateral exercises) • Mobilization exercises: 1x30 repetitions • Stretching exercises: 2x20 seconds ➔ All one-sided exercises were conducted alternately	• Muscle building with higher intensities and lower repetition numbers • Becoming familiar with further exercise variations with higher intensities • Further improvement of balance and range of motion • Increased ability to independently select and adapt exercise difficulty and load dosage depending on the perception of exertion and pain • Possibility to choose between two different intensity levels for strengthening exercises

Table A2: Exercise program.

App-based home exercise program • 3 sessions à 5 exercises per week • Each session lasting 25-30 minutes • Training material: chair, ball or pillow, elastic resistance bands (provided by the study) • Primary focus was to strengthen knee extensors, knee flexors and hip abductors; further exercises comprised balance, mobilization and stretching • Patients were asked to conduct strengthening exercises with an intensity of 7-9 ("exhausting to very exhausting" on a scale 0-10) • Balance tasks should be challenging, but always able to be performed correctly			
1. Strengthening exercises			
Knee extension	Supine	S1. Knee extension	**Progression:** without ground contact
	Seated	S2. Knee extension	**Progression:** without ground contact
		S3. Resistive knee extension	**Progression:** without ground contact
	Standing	S4. Knee extension with band	**Progression:** without ground contact, increase resistance with elastic band
Knee flexion	Standing	S5. Knee flexion	**Progression:** without ground contact
		S6. Knee flexion with band	**Progression:** without ground contact, increase resistance with elastic band
		S7. Resistive knee flexion	**Progression:** without ground contact
Hip abduction	Seated	S8. Hip abduction	**Progression:** with elastic band, increase resistance with elastic band
	Standing	S9. Hip abduction with band	**Progression:** without ground contact, increase resistance with elastic band
Hip flexion	Supine	S10. Hip flexion	**Progression:** without ground contact
		S11. Lift stretched leg	**Progression:** without ground contact
	Seated	S12. Hip flexion	**Progression:** without ground contact
		S13. Hip flexion with extended leg	**Progression:** without ground contact
	Standing	S14. Hip flexion without band	**Progression:** without ground contact
		S15. Hip flexion with band	**Progression:** without ground contact, increase resistance with elastic band
Hip extension	Standing	S16. Hip extension without band	**Progression:** without ground contact
		S17. Hip extension with band	**Progression:** without ground contact, increase resistance with elastic band
Sit-to-stand	Seated	S18. Getting up from the seat	**Progression:** without arm support
		S19. Getting up from the seat with band	**Progression:** without arm support, increase resistance with elastic band
		S20. Single legged getting up from the seat	**Progression:** without arm support
Squat variation	Standing	S21. Mini squat	**Progression:** upper body vertical
		S22. Mini squat single-legged	**Progression:** upper body vertical
		S23. Wall slide	**Progression:** upper body vertical
		S24. Wall slide with band	**Progression:** upper body vertical, increase resistance with elastic band
		S25. Wall slide with ball	**Progression:** upper body vertical
		S26. Single leg wall slide	**Progression:** upper body vertical
		S27. Stairs upwards	**Progression:** without ground contact
		S28. Stairs downwards	**Progression:** without ground contact
2. Balance exercises			
	Standing	B1. Double legged standing stable	**Progression:** eyes closed
		B2. Double legged standing stable with destabilization of the arms	
		B3. Tandem standing stable	**Progression:** eyes closed
		B4. Tandem standing with destabilization of the arms	
		B5. Single-leg standing stable	**Progression:** eyes closed
		B6. Step position with weight shift to the front	
		B7. Step position with weight shift to the back	
3. Mobilization exercises			
	Supine	M1. Knee extension/flexion	
	Seated	M2. Knee extension/flexion	
		M3. Patella relief	
4. Stretching exercises			
	Seated	St1. Stretch musculature of the thigh back (ischiocrural musculature)	
	Standing	St2. Stretch musculature of the thigh back (ischiocrural musculature)	
		St3. Stretching the front of the thigh	

App features and course of a training session

1. Home screen

Figure A1: Home screen after login.

2. Overview training schedule

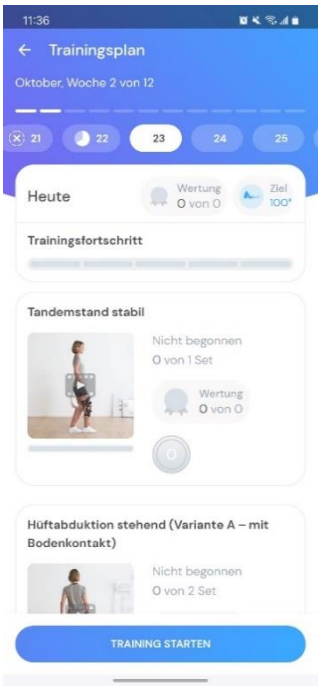

Figure A2: Daily training schedule with overview of scheduled exercises.

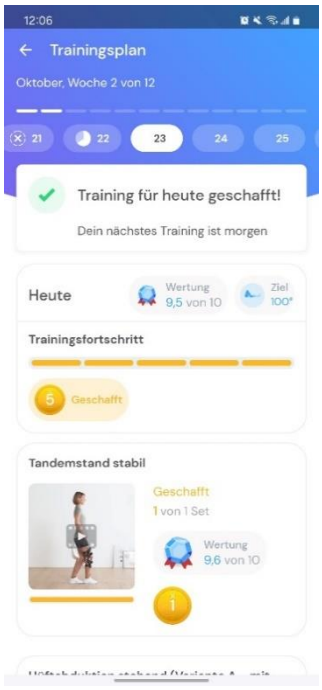

Figure A3: Daily training schedule after completing the exercises.

3. Process of connecting and calibrating sensors

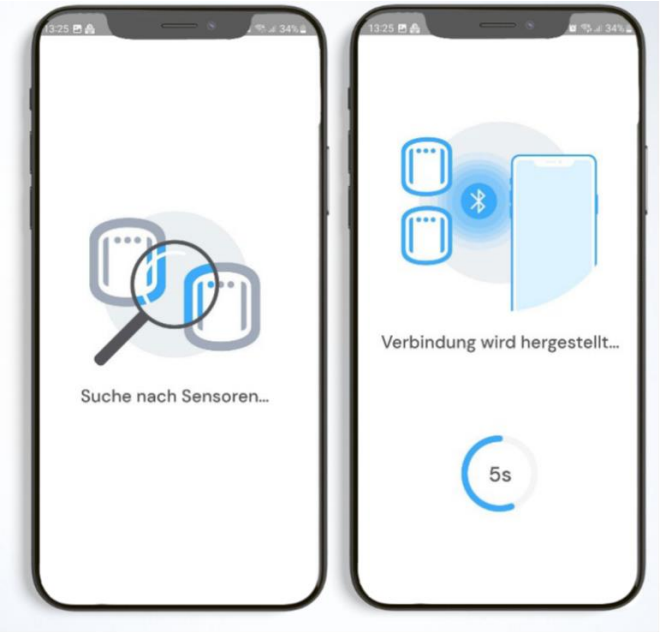

Figure A4: Connecting the sensors

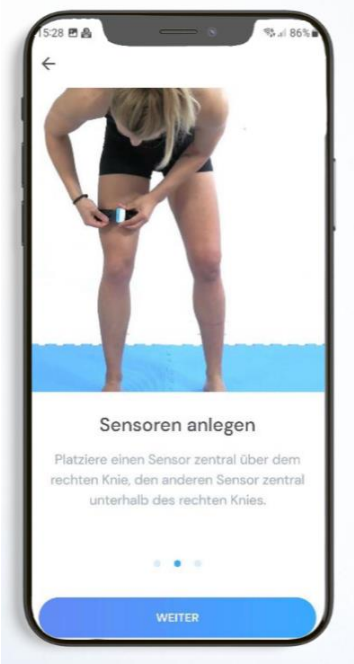

Figure A5: Attaching sensors proximally and distally to the osteoarthritis-affected knee joint.

Figure A6: Movement task during calibration in supine position.

Figure A7: Movement task during calibration in standing position.

4. Training process
    I. Exercise description and video

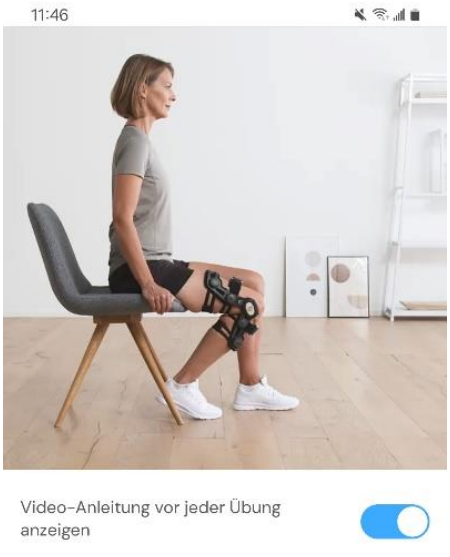

Figure A8: Video for the exercise execution.

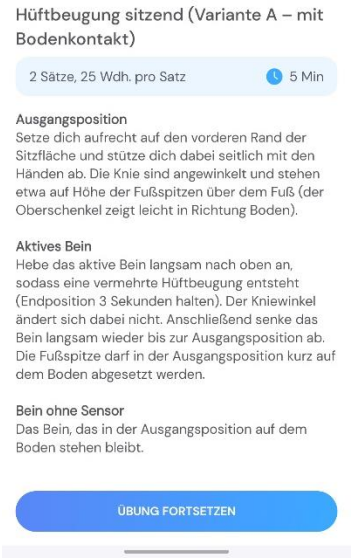

Figure A9: Text description for the exercise execution.

II. Avatar

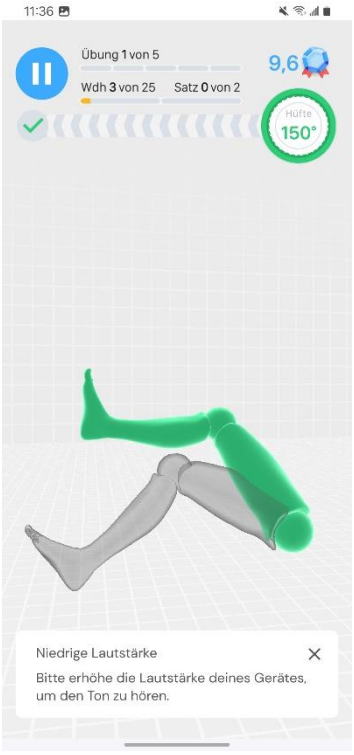

Figure A10: The patient must align his virtual limb (green) to the target condition displayed with another avatar (grey) regarding pre-defined range of motion, movement velocity, and number of repetitions.

III. Movement bar

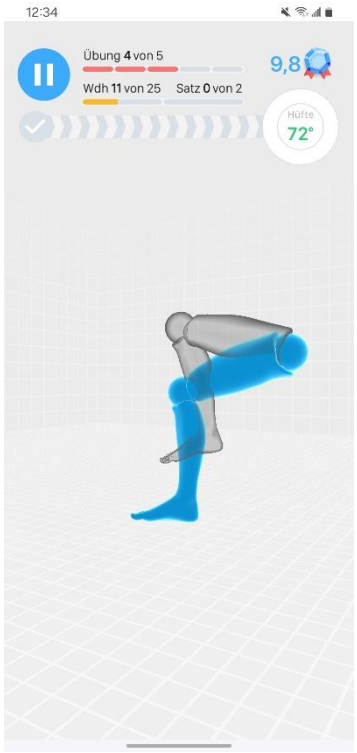

Figure A11: The own training leg is blue in the starting position. The movement bar with the target angle is displayed on the top.

Figure A12: The own training leg and the movement bar turn green when the target position is reached.

IV. Repetition counting

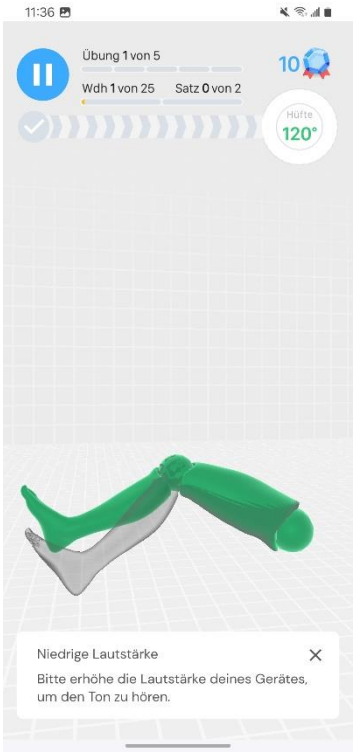

Figure A13: Repetitions and the number of sets are displayed above the movement bar and registered when performed correctly.

V. Correction of exercise execution

Figure A14: Advice: Knee should be extended more.

Figure A15: Advice: Thigh should be hold in a higher position.

VI. Perceived pain and strain

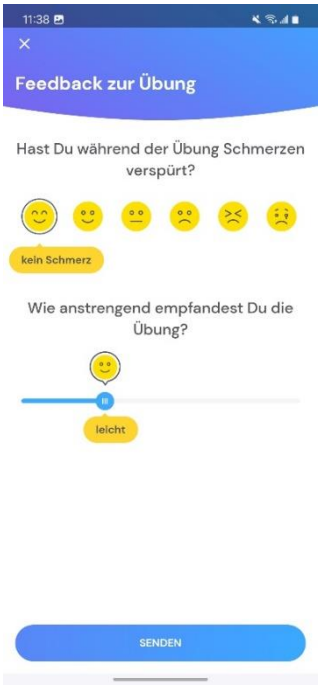

Figure A16: Pain and strain query after each exercise.

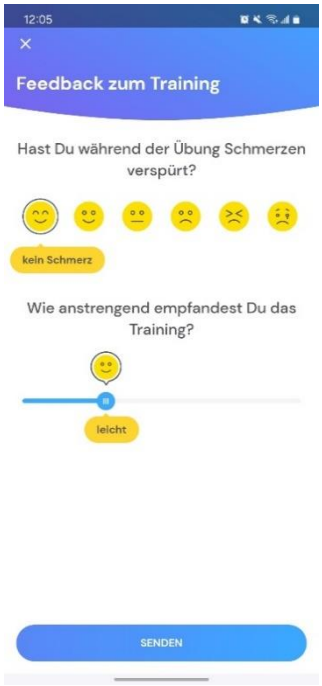

Figure A17: Pain and strain query after the exercise session.

VII. Change exercise variation or skip exercise

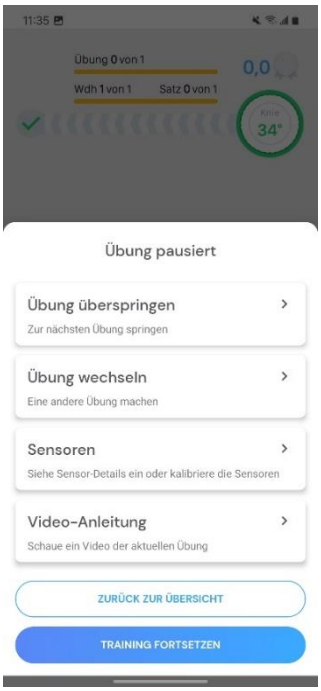

Figure A18: Exercises can be paused or skipped.

Figure A19: Users can choose one of two difficulty levels for strengthening exercises.

5. Monitoring / Statistics

Figure A20: Monitoring of exercise adherence.

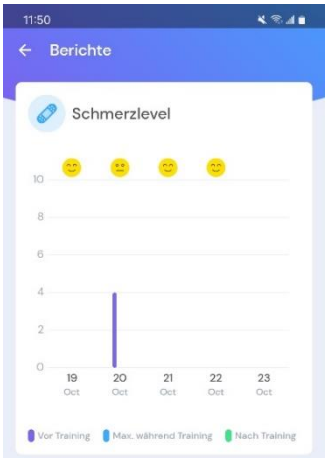

Figure A21: Monitoring of perceived pain level.

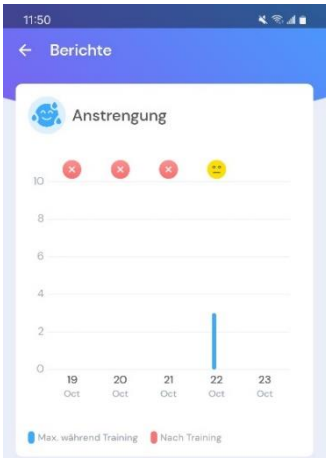

Figure A22: Monitoring of perceived exertion.

6. In-App Chat support

Figure A23: In-App Chat support.

Table A3: Outcome measures and study instruments.[a]

Outcome Description	Instrument [ref]	Scale & Score	Items	Sample	Timepoints
Socio-demographic data, anthropometric data, other baseline data	Variables and definitions according to the International Standard Set of Outcome measures for patients with hip or knee OA (9).	NA	NA	IG, CG	t0
Technical affinity towards electronic devices	Self-reported questionnaire on subjective technical affinity (Technical Affinity - Electronic Devices (TA-EG)) (10)	5-point Likert (b2w), -2-14 (w2b)	17	IG, CG	t0
Outcome expectation	Expectation for Treatment Scale (ETS, German version) (11)	4-point Likert (w2b), 5-20 (w2b)	5	IG, CG	t0
Fear of Movement	Tampa Scale for Kinesiophobia (German Version, TSK-GV) (12)	4-point Likert (w2b), 6-24 (b2w)	6	IG, CG	t0
Subscale knee pain (Co-1° outcome)	Knee Osteoarthritis Outcome Score (KOOS) (13, 14): A disease related questionnaire asking for patient's opinion about their knee complaints.	5-point Likert (b2w), 0-100 (w2b)	9	IG, CG	t0, t1
Subscale physical function (Activities in daily living, ADL) (Co-1° outcome)	Knee Osteoarthritis Outcome Score (KOOS) (13, 14): A disease related questionnaire asking for patient's opinion about their knee complaints.	5-point Likert (b2w), 0-100 (w2b)	17	IG, CG	t0, t1
Subscales symptoms, function in sport and recreation (Sport/Rec), knee-related quality of life (QoL)	Knee Osteoarthritis Outcome Score (KOOS) (13, 14): A disease related questionnaire asking for patient's opinion about their knee complaints.	5-point Likert (b2w), 0-100 (w2b)	7, 5, 4	IG, CG	t0, t1
Patient's global assessment (PGA)	Patient Global Assessment of osteoarthritis – Knee (15)	5-point Likert (b2w)	1	IG, CG	t0, t1
Health-related quality of life (HRQoL) – physical component score (PCS)	Veterans RAND 12-Item Health Survey (VR-12) (16, 17): A generic questionnaire to assess the patient's opinion about their health-related quality of life (HRQoL).	3-point, 5-point, or 6-point Likert, 0-100 (w2b)	12	IG, CG	t0, t1
Health-related quality of life (HRQoL) – mental component score (MCS)	Veterans RAND 12-Item Health Survey (VR-12) (16, 17): A generic questionnaire to assess the patient's opinion about their health-related quality of life (HRQoL).	3-point, 5-point, or 6-point Likert, 0-100 (w2b)	12	IG, CG	t0, t1
Subjective assessment of overall change, change in pain and change in function compared to three months ago	Transition question according to Angst, Benz (18)	5-point Likert (b2w), dichotomized into improved (somewhat/much better) and not improved (unchanged, somewhat/much worse)	3	IG, CG	t1
Functional strength measure for the lower extremities	30-sec Chair Stand Test (19)	Number of repetitions	NA	IG, CG	t0, t1
Treatment progression	Variables and definitions according to the International Standard Set of Outcome measures for patients with hip or knee OA (9).	NA	NA	IG, CG	t0, t1
Care utilization		NA	NA	IG, CG	t0, t1 + after 4 and 8 weeks
Usability of the app	m-Health App Usability Questionnaire (MAUQ) (20)	7-point Likert (w2b), 1-7 (w2b)	18	IG	t1
Patient satisfaction with the app	Patient satisfaction questionnaire (ZUF-8) (21)	4-point Likert, 8-32 (w2b)	8	IG	t1
Patient satisfaction with the results of the treatment	Satisfaction with the results (9)	5-point Likert (b2w)	1	IG, CG	t1
Adherence to exercise	Logfiles relate to overall exercise session adherence (percentage of conducted exercise sessions relative to the overall number of prescribed exercise sessions) and exercise repetition adherence (percentage of all valid repetitions in percent with a maximum value of 100%).	NA	NA	IG	continuously during intervention phase
Active time	Logfiles: crude time for exercising with the sensor-equipped leg without login, calibration, video watching, and feedback on pain and exertion.	NA	NA	IG	continuously during intervention phase

Table A3: Outcome measures and study instruments (continued).

Rating of perceived exertion (RPE) during and after exercising	Entry into the app after each exercise and after the training using an adapted RPE-Scale (NRS 0-10).	0-10 (no exertion to maximal exertion)	NA	IG	continuously during intervention phase
Rating of perceived pain • Delta pain (rating of perceived pain after – before exercising) • Perceived pain during exercising	Entry into the app before/after the training and after each exercise using a faces pain scale referring to the numbers 0, 2, 4, 6, 8, 10.	0-10 (no pain to highest pain)	NA	IG	continuously during intervention phase
Exercise-related pain	Retrospective questions concerning exercise-related pain (single exercise or whole exercise session) including frequency, duration, and intensity	NA	NA	IG, CG	t1
Adverse event report	Direct contact to study personal	NA	NA	IG, CG	if reported

[a] b2w=best to worse. w2b=worse to best. IG=intervention group. CG=control group. t0=timepoint 0, collection point at baseline. t1=timepoint 1, collection point after three months. NRS=Numerical Rating Scale.

Sample size

The following excerpt is taken from the published study protocol (22).

"The two primary endpoints of the study are the KOOS subscales of pain and ADL. The results of a pilot study comparing the KOOS pain subscale and KOOS ADL subscale of 29 patients in the control group (usual care) with 15 patients in the intervention group (re.flex) using baseline adjusted analysis of covariance revealed effect sizes of 1.16 (Pain subscale) and 1.03 (ADL subscale). A recent meta-analysis on exercise interventions in patients with knee OA reported a standardized mean difference of 0.5 (95% CI 0.37 to 0.63) for pain reduction immediately posttreatment in comparison to usual care or minimal treatment (23). Additionally, minimal clinically important differences (MCIDs) were reported between 5.5 and 8.7 points on the WOMAC pain subscale (score 0–100) for nonsurgical treatment strategies in patients with knee OA (24, 25). These correspond to standardized mean differences between 0.59 and 0.94. Based on the preceding, rather heterogeneous results with effect sizes between 0.5 and 1.2 from the results of the pilot study (8) and findings and recommendations of other sources, the planned study is powered to demonstrate a MCID of 5 points (0–100) on the KOOS Pain Subscale between the intervention and control group with a standard deviation of 10. This leads to an effect size of 0.5 and to a sample size of evaluable participants of 2*78=156. For adjustment of baseline, aetiology, medication and laterality, 4 additional degrees of freedom are spent, and the sample size is increased to 160. Considering a drop-out rate of ~ 20%, 200 patients will be recruited to achieve a power of 80% with a type 1 error of 0.025 (two-sided Bonferroni correction for two confirmatory outcomes) by baseline adjusted comparison of outcome values at t1 between study arms (analysis of covariance, ANCOVA)."

Table A4: Baseline characteristics of participants (incl. comparison between study groups).[a]

	Total	re.flex group (n=98)	Usual care group (n=96)	*P* value
Demographics				
Age, years	61.9 (7.7)	61.6 (8.0)	62.1 (7.5)	.65[b]
Gender				.31[c]
Female	132 (68%)	70 (71%)	62 (65%)	..
Male	62 (32%)	28 (29%)	34 (35%)	..
Anthropometry				
Body Height, cm	168.9 (9.0)	168.2 (8.8)	169.5 (9.3)	.30[b]
Body Weight, kg	81.8 (72.0-93.4)	82.2 (74.8-93.0)	81.6 (69.0-93.7)	.37[d]
Body-mass-index, kg/m²	28.1 (25.9-31.9)	28.4 (26.8-32.2)	27.8 (25.0-31.4)	.08[d]
Stratification factors				
Laterality				.97[c]
One-sided knee OA	73 (38%)	37 (38%)	36 (38%)	..
Both-sided knee OA	121 (62%)	61 (62%)	60 (62%)	..
Etiology				.88[c]
Primary knee OA	167 (86%)	84 (86%)	83 (87%)	..
Secondary knee OA	27 (14%)	14 (14%)	13 (13%)	..
Medication (knee OA-related)				.80[c]
No or sporadic	181 (93%)	91 (93%)	90 (94%)	..
Regularly	13 (7%)	7 (7%)	6 (6%)	..
Socio economics				
Nationality				.98[c]
German	188 (97%)	95 (97%)	93 (97%)	..
Others	6 (3%)	3 (3%)	3 (3%)	..
Life situation				.29[c]
Working	109 (56%)	61 (62%)	48 (50%)	..
Unemployed	1 (1%)	0 (0%)	1 (1%)	..
Retired	77 (40%)	34 (35%)	43 (45%)	..
Others	7 (4%)	3 (3%)	4 (4%)	..
Education				.53[c]
Low (<10 years)	17 (9%)	8 (8%)	9 (9%)	..
Middle (≥10 years)	70 (36%)	36 (37%)	34 (35%)	..
High (university entrance qualification)	97 (50%)	49 (50%)	48 (50%)	..
Others	10 (5%)	5 (5%)	5 (5%)	..
Job Qualification				.38[c]
None	3 (2%)	1 (1%)	2 (2%)	..
Apprenticeship	98 (51%)	50 (51%)	48 (50%)	..
Administration	5 (3%)	4 (4%)	1 (1%)	..
University of appl. sciences	22 (11%)	12 (12%)	10 (10%)	..
University	33 (17%)	12 (12%)	21 (22%)	..
PhD	10 (5%)	7 (7%)	3 (3%)	..
Others	23 (12%)	12 (12%)	11 (12%)	..
Housing				.99[c]
Together with partner	165 (85%)	83 (85%)	82 (85%)	..
Alone	27 (14%)	14 (14%)	13 (14%)	..
Others	2 (1%)	1 (1%)	1 (1%)	..
Anamnesis				
Time since diagnosis of knee osteoarthritis, months	63 (24-120)	65 (24-120)	61 (24-120)	.85[d]
Osteoarthritis				..
Right knee	159 (82%)	80 (82%)	79 (82%)	.91[c]
Left knee	154 (79%)	79 (81%)	75 (78%)	.67[c]
Right hip	3 (2%)	1 (1%)	2 (2%)	.55[c]
Left hip	6 (3%)	5 (5%)	1 (1%)	.10[c]
Signal joint - Knee				.38[c]
Right	109 (56%)	52 (53%)	57 (59%)	..
Left	85 (44%)	46 (47%)	39 (41%)	..
Difficulty/pain severity of the knee osteoarthritis[f]				.73[c]
No	1 (1%)	0 (0%)	1 (1%)	..
Mild	52 (27%)	27 (28%)	25 (26%)	..
Moderate	123 (63%)	61 (62%)	62 (65%)	..
Severe	18 (9%)	10 (10%)	8 (8%)	..
Extreme	0 (0%)	0 (0%)	0 (0%)	..
History of injury/disease				
Ligament injury	43 (22%)	22 (22%)	21 (22%)	.92[c]
Meniscus damage	107 (55%)	50 (51%)	57 (59%)	.24[c]
Trauma	24 (12%)	11 (11%)	13 (14%)	.62[c]
Developmental disorder	8 (4%)	4 (4%)	4 (4%)	.98[c]
Other joint disease	7 (4%)	4 (4%)	3 (3%)	.72[c]
No previous history	56 (29%)	31 (32%)	25 (26%)	.39[c]
Prior Therapy				
Anterior cruciate ligament (ACL) reconstruction right	12 (6%)	8 (8%)	4 (4%)	.26[c]
Anterior cruciate ligament (ACL) reconstruction left	16 (8%)	7 (7%)	9 (10%)	.56[c]
Meniscus operation right	52 (27%)	28 (29%)	24 (25%)	.61[c]
Meniscus operation left	47 (24%)	21 (21%)	26 (27%)	.36[c]

Table A4: Baseline characteristics of participants (incl. comparison between study groups) (continued).

	Total	re.flex group (n=98)	Usual care group (n=96)	*P* value
Osteotomy right	6 (3%)	3 (3%)	3 (3%)	.97[c]
Osteotomy left	2 (1%)	1 (1%)	1 (1%)	.98[c]
Joint replacement right	4 (2%)	1 (1%)	3 (3%)	.29[c]
Joint replacement left	7 (4%)	3 (3%)	4 (4%)	.67[c]
Number of total hip arthroplasty				.03[g]
0	183 (94%)	89 (91%)	94 (98%)	..
1	8 (4%)	6 (6%)	2 (2%)	..
2	3 (2%)	3 (3%)	0 (0%)	..
No surgeries	83 (43%)	43 (44%)	40 (42%)	.76[c]
Comorbidities				
Heart disease	14 (7%)	6 (6%)	8 (8%)	.58[c]
Hypertension	68 (36%)	35 (37%)	33 (34%)	.72[c]
Stroke (burden)	0 (0%)	0 (0%)	0 (0%)	..
Circulatory disorder	3 (2%)	2 (2%)	1 (1%)	.55[c]
Lung	12 (6%)	7 (7%)	5 (5%)	.55[c]
Diabetes	6 (3%)	3 (3%)	3 (3%)	1.00[c]
Kidney	1 (1%)	1 (1%)	0 (0%)	.32[c]
Neurological Disease	1 (1%)	0 (0%)	1 (1%)	.32[c]
Liver	3 (2%)	1 (1%)	2 (2%)	.56[c]
Cancer	9 (5%)	6 (6%)	3 (3%)	.31[c]
Depression	8 (4%)	4 (4%)	4 (4%)	1.00[c]
Back	22 (12%)	14 (15%)	8 (8%)	.17[c]
Activity and training variables				
Physical activity (per week)				.82[c]
No	5 (3%)	3 (3%)	2 (2%)	..
30 minutes	14 (7%)	9 (9%)	5 (5%)	..
1 hour	40 (21%)	20 (20%)	20 (21%)	..
2 hours	39 (20%)	20 (20%)	19 (20%)	..
More than 2 hours	96 (50%)	46 (47%)	50 (52%)	..
Previous experience with strength training				.02[c]
Very high	13 (7%)	2 (2%)	11 (11%)	..
High	38 (20%)	22 (22%)	16 (17%)	..
Medium	92 (47%)	49 (50%)	43 (45%)	..
Low	39 (20%)	22 (22%)	17 (18%)	..
Very low	12 (6%)	3 (3%)	9 (9%)	..
Previous experience with exercise therapy (e.g. training with a physiotherapist or sports therapist				.16[c]
Very high	16 (8%)	5 (5%)	11 (12%)	..
High	46 (24%)	24 (25%)	22 (23%)	..
Medium	85 (44%)	45 (46%)	40 (42%)	..
Low	33 (17%)	20 (20%)	13 (14%)	..
Very low	14 (7%)	4 (4%)	10 (10%)	..
Previous experience with hip or knee group training				.40[c]
Yes	15 (8%)	6 (6%)	9 (9%)	..
No	179 (92%)	92 (94%)	87 (91%)	..
Others				
Technical affinity [-2; 14][h]	7.5 (2.0)	7.4 (2.1)	7.7 (1.9)	.45[b]
Outcome expectation [5; 20][i]	14.4 (3.1)	14.4 (3.3)	14.3 (2.9)	.66[b]
Fear of Movement [6; 24][j]	9.6 (3.0)	9.8 (3.3)	9.5 (2.6)	.46[b]

[a] Data are mean (SD), n (%), or median (IQR). Some percentages might not add to 100% due to rounding. OA=Osteoarthritis.

[b] t-test for independent samples, mean (SD)

[c] Chi-Square test for 2*2 Tables

[d] Mann-Whitney test, median (IQR)

[e] Chi-Square test full degrees of freedom (nominal variables)

[f] Knee Osteoarthritis Outcome Score subscale pain scores were categorized into on average no (>87.5 points), mild (>62.5 – 87.5 points), moderate (>37.5 – 62.5 points), severe (>12.5 – 37.5 points) or extreme (0 – 12.5 points) difficulty/pain severity.

[g] Chi-Square test for linear trend (ordinal variables)

[h] Technical affinity was assessed with the Technical Affinity – Electronic Devices (TA-EG) questionnaire using a 5-point Likert scale with options of "completely applicable", "rather applicable", "partly", "rather not applicable", and "not applicable at all". Higher scores reflect a better technical affinity.

[i] Outcome expectation was assessed with the Expectation for Treatment Scale (ETS, German version) using a 4-point Likert scale with options of "partially disagree", "partially agree", "agree", and "definitely agree". Higher scores reflect a higher outcome expectation.

[j] Fear of Movement was assessed with the Tampa Scale for Kinesiophobia (TSK-GV, German version) using a 4-point Likert scale with options of "strongly disagree", "disagree", "agree", and "strongly agree". Higher scores reflect greater fear of movement.

Table A5: Mean (SD) scores on primary and secondary outcome measures for baseline (t0) and after three months (t1), by study group.[a]

	Baseline (t0)		3 months (t1)[b]	
	re.flex group (n=98)	Usual care group (n=96)	re.flex group (n=98)	Usual care group (n=96)
Primary outcomes				
Pain (KOOS Pain)	53.9 (14.4)	54.9 (12.8)	63.6 (16.3)	59.3 (14.6)
Physical function (KOOS ADL)	66.7 (15.1)	67.7 (15.2)	75.6 (16.6)	72.4 (15.2)
Secondary outcomes				
Symptoms (KOOS Symptoms)	56.0 (17.9)	57.1 (17.1)	65.6 (17.5)	62.1 (17.0)
Function in sport and recreation (KOOS Sport/Rec)	33.6 (17.2)	33.1 (18.2)	43.2 (23.0)	38.3 (20.7)
Knee-related quality of life (KOOS QoL)	32.3 (16.5)	32.8 (14.2)	36.5 (17.9)	34.4 (15.2)
Patients Global Assessment	2.7 (0.8)	2.8 (0.7)	2.6 (0.9)	2.7 (0.7)
VR-12 PCS	37.6 (7.7)	37.2 (7.9)	39.4 (8.5)	36.8 (7.7)
VR-12 MCS	51.5 (10.5)	50.9 (9.5)	50.9 (10.7)	50.6 (10.0)
30s Chair Stand Test	10.7 (2.4)	10.6 (2.5)	12.4 (2.6)	12.0 (2.6)

KOOS=Knee Osteoarthritis Outcome Score (0-100, worse to best); ADL=Activities in Daily Living. Patients Global Assessment is score 1-5 (best to worse). VR-12=Health related quality of life (0-100, worse to best, normalized to a mean value of 50 and SD of 10). PCS=Physical Component Score; MCS=Mental Component Score.

[b] Missing values were replaced with multiple imputation method jump to reference

Table A6: Sensitivity analyses for primary and secondary outcomes.[a]

	Analysis	n IG (3 months)	n CG (3 months)	Difference crude (3 months minus baseline)[b]	Coefficient b (95% CI)	SE	*P* value	Cohen's d
Pain (KOOS Pain)[c]	MI (ITT)	98	96	10.2 4.5	5.3 (1.1 to 9.4)	2.1	.01	0.38
	PP	62	91	9.5 4.6	5.3 (1.2 to 9.5)	2.1	.01	0.36
	CC	88	91	9.5 4.6	5.3 (1.2 to 9.5)	2.1	.01	0.32
	LOCF	98	96	8.5 4.3	3.8 (-0.2 to 7.8)	2.0	.06	0.28
Physical function (KOOS ADL)[c]	MI (ITT)	98	96	9.3 4.7	4.3 (0.4 to 8.2)	2.0	.03	0.33
	PP	63	91	10.0 4.7	5.8 (2.1 to 9.6)	1.9	.003	0.42
	CC	89	91	8.9 4.7	4.3 (0.3 to 8.2)	2.0	.03	0.29
	LOCF	98	96	8.1 4.5	3.3 (0.5 to 7.1)	1.9	.08	0.26
Symptoms (KOOS Symptoms)[c]	MI (ITT)	98	96	10.0 5.0	4.5 (0.2 to 8.9)	2.2	.04	0.31
	PP	63	91	9.2 5.1	4.1 (-2.3 to 6.8)	2.2	.07	0.27
	CC	89	91	10.1 5.1	4.5 (0.1 to 8.9)	2.4	.04	0.29
	LOCF	98	96	9.1 4.9	3.8 (-0.3 to 8.0)	2.1	.07	0.26
Function in sport and recreation (KOOS Sport/Rec)[c]	MI (ITT)	98	96	10.0 5.2	5.0 (-0.3 to 10.2)	2.7	.07	0.27
	PP	63	90	10.8 5.6	5.2 (-0.4 to 10.7)	2.8	.07	0.29
	CC	89	90	9.9 5.6	4.5 (-0.8 to 9.9)	2.7	.09	0.23
	LOCF	98	96	9.0 5.3	3.8 (-1.2 to 8.7)	2.5	.13	0.20
Knee-related quality of life (KOOS QoL)[c]	MI (ITT)	98	96	4.4 1.6	2.7 (-1.4 to 6.7)	2.1	.20	0.19
	PP	63	91	4.8 1.9	2.9 (-1.2 to 7.1)	2.1	.16	0.20
	CC	89	91	4.4 1.9	2.7 (-1.5 to 6.7)	2.1	.21	0.17
	LOCF	98	96	4.0 1.8	2.1 (-1.7 to 5.9)	1.9	.27	0.15

Table A6: Sensitivity analyses for primary and secondary outcomes (continued).

	Analysis	n IG (3 months)	n CG (3 months)	Difference crude (3 months minus baseline)[b]	Coefficient b (95% CI)	SE	*P* value	Cohen's d
Patients Global Assessment[d]	MI (ITT)	98	96	-0.1 -0.1	-0.1 (-0.3 to 0.1)	0.1	.36	0.11
	PP	63	91	-0.2 -0.1	0.2 (0.0 to 0.5)	0.1	.03	0.26
	CC	89	91	-0.1 -0.1	0.1 (-0.1 to 0.3)	0.1	.30	0.10
	LOCF	98	96	-0.1 -0.1	0.1 (-0.1 to 0.3)	0.1	.37	0.09
VR-12 PCS[c]	MI (ITT)	98	96	2.0 -0.4	2.6 (0.5 to 4.7)	1.1	.01	0.31
	PP	63	91	2.6 -0.4	3.5 (1.5 to 5.6)	1.0	.001	0.41
	CC	89	91	1.9 -0.4	2.7 (0.6 to 4.7)	1.1	.01	0.28
	LOCF	98	96	1.7 -0.3	2.3 (0.3 to 4.2)	0.9	.02	0.27
VR-12 MCS[c]	MI (ITT)	98	96	-0.6 -0.3	0.1 (-2.6 to) 2.4)	1.3	.95	0.04
	PP	63	91	0.8 0.3	1.3 (-3.9 to 1.4)	1.3	.35	0.12
	CC	89	91	-0.5 -0.3	-0.1 (-2.6 to 2.5)	1.3	.95	0.03
	LOCF	98	96	-0.5 -0.3	0.0 (-2.3 to 2.4)	1.2	.98	0.02
30s Chair Stand Test[c]	MI (ITT)	98	96	1.7 1.4	0.3 (-0.3 to 1.0)	0.3	.31	0.16
	PP	63	75	1.8 1.5	0.4 (-0.3 to 1.1)	0.4	.23	0.17
	CC	89	91	1.7 1.5	0.3 (-0.3 to 0.9)	0.3	.34	0.12
	LOCF	98	96	1.4 1.1	0.3 (-0.2 to 0.8)	0.3	.28	0.14

[a] Differences in change between groups are adjusted for baseline and stratification variables.
IG=intervention group. CG=control group. MI=Multiple imputation. ITT=Intention to treat. PP=per Protocol. CC=Complete Case. LOCF=Least (=baseline) observation carried forward. KOOS=Knee Osteoarthritis Outcome Score (0-100, worse to best). ADL=Activities of Daily Living. Patients Global Assessment is scored 1-5 (best to worse). VR-12=Health related quality of life (0-100, worse to best, normalized to a mean value of 50 and SD of 10). PCS=Physical Component Score. MCS=Mental Component Score.
[b] Upper entry intervention group, lower entry control group.
[c] For change within groups, positive changes indicate improvement. For difference in change between groups, positive differences favour intervention group (re.flex).
[d] For change within groups, negative changes indicate improvement. For difference in change between groups, negative differences favour intervention group (re.flex).

Subgroup analyses

Table A7: Knee osteoarthritis related concomitant care during the 12-week intervention phase.[a]

Category		CG (usual care)	IG (re.flex)
Orthopaedic consultation	before and during[b]	11	9
	new during[c]	6	5
	total number[d]	17	14
Injection	before and during[b]	3	1
	new during[c]	3	3
	total number[d]	6	4
Hard frame knee orthosis	before and during[b]	5	3
	new during[c]	2	0
	total number[d]	7	3
Insoles[e]	before and during[b]	23	21
	new during[c]	11	5
	total number[d]	34	26
Patient information	before and during[b]	3	1
	new during[c]	7	6
	total number[d]	10	7
Physiotherapy[e]	before and during[b]	21	14
	new during[c]	6	6
	total number[d]	27	20
NSAID (incl. cremes)[e, f]	before and during[b]	11	12
	new during[c]	6	2
	total number[d]	17	14

[a] CG=control group. IG=intervention group.
[b] Concomitant care was already made use of in the previous 12 months.
[c] Concomitant care was initiated during the 12-week intervention phase.
[d] Total number of participants who used concomitant care during the intervention period.
[e] Those included into the subgroup analysis are highlighted in bold.
[f] NSAID= Non-steroidal anti-inflammatory drugs intake on a regular base (weekly or daily).

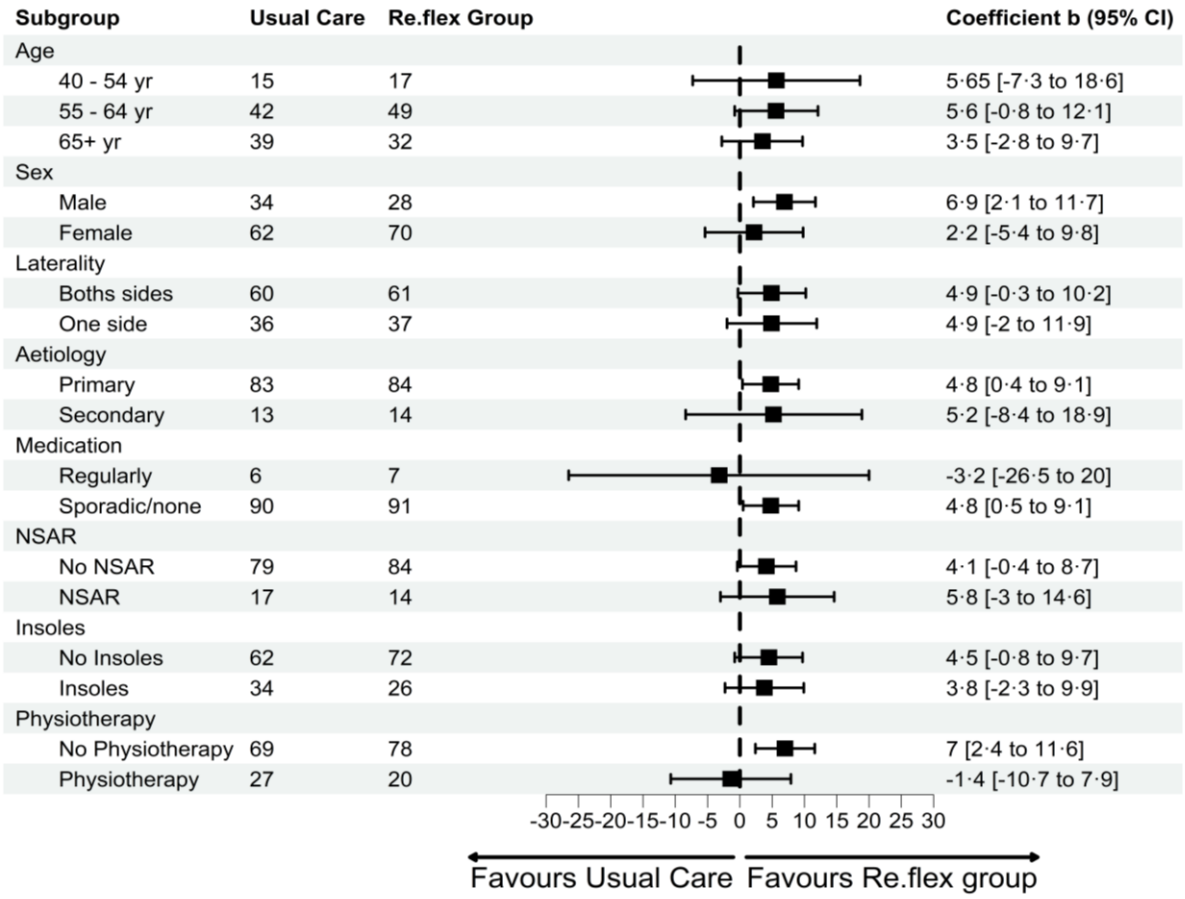

Figure A24: Subgroup analyses for Knee Osteoarthritis Outcome Score (KOOS) Subscale Pain. For difference in change between groups (coefficient b), positive differences favour re.flex group (intervention group).

Subgroup	Usual Care	Re.flex Group	Coefficient b (95% CI)
Age			
40 - 54 yr	15	17	2·7 [-8·7 to 14·2]
55 - 64 yr	42	49	3·7 [-2·6 to 10·1]
65+ yr	39	32	4·3 [-1·2 to 9·8]
Sex			
Male	34	28	4·9 [0 to 9·8]
Female	62	70	2·2 [-4·1 to 8·6]
Laterality			
Boths sides	60	61	4 [-1·1 to 9]
One side	36	37	4 [-2·3 to 10·2]
Aetiology			
Primary	83	84	4·4 [0·3 to 8·5]
Secondary	13	14	0·4 [-13·1 to 13·8]
Medication			
Regularly	6	7	11·6 [-12·4 to 35·6]
Sporadic/none	90	91	3·5 [-0·6 to 7·6]
NSAR			
No NSAR	79	84	3·9 [-0·2 to 8]
NSAR	17	14	0·2 [-9·7 to 10]
Insoles			
No Insoles	62	72	4·3 [-0·5 to 9·1]
Insoles	34	26	2·1 [-2·8 to 8·6]
Physiotherapy			
No Physiotherapy	69	78	6 [1·8 to 10·2]
Physiotherapy	27	20	-3·2 [-12·5 to 6·2]

Figure A25: Subgroup analyses for Knee Osteoarthritis Outcome Score (KOOS) subscale Activities in daily living (ADL). For difference in change between groups (coefficient b), positive differences favour re.flex group (intervention group). The only significant interaction was found for physiotherapy (*P*=.03).

Adverse Events

Participants of the re.flex group were asked to document any adverse events (AE) occurring during the study period. Participants of the intervention group were further instructed to interrupt the training program in case of any suspicious symptoms, fatigue or excessive pain during the exercise intervention. Minor AEs had to be reported to the responsible study personal within one week (via email, telephone). AEs causing the need for referral to a physician or hospital had to be reported to the responsible study personal immediately. The decision on how to proceed was up to the study physician and the study personal (sports scientist/physiotherapist) and included actions like modifying, pausing, or completely ceasing the training program. In case of persistent complaints, patients were presented again to the physician to initiate further medical interventions, if necessary.

Table A8: Adverse Event Reporting.[a]

ID[b]	Harm	Type[c]	Exp[d]	Link[e]	MC[f]	CoI[g]
006	Back and groin pain	AE	UE	S	no	stop
087 (DO)	Increased pain due to device-initiated overload (repetition count failure due to movement restrictions of OA knee)	AE	UE	S	no	stop
140	Increasing knee pain associated with specific exercise	AE	UE	S	yes	stop
063	Severe pain in the knee joint during rest. Irritated knee.	AE	EE	S	no	pause
129	Pain during specific exercises	AE	EE	S	no	mod
025	Increasing buttock/sciatica pain during specific exercises, sometimes also at night	AE	UE	L	yes	stop
051 (DO)	Activated knee OA with effusion	AE	UE	L	yes	stop
107 (DO)	Increasing pain at the sacroiliac joint due to device-initiated overload (repetition count failure due to movement restrictions of OA knee)	AE	UE	L	no	stop
035	Pain like muscle strain after the first exercise session (short-term)	AE	EE	L	no	none
152	Knee inflammation	AE	UE	L	no	pause
123	Increasing knee joint pain	AE	EE	P	yes	stop
010	Increased knee pain	AE	EE	P	no	pause
003	Covid-19 and Bursitis at the hip	AE	UE	U	yes	stop
020	Hayfever, associated with rheumatic flare	AE	UE	U	yes	stop
130 (DO)	Pain in back and knee. According to report of patient, no link to intervention. Wants to cease study.	AE	NA	U	no	stop
019	Meniscal surgery due to a prior injury before the start of the study	SAE	UE	U	yes	pause
038	Hospital stay because of gallstones	SAE	NA	N	yes	pause
100 (DO)	Stroke (Trans Ischemic attack)	SAE	NA	N	yes	stop
110	Knee arthroscopy after advice from external physician in the context of usual care	SAE	NA	N	yes	pause
119	Hospital stay because of heart catheter	SAE	NA	N	yes	pause

[a] Reports were classified into AE=adverse event, and SAE=serious adverse events (events related to death, life-threatening illness or injury, in-patient hospitalization). They were further classified into EE=expected, and UU=unexpected events, and the link to intervention was differentiated into S=sure, L=likely, P=possible, U=unlikely, N=no. Actions taken were classified into need (=yes)/no need (=no) for immediate medical care (e.g. referral to orthopaedist, physiotherapy, medication) and change of intervention modalities (e.g. mod=modification, pause=pausing, stop=stopping, none=no change).

[b] DO=Drop-out; [c] Type of event; [d] Expectation: NA=not applicable/no link; [e] Link to intervention; [f] MC=Medical care; [g] Change of intervention

Exercise-related pain

Exercise pose, duration, load, wrong movement execution, or exercise-related muscle soreness were mentioned by 24 (27%) participants, 10 (11%) participants mentioned symptoms other than osteoarthritis causing pain, 7 (8%) participants related pain to prevalent knee osteoarthritis, and 12 (14%) participants named other or unknown reasons.

Related adaptations of the training behaviour were reported by 22 participants of which 12 (13.5%) modified exercises, 7 (8%) stopped training, 3 (3%) focused on better exercise execution and 1 (1%) took medication to manage exercises. Table 9 gives an overview on pain incidence, frequency, duration, and intensity.

Table A9: Frequency of self-reported exercise-related pain during exercise (at three months, n [% intervention group]).

Incidence		Frequency		Duration		Intensity[a]	
Yes	53 (52%)	Always	4 (4%)	Min to few h	29 (30%)	2	16 (16%)
		Frequently	7 (7%)	1 day	13 (13%)	4	11 (11%)
		Sometimes	39 (40%)	≤ 1 week	5 (5%)	6	16 (16%)
		Once	3 (3%)	> 1 week	6 (6%)	8	9 (9%)
						10	1 (1%)
No pain	36 (37%)	No pain	36 (37%)	No pain	36 (37%)	No pain	36 (37%)
Missing[b]	0 (0)	Missing	0 (0)	Missing	0 (0)	Missing	0 (0)
DO t1	9 (9%)	DO t1	9 (9%)	DO t1	9 (9%)	DO t1	9 (9%)

[a] Likert scale scored 0 (no pain), 2 (little pain), 4 (moderate pain), 6 (much pain), 8 (very much pain) or 10 (highest imaginable pain).

[b] Missing data do not include drop-outs (DO) at three months (DO t1) of the intervention group (n = 9).

Table A10: Logfile data for week 1, week 12, and overall.

	Patients of the re.flex group		
	Week 1	**Week 12**	**Overall**
Attrition rate (%)[b, c]	2	28	..
Exercise session adherence (%)[c, d]	94	65	77
Exercise repetition adherence (%), mean (SD)[c, e]	91 (27)	63 (47)	74 (43)
Active time (min), mean (SD)[f]	21 (5)[g]	11 (4)[h]	18 (6)[i]

[a] Missing date were not replaced with multiple imputation.
[b] Attrition rate is the percentage of participants who did not log into the re.flex app at least once a week.
[c]Data refer to all patients of the re.flex group (n=98); 12 weeks with 3 exercise sessions per week.
[d] Exercise session adherence is the percentage of conducted exercise sessions relative to the overall number of prescribed exercise sessions during the study period.
[e] Exercise repetition adherence is the percentage of all valid repetitions in percent with a maximum value of 100%.
[f] Active time is the crude time for exercising with the sensor-equipped leg without login, calibration, video watching, and feedback on pain and exertion.
[g] Data refer to 276 exercise sessions.
[h] Data refer to 192 exercise sessions.
[i] Data refer to 2706 exercise sessions.

Table A11: Perceived exertion and pain outcomes before, during, and after exercising.

	Values, mean (SD)	**Values, median (IQR)**	**Range**
Perceived exertion during exercise[a, b]	3.5 (1.1)	3.0 (1.0)	0.0-10.0
Perceived exertion after exercise[a, b]	2.8 (1.7)	3.0 (0.0)	0.0-10.0
Delta pain[a]	0.3 (1.2)	0.0 (0.0)	-8.0-8.0
Perceived pain during exercise[a, c]	0.9 (1.5)	0.0 (2.0)	0.0-10.0

[a] Data out of 2705 exercise sessions.
[b] 10-point scale from 0 (no exertion at all) to 10 (maximum conceivable exertion).
[c] 10-point scale from 0 (no pain) to 10 (highest imaginable pain).

Table A12: Patient satisfaction of the re.flex app and treatment satisfaction.

	re.flex group (n=89)	**Usual care group (n=91)**
Patient satisfaction (ZUF-8)[a], mean (SD)	24.9 (5.0)	..
Treatment satisfaction, n (%)		
Very satisfied	23 (25.8)	6 (6.6)
Satisfied	33 (37.1)	14 (15.4)
Neither/nor satisfied	24 (27.0)	59 (64.8)
Unsatisfied	7 (7.9)	11 (12.1)
Very unsatisfied	2 (2.2)	1 (1.1)

[a] ZUF-8=Patient satisfaction questionnaire (8-32, higher values indicating higher patient satisfaction with the app).

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5 Discussion

The scientific program of the present dissertation aimed to evaluate the self-directed m-health exercise intervention re.flex for patients with knee OA from a quantitative and qualitative perspective. The findings of the included research articles demonstrated superiority of re.flex in comparison to usual care for the primary outcome of knee-related pain at three months. However, mean differences between the re.flex group and the usual care group, as well as effect sizes, were found to be smaller in the confirmatory RCT when compared to the pilot RCT. Divergent findings were observed for the PROM physical function, for which statistically significant differences between both groups were only evident in the pilot RCT. Furthermore, for secondary outcomes, beneficial treatment effects in favor of re.flex were found for other OA-specific complaints (symptoms, sports and recreation, and quality of life subscales) in the pilot RCT, as well as for the physical component score of the general HrQoL in the pilot and confirmatory RCT. The performance measures did not demonstrate statistically significant improvements in favor of the re.flex intervention in either of the two studies. Notably, in both RCTs, the study intervention showed high adherence rates, and no intervention-related serious adverse events were observed. The qualitative study corroborated these findings, as most participants reported positive outcomes, such as reduced pain, improvements in function and activities of daily living, or a subjective increase in muscle strength. Moreover, the participants demonstrated a high level of acceptability for the self-directed m-health exercise intervention, valuing the ease of use, the comprehensibility, and the flexibility with which exercises can be conducted. In addition, from the patients' perspectives, app features including videos, real-time biofeedback, and reminders for upcoming exercise sessions were found to be useful, supportive, and motivational for regular exercise participation. However, a proportion of patients would prefer to have at least some kind of human interaction in combination with the m-health intervention.

5.1 Overall discussion of key findings of the self-directed m-health exercise intervention

5.1.1 Patient-reported outcome measures: pain and physical function

Superiority of the self-directed m-health exercise program re.flex over usual care for the patient-reported outcome pain could be demonstrated in both RCTs (study 1 and study 3). This is in accordance with several meta-analyses on the short-term effectiveness of non-digital and digital delivered exercise interventions in patients with knee OA (Chen et al., 2021; Fransen et al., 2015; Holden et al., 2023; Lawford et al., 2024; Yang et al., 2023). However, some

discrepancies have been observed in the magnitude of the between-group differences and standardized mean differences (SMD) across studies (see Table 4). The findings of between-group differences and SMD for pain were substantially greater in the pilot RCT than in the confirmatory RCT, but were comparable in size to those in the current 2024 Cochrane meta-analysis (Lawford et al., 2024). However, Lawford and colleagues (2024) criticized the inclusion of trials with small sample sizes and inadequate quality, which could have led to an overestimation of effects in their analysis. Thus, findings from the 2015 Cochrane meta-analysis (Fransen et al., 2015) and the sensitivity analysis (which included only trials at low risk of bias and were fully powered) of the 2024 Cochrane meta-analysis (Lawford et al., 2024) appear to provide a more appropriate benchmark. Furthermore, divergent findings were reported in terms of improvements in physical function. While the pilot RCT and Cochrane meta-analyses (Fransen et al., 2015; Lawford et al., 2024) demonstrated beneficial effects of exercise over usual care or no treatment, Holden and colleagues (2023) in their IPD meta-analysis, as well as the digital-based meta-analyses (Chen et al., 2021; Yang et al., 2023) and the confirmatory RCT integrated in this dissertation cast doubt on the effectiveness of exercise in improving physical function. Notably, the digital-based meta-analyses included non-digital treatments (e.g. in-person exercise treatment) as control conditions, in addition to usual care and no care (Chen et al., 2021; Yang et al., 2023). Based on a subsequent subgroup analysis within one of these meta-analyses, notable improvements in physical function of digital-based exercise interventions could be demonstrated when compared to usual care alone (Yang et al., 2023). In contrast, the other meta-analysis did not further distinguish between control conditions and was unable to identify a positive treatment effect (Chen et al., 2021). Moreover, evidence for significant improvements was observed when only utilizing the delivery type app (Yang et al., 2023). The potential benefits of web- and app-based exercise programs have been associated with the incorporation of special features (e.g. video-based exercise demonstrations, automated reminders to perform exercises, incorporation of educational material, sensor-based motion and physical activity tracking). Exercise programs that have integrated these features have demonstrated greater improvements in patient outcomes in comparison to programs that did not include these features (Chen et al., 2021). However, given that only five (Yang et al., 2023) respectively four studies (Chen et al., 2021) with the delivery type app or web-based could be included in the meta-analyses, and in addition, those studies were characterized by high heterogeneity of study interventions, absence or involvement of human interaction, and sample characteristics, the quality of evidence is low. Nevertheless, even though non-digital, in-person exercise interventions that have been demonstrated to exhibit small to medium effects in reducing pain and improving physical function remain the current gold standard, digital-based exercise programs have been shown to be at least equally

effective (Hinman et al., 2024; Yang et al., 2023). Considering these findings, digital exercise delivery has been shown to offer advantages that justify its utilization and implementation in the future treatment of patients with knee OA. Specifically, the pilot RCT depicted in this dissertation has already indicated this potential, although it could not be fully confirmed in the confirmatory RCT. However, in this context, the small sample size in the pilot RCT may have led to an overestimation of the substantial improvements in pain reduction and physical function observed with the use of re.flex compared to usual care and thus limit the generalizability of the results. Furthermore, the discrepancies observed between the results of the pilot and confirmatory RCT may be attributable to the control group. In the pilot RCT, the control group remained stable or even experienced slightly worse outcomes for measurements of pain and physical function at follow-up. In contrast, in the confirmatory RCT, the control group showed relevant symptom relief, thereby reducing the between-group differences. Another potential explanation for these discrepancies could be attributed to the lockdown situation of the COVID-19 pandemic during the pilot RCT, in which access to concomitant care was limited. Unfortunately, for the pilot RCT only data on concomitant pharmacological care are available, but not on concomitant use of physiotherapy. The analysis of descriptive statistics indicated that approximately 20% of patients in both groups utilized NSAIDs or analgesics on a daily or weekly basis. However, due to the small sample size, no subgroup analyses were performed. In the confirmatory RCT, the most frequently utilized concomitant care included physiotherapy, NSAIDs (taken on a daily or weekly basis), and insoles. Intake of NSAIDs demonstrated comparable rates across groups (14-18%), and the subgroup analysis did not reveal significant interactions with study arm, suggesting no relevant influence on intervention effects. In contrast, physiotherapy demonstrated a significant interaction with the study arm ($p = .03$) for physical function. The findings indicated that patients in the control group who received concomitant physiotherapy demonstrated greater improvements compared to those using physiotherapy in the re.flex group. Conversely, patients in the re.flex group who did not receive physiotherapy showed greater improvements than the control group. A similar but non-significant trend was observed for pain. Overall, the risk of bias influencing the effects of the re.flex intervention by concomitant treatments is considered low. Nevertheless, this finding may partly explain the improvements observed in the control group of the confirmatory RCT, which, in contrast, were not seen in the pilot RCT. A further aspect that could explain the smaller effects observed in the confirmatory RCT may be the regression to the mean phenomenon, which frequently occurs after higher-than-average treatment effects in pilot studies, with uncertainty regarding whether an effect is due to treatment or rather due to chance (Duan, 2013). Lastly, in the pilot RCT effects could be larger, as some of the patients wore an additional knee brace during exercise, which was demonstrated in subgroup analyses

to increase benefits even when they were not statistically superior to the non-brace exercise group. However, the present dissertation does not intend to address the additional effects of knee brace use or non-use in greater detail.

Table 4: Overview of between-group differences and standardized mean differences (SMD) of the patient-reported outcome pain and physical function for the pilot randomized controlled trial (RCT), confirmatory RCT, and several meta-analyses or systematic reviews. All studies compared exercise interventions with usual care, minimal care, or no care. Chen et al. (2021) and Yang et al. (2023) additionally incorporated non-digital treatment as a control condition.

Reference	Pain		Physical function	
	Between-group difference (95% CI)	**SMD**	**Between-group difference (95% CI)**	**SMD**
Dieter et al. (2024) (pilot RCT)	13.2 (7.3 to 19.1)	0.76	12.0 (5.9 to 18.1)	0.64
Dieter, Martus, et al. (2025) (confirmatory RCT)	4.8 (0.7 to 8.9)	0.35	3.9 (0.0 to 7.9)	0.31
Fransen et al. (2015)[1]	12 (10 to 15)	0.49	10 (8 to 13)	0.52
Lawford et al. (2024)[2]	13.1 (10.4 to 15.9)	0.71	12.5 (9.7 to 15.3)	0.72
Lawford et al. (2024)[3]	10.0 (6.7 to 13.5)	0.54	8.9 (5.6 to 12.0)	Not reported
Holden et al. (2023)[4]	6.4 (4.3 to 8.5)	Not reported	4.5 (3.0 to 6.0)	Not reported
Chen et al. (2021)[5]	6.6[6]	0.29	Not reported	0.22
Yang et al. (2023)[7]	Not reported	0.28	Not reported	0.17

SMD Standardized Mean Difference; CI Confidence Interval; RCT Randomized Controlled Trial

[1]Included land-based exercise interventions for patients with knee osteoarthritis; no digital delivered interventions.

[2]Overall analysis (including outliers), included n=56 studies for pain and n=54 studies for physical function. All studies included land-based non-digital or digital exercise interventions.

[3]Only trials at low risk of bias and fully powered, included n=14 studies for pain and n=11 studies for physical function. All studies Included land-based non-digital or digital exercise interventions.

[4]Included patients with knee and hip osteoarthritis, and non-digital or digital land-based and aquatic exercise interventions.

[5]Included digital-based exercise interventions (e.g. via telephone, web, app) for patients with knee osteoarthritis.

[6]Extrapolated from a pain change of 1.31 on a scale of 0-20. 95% CI was not reported.

[7]Included digital-based exercise interventions (e.g. via telephone, web, app) for patients with knee osteoarthritis.

The qualitative study of the present work investigating patients' experiences of the 12-week self-directed m-health exercise intervention confirmed the findings of beneficial effects on patient-reported outcomes pain and physical function. Most participants reported positive outcomes after completing the exercise program, including reduced pain, a reduced need for pain medication, improvements in function and daily activities (e.g. cycling, walking, climbing and descending stairs), and an increase in subjective muscle strength and knee stability. Similar improvements have been reported in other qualitative studies in the field of digital-based exercise therapy for patients with knee OA (Cronström et al., 2019; Nelligan et al., 2020), although it should be noted that patients' responses to exercise therapy can vary and not all patients will benefit equally.

5.1.2 Adherence

In the management of knee OA, improvements in pain and physical function are closely associated with patients' adherence to exercise programs. The active and ongoing participation in exercise is crucial for the achievement and maintenance of the beneficial treatment effects (K.L. Bennell et al., 2014). Thereby, several intrinsic and extrinsic factors, including motivational level or environmental factors, were identified as influencing variables (Petursdottir et al., 2010). In order to enhance adherence, strategies such as regular supervision, patient education, BCTs, self-monitoring tools, and digital health technologies have been shown to play an important role in overcoming barriers and promoting sustained participation (Hurley et al., 2010; Meade et al., 2019; Pérez-Maletzki et al., 2024; Pisters et al., 2010; Roddy et al., 2005; Schafer et al., 2018). The qualitative study described in this dissertation corroborates these assumptions. From the patients' perspective, the flexibility to conduct exercises at any time and in any location, the various app features (e.g. motion sensors that provide a control mechanism and objective monitoring, positive verbal feedback, reminder notifications for upcoming exercise sessions), and positive experiences were determined to be important facilitators to increase motivation and regularity for the use of the digital exercise program. Conversely, for a subset of patients, the absence of human supervision and the lack of interaction with a health professional when needed, as well as technical issues, had a detrimental effect on motivation and exercise completion. This assumption is consistent with the findings of other qualitative studies, which have indicated that a certain level of human connection associated with the digital health intervention could facilitate regular exercise participation, e.g. by receiving regular SMS messages or communicating with the physiotherapist via chat, videoconferencing, or telephone (Cronström et al., 2019; Hinman et al., 2017; Lawford et al., 2018). However, it was also stated that enhancing self-efficacy and self-management in patients appear to be important factors in

increasing adherence and empowering individuals to exercise without the need for supervision (Fernandes et al., 2022; Hinman et al., 2017).

According to the quantitative analysis of adherence rates derived from the two RCTs included in this dissertation (study 1 and study 3), 92.5% in the pilot RCT and 77% in the confirmatory RCT of all prescribed exercise sessions were completed. However, a direct comparison of these adherence rates across both studies should be avoided. In the pilot RCT, only intervention finishers who completed >50% of all exercise sessions and were still active in weeks 11 and 12 of the intervention phase were considered. Conversely, the confirmatory RCT focused on adherence among those who had initially started the program. However, the observed adherence rates in both studies correspond to the documented rates of 68-88% reported in the extant literature for digital home exercise programs for patients with knee OA that were guided via apps, web-based platforms, or videoconferencing tools (Alasfour & Almarwani, 2020; Bennell et al., 2017; Doiron-Cadrin et al., 2020; Gohir et al., 2021; Mecklenburg et al., 2018). In this regard, the study by Mecklenburg and colleagues (2018) employed a design and technological set-up similar to the re.flex intervention, incorporating an app with narrated videos to demonstrate the exercises along with motion sensors that tracked exercise performance and provided real-time feedback. The adherence rates of this study have been found to be 76% among participants who initially commenced the 12-week exercise program and 95% among those who completed it. Accordingly, there is a strong alignment between these data and those from the confirmatory and pilot RCT of the re.flex intervention. In this context, the specific group of sensor-based apps constitutes a distinct category that has the potential to further enhance adherence rates by offering additional information and guidance on exercise execution and training load (e.g. frequency and duration), as well as providing real-time biofeedback to prevent incorrect movement execution and promote the acquisition of correct movement patterns. As a result, they are able to mimic human supervision, at least to a certain extent. Notably, adherence to digital exercise programs has been found to exceed the rates reported for non-digital home exercise programs (62-75% completion of the prescribed exercise sessions) (Ay et al., 2016; Pisters et al., 2010) and seems to improve adherence at least in the short term (Liu et al., 2025). However, in the medium and long term, there is no evidence that adherence to digital exercise programs could exceed that of non-digital exercise delivery (Liu et al., 2025). A critical point to note pertains to the fact that to date, the majority of studies have relied on self-reported adherence rates, which are subject to bias due to the risk of overreporting resulting from inadequate recall and social desirability. Consequently, the findings from the RCTs that have demonstrated high adherence rates to the re.flex intervention appear to be of even greater value. Future assessments of

adherence should be supported by objective data derived from wearable devices or apps, in order to collect more detailed information on exercise dosage and performance quality (Liu et al., 2025).

5.1.3 Safety

In the two RCTs incorporated in this dissertation, no serious adverse events were reported during the intervention periods. A total of 4 (13%) respectively 12 (12%) minor adverse events were observed in the pilot and confirmatory RCT that were potentially associated with the re.flex intervention. The complaints reported were predominantly of musculoskeletal nature, with symptoms such as increased knee pain. This observation is consistent with the findings from other supervised or self-directed digital exercise programs in patients with knee OA, which also did not report any serious adverse events in conjunction with the respective interventions (Bennell et al., 2022; Gohir et al., 2021; Nelligan et al., 2021). Additionally, the incidence of minor adverse events has been observed to be consistent with that of another self-directed web-based exercise program, which reported 13 cases (16%) of adverse events among the intervention group including n=90 participants. Of these, 8 cases were associated with increased knee pain (Nelligan et al., 2021). According to the findings of a 6-month, supervised, telehealth-delivered exercise program, non-serious adverse events were experienced by 49% of patients, including symptoms such as knee joint pain, knee swelling, and other lower limb musculoskeletal complaints (Bennell et al., 2022). Compared to these findings, the results of our RCTs were even less prevalent. Overall, the findings of the pilot and confirmatory RCTs as well as those from the digital exercise programs in the extant literature are consistent with the ratings of various guidelines, meta-analyses, and reviews of exercise therapy for knee OA that are based on the non-digital provision of exercise (Bannuru et al., 2019; K.L. Bennell et al., 2014; Fransen et al., 2015). These authors conclude that all types of therapeutic exercise are considered safe, irrespective of the presence of comorbidities and with minimal risk of side effects. Moreover, it was stated that the probability of severe adverse events is negligible (Holden et al., 2021). The reported adverse events were found to be associated with increased knee, hip, or back pain (Bannuru et al., 2019; Fransen et al., 2015). Additionally, the available literature reveals evidence that no notable differences were observed between group-based and home-based settings, with both demonstrating low incidences of adverse events (K.L. Bennell et al., 2014). Nevertheless, the supervision of exercise sessions, at least in the initial stage of exercise programs, may prevent adverse events by ensuring correct execution and selection of exercises, and an appropriate tailoring of exercise intensity (Holden et al., 2021). However, to ensure the generalizability of this assertion, it is necessary to investigate whether this also applies to supervised or via motion sensors imitated supervised digital delivered

exercise interventions. This appears to be of particular importance given that, in certain instances within the pilot and confirmatory RCTs, there were patients who may have required additional support. In certain cases, when the sensor-based exercise app with its technical features was not utilized correctly, there was a potential risk for overtraining and incorrect movement performance. Some patients reported accepting incorrect exercise execution in order to cheat the app in the absence of repetition counting due to failed sensor registration. In doing so, they sometimes performed more repetitions than specified in order to register all repetitions as completed in the app. Although the probability of such training errors was minimized by the system's design to alert users to malfunctions and incorrect exercise execution, this may have also resulted in some of the minor adverse events that could potentially be prevented by the supervision of a health professional. Furthermore, some patients identified difficulties related to exercises requiring high knee flexion in combination with high load on the affected leg (e.g. one-sided exercises, wall squat). This phenomenon was particularly evident among patients with a high body mass index and strengthens the conclusion drawn by Durst and colleagues (2020). Their research revealed that the movement quality associated with exercise demonstration via mobile app was acceptable for exercises that are easy to conduct and instruct, but require more instruction for more complex exercises (e.g. by the expertise of a physiotherapist).

5.1.4 Usability and acceptability

Usability is defined as the “extent to which a product [in this case the digital health technology re.flex] can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use” (Grassi et al., 2017). In addition, the term “acceptability” describes a construct that reflects patients’ experiences and needs in relation to the requirements placed on the digital health technology (in this case re.flex) as a suitable method for exercise delivery. These specific topics were addressed in the qualitative study (study 2) of this dissertation. Thereby, participants positively valued the ease of use, comprehensibility, and self-explanatory nature of the self-directed app-based exercise program. Other qualitative studies examining self-directed or supervised digital exercise interventions in patients with knee OA corroborated these findings, highlighting the potential impact of simplicity and comprehensibility in the use of digital health technologies on adherence and motivation (Danbjorg et al., 2018; De Vries et al., 2017; Nelligan et al., 2020). Conversely, technical issues had a detrimental effect on motivation and adherence to exercise of some participants. In addition, patients in the qualitative study on the re.flex intervention found the app features including videos, real-time biofeedback, verbal feedback, and reminders for upcoming exercise sessions via push-notifications to be useful, supportive, and

motivative in order to guide and control regular exercising. These findings align with those reported in other qualitative studies, which identified similar features as facilitators and motivators for successful exercise participation (Cronström et al., 2019; Nelligan et al., 2020). Moreover, one study found a positive effect related to monitoring, particularly in cases where patients were aware that their actions were being supervised (Danbjorg et al., 2018). Furthermore, the flexibility to perform exercises at any time and in any location was identified as a key benefit by patients using the re.flex intervention as well as in other studies that employed digital health technologies either without human support or with asynchronous chat support (Bossen et al., 2013; Cronström et al., 2019). However, despite the numerous advantages and facilitators associated with participating in the m-health delivered exercise program, some patients expressed that they would have found a combination of human supervision and the digital exercise intervention to be even more beneficial. This finding is consistent with the results of previous studies on self-directed digital exercise interventions in patients with knee OA, which suggested the provision of human support when needed (e.g. for clinical questions) (Bossen et al., 2013; Nelligan et al., 2020). In this context, hybrid formats such as telehealth or blended care may offer notable benefits by combining digital health technologies with support by a health professional. The integration of asynchronous, synchronous, or in-person communication within digital exercise programs allows for the adaptation of exercise programs according to patients' needs and enables the preparation of patients for upcoming exercise sessions by empowering them for correct and safe exercise technique. In addition, this enables answering upcoming questions, the provision of reassurance, motivation, feedback, and the management of technological issues (Cronström et al., 2019; De Vries et al., 2017; Hinman et al., 2017; M Ezzat et al., 2025; Pearson et al., 2016). In this context, it has been demonstrated that patients who already possess a very positive attitude toward technology may develop a mastery experience, which is important for self-efficacy and future exercise behavior, alone by using a self-directed app-based exercise program. Conversely, for patients who do not have such positive technological attitudes, exercise programs that are, at least initially, supported by health professionals appear to be preferable (Sassenberg et al., 2022).

The quantitative analysis of the confirmatory RCT, which reported a high level of usability and satisfaction with the re.flex app and a high treatment satisfaction, corroborated the findings from the qualitative evaluation of mostly positive patient experiences, usability, and acceptability. Nevertheless, the occurrence of minor adverse events, the dissatisfaction with treatment results, and negative experiences observed in a small number of patients also indicate that a self-directed m-health exercise intervention might not be a one-size-fits-all

solution. In summary, flexible, comprehensive, and user-friendly digital health technologies that include appropriate app features for exercise guidance, feedback, and monitoring are highly accepted and have the potential to facilitate access to conservative OA treatment. However, the extent to which additional human support should be provided must be tailored to the patient's preferences and needs.

Summary chapter 5.1

In summary, the findings indicated that the self-directed m-health exercise intervention re.flex proved to be superior to usual care in reducing pain among patients with knee OA. Conversely, effects on physical function were less consistent. The findings align with the extant literature on digital and non-digital exercise interventions, although the observed effects of the confirmatory RCT remain at the lower end of the range reported in the reference literature. Nevertheless, digital exercise programs have been shown to be at least as effective as non-digital, in-person exercise interventions. The discrepancies observed between the effects of the pilot and confirmatory RCTs may be attributable to a variety of factors, including the small sample size of the pilot RCT, the outcomes of the control group and the potential influence of concomitant care on their progress, the phenomenon of regression to the mean, and the knee brace use in the pilot RCT. The qualitative research supports the findings with observed patient-reported benefits in terms of pain, function and daily activities, subjective muscle strength, and reduced need for pain medication. Exercise adherence rates in both RCTs were high (pilot RCT: 92.5 % in intervention finishers, confirmatory RCT: 77% in those who initially started the program). These data align with prior studies of digital-based home exercise programs and exceed reported rates for non-digital home exercise interventions in patients with knee OA. Furthermore, in both RCTs, no serious adverse events were reported, and the incidence of minor adverse events (e.g. increased knee pain) was low. These findings are again consistent with studies, guidelines, and meta-analyses of digital and non-digital exercise interventions for patients with knee OA, which similarly reported only a minimal risk of side effects. Facilitators for increased motivation and regular exercise participation that were identified in the qualitative study can be seen in the flexibility, various app features (e.g. motion sensors, reminders, feedback), and positive user experiences with the re.flex intervention. These elements in combination with the comprehensibility and user-friendliness of the digital exercise intervention also contributed to its high usability, satisfaction, and acceptability. Quantitative analysis derived from the confirmatory RCT corroborated this finding. Conversely, the absence of human supervision and technical issues reduced engagement and satisfaction for some patients, indicating that self-directed m-health exercise interventions may not be equally suitable for all patients. Importantly, sensor-based technologies (such as re.flex) can

partially substitute human supervision, by providing real-time biofeedback, guidance on exercise execution, and support in regulating training load. However, although the re.flex system was designed to minimize the risk of training errors by alerting users to malfunctions and incorrect exercise execution, in a small number of patients signs of overtraining and incorrect movement performance were still observed. Overall, these findings were consistent with those of other qualitative and crossover studies in the literature that examined digital exercise interventions in patients with knee OA. These studies also highlighted that some patients could benefit from additional support from a health professional, particularly when engaging in more complex exercises or when having a less positive attitude toward technology. In this context, for some patients blended care models or supervised digital exercise interventions that combine digital health technologies with tailored support by a health professional may provide an optimal alternative. Finally, re.flex makes a significant contribution to the field of self-directed app-based exercise delivery in knee OA by providing high-quality data in a domain where few studies of low quality are currently available. Overall, the findings demonstrated clinical benefits, high adherence, usability, acceptability, and safety of the re.flex exercise intervention in patients with knee OA. Nevertheless, self-directed exercise interventions are not a one-size-fits-all-solution. In this work, this was demonstrated by patient dissatisfaction with treatment outcomes and minor adverse events occurring in a small number of patients.

5.2 Clinical relevance

Although the findings of a clinical study (e.g. within-group change scores or between-group differences) may demonstrate statistical significance for an outcome, it cannot be assumed that they necessarily represent clinically meaningful treatment effects. Consequently, current research faces the challenge of developing guidelines and standards that facilitate interpretation of which outcome changes or differences reflect relevant clinical improvements (Jaeschke et al., 1989). Unfortunately, in the current literature, different approaches and terminologies determining a clinically meaningful treatment effect, such as the Minimal Important Change (MIC), Minimal Important Difference (MID), and MCID are often mixed together, even though they consider different constructs of a health outcome. In this regard, Dekker and colleagues (2024) have developed a framework that structures the various approaches and provides a comprehensive overview of their potential areas of application. Table 5 summarizes this overview of concepts, methods, and criteria that can be used to evaluate a minimal important change or difference. A key aspect of the framework pertains to the distinction between interpreting the outcome of interest at individual or group level, and assessing the minimal important change or difference. In this context, the term "change" refers

to within-person or within-group change over time, whereas the term "difference" refers to a difference between persons or groups regarding a change over time.

At individual level, clinical relevance can be ascertained by categorizing patients as either responders or non-responders based on a prespecified MIC or defined responder criteria. By definition, the MIC is “a threshold for a minimal within-person change over time above which the individual’s change is considered to be important” (Dekker et al., 2024). Additionally, the MIC can be utilized at group level, where the criteria for clinical importance is met if the within-group average change score exceeds the specified MIC or a relevant proportion of responders exceeding the MIC can be identified. Consequently, the MIC method is applicable for within-person or within-group changes; however, it is not suitable for the interpretation of between-group differences. In order to determine the MIC, various calculation methods can be employed, including distribution-based, anchor-based, and consensus-based approaches. Distribution-based methods rely on statistical criteria concerning the distribution of the outcome of interest (e.g. effect size, standard error of measurement [SEM]) as a value for MIC (Dekker et al., 2024). The anchor-based methods use an external criterion called “anchor” derived from a measure of change, e.g. global rating of change scales (Dekker et al., 2024; Kamper et al., 2009). Thereby, the MIC is calculated based on the mean within-group change of the subgroup who rated their change in the related outcome of interest “a little better/somewhat improved” (= mean change method, mostly using a 5-point or 7-point Likert scale) or by using receiver operating characteristics (ROC). Finally, the consensus-based MIC pertains to the consensus that is reached by relevant stakeholders (e.g. in a Delphi study). The MID is an approach that was intended by certain researchers to be employed for the evaluation of between-group differences (Silva et al., 2023). However, the reported data also rely on a within-group design, addressing the same context as MIC. This can lead to confusion as it is utilized for the same construct as "MIC", but uses the term “difference”.

In the context of interpreting the clinical importance of between-group differences, two approaches can be differentiated. The responder approach uses consensus-based cut-off values for the statistical parameters Number Needed to Treat (NNT) and Risk Ratio (RR) to determine clinical relevance, while the group average approach applies anchor-based (e.g. using the mean change method or ROC method, even though there is no information yet about how the data from both comparison groups is included in the calculation) or consensus-based MCID values (Dekker et al., 2024). Jaeschke and colleagues (1989) were the first to introduce the concept of MCID and defined it as being “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management”.

Table 5: Overview of concepts, methods, and criteria of minimal important change and difference with the differentiation to the interpretation in individuals or groups (modified according to Dekker et al. (2024)).

Level	Concept	Methods	Criteria for clinical importance
Individual level (change within an individual)	Responder	MIC (distribution-based, anchor-based, or consensus-based) or responder criteria	Within-person change >MIC
Group level - Responder approach			
Within-group change	Proportion of responders	Cut-off for minimal important within-group change (consensus-based)	Proportion of responders >cut-off
Between-group difference in within-group change		Cut-off for NNT or RR (consensus-based)	NNT <cut-off RR <cut-off
Group level - Group average approach			
Within-group change	Average change	MIC (distribution-based, anchor-based, or consensus-based)	Within-group change >MIC
Between-group difference in within-group change		MCID (anchor-based, consensus-based)	Between-group difference >MCID

MIC Minimal Important Change; NNT Number Needed to Treat; RR Risk Ratio; MCID Minimal Clinically Important Difference

Dekker and colleagues (2024) further specified MCID as "the smallest difference in change between group A and group B that is considered to be important", thereby clarifying its application for the interpretation of between-group differences. The MIC or MCID of an outcome is highly dependent on context variables, including patient characteristics (e.g. disease severity or patient expectations) and clinical conditions (e.g. specific disease, type of intervention). Therefore, when interpreting a MIC or MCID, it is essential to consider whether the patient population and clinical context in which it was calculated are representative of that in which it should be applied (Sedaghat, 2019). For instance, given that the magnitude of a change score in an outcome has a different meaning for a patient group with lower or higher scores at baseline, it is imperative to consider this aspect when interpreting the results (Beaton et al., 2002). Furthermore, it is recommended that the clinical relevance of group differences be evaluated not solely by a single threshold, but rather by employing a multifactorial evaluation. This can include the consideration of costs, safety, percentages of responders, the evaluation of secondary outcomes, patient adherence, availability of alternative therapies and their benefit-risk profiles, and other factors, in addition to the clinical benefits of the intervention. When focusing only on group mean differences, meaningful improvements in specific subgroups of patients, as identified by responder analyses, may be obscured (Dworkin et al., 2009). To address this issue, the concept of the Smallest Worthwhile Effect (SWE) is proposed to be added to the MCID approach, defining "the smallest beneficial effect of intervention that justifies the costs, risks, and inconveniences of that intervention" (Dekker et al., 2024).

The above presented conceptual summary of current terminologies, calculation methods, and criteria that are used to assess the clinical relevance of health outcomes in relation to the differentiation between interpretation in individuals or groups demonstrates the complexity related to this topic, which is also heavily discussed in current literature on the treatment of patients with OA (Holden et al., 2023; Lawford et al., 2024). Existing recommendations rely mainly on responder criteria or MIC values for within-person or within-group evaluation. For instance, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) recommend setting the MIC at 15% scale range of the assessment tool (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2023). Furthermore, in the context of OA, the OMERACT-OARSI initiative have established specific responder criteria (Pham et al., 2003). Additionally, a number of studies have reported anchor-based (calculated by the mean change method or ROC) MICs ranging from 5.6 to 19.9 points for patient-reported outcomes of pain (scale range 0-100) and from 7.6 to 14.5 points for physical function (scale range 0-100) among patients with knee OA undergoing non-surgical treatment (e.g. self-management, pharmacological interventions, exercise,

physiotherapy, rehabilitation) over a time period from two weeks to 12 months (Angst et al., 2018; Mills et al., 2016; Mostafaee et al., 2022; Tubach et al., 2005). However, even within a single study, discrepancies in MIC (denoted as MID in this study) of more than 11 points were identified, contingent on the calculation method (mean change method or ROC) employed (Mills et al., 2016). This demonstrates the substantial inconsistencies in the extant literature and the dependence of MIC values on the calculation method or study intervention, thereby still raising the question of what standard the results should be classified against. The only work found determining an MCID for group comparison in patients with knee OA is from 1992, using a consensus-based Delphi technique to determine achievable deltas for different outcome measures between two NSAID groups (Bellamy et al., 1992). Thereby, an MCID of 17.5 was established for the outcome pain on movement determined on a VAS (0-100mm). To the best of my knowledge, other, newer MCID values specific for patients with knee OA who underwent non-surgical or mainly exercise treatments and which were calculated for between-group differences based on the definition outlined above are not currently available. Existing studies that report having assertedly calculated MCID or MID values for the interpretation of between-group differences were also based solely on a within-group design. Consequently, the findings of these studies are not suitable to be used for between-group differences.

For the present dissertation, the interpretation of between-group differences are of the greatest importance, as the included RCTs (study 1 and study 3) have evaluated the effectiveness of the intervention re.flex compared to usual care. Thereby, the main focus was given to the PROMs of pain and physical function. As previously discussed, statistically significant improvements were observed for pain in both RCTs and for physical function only in the pilot RCT. Subsequently, these findings will be discussed in the context of their clinical relevance. For both outcomes, pain and physical function, the clinical relevance of the between-group differences has previously been called into question in two meta-analyses (Holden et al., 2023; Lawford et al., 2024). However, the MCID cut-offs applied in the Cochrane meta-analysis (Lawford et al., 2024) (12 for pain and 13 for physical function) were calculated using interventions ranging from non-surgical to surgical, thereby limiting the comparability of the results (Devji et al., 2017). The systematic review reporting these MCID cut-offs themselves demonstrated in subgroup analyses that the type of intervention (in this case surgical vs non-surgical) was significantly associated with the magnitude of the MCID (they called it MID), with extensively higher changes needed for important improvements in surgical (25 resp. 28) interventions compared to non-surgical (8 resp. 10) interventions for pain and physical function outcomes. Moreover, the range of MCIDs reported was very wide and a closer examination on

the 13 included studies revealed that all of them actually used a within-group design for calculating the MCID. Thus, correctly the reported data describe the MIC, that can be only used for the interpretation of within-person or within-group changes. The confirmatory RCT succumbed to the same pitfall associated with the misuse of MIC values for group comparison. In the initial sample size calculation, the between-group difference in pain outcome was powered for a MCID of 5 points, even though it subsequently turned out that using an MCID derived from minimal important improvements of within-group changes (MIC) to evaluate group differences was inadequate. Overall, the extant literature does currently not appear to provide appropriate MCID values for patients with knee OA receiving exercise treatment with regard to the PROMs pain and physical function that can be used to evaluate between-group differences. Consequently, it is currently not possible to classify the clinical relevance of the between-group differences in the RCTs (pilot and confirmatory) evaluated in this dissertation using MCID cut-offs. Accordingly, in the confirmatory RCT the alternative responder approach in a slightly modified design was employed, utilizing NNT and RRs for the interpretation of clinical relevance. Meanwhile NNT can be used for comparisons across studies of different treatments, but with a comparable diagnosis, RRs determine the likelihood of “response” between two treatment arms in a study (Smith et al., 2020). However, in contrast to Dekker and colleagues' recommendation to use MIC to determine the proportion of responders in the two comparison groups (Dekker et al., 2024), an anchor-based own responder criterion was used in the confirmatory RCT. This is of particular importance given that the proportion of responders form the basis for calculating RR and NNT. In doing so, transition questions were used as anchor questions and patients were able to indicate subjective changes of their OA-related health status overall, for pain, and for function compared to the status three months ago. These changes were assessed using a 5-point Likert scale. For the responder analysis, the answers were then dichotomized into two groups: improved (much better/somewhat better) and not improved (unchanged/somewhat worse/much worse). Patients in the improved group were designated as responders, while the remaining patients were classified as non-responders. The RRs between the re.flex and usual care group and the NNT were used as effect measures. For each of the three transition scales, a statistically significant higher proportion of responders in the re.flex group compared to the usual care group was observed. It was shown that the risk for subjective improvement was between 2.1 and 2.7-fold in the re.flex group in comparison to usual care and NNT were 2.6 (overall), 3.3 (pain) and 3.4 (function). However, once more, the extant literature lacks clearly defined standards for NNT and RR cut-offs for the final evaluation of the clinical relevance associated with the treatment of patients with knee OA. Nevertheless, subsequently, these findings from the embedded confirmatory RCT will attempted to be situated according to similar studies with a comparable

intervention design and patient population. In this context, a self-directed web-based strengthening exercise and physical activity program for patients with knee OA has found slightly lower RRs than reported in our confirmatory RCT (2.1 vs 2.7 for overall change, 1.7 vs 2.1 for pain, 1.7 vs 2.2 for function) (Nelligan et al., 2021). However, a discrepancy emerges with respect to the data acquisition methods. The RRs for overall, pain, and function change in our confirmatory RCT derived from anchor-based patients' perceptions, whereas in the RCT conducted by Nelligan and colleagues (2021), the overall change derived from anchor-based patients' perceptions and the change in pain and function were based on MCID responder criteria (what would be in the above introduced terminology rather a MIC) derived from existing literature. This methodological discrepancy can potentially limit the comparability and generalizability of the findings. Furthermore, responder rates of the intervention group in our confirmatory RCT (54% to 61%) were slightly lower when compared to the range of 57% to 72% reported in the aforementioned RCT for the various domains. Nevertheless, given that our confirmatory RCT documented a lower number of responders in the control group, the RRs were still higher. Moreover, NNT in our confirmatory RCT were smaller than NNT reported in the 2015 Cochrane Review on land-based exercise therapy in knee OA derived from continuous variables (self-reported pain and physical function score on a scale 0-100, best to worst) (Fransen et al., 2015).

Consequently, even when between-group differences in our confirmatory RCT were small, a relevant proportion of participants in the re.flex group experienced patient benefits derived from the self-directed m-health exercise intervention. The findings of the responder analysis, NNT, and RRs in conjunction with the high adherence rate and the minor adverse events imply that at least with respect to pain reduction, the observed findings could be classified as clinically relevant. With regard to physical function, the between-group differences were not statistically significant in the confirmatory RCT, thus questioning their eligibility to be interpreted for clinical important improvements. In this context, it should be noted that the re.flex intervention is no one-size-fits-all solution and not all patients seemed to benefit in the same manner. This observation was corroborated by the results of the responder analysis (considering the proportion of patients in the non-responder group), as well as the fact that some of the patients also encountered minor exercise- and app-related adverse events and expressed dissatisfaction, suggesting that they would require more supervised and individualized treatment. Accordingly, personal context factors should be considered when choosing the most suitable delivery mode for exercises. Ultimately, re.flex was not permanently listed in the DiGA directory in Germany, as the clinical relevance was questioned by the decision-making committee. Notably, this decision is also of societal value, as exercise is recommended as a

first-line treatment for patients with knee OA (Conley et al., 2023), and digital health apps could address the undersupply of current healthcare treatment options. At present, there is a lack of consensus from both regulatory and scientific viewpoints concerning the establishment of defined standards for evaluating the clinical relevance of between-group differences in non-surgical interventions among patients diagnosed with knee OA. Accordingly, and in view of the fact that the discussion of clinical relevance is a recurring issue in the extant literature, there is an urgent need for the development of precise criteria for clinical relevance in conservative OA therapy in the future.

Summary chapter 5.2

In clinical studies, statistical significance does not necessarily imply clinical relevance for an outcome. However, the interpretation of clinical relevance in current literature is challenging, as there exists considerable inconsistency in the terminologies (MIC, MID, MCID) and calculation methods (distribution-based, anchor-based, consensus-based) used to determine minimal important change or difference. As a result, establishing reliable standards is complicated. While responder criteria and MIC values are applied to within-person or within-group changes, MCID thresholds or cut-offs for RR and NNT can be used for between-group differences. However, the current use in the extant literature is frequently not appropriate, as the MIC approach is misused to interpret a between-group difference for which it is not suitable. Furthermore, despite the fact that MIC and MCID values are highly dependent on context variables (e.g. patient characteristics, clinical conditions), some meta-analyses have calculated thresholds derived from heterogeneous interventions ranging from non-surgical to surgical methods. In general, in current literature, appropriate MCID values to evaluate clinical relevance in PROMs pain and physical function for group comparisons in patients with knee OA receiving conservative treatment are not available. Against this background, the present dissertation employed a responder approach in the confirmatory RCT, using patient-reported transition questions (in domains overall, pain, and function) as anchors to calculate RRs and NNT. The results demonstrated significantly higher responder rates in the re.flex group compared to the usual care group, with RRs ranging from 2.1 to 2.7 and NNTs between 2.6 and 3.4. In the context of knee OA, research findings indicated that RRs were slightly higher than those observed in a comparable study on a self-directed web-based strengthening exercise and physical activity program, and NNTs were found to be smaller than those reported in the 2015 Cochrane review on land-based exercise therapy. However, methodological differences in responder definitions may potentially limit direct comparability with the aforementioned references. In conclusion, despite the between-group differences in pain and physical function observed in the confirmatory RCT were small, a relevant proportion of

patients in the re.flex group experienced a clinical benefit derived from the self-directed m-health exercise intervention. Of course, there were also patients who seemed not to benefit in the same manner, indicating that the re.flex intervention is no one-size-fits-all solution. Yet, based on a multifactorial evaluation including the responder analysis, RRs, NNT, high patient adherence, and the low number of minor adverse events, it can be concluded that the observed findings could be classified as clinically relevant, at least in terms of pain reduction. Nevertheless, the re.flex intervention was not permanently listed in the DiGA directory in Germany, as the clinical relevance was questioned by the decision-making committee. This decision may align with two meta-analyses which also previously cast doubt on the clinical importance of exercise-related treatment effects in pain and physical function. However, at present, there is no established standard against which the clinical relevance of between-group differences in conservative OA therapy can be assessed. Accordingly, there is an urgent need for the development of precise and context-specific criteria for future evaluations.

5.3 Strengths and limitations

This chapter will discuss the strengths and limitations of the included studies in this dissertation. A critical analysis of the strengths and limitations is essential for the interpretation of the results and the conclusion of this work.

Firstly, an overview of the strengths and limitations of the two RCTs (study 1 and study 3) will be provided.

Sample size

A notable strength of the confirmatory RCT was its large sample size, whereas this was a limitation in the pilot RCT. Consequently, the findings of the pilot RCT may lack generalizability due to the limited sample size. However, the primary objective of pilot studies should not be the attainment of statistical significance, but rather the acquisition of early insights into the research question, study design, and intervention.

Missing values

In both RCTs only few missing outcome data (<10%) were observed. However, only the confirmatory RCT implemented a rigorous statistical analysis, incorporating jump-to-reference for multiple imputation and conducting various sensitivity analyses (intention-to-treat, complete case, per protocol, last (=baseline) observation carried forward), to substantiate the robustness of the findings. In the pilot RCT, only a complete case analysis without the imputation of missing values was conducted as the primary analysis. At least, sensitivity analyses (last observation (=baseline) carried forward, mean imputation method) did not reveal significant

differences. However, it must be mentioned that the last observation carried forward method is no longer state of the art and multiple imputation is the current standard.

Lack of blinding

Due to obvious group assignments, there is a lack of blinding of participants. Consequently, in both RCTs, a reporting bias of self-reported outcome measures cannot be ruled out.

Assessment of adherence data

A strength of both RCTs was the use of motion sensors to collect accurate data on adherence to exercise.

External validity

A high degree of external validity of the trial findings can be assumed in both RCTs. The baseline characteristics (e.g. age, sex, BMI) and baseline outcome measures for pain and physical function align with those of an IPD meta-analysis with more than 4240 participants with knee and hip OA (Holden et al., 2023). This indicates that findings should be generalizable to other OA patients with similar disease severity in predominantly industrialized countries. However, as eligibility required a pain score of <60 (out of 0-100, worst to best), findings may not be generalizable to individuals with milder symptoms.

Selection bias

The baseline data demonstrate higher educational levels and a relatively small proportion of foreigners in comparison to the age-equal native German population in the study sample of both RCTs. Consequently, a selection bias towards socio-demographic characteristics cannot be excluded.

Randomization process

The risk of randomization bias was minimized in both RCTs, resulting in well-balanced baseline characteristics between study groups.

Reported results

In the confirmatory RCT, the risk of bias in the selection of reported results can be excluded, as the analysis was conducted according to the pre-specified published study protocol. The pilot RCT was pre-registered, but a study protocol was not published.

Deviations from intended interventions

The confirmatory RCT exhibited a low risk of bias related to deviations from the intended interventions, as concomitant treatments during the intervention period were comparable in

both groups. Concomitant treatments in the pilot RCT were assessed retrospectively and only for medication intake at the follow-up of the study.

Exercise intensity

In both RCTs, it is possible that the exercise intensity at which the participants exercised was insufficient to trigger adaptations in muscle gains. The values recorded for perceived exertion during the exercise sessions indicated moderate to somewhat strenuous intensity levels. However, an efficacious training load would be considered to be within a strenuous to very strenuous range. This could also have affected outcomes related to pain and physical function.

MCID

With regard to the confirmatory RCT it must be acknowledged that using a MCID derived from minimal important improvements of within-group changes to evaluate between-group differences was inadequate.

Subsequently, strengths and limitations associated with the qualitative study will be addressed.

Data collection

All participants completed interviews within 2–5 weeks after completing the intervention, ensuring better recall of the mobile app and the exercise program.

Investigator triangulation

The development of themes and subthemes was conducted independently by two researchers and subsequently reviewed and discussed by a third researcher.

Reflexive strategies and reliability

The incorporation of audio-recording, investigator triangulation, and reflexivity strategies (e.g. documentation sheets) in the research design served to increase the reliability of the findings.

Researcher bias

The researcher who developed the coding system was not involved in the design of the study or the collection of the data, thereby reducing the risk of bias.

Interview design

The conduction of telephone interviews may have limited the depth of information and led to superficial responses due to the absence of personal interaction.

Data saturation

The sample size was determined a priori. Despite this limitation, both inductive and a priori thematic saturation could be confirmed in the dataset.

Selection bias

A selection bias is possible, as no purposive sampling (e.g. based on age, sex, technical affinity, positive or negative outcome) was conducted. This may limit the generalizability of the findings, as certain patient characteristics could be underrepresented in the study sample. Moreover, participants self-selected to participate in the related RCT. This may have indicated an existing interest in digital exercise programs, which could have led to a more positive attitude toward the use of digital technologies.

Researcher involvement

Two researchers were involved in the development of the exercise program and the data collection of the RCT, which could have affected the findings.

6 Conclusion and implications for practice and future research

The four research articles included in this dissertation provide evidence for the superiority of the self-directed sensor-based m-health exercise program re.flex in comparison to usual care among patients with knee OA. The findings demonstrated statistically significant and clinically relevant improvements in pain reduction. In this context, the responder analysis in the confirmatory RCT identified a relevant proportion of patients in the re.flex group which experienced a clinical benefit derived from the self-directed m-health exercise intervention. However, despite the promising results observed in the pilot RCT, the improvements in physical function could not be confirmed in the confirmatory RCT conducted with a larger sample size. With regard to subgroup analyses from the confirmatory RCT, concomitant care (e.g. physiotherapy, NSAID) did not positively influence the effects derived from the re.flex intervention. Furthermore, the high adherence rates, usability, and satisfaction with the exercise app that has been demonstrated in all three studies, indicate that the implementation of a self-directed digital-delivered exercise program is well-accepted by the majority of patients. In particular, the ease of use, comprehensibility, flexibility, and certain app features (e.g. push-notifications as reminders, instructional videos, real-time biofeedback) appeared to facilitate guidance, control, and motivation to engage in digital exercise participation. Moreover, the re.flex intervention can be regarded as safe, with no reports of serious adverse events. Nevertheless, the occurrence of minor adverse events and dissatisfaction in some patients, as well as the observed proportion of non-responders, reveal that self-directed digital exercise interventions are no one-size-fits-all solution. For future practice, when selecting an appropriate treatment option for patients with knee OA, it is essential to consider the personal context factors, patients' prerequisites and needs. In particular, as some patients have lacked human support, there is a growing need for hybrid forms of digital health interventions. For instance, the combination of an m-health-based exercise program with initial sessions conducted by a physiotherapist might be a conceivable option. Regrettably, despite the potential of digital exercise interventions to enhance accessibility to effective and safe first-line treatments, to date, no DiGA specifically designed for patients with knee OA is reimbursable in Germany. Unfortunately, the intervention re.flex was also rejected for inclusion in the DiGA directory by the evaluating federal ministry. Nevertheless, the studies included in this dissertation make a significant contribution to further improve evidence in the field of self-directed app-based exercise delivery in knee OA by providing high-quality data in a domain where few studies of low quality are currently available.

In the future, research should further focus on a better understanding of responder characteristics, identifying subgroups of people who may benefit most, and determining the

optimal exercise type, dosage, and delivery mode for these groups (for this purpose the data of the pilot and confirmatory RCTs could also be used). In this context, it would be important to develop selection criteria that allow for the accurate allocation of patients to the most suitable exercise intervention, ranging from digital self-directed over digital supervised to traditional face-to-face treatment. In this regard, a stepped-care model in which individuals move through a hierarchical sequence of evidence-based interventions depending on their treatment success is also a conceivable approach. Additionally, further high-quality evidence distinguishing between self-directed and supervised digital exercise programs must be obtained. Moreover, as the discussion of clinical relevance is a recurring issue in research and a number of inadequate MCIDs can be found in the extant literature, there is an urgent need for the development of precise criteria to determine which outcome improvements for between-group differences can be rated as clinically relevant in conservative OA therapy. Finally, in order to further optimize the re.flex exercise intervention, the implementation of an automated feedback system that reacts to exertion and pain levels from previous exercise sessions could lead to a more individualized and tailored exercise intervention. The implementation of educational information (e.g. by providing knowledge on the exercise regimen and adjustments that should be made for appropriate exercise intensity) could further improve the effectiveness.

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Affidavit

I hereby declare that I have independently written the dissertation submitted for doctoral qualification entitled 'Self-directed m-health exercise interventions for patients with knee osteoarthritis: Insights from a mixed methods evaluation', using only the indicated sources and aids, and that I have clearly marked any passages taken verbatim or in content as such.

I declare under oath that this information is true and that I have not concealed anything. I am aware that making a false declaration under oath is punishable by imprisonment for up to three years.

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Place, date, signature