MOVING FORWARD

Towards a proactive, integrated and blended care intervention in patients with moderate medically unexplained physical symptoms

SUZE TOONDERS

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Een stap vooruit
Richting een proactieve, geïntegreerde en blended interventie voor patiënten met matige somatische onvoldoende verklaarde lichamelijke klachten

(met een samenvatting in het Nederlands)

Proefschrift

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Promotor:

Prof. dr. C. Veenhof

Copromotoren:

Dr. M.F. Pisters

Dr. P.E. van Westrienen

Beoordelingscommissie:

Prof. dr. J. Nijs

Prof. dr. J.J. van Os

Prof. dr. R.W.J.G. Ostelo

Prof. dr. F.E. Scheepers

Prof. dr. T.J.M. Verheij

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‘Not everything that is faced can be changed.
But nothing can be changed until it is faced’

– James Baldwin

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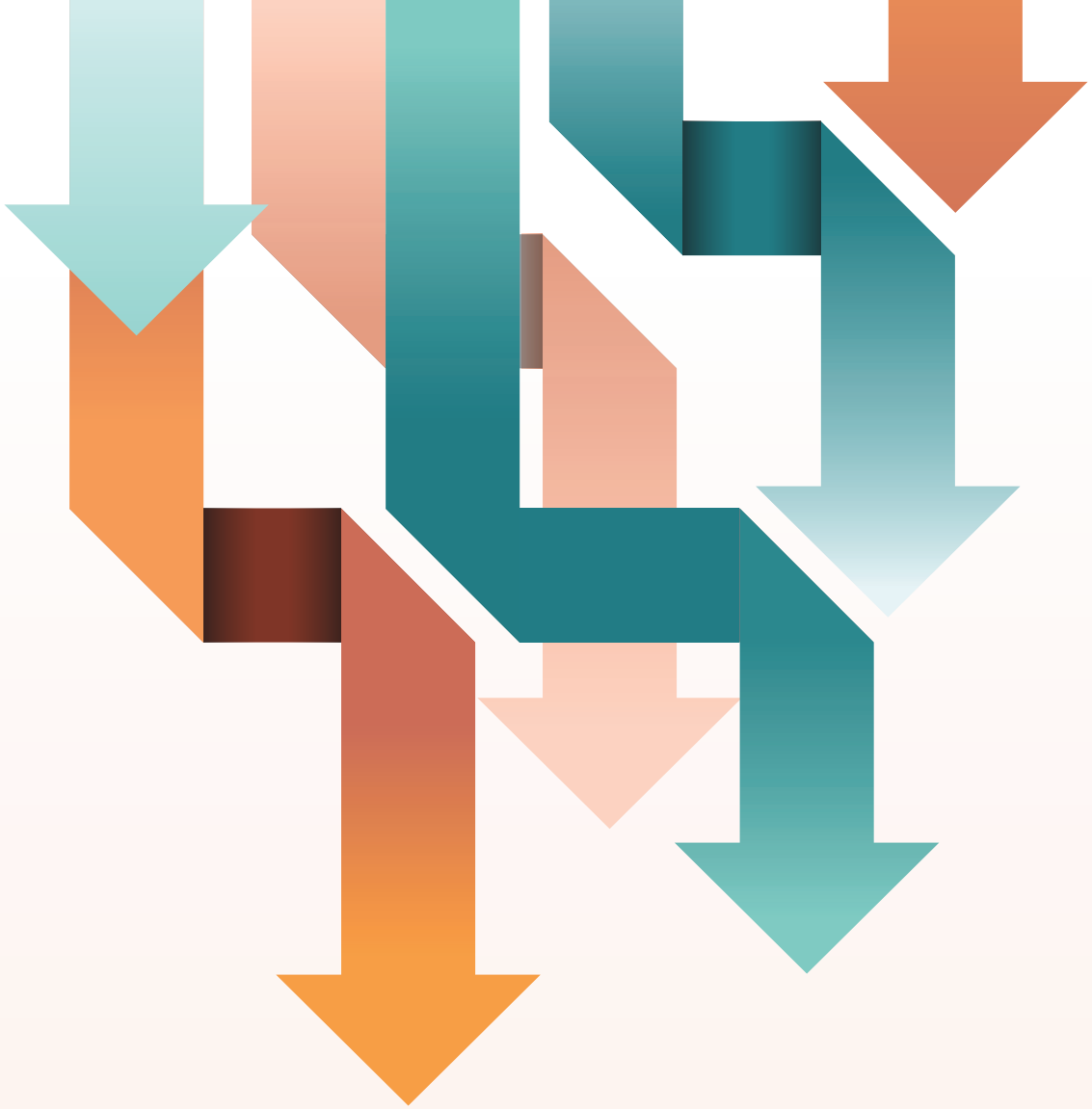

CHAPTER 1

General introduction

A TRANSITION IN HEALTHCARE: MOVING FROM CURE AND CARE TOWARDS BEHAVIOR AND HEALTH

With rising healthcare costs, an aging society and technological innovations that offers more opportunities, healthcare in the Netherlands is facing a challenge to keep healthcare accessible and affordable with a good quality of care [1]. To meet these challenges, policy in the Netherlands is aimed at changing the way healthcare is organized, moving from cure and care to behavior and health [2].

This transition in healthcare requires organizational changes and the development of innovative, proactive and preventive treatments [3]. Such treatments strive to engage patients early, enabling professionals and patients to work together to address health issues before they become chronic [4]. This can improve patient outcomes through lifestyle changes, with the use of self-management. Self-management refers to the patient's ability to cope with the physical, psychological and social consequences of a condition and associated lifestyle changes in conjunction with the social environment [5]. The use of eHealth can be of support, defined as the delivery of personalized healthcare at a distance through the use of technology [6]. There are different ways eHealth can be implemented: as an addition to face-to-face care (i.e. blended care), or as a complete replacement for physical consults [7,8].

This dissertation studies a newly developed innovative approach to care for patients with moderate Medically Unexplained Physical Symptoms (MUPS). For this patient group, the transition in healthcare has been translated into a proactive, integrated, blended care intervention in which self-management is stimulated with the aim of preventing chronicity of complaints. The moderate MUPS population has a high prevalence in primary care, while little research has been done into the prevention of their chronic complaints. Furthermore, as of date there is no appropriate treatment to reduce the burden for these patients, thereby also straining healthcare professionals and leading to high healthcare and societal costs. Research questions in this dissertation determine the effectiveness of remote eHealth interventions in general and show the extent to which a specific proactive, integrated, blended care intervention is of added value, both from the viewpoint of effectiveness and of efficiency. Secondly, it seeks to find out how such an intervention is implemented in daily practice, gathering the experiences of involved patients and healthcare professionals. Finally, it asks whether it is possible to distinguish clusters of patients with similar characteristics, using in-depth analyses of gathered data on self-management skills and movement behavior.

MEDICALLY UNEXPLAINED PHYSICAL SYMPTOMS (MUPS)

Most people at times experience physical symptoms such as pain, fatigue or dizziness [9]. Surveys show that approximately 90% of the Dutch general population experienced at least one physical symptom in the past two weeks [10]. While in most cases symptoms disappear spontaneously, in certain cases symptoms persist for a few weeks or even months without having an identifiable underlying explanation after examination [11]. Whether people visit their general practitioner with concerns about these symptoms is strongly related to the impact on daily life and ideas about these symptoms [10]. A common classification among patients identified with MUPS based on the frequency of consulting a general practitioner, the duration of symptoms, and the physical and psychological dysfunctions experienced, are mild, moderate, and chronic [12]. Patients with mild symptoms usually improve within 2 weeks [13] and have an estimated prevalence of 70 – 80% in primary care [12,14]. Patients with moderate symptomatology have an estimated prevalence of approximately 15% and mostly still experience symptoms after three months [13]. Patients with chronic symptoms typically experience symptoms for at least 6 months and are diagnosed with a functional somatic syndrome (i.e. fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome) or a somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th edition [12,15]. The prevalence of chronic MUPS in primary care is approximately 2.5% [16]. MUPS often goes along with maladaptive cognitions, emotions and behavior and are more common when patients are concerned and develop negative catastrophizing beliefs [17,18,19]. Theories on developing MUPS are based on symptom perception, somatic causes, illness behavior and predisposition [20]. MUPS can have a high impact on quality of life and daily functioning, impairing social, physical and psychological functioning [14,21].

In comparison with other patient groups, the quality of life of patients with MUPS is among the poorest [21]. A previous study found differences in quality of life between patients with moderate and chronic MUPS, also when compared to the general population. Although patients with moderate MUPS experience a higher quality of life compared to patients with chronic MUPS, their quality of life is worse when compared to the general population [22].

The extensive use of healthcare services by patients with chronic MUPS is associated with high societal costs [23,24]. These are associated with receiving, often unnecessary, diagnostic procedures and medication [25,26]. The use of inpatient and outpatient care is approximately twice as high in patients with chronic MUPS compared to patients without

MUPS [27]. Societal costs are further increased by the high levels of presentism and absenteeism related to MUPS [28]. The average total societal cost per patient with MUPS is estimated at EUR 6,815 per year [29]. Prevention of the development of chronic MUPS is therefore important from a societal cost-perspective.

EARLY IDENTIFICATION AS A FIRST STEP

Proactive and preventive healthcare aims to prevent illness, decrease the burden of disease and/or associated prognostic risk factors [30]. A first step in proactive and preventive care is identification and selection: patients who are at risk for developing chronicity of complaints [31]. Timely diagnosis of moderate MUPS can contribute to preventing chronicity, requiring early identification by the GP. However, for GPs identification of patients with MUPS is challenging [32]. GPs often experience frustration and stress during consultations out of fear of missing a serious medical illness [32]. Proactive periodical screening of electronic medical records provides a quick overview of patients at risk, and could support the GP in timely diagnosis by identifying patients with characteristics of MUPS. This efficient identification technique is referred to as 'panel management'. Panel management is the combination of risk assessment, followed by a proactive and preventive intervention [31]. The focus of care then shifts from patients consulting their GP with their health problems to GPs proactivity approaching patients at risk, whether or not these patients seek care. The PRESUME screening method allows patients with moderate MUPS to be identified using electronic medical records of the GP [33]. This screening method selects patients in three steps: firstly, selecting only patients of 18 years or older, with at least five general practice consultation in the past twelve months. Subsequently, among these patients, those with medical and/or psychiatric diagnosis (i.e. chronic obstructive pulmonary disease, hypertension or diabetes mellitus; schizophrenia, anxiety disorder or depressive disorder) were excluded. Finally, remaining patients were identified with an increased risk of mild or moderate MUPS, based on the presence of MUPS related symptoms, or chronic MUPS, based on an established chronic MUPS diagnosis (e.g. fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome). All other patients were considered as non MUPS patients.

THE ROLE OF EHEALTH

EHealth has the potential to improve access to healthcare services, can make healthcare professionals work more efficiently, contribute to improve quality of life of patients and decrease healthcare costs [6]. Despite the potential of eHealth, challenges remain, as there

is still uncertainty about the effectiveness in different populations [34,35]. Furthermore, often overlooked are strategies to implement eHealth initiatives in daily practice [36]. Online intervention cannot only support usual therapeutic guidance, but can also be integrated as a substantial element of interventions [37,38], so called blended care. Personal attention of a healthcare professional in face-to-face treatments next to an accessible online tool is seen as highly promising, as it can stimulate patients to take an active role in their disease management [39]. For instance, preparation can be done independently online, and questions can be discussed at face-to-face meetings with healthcare professionals.

The first study in this dissertation seeks to add more knowledge about the effectiveness of remote physical therapy eHealth interventions on pain in patients with musculoskeletal disorders and explore the relative proportion of face to face treatments and eHealth, when eHealth is integrated in treatment.

TREATING PATIENTS WITH MODERATE MUPS

So far no effective preventive interventions for patients with moderate MUPS in primary care exist, partly due to the fact that adequate methods for early identification are lacking. Existing literature focuses on effective interventions for patients with chronic MUPS [40,41,42]. Here, frequently used management strategies are information and explanation, medication, cognitive behavioral therapy, physical therapy and exercise therapy [43]. Neurosciences-based therapeutic education, cognitive behavioral therapy, and exercise therapy have also been shown to be effective treatment modalities in patients with chronic MUPS [44]. This literature also shows combining physical and mental health interventions is a promising approach, and shows it may be more effective than monotherapy, since patients with chronic MUPS are generally not willing to accept only psychological interventions [45]. To gain more insights into themes which should be integrated in an intervention for patients with moderate MUPS, a qualitative study with GPs, physical therapists, mental health nurses and healthcare psychologists was performed [46]. This led to the following major treatment modalities: 1) coaching to a healthier lifestyle, 2) education regarding psychosocial factors, 3) therapeutic neuroscience education, 4) multidisciplinary intake, 5) multidisciplinary cooperation and coordination, 6) relaxation or body awareness exercises, 7) clear communication by professionals to the patients and 8) graded activity.

In sum, a treatment for patients with moderate MUPS is lacking. Based on the above modalities, this dissertation sets out to develop a proactive, integrated and blended care

approach for patients with moderate MUPS, as well as study its short- and long-term effectiveness. Furthermore, it seeks to study the cost-effectiveness of this intervention, as early treatment can prevent high costs for society.

END-USER EXPERIENCE

An innovative intervention requires a strategy for implementation in daily practice, often lacking. Attention should be paid to the experiences, expectations and needs of end users [47], here both patients and health care professionals. This can increase the effectiveness of an intervention, as it helps determining which problems end users experience, which improvements can be made, and can better tailor interventions to the patient's needs [48]. Also, when implementing an innovative intervention, experiences, expectations and needs of healthcare professionals are of importance, as much is often asked of them, requiring them to change their healthcare delivery from a traditional expert to a patient-centered approach [49], thus shifting from a therapist role to being more of a coach [50].

Given this importance of the experiences of end users, this dissertation hence sets out to understand barriers and facilitators from both patients' and healthcare professionals' perspective with regards to the usability of the proactive, integrated blended care intervention in patients with moderate MUPS.

IDENTIFYING PATTERNS

In general, the effectiveness of self-management interventions for patients with chronic MUPS are often found to be high in the short term, yet have no sustainable long-term effects [51,52]. A possible explanation for these disappointing results might be that these interventions generally target a heterogeneous population [53]. Patients with MUPS (mild, moderate and chronic) vary greatly in their abilities and limitations, goals, and lifestyle and therefore can benefit from guidance that is tailored to their specific needs [54]. Tailoring to these patients' specific needs can significantly contribute to their motivation, self-efficacy, and adherence [55].

Hence, this dissertation seeks to distinguish groups of patients with moderate MUPS according to self-management skills and movement behavior to better grasp the heterogeneity of this patients population. Such knowledge on subgroups based on self-management skills and movement behavior patterns is currently lacking, and direction for better tailoring treatment on these outcomes is hence also lacking.

OBJECTIVES AND OUTLINE OF THIS THESIS

This dissertation aims to add knowledge on the evaluation of effectiveness and experiences of a proactive, integrated and blended care intervention in a randomized clinical trial in primary care for patients with moderate MUPS. The second aim was to identify subgroups based on patterns in self-management skills and movement behavior.

Chapter 2 provides insight in the effectiveness of physical therapy eHealth interventions on pain in patients with musculoskeletal complaints. This systematic review gave a broad understanding of the role of eHealth in treatment for patients with chronic pain conditions, which accounts for a large proportion of patients with moderate MUPS. **Chapter 3** contains a protocol of the development of an indicated blended care intervention in primary care for patients with moderate MUPS with the aim to prevent chronicity (PARASOL). In **chapter 4** we present data on the short- and long-term effectiveness of the PARASOL intervention compared to usual care. In a multicenter randomized clinical trial we evaluated the effectiveness of the PARASOL intervention on subjective symptom impact and quality of life. In **chapter 5** we present the results of the cost-effectiveness of the PARASOL intervention compared to usual care from a societal and healthcare perspective. **Chapter 6** includes the patients' perspective on the implementation of a proactive, indicated blended care intervention to gain more understanding on their usability. **Chapter 7** describes the concept of usability from the healthcare's professional perspective. To gain more insight in subgroups, we present data in **chapter 8** on the identification of patterns in self-management skills and compare these on the patient reported outcome measures of physical functioning, pain and fatigue. In **chapter 9** patterns in movement behavior and their related clinical variables are presented. Finally, **chapter 10** will summarize the main findings of this dissertation and discuss clinical relevance, methodological considerations and recommendations for clinical practice, future research and education. A summery in English and Dutch concludes this dissertation in **chapter 11**.

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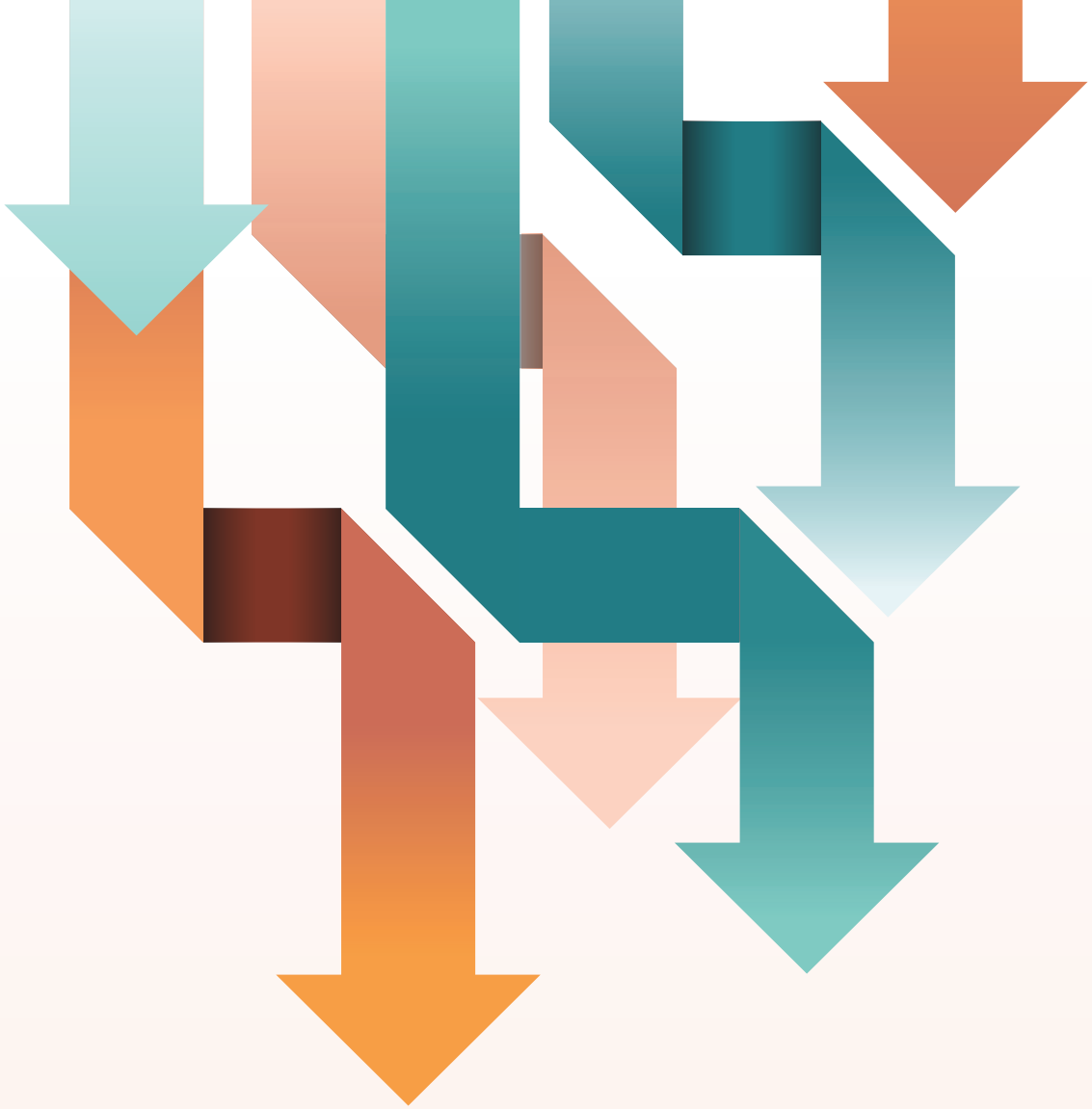

2

CHAPTER

Effectiveness of remote physiotherapeutic e-Health interventions on pain in patients with musculoskeletal disorders: a systematic review

Suze A. J. Toonders
Hedwig A. van der Meer
Thijs van Bruxvoort
Cindy Veenhof
Caroline M. Speksnijder

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ABSTRACT

Purpose

To systematically review the literature on effectiveness of remote physiotherapeutic e-Health interventions on pain in patients with musculoskeletal disorders.

Materials and methods

Using online data sources PubMed, Embase, and Cochrane in adults with musculoskeletal disorders with a pain-related complaint. Remote physiotherapeutic e-Health interventions were analysed. Control interventions were not specified. Outcomes on effect of remote e-Health interventions in terms of pain intensity.

Results

From 11,811 studies identified, 27 studies were included. There is limited evidence for the effectiveness for remote e-Health for patients with back pain based on five articles. Twelve articles studied chronic pain and the effectiveness was dependent on the control group and involvement of healthcare providers. In patients with osteoarthritis (five articles), total knee surgery (two articles), and knee pain (three articles) no significant effects were found for remote e-Health compared to control groups.

Conclusions

There is limited evidence for the effectiveness of remote physiotherapeutic e-Health interventions to decrease pain intensity in patients with back pain. There is some evidence for effectiveness of remote e-Health in patients with chronic pain. For patients with osteoarthritis, after total knee surgery and knee pain, there appears to be no effect of e-Health when solely looking at reduction of pain.

INTRODUCTION

Musculoskeletal disorders contain over 150 diagnoses from the locomotor system and are prevalent in over 50% of the adult population [1,2,3]. The global disability-adjusted life years (DALYs) for musculoskeletal disorders increased by 61.6% between 1990 and 2016, making this the second largest problem in terms of years lived with disability [1]. Pain is the most common complaint in patients with a musculoskeletal disorder. This musculoskeletal pain leads to a decrease in functioning on daily basis [4].

Physiotherapists are specialized in treating musculoskeletal disorders and support patients to increase their daily functioning [5]. The focus of physiotherapeutic treatment in patients with musculoskeletal pain is on offering individualised patient care to develop strategies for managing pain, rehabilitate and restore physical function by delivering education, exercises, and encouragement to engage in regular physical activity [6]. Physiotherapists may use e-Health in their treatment, as e-Health can serve as a supportive tool for education, exercises, and encouragement [7].

E-health can be defined as the delivery of personalized healthcare at a distance through the use of technology [8]. This technology can be computers and mobile phones, but also satellite communications [9]. When smart or portable devices are specifically used, for instance using mobile applications, this often is referred to as mobile health (mHealth) [9]. Besides the mode of delivery (i.e. computer, mobile, tablet), the moment of delivery can also vary. For instance, e-Health can be used in both the diagnostic process (e.g. intake, questionnaires) [10] and therapeutic process (e.g. videoconferencing, online exercises, education) [11,12,13,14]. The types of e-Health interventions vary from interactive websites, to internet delivered programs, and to mobile applications. Furthermore, there are different ways e-Health can be implemented: as an addition to face-to-face care (i.e. blended care), or as a complete replacement for physical consults [13,15,16].

In several countries including the Netherlands during the 2019 novel coronavirus (COVID-19) pandemic [17,18], all physiotherapeutic care had to be offered at distance. By applying remote e-Health tools, patients with (chronic) pain still received care during this pandemic. From the available literature it is known that e-Health generally can be just as effective or slightly more effective than usual face-to-face care [19,20]. However, the challenge remains the uncertainty about the effectiveness in different populations [18,19,21]. It is currently still unknown what the effectiveness is of these remote e-Health interventions on patients with musculoskeletal pain-complaints. Therefore, the aim of this study was to systematically review the literature on the effectiveness of remote physiotherapeutic e-Health interventions on pain in patients with musculoskeletal disorders.

METHODS

Protocol and registration

Reporting of this review has been done according to PRISMA recommendations [22], and is registered on PROSPERO (registration number CRD42018055386).

Eligibility criteria

Randomized controlled trials of remote physiotherapeutic e-Health interventions in adults with complaints of the musculoskeletal system were included. Inclusion criteria for the studies applied were: 1) the primary or secondary outcome measure had to be pain related (e.g. pain intensity, pain days, pain-related disability); and e-Health interventions must be: 1) remotely transmitted, 2) applied within the field of physiotherapy for patients with musculoskeletal complaints. The inclusion criteria show that interventions that are within the physiotherapeutic domain (e.g., counselling, exercises) [23] are included as long as patients do not go to the clinic to receive their physiotherapeutic treatment, but their physiotherapeutic treatment is given at distance through an e-Health application (interactive websites, internet delivered programs, video consultations or mobile applications). The therapy could consist of exercises, [24] pain education [25,26] or any other intervention that aimed at decreasing pain-related complaints, for example encouragement to engage in regular physical activity.

Exclusion criteria applied were: (1) the e-Health intervention is a complement to usual face-to-face physiotherapeutic care (e.g. blended care), (2) the e-Health intervention is not patient-oriented (i.e. educational intervention for healthcare professionals), (3) the outcome measures were incomplete for baseline or follow-up, (4) the full text article is not available in English or Dutch, and (5) feasibility studies of e-Health.

Information sources

Literature searches were performed in the electronic databases PubMed [1966 – 2022], Embase [1947 - 2022], and Cochrane [1898 – 2022] to identify randomized controlled trials examining the effects of e-Health interventions on patients with musculoskeletal complaints. Database searches were performed on February 25, 2022.

Search

Combinations of keywords, free text and medical subject headings related to telemedicine, Internet, e-Health interventions, musculoskeletal disorders and physiotherapy were the

core of the search strategy. The search strategy was developed in PubMed (see Appendix 1) and thereafter fitted for other online databases. Keywords and medical subject heading terms used in the search were: (1) e-health OR e-Health OR web OR Internet OR online OR computer OR telemedicine OR telerehabilitation, AND (2) musculoskeletal disorders OR physiotherapy, AND (3) intervention OR randomized controlled trial. Screening of articles was done by two researchers (HvdM, ST), a third researcher (CMS) screened those articles with no consensus independently to be included or excluded. The process of screening was based on relevance and pre-set inclusion and exclusion criteria. References of remaining articles were screened for additional studies. The search results were downloaded in a database created using Covidence [27].

Study selection

Inclusion criteria were applied to the titles and abstracts of all retrieved records by two researchers blinded for each other's results (ST, HvdM) after removal of duplicates. For eligibility this process was repeated for full text screening of the remaining articles. A third reviewer (CMS) made the decision regarding inclusion of the article when the two reviewers did not reach consensus.

Data collection process, data items and summary measures

Two reviewers (ST, TvB) performed data extraction from the included articles. A third reviewer (HvdM) checked the extracted data for accuracy. The following key data were extracted from the included articles: (1) study characteristics: sample size; (2) participant characteristics: age and gender; (3) intervention & control characteristics: type of (control) intervention(s), frequency, follow-up of interventions; and (4) outcome measures. For the follow-up data the longest available term was included in this systematic review. Mean and standard deviations were derived from the included studies, where possible, for further statistical analysis. When the p-values for the between-group results were not available, these were calculated using the mean and standard deviations from the publication.

Risk of bias in individual studies

The Cochrane 'risk of bias' (RoB) tool assessment was used to assess the risk of bias of the included studies. The RoB tool assesses whether a study has high, low or unclear risk of bias, which may influence study validity, across six domains [28]. The tool does

not lead to a quality score but solely focuses on internal validity [28]. Two researchers (HvdM, ST) assessed the methodological quality and risk of bias independently. In case of disagreement, a third reviewer (CMS) made the decision. Results of the RoB assessment were also presented graphically individually and in a summary graph using Review Manager (RevMan) [29]. For the assessment of methodological quality, the Physiotherapy Evidence Database scale (PEDro) was used. The PEDro scale is a valid instrument to measure the methodological quality of clinical trials [30]. The PEDro scale consists of 11 items of which ten of the items assess the internal and/or external validity of the article [31]. The sum score of the ten items is used to rate the methodological quality of the article. An article can score a 9 to 10 (excellent); 6 to 8 (good); 4 to 5 (moderate); or 0 to 3 (poor) [31].

Synthesis of results

Meta-analysis of the results was not possible due to heterogeneity. So, the evidence was weighed based on the present methodological quality of the included studies. A best evidence synthesis was applied, based on the criteria as described by van Tulder et al. (see Table 1) [32]. The synthesis of the between-group results were described per patient population, as well as the level of involvement of the healthcare provider in the intervention group. This level could be when patients had online interactions with their healthcare provider, described as minimal involved, or when patients had no interaction at all with their healthcare provider. Finally, a distinction was made in the comparison of the intervention with the control group. The control group was subdivided into no care (eg, waiting list, assessment only) or usual care (eg, face-to-face treatment).

Additional analysis

For each study, within-group effect sizes were calculated according to the standard mean difference [33]. Effect sizes (ES) were classified as small (<0.20), moderate (around 0.50) or large (>0.80), according to Cohen's criteria [34]. For between-group analysis the p-value was calculated.

Table 1: Best Evidence Synthesis

Strong evidence	Provided by consistent, statistically significant findings in outcome measures in at least two high quality RCTs†
Moderate evidence	Provided by consistent, statistically significant findings in outcome measures in at least one high quality RCT and at least one low quality RCT or high quality CCT†
Limited evidence	Provided by statistically significant findings in outcome measures in at least one high quality RCT†, or provided by consistent, statistically significant findings in outcome measures in at least two high quality CCTs† (in the absence of high quality RCTs)
Indicative findings	Provided by statistically significant findings in outcome and/or process measures in at least one high quality CCT or one low quality RCT† (in the absence of high quality RCTs), or provided by consistent, statistically significant findings in outcome and/or process measures in at least two ODs with sufficient quality (in absence of RCTs and CCTs)†
No evidence	In cases of results of eligible studies that do not meet the criteria for one of the above-stated levels of evidence, or in case of conflicting results among RCTs and CCTs, or in case of no eligible studies

RTCs: randomized controlled trials; CCTs: controlled clinical trials; ODs: other designs.

† If the proportion of studies that show evidence is <50% of the total number of studies within the same category of methodological quality and study design (RCTs, CCTs or ODs), we state no evidence.

RESULTS

Study selection

The search strategy revealed 11,811 initial articles from PubMed, Pedro and Cochrane (see Figure 1). Two articles were identified through hand search. After removing double references, 10,424 titles and abstracts were screened for eligibility, resulting in 201 articles which were screened full-text. Finally, 27 articles were included [35-62], and 175 were excluded because inclusion criteria were not met on the study design (n=41), the patient population (n=44), the intervention (n=53), the outcome measures (n=19), or other reasons (n=18). A list of excluded references can be found in Appendix 2.

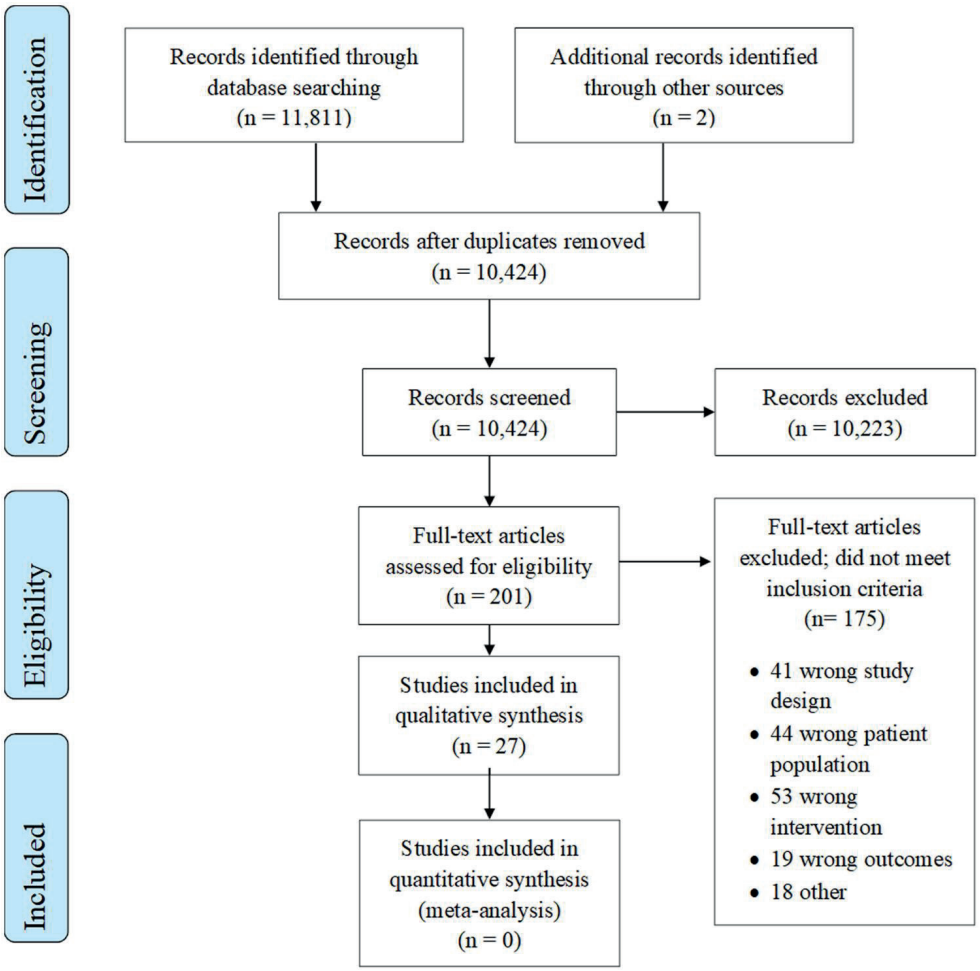

Figure 1: Flowchart of the study

Study characteristics

Overall, the intervention groups consisted of 2,311 patients with a range in age of 35 to 68 years (Table 2). Five articles focused on back pain [36,45,52,61,62], twelve on musculoskeletal chronic pain [38,40-42,46,48,51,53,57-60], five on osteoarthritis [35,43,44,47,54], two on total knee surgery [49,50] and three articles on knee pain [37,55,56]. Applied e-Health interventions were interactive websites (n=8) [36,38,40,46,47,49,52,62], internet delivered programs (n=15) [35,37,41-43,45,48,50,51,56-60] and mobile applications (n=5) [44,53-55,61]. Study duration ranged from 6 weeks to 12 months. Six studies [41,49,50,53,58,60] measured pain intensity by the Visual Analog Scale (VAS), a 100 mm

line (0 mm: no pain; 100 mm: extreme pain) [63]. Nine studies [35,37,38,42,43,54,56,57,61] measured pain intensity by the Numeric Pain Rating Scale (NPRS), an 11-point scale (0: no pain; 10: extreme pain). Two studies [36,46] used the pain severity subscale of the Multidimensional Pain Inventory (MPI) [64]. Five studies [40,48,51,59,62] used the Brief Pain Inventory (BPI) [65]. Furthermore, three studies [43,50,56] used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [66] pain subscale, one study used the Arthritis Impact Measurement Scale 2 (AIMS2) [67] pain subscale [47], one study [55] PROMIS pain and one study [44] used the Hip Disability and Osteoarthritis Outcome Score (HOOS) [68] and Knee Injury and Osteoarthritis Outcome Score (KOOS) [69].

Risk of bias and methodological quality within studies

Of the six bias domains assessed with the Cochrane RoB tool (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias), all except attrition bias had at least 25% unclear or high risk of bias (Figure 2). Attrition bias and detection bias had the lowest risk of interfering with the results, and detection bias had a 100% high risk of bias score throughout as patients were the outcome assessors for the outcome measure 'pain intensity'. Figure 3 depicts the RoB per domain for each individual study. All included studies scored a high risk of bias on at least two domains. Seven studies received a high risk of bias on three or more domains and they also had minimally one other domain with an unclear risk of bias [36,46,48,51,52,61,62]. Two studies did not have any low risk of bias scores [51,62].

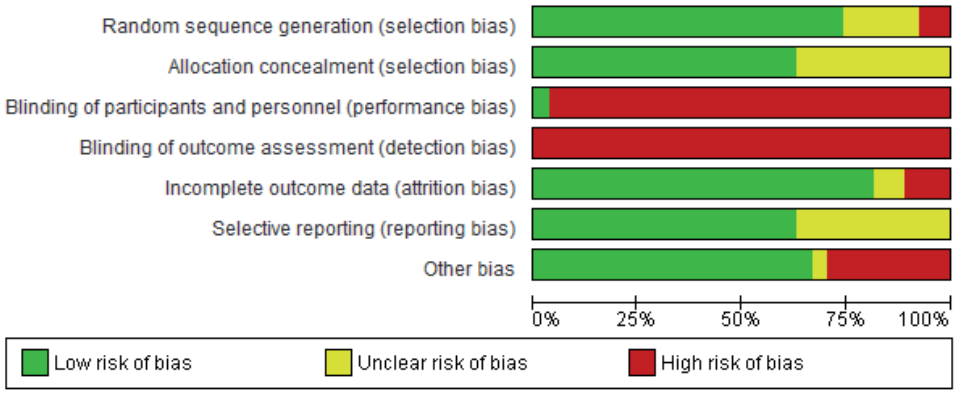

Figure 2: Risk of bias graph. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Created with RevMan 5.4.1.[29]

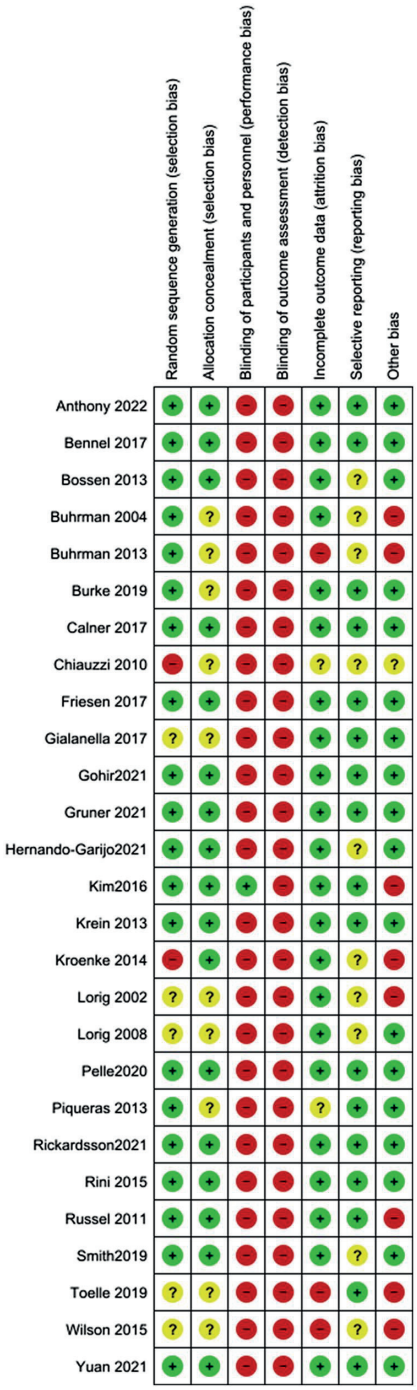

Figure 3: Risk of bias summary. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Created with RevMan 5.4.1.[29]

Table 3 depicts the PEDro scores per study. The scores for methodological quality ranged from 5 to 8 points, which indicates that all included studies are of moderate to good methodological quality. None of the studies, except for one [37], blinded the participants or therapists and all reported between-group statistical comparisons and point measures for key outcomes.

Results of studies per patient population

The results of the individual studies and the synthesis of the results are described below per patient population. The between-group effects are used for synthesis of the results as described in the methods. All results are depicted in Table 2.

Back pain

Three studies of moderate methodological quality [36,52,61] and two studies of good methodological quality [45,62] assessed the effectiveness of remote e-Health on pain intensity in patients with back pain. Three articles used the NPRS [45,52,61], one study used BPI [61], and one study used both MPI and the VAS through a pain diary [36].

Two studies [36,52] investigated minimally involved care through e-Health and compared their interventions to no care. One study [52] of moderate methodological quality investigated an interactive website which contained a closed moderated discussion group including a book and video about back pain, which was significantly effective on the NPRS compared to the control group [52]. The other study [36], also of moderate methodological quality, used an interactive website for an online self-help program with telephone support as intervention. Compared to the control group, there was no significant effect found on the MPI [36]. Due to inconsistent between-group findings, moderate methodological quality and high risk of bias was found in both studies [36,52]; there is currently no evidence that e-Health with minimal involvement of a healthcare provider is more effective than no care in patients with back pain.

Three studies [45,61,62] described full online programs without healthcare provider involvement. One study [45] compared a group receiving an internet delivered physical activity program where patients received activity trackers, with a group that would upload pedometer data and received email updates. This study was of high methodological quality, low risk of bias and found no statistical difference between both groups on the NPRS. Another study [62] compared an interactive website for an online self-help program to a back pain guide. This study was of good methodological quality, had a high

risk of bias and found a significant effect in favour of the intervention on the BPI. These two studies [45,62] compared the online intervention to reading material, but showed conflicting results. The third study [61] which was of moderate methodological quality and had a high risk of bias compared a mobile application to face-to-face physiotherapy and found a significant effect in favour of the mobile application. As this is a moderate quality study, there are indicative findings that e-Health is more effective than face-to-face therapy for patients with back pain.

Overall, there is limited evidence that remote e-Health is more effective than a control intervention on pain intensity in patients with back pain.

Chronic pain

Five studies [38,46,51,58,60] of moderate methodological quality and six studies [41,42,48,53,57,59] of good methodological quality and one article [40] of excellent quality assessed the effectiveness of remote e-Health in patients with chronic or persistent pain. Four studies [40,48,51,59] used the BPI total intensity score, one study [46] used the MPI, three studies [38,42,57] used the NPRS and the VAS was used in four studies [41,53,58,60].

Ten of the interventions used were online with no involvement of the healthcare provider and consisted of internet delivered programs or interactive websites with cognitive behavioural aspects [42,46,51,57,59], telecare management [41,48,53] or a self-guided web-based program [40,58]. Four studies [40,41,48.58] compared their intervention to face-to-face interventions, of which two studies [41,48] found a significant effect for the intervention group, but the other two studies [40,58] did not. Therefore, there is currently no evidence that remote e-Health without involvement of the healthcare provider is more effective than face-to-face interventions in patients with chronic or persistent pain [40,41,48,58]. Four other studies [42,51,57,59] compared their intervention to no intervention and three studies [42,57,59] found a significant difference, indicating that there is moderate evidence for the effectiveness of remote e-Health in patients with chronic or persistent pain when compared to no intervention [42,51,57,59]. One study [46] compared e-Health to an online discussion forum and one study [53] compared e-Health to an paper book, and neither study found statistical differences between groups.

Two studies described e-Health interventions with minimal involvement of a healthcare provider, including telecare management [38,60]. They compared the intervention to usual care, of which both [38,60] found a significant result in favour of the intervention. These findings suggest that there is strong evidence for e-Health interventions with

minimal involvement in patients with chronic or persistent pain when compared to a control group (usual care or online).

Osteoarthritis

Five studies [43,44,47,54,70] looked at the effect of different remote e-Health interventions on pain in patients with osteoarthritis. These articles were all assessed as good methodological quality (Table 3) and consists of internet-based self-management program with minimal involvement of a healthcare provider [43,47] and a fully automatic web-based program or mobile application for patients with osteoarthritis [35,44,54]. Pain intensity was measured with AIMS2 [47], NPRS [35,43,54], WOMAC [43], and HOOS/KOOS [44]. Three interventions [35,47,54] were not significantly more effective than no care and therefore there is currently no evidence for the effectiveness of remote e-Health on pain intensity in patients with osteoarthritis compared to no care. Two studies compared the e-Health intervention to usual care, of which one study found a statistical between-group difference [43] and the other study did not [44]. Therefore, there is currently no evidence for the effectiveness of remote e-Health on pain intensity in patients with osteoarthritis compared to usual care.

Total Knee Surgery

Two studies [49,50] looked at remote tele-rehabilitation with minimal involvement of a healthcare provider after total knee surgery. The studies were of moderate [49] and high [50] methodological quality and showed no significant improvement on pain measured with the VAS [49,50] and WOMAC [50] when compared to no care. Therefore, there is moderate evidence that e-Health is not effective on pain intensity for patients after total knee surgery compared to no care.

Knee pain

Three studies [37,55,56] investigated on pain outcome in a population of knee pain with online modules measured with NPRS, WOMAC and PROMIS and compared this intervention to a handout with exercises [37], online education [56] and conventional physiotherapy [55]. Two studies [37,56] had good methodological quality and one study [55] with excellent quality showed conflicting results on significance compared to their control group. Therefore, there is limited evidence that e-Health is effective on pain intensity for patients with knee related complaints.

Table 2: Study characteristics

Author, year	Complaints	Intervention group			Control group			Follow-up	Pain outcome measurement tool	Within-group						Between-group
		Population	Intervention		Population	Control intervention				Intervention group			Control group			
		N (%F) Mean age±SD	Description	Study duration	N (%F) Mean age±SD	Description	Study duration			B m (SD)	FU m (SD)	ES *Cohen's d*	B m (SD)	FU m (SD)	ES *Cohen's d*	p-value
BACK PAIN																
Buhrman, 2004 [36]	Low back pain	21 (64) 44 ±10	Internet-based cognitive-behavioral intervention with telephone support	8 wk	29 (62) 45±11	Waiting-list crossover to intervention	N.A.	3 mo	MPI	3.8 (1.9)	3.0 (1.3)	0.5	5.0 (1.7)	3.1 (1.2)	1.3	0.78
									Pain diary avg.	37.4 (18.2)	36.2 (20.4)	-0.1	44.4 (14.2)	32.6 (21.6)	-0.7	0.56
Chiauzzi, 2010 [62]	Chronic back pain	95 (67) 47±12	Self-guided website with lessons, interactive tools, personalized assessments, and articles	4 wk	104 (68) 45±12	Participants were emailed a back-pain guide, they were asked to read the guide	4 wk	6 mo	BPI	5.6 (0.2)	4.8 (0.3)	-3.6	5.6 (0.2)	5.2 (0.2)	-2.1	0.00*
Krein, 2013 [45]	Low back pain	111 (11) 51±13	Internet-mediated walking program with pedometer	12 mo	118 (14) 52±13	Uploading pedometer and monthly e-mail reminders	N.A.	12 mo	NPRS	6.0 (1.9)	5.4 (2.2)	-0.3	6.1 (1.6)	5.6 (2.0)	-0.3	0.81
Lorig, 2002 [52]	Low back pain	190 (39) 47± -	Closed, moderated e-mail discussion group including a book and video about back pain	12 mo	231 (40) 45± -	Subscription to a non-health related magazine of personal choice	12 mo	12 mo	NPRS	4.0 (2.4)	2.5 (2.6)	-0.6	3.8 (2.4)	2.8 (2.6)	-0.4	0.05*
Toelle, 2019 [61]	Non-specific low back pain	48 (73) 41±11	Multidisciplinary mHealth back pain app	3 mo	46 (67) 43±11	Six individual physiotherapy sessions	6 wk	12 wk	NPRS	5.1 (1.1)	2.7 (1.5)	-1.8	5.4 (1.2)	4.1 (1.4)	-1.0	0.02*
MUSCULOSKELETAL CHRONIC PAIN																
Burke, 2019 [57]	Chronic pain, spinal cord injury	35 (29) 50±12	Internet delivered cognitive behavioural therapy	12 wk	34 (21) 52±14	No intervention	N.A.	12 wk	NPRS	5.3 (2.1)	5.0 (2.2)	-0.1	4.4 (2.2)	4.6 (2.3)	0.1	0.02*

Author, year	Complaints	Intervention group			Control group			Follow-up	Pain outcome measurement tool	Within-group						Between-group
		Population	Intervention		Population	Control intervention				Intervention group			Control group			
		N (%F) Mean age±SD	Description	Study duration	N (%F) Mean age±SD	Description	Study duration			B m (SD)	FU m (SD)	ES *Cohen's d*	B m (SD)	FU m (SD)	ES *Cohen's d*	p-value
Buhrman, 2013 [46]	Chronic pain	36 (72) 40±9	Online cognitive behavioral training and education program	8 wk	36 (72.2) 40±9	A moderated online discussion forum	8 wk	8 wk	MPI	3.8 (1.0)	3.7 (1.1)	-0.1	4.0 (1.1)	4.2 (1.2)	0.1	0.07
Calner, 2017 [58]	Persistent musculoskeletal pain	55 (86) 44±10	Self-guided, web-based programme &MMR	16 wk	44 (84) 42±11	Multimodal rehabilitation (MMR)	N.A.	12 mo	VAS	66.1 (16.7)	56.6 (20.7)	-0.5	64.7 (16.2)	57.3 (22.5)	-0.4	0.89
Friesen, 2017 [59]	Fibromyalgia	30 (93) 49±10	Internet delivered cognitive behavioural pain management cours	8 wk	30 (97) 46±13	Waiting list	N.A.	8 wk	BPI	5.5 (1.1)	5.0 (1.7)	-0.3	6.0 (1.4)	6.3 (1.3)	0.2	0.00*
Gialanella, 2017 [60]	Chronic neck pain	47 (89) 56±14	Home based telemedicine program with scheduled phone calls	6 mo	47 (89) 60±11	Recommendation to continue exercising at home	N.A.	6 mo	VAS	6.8 (1.3)	3.9 (1.8)	-1.9	6.6 (1.5)	5.1 (1.9)	-0.9	0.00*
Hernando-Garijo, 2021 [41]	Fibromyalgia	17 (100) 52±9	Telerehabilitation aerobic exercise program	15 wk	17 (100) 55.±9	Usual care	N.A.	15 wk	VAS	7 (1.5)	4.9 (2)	-1.2	7.3 (1.1)	6.5 (1.9)	-0.5	0.02*
Kroenke, 2014 [48]	Chronic pain	124 (12) 55±9	Telecare management	12 mo	126 (22.2) 55±8	Pain care as usual from their primary care physicians	12 mo	12 mo	BPI	5.3 (1.8)	3.6 (2.2)	-0.9	5.1 (1.8)	4.6 (2.1)	-0.3	<0.00*
Lorig, 2008 [38]	Arthritis and Fibromyalgia	441 (90) 52±11	Web-based self-management program with moderated online workshops	6 wk	425 (91) 53±12	Usual care	N.A.	12 mo	NPRS	6.1 (2.4)	5.8 (2.5)	-0.1	6.4 (2.2)	6.5 (2.3)	0.1	0.00*
Rickardsson, 2021 [42]	Chronic pain	57 (72) 48±13	iACT – a novel format of Internet - ACT using exercises	8 wk	56 (79) 51±11	Waiting list	N.A.	Post treatment	NPRS	5.2 (1.5)	3.7 (0.3)	-1.4	5.8 (1.5)	5.4 (0.3)	-0.4	0.00*

Author, year	Complaints	Intervention group			Control group			Follow-up	Pain outcome measurement tool	Within-group						Between-group
		Population	Intervention		Population	Control intervention				Intervention group			Control group			
		N (%F) Mean age±SD	Description	Study duration	N (%F) Mean age±SD	Description	Study duration			B m (SD)	FU m (SD)	ES *Cohen's d*	B m (SD)	FU m (SD)	ES *Cohen's d*	p-value
Smith, 2019 [40]	Chronic pain	41 (90)	Web-based self-mangement program	16 wk	39 (84)	Usual care	16 wk	16 wk	BPI	5.4 (1.7)	4.44 (1.6)	-0.6	5.05 (1.7)	4.73 (1.7)	-0.2	0.42
Wilson, 2015 [51]	Persistent Pain	45 (37) 49±12	Internet-based self-management program	8 wk	47 (41) 50±11	Delay (wait-list comparison).	N.A.	8 wk	BPI	5.6 (1.6)	5.3 (1.9)	-0.2	5.0 (1.7)	5.1 (1.8)	0.1	0.60
Yuan, 2021 [53]	Fibromyalgia	20 (95) 43.3 ± 8.4	Mobile app	6 wk	20 (100) 42.1 ± 11.8	Paper book	6 wk	6 wk	VAS	5.9 (2.2)	5.1 (2.6)	-0.33	5.7 (2.2)	5.3 (2.3)	-0.18	0.798
						OSTEOARTHRITIS										
Anthony, 2022 [54]	Osteoarthritis, waiting list for knee or hip surgery	45 (37.8) 63	Acceptance and commitment therapy (ACT) delivered via a mobile phone	2 wk	54 (33.3) 65	Assessment only	2 wk	2 wk	NRPS	5.4 (2.1)	5.5 (2.2)	0.05	5.9 (1.9)	6.2 (2.2)	0.15	0.22
Bossen, 2013 [35]	Osteoarthritis	100 (60) 61 ± 5.9	Fully automated Web-based intervention that contains automatic functions without human support	9 wk	99 (69) 63 ± 5.4	Waitling list	9 wk	12 mo	NRPS	5.4 (1.2)	3.5 (1.1)	-1.7	4.9 (1.2)	3.8 (1.1)	-0.9	0.33
Gohir, 2021 [43]	Osteoarthritis	48 (71) 65.2 ± 9.7	Digitally delivered program with daily exercises and informative texts	6 wk	57 (65) 68 ± 8.6	Usual care	N.A.	6 wk	NRPS	4.4 (2.0)	2.6 (N.A)	(N.A)	4.7 (2.1)	4.3 (N.A)	(N.A)	<.00*
									WOMAC Pain	8.0 (3.9)	5.8 (N.A)	(N.A)	7.8 (3.7)	6.6 (N.A)	(N.A)	0.02*
Pelle 2020 [44]	Osteoarthritis	214 (69) 62.1 ± 7.7	Standalone eHealth application	N.A.	213 (75) 62.1 ± 7	Usual care	N.A.	6 mo	HOOS/ KOOS	57.5 (15.5)	59.4 (17.7)	0.1	58.2 (17.8)	57.5 (18.0)	-0.1	0.27
Rini, 2015 [47]	Osteoarthritis	58 (79) 69±8	Internet-based self-management program.	8 wk	55 (82) 67±11	Assessment only	6-9 wk	Post-intervention	AIMS2	4.8 (1.7)	4.1 (2.0)	-0.4	5.1 (1.8)	4.6 (1.8)	-0.3	0.17

Author, year	Com-plaints	Intervention group			Control group			Follow-up	Pain outcome							
										Within-group						Between-group
		Popula-tion	Intervention		Popula-tion	Control intervention			measure-ment tool	Intervention group			Control group			
		N (%F) Mean age±SD	Description	Study duration	N (%F) Mean age±SD	Description	Study duration			B m (SD)	FU m (SD)	ES *Co-hen's d*	B m (SD)	FU m (SD)	ES *Co-hen's d*	p-value
TOTAL KNEE SURGERY																
Piqueras, 2013 [49]	Total Knee	72(83) N.A.	Interactive virtual telerehabilitation system	2 wk	70 (63) N.A.	Conventional out-patient phys-iotherapy	N.A.	3 mo	VAS	3.8 (2.0)	2.0 (2.0)	-0.9	4.3 (1.9)	2.0 (2.5)	-1.0	1.00
Russell, 2011 [56]	Total Knee	31 66±8	Internet-based telerehabilitation system	6 wk	34 70±7	Usual face-to-face	N.A.	6 wk	WOMAC Pain	4.3 (2.7)	3.0 (2.3)	-0.6	3.7 (1.8)	2.2 (1.8)	-0.8	0.24
									VAS	4.4 (1.4)	3.1 (1.6)	-0.9	5.2 (1.5)	3.3 (1.3)	-1.3	0.22
KNEE PAIN																
Bennell, 2017 [85]	Knee pain	74 (58) 61±7	Internet-delivered physiotherapist prescribed home exercise and pain coping skills training	N.A.	74 (54) 62±8	Online educa-tion	N.A.	9 mo	NPRS	6.1 (1.4)	3.6 (2.2)	-1.4	6.2 (1.3)	4.7 (2.5)	-0.8	0.00*
									WOMAC pain	9.0 (2.4)	5.1 (2.9)	-1.5	9.2 (2.5)	6.9 (3.5)	-0.8	<0.00*
Gruner, 2021 [55]	Knee pain	31 (50) 58.5±3.7	Digital exercise therapy application	8 wk.	29 (34.6) 55.9 ±13.3	Conventional physiotherapy	8 wk	8 wk	PROMIS_ PI	58.8 (6.7)	52.7 (6.8)	-0.9	57.0 (5.3)	55.5 (7.5)	-0.23	0.14
Kim, 2016 [44]	Knee pain	284 (61) 52	Online exercises	6 wk	286 (61) 52	Static handout of exercises	6 wk	6 wk	NPRS	4.4 (2.2)	3.9 (2.0)	-0.2	3.9 (1.7)	3.7 (1.8)	- 0.1	0.11

B: baseline; BPI: Brief Pain Inventory; ES: effect size; F: female; FU: follow-up; m: mean; mo: month(s); MPI: multidimensional pain inventory; NA; not applicable N: number of participants; NPRS: numeric pain rating scale; SD: standard deviation; VAS: visual analogue scale; Wk: week(s); *significance level ≤0.05

Table 3: Methodological quality assessment based on the PEDro scale

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total score
Anthony, 2022	y	1	1	1	0	0	0	1	1	0	1	06/10
Benell, 2017	y	1	1	1	0	0	0	1	1	1	1	07/10
Bossen, 2013	y	1	1	1	0	0	0	0	1	1	1	06/10
Buhrman, 2004	y	1	0	1	0	0	0	1	0	1	1	05/10
Buhrman, 2013	y	1	0	1	0	0	0	0	1	1	1	05/10
Burke, 2019	y	1	0	1	0	0	1	1	0	1	1	06/10
Calner, 2017	y	1	1	1	0	0	0	0	0	1	1	05/10
Chiauzzi, 2010	y	1	0	1	0	0	0	1	1	1	1	06/10
Friesen, 2017	y	1	1	1	0	0	0	1	0	1	1	06/10
Gialanella, 2017	y	1	0	1	0	0	0	1	0	1	1	05/10
Gohir, 2021	y	1	1	1	0	0	0	0	1	1	1	06/10
Gruner, 2021	y	1	1	1	0	1	1	1	1	1	1	09/10
Hernando-Garijo,2021	y	1	0	1	0	0	1	1	1	1	1	07/10
Kim, 2016	y	1	1	1	0	1	1	0	1	1	1	08/10
Krein, 2013	y	1	1	1	0	0	1	1	1	1	1	08/10
Kroenke, 2014	y	1	1	1	0	0	1	1	1	1	1	08/10
Lorig, 2008	y	1	0	1	0	0	0	0	1	1	1	05/10
Lorig, 2002	y	1	0	1	0	0	0	0	1	1	1	05/10
Pelle,2020	y	1	1	1	0	0	0	0	1	1	1	06/10
Piqueras, 2013	y	1	0	1	0	0	1	0	0	1	1	05/10
Rickardsson,2021	y	1	1	1	0	0	0	1	1	1	1	07/10
Rini, 2015	y	1	1	1	0	0	1	1	1	1	1	08/10
Russell, 2011	y	1	1	1	0	0	1	1	1	1	1	08/10
Smith, 2019	y	1	1	1	0	1	1	1	1	1	1	09/10
Toelle, 2019	y	1	0	1	0	0	0	1	0	1	1	05/10
Wilson, 2015	Y	1	0	1	0	0	1	1	0	1	1	06/10
Yuan, 2021	y	1	1	1	0	0	1	1	1	1	1	08/10

Q1: eligibility criteria were specified (n = no, y= yes; *not taken into consideration for total score*); **Q2**: subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); **Q3**: allocation was concealed; **Q4**: the groups were similar at baseline regarding the most important prognostic indicators; **Q5**: there was blinding of all subjects; **Q6**: there was blinding of all therapists who administered the therapy; **Q7**: there was blinding of all assessors who measured at least one key outcome; **Q8**: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; **Q9**: all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"; **Q10**: the results of between-group statistical comparisons are reported for at least one key outcome; **Q11**: study provides both point measures and measures of variability for at least one key outcome. For all items 0 = no, 1 = yes.

DISCUSSION

This systematic review showed that there is limited evidence for the effectiveness of e-Health on pain intensity in patients with back pain regardless of the extent to which the healthcare professional was involved in the online intervention and regardless of which control group was used. In patients with chronic pain, there is no evidence that remote e-Health without involvement of the healthcare providers is more effective than face-to-face interventions, but there is moderate evidence that it is more effective than no treatment. There is strong evidence that remote e-Health with minimal involvement of the healthcare provider is more effective than a control intervention in patients with chronic pain. For patients after total knee surgery, there appears to be a moderate effect of e-Health intervention with minimal involvement in the reduction of pain compared to no care. While for patients with osteoarthritis and knee pain there was no effect on the pain related outcome.

When we look at the between-group effect, this systematic review shows that there is no evidence between minimal healthcare provider involvement and no care in patients with back pain. There is, however, an indication that remote autonomous e-Health is more effective compared to face-to-face (usual care) treatments. Actually, according to another systematic review, autonomous e-Health interventions were not more effective than usual care in patients with low back pain [71]. According to the conflicting results in patients with low back pain, it may be that the interventions are insufficient tailored. Gains can be made when interventions are more adapted to individual needs and wishes. For low back pain, for example, the StarT-back screening tool is developed in which a treatment guideline is specified based on the risk profile [72]. The stepped care principle can also support personalized care, because the inclusion of giving autonomous home-based e-Health, blended care of face-to-face treatment requires careful consideration of whether a patient has motivation, access to digital services and the ability to process information [73]. The current systematic review looked into remote e-Health interventions. As it has been shown that a physiotherapist can positively influence treatment outcomes by providing positive feedback, giving answers on patient's questions, and providing clear instructions for home practice [74], it could be useful to see with the studies included in the current review what the effect of just the e-Health application is, rather than the influence of the physiotherapist.

For patients with chronic pain, we found conflicting results regarding the effectiveness of remote e-Health interventions depending on the involvement of the healthcare

provider and the control group. This study showed that when the online involvement of the healthcare provider increases, the evidence of effectiveness of remote e-Health compared to usual care also increases. Autonomous e-Health is more effective than no treatment, but not more effective than usual care unless there is minimal involvement of the healthcare provider. This is comparable to other studies in which they have shown that there is no evidence that autonomous remote e-Health has additional value next to usual care in patients with chronic pain [75], other than their cost-effectiveness [12,14,76,77]. Therefore, when applying e-Health in this population, it should be integrated in the intervention, also known as blended care, to provide effective treatment with lower costs [13,78].

The amount of effect of e-Health depends on usage and adherence [79]. Usage contains activity on the e-Health application, such as number of logins, minutes or activities completed [80]. Adherence is the extent to which a person uses the e-Health application as intended [80]. The studies included in the current review show contradictory evidence regarding usage, adherence and effect of the e-Health intervention [47,51,57,58,60,61]. For instance, some studies report low adherence rates but did not correct for this in the assessment of effectiveness [51,57,58]. In case of low adherence, i.e. the e-Health intervention was often not completely followed as intended, interpretation of the findings becomes more challenging [80].

In this systematic review, no significant effect was found in the population of osteoarthritis or patients with knee pain or knee surgery. Reasons why no effect was found is because of the relatively low number of studies included in this systematic review. Another explanation is that the pain outcome measure may not be the most obvious physical outcome measure for these populations. When looking at other outcome measures, for example physical activity, there is a significant long-term effect in favour of remote e-Health. At last, there might be a potential ceiling effect of the amount of therapy a patient can receive in which additional treatment would no longer lead to improved recovery [81]. In the case of pain intensity, evidence suggests that the content of the intervention is more important than the mode of delivery (i.e. in person or e-Health) [81]. Furthermore, there are big within-patient differences in the course of pain in patients with knee osteoarthritis [82], so with small sample sized and limited number of studies the interpretation of these results should be done with caution.

Limitations and strengths

A limitation is that even though this review only included remote e-Health interventions, there was still a large variety of intervention types (e.g. interactive websites, internet delivered programs and mobile applications) and pain related outcome measurements (VAS, NPRS, MDI, etc). Because of this, it was not possible to do a meta-analysis and interpretation of results must be done with caution. Another reason to be cautious is that the interventions in this review sometimes were given by a professional other than physiotherapists, for example by a physician-pain specialist [48], psychologists [42], nurse [60] or undefined therapists [38,40,45,51,62]. However, all included interventions can be delivered by physiotherapists as they are part of the modality physiotherapist have in the management of pain related complaints [23]. The final limitation of this study is that only within-group effect sizes are presented. It indicates the direction of the effectiveness of the intervention itself. Unfortunately, we were unable to abstract enough information from the articles to calculate the between-group effect sizes. Therefore, we extracted the P value of the between group effects per article which are presented in table 2. A strength of this study is that all included articles were at least of moderate methodological quality, as assessed with the PEDro scale. All steps of this review were done with minimally two researchers independent from each other, which increases the reliability of the results. Additionally, both Pedro scale and Cochrane RoB tool were used so a more accurate conclusion can be drawn, as there are some slight discrepancies between the two tools.

Recommendations for future research and clinical practice

Based on the heterogeneity of interventions and outcome measures, we recommend to describe the used e-Health intervention carefully in future research so these interventions can be reproduced optimally. For example, by using the TIDieR checklist which aims to improve the completeness of reporting of interventions [83]. The TIDieR checklist includes 12 items, like brief name, why, what (materials), what (procedure), who provided, how, where, when and how much, tailoring, modifications and how well (planned) [83]. Additionally, future studies should look into the impact of patients' experience of pain on daily functioning, and how e-Health can contribute to decrease the impact of pain.

While remote e-Health and usual care has no preference based on pain-outcome, literature shows in some cases that e-Health is more cost-effective than usual care [78,84]. The cost-effectiveness is in most studies still unclear and should be studied. It would be interesting for instance to determine the cost-effectiveness of e-Health interventions in chronic pain populations because of their social and economic burden [76,85].

When applying e-Health in the clinical practice, the amount of e-Health should be able to tailor specific needs of patients [86]. Some patients may have limited motivation to online consultation or other aspects of e-Health and patient preferences are an important aspect of evidence-based practice [87]. Another aspect of evidence-based practice is available evidence, to which this review contributes and shows that e-Health can be an effective way of reducing pain in some populations. However, this review is regarding autonomous e-Health interventions, and most physiotherapists will apply blended e-Health to ensure their full skillset, including hands-on therapy, can be used to help their patient with pain complaints [88,89,90].

CONCLUSION

There is limited evidence for the effectiveness of remote physiotherapeutic e-Health interventions to decrease pain intensity in patients with back pain. Autonomous e-Health is more effective than no treatment in patients with chronic pain, but not more effective than usual care unless there is minimal involvement of the healthcare provider. For patients with osteoarthritis, after total knee surgery and knee pain, there appears to be no effect of e-Health in the reduction of pain.

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APPENDIX 1: SEARCH STRATEGIES

Database	Search strategy *Last performed: February 25, 2022*	Results
Pubmed	("mobile health"[Title/Abstract] OR "web based"[Title/Abstract] OR web-based[Title/Abstract] OR "web"[Title/Abstract] OR "internet"[Title/Abstract] OR "computer"[Title/Abstract] OR mobile health[MeSH Terms] OR internet[MeSH Terms] OR ehealth[MeSH Terms] OR telehealth[MeSH Terms] OR "telehealth"[Title/Abstract] OR "telemedicine"[Title/Abstract] OR telemedicine[MeSH Terms] OR "ehealth"[Title/Abstract] OR "e health"[Title/Abstract] OR "mobile health"[Title/Abstract] OR "online"[Title/Abstract]) AND (musculoskeletal pain[MeSH Terms] OR "musculoskeletal"[Title/Abstract] OR musculoskeletal disease[MeSH Terms] OR physical therapy modalities[MeSH Terms] OR physical therap*[Title/Abstract] OR physiotherap*[Title/Abstract] OR exercise therapy[Title/Abstract] OR exercise therapy[MeSH Terms] OR "tension" OR "muscular" OR "myogenic" OR "myogenous" OR "myofascial") AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract] OR randomized controlled trial[MeSH Terms] OR clinical trial[MeSH Terms]) NOT (("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	7510
EMBASE	telehealth:ab,ti OR ehealth:ab,ti OR internet:ab,ti AND ('physiotherapy'/exp OR physiotherapy OR 'musculoskeletal disease'/exp OR 'musculoskeletal disease') AND (random*:ab,ti OR (clinical NEXT/1 trial*):de,ab,ti OR 'health care quality'/exp)	2023
Cochrane	("Musculoskeletal Disease" or "Musculoskeletal Pain" or Muscul* or "Physical Therapy":ti,ab,kw) and (eHealth or e-health or internet* or web* or tele* or online* or computer*:ti,ab,kw) *Filter: trials*	3098

APPENDIX 2: LIST OF EXCLUDED ARTICLES

175 were excluded because:

- the study design was not a RCT or had other issues (n=41) [1-41],
- the patient population was not in line with our in- and exclusion criteria (n=44) [42-85],
- the intervention was not in line with our in- and exclusion criteria (n=53) [86-138],
- the outcome measures were not in line with our in- and exclusion criteria (n=19) [139-157],
- other reasons (n=18) [158-175].

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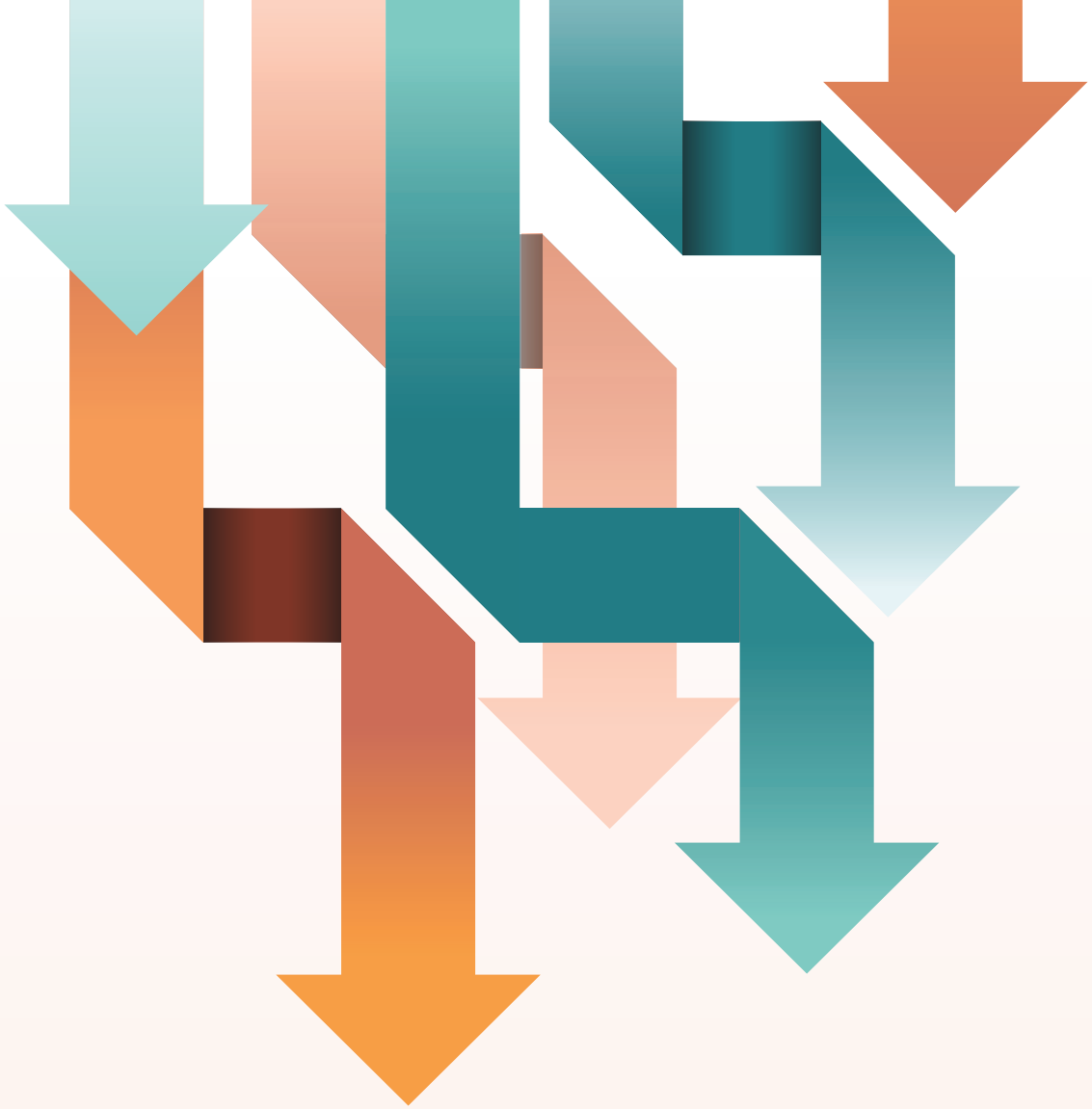

3

CHAPTER

Effectiveness of a blended and integrated mental health and physical therapy intervention program (PARASOL) for patients with moderate medically unexplained physical symptoms to prevent chronicity: study protocol of a cluster randomized clinical trial

Paula E. van Westrienen
Martijn F. Pisters
Suze A.J. Toonders
Marloes Gerrits
Cindy Veenhof
Niek J. de Wit

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ABSTRACT

Background

Medically unexplained physical symptoms are an important health problem in primary care, with a spectrum from mild to chronic. The burden of chronic medically unexplained physical symptoms is substantial for patients, health care professionals, and society. Therefore, early identification of patients with moderate medically unexplained physical symptoms is needed in order to prevent chronicity. The preventive screening of medically unexplained physical symptoms (PRESUME) screening method was developed using data from the electronic medical record of the patients' general practitioner and demonstrated its prognostic accuracy to identify patients with moderate medically unexplained physical symptoms. In the next step, we developed a proactive blended and integrated mental health and physical therapy intervention program (PARASOL) to reduce complaints of moderate medically unexplained physical symptoms, stimulate self-management, and prevent chronicity.

Objective

The primary objective of this study is to investigate the effectiveness of the blended PARASOL intervention on the impact of symptoms and quality of life in patients with moderate medically unexplained physical symptoms compared with usual care. Secondary objectives are to study the effect on severity of physical and psychosocial symptoms, general health, physical behavior, illness perception, and self-efficacy in patients with moderate medically unexplained physical symptoms as well as to determine the cost-effectiveness of the program.

Methods

This paper presents the study protocol of a multicenter cluster randomized clinical trial. Adult patients with moderate medically unexplained physical symptoms will be identified from electronic medical record data using the PRESUME screening method and proactively recruited for participation in the study. Cluster randomization will be performed at the level of the participating health care centers. In total 248 patients with moderate medically unexplained physical symptoms (124 patients per arm) are needed. The PARASOL intervention is a 12-week blended primary care program consisting of 4 face-to-face consultations with the mental health nurse and 5 physical therapy sessions, supplemented with a Web-based program. The Web-based program contains (1)

information modules and videos on self-management and educative themes, (2) videos and instructions on prescribed home exercises, and (3) assignments to gradually increase the physical activity. The program is directed at patients' perception of symptoms as well as modifiable prognostic risk factors for chronicity using therapeutic neuroscience education. It encourages self-management, as well as an active lifestyle using a cognitive behavioral approach and graded activity. Primary outcomes are impact of symptoms and quality of life. Secondary outcomes are severity of physical and psychosocial symptoms, general health, physical behavior, illness perceptions, self-efficacy, and cost-effectiveness. All measurements will be performed at baseline, 3 and 12 months after baseline. Retrospective cost questionnaires will also be sent at 6 and 9 months after baseline and these will be used for the cost-effectiveness analysis.

Results

The intervention has been developed, and the physical therapists and mental health nurses in the participating experimental health care centers have received two days of training on the content of the blended PARASOL intervention. The recruitment of health care centers started in June 2016 and inclusion of patients began in March 2017. Follow-up assessments of patients are expected to be completed in March 2019.

Conclusions

This study is the first randomized clinical trial to determine the effectiveness (including cost-effectiveness) of a proactive, blended, and integrated mental health and physical therapy care program for patients with moderate medically unexplained physical symptoms. The findings will help to improve the treatment for patients with moderate medically unexplained physical symptoms and prevent chronicity.

INTRODUCTION

Medically unexplained physical symptoms (MUPS), especially pain, dizziness, and fatigue are frequent in primary care, in fact 25%-50% of all symptoms presented during consultations cannot be adequately medically explained [1]. If there are physical complaints for which no medical condition can be found after adequate medical examination, they will be defined as MUPS [2,3].

MUPS can be regarded as a spectrum ranging from mild unexplained physical symptoms (low incidence, one or two domains, low impact), to moderate symptoms (more frequent, two or three domains, higher impact) and finally to persisting or chronic MUPS (high impact, more clusters involved, chronic; eg, fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome) [3,4]. In this spectrum, mild MUPS have an estimated prevalence of 70% to 80% [4,5]. These patients consult their general practitioner (GP) for a symptom that cannot be explained immediately, but the symptoms improve within 2 weeks [6]. Moderate MUPS have an estimated prevalence of approximately 15%, where patients still experience unexplained symptoms after three months without a diagnosis of a functional somatic syndrome [6]. Patients with chronic MUPS will have a symptom duration of at least six months, with the presence of a functional somatic syndrome, such as fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome, or a somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [4,6,7]. Patients with chronic MUPS occur in approximately 2.5% in primary care, and 3% of the GP consultations are MUPS consultations [1,8].

Despite the low prevalence of chronic MUPS, the burden is substantial [1], with a high impact on patients' quality of life and daily functioning. Compared with the general population, as well with other patient groups such as major depressive disorder and cancer patients, patients with chronic MUPS report a lower quality of life [9,10]. Moreover, patients with MUPS consult a GP more frequently, but GPs find adequate management of MUPS challenging [11]. GPs frequently focus on exclusion of a somatic disease by recommending somatic interventions such as drug prescriptions, an investigation or a referral to a specialist; while patients often do not request for somatic interventions [12]. Furthermore, GPs face difficulty in the timely recognition of patients with MUPS [13]. On average, it takes two years to obtain a diagnosis. During this time period patients have on average 15 GP consultations, 8 visits to a hospital specialist and 14 sessions with the physical therapist [10]. Almost 40% of patients with MUPS report absenteeism from work [10]. As a result, MUPS are associated with increased direct and indirect costs related to health care expenditure as well as work and insurance related costs [10,14].

Much research has been conducted on effective interventions for chronic MUPS. Neurosciences-based therapeutic education, cognitive behavioral therapy, and exercise therapy have been shown to be effective treatment modalities in patients with MUPS [15,16,17,18]. Overall, the vast majority of these studies included patients with chronic MUPS. So far little research has been conducted in patients with moderate MUPS, partly due to the fact that adequate methods for early identification are lacking. Early identification of patients with moderate MUPS would enable interventions directed at prevention of chronicity, which ultimately might decrease the burden of these symptoms for patients, health care professionals and society.

Recently, a screening method (PRESUME; preventive screening of medically unexplained physical symptoms) has been developed to identify patients with moderate MUPS using data from the electronic medical record of the patient's GP as shown in Figure 1 [19]. The PRESUME screening method showed acceptable prognostic accuracy over a five-year follow-up [19]. For patients with moderate MUPS, we developed a proactive, blended, and integrated mental health and physical therapy care program to prevent chronicity. This is a 12-week program consisting of 4 face-to-face consultations with the mental health nurse and 5 physical therapy sessions, which are supplemented with a Web-based program (e-Exercise). Blended care has already proven to be effective in other studies [20,21] and it helps to promote self-management.

The primary objective of the present study is to investigate the effectiveness of the proactive, blended and integrated mental health and physical therapy care program (PARASOL) on impact of symptoms, as well as the physical and mental dimensions of quality of life in patients with moderate MUPS in comparison with usual care. Secondary objectives are to study the effect on severity of (psychosocial) symptoms, general health, physical behavior, illness perception, and self-efficacy in patients with moderate MUPS as well as to determine the cost-effectiveness of this program.

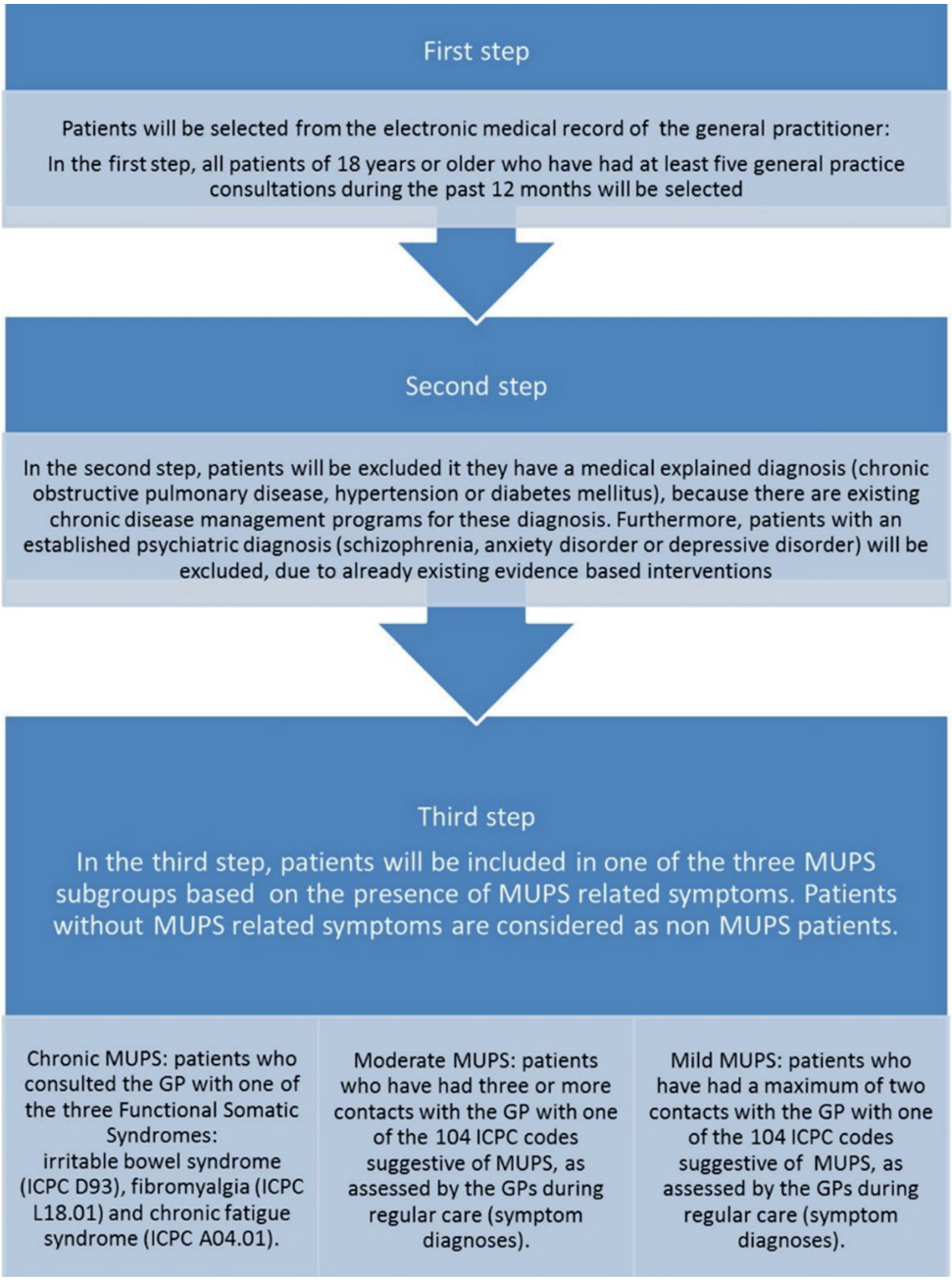

Figure 1: PRESUME screening method

METHODS

Study Design

A prospective, multicenter cluster randomized clinical trial will be conducted. The study has been approved by the Medical Ethical Committee of University Medical Center Utrecht, the Netherlands. The blended PARASOL intervention will be compared with usual care. An overview of the study procedure is shown in Figure 2.

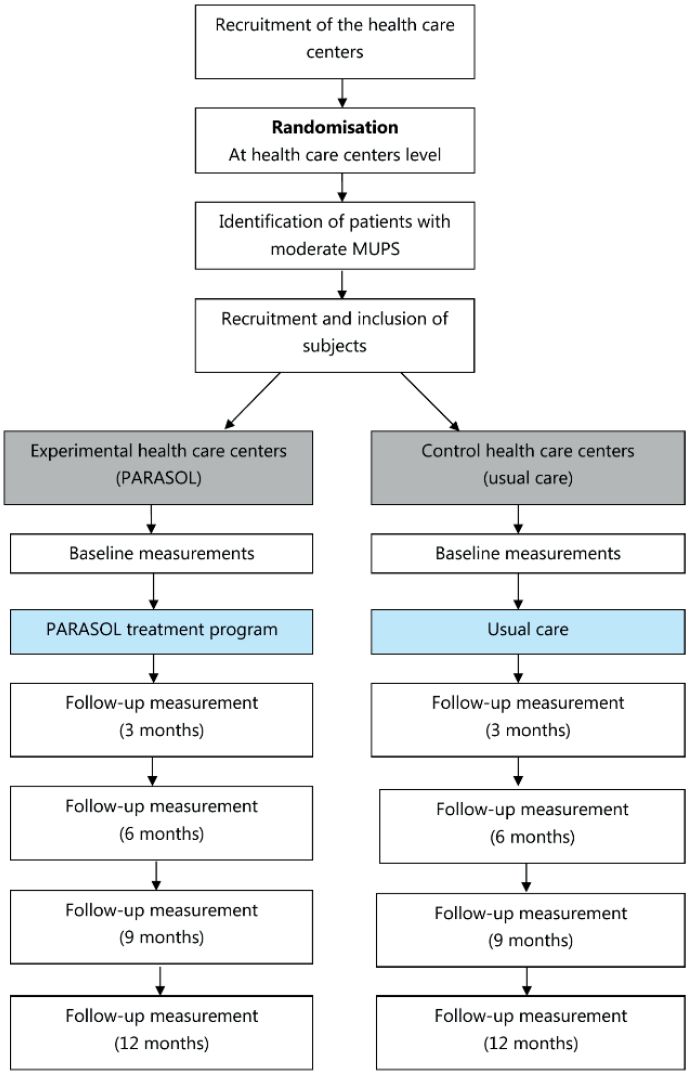

Figure 2: Overview of the study

Participants

Patient selection

Patients with moderate MUPS will be identified in the participating practices using 3 strategies. The first strategy is to use the PRESUME screening method. All patients in the routine care database of a GP are anonymously screened in a stepwise selection, based on a consultation frequency above five, with exclusion of chronic diseases (eg, chronic obstructive pulmonary disease, hypertension or diabetes mellitus) and psychiatric diagnoses (eg, schizophrenia, anxiety disorder or depressive disorder) and the presence of any of the 104 MUPS related International Classification of Primary Care codes. The prognostic accuracy of this PRESUME screening method for identification of moderate MUPS patients is moderate [19].

Since the PRESUME screening method is over inclusive and not meant to set an accurate diagnosis of MUPS in individual patients, all identified patients with moderate MUPS will be screened by their GP for eligibility [19]. As a consequence, the expected prevalence of patients with moderate MUPS is less than the 2.4% according to the PRESUME screening method [19]. The GP will exclude patients based on the following criteria: (1) having another chronic somatic or psychiatric disease, (2) receiving a medically explained diagnosis between identification using the PRESUME screening method and the time of inclusion, (3) having complaints with a duration of less than 1 month, in which case further diagnostic evaluation of the symptoms is needed, and (4) unable to participate as determined by the GP, due to a life-threatening condition, a shortened life expectancy, a major life event in the past month or a MUPS targeted multidisciplinary intervention in the past 12 months. All remaining eligible patients will proactively be approached by their GP, by sending them an invitation letter with study information. Secondly, GPs will recruit patients during consultations if they meet the following criteria: ≥18 years of age, ≥5 general practice consultations during the past twelve months, medically unexplained physical symptoms, and the diagnostic phase is completed. When a patient is eligible, the GP can give the contact details of the researchers of the PARASOL study to the patient. The last strategy will be open recruitment in participating health care centers. Flyers with information about the PARASOL study will be provided in the waiting rooms and included in the newsletter of the health care centers. Patients who are willing to participate can contact the researcher by phone or by mail. Subsequently, the researcher will determine whether the patient is eligible by asking if the patient is older than 18 years, has had ≥5 general practice consultations during the past twelve months, and if the patient has medically unexplained physical symptoms.

All patients who are willing to participate in the PARASOL study, will have to have access to the internet and have mastered the Dutch language. When a patient is willing to participate, they can contact the researcher by phone or email. The researcher will answer any possible questions, give further information, and will make an appointment for the patient to sign informed consent and a baseline measurement evaluation. Additionally, patients in the intervention group will be invited to participate in the blended PARASOL intervention

Study centers

The Leidsche Rijn Julius Health Care Centers (LRJG; 5 health care centers with 40,000 patients) and the Eindhoven Corporation of Primary Health Care Centers (SGE; 10 health care centers, 70,000 patients) will participate in the study. All relevant disciplines—general practitioners, physical therapists, and mental health nurses—are available and willing to participate.

Randomization Procedure

Cluster randomization will be performed at the level of the participating health care centers. Health care centers will randomly be assigned to either the intervention group or the control group (usual care) using a Web-based random generation of a sequence of numbers. Through cluster randomization, we will avoid professionals within one health care center offering both the blended PARASOL intervention and usual care, as this could cause potential contamination effects [22]. A higher drop-out rate in the intervention group is expected since psychological therapies have a 7% higher proportion of drop outs compared with usual care [18]. The blended PARASOL intervention combines both mental health and physical therapy sessions. Therefore, an unequal randomization on cluster level will be conducted. Of the 15 included health care centers, 8 will be randomized to the blended PARASOL intervention and 7 will be randomized to the control group. After randomization of the health care centers, the selection and inclusion procedure of patients with moderate MUPS will be performed.

Intervention Program

The health care program is a proactive, blended, and integrated care program offered by a physical therapist and mental health nurse. The program will start with a physical approach since patients' perception of the symptoms usually has a somatic focus and

MUPS patients are often reluctant to accept psychological oriented treatments [23,24]. The aim of the health care program is to reduce complaints of moderate MUPS, stimulate self-management, and prevent chronic MUPS. The health care program is focused on patients' insight, perception of symptoms, and modifiable prognostic risk factors for the development of chronic MUPS, using a cognitive behavioral approach and therapeutic neuroscience education as well as encouraging self-management and an active lifestyle using graded activity (details are provided in Appendix 1). It consists of 3 steps and the face-to-face sessions will be integrated with eHealth modules, called blended health care. The content of the eHealth modules will be discussed during the face-to-face sessions. Details of the 3 steps are listed below:

1. Intake: The program will start with an intake session with both the physical therapist and the mental health nurse. During the intake session the complaints, treatment goals, treatment demand, and perpetuating factors of the patient will be identified according to the somatic, cognitive, emotional, behavioral, and social factors (SCEGS) model [3]. After the intake the physical therapist and mental health nurse discuss the complaints, treatment goals, and treatment demand.

    a. The physical therapist will focus on the somatic complaints (ie, physical symptoms, duration and course of symptoms, severity of symptoms, and physical functioning) and will conduct a physical examination to get insight to factors that are related to the content of the health care program (eg, posture and movement, breathing patterns, and muscle tension) and to determine if symptom specific exercises are needed.
    b. The mental health nurse will focus on cognitive, emotional, behavioral and social complaints.

2. Face-to-face sessions:

    a. Patients will have 4 face-to-face sessions with the physical therapist (week 1, week 3, week 6 and week 12) where the focus will be on the perception and acceptation of physical complaints of the patients. The physical therapist will start with education regarding the unexplained symptoms. Therapeutic neuroscience education according to the sensitization model is of particular interest due to patient's somatic fixation and anxiety for a severe disease [17]. Concurrently, graded activity will be used to gradually expand activities performed by the patient using principles of operant conditioning [25,26]. The

graded activity schedule can be performed in daily life. In week 6, the physical therapist will discuss the patients' lifestyle (eg, exercise, sleep, and relaxation) with the focus on behavioral changes to promote a healthy lifestyle. In week 12, the physical therapist will discuss long-term goals as well as how patients can maintain a physically active lifestyle.

b. Patients will have 3 face-to-face sessions with the mental health nurse (week 1, week 3, and week 6). In all 3 face-to-face sessions the mental health nurse will train coping strategies according to perpetuating factors and operant conditioning [25], with the focus on changing perception and acceptation. The mental health nurse will start with education regarding general perpetuating factors with the link to possible perpetuating factors of the patient. In the next 2 face-to-face sessions, the link between the perpetuating factors and patients coping strategies will be made, with the focus on behavioral change.

3. eHealth modules: The Web-based part of the health care program consists of exercises (instruction videos) and information modules on self-management and educative themes (description and videos). The modules consist of 3 components which are listed below.

    a. Graded activity, an activity-focused method with operant conditioning behavioral principles with 3 consecutive phases. In the starting phase, the patient will choose an activity they want to expand gradually. The patient will perform the chosen activity to their tolerance level (ie, until pain or fatigue drives them to stop; this will be pain-contingent) while their performance is recorded in distance units, time, or number of repetitions. After at least 3 pain-contingent measurements, occurring over several days, a baseline will be determined, and the patient sets his or her individual treatment goal. In the treatment phase, the chosen activity will be increased gradually (ie, time-contingent) and an individual scheme will be drawn up. In the integration phase, patients will be stimulated to adhere to the activity in their daily living [25,26]

    b. Videos of prescribed home exercises by their physical therapist

    c. Videos and information on self-management and educational themes such as central sensitization, perpetuating factors, graded activity, behavioral change, stress, coping, relaxation, lifestyle advice, creating and performing an exercise plan, and avoiding a relapse.

Usual Care

Patients in the control health care centers will get care as per usual without any restrictions. This care could include care of the GP, physical therapist, mental health nurse, and psychologist.

Outcomes

Primary Outcome

The primary outcome measures are impact of symptoms and quality of life.

Secondary Outcomes

Several secondary parameters will be measured to determine the influence of the blended e-Exercise health care program on severity of physical and psychosocial symptoms, general health, physical behavior, illness perceptions, self-efficacy, and cost-effectiveness.

Measurements

Three time points (baseline, 3-month, and 12-month follow-up) will be used for data collection. In addition, cost questionnaires will also be sent to the patients at 6 and 9 months. Furthermore, the impact of symptoms will be measured weekly between 0 and 3 months, followed by monthly measurements between 6 and 12 months. We offer no financial incentives to complete questionnaires or to carry the Acitv8 activity monitor. The measures that will be collected are listed below and Table 1 gives a summary of all measures that will be collected.

- Impact of symptoms, which addresses adequate relief using a validated single question, which is scored on a dichotomous scale (“Over the past week have you had adequate relief of your symptoms?”) [27,28]. A responder for adequate short-term relief is defined as a patient who will report adequate relief of their symptoms for at least six of the twelve weeks between the baseline and three-month follow-up. In addition, a responder for adequate long-term relief will report adequate relief of their symptoms for at least three of the six months between the 6- and 12-month follow-up. Otherwise, a patient will be defined as a nonresponder. Adequate relief is a validated clinically relevant endpoint and is defined at the point where the individual patient is satisfied with treatment [29].

- Quality of life will be measured with the 36-Item Short Form Health Survey (RAND-36) health survey. The RAND-36 is a valid and reliable self-reported questionnaire [30]. The questionnaire consists of eight subscales, namely physical functioning, social functioning, role-physical or emotional problems, mental health, vitality, bodily pain, and general health. A higher score on the scale of 0-100 indicates a better quality of life [30,31].
- Severity of symptoms, defined as self-perceived pain and fatigue in the past week, will be measured with an 11-point numeric scale (score 0-10) [32].
- Severity of psychosocial symptoms will be measured with the Four-Dimensional Symptom Questionnaire (4DSQ) questionnaire. This questionnaire consists of 4 subscales, namely distress, depression, anxiety, and somatization [33,34].
- Self-perceived health will be measured with the EuroQol-5D (EQ5D) questionnaire. This questionnaire will measure the perceived health on five levels (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [35].
- Physical movement behavior will be measured with the Activ8 activity monitor [36]. The Activ8 is a validated activity monitor to measure physical behavior by measuring several activities and postures (lying, sitting, standing, walking, running, and cycling). Patients will wear the Activ8 activity monitor for 1 week at varying intervals during the study. They will wear it at baseline, at 3 months follow-up, and at 12 months follow-up.
- Illness perceptions will be measured using the Brief Illness Perception Questionnaire. This questionnaire is an eight-item scale designed to assess cognitive and emotional representations of illness on an ordinal scale (0-10) [37,38].
- Self-efficacy will be measured with the Hei-Q questionnaire, which is a user friendly, valid, and reliable questionnaire specifically developed to evaluate patients' education and self-management programs for patients with chronic complaints [39].
- Health care use and indirect costs through illness and absenteeism will be measured with Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness (TIC-P) questionnaire to evaluate the cost-effectiveness of the program in terms of costs per Quality Adjusted Life Years (QALYs) [40]. Patients will be asked to complete the cost questionnaire every 3 months, since this questionnaire focuses on health-related costs in the past 3 months.

QALYs will be measured using the EQ-5D scores [41]. In this way, we will get information of patients' healthcare utilization and (unpaid) productivity losses.

- Besides the above parameters, the efficacy, barriers, and facilitators of the Web-based component of the blended PARASOL intervention from a patient's perspective will be measured using the System Usability Scale (SUS). The SUS will be completed by patients of the intervention group at the end of the health care program (3-month follow-up). The questionnaire will measure the perceived usability by ten statements which can be scored on a 5-point Likert scale ('totally agree' to 'totally disagree'). The SUS is a simple, valid, and reliable measurement and is often used the evaluate the usability of eHealth applications [42].

Other Measures

Demographic and clinical variables such as age, gender, education level, work situation, duration of complaints, and possible comorbidities will be measured at baseline. Possible comorbidities will be measured again at 3 and 12 months after baseline to determine if patients have developed comorbidities or any chronic MUPS syndromes such as fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome.

Sample Size

The number of eligible patients was calculated according to Campbell et al for cluster randomized trials [43]. The power calculation is based on an intracluster correlation coefficient of 0.04 [44,45] and a minimum of 20 patients per health care center. Additionally, we assume a minimal clinical detectable change of >10 points in the sum score of physical functioning of the RAND-36 questionnaire, and a SD of 23.8 [10]. Based on these assumptions and a power of 80% (alpha=.05), at least ten health care centers and 206 participating patients are needed. With an expected drop-out rate of 20%, a total of 248 participating patients (124 patients per arm) are needed for the study

Table 1: Summary of measures to be collected

Outcome measures	Data collection instrument	Follow-up measurements				
		Baseline	3 months	6 months	9 months	12 months
Primary outcome measures						
Impact of symptoms[a]	Adequate Relief question	✓	✓			✓
Quality of life	36-Item Short Form Health Survey (RAND-36)	✓	✓			✓
Secondary outcome measures						
Pain	Numeric Rating Scale	✓	✓			✓
Fatigue	Numeric Rating Scale	✓	✓			✓
Severity of psychosocial symptoms	Four-Dimensional Symptom Questionnaire	✓	✓			✓
General health	EuroQol-5 Dimensions	✓	✓			✓
Physical behaviour	Activ8 activity monitor	✓	✓			✓
Illness perceptions	Brief Illness Perception Questionnaire	✓	✓			✓
Self-efficacy	Health Education Impact Questionnaire	✓	✓			✓
Cost-effectiveness	Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness	✓	✓	✓	✓	✓
Barriers and facilitators of the blended e-Exercise health care program	System Usability Scale		✓			
Other measures						
Age	Questionnaire	✓				
Gender	Questionnaire	✓				
Education level	Questionnaire	✓				
Work situation	Questionnaire	✓				
Duration of complaints	Questionnaire	✓				
Possible co-morbidities	Questionnaire	✓	✓			✓

[a] Measured weekly between baseline and 3 months follow-up, and monthly between 6 and 12 months follow-up.

Statistical Analysis

Statistical analysis will be performed using IBM SPSS 22. Statistical analysis will be performed according to the intention-to-treat principle. Any missing values will be imputed with the Multivariate Imputation by Chained Equations. Descriptive statistics will be used to describe the number of patients with moderate MUPS (as identified using the PRESUME screening method) which are excluded by their GPs, how many patients are recruited with the 3 different strategies, as well as how many patients do not complete the blended PARASOL intervention. Additionally, descriptive statistics (frequencies, t-test and chi-square test) will be used to describe the demographic characteristics of the study population and to explore baseline comparability. Differences in effectiveness of the blended PARASOL intervention will be analyzed using longitudinal mixed methods analyses. In this way, we can correct for independence of observations within patients as well as take into account possible variations between clusters and health care professionals. Analyses will be corrected for potential confounders (eg, age, gender, and psychiatric comorbidity) and potential interactions terms (eg, age in the use of the Web-based component of the PARASOL intervention) will be checked. Furthermore, the cost-effectiveness of the blended PARASOL intervention will be clarified with an incremental cost-effectiveness ratio based on the costs per QALY. All costs measured by the TIC-P (health care use and indirect costs of illness and absenteeism) are used to calculate the incremental cost-effectiveness ratio.

RESULTS

The components of this intervention are based on results of a literature search and focus groups with experts (general practitioners, physical therapists, mental health nurses, and psychologists) [46]**.** The content of the information, self-management, and exercise modules were specifically developed for the current study. The functionality of the online program used in this study is based on the blended exercise intervention for patients with hip or knee osteoarthritis (e-Exercise) [47].

Before the start of the intervention program, physical therapists and mental health nurses of the experimental health care centers received two days of training on the content of the blended PARASOL intervention. The training consisted of presentations on the study population, central sensitization, therapeutic neuroscience education, graded activity, and perpetuating factors for all professionals involved in the study. Furthermore, the training included discussion of the content of the online modules and instructions on their implementation. During the study, a follow-up training session for the therapists

will be conducted to ensure adherence to the treatment protocol. The recruitment of health care centers started in June 2016 and inclusion of patients began in March 2017. Follow-up assessments of patients are expected to be completed in March 2019.

DISCUSSION

In this randomized clinical trial, the effectiveness (including cost-effectiveness) of the PARASOL intervention, a proactive blended and integrated mental health and physical therapy intervention program, will be studied.

Although the study is well-planned and involves all relevant stakeholders, the conduction of the study will present several operational challenges. The first challenge has been identified as GPs motivation to actively participate in the recruitment of patients with moderate MUPS. Patients with MUPS are a difficult patient group for GPs and often the patient-doctor relationship is under pressure due to mismatches between the expectations of the patient and doctor [48]. To motivate GPs to recruit patients with moderate MUPS, information about the PARASOL study will be sent to them beforehand. During the study, GPs will be individually informed if one of their patients is participating in the PARASOL study. Furthermore, all participating GPs will be sent updates at 3-month intervals informing them about total patient inclusion in the study, as well as patient inclusion per GP.

A second challenge identified is the recruitment of adequate patient numbers to achieve the desired statistical power. Patients with moderate MUPS will be identified using the PRESUME screening method, following which they will be proactively approached by their GP. This proactive approach may lead to patients in a non-symptomatic phase or without a treatment demand being contacted. Consequently, these patients might be less motivated to follow the blended PARASOL intervention aiming to prevent chronicity of MUPS. To deal with this challenge, setting individual treatment goals has been identified as an important part of the intake session. It should be noted that the face-to-face sessions are not performed on a weekly basis to not only reduce the burden for patients, but more importantly to encourage self-management. A third challenge is the potential drop-out rate in the control group since these patients will not be receiving the blended PARASOL intervention and therefore may be less motivated to participate in the study. To deal with this challenge, patients in the control group will be offered to follow the blended PARASOL intervention after the study ends.

A final identified challenge is the non-usage of the Web-based component of the blended PARASOL intervention. Previous studies have shown that patients in online interventions

are less motivated and feel less pressure to continue with the intervention compared to face-to-face interventions [49]. To combat this, patients will receive email reminders for the eHealth modules weekly. Furthermore, the PARASOL intervention has been designed as a blended care program, and this is therefore expected to maximize adherence compared to self-guided internet interventions [50].

Besides these challenges, there are several strengths and limitations in the design of the study that should be noted. The first strength of this study is that physical therapists and mental health nurses will participate in two days of intensive training about the content of the blended PARASOL intervention. This will minimize the differences in the care offered by professionals at different health care centers during the health care program [51]. In addition, a meeting with the participating physical therapists and mental health nurses will be organized after 6 months to discuss the content of the blended PARASOL intervention as well as any possible difficulties faced. The 12-month follow-up measurement is another strength of this study as it will result in data being obtained about long-term effectiveness (and cost-effectiveness) of the program. The PARASOL intervention stimulates self-management by focusing on achieving a healthier lifestyle as well as the adoption and maintenance of exercise behavior. Since the process of adopting a change to maintaining a change takes at least six months, a long-term follow-up is of particular interest [52]. A third strength of this study is performing cluster randomization at the level of the health care centers as this ensures that a contamination-effect will be avoided [22]. Finally, this is the first study, to the best of our knowledge, that investigates the effectiveness of an intervention program for patients with moderate MUPS to prevent chronicity.

The first identified limitation of this study, is that it is unblinded. Patients, health care professionals, and the researchers are aware all of the group allocated to the blended PARASOL intervention. This may lead to bias mechanisms such as response bias or observer bias being present in the data [53]. One of the aims of the training provided to the healthcare professionals involved in the study is to avoid response bias from the health care professionals. Observer bias will be avoided by using a measurement protocol, well trained observers, and standardized outcome measures. A second limitation is that overtreatment may occur since not all patients with moderate MUPS will be prevented from developing chronic MUPS after completing the PARASOL intervention. This could lead to higher health care costs if patients are still consulting health care professionals after completing the PARASOL intervention. However, an early intervention for patients with moderate MUPS may lead to a decrease of direct and indirect costs on long term if

chronic MUPS is prevented. Therefore, one of the secondary objectives is to determine the cost-effectiveness of the PARASOL intervention. A third limitation is complexity of the design of the study due to the use of cluster randomization. Cluster randomized trials are more complex, require more patients to obtain equivalent statistical power, and require more complex analysis [43]. However, in the sample size calculation and statistical analysis, this possible design effect has been taken into account.

This study is the first trial that investigates the effectiveness (including cost-effectiveness) of a blended care program in patients with moderate MUPS. Therefore, this study will provide relevant results regarding short- and long-term effectiveness of a multidisciplinary, blended care program to prevent chronic MUPS.

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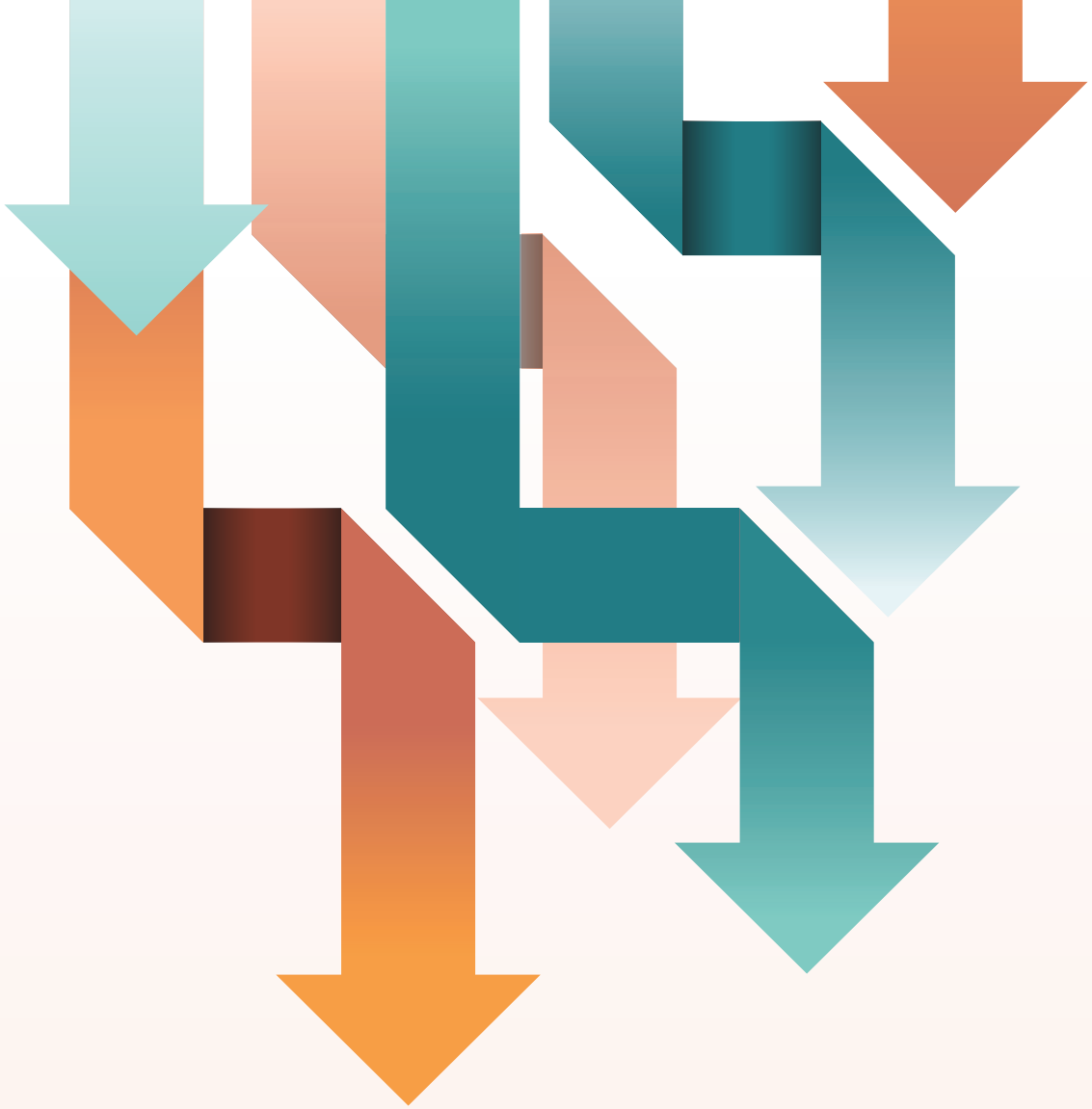
APPENDIX 1: SCHEMATIC VIEW OF THE BLENDED HEALTH CARE PROGRAM

Schematic view of the blended health care program		
Intake	Physical therapist	Anamnesis and physical examination
		Providing information about the web-based part of the health care program
	Mental health nurse	Anamnesis according to the SCEGS
Week 1	Physical therapist	Education about therapeutic neuroscience education
		Providing information about the 3-day baseline self-test
	Mental health nurse	Education about perpetuating factors
	Web-based component	Module 1: Central sensitisation & perpetuating factors
		Performance of a 3-day baseline test
Week 2	Web-based component	Module 2: Graded activity & Behavioural change
Week 3	Physical therapist	Evaluation of education week 1
		Education about graded activity
		Evaluation results from the 3-day self-test
		Determining short term goal
		Discussing the gradual increase of the selected activity
	Mental health nurse	Patient specific inventory on perpetuating factors
		Education about coping strategies
	Web-based component	Starting gradually increase selected activity
Week 4	Web-based component	Module 4: Stress
Week 5	Web-based component	Module 5: Coping with physical complaints
Week 6	Physical therapist	Evaluation of graded activity
		Evaluation of online modules
		Coaching on lifestyle
	Mental health nurse	Evaluation of perpetuating factors
		Evaluation of the coping strategies
Week 7	Web-based component	Module 7: Relaxation
Week 8	Web-based component	Module 8: Lifestyle
Week 9	Web-based component	Module 9: Creating an exercise plan
Week 10	Web-based component	Module 10: Performing the exercise plan
Week 11	Web-based component	Module 11: Maintaining an active lifestyle and avoiding a relapse
Week 12	Physical therapist	Discussing long-term goals
		Support to maintain a physically active lifestyle



4

CHAPTER

Effectiveness of a blended multidisciplinary intervention for patients with moderate medically unexplained physical symptoms (PARASOL): a cluster randomized clinical trial

Paula E. van Westrienen
Niek J. de Wit
Suze A.J. Toonders
Cindy Veenhof
Marloes M.J.G. Gerrits
Martijn F. Pisters

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ABSTRACT

Introduction

In patients with moderate Medically Unexplained Physical Symptoms (MUPS), interventions focusing on both physical and psychological aspects are recommended. A proactive, blended and integrated physical therapy and mental health nurse intervention (PARASOL) might reduce complaints, stimulate self-management and prevent chronicity.

Objective

To investigate short- and long-term effectiveness of the PARASOL intervention compared to usual care on subjective symptom impact and quality of life in patients with moderate MUPS.

Methods

We conducted a cluster randomized clinical trial. The 12-week intervention integrated face-to-face sessions with the physical therapist and mental health nurse and access to a web-based program consisting of graded activity, exercises and information modules. Primary outcomes were subjective symptom impact, as registered with the adequate relief question, and quality of life. Secondary outcomes were severity of (psychosocial) symptoms, overall current health, physical behaviour, illness perceptions, and self-management skills. Assessment took place at baseline, after three and twelve months.

Results

Compared to usual care (n=80), the number of patients in the PARASOL intervention (n=80) that reported adequate short-term relief was higher (31.2% in intervention group vs. 13.7% in control group). On quality of life and secondary outcomes no significant between group differences in short- and long-term were found.

Conclusions

The PARASOL intervention does improve subjective symptom impact of patients with moderate MUPS on short-term. No additional beneficial effects on the other outcomes and the long-term were found.

INTRODUCTION

Medically unexplained physical symptoms (MUPS) are defined as physical complaints such as pain, fatigue and/or dizziness for which no pathophysiological explanation can be found after adequate medical examination[1,2,3]. MUPS is classified in a continuum from mild, to moderate, to chronic MUPS[1]. The majority (75%) of the patients have mild MUPS, in whom symptoms generally recover within 1-3 months[4,5,6]. These symptoms usually have a low impact in one or two domains and are in many patients transient. Twenty percent of the patients with MUPS have persisting symptoms after three months. Most of them have moderate MUPS[4], and experience severe unexplained symptoms in two or three domains with a higher impact in daily life, with psychological and physical distress, but without a diagnosis of a functional somatic syndrome (FSS), or a somatic symptom disorder (SSD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition[4,7]. Patients with moderate MUPS experience a better quality of life than patients with chronic MUPS[8]. The remaining 5% have chronic MUPS, defined by the presence of FSS, such as fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome, or SSD[4,7]. Patients with chronic MUPS have more severe symptoms and experience psychological and physical dysfunction[4]. Chronic MUPS has a high impact on patients' quality of life and daily functioning[9,10], and are associated with mental health disorders as depression and anxiety[11]. MUPS can be clarified by the biopsychosocial model, based on the theory of Engel[12]. Physical, psychological and social factors are considered to be contributors to the symptoms and experienced disability.

Many patients with MUPS have a good prognosis. Fifty to 75% of the patients with MUPS improve within one year. Yet, unfortunately approximately 10 to 30% deteriorate[13]. An unfavourable course towards chronicity is expected when patients have a multiple number of physical symptoms within different clusters, experience more severe symptoms, have poorer physical functioning, have financial problems or have a history of childhood physical abuse[13,14]. Furthermore, female gender and an older age seems to be associated with unfavourable disease course, but results are inconsistent[14,15].

Much research has been conducted on effective interventions for chronic MUPS. Neurosciences-based therapeutic education, cognitive behavioral therapy, and exercise therapy have been shown to be effective treatment modalities in patients with chronic MUPS[16,17,18,19]. Most pharmacological interventions focused on antidepressants in patients with chronic MUPS. No pharmacological interventions are known that sufficiently treat all symptoms while avoiding the risk of adverse events[20]. The guideline therefore

recommend to be reluctant with pharmacotherapy in MUPS[2]. Overall, the vast majority of these studies included patients with chronic MUPS. So far little research has been conducted in patients with moderate MUPS.

For GPs, adequate management of chronic MUPS is challenging, given the unexplained background and high consultation frequency[10,21]. For society, the high health care utilization in chronic MUPS creates a financial burden[10,22]. Because of the high impact of chronic MUPS there is a need for early identification of patients with moderate MUPS and (cost-)effective interventions to prevent chronicity.

We demonstrated in earlier research that patients with moderate MUPS can be adequately identified using data of the electronic medical records of the GP[23]. Subsequently patients can be proactively approached by the GP for intervention. However, so far, no effective interventions for patients with moderate MUPS are known. Currently, Dutch multidisciplinary guidelines recommend focus on both physical and mental aspects in treatment[2]. In the Dutch gatekeeper system, patients consult their GP first. Within Dutch general practices, GPs work together with a mental health nurse. Mental health nurses work under the supervision of the GP[24] . They have received higher vocational training in nursing or psychology and deliver short-term care to patients with psychosocial problems[24]. The GP is suggested to act as case manager, in close collaboration with the mental health nurse and/or physical therapist with a special interest in MUPS. So far solid evidence for effectiveness of this integrated approach is lacking[2,25].

We developed a proactive, blended and integrated multidisciplinary intervention (PARASOL) for patients with moderate MUPS in primary care with the aim to prevent chronicity[26]. The intervention integrates face-to-face sessions with the physical therapist and mental health nurse with a web-based program of graded activity, information modules and exercises. This blended care approach provides patients 24/7 access to an online eCoachings platform, ensuring continuity of care and encouragement of self-management. Therefore, the aim of this study was to evaluate the effectiveness of the PARASOL intervention on subjective symptom impact and quality of life of patients with moderate MUPS in primary care, as compared to usual care. As our intervention can be considered a complex intervention, the Medical Research Council framework was used for the evaluation of PARASOL[27].

MATERIALS AND METHODS

Design

A prospective, multicenter cluster randomized clinical trial in primary care, reported according to the CONSORT Cluster Trial checklist.

Setting and participants

Fifteen multidisciplinary health care centers, with in total 110.000 patients, participated. Patients were eligible if they were 18 years or older, had at least five GP's consultations in the past 12 months, of which three or more resulted in a diagnosis suggestive of MUPS. Furthermore, patients with an established chronic MUPS diagnosis (i.e. fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome) and a confirmed medical and/or psychiatric diagnosis (i.e. chronic obstructive pulmonary disease, hypertension or diabetes mellitus schizophrenia, anxiety disorder or depressive disorder) were excluded.

Eligible patients were approached using three strategies[23]. In the first strategy patients with moderate MUPS were identified in the electronic medical records of the GP using the previously reported PRESUME screening method[23]. All identified patients were proactively approached with an invitation letter of their GP explaining the study. In the second strategy participating GPs of the fifteen health care centers actively recruited patients with moderate MUPS during consultations, and – if met the PRESUME criteria for moderate MUPS – linked the patient to the research group for inclusion. In the third strategy patients were recruited through flyers in the waiting rooms in the fifteen participating health care centers by placing and study information in the centers' newsletters. Patients who were willing to participate were encouraged to contact the researcher by phone or by mail. Subsequently, the researcher checked the diagnosis (moderate MUPS according to the PRESUME criteria), and confirmed that patients had access to internet and master the Dutch language. After receiving detailed information about the study's aims and procedures, patients were asked to provide written informed consent.

Intervention program

The twelve week PARASOL intervention integrates five face-to-face sessions with the physical therapist, four face-to-face sessions with the mental health nurse and access to a web-based program focusing on 1) graded activity, 2) exercises and 3) information modules (shown in Fig 1). The components of the intervention were based on results of a literature search and focus groups with experts (GPs, psychosomatic physical therapists,

mental health nurses and health care psychologists)[28]. The structure of the web-based program was based on the e-Exercise intervention for patients with hip or knee osteoarthritis[29].

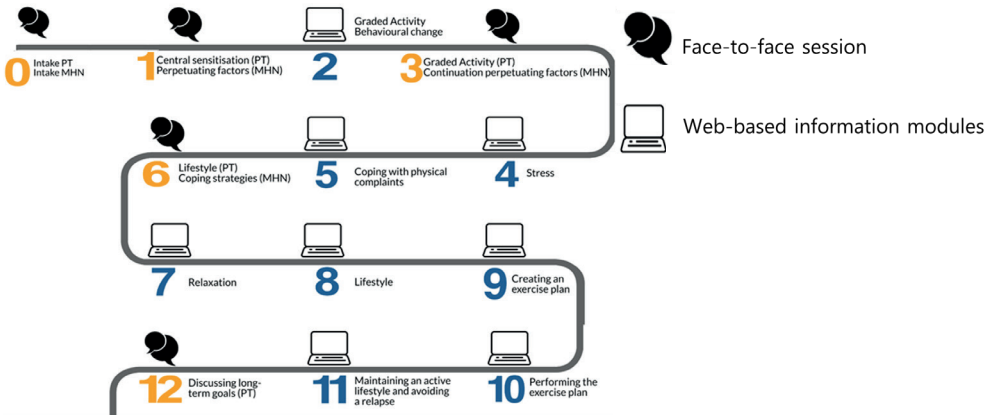

Figure 1: Overview of the PARASOL intervention

The intake started with the physical therapist since participants' perception of the symptoms usually has a somatic focus and patients with MUPS are often reluctant to focus on the psychosocial complaints [30,31]. The physical therapist focused on the somatic complaints and conducted a physical examination to get insight in the physical status (e.g. posture and movement, breathing patterns and muscle tension). Afterwards, the physical therapist created an account for the web-based program and added symptom specific exercises in the web-based program and informed the participant about the first information modules with corresponding home assignments. In the second part of the intake, the mental health nurse focused on cognitive, emotional, behavioural and social aspects of the complaints[32]. Patients' treatment goals and treatment demand were also identified during the intake. After completing the intake the two professionals discussed the complaints, the background, the expectations and the treatment goals of the patient.

After the intake, participants had four follow-up sessions with the physical therapist and three with the mental health nurse, combined with home assignments in the web-based program. The home assignments and the themes of the information modules (videos and descriptions) were discussed during the face-to-face sessions. Participants followed an online graded activity program and received instructions for exercises at home (shown in Fig 1). Participants received automatic support during their graded activity program

and home exercises of the web-based program. Weekly automatic emails informed and reminded participants about new assignments and content. The content of the intervention was described in more detail elsewhere[26].

Usual care

Usual care was defined as routine GP care for patients with MUPS, which could be provided by the GP, physical therapist, mental health nurse and psychologist, without restrictions. The physical therapists and mental health nurses of the health care centers in the control group were blinded to the intervention, i.e. they were not aware of the content of the PARASOL intervention. After the end of the study, participants in the control group were offered to follow the PARASOL intervention.

Outcomes

Study outcomes were assessed at baseline, three months (short-term) and twelve months (long-term). Participants were asked to fill out questionnaires and wear an activity monitor for a week. Participant characteristics such as age, gender, marital status, education level, work situation, duration of complaints, and possible comorbidities were measured at baseline. If participants did not complete the questionnaires, a first reminder was sent after one week and a second reminder or a phone call after two weeks. No financial incentives were offered to complete the measurements.

Primary outcome measures

We used two primary outcomes to evaluate the PARASOL intervention. The first one was subjective symptom impact, as registered with the adequate relief question. This is a validated single question measurement, which is scored on a dichotomous scale ("Over the past week have you had adequate relief of your symptoms?")[33,34]. Adequate short-term relief was defined as a participant who reported adequate relief of their symptoms for at least six of the twelve weeks between the baseline and three-month follow-up. If not, a participant was defined as a non-responder[35]. Adequate long-term relief was defined as a participant who reported adequate relief of their symptoms for at least four of the seven months between the 6- and 12-month follow-up. The second primary outcome was quality of life, as assessed with the 36-Item Short Form Health Survey (RAND-36) health survey[36,37]. The RAND-36 consists of eight subscales, which were merged into two summary component scales: "Physical Component Scale" (PCS)

and Mental Component Scale" (MCS). The norm-based score for the PCS and MCS was 50, where a score below 50 meant a less favourable physical and mental health state[38,39].

Secondary outcome measures

Symptom severity for pain and fatigue was assessed using a numeric rating scale ranging from 0 (no pain/no fatigue) to 10 (worst possible pain/fatigue)[40]. Severity of psychosocial symptoms was assessed with the Four-Dimensional Symptom Questionnaire (4DSQ) [41,42]. The questionnaire consists of four subscales, namely distress with a score range of 0-32, depression with a score range of 0-12, anxiety with a score range of 0-24 and the somatisation scale with a score range of 0-32. A higher score defines an increased probability of a disorder. Overall current health was assessed with the EuroQol visual analogue scale (EQ VAS)[43]. Scores ranged from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Physical behaviour was assessed with the Activ8 activity monitor[44]. The Activ8 is an activity monitor that measures physical behaviour by measuring several activities and postures (lying, sitting, standing, walking, running and cycling). Data were converted into total sedentary time and the average amount of hours of moderate or vigorous physical activity (MVPA). Total sedentary time (average hours per day) included any waking behaviour characterized by an energy expenditure $\leq$1.5 metabolic equivalents, while in a sitting, reclining or lying posture. MVPA was measured, to determine if participants met the Dutch Standard for Healthy Physical Activity criteria. Participants met the Dutch Standard for Healthy Physical Activity if they had at least 150 minutes of moderate intense physical activity every week, spread over several different days[45]. Illness perceptions were assessed with the Brief Illness Perception Questionnaire[46,47]. The questionnaire consists of eight items and has a score range of 0-10. Higher scores on personal control beliefs, treatment control beliefs and coherence beliefs indicates an improvement in perception, whereas on consequences beliefs, timeline beliefs, identity beliefs, concern beliefs and emotional response beliefs a lower score indicates an improvement in perception. Self-management skills were assessed with the Health Education Impact Questionnaire. The questionnaire consists of eight subscales and were scored on a 4-point Likert scale ("totally disagree" to "totally agree") [48]. A higher score indicates a higher level of self-management.

Sample size

The power calculation was based on the recommendations of Campbell et al[49] for cluster randomized trials and performed for the primary outcome measure quality of life (power = 0.8; alpha = 0.05). An intraclass correlation coefficient of 0.05 was assumed and a minimum cluster size of 20. In addition, to detect a clinically relevant difference between groups, a difference of >10 points in the sum score of physical functioning of the RAND-36 questionnaire and a SD of 23.8 were used in sample size calculation[50]. With an expected dropout rate of 20%, a total of 248 participants (n=124 per arm) were needed.

Randomization

We used cluster randomization on health care center level to prevent contamination effects. Of the 15 health care centers, eight were randomized to the PARASOL intervention and seven the control group. Concealment of allocation was ensured since a person outside of the research team performed the randomization. The health care centers were informed about their allocation by email. The health care professionals and patients were not blinded. The main investigators were also not blinded to group assignment.

Physical therapists and mental health nurses of the health care centers assigned to the intervention group were asked if they had a special interest or already experience in treating patients with MUPS. The physical therapists and mental health nurses signed up were instructed how to treat patients with moderate MUPS during a two-day training on the content of the PARASOL intervention. Furthermore, a booster session after six months was conducted to ensure adherence to the treatment protocol. The physical therapists and mental health nurses of the control health care centers were not trained.

Ethics

The trial protocol and study material was approved by the Medical Ethical Committee of University Medical Center Utrecht, the Netherlands (number 16/532). The trial was registered in the Dutch trial register with number NL6581. The authors confirm that all ongoing and related trials for this intervention are registered. Participants were informed about the design and conduct of the study and asked for informed consent. They were assigned to a unique trial code and participant information was stored separately from outcome data.

Statistical analysis

Descriptive statistics were used to describe participants' general characteristics. Frequencies, t tests and chi-square tests were used to explore agreement in demographics between both groups on general characteristics. The primary analyses were performed according to the intention-to-treat principle. Per-protocol analyses were performed for participants who attended all face-to-face meetings of the PARASOL intervention and for all participants in the usual care group, despite per-protocol analyses were not planned in the initial study protocol[26]. Missing values were imputed with the Multivariate Imputation by Chained Equations.

We performed univariate and multivariate analyses to determine the effectiveness of the PARASOL intervention on mean differences in the primary and secondary outcome measures on short- and long-term. In both univariate and multivariate analyses, the baseline value was included as covariate[51]. In the multivariate analyses, we controlled for recruitment strategy, marital status, age and duration of symptoms, since these variables had a more than 10% change-in-estimate of the effect. The primary outcome subjective symptom impact was analyzed by logistic regression. All other outcome measures were analyzed with a linear regression model. From these models, we estimated the mean of the outcomes for the intervention group and control group, mean differences within groups and mean differences between groups (with 95% CIs).

To determine if linear mixed model analysis with a 2-level hierarchy was necessary, heterogeneity was assessed across health care centers on quality of life as primary outcome measure by calculating the ICC. The highest ICC was found to be 0.034. Linear mixed model analyses were performed, but no variations between clusters was observed. Therefore, only univariate and multivariate intention-to-treat analyses are presented in the tables.

Per-protocol analyses consisted of multivariate analyses controlling for the same variables as the primary analyses. Additional sensitivity analyses were performed by comparing the results of the main analysis of subjective symptom impact for different cut-off points to ensure the validity of the results. On short-term, we adjusted the cut-off points by defining a responder as a participant who reported adequate relief of their symptoms for at least 40% or at least 60% of the measurements. On long term, we adjusted the cut-off points by defining a responder when a participant reported adequate relief of their symptoms for at least 40% or at least 70%. Analyses were carried out using SPSS Statistics 25.0 (IBM SPSS, Chicago, Illinois).

RESULTS

Participant flow

After randomisation, one health care center allocated to the intervention group declined to participate due to lack of time of the health care professionals. In the remaining 14 health centers, 169 eligible patients were included between March 2017 and April 2018. Of these, 139 (82%) participants were identified through the PRESUME approach, 5 (3%) were recruited during GP's consultation and 25 (15%) via flyers in the waiting rooms and study information in the centers' newsletters. On average, five participants were included per health care center (range 2 to 34). Nine eligible patients did not provide informed consent, because of lack of time (n=1), priority for another treatment (n=1) or other/ unknown (n=7). Of the remaining 160 participants, 80 originated from health care centers allocated to the intervention group and 80 from health care centers allocated to the control group. The inclusion stopped after the originally planned 12 months because of the financial budget restrictions of the project. Seven physical therapists and six mental health nurses from the health care centers allocated to the PARASOL intervention, were trained in the PARASOL intervention. On average they each treated 12 participants (range 5 to 26). No adverse effects of the intervention were reported.

The response rate for the questionnaires was 100% at baseline, 82% at three months, and 71% at twelve months (Fig 2). Eligible activity monitor data at baseline, three months and twelve months were available for 96%, 71%, and 60% of the 160 participants, respectively. Overall dropout rate in the intervention group was 33% and 25% in the control group. In the intervention group dropouts were significantly older and had a significantly shorter duration of symptoms compared to the non-drop outs. In the control group dropouts and non-dropouts did not differ. Furthermore, the two patient groups did differ significantly in recruitment strategy (Table 1).

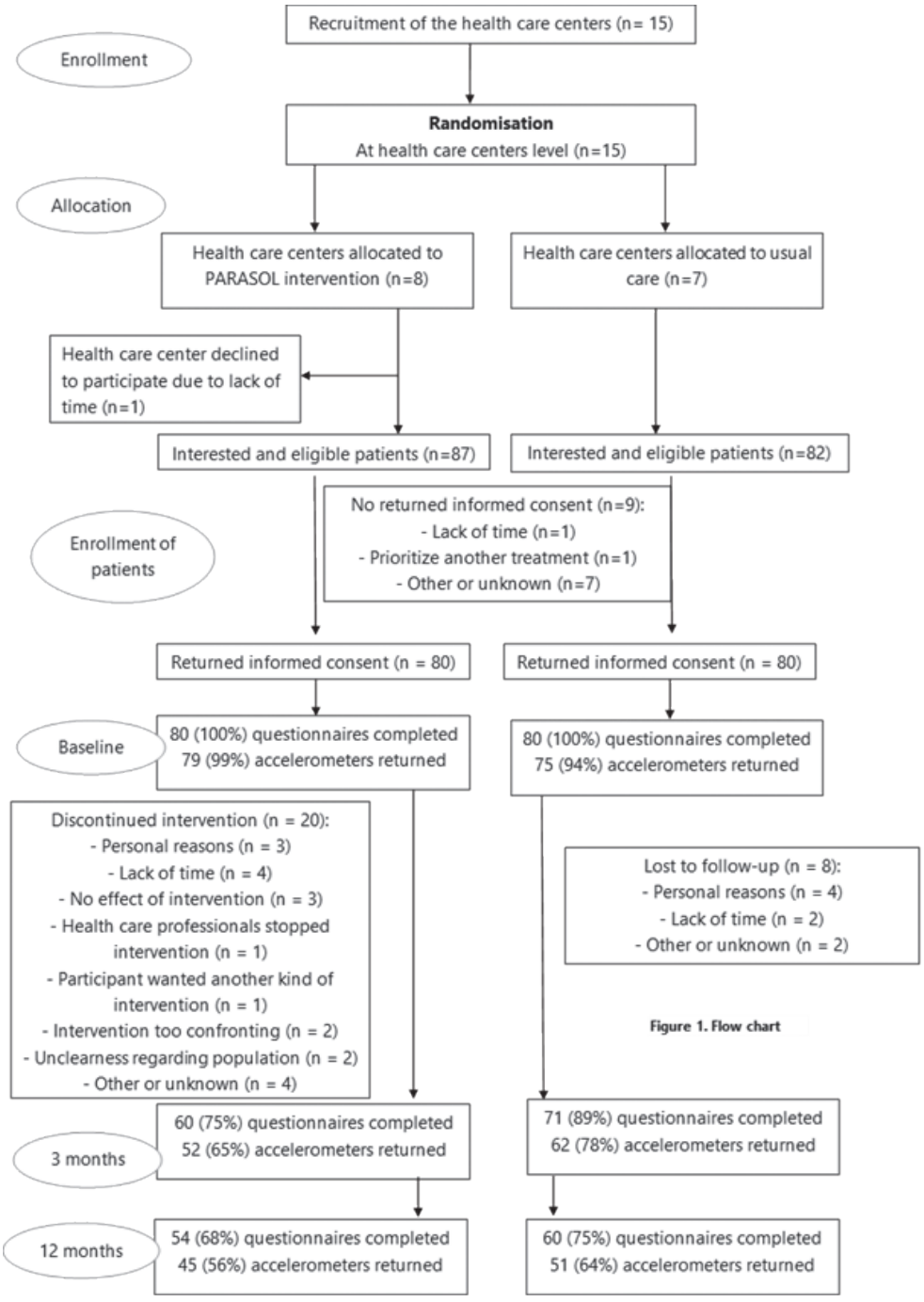

Figure 2: Flow chart

Table 1: Characteristics of participants[a]

Characteristic	Baseline		
	All participants (n = 160)	Exp (n= 80)	Con (n = 80)
Gender, female	119 (74.4)	57 (71.3)	62 (77.5)
Age *(yr)*, mean (SD)	48.4 (13.7)	47.1 (12.4)	49.7 (14.9)
Duration of symptoms			
0 mo. – 1 y.	22 (13.7)	8 (10)	14 (17.5)
≥1 y.	138 (86.3)	72 (90)	66 (82.5)
Education level			
Low	41 (25.6)	18 (22.5)	23 (28.8)
Middle	65 (40.6)	38 (47.5)	27 (33.8)
High	54 (33.8)	24 (30)	30 (37.5)
Work status			
Student	2 (1.3)	1 (1.3)	1 (1.3)
Employed	103 (64.4)	53 (66.3)	50 (62.5)
Unemployed	27 (16.9)	13 (16.3)	14 (17.5)
Retired	22 (13.8)	10 (12.5)	12 (15)
Volunteer	6 (3.8)	3 (3.8)	3 (3.8)
Marital status[b]			
Unmarried	56 (35)	22 (27.5)	34 (42.5)
Married/living with a partner	103 (64.4)	57 (71.3)	46 (57.5)
No. of comorbidities			
0	85 (53.1)	45 (56.2)	40 (50)
1	31 (19.4)	15 (18.8)	16 (20)
≥2	44 (27.5)	20 (25)	24 (30)
Recruitment strategy			
PRESUME screening	130 (81.3)	57 (71.3)	73 (91.3)
GP during consultation	5 (3.1)	5 (6.3)	0 (0)
Open recruitment	25 (15.6)	18 (22.5)	7 (8.8)

[a]Data are reported as number (percentage) of participants unless otherwise indicated.

[b]One participant included in the experimental group refused to answer here marital status.

Exp = experimental group, Con = control group

Short-term effectiveness

After completing the intervention, 31.2% of patients reported adequate relief, as compared to 13.7% in the control group (Table 2). This between group difference persisted after adjustment for recruitment strategy, marital status, age and duration of symptoms in multivariate analysis (Table 3). The quality of life of patients within the intervention group improved significantly both for PCS and MCS (Table 2). However, no between group differences in quality of life were found. Adjustment for potential confounders showed similar results (Table 3).

As for the secondary outcomes, patients within the intervention group improved significantly on overall current health, severity of psychosocial symptoms subscale distress and subscale somatization, and the illness perception items personal control, coherence, and emotional response (S1 Table). In contrast, in the usual care group, none of the outcome measures showed any significant within group differences over time. However, no significant between group differences were found on the secondary outcome measures (S1 Table). Adjustment for potential confounders showed similar results (Table 3).

Short-term results of the per-protocol analyses showed similar results on the primary outcome measures as the intention-to-treat analyses (S2 Table). Both sensitivity analyses, where different cut-off points were compared, demonstrate comparable findings on subjective symptom impact (S3 Table).

Long-term effectiveness

In 12-month follow-up, the percentage of patients with adequate relief in the intervention group was 41.3%, as compared to 31.2% in the control group. Between group differences were not statistically significant after adjustment for potential confounders (Table 3). Quality of life improved significantly on PCS and MCS in patients from the intervention group (Table 2). However, no between group differences in quality of life were found on the long-term. Adjustment for potential confounders showed similar results(Table 3).

As for the secondary outcomes, patients within the intervention group improved significantly on overall current health, severity of symptoms pain and fatigue, severity of psychosocial symptoms subscale distress, subscale anxiety and subscale somatization, and the illness perception items consequences, personal control and identity (S1 Table). Short and long-term results were similar for the secondary outcome measures. No significant between group differences were found on the secondary outcome measures (Table 3).

Long-term results of the per-protocol analyses showed similar results on the primary outcome measures as the intention-to-treat analyses. Only on the secondary outcome measures, heiQ subscale “self-monitoring and insight”, a statistically significant difference between groups was found (S2 Table). The sensitivity analyses, where different cut-off points were compared, demonstrated comparable findings on subjective symptom impact (S3 Table).

Table 2: Unadjusted primary outcome measures. Mean (SD) of groups, mean (SD) difference within groups, and mean difference (95% CI) or odds ratio (95% CI) between groups

Outcome	Groups						Difference within groups				Difference between groups	
	Week 0		3 months		12 months		3 months minus Week 0		12 months minus Week 0		3 months minus Week 0	12 months minus Week 0
	Exp (n = 80)	Con (n = 80)	Exp	Con	Exp	Con	Exp	Con	Exp	Con	Exp minus Con	Exp minus Con
Quality of Life RAND-36 *(0-100)*												
Physical Component Scale	42.7 (7.3)	42.7 (10.1)	46.5 (13.1)	43.9 (12.8)	46.5 (15.1)	43.9 (14)	MD 3.7 (1.4 to 6)	MD 1.3 (-1 to 3.5)	MD 3.7 (0.8 to 6.7)	MD 1.3 (-1.6 to 4.1)	MD 2.5 (-0.7 to 5.7)	MD 2.5 (-1.9 to 6.6)
Mental Component Scale	41.9 (12.7)	46 (11.6)	46.5 (20.1)	49 (15.2)	46.6 (17.2)	48.1 (14.7)	MD 4.6 (1.1 to 8.1)	MD 3 (-0.3 to 6.4)	MD 4.7 (1.3 to 8.1)	MD 2.1 (-1.2 to 5.3)	MD -0.3 (-5.5 to 4.8)	MD 0.4 (-4.3 to 5.1)
Impact of symptoms Adequate relief *(yes/no)* [a]												
Responder, n(%)	..	..	25 (31.2)	11 (13.7)	33 (41.3)	25 (31.2)	..	..	..	..	OR 2.9 (1.2 to 6.9)	OR 1.6 (0.7 to 3.4)

Exp = experimental group, Con = control group

MD = Mean Difference

Table 3: Adjusted multivariate comparisons of primary and secondary outcome measures per group based on intention-to-treat analysis at 3 and 12 months

	Difference between groups					
	3 months minus Week 0	Between- group difference (P)	Between-group effect size	12 months minus Week 0	Between- group difference (P)	Between-group effect size
	Exp minus Con			Exp minus Con		
Quality of Life RAND-36 *(0-100)* *						
Physical Component Scale	2.3 (-1.2 to 5.8)	0.19	0.17	2.9 (-1.5 to 7.3)	0.19	0.13
Mental Component Scale	0.3 (-5.1 to 5.7)	0.91	0.07	0.6 (-4.2 to 5.5)	0.79	0.11
Impact of symptoms						
Adequate relief (yes/no)†	2.8 (1.1 to 7.3)	0.04	0.18[a]	1.5 (0.7 to 3.4)	0.33	0.10[a]
Severity of symptoms NRS *(0-10)**						
Pain	-0.7 (-2.3 to 0.8)	0.35	-0.10	-0.9 (-2 to 0.3)	0.13	-0.18
Fatigue	-0.7 (-2.1 to 0.7)	0.34	-0.12	-0.4 (-1.4 to 0.7)	0.51	-0.11
Severity of psychosocial symptoms 4DSQ *						
Distress *(0-32)*	-0.8 (-4.7 to 3.2)	0.71	-0.07	-0.3 (-3.7 to 3)	0.84	-0.08
Depression *(0-12)*	-0.3 (-1.4 to 0.8)	0.63	-0.09	-0.2 (-1.4 to 1)	0.78	-0.07
Anxiety *(0-24)*	-0.3 (-2 to 1.3)	0.71	-0.09	-0.2 (-1.5 to 1.1)	0.79	-0.09
Somatization *(0-32)*	-1.6 (-4.4 to 1.2)	0.27	-0.15	-1.7 (-4.5 to 1)	0.21	-0.16
Physical behaviour *(h/d)**						
Sedentary behaviour	0.4 (-1 to 1.7)	0.61	0.03	0.3 (-0.7 to 1.4)	0.52	0.06
Moderate or vigorous physical activity	0.1 (-0.3 to 0.5)	0.66	0.09	-0.1 (-0.4 to 0.2)	0.37	-0.02
EQ VAS *(0-100)**						
Overall current health	5.8 (-4.7 to 16.3)	0.28	0.18	3.6 (-4.2 to 11.4)	0.36	0.16
Illness perceptions IPQ-k *(0-10)**						
Consequences	-0.1 (-1.7 to 1.6)	0.95	-0.05	-0.3 (-1.5 to 0.8)	0.58	-0.10

	Difference between groups					
	3 months minus Week 0	Between- group difference (P)	Between-group effect size	12 months minus Week 0	Between- group difference (P)	Between-group effect size
	Exp minus Con			Exp minus Con		
Timeline	0 (-1.9 to 1.8)	0.97	0	0.6 (-0.8 to 2)	0.42	0.08
Personal control	0.8 (-1 to 2.7)	0.37	0.10	0.7 (-0.6 to 2)	0.32	0.14
Treatment control	0.8 (-1.1 to 2.6)	0.42	0.01	0 (-1.5 to 1.5)	0.98	-0.13
Identity	0.1 (-1.2 to 1.3)	0.93	-0.03	-0.5 (-1.6 to 0.5)	0.31	-0.14
Concern	0.3 (-1.4 to 2)	0.73	-0.01	0.1 (-1.1 to 1.3)	0.83	-0.05
Coherence	0.6 (-0.9 to 2.2)	0.42	0.12	0.4 (-0.9 to 1.7)	0.53	0.15
Emotional response	0.5 (-1.2 to 2.3)	0.53	0.01	0.4 (-0.8 to 1.6)	0.51	-0.02
Self-management skills HEI-Q *(1-4)**						
Health-directed activity	0.06 (-0.27 to 0.38)	0.73	0.15	-0.08 (-0.36 to 0.21)	0.61	0.14
Positive and active engagement in life	0.04 (-0.23 to 0.30)	0.78	0.06	0.10 (-0.15 to 0.36)	0.42	0.13
Self-monitoring and insight	0.18 (-0.11 to 0.47)	0.22	0.19	0.18 (-0.04 to 0.40)	0.10	0.24
Constructive attitude and approaches	-0.01 (-0.29 to 0.27)	0.93	0.04	0.06 (-0.16 to 0.28)	0.61	0.11
Skill and technique acquisition	0.18 (-0.22 to 0.58)	0.38	0.19	0.15 (-0.09 to 0.39)	0.22	0.27
Social integration and support	0.07 (-0.28 to 0.42)	0.70	0.07	-0.12 (-0.37 to 0.13)	0.35	-0.04
Emotional distress	0.01 (-0.29 to 0.31)	0.96	0.07	0.01 (-0.25 to 0.26)	0.94	0.07
Health service navigation	0.01 (-0.31 to 0.32)	0.96	0.01	-0.01 (-0.24 to 0.23)	0.95	0

*Data are differences in mean (95%CI)

†Data are odds ratio (95% CI)

[a]Data are risk differences

Exp = experimental group, Con = control group

DISCUSSION

This is the first multicenter cluster randomized clinical trial of a proactive, blended and integrated intervention with a physical therapist and mental health nurse for primary care patients with moderate MUPS aiming at prevention of chronicity. The results showed more patients with short-term adequate relief after treatment with the PARASOL intervention compared to the usual care group. Unfortunately, this between group difference in favour of the PARASOL intervention did not sustain in long-term. Although quality of life improved within the PARASOL group after the intervention, this improvement did not differ from the usual care group. No additional beneficial effects of the PARASOL intervention on the secondary outcomes were found, neither in short-term nor in long-term follow-up.

Subjective symptom impact was one of the primary outcome measures because this subjective outcome adequately reflects the perception of symptoms. Better adequate short-term relief was not accompanied by significant improvements on severity of symptom scores. The explanation for this finding might be that the intervention focused on patients' insight, perception of symptoms and modifiable prognostic risk factors. Thus the main effect of the PARASOL intervention might be diminishing the impact of symptoms on patients by improving coping strategies and perception of symptoms, without having an effect on symptom severity.

The PARASOL intervention is the first blended care intervention in patients with moderate MUPS. It is hypothesized that blended care can help to stimulate self-management. Although self-management skills improved after the intervention, this improvement did not differ from the usual care group. A possible explanation might be that patients had a lack of intrinsic motivation due to the proactive approach of the GP since the presence of motivation is an important aspect for patients' self-management[52]. Therefore, insight in patients' self-management skills should be assessed for personalization of the intervention, to enable stimulation of self-management in the right patients.

Although not statistically significant, a positive trend in the between group differences on quality of life in favour of the PARASOL intervention was found. Not achieving the preset sample size might be an important reason why we were not able to demonstrate the effectiveness of the PARASOL intervention. The size of the effect on quality of life at the end of treatment was similar to earlier research, but differ with a more recent primary care intervention in patients with MUPS[19,53]. Sitnikova et al. found a significant effect on the physical component of quality of life at the end of the treatment, but this effect did

not sustain on long-term. This is remarkable compared to our results, since our results showed a sustained long-term improvement, although not different from the usual care group. The sustained long-term improvement might be due to the fact that the PARASOL intervention focused on adopting and maintaining a behavioral change. Taking into account the sustained long-term improvement on quality of life and the short-term effect on subjective symptom impact, despite the low power, we recommend to optimize the PARASOL intervention. An idea for optimization is adding a booster session a few weeks after the end of the intervention, to enhance long-term effectiveness and reinforce changes.

Strengths and limitations

The strength of this study is that we opted for cluster randomization, in order to keep the effect of the intervention as pure as possible to prevent a contamination effect. The following limitations of the present study need to be taken into account. First, we only included 160 participants while the desired number of participants was 248. Since the number of interested patients was lower than expected in the first recruitment strategy, we added the second and third recruitment strategy and extended the inclusion period with another six months, but we still did not achieve our sample size needed. This may raise questions regarding the validity of our results. However, absence of evidence is not evidence of absence[54]. So it might be that the absence of a statistically significant effect is due to a small sample despite a positive trend in difference in endpoints. However, on the other hand the non-significant between group differences in quality of life on the short term and long-term differences on the primary outcomes can be considered small effect sizes. Besides the low number of participants, the inclusion of participants using the three recruitment strategies differed substantially between both groups, which may be considered as bias. Secondly, we had to deal with high drop-out rates: 18% after three months and 29% after twelve months. Percentages of missing data in our activity monitor data were even higher. The low number of participants and the high drop-out rates might be attributed to a relatively long follow-up period, the number and length of the measurements and the recruitment strategy where patients were proactively approached by the GP and therefore might be less motivated to change. Retrospectively, conducting a pilot study first might have been better in terms of recruitment success and a lower drop-out rate. Thirdly, our included patient group is very heterogeneous. Patients with moderate MUPS differ on severity of symptoms, duration of symptoms and might have varying needs. The heterogeneity might have contributed to more outliers and a wide dispersion across participants. Fourthly, the 2-day training session for the

physical therapists and mental health nurses of the health care centers assigned in the intervention group was a bit short. Blended care is a relatively new way of delivering care, which requires a different way of working for health care professionals. Therefore, training of the health care professionals is a target for improvement. Future training should also have more focus on gaining insight in the added value of integrated care and how this supports patients' self-management. Another limitation are the established baseline differences between groups on both primary and secondary outcome measures despite randomization, which might have influenced our findings[51]. Overall, the intervention group had a lower score on baseline measurements as compared to the control group. As a consequence, patients in the intervention group had a higher potential to improve. This might be attributable to the fact that only patients with more severe complaints wanted to participate, after which the symptoms generally improve during the trial, also known as regression to the mean. In addition, in both groups a proportion of the patients might have improved spontaneously[23]. A final limitation is that the psychometric properties of the adequate relief question in patients with moderate MUPS are unknown. The adequate relief question is a validated clinically relevant endpoint in patients with irritable bowel syndrome, an established chronic MUPS diagnosis. This may raise questions regarding the relevancy in patients with moderate MUPS. However, we chose the adequate relief question since this subjective outcome reflects on the perception of symptoms which is as important as actual symptom severity in patients with functional disorders[55].

Clinical Implications and Future Directions

The current trend in daily practice is a stepped care strategy with attention to self-management. This includes that patients are treated in accordance with their symptom severity by the right health care professional in the right place at the right time. In the Netherlands health care insurance companies require that patients follow a primary care intervention first before they can be referred to secondary care. In our opinion, the PARASOL intervention, if optimized, suits in this requirement. In case of deterioration of symptoms or unsatisfying results, patients could be referred to secondary care.

Given the adequate short-term relief and the improvements within the intervention group on short- and long-term, PARASOL has the potential to become a valuable primary care intervention. The PARASOL intervention can prevent high costs for society, including health care costs. Therefore, cost-effectiveness from a societal perspective of the PARASOL intervention compared to usual care in patients with moderate MUPS will be evaluated in another study.

CONCLUSION

In conclusion, a relatively short multidisciplinary intervention in primary care, integrating face-to-face sessions with a web-based program does improve subjective symptom impact of patients with moderate MUPS on short-term. No additional beneficial effects on the other outcomes were found on the short and long-term.

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S1 Table: Unadjusted secondary outcome measures. Mean (SD) of groups, mean (SD) difference within groups, and mean difference (95% CI) or odds ratio (95% CI) between groups

Outcome	Groups						Difference within groups				Difference between groups	
	Week 0		3 months		12 months		3 months minus Week 0		12 months minus Week 0		3 months minus Week 0	12 months minus Week 0
	Exp (n = 80)	Con (n = 80)	Exp (n = 80)	Con (n = 80)	Exp (n = 80)	Con (n = 80)	Exp	Con	Exp	Con	Exp minus Con	Exp minus Con
Severity of symptoms NRS *(0-10)*												
Pain	5.2 (2.4)	4.8 (2.5)	4.2 (5.7)	4.5 (4.1)	3.9 (3.8)	4.5 (3.7)	MD -1 (-2.3 to 0.2)	MD -0.3 (-1.4 to 0.7)	MD -1.3 (-2.3 to -0.3)	MD -0.3 (-1.3 to 0.7)	MD -0.5 (-2 to 0.9)	MD -0.8 (-1.9 to 0.3)
Fatigue	6.2 (2.6)	5.7 (2.6)	5.2 (5.3)	5.4 (4.1)	5 (2.8)	5.1 (3.4)	MD -1.1 (-2.3 to 0.1)	MD -0.3 (-1.4 to 0.8)	MD -1.2 (-2.2 to -0.2)	MD -0.6 (-1.6 to 0.3)	MD -0.5 (-1.9 to 0.9)	MD -0.3 (-1.3 to 0.8)
Severity of psychosocial symptoms 4DSQ												
Distress *(0-32)*	13.5 (8.6)	11.2 (8.4)	10.5 (15.8)	9.5 (11.3)	10.4 (10.7)	9.4 (10)	MD -3 (-5.6 to -0.4)	MD -1.7 (-4.1 to 0.7)	MD -3.1 (-5.4 to -0.7)	MD -1.8 (-4.1 to 0.5)	MD -0.5 (-4.3 to 3.4)	MD 0.1 (-3.1 to 3.2)
Depression *(0-12)*	2 (3)	1.3 (2.6)	1.4 (4.6)	1.1 (3.5)	1.3 (4.1)	1 (3.4)	MD -0.6 (-1.6 to 0.4)	MD -0.2 (-1 to 0.7)	MD -0.7 (-1.7 to 0.4)	MD -0.3 (-1.3 to 0.7)	MD -0.3 (-1.3 to 0.8)	MD 0 (-1.1 to 1.1)
Anxiety *(0-24)*	3.2 (4.3)	2.4 (4.5)	2.2 (6.5)	2.1 (5.3)	1.8 (4.1)	1.7 (4.3)	MD -1 (-2.3 to 0.4)	MD -0.3 (-1.5 to 0.8)	MD -1.4 (-2.7 to -0.2)	MD -0.7 (-2 to 0.6)	MD -0.3 (-1.9 to 1.2)	MD -0.1 (-1.3 to 1.1)
Somatization *(0-32)*	13.4 (6.9)	12 (6.9)	10.4 (11.1)	10.8 (8.4)	9.7 (9.5)	10.4 (9.3)	MD -3 (-5 to -1.1)	MD -1.2 (-3 to 0.6)	MD -3.7 (-5.7 to -1.6)	MD -1.6 (-3.6 to 0.4)	MD -1.4 (-4 to 1.2)	MD -1.4 (-3.9 to 1.2)
Physical behaviour *(h/d)*												
Sedentary behaviour	9 (2.4)	9 (2.2)	9.2 (5.3)	9 (4)	8.6 (3.5)	8.3 (3.4)	MD 0.2 (-1.1 to 1.5)	MD 0 (-1.1 to 1.2)	MD -0.3 (-1.4 to 0.7)	MD -0.7 (-1.7 to 0.4)	MD 0.2 (-1.1 to 1.5)	MD 0.3 (-0.7 to 1.3)
Moderate or vigorous physical activity	0.4 (0.5)	0.6 (0.6)	0.6 (1.3)	0.6 (1)	0.4 (0.8)	0.6 (0.9)	MD 0.1 (-0.4 to 0.7)	MD 0 (-0.4 to 0.4)	MD 0 (-0.4 to 0.4)	MD 0 (-0.4 to 0.4)	MD 0.1 (-0.3 to 0.5)	MD -0.1 (-0.4 to 0.1)
EQ VAS *(0-100)*												
Overall current health	60.7 (19.3)	67.2 (17)	72.2 (38.8)	70.5 (28.6)	69.3 (26.8)	69.6 (24)	MD 11.4 (5.4 to 17.5)	MD 3.2 (-2.6 to 9.1)	MD 8.6 (3 to 14.1)	MD 2.4 (-3.1 to 7.9)	MD 4.9 (-5.2 to 15)	MD 1.6 (-5.9 to 9.1)

Outcome	Groups						Difference within groups				Difference between groups	
	Week 0		3 months		12 months		3 months minus Week 0		12 months minus Week 0		3 months minus Week 0	12 months minus Week 0
	Exp (n = 80)	Con (n = 80)	Exp (n = 80)	Con (n = 80)	Exp (n = 80)	Con (n = 80)	Exp	Con	Exp	Con	Exp minus Con	Exp minus Con
Illness perceptions IPQ-k *(0-10)*												
Consequences	5.8 (2.7)	5.2 (2.7)	5.4 (5.8)	5.2 (4.2)	4.8 (3.6)	4.7 (3.8)	MD -0.5 (-1.7 to 0.8)	MD -0.1 (-1.2 to 1)	MD -1 (-2 to -0.1)	MD -0.5 (-1.5 to 0.4)	MD -0.1 (-1.6 to 1.4)	MD -0.2 (-1.3 to 0.8)
Timeline	7.4 (2.6)	7.5 (3.3)	7.3 (7.1)	7.5 (5.3)	7.3 (4.7)	7 (4.6)	MD -0.1 (-1.5 to 1.3)	MD -0.1 (-1.3 to 1.2)	MD -0.1 (-1.2 to 1.1)	MD -0.6 (-1.7 to 0.6)	MD -0.1 (-1.9 to 1.7)	MD 0.4 (-0.9 to 1.7)
Personal control	4.3 (2.3)	4.6 (2.7)	5.8 (6.4)	5.2 (4.5)	5.7 (4.1)	5.1 (4)	MD 1.5 (0.1 to 2.9)	MD 0.6 (-0.6 to 1.9)	MD 1.4 (0.2 to 2.5)	MD 0.5 (-0.6 to 1.6)	MD 0.6 (-1.1 to 2.3)	MD 0.6 (-0.6 to 1.9)
Treatment control	6 (2.2)	4.9 (3)	6.2 (6.8)	5 (4.8)	5.4 (4.6)	5.2 (4.8)	MD 0.2 (-1.2 to 1.6)	MD 0.1 (-1.1 to 1.4)	MD -0.6 (-1.9 to 0.6)	MD 0.3 (-1 to 1.5)	MD 0.7 (-1 to 2.5)	MD 0 (-1.5 to 1.4)
Identity	6.4 (2.1)	6 (2.3)	5.9 (4.5)	5.6 (3.3)	5.2 (3.6)	5.5 (3.6)	MD -0.5 (-1.5 to 0.6)	MD -0.3 (-1.2 to 0.6)	MD -1.2 (-2.1 to -0.2)	MD -0.5 (-1.4 to 0.4)	MD 0 (-1.1 to 1.2)	MD -0.5 (-1.5 to 0.5)
Concern	5.7 (2.7)	5 (2.9)	5.1 (6)	4.5 (4.5)	4.8 (4.1)	4.4 (3.6)	MD -0.6 (-1.9 to 0.7)	MD -0.5 (-1.6 to 0.7)	MD -0.9 (-1.9 to 0.2)	MD -0.6 (-1.7 to 0.4)	MD 0.2 (-1.4 to 1.8)	MD 0.2 (-0.9 to 1.3)
Coherence	5.3 (2.2)	5.9 (3.2)	6.8 (5.6)	6.5 (4.2)	6.3 (4.2)	5.9 (4.3)	MD 1.5 (0.2 to 2.8)	MD 0.6 (-0.5 to 1.8)	MD 1 (-0.2 to 2.1)	MD 0 (-1.2 to 1.2)	MD 0.6 (-1 to 2.1)	MD 0.5 (-0.7 to 1.8)
Emotional response	6.1 (2.7)	5.2 (3.2)	5.2 (6.3)	4.2 (4.3)	5.1 (3.8)	4.3 (4)	MD -0.9 (-0.1 to -1.8)	MD -1 (-2.1 to 0.1)	MD -1 (-2 to 0.1)	MD -0.9 (-2 to 0.2)	MD 0.5 (-1.2 to 2.1)	MD 0.5 (-0.7 to 1.6)
Self-management skills HEI-Q *(1-4)*												
Health-directed activity	2.94 (0.69)	3.27 (0.64)	3.16 (1.29)	3.29 (0.91)	3.13 (0.88)	3.27 (0.76)	MD 0.23 (-0.27 to 0.73)	MD 0.02 (-0.37 to 0.41)	MD 0.19 (-0.22 to 0.59)	MD 0 (-0.38 to 0.37)	MD 0.06 (-0.25 to 0.37)	MD -0.07 (-0.34 to 0.20)
Positive and active engagement in life	2.96 (0.55)	3.05 (0.55)	3.05 (0.97)	3.08 (0.70)	3.09 (0.84)	3.04 (0.77)	MD 0.09 (-0.31 to 0.50)	MD 0.02 (-0.31 to 0.35)	MD 0.13 (-0.26 to 0.52)	MD -0.01 (-0.36 to 0.33)	MD 0.04 (-0.21 to 0.28)	MD 0.09 (-0.15 to 0.33)

Outcome	Groups						Difference within groups				Difference between groups	
	Week 0		3 months		12 months		3 months minus Week 0		12 months minus Week 0		3 months minus Week 0	12 months minus Week 0
	Exp (n = 80)	Con (n = 80)	Exp (n = 80)	Con (n = 80)	Exp (n = 80)	Con (n = 80)	Exp	Con	Exp	Con	Exp minus Con	Exp minus Con
Self-monitoring and insight	2.80 (0.44)	2.93 (0.45)	3.00 (1.09)	2.90 (0.79)	3.03 (0.70)	2.91 (0.73)	MD 0.21 (-0.25 to 0.66)	MD -0.03 (-0.39 to 0.32)	MD 0.23 (-0.15 to 0.60)	MD -0.01 (-0.35 to 0.33)	MD 0.19 (-0.09 to 0.47)	MD 0.16 (-0.04 to 0.37)
Constructive attitude and approaches	3.02 (0.53)	3.13 (0.59)	3.09 (1.05)	3.16 (0.79)	3.15 (0.77)	3.15 (0.69)	MD 0.08 (-0.35 to 0.50)	MD 0.03 (-0.32 to 0.38)	MD 0.13 (-0.20 to 0.47)	MD 0.02 (-0.32 to 0.36)	MD 0.01 (-0.25 to 0.27)	MD 0.05 (-0.15 to 0.26)
Skill and technique acquisition	2.51 (0.54)	2.81 (0.58)	2.90 (1.55)	2.84 (1.06)	2.86 (0.76)	2.85 (0.76)	MD 0.39 (-0.18 to 0.96)	MD 0.03 (-0.42 to 0.49)	MD 0.35 (-0.02 to 0.71)	MD 0.04 (-0.33 to 0.41)	MD 0.16 (-0.21 to 0.54)	MD 0.21 (-0.11 to 0.35)
Social integration and support	2.76 (0.67)	2.86 (0.63)	2.92 (1.31)	2.91 (0.90)	2.83 (0.87)	2.98 (0.93)	MD 0.16 (-0.35 to 0.66)	MD 0.05 (-0.33 to 0.42)	MD 0.07 (-0.32 to 0.46)	MD 0.12 (-0.30 to 0.54)	MD 0.07 (-0.26 to 0.39)	MD -0.11 (-0.36 to 0.14)
Emotional distress	2.87 (0.65)	3.06 (0.63)	3.05 (1.19)	3.14 (0.89)	3.10 (0.95)	3.20 (0.86)	MD 0.17 (-0.29 to 0.64)	MD 0.08 (-0.29 to 0.45)	MD 0.23 (-0.17 to 0.63)	MD 0.14 (-0.25 to 0.53)	MD 0.04 (-0.25 to 0.32)	MD -0.02 (-0.26 to 0.23)
Health service navigation	2.98 (0.53)	2.99 (0.56)	3.04 (1.22)	3.03 (0.94)	3.06 (0.75)	3.07 (0.85)	MD 0.05 (-0.42 to 0.53)	MD 0.04 (-0.34 to 0.41)	MD 0.08 (-0.28 to 0.44)	MD 0.08 (-0.31 to 0.47)	MD 0.02 (-0.28 to 0.31)	MD 0 (-0.23 to 0.22)

Exp = experimental group, Con = control group

S2 Table: Primary and secondary outcome measures based on per-protocol analysis at 3 and 12 months

	Difference between groups	
	3 months minus Week 0	12 months minus Week 0
	Exp minus Con	Exp minus Con
Quality of Life RAND-36 *(0-100)* *		
Physical Component Scale	3 (0 to 6)	3.1 (-1 to 7.3)
Mental Component Scale	1 (-3.6 to 5.5)	1.4 (-3.4 to 6.3)
Impact of symptoms	2.8 (1 to 8)	1.3 (0.5 to 3.2)
Adequate relief (yes/no)†		
Severity of symptoms NRS *(0-10)**		
Pain	-1 (-2.1 to 0.2)	-1 (-2.1 to 0.2)
Fatigue	-1 (-2.2 to 0.1)	-0.4 (-1.5 to 0.7)
Severity of psychosocial symptoms 4DSQ*		
Distress *(0-32)*	-1.1 (-4.4 to 2.1)	-0.2 (-3.3 to 2.9)
Depression *(0-12)*	-0.3 (-1.3 to 0.6)	-0.2 (-1.3 to 1)
Anxiety *(0-24)*	-0.4 (-1.8 to 1)	-0.1 (-1.4 to 1.2)
Somatization *(0-32)*	-1.8 (-4 to 0.4)	-1.2 (-3.7 to 1.4)
Physical behaviour *(h/d)**		
Sedentary behaviour	0.3 (-0.8 to 1.5)	0.5 (-0.5 to 1.5)
Moderate or vigorous physical activity	0.1 (-0.2 to 0.4)	-0.1 (-0.4 to 0.1)
EQ VAS *(0-100)**		
Overall current health	5.8 (-2.3 to 13.8)	5.4 (-2.4 to 13.2)
Illness perceptions IPQ-k *(0-10)**		
Consequences	-0.1 (-1.4 to 1.2)	-0.2 (-1.4 to 0.9)
Timeline	0 (-1.5 to 1.4)	0.9 (-0.5 to 2.4)
Personal control	1 (-0.4 to 2.4)	0.6 (-0.6 to 1.8)
Treatment control	1.1 (-0.5 to 2.7)	-0.1 (-1.6 to 1.3)
Identity	-0.3 (-1.3 to 0.6)	-0.7 (-1.8 to 0.3)
Concern	0.2 (-1.2 to 1.6)	0.2 (-1 to 1.4)
Coherence	0.8 (-0.5 to 2.1)	0.4 (-0.9 to 1.7)
Emotional response	0.6 (-0.7 to 1.9)	0.5 (-0.8 to 1.8)
Self-management skills HEI-Q *(1-4)**		
Health-directed activity	0.06 (-0.20 to 0.31)	-0.05 (-0.30 to 0.21)
Positive and active engagement in life	0 (-0.21 to 0.21)	0.13 (-0.10 to 0.36)
Self-monitoring and insight	0.22 (0 to 0.45)	0.22 (0.01 to 0.43)
Constructive attitude and approaches	-0.03 (-0.25 to 0.20)	0.09 (-0.14 to 0.30)
Skill and technique acquisition	0.21 (-0.13 to 0.54)	0.18 (-0.06 to 0.41)
Social integration and support	0.05 (-0.23 to 0.32)	-0.14 (-0.40 to 0.13)
Emotional distress	-0.01 (-0.25 to 0.23)	0.01 (-0.26 to 0.27)
Health service navigation	0.01 (-0.24 to 0.27)	-0.01 (-0.23 to 0.22)

*Data are differences in mean (95%CI).

†Data are odds ratio (95% CI).

Exp = experimental group (n=57), Con = control group (n=80)

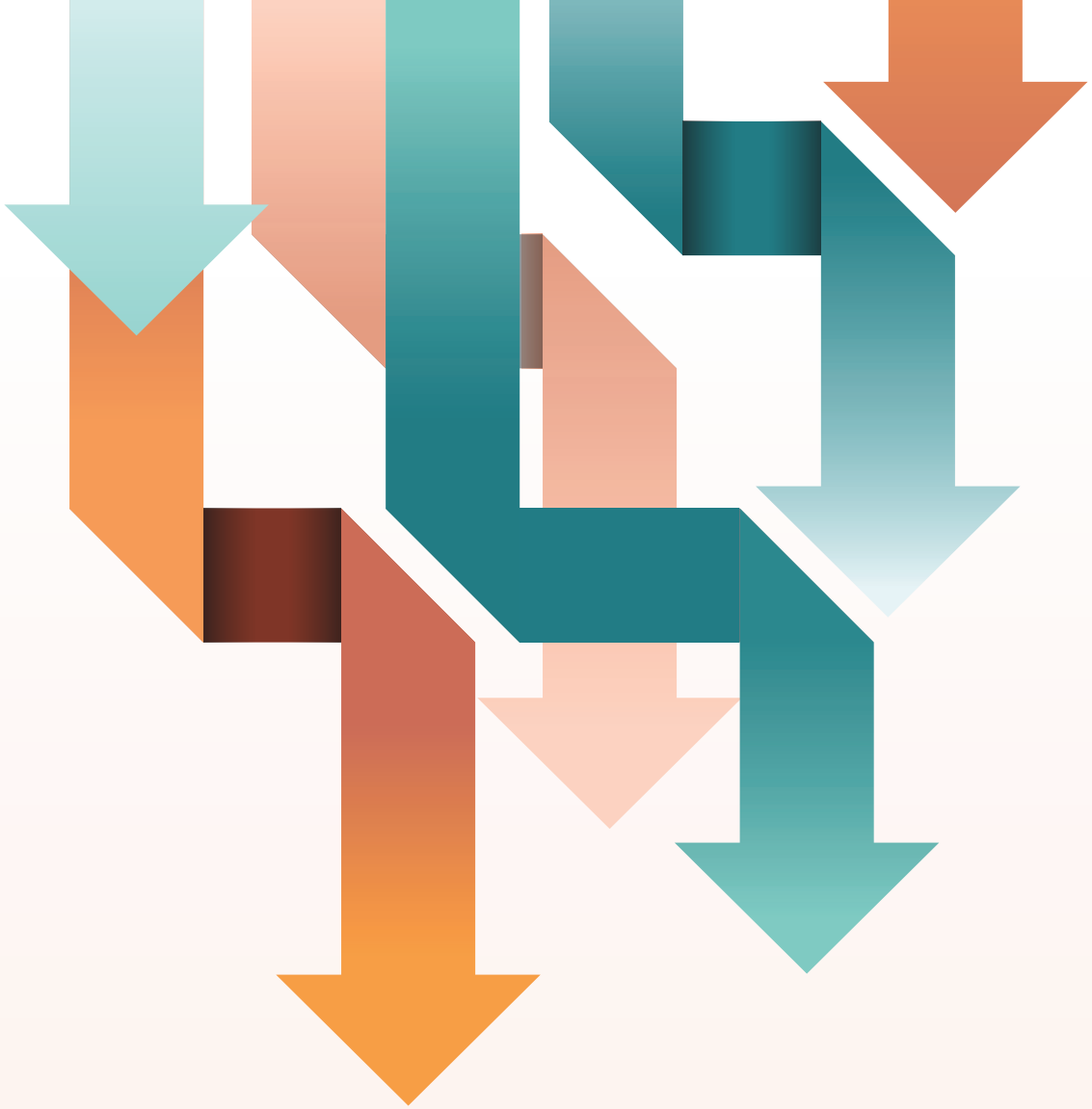
S3 Table: Sensitivity analyses of subjective symptom impact

At least 60% adequate relief on short-term	Groups		Difference between groups
	Exp	Con	Exp minus Con
Impact of symptoms Adequate relief *(yes/no)*			
Responder, n(%)	25 (31%)	11 (14%)	OR 3.0 (1.2 to 7.6)
Exp = experimental group, Con = control group			

At least 40% adequate relief on short-term	Groups		Difference between groups
	Exp	Con	Exp minus Con
Impact of symptoms Adequate relief *(yes/no)*			
Responder, n(%)	42 (53%)	20 (25%)	OR 3.8 (1.7 to 8.2)
Exp = experimental group, Con = control group			

At least 70% adequate relief on long-term	Groups		Difference between groups
	Exp	Con	Exp minus Con
Impact of symptoms Adequate relief *(yes/no)*			
Responder, n(%)	28 (35%)	27 (34%)	OR 1.2 (0.5 to 3)
Exp = experimental group, Con = control group			

At least 40% adequate relief on long-term	Groups		Difference between groups
	Exp	Con	Exp minus Con
Impact of symptoms Adequate relief *(yes/no)*			
Responder, n(%)	50 (63%)	33 (41%)	OR 2.2 (1 to 4.8)
Exp = experimental group, Con = control group			



5

CHAPTER

The cost-effectiveness of an indicated blended care intervention in primary care compared to usual care in patients with moderate medically unexplained physical symptoms

Suze A.J. Toonders
Paula E. van Westrienen
Niek J. de Wit
Johanna M. van Dongen
Marloes M.J.G. Gerrits
Martijn F. Pisters
Cindy Veenhof

Under review

ABSTRACT

Introduction

Appropriate treatment for people with an increased risk for developing chronic Medically Unexplained Physical Symptoms (MUPS) is of great importance at an early stage to improve quality of life and prevent high costs for society.

Objective

To evaluate the cost-effectiveness of an integrated blended care intervention compared to usual care for QALYs, subjective symptom impact and physical and mental health status in patients with moderate MUPS.

Methods

This economic evaluation was conducted alongside a 12-month prospective, multicenter cluster randomized controlled trial in Dutch primary care. 80 participants received the intervention and 80 participants received usual care. Seemingly unrelated regression analyzes were performed to estimate cost and effect differences. Missing data were imputed using multiple imputation. Bootstrapping techniques were used to estimate uncertainty.

Results

We found no significant difference in total societal costs. Intervention, primary and secondary healthcare and absenteeism costs were higher for the intervention group. The ICER for QALYs demonstrated that the intervention was on average less costly and less effective compared to usual care. For the subjective symptom impact and physical health, the ICER indicated that the intervention group was on average less costly and more effective. For mental health, the intervention was on average more costly and less effective.

Conclusion

We didn't find an integrated blended primary care intervention to be cost-effective compared to usual care. However, when looking on relevant, but specific outcome measures (subjective symptom impact and physical health) for this population, there seems to be a positive trend of lower average costs and more effectiveness.

INTRODUCTION

Medically Unexplained Physical Symptoms (MUPS) are defined as pain, fatigue, and/or dizziness or a combination of these which last at least several weeks and for which no sufficient explanation can be found after proper medical examination [1,2,3]. MUPS are very common, especially in primary care. Around 25–50% of the complaints that patients present to their general practitioner (GP) can be classified as MUPS [4]. Based on severity and disease impact, MUPS can be classified as mild, moderate or chronic [5]. In mild symptoms, symptoms recover generally within 3 months [5]. Patients with moderate MUPS experience severe unexplained symptoms, with psychological and physical distress, but without a diagnosis of a functional somatic syndrome (FSS), or a somatic symptom disorder (SSD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [6,7]. Patients with chronic MUPS experience severe physical symptoms and a high level of psychological distress with a major impact on daily functioning and quality of life [8,9,10].

Early identification of patients with an increased risk of developing chronic MUPS is of great importance [7,11]. After identification, these patients can then be offered an intervention with the focus on improving coping strategies and disease perception [12]. This is an example of proactive care where the aim is to prevent chronicity and subsequent long-term care [13]. Support in patients' self-management and integration of technology is an efficient way to provide this type of care [14,15,16]. For patients with moderate MUPS, a 12- week primary care intervention (PARASOL) has recently been introduced with the aim to prevent chronicity. First, patients were identified, after which they received the PARASOL intervention. The intervention was offered in a blended way, meaning that face-to-face sessions with a physical therapist and a mental health nurse were integrated with a web-based program [17]. On short-term, at the end of the intervention, this intervention was found to be effective in improving the subjective symptom impact of patients with moderate MUPS compared to usual care. However, no significant short- and long-term differences in quality of life were found [18].

Beyond the effects of the intervention on the quality of life of patients, interventions of this type might also prevent high costs for society by offering early treatment. Literature shows that patients with chronic MUPS make extensive use of healthcare services, with is in turn associated with high societal costs [19]. Amongst others, these costs are associated with receiving, often unnecessary, diagnostic procedures and medication [20,21]. The use of inpatient and outpatient care is approximately twice as high in patients with chronic

MUPS compared to patients without MUPS [22]. Societal costs are further increased by the high levels of presenteeism and absenteeism related to MUPS [23]. The average total societal cost per patient with MUPS in general is estimated at EUR 6,815 per year [10].

Prevention of the development of chronic MUPS is therefore important especially from a societal cost-perspective. Therefore, this study evaluates the cost-effectiveness of the PARASOL intervention compared to usual care in patients with moderate MUPS from a societal perspective.

METHODS

Design overview

An economic evaluation is conducted alongside a 12-month prospective, multicenter cluster randomized clinical trial in primary care. The trial protocol and study materials were approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht (MREC document number: NL57931.041.16). The trial was registered in the Dutch trial register with number NL6581. This study is reported according to The Consolidated Health Economic Evaluation Reporting Standards (CHEERS). A total of fifteen Dutch multidisciplinary healthcare centers, with in total 110,000 patients, participated. The healthcare centers were randomized using a web-based random generation of a sequence of numbers. Cluster randomization was performed at the healthcare center level to avoid professionals within one healthcare center offering both the PARASOL intervention and usual care. Eventually, eight healthcare centers were randomized to the PARASOL intervention and seven to usual care. The healthcare centers were informed about their allocation by email. Due to the nature of the intervention, the participating healthcare professionals and patients could not be blinded. The main investigators were also not blinded to group assignment. The physical therapists and mental health nurses of the healthcare centers assigned to the intervention group were trained in how to treat patients with moderate MUPS during a two-day training on the content of the PARASOL intervention. The physical therapists and mental health nurses of the seven control healthcare centers were not instructed, but treated patients as usual. Enrollment of 160 eligible patients lasted from March 2017 till April 2018, after which they were followed-up for 12 months.

Participants

Patients were proactively approached for participation if identified with moderate MUPS. Identification of patients was based on the PRESUME screening method, which

included the presence of MUPS-related symptoms, aged ≥18 years with five or more GP consultations [7]. Patients with an established psychiatric and/or medical diagnosis who were part of a chronic disease management program for chronic obstructive pulmonary disease, hypertension, or diabetes mellitus were excluded. Patients were also excluded when identified with chronic MUPS, based on an established chronic MUPS diagnosis. Besides the proactive approach, two other recruitment strategies were used to recruit participants. Participating GPs actively approached patients with moderate MUPS during consultations, and - if they met PRESUME criteria - matched them to the study group for inclusion. Finally, patients were recruited via flyers and newsletters in the waiting rooms of the participating healthcare centers. Patients with moderate MUPS who were interested in participating were accepted if they met PRESUME criteria, had access to the internet and had mastered the Dutch language. All of the patients gave their written informed consent after receiving detailed information about the study's aims and procedures.

Intervention: PARASOL

The PARASOL intervention comprised of a 12-week integrated blended primary care program, consisting of four face-to-face consultations with a mental health nurse and five physical therapy sessions, supplemented with an integrated web-based program. The web-based program consisted of (1) information modules and video's on self-management and educative themes, (2) video's and instructions on prescribed home exercises, and (3) assignments to gradually increasing physical activity. The intervention uses a cognitive-behavioral approach and therapeutic neuroscience education, and encourages self-management and an active lifestyle using graded activity. The web-based program was based on expert opinions [24].

Control: usual care

Usual care was defined as routine care for patients with MUPS as provided by the GP, physical therapist, mental health nurse and psychologist, without restrictions. The physical therapists and mental health nurses of the control healthcare centers were not instructed, and treated patients as they would otherwise.

Outcome measures

This economic evaluation consisted of utility and clinical outcomes. An overview of the corresponding questionnaires and timing of administering them can be found in Table 1.

- The EQ-5D-5L was assessed at baseline, 3 and 12 months and measures the patients' health state on a 5-point scale of complaints on five health domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Scores generally range from less than 0 (where 0 is the value of a health state equivalent to dead; negative values representing values as worse that dead) to 1 (the value of full health), with higher scores indicating higher health utility. Health states were converted into utility values using the Dutch tariff [25]. Quality Adjusted Life Years (QALYs) were estimated by multiplying the duration a patient spent in a certain health state by the utility value of that health state, using linear interpolation between measurement points.

- The subjective symptom impact was assessed with the adequate relief question. This is a validated single question measurement, which is scored on a dichotomous scale on weekly basis ("Over the past week have you had adequate relief of your symptoms?") [26,27]. Adequate short-term relief is defined as a participant who reported adequate relief of their symptoms for at least six of the twelve weeks between the baseline and three-month follow-up. If not, a participant is defined as a non-responder [27]. Adequate long-term relief is defined as a participant who reported adequate relief of their symptoms for at least four of the seven months between the 6- and 12-month follow-up.

- Health related quality of life was assessed at baseline, 3 and 12 months with RAND 36-Item Health Survey (RAND-36) [28]. The RAND-36 consists of eight subscales, which were merged into two summary component scales: "Physical Component Scale" (PCS) and "Mental Component Scale" (MCS). The norm-base score or the PCS and MCS is 50, where a score below 50 mean a less favorable physical and mental health state [29].

Table 1: Overview of outcome measures

Outcome measures	Data collection instrument	Follow-up measurements				
		Baseline	3 months	6 months	9 months	12 months
Baseline characteristics	Questionnaire	√				
Quality of life	36-Item Short Form Health Survey (RAND-36)	√	√			√
Subjective symptom impact	Adequate relief question	√ *Weekly between baseline and 3 months*	√ *Monthly between 6 and 12 months*	√	√	√
General health	EuroQol-5 Dimensions	√	√			√
Cost-effectiveness	Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness	√	√	√	√	√

Cost outcome measures

Costs were determined during the 12 months of follow-up using a retrospective 3-monthly cost questionnaire 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness' (TIC-P) [30].

- The intervention costs were estimated using a bottom-up micro-costing approach. That is, information was gathered about the patients' total number of appointments with the physical therapist and mental health nurse, which were in turn valued using Dutch standard costs [31]. In addition, we estimated the development costs of the PARASOL intervention per patient. For this, we estimated the expected number of patients with MUPS that would be eligible for PARASOL during the first 5 years after implementation and assuming an implementation rate of 10% in primary care. With total development costs of 9900 euros, this resulted in a total cost of EUR 0.39 per patient.

- Healthcare utilization was divided into the use of primary and secondary care and medication. Healthcare utilization was valued using Dutch standard costs [31]. If unavailable, prices according to professional organizations were used. Medication use was valued using priced derived from http://www.medicijnkosten.nl.

- Absenteeism was assessed by asking patients to report their total number of work-related sick days. In agreement with the Friction Cost Approach (FCA), sick days were valued using gender-specific price weights [32][33]. The FCA assumes that production losses are confined to the "friction period" (i.e. time needed to replace; 12 weeks or 60 days).

- Presenteeism was defined as being less productive at work, assessed by asking patients about their total number of working days on which patients had complaints and rated using gender-specific price weights.

- Unpaid productivity loss was valued using the Dutch recommended shadow price of 15.15 Euro/h [31] and consist of unpaid work that the patient can no longer do due to their physical or psychological problems.

- All costs were converted to Euros 2020, using consumer price indices provided by Statistics Netherlands.

Demographics

Patient characteristics, including age, sex, educational level, duration of complaints, work status, marital status and the presence of comorbidities and recruitment strategy were measured at baseline.

Statistical analyses

Statistical analyses were performed according to the intention-to-treat principle. Descriptive statistics were used to describe and compare general characteristics of patients in the PARASOL intervention and the usual care group. Missing data were multiply imputed (MI) using the MICE procedure [34] with predictive mean matching. Ten complete data sets were created in order for the loss of efficiency to be <5%. The imputation model consisted of confounder variables that have more than 10% change in the estimate of the effect. These variables were recruitment strategy, marital status, age, and duration of symptoms. In addition, we included all available baseline and follow-up costs variables and variables at baseline and follow-up related to the cost, utility, and clinical outcomes. Imputed datasets were analyzed as outlined below. Pooled estimates were calculated using Rubin's rules.

Average aggregate and disaggregate cost differences between groups were calculated. Seemingly unrelated regression analyzes (SUR) were performed to estimate cost and effect differences, while adjusting for baseline values, confounders, and their possible correlation [35,36]. The 95%CIs around the cost differences were estimated using bias-corrected and accelerated bootstrap intervals with 5000 replications. Incremental Cost-Effectiveness Ratios (ICERs) were calculated by dividing the differences in total costs between the two groups by the difference in effects. Bootstrapped incremental cost-effect pairs were plotted on cost-effectiveness planes. Cost-effectiveness acceptability curves (CEAC) were estimated, which indicate the probability that the PARASOL intervention is cost-effective compared to usual care at different values of willingness to pay. For the societal perspective, willingness to pay threshold values of EUR 10,000 to EUR 80,000 per QALY are used in the Netherlands [37]. For the other outcomes, willingness to pay threshold values are lacking. The primary analysis was carried out from the societal perspective and a secondary analysis was performed from the healthcare perspective. The societal perspective consists of the total costs related to MUPS, regardless of who paid for it. The healthcare perspective only includes costs accruing to the formal Dutch healthcare sector.

As in the majority of trial-based economic evaluations, the power/sample size estimates were not performed for this study because cost data are right skewed and therefore require larger sample sizes to detect relevant differences. Such large sample sizes, however, may be neither feasible nor ethically acceptable [38]. All analyses were performed using STATA 13.0. For the cost and effect differences, a two-sided significance level of 0.05 was considered statistically significant.

Sensitivity Analysis

Three sensitivity analyses were performed to test the robustness of the results. First, the analysis used data at three months as the final measurement instead of 12 months. A second sensitivity analysis was performed, in which outliers were selected (more than 3 standard deviations from the mean) and removed. Finally, results were analyzed separately for employed and unemployed patients.

RESULTS

Of the 160 included participants, 130 (81%) participants were identified with the PRESUME method, five (3%) were recruited during the GP consultation and 25 (16%) through flyers in the waiting rooms and study information in the newsletters of the participating healthcare centers. On average, five participants per healthcare center were included (range=2-34). After randomization, 80 patients were allocated to the intervention group and 80 in the control group (usual care). The two patient groups did not considerably differ in demographic characteristics (Table 2).

Resource use and costs. Difference in costs between the PARASOL intervention and usual care

Total healthcare costs of the PARASOL intervention were found to be significantly higher (MD: 753€; 95% CI: 122 to 1384) compared to usual care. From the societal perspective, however, we found no significant difference in total societal costs when comparing the PARASOL intervention to usual care (MD: -213€; 95% CI: -2072 to 1647). As for the disaggregate cost categories, the cost of the intervention, primary and secondary healthcare costs and absenteeism were higher for the PARASOL intervention group compared to usual care. Lower costs were found for medication, presenteeism and unpaid productivity. Of the disaggregate cost differences, only the difference in unpaid productivity was significantly in favor of PARASOL (MD: -1294€; 95% CI: -2571 to -16). An overview of the costs per group and the differences in costs can be found in Table 3.

Cost-effectiveness analysis, primary analysis; societal perspective

For QALYs, the ICER was 33,798, demonstrating that a QALY lost in the PARASOL intervention group was on average associated with a societal cost saving of EUR 33,799 compared to usual care (Table 4). However, as shown by the CEAC and CE–plane, the uncertainty surrounding this ICER was large (Fig. 1 and Fig. 2). The CEAC also showed that if one is willing to pay EUR 0 per QALY gained, the probability that the PARASOL intervention is cost-effective compared with usual care was 0.6. However, this probability decreases to a minimum of 0.5, at a willingness to pay of EUR 50,000 per QALY.

The ICER for the subjective symptom impact demonstrated that the PARASOL intervention was on average associated with a societal cost saving of EUR 708 compared with usual care per point improvement on subject symptom impact. Again, however, the uncertainty surrounding the ICER was large. The CEAC showed that at a willingness to pay of EUR 0 on the subjective symptom impact, the probability that PARASOL intervention being cost-effective compared with usual care was 0.5. At the willingness to pay level of EUR 10,000, the probability that PARASOL intervention being cost-effective compared with usual care increased to 0.8.

For the physical and mental scale on the RAND-36 the ICER was EUR -99 and 279, respectively. For the physical scale, the ICER indicated that the PARASOL intervention group dominated usual care (i.e. on average less costly and more effective). The CEAC showed a probability of 0.6 at a willingness to pay of EUR 0 per point improvement. The probability increased to more than 0.9 at a willingness to pay level of EUR 10.000 per point improvement. The ICER for the mental scale, however, indicated that the PARASOL intervention was on average more costly and less effective than usual care. Here, the CEAC showed that at a willingness to pay of EUR 0 per point improvement, the probability of PARASOL to be cost-effective compared to usual care was 0.6. At increasing levels of willing to pay, this probability decreased.

Table 2: Characteristics of participants at baseline [a]

Characteristics	Baseline		
	All participants (n = 160)	PARASOL intervention (n= 80)	Usual care (n = 80)
Gender, female	119 (74.4)	57 (71.3)	62 (77.5)
Age *(yr)*, mean (SD)	48.4 (13.7)	47.1 (12.4)	49.7 (14.9)
Duration of symptoms			
0 mo. – 1 y.	22 (13.7)	8 (10)	14 (17.5)
≥1 y.	138 (86.3)	72 (90)	66 (82.5)
Education level			
Low	41 (25.6)	18 (22.5)	23 (28.8)
Middle	65 (40.6)	38 (47.5)	27 (33.8)
High	54 (33.8)	24 (30)	30 (37.5)
Work status			
Employed	103 (64.4)	53 (66.3)	50 (62.5)
Unemployed	57 (16.9)	27 (33.8)	30 (37.5)
Marital status [b]			
Unmarried	56 (35)	22 (27.5)	34 (42.5)
Married/living with a partner	103 (64.4)	57 (71.3)	46 (57.5)
No. of comorbidities			
0	85 (53.1)	45 (56.2)	40 (50)
1	31 (19.4)	15 (18.8)	16 (20)
≥2	44 (27.5)	20 (25)	24 (30)
Recruitment strategy			
PRESUME screening	130 (81.3)	57 (71.3)	73 (91.3)
GP during consultation	5 (3.1)	5 (6.3)	0 (0)
Open recruitment	25 (15.6)	18 (22.5)	7 (8.8)

[a] Data are reported as number (percentage) of participants unless otherwise indicated.

[b] One participant included in the experimental group refused to answer here marital status.

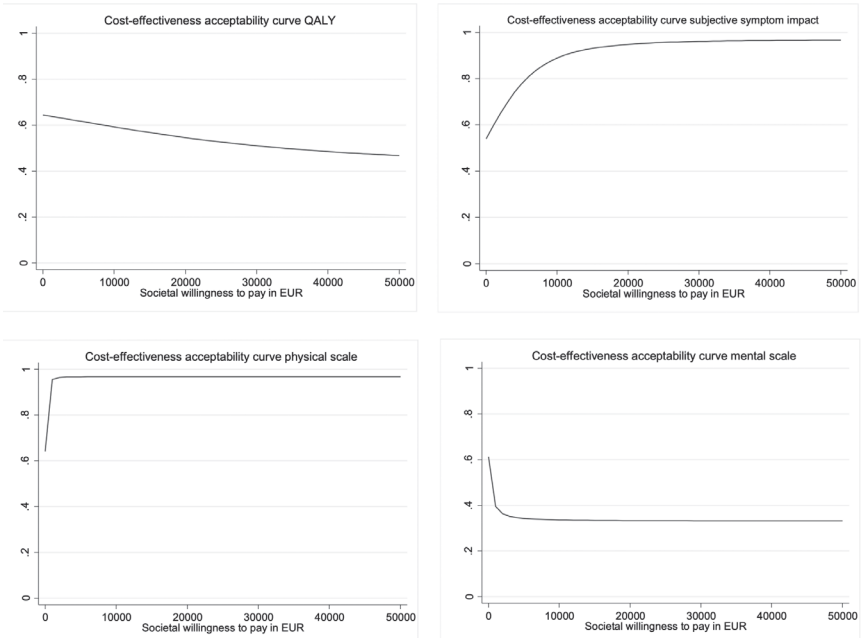


Figure 1: Cost-effectiveness acceptability curve indicating the probability of cost-effectiveness for different values (€) from a societal perspective

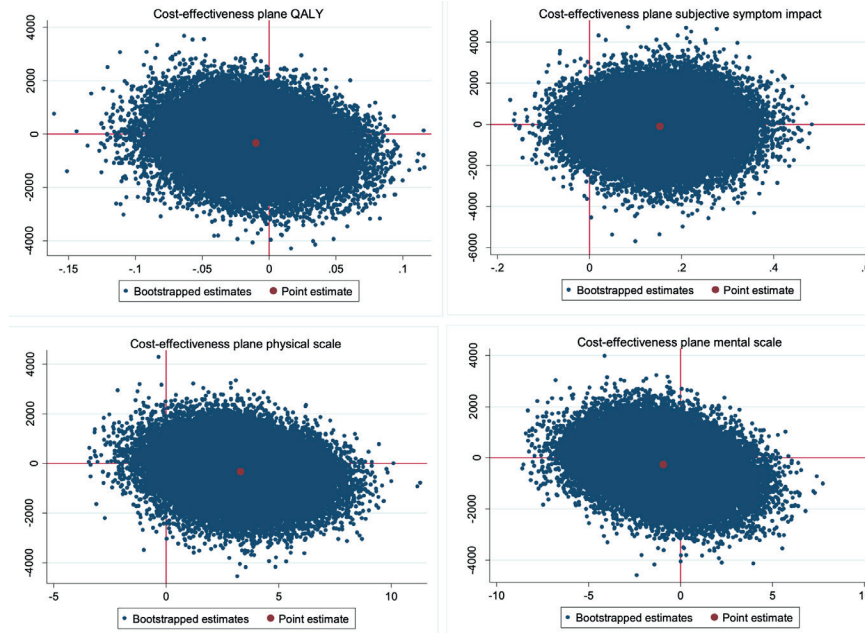


Figure 2: Cost-effectiveness plane indicating the uncertainty around the incremental cost-effectiveness ratio from a societal perspective

Table 3: Unadjusted and adjusted between-group differences in the PARASOL intervention group and usual care group during 12 months follow-up

	PARASOL intervention	Usual Care	Unadjusted mean cost difference in € (95% CI)	Adjusted[b] mean cost difference in € (95% CI)	Adjusted[b] mean cost difference in € (95% CI) Employed	Adjusted[b] mean cost difference in € (95% CI) Unemployed
	(n=80)	(n=80)	(n=160)	(n=160)	(n=110)	(n=50)
Cost category	Mean Costs in € (SEM)	Mean Costs in € (SEM)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Intervention	408	-	-	-	-	-
Primary Healthcare	974 (153)	825 (118)	149 (-221 to 518)	79 (-208 to 367)	160 (-98 to 418)	-155 (-1065 to 755)
Secondary Healthcare	821 (252)	530 (144)	292 (-305 to 889)	267 (-279 to 812)	279 (-250 to 807)	634 (-976 to 2244)
Medication	36 (4)	38 (4)	-1 (-13 to 10)	-1 (-13 to 10)	0 (-13 to 13)	-4 (-32 to 24)
Absenteeism	1779 (372)	915 (249)	864 (20 to 1707)[a]	364 (-395 to 1124)	798 (-189 to 1784)	0
Presenteeism	268 (45)	234 (37)	34 (-70 to 137)	-36 (-137 to 65)	9.6 (-116 to 135)	0
Unpaid productivity	1091 (409)	1988 (468)	-897 (-2171 to 376)	-1294 (-2571 to -16)[a]	-910 (-2611 to 790)	-1589 (-3713 to 535)
Healthcare costs[c] total	**2240 (323)**	**1393 (218)**	**847 (54 to 1640)[a]**	**753 (122 to 1384)[a]**	**847 (176 to 1517)**	**882 (-887 to 2653)**
Social costs[d] total	**5376 (831)**	**4539 (672)**	**847 (-1303 to 2997)**	**-213 (-2072 to 1647)**	**744 (-1731 to 3219)**	**-775 (-3827 to 2278)**

[a] Significant difference between the PARASOL intervention and usual care (p≤0.05)

[b] Adjusted for age, recruitment, marital status, duration of complaints, HC at baseline, SC at baseline, health related quality of life score at baseline and utility score at baseline

[c] Healthcare costs are the sum of intervention, primary and secondary healthcare costs and medication

[d] Societal costs are the sum of the healthcare, absenteeism, presentism and unpaid productivity costs

Costs are expressed in 2020 Euros

Table 4: Differences in pooled mean costs and effects (95% CI), incremental cost-effectiveness ratios, and the distribution of incremental cost-effect pairs around the quadrants of the cost-effectiveness planes

	n		Outcome	ΔC (95% CI)	ΔE (95% CI)	ICER	Distribution CE-plane (%)			
Analysis	**PARASOL**	**Usual care**		**€**	**Points**	**€/point**	**NE [a]**	**SE [b]**	**SW [c]**	**NW [d]**
Main analysis (imputed dataset)										
Societal perspective	80	80	QALY (0-1)	-333 (-1816 to 1066)	-0.01 (-0.07 to 0.05)	33799	10.9	27.2	37.8	24.1
	80	80	Subjective Symptom impact (y/n)	-108 (-2159 to 1914)	0.15 (-0.01 to 0.31)	-708	43	53.8	1.7	1.5
	80	80	Physical scale RAND-36 (0-100)	-328 (-1828 to 1116)	3.31 (-0.21 to 6.82)	-99	33.4	63.6	1.4	1.6
	80	80	Mental scale RAND-36 (0-100)	-259 (-1687 to 1215)	-0.93 (-5.07 to 3.21)	279	8.3	24.3	38.6	28.8
Healthcare perspective	80	80	QALY (0-1)	848 (443 to 1612)	-0.01 (-0.07 to 0.05)	-86180	37.8	0	0	62.2
	80	80	Subjective Symptom impact (y/n)	897 (180 to 2616)	0.15 (-0.01 to 0.31)	5863	95	1.7	0.4	3
	80	80	Physical scale RAND-36 (0-100)	803 (399 to 1497)	3.31 (-0.21 to 6.82)	243	96.9	0	0	3.1
	80	80	Mental scale RAND-36 (0-100)	800 (405 to 1505)	-0.93 (-5.07 to 3.21)	-860	32.6	0	0	67.4

[a] Refers to the northeast quadrant of the CE-plane, indicating PARASOL intervention is more effective and more costly than usual care

[b] Refers to the southeast quadrant of the CE-plane, indicating PARASOL intervention is more effective and less costly than usual care

[c] Refers to the southwest quadrant of the CE-plane, indicating PARASOL intervention is less effective and less costly than usual care

[d] Refers to the northwest quadrant of the CE-plane, indicating PARASOL intervention is less effective and more costly than usual care

Costs are expressed in 2020 Euros

ICER = incremental cost-effectiveness ratio

CE = cost-effectiveness

C = Costs

E = Effects

QALY = Quality-Adjusted Life Years

Cost-effectiveness analyses, secondary analysis; healthcare perspective

The ICER for QALY from the healthcare perspective was -86,180 suggesting an increase of QALY is associated with a healthcare cost of EUR 86,180 for PARASOL intervention compared to usual care (Table 4). The majority of the cost-effect pairs were located in the Northwest quadrant (62.2%), suggesting that the PARASOL intervention was on average more costly and less effective than usual care. The CEAC showed at a willingness to pay of EUR 50,000, the probability of the intervention being more cost-effective than usual care increased to a maximum of 0.2 per point improvement (Appendix I and II).

For the subjective symptom impact the ICER was 5,863. The cost-effect pairs were mostly located in the northeast quadrant (95%), indicating that the PARASOL intervention was on average more costly, yet more effective than usual care. At a willingness to pay of EUR 0 the probability of the intervention being more cost-effective than usual care was 0.1 and increased to 0.8 at a willingness to pay of EUR 10,000 per point improvement. The same results were found on the physical scale, with an ICER of 243 and 96.9% of all points in the northeast quadrant. With a willingness to pay of EUR 10,000, the probability of PARASOL being more cost-effectiveness than usual care was more than 90 percent. The ICER on the mental scale was found to be -860, where the CEAC showed that the PARASOL intervention was on average less effective with higher costs. The probability that the PARASOL intervention was more cost-effective compared to usual care was 0.3 at a willingness to pay of EUR 10,000 (Appendix I and II).

Sensitivity analysis

The sensitivity analysis showed similar results when including employment as an additional confounder. Furthermore, when running the analysis for employed (N=110) and for unemployed (N=50) participants only, no significant differences between both groups were found (Table 3), demonstrating that the results were not influenced by employment. As for on the other sensitivity analyses (firstly using three months as final measurement and secondly removing outliers), no significant differences were found between the results of the primary analysis and the sensitivity analysis. Furthermore, we found no significant differences over time in the average societal costs between the intervention and control group. This also holds when comparing total healthcare costs (Appendix III). By removing outliers, it became clear that the societal cost-differences between the PARASOL intervention group and usual care was driven by outliers on cost items ‘secondary care costs’ and ‘absenteeism’.

DISCUSSION

Main findings

In this study, we could not demonstrate that the PARASOL intervention was cost-effective as compared to usual care. The total healthcare costs of the PARASOL intervention appear to be significantly higher, with the total societal costs not being significantly different compared to usual care. The results of the cost-effectiveness analysis from a social perspective, using QALY as an outcome measure, found the intervention to be less effective, yet less costly compared to usual care. For the outcome measures subjective symptom impact and the physical scale of the RAND-36, there seems to be a positive trend of lower average costs and more effectiveness in the PARASOL intervention group compared to usual care. However, the differences are small and not significant. For the mental scale of the RAND-36, we couldn't demonstrate the cost-effectiveness of the intervention compared to usual care.

One of the explanations for the lack of cost-effectiveness of the PARASOL intervention maybe the duration of the follow-up. The follow-up in this study was 12 months, yet as the intervention was offered proactive to prevent chronic MUPS in patients, cost differences may only appear after a longer period. Over time, severity of complaints may increase, increasing their impact on daily life and utility. Hence, the 12-month follow-up period might have been too short for the additional costs incurred by proactively offering this preventive intervention (EUR 408) to be made up in lower overall societal costs. However, these additional costs probably explains the significant difference in total healthcare costs. Literature supports this finding that a 12-month follow-up period may not be sufficient to demonstrate cost-effectiveness [39].

A second explanation for the lack of cost-effectiveness of the PARASOL could lie in the included population. That is, the PARASOL intervention only includes patients with moderate MUPS. These patients suffer from less severe complaints in daily life compared to chronic MUPS patients [40], and hence may have had lower costs to begin with. Cost differences between usual care and the intervention are hence likely to be smaller and therefore differences are harder to demonstrate. This reasoning is underscored by literature. That is, the mean total societal costs in our study were EUR 5,376 for the PARASOL intervention and EUR 4,539 for usual care Per Patient Per Year (PPPY). Literature on chronic MUPS finds higher average societal costs due to PSS of EUR 6,816 PPPY [10]. The same holds for total healthcare costs. We found an average of EUR 2,240 in the intervention group and an average of EUR 1,393 in the usual care group PPPY. Literature on chronic MUPS patients founds an average of EUR 3,123 PPPY [10].

Although not statistically significant, a positive trend on the subjective symptom impact and the PCS in favor of the PARASOL intervention was found. This outcome is consistent with literature on a primary care intervention for patients with chronic MUPS. The authors suggest that the improvement in PCS was reflected by an improvement in the ability to carry out daily tasks [41]. This may be explained by the fact that patients with PSS often experience physical limitations due to their symptoms, and are therefore not able to carry out daily tasks on their own [42]. At a willingness to pay of EUR 10,000, the probability of cost-effectiveness of PARASOL on PCS is more than 0.8 compared to usual care. There is, however, no data on what one is willing to pay for this outcome measure. The amount that has to be invested for an improvement seems high when comparing what an insurance company is willing to pay for a lifestyle intervention. Insurance companies reimburse at maximum EUR 2,500 for lifestyle interventions [43].

Strengths and limitations

This study was the first trial to investigate the cost-effectiveness of an integrated blended primary care intervention in patients with moderate MUPS. Therefore, this study provides relevant results regarding cost-effectiveness of a multidisciplinary, blended care intervention to prevent chronic MUPS. A strength of this economic evaluation is that we analyzed the data both from the societal perspective as well as the healthcare perspective. In addition, to the different perspectives, various sensitivity analyses were performed to assess the robustness of the study results.

A limiting factor of this study is that little is known about the willingness to pay for the three clinical outcome measures, i.e. subjective symptom impact, PCS and MCS. This makes it impossible to make strong statements about the cost-effectiveness of the PARASOL intervention for these outcomes. In addition, the sample size is too small for analyses of cost-effectiveness in subsets of the sample, requiring the inclusion of more patients. The last limiting factor is the follow up period of 12 months which may not show an effect on costs.

CONCLUSION

Overall, we didn't find an integrated blended primary care intervention to be cost-effective compared to usual care, both from a societal and healthcare perspective. However, when looking on relevant, but specific outcome measures (subjective symptom impact and physical health) for this population, there seems to be a positive trend of lower average costs and more effectiveness for the integrated blended primary care intervention compared to usual care.

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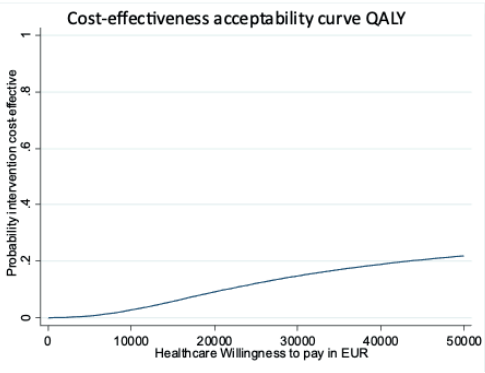
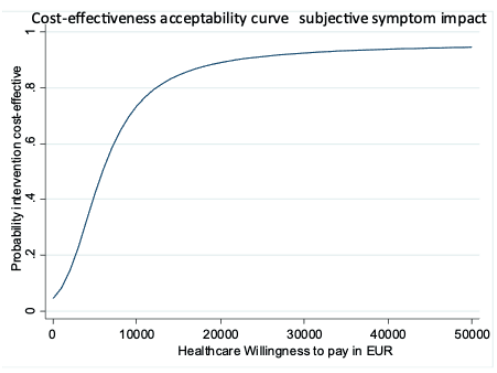
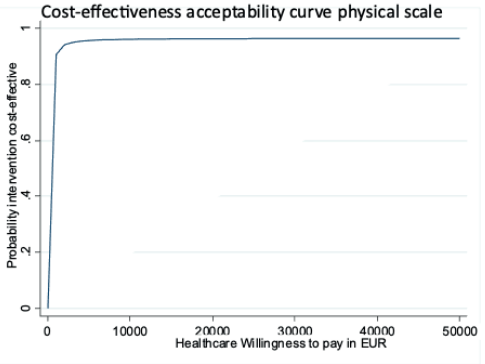
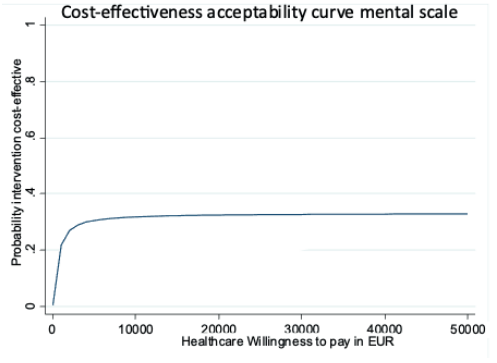
APPENDIX I: COST-EFFECTIVENESS ACCEPTABILITY CURVE INDICATING THE PROBABILITY OF COST-EFFECTIVENESS FOR DIFFERENT VALUES (€) FROM A HEALTHCARE PERSPECTIVE

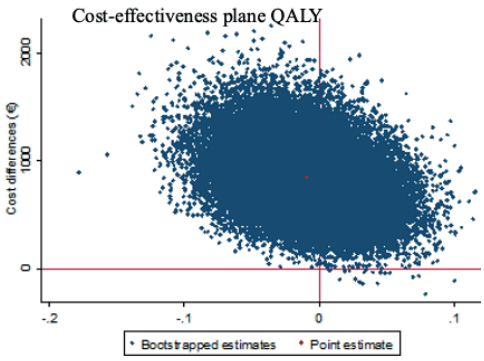


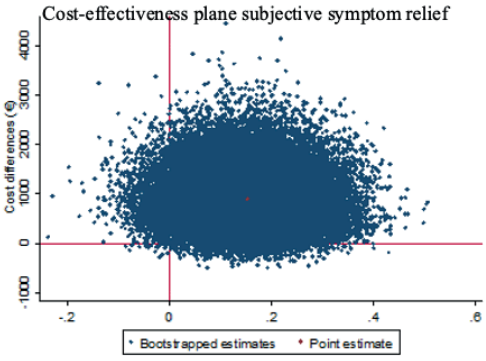


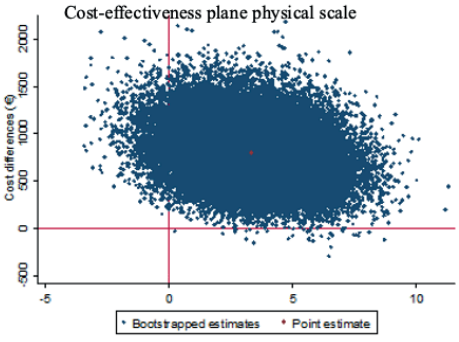


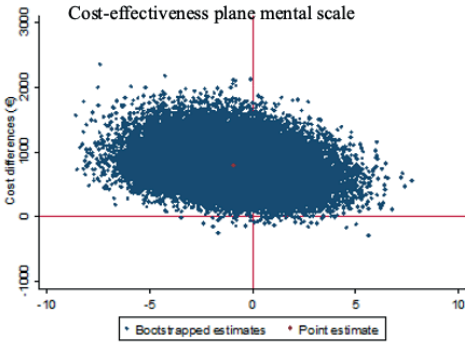


APPENDIX II: COST-EFFECTIVENESS PLANE INDICATING THE UNCERTAINTY AROUND THE INCREMENTAL COST-EFFECTIVENESS RATIO FROM A HEALTHCARE PERSPECTIVE

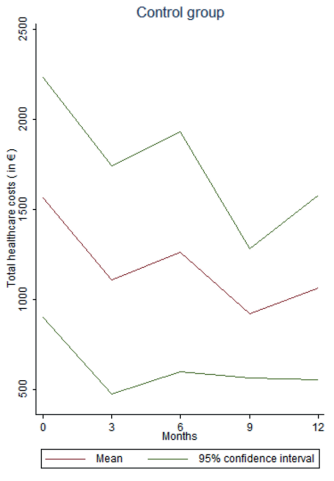


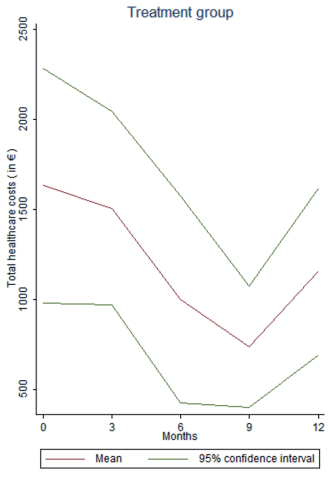


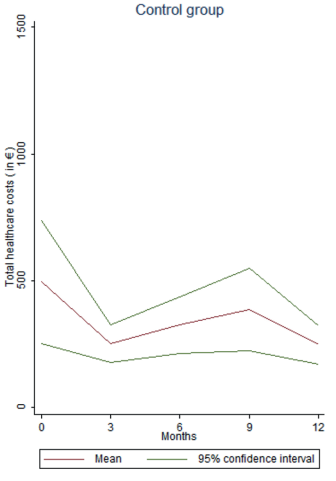


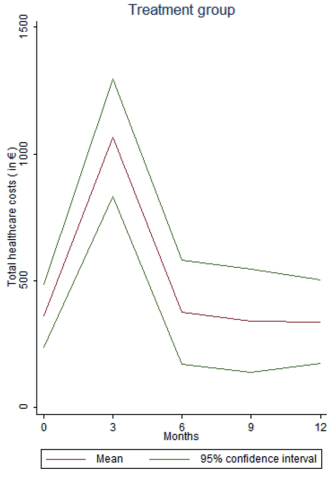


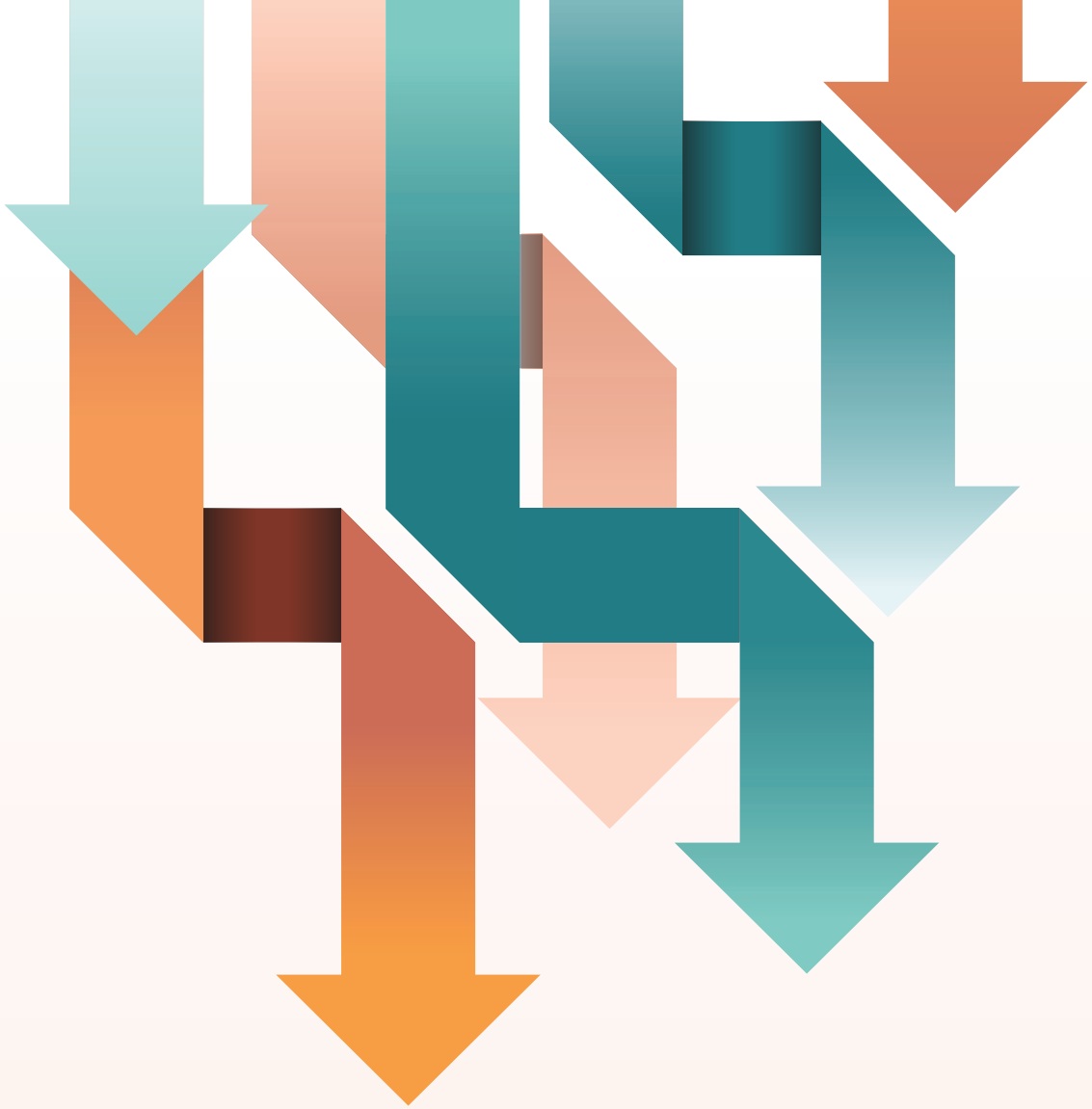
APPENDIX III TOTAL COST OVER TIME, FROM THE SOCIETAL (FIGURES ON THE LEFT) AND A HEALTHCARE PERSPECTIVE (FIGURES ON THE RIGHT)











6

CHAPTER

Patients' Perspectives on the Usability of a Blended Approach to an Integrated Intervention for Patients With Medically Unexplained Physical Symptoms: Mixed Methods Study

Suze A.J. Toonders
Paula E. van Westrienen
Sophie Konings
Marianne E. Nieboer
Cindy Veenhof
Martijn F. Pisters

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ABSTRACT

Background

Medically Unexplained Physical Symptoms (MUPS) are physical symptoms such as pain, fatigue and/or dizziness, that persist for more than a few weeks and cannot be explained after adequate medical examination. Treatment to prevent chronicity of symptoms is recommended. A promising approach is firstly identifying patients at risk and subsequently offering a blended care intervention, with a focus on stimulating self-management, while using eHealth as supportive tool. When these interventions match with patient's expectations, its effectiveness grows.

Objective

This study aimed to get more insights into the usability from the patients' perspective and hence can improve future interventions.

Methods

A mixed-method design was adopted, using qualitative and quantitative data. Through semi-structured interviews in-depth insights were gained into patients' perspectives on usability. The analysis process was continuous and iterative. Data was synthesised and categorized along different themes. The System Usability Scale, measuring the usability of a system, was used to compare participants that found usability to be low, medium and high.

Results

Saturation was reached after interviewing thirteen participants. Four themes emerged from the interviews: motivations and expectations prior to participating in the program, the applicability of e-Coaching, the role of healthcare professionals and the integrated design of the blended approach.

Conclusions

Successful implementation of integrated blended care interventions from the patients' perspective requires matching treatment to patients' individual situation and motivation. Furthermore, personalizing the relative frequency of face-to-face appointments and e-Coaching can improve usability.

INTRODUCTION

Medically Unexplained Physical Symptoms (MUPS) are physical symptoms that persist for more than a few weeks and cannot be explained after adequate medical examination [1]. MUPS are a serious concern, since approximately 25-50% of symptoms remain unexplained in primary care [2,3]. Patients with MUPS experience symptoms such as pain, fatigue and/or dizziness [4]. These symptoms often have a major impact on daily life, with a high burden for patients with MUPS [5]. MUPS can be divided into the following three stages: mild, moderate, and chronic [6]. These stages are based on the frequency of consultations to the General Practitioner (GP), the duration of symptoms and the physical and psychological dysfunctions experienced [6]. Existing research on treatment in the chronic stages of MUPS provides valuable insights, with recommended interventions including cognitive behavioral therapy, exercise therapy and neuroscience education [7]. Treatment for preventing the chronicity of symptoms has been recommended in order to reduce the severity of symptoms and the direct and indirect costs of care [8,9]. This is in line with the general trend in health care policy; policies nationwide aim to strengthen health programs to prevent diseases and address risk factors [10]. Healthcare is thereby changing its focus from cure and care to behavior and health [11].

In order for programs to succeed in shifting the focus to behavior and health, these programs must include proactive and indicated prevention [12]. A first step is identifying patients who are at risk for developing chronicity [13,14]. Moreover, literature has shown that programs and interventions should focus on promoting patients' self-management [15,16]. eHealth can serve as a supportive tool for both personalization and the promotion of self-management [17,18]. eHealth is not only supportive of usual therapeutic guidance but is also a substantial

element of interventions as a whole [19]. This is referred to as *blended care* - the combination of face-to-face contact with integrated web-based applications [20] - or as *e-coaching*, which is defined as "the use of technology during coaching to motivate and stimulate (groups of) people to change attitudes, behaviors, and rituals"[21,22].

When these interventions match patients' expectations, sustainable changes in patients are achieved more effectively [23]. More insights into usability from the patient perspective can further improve these interventions [24,25]. For example, from the patient perspective, interventions should be easy to use and acceptable. This usability, which is defined as "the quality of a system with respect to ease of learning, ease of use and user satisfaction"[26], can be measured.

The objective of this study was to gain more understanding into patients' perspectives on the usability of integrated blended care interventions. In order to do so, this study analyzed a recent proactive, multidisciplinary, and integrated blended care intervention that was developed to prevent chronicity in patients with MUPS in primary care [27,28]. At-risk patients were identified by using electronic medical records [29]. e-Coaching was used to integrate technology into the intervention. The main goals were to (1) promote self-management among patients and (2) provide patients with insights into dealing with their complaints.

METHOD

Study design and Setting

A mixed methods design (ie, the use of qualitative and quantitative data) was used. Through semistructured interviews, qualitative data were gathered in order to gain an in-depth understanding of usability from patients' perspectives. System Usability Scale (SUS) scores (low, medium, and high) were compared to responses in the interviews, which allowed us to gain better insight into the relationship between identified themes from interviews and experienced usability. This study was approved by the Medical Ethical Committee of University Medical Center Utrecht (approval number: 17-391/C).

Participants

Patients who participated in the PARASOL intervention were eligible for inclusion. To be included in the intervention, all patients (aged ≥18 years) must have had ≥5 consultations with their general practitioner in the past 12 months. Of these consultations, ≥3 had to be classified as "suggestive of MUPS" based on 1 of the 104 International Classification of Primary Care codes. Patients with medical and psychiatric diagnoses were excluded[28]. Only participants in the PARASOL intervention who provided informed consent for this follow-up study were invited. In order to obtain rich data, stratified purposeful sampling was conducted based on the outcomes of the SUS. Patients with validated SUS scores of <70, between 70 and 80, and >80 were included; these represent low, medium, and high scores for usability, respectively[30].

Measurements

Qualitative data were collected in one-to-one semistructured interviews, which were conducted at an agreed-upon location. A second researcher was available to play the

role of observer. The topic list of the interview was based on the theoretic construct of De Bleser et al [26] and supplemented with the determinants of health care innovation that were selected and developed by the Netherlands Organization for Applied Scientific Research [31] (Textbox 1). The quantitative data consisted of the outcomes of the SUS. The SUS has high reliability[30] and contains 10 questions on the usability of a system [32]. Questions were answered on a numeric rating scale with scores that range from 1 to 5 ("strongly agree" to "strongly disagree"). The SUS was administered at the end of the intervention. The demographic data consisted of age, gender, and educational level (basic, intermediate, and high). Educational levels were derived from the Standard Classification of Education used by Statistics Netherlands[33].

Procedure

Qualitative data were collected from semi-structured interviews within 4 weeks after participants completed the PARASOL intervention to avoid recall bias. Interviews took place in patients' homes or in one of the participating healthcare centres, depending on the preferences of the patient. Before the interview started, procedures regarding sound recording and the coding of data were explained, after which permission was requested from the participants. Quantitative data were collected for the randomized controlled trail PARASOL (Evaluation of a proactive preventive program in patients with medically unexplained physical symptoms, NL57931.041.16) [28]. Demographic data were retrieved from baseline measurements. After 3 months, upon the completion of the PARASOL intervention, SUS scores were gathered.

Textbox 1: Outline of interview guide [26]. The key areas are shown

Performance
- Impact of use environment
- Impact of user characteristics
- Ease of manipulation of device

Satisfaction
- Physical dimension
- Privacy dimension
- Human interaction
- Self-concept
- Routine
- Sustainability

Acceptability
- Acceptance for daily life use
- Willingness to pay for device

PARASOL intervention

The PARASOL intervention was a 12-week integrated blended care intervention that consisted of 4 face-to-face consultations with a mental health nurse and 5 physical therapy sessions and was supplemented with e-coaching. e-Coaching consisted of information modules and videos on self-management and educative themes, videos and instructions on prescribed home exercises, and assignments for gradually increasing physical activity. The intervention aimed to improve patients' perceptions of symptoms and identify modifiable risk factors of chronicity by providing therapeutic neuroscience education and promoting self-management. The intervention also aimed to promote an active lifestyle by using a cognitive behavioral approach and graded activities. Health care professionals were instructed on how to treat patients with moderate MUPS during a 2-day training session. Beyond the program itself, instructions included presentations on the study population, central sensitization, therapeutic neuroscience education, graded activities, and perpetuating factors. Furthermore, health care professionals were instructed on how to integrate e-coaching during the intervention. They were, for instance, guided on how to personalize general themes and instructed to ask patients about whether they understood information that is given on web-based platforms. All health care professionals received a guideline after finishing the training.

Data analysis

Interviews were recorded and transcribed verbatim, and transcriptions were checked by 2 researchers. Within 1 week after completing the interviews, a summary was sent to all participants. This member check verified whether interpretations were correct. After the initial interviews were conducted, the interviewer added other questions based on the themes that emerged from these interviews. Both researchers encoded meaningful text fragments independently, and a set of preliminary concepts and codes was generated. The analysis process was continuous and iterative. Data were synthesized and categorized into 4 different themes. In the last stage of the analysis, for each theme, interview responses were compared on the basis of participants' SUS ratings. This allowed us to gain better insight into the relationship between identified themes from interviews and experienced usability.

RESULTS

Saturation was reached after 13 interviews. Interviews lasted for approximately 20 to 50 minutes and had a mean duration of 33 minutes. Participants' mean age was 42 years. A

majority of participants were female (10/13, 77%). Further, 5 participants had an SUS score of <70, 5 participants had a score of between 70 and 80, and 3 participants had a score of >80. The demographic characteristics of the study population can be found inTable 1.

These interviewees form a subset of participants in the PARASOL intervention (n=80), with a mean age of 47 years and 71% female. These overall averages of the PARASOL intervention participants are hence comparable to those selected for interviews on the basis of purposeful sampling. The overall mean SUS score in the PARASOL intervention (n=55) was 74,6. A total of 19 participants had a SUS score of <70, fifteen participants had a SUS between 70-80 and 21 participants had a SUS above 80 points. Twenty participants in the PARASOL intervention did not complete the intervention and five questionnaires were not submitted.

As the use of e-Coaching integrated in treatment is relatively new, participants were asked about their general experience and interest in technology in healthcare. Every participant had used some form of technology in the broadest sense of the word. The use of a PC, smartphone and tablet were mentioned. The integration of technology in healthcare was only previously experienced by two of the participants. When asked about technology in healthcare, participants mentioned the use of pedometers, health apps and websites. Participants' interest of technology differs, as can be seen from Table 2.

Table 1: Demographic characteristics

Participant number	Age (years)	Sex	Educational level	Previous experience in blended- care	Interest in technology in the field of healthcare	System Usability Scale score
1	35	Female	Intermediate	No	Yes	67.5
2	48	Female	Intermediate	No	No	60.0
3	38	Female	Intermediate	No	Neutral	77.5
4	23	Female	Intermediate	No	Neutral	57.5
5	42	Female	Basic	No	Neutral	55.0
6	42	Male	Intermediate	No	Yes	50.0
7	48	Female	High	Yes	Yes	77.5
8	43	Female	Intermediate	No	Yes	85.0
9	47	Female	High	Yes	Yes	80.0
10	38	Male	High	No	No	72.5
11	31	Female	High	No	Yes	72.5
12	52	Male	High	No	Yes	87.5
13	57	Female	High	No	No	95.0

The 13 interviewees formed a subset of participants from the PARASOL intervention arm (n=80; age: mean 47 years; female: 57/80, 71%). The overall averages of the PARASOL intervention participants were hence comparable to those who were selected for interviews on the basis of purposeful sampling. The overall mean SUS score in the PARASOL intervention arm (n=55) was 74.6. A total of 19 participants had an SUS score of <70, 15 participants had an SUS score of between 70 and 80, and 21 participants had an SUS score of >80. Further, 20 participants in the PARASOL intervention did not complete the intervention, and 5 questionnaires were not submitted.

As the use of e-coaching integrated in treatment is relatively new, participants were asked about their general experience with and interest in technology in health care. Every participant had used some form of technology (in the broadest sense of the word). The use of a PC, smartphone, and tablet were mentioned. The integration of technology in health care was only previously experienced by 2 of the participants. When asked about technology in health care, participants mentioned the use of pedometers, health apps, and websites. Participants' interest in technology differed, as can be seen in Table 1.

A total of 4 themes emerged from the interviews. These themes provided insight into the usability of a blended approach to an integrated intervention from patients' perspectives.

Theme 1: Motivation and expectations prior to participation in the intervention

There was no consensus on participants' expectations prior to the intervention. Some participants stated that they had no expectations or no expectations that the complaints would disappear by participating in the intervention. Others expected fewer complaints and more physical activity, and some expected that their pain would go away. A recurring statement reflected the hope that someone would seriously consider their complaints:

That someone finally thinks about the fact that these complaints are really there, and that a program is being made. [Participant #3]

In terms of motivation, some participants participated mainly for personal interest. Other participants were just curious and saw no disadvantages, and some started the intervention because of a referral from their general practitioner. Experiencing intense pain was a motivation for participating in the intervention, and some participants mentioned that there were no other options for treatment with regard to their complaints. One participant stated:

I take this, because elsewhere a program is never really offered. [Participant #8]

When the results were analyzed based on SUS score groups, they showed that higher overall SUS scores were related to quotes regarding autonomy and intrinsic motivation (Textbox 2). In terms of expectations related to the intervention program, there was no difference among SUS groups (Textbox 3).

Textbox 2: Quotes related to motivation. The quotes are stratified by System Usability Scale (SUS) score groups

SUS score group: <70
- "I participate to stay active"
- "Advice from GP"

SUS score group: 70-80
- "Interesting to see whether the mental and physical aspects come together"
- "I don't understand my complaints and want to know what they are, and how I can deal with them"

SUS score group: >80
- "I have to make use of this opportunity, as I have been looking for ways to deal with my complaints for two years"
- "I had no way to resolve my complaints, and perhaps this will help me"

Textbox 3: Quotes related to expectations. The quotes are stratified by System Usability Scale (SUS) score groups

SUS score group: <70
- "I don't know if it will work"
- "I have no idea what to expect"

SUS score group: 70-80
- "I'm curious, rather than have any expectations"
- "I thought, this must really work"

SUS score group: >80
- "I was open to something new"

Theme 2: Applicability of e-Coaching

References were made to e-coaching during interviews twice. The first reference concerned the look and feel of the application, and the second concerned the application's acceptability. Some participants mentioned that they spent a long time searching within the application and found the web-based portion to be confusing. For example:

I had to watch instruction videos but I could not find them. [Participant #3]

Other participants however found the site to be well structured. There was no consensus on the ease with which documents or instruction videos could be found. Many participants

had problems with logging in. In addition, the application often had bugs. This did not promote the use of e-coaching. One participant said:

I did my exercises every day but the program did not work so I just did not fill it in. [Participant #13]

Another participant missed an evaluation that would have given insight into their progress. The ability to ask questions on web-based platforms and the fact that people can use the intervention anywhere were mentioned as facilitators. Participants stated that the planning assignments and exercises were clear every week. One participant said:

What I found very clear was that you could just click and do your exercises and activities on a weekly and daily basis. [Participant #8]

Participants appreciated the ability to tick off the followed modules so that it was immediately clear which modules had been completed and which were still open. There was no consensus on whether obtaining information through text or film was preferred. Participants gave the following tips for the use of e-coaching:

Add forms on the site to leave notes on progress, e.g. how many minutes one walked. [Participant #9 and Participant #11]

Make assignments more accessible by using visual support (colors, shapes). [Participant #7]

The higher the satisfaction (as measured by the SUS), the more participants understood and used the web-based environment (Textbox 4).

Textbox 4: Quotes related to the applicability of e-coaching. The quotes are stratified by System Usability Scale (SUS) score groups

SUS score group: <70
- "It is unclear for me how to use the website"
- "I can't enter the system, I never accessed the online part"
- "I often did not fill out the online sections, I prefer face-to-face treatments"

SUS score group: 70-80
- "I could not find the video, so I used text"
- "Clear and easy to use"

SUS score group: >80
- "The videos are clear and easy to use in daily life"
- "The site was clear"
- "It was easy to get the hang of the application"

Theme 3: The role of healthcare professionals

An often-mentioned facilitator of the treatment was agreement among health care professionals. Participants felt that they were receiving the same information from different angles. In face-to-face treatments, which participants felt to be useful, health care professionals provided psychoeducation, in which reminders and repetition were introduced to patients. A participant stated:

Because both the mental health nurse and the physical therapist spoke about interpreting pain, for example, and the physical therapist explains it more anatomically. [Participant #11]

The important roles of health care professionals were found to be discussing exercises, providing information, setting goals, and helping patients reach these goals. Participants also appreciated the fact that health care professionals supported reflections on behaviors and thoughts via confrontation, convincement, and motivation. For example:

Holding up a mirror to me, that there was a confrontation, it was very helpful that the physical therapist was confrontational. [Participant #12]

Another facilitator was the approachability of the mental health nurse. Participants recommended increasing the involvement of the general practitioner to increase the amount of feedback and encouragement that they receive. One participant stated:

I can imagine that people with these complaints do not always immediately think the mental health nurse and the physical therapist are going to solve the problem, so I think that the GP is still important for encouragement. [Participant #3]

Participants also did not expect physical therapists to engage in conversations as much as they did:

I think physical therapy is important only when giving exercises and not for conversations. [Participant #10]

The higher the SUS score, the more patients understood that health care professionals acted as coaches rather than as therapists (Textbox 5). There was no difference among subgroups with regard to interprofessional collaboration (Textbox 6).

Textbox 5: Quotes related to the role of professionals. The quotes are stratified by System Usability Scale (SUS) score groups

SUS score group: <70
- "I feel the need to have my own say more"
- "Sometimes I feel I have the same conversation twice, the physical therapist and I were a better match and we could converse more easily"

SUS score group: 70-80
- "The physical therapist remember me and my story, and that made me feel good"
- "I expected more from the physical therapist, just conversing and no exercises"

SUS score group: >80
- "The professionals were very involved"
- "It's good that the professionals held up a mirror to me"

Textbox 6: Quotes related to interprofessional collaboration. The quotes are stratified by System Usability Scale (SUS) score groups

SUS score group: <70
- "Good cooperation, same advice"
- "The same advices, did not notice cooperation, I did know they coordinated amongst the two of them"

SUS score group: 70-80
- "The combination of the mental health nurse and the physical therapist was good"
- "There was an overlap, but that did not bother me, it was complementary"

SUS score group: >80
- "I know they coordinated, they did not enter each other's domains"
- "One was more physical, the other was more psychological"

Theme 4: Integrated design of the blended approach

Given that only 2 participants had previous experience with blended care, interview questions about this new method of delivering health care were asked. Some participants were satisfied with the higher frequency of face-to-face appointments at the start of the intervention, while others were not. The time between appointments increases the chance of forgetting parts of the treatments. The face-to-face sessions served as a reminder:

Because I forget a lot, so it's nice that I can have feedback reminder. [Participant #5]

Participants suggested making the number of face-to-face sessions dependent on individual preferences. One participant said:

I think you should personally consult with each individual on the number of appointments. [Participant #13]

Others indicated that the number of face-to-face appointments should be made dependent on one's experience with web-based applications. For example:

I think for me personally I could have done with fewer appointments, as I am used to work online. [Participant #8]

Participants also mentioned that it was important for face-to face sessions and e-coaching to be coordinated. One participant stated:

You are encouraged to do the online program and then you come to practice and can get the information again, it connects. [Participant #7]

Another stated that face-to-face sessions filled the gap that was left on web-based platforms:

In fact, I first had to read the explanation on the website and then my questions were discussed. [Participant #10]

The possibility to schedule therapy based on personal preferences however was seen as an advantage. For example:

I liked the times. It was possible for me to make an appointment at the end of the day. [Participant #7]

The advantage of e-coaching was that participants could prepare specific questions that could be asked during the face-to-face sessions (eg, "I could ask specific questions I prepared myself"

[Participant #10]). Further, participants generally perceived blended care as positive (eg, "But that you can check it yourself at home. I think this is very good" [Participant #7]). Participants appreciated the integrated design of the intervention across all of the different SUS score groups (Textbox 7).

Textbox 7: Quotes related to the integrated design of the blended approach. The quotes are stratified by System Usability Scale (SUS) score groups

SUS score group: < 70
- "Because feedback is more specific for my own situation"
- "Face-to-face was a reminder…I find personal contact to be very important"

SUS score group: 70-80
- "The proportion [face-to-face and online] and frequency was good"
- "Face-to-face and online matched"
- "Repetition made it easier to remember"

SUS score group: >80
- "I find it easy to combine with other activities, I could do with less appointments"
- "The number of appointments should be based on personal preferences"

Overall, the results of this study show that participants experienced the intervention positively. This integrated blended care intervention aimed to promote self-management among patients and provide patients with insights into dealing with their complaints. Participants stated that they learned about self-management:

Now, I can estimate what I can do and cannot do. [Participant #9]

I can actually do it all by myself. [Participant #8]

Participants also gained more insights into dealing with their complaints:

Knowing nothing is broken, that idea has reassured me. [Participant #4]

Because of graded activity, pain turns into pride; I am happier, undertake more, sing more; I'm enjoying more. [Participant #11]

Textbox 8 includes all of the core themes that emerged from the semistructured interviews and hence summarizes usability from patients' perspectives. It shows the factors that were appreciated and lessons learned for improving usability.

Textbox 8: Summary of findings

Facters that patients appreciated	Lessons learned from improving usability
• Information being recognizable • The intervention as an incentive • The personal approach • The holistic approach • Inter-professional collaboration	• Connect the intervention to the individual's situation and motivation • Improve the accessibility of and technology support in e-coaching • Introduce the possibility of asking questions on web-based platforms • Personalize the intervention with respect to the amount of personal guidance alongside e-coaching

DISCUSSION

In this study, we evaluated patients' perspectives on the usability of an integrated blended care intervention. All included patients participated in a 12-week proactive blended care intervention in primary care with the aim of preventing the chronicity of MUPS. Participants were all generally positive about the received care. Various aspects of usability were highlighted, and responses were categorized into 4 themes.

The first theme which arose from interviews was motivation and expectation of patients prior to the intervention. Existing literature shows that interventions that match patients'

expectations are more effective in reaching sustainable change in patients [23]. This especially holds true for intrinsic motivation rather than extrinsic motivation, which increases one's willingness to spend more time on assignments [34] and leads to better health care outcomes [35]. Motivation also seems to be a factor of patients' adherence to eHealth [36]. In this study, we found differences in motivation related to satisfaction. When the overall results of the interviews were compared based on SUS scores, intrinsic motivation seemed to be an important factor related to experienced usability. Another factor that may influence a patient's motivation is patient selection. In this study, an electronic screening method involving the use of data from the electronic medical records of general practitioners' patients was used[29All eligible patients who were at risk for the chronicity of complaints were proactively approached by their general practitioners via an invitation letter. The selection of patients via this approach also has implications for patients' motivation, as the chance of approaching patients who may be less motivated may increase. To achieve adherence in patients, one should therefore take motivation into account in future interventions.

Many participants were not satisfied with the technical support provided in e-coaching, as technical functions did not work and logging in was a problem. The degree of satisfaction, which was measured with the SUS, increases when the web-based environment is understood and can be used. When patients were uncertain about the usefulness of e-coaching, the e-coaching modules were not used. This phenomenon has also been found in literature. Adapting eHealth to users' understanding and capabilities leads to a more usable and useful system[23]. When comparing the ages and educational levesl of the participants in the low and high SUS score groups, a finding that stood out was that those with lower satisfaction were substantially younger and had lower educational level. Existing literature shows that individuals with less education have worse actual and self-rated skills for evaluating the quality of web-based health information and lower trust in web-based health information compared to those with more education[37]. Studies however have found no consensus regarding the relationship between satisfaction and age [37].

Irrespective of the differences in satisfaction with e-coaching, participants were satisfied with the interprofessional collaboration. The holistic approach, through which physical therapists and mental health nurses provided information from different angles, was positively received by the participants. The expectations of participants regarding the role of health care professionals however differed among the SUS score groups. The higher the SUS score, the more patients understood that health care professionals acted as

coaches rather than as therapists. Participants in the lower SUS score group, for instance, felt that they had to explain their complaints twice and expected that the roles of physical therapists would include more than just engaging in conversations and providing exercises. As the organization of health care has changed (ie,focusing more on prevention) [38], the role of health care professionals will change, health care professionals will shift their focus from being a therapist to being more of a coach[39]. It seems important to explain this new role at the start of integrated blended care interventions in order to better shape the expectations of patients. Aside from interprofessional collaboration, attention should also be given to the collaboration between professionals and patients. Shared decision-making can support this process[40].

Participants appreciated the integrated design of the intervention across all of the different SUS score groups. They positively evaluated the possibility of saving texts and videos for future reference and the repetition of information in e-coaching combined with face-to-face sessions. The ability to personalize face-to-face sessions by allowing patients to prepare specific questions after studying the general information in the e-coaching modules was appreciated. Earlier studies have underlined the importance of face-to-face treatment combined with web-based care, as this has been found to improve and preserve outcomes[35,36,41]. The extent to which the intervention was tailored to participants made interventions and information recognizable. Participants also mentioned that an important yet missing part of the intervention was a diary or a free space for taking notes on exercises. The option to tick off exercises and modules and the explanation of exercises were considered to be helpful. These findings are supported by literature stating that the key components of the positive effect that eHealth has on health outcomes are personalization, stimulation, goal setting, and the integration of e-coaching[21]. All these elements were available in the integrated blended care intervention.

The results of this study demonstrate the usability of an integrated blended care program for patients with MUPS. More research is needed to investigate whether these results are patient-specific or whether the results of this patient population are unique. What remains important is ensuring that the use of technology in treatment fits the participants [42]. A checklist can help health care professionals, together with patients, to decide whether a patient is eligible for this program and whether the program matches a patient's characteristics (eg, abilities, needs, and preferences) and prior experiences with blended care[41].

Strengths and limitations

A limitation of this qualitative study is that all information is based on a specific integrated blended care intervention—the PARASOL intervention. Therefore, some items of the core themes are directly linked to this specific intervention. However, recommendations are insightful in general when starting an integrated intervention with a blended approach.

The theoretical construct of Bleser et al [26] was chosen. This construct contains the performance, satisfaction, and acceptability features. Other theoretical constructs for gathering insights into usability also exist, such as the Unified Theory of Acceptance and Use of Technology and the Technology Acceptance Model. These other constructs however largely overlap [43,44]. The Unified Theory of Acceptance and Use of Technology focuses more on social influences related to behavioral intention, whereas the Technology Acceptance Model focuses on perceived usefulness and ease of use. Given the findings of this study, including other measuring instruments, such as the Intrinsic Motivation Inventory and the Rotter locus of control scale, could be an interesting addition in future research. These could shed more light on patients' motivations at the start of the program. The strengths of this study are the use of an iterative process during the analysis of the results and the use of triangulation methods during the whole research process. Furthermore, patient involvement was sought in all research phases.

CONCLUSIONS

The successful implementation of integrated blended care interventions based on patients' perspectives requires matching treatments to patients' individual situations and motivations. In addition, personalizing the relative frequency of face-to-face appointments and e-coaching is of importance.

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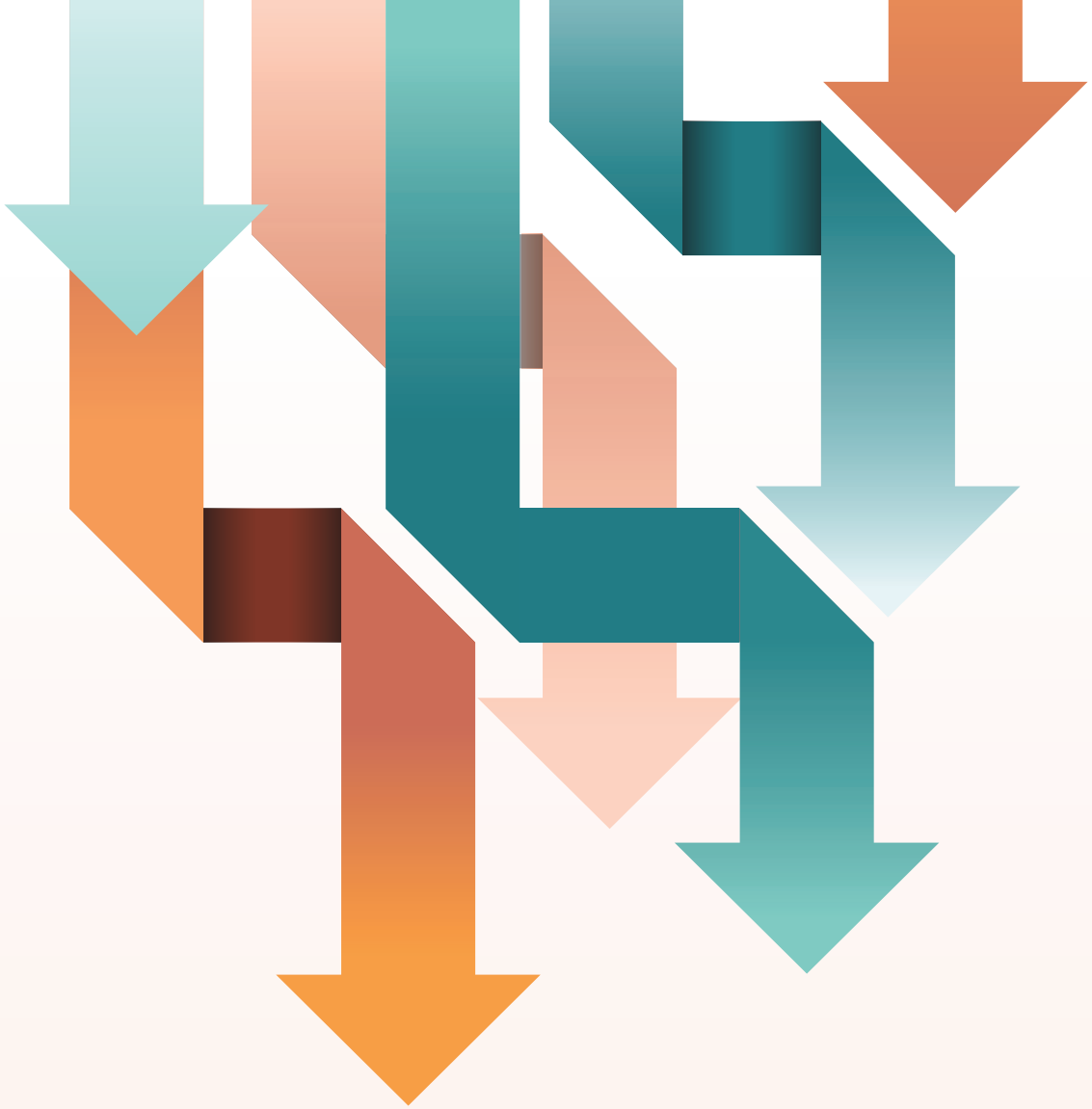

7

CHAPTER

Healthcare professionals' perspectives on a blended care program in primary care: A qualitative study

Suze A.J. Toonders
Eva Y. Poolman
Marianne E. Nieboer
Martijn F. Pisters
Cindy Veenhof

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ABSTRACT

Increasingly, healthcare policies have changed focus from cure and care to behaviour and health. Prevention is becoming more important, which requires a change in the role of healthcare professionals. Healthcare professionals' role is changing from being a therapist to taking on the role of a coach. To prevent chronicity in Medically Unexplained Physical Symptoms (MUPS), an integrated blended care program was developed. To apply this new program in daily practice, it is important to gain insight into the usability. From the healthcare professionals' point of view the concept of usability consists of performance, satisfaction and acceptability. In this qualitative study participants were recruited after participating in the PARASOL program. Demographics were collected. Semi-structured interviews were conducted and analysed using thematic analysis. Ten healthcare professionals (six physical therapists and four mental health nurses) were interviewed. Four themes on usability were identified: *(1) Who fits in the program, (2) preparation, (3) experience with the program and (4) interprofessional collaboration.* This study gathered healthcare professionals' experiences with and attitudes towards integrating healthcare and offering blended care programs. An integrated blended care program offers the possibility to personalize treatment. Findings show attention should be given to the new responsibilities of healthcare professionals, and their role in integrated and blended care. This new approach of delivering healthcare can facilitate interprofessional collaboration. Achieving sustainable change in patients however still requires instruction and support for healthcare professionals implementing behavioural change techniques.

INTRODUCTION

Over 75% of the Dutch population visited the general practitioner (GP) in 2018 with an average of 4.5 visits per person per year [1]. About 30% of symptoms, e.g., pain, fatigue or dizziness [2] remain medically unexplained after patients visits their GP [3,4]. In most patients these symptoms disappear spontaneously after a few weeks. Nevertheless, for 2.5% of these patients, symptoms sustain and have a high impact on daily life [3,5] These so called Medically Unexplained Physical Symptoms (MUPS) are physical complaints that last for at least a few weeks, where no somatic condition is found that explains the complaints with adequate medical examination [2].

Providing appropriate treatment for people with MUPS at an early stage, with the use of neurosciences-based therapeutic education, cognitive behavioural therapy and exercise therapy which have been shown to be effective treatment modalities in patients with chronic MUPS, has multiple advantages [3]. Literature shows effective outcomes on the reduction of unnecessary medical consumption, and increased job participation [6,7]. MUPS can be divided into three consecutive stages, ranging from mild, to moderate to chronic stages. These stages are based on the frequency of consultations to the GP, duration of symptoms and experienced physical and/or psychological dysfunction [8]. Prevention in relation to MUPS seeks to identify individuals who show early signs of MUPS [9].

In order to maintain healthcare accessibility and affordability, policy in the Netherlands has sought to change the way in which healthcare is organized. Moving from a focus on cure and care to behaviour and health [10]. This change requires a shift in healthcare delivery with more focus on prevention, from a traditional expert to a patient-centred approach [11]. Therefore, the role of healthcare professionals also has to change, moving from focus on being a therapist to focus on being a coach [12].

Recently, such an integrated blended care program to prevent chronicity in MUPS, the PARASOL program, has been developed in collaboration with healthcare professionals and patients [13]. This specific program focuses on increasing insight into patients' perception of symptoms and modifiable prognostic risk factors for chronicity using therapeutic neuroscience education and encouraging self-management as well as an active lifestyle using a cognitive behavioural approach and graded activity [13]. Blended care is the combination of online care and therapeutic guidance [14]. The face to face sessions took place in the healthcare centre and lasted 30 minutes. Patients received 4 face-to-face sessions with the physical therapist (week 1, week 3, week 6 and week

12) where the focus was on the perception and acceptation of physical complaints. Patients received 3 face-to-face sessions with the mental health nurse (week 1, week 3, and week 6). In all 3 face-to-face sessions the mental health nurse was training coping strategies according to perpetuating factors and operant conditioning[15], with the focus on changing perception and acceptation. Online care was provided using e-Coaching defined as 'the of technology during coaching to motivate and stimulate (groups of) people to change attitudes, behaviours, and rituals' [16,17]. E-coaching provides information modules, personalised exercises and assignments to gradually increase the physical activity in a web based application and is not a standalone, but integrated in care. Online programs can not only be supportive of usual therapeutic guidance, but can also be a substantial element of the intervention as a whole [18,19]. The combination of personal attention of a healthcare professional and the accessibility of an online tool is seen as highly promising, as it can stimulate patients to take an active role in their disease management [20], as preparation can be done independently online and specific or substantive questions can be discussed at face-to-face meeting with professionals.

To implement a successful innovation, attention should be given to the unique position of end-users [17]. The involvement of end-users provides direction for the development of integrated blended care programs. Co-creation, the engagement of users throughout the development process, is an important strategy in order to meet the values and needs [21]. The objective of this study is to gain insight into the concept of usability, consisting of performance, satisfaction and acceptability from the healthcare professionals' perspective. Usability refers to 'the quality of a system with respect to ease of learning, ease of use, user satisfaction and needs to be tested subjectively, from end-users perspective' [22].

METHODS

A qualitative design was chosen. Data were collected through semi-structured interviews with healthcare professionals recruited after participating in the clinical trial PARASOL [13].

PARASOL program

The PARASOL program is a protocolled 12- weeks integrated blended care program. The program consists of five face-to-face consultations with a physical therapist and four sessions with a mental health nurse in primary care, supplemented with e-Coaching [13].

Physical therapists and mental health nurses received instructions about the program during a two-day training session. These instructions included presentations on the study population, central sensitization, therapeutic neuroscience education, graded activity, and perpetuating factors [13]. Furthermore, professionals were instructed on how to integrate E-coaching. All healthcare professionals received a protocol. Three months after the two-day training the PARASOL program started.

The e-Coaching modules consisted of information modules and videos on self-management and educative themes, videos and instructions on prescribed home exercises and assignments to gradually increase physical activity. Content was directed at patients' perception of symptoms, and modifiable prognostic risk factors for chronicity using therapeutic neuroscience education and encouraging self-management as well as an active lifestyle using a cognitive behavioural approach and graded activity. The e-Coaching modules complemented face-to-face treatments in order to introduce general themes, while during the contact with healthcare professionals, treatment could be personalized. Furthermore, during face-to-face treatment patients could pose questions to healthcare professionals. The basic functionality of e-Coaching used is based on the blended exercise intervention for patients with hip or knee osteoarthritis, called e-Exercise [23].

Sample

Convenience sampling was used whereby the inclusion criterion was that healthcare professionals were eligible if they were involved in the PARASOL trial (seven physical therapists and six mental health nurses). All were approached to participate by the researcher (ST). We expected saturation at a sample size of eight to ten participants, based on similar published literature [24]. Instructions were given by phone, information was sent by email and an appointment was made. Subsequently, informed consent was obtained.

Data collection

At the start of the semi-structured interview, demographic data such as age, gender, profession, work experience, number of patients treated in the PARASOL program and the System Usability Scale (SUS) score were collected. Semi-structured interviews were conducted by ST. A second researcher was present for non-verbal observation and verified if all questions were asked. The interview guide was based on the theoretic

construct of De Bleser et al 2011, offering direction to the interviews [22]. This construct test existing electronic monitoring devices and divides criteria in objective and subjective dimensions. This study focused on the subjective dimension, containing user performance, satisfaction and acceptability [22]. The interview guide was supplemented by determinants of healthcare innovation selected and developed by TNO (Netherlands Organisation for Applied Scientific Research) [25]. After the first interviews were conducted, the interviewer added questions based on topics that emerged from previous interviews (for example '*How is your interest in technology in general?' and 'For which patients would this program be suitable?').*The SUS consists of ten questions about the usability of a system [26]. The questions were answered on a numeric rating scale with a score range of one to five. A score of one stands for 'strongly disagree' and a score of five stands for 'strongly agree'. The validated classification of the SUS of <70, a score between 70-80 or a score >80 respectively represent low, medium and high user usability. The SUS has a high reliability (α=0.911) [27]. SUS scores were collected before the interview started and give information on the extent to which usability varies.

Data analysis

Interviews were recorded and transcribed verbatim and the audio interviews were checked by two researchers (ST & EP). Within one week after completing the interview, a brief summary was sent to all participants to ensure all information was interpreted correctly from the transcript. Thematic analysis was conducted [28], whereby inductive codes were assigned to quotations that were related to the research question. Data were analysed manually and independently by two researchers (ST & EP). During the initial process of coding, transcripts were analysed line by line allowing the data to be fractured. These codes were highlighted and labelled within the text. During the axial coding process, fragments were put together. These fragments were categorized according to their similarities, after which main themes emerged, which were described and discussed by the researchers (ST, EP & MN). Finally, within the themes factors were labelled whether they were a facilitator or a barrier.

Validity

Validity was increased by creating a non-judgmental atmosphere in an independent position during the interviews and emphasizing the need to learn from the healthcare professionals. Fully transcribing the interviews decreases the chance of information bias, hence increasing accuracy and precision of the data collection that follows the interviews.

The involvement of more than one researchers in collecting and analysing data increased the validity. Furthermore, the interpretation of the given answers was checked by the member check.

Ethical considerations

The study was approved by the Medical Ethical Committee Utrecht, by number 17/391. The dataset, including the interview guide, used and analysed during the current study are available from the corresponding author on reasonable request.

RESULTS

Among the healthcare professionals contacted (seven physical therapists and six mental health nurses), two refused participation because they were not interested. One healthcare professional did not respond. In total ten healthcare professionals (six physical therapists and four mental health nurses) were interviewed. Of the ten participants, eight were female. Participants ranged in age from 25 to 62 years with a mean age of 35 years. Work experience ranged between 1.5 to 34 years. The number of patients treated with the PARASOL program ranged from 6 to 17. SUS scores ranged from 30 to 82.5, which implies eight healthcare professionals scored a low usability score, one a medium score and one healthcare professional scored a high usability score [27]. The interviews lasted between 30 to 45 minutes.

Besides demographics, questions about previous experiences with blended care (interest in blended care, expectations of integrated blended care programs) were asked. Most healthcare professionals volunteered to participate in this study out of personal interest in the subject matter. Although not everyone had previous experience with blended care, expectations of the blended program were cited as something new that fitted them well, and seen as the future of primary care. Although the healthcare professionals were optimistic about blended care, some were also afraid that the online program would take over their jobs. Through questions about usability from healthcare professionals point of view, facilitators and barriers to implement an integrated blended care program were found. These are summarized in table 1.

Table 1: Summary of facilitators and barriers linked to the (sub) themes

Core theme	Facilitator	Barrier
Who fits in the program?	Intrinsic motivation of patients	Chronicity of complaints
Preparation	The use of a protocol	Duration between training and doing
	The number of patients treated	
Experience with the program	Achieving in depth treatment within the duration of a face-to-face session	Absence of evaluation time at the end of a program
		Difficulties setting (long-term) goals
		Difficulties in delivering care remotely, like e-Coaching
	Quality and structure of content	Technical issues
	Providing information interactively (text and video)	
Interprofessional collaboration	Holistic approach	Lack of feedback or confirmation from other disciplines
	Support of colleagues	

As seen in table 1, the analysis resulted in four core themes. The themes are presented according to the sequence of the integrated blended care program.

Who fits in the program?

In the interviews, multiple situations were reported that hindered or favoured participation of patients in this integrated blended care program. The fact that the patient population strongly varied was repeatedly mentioned. Interviewees felt this integrated blended care program was not suitable for all included patients, specifically patients suffering from MUPS for a long time. Those interviewed felt that the intrinsic motivation of patients plays an important role in successfully completing the program. When describing their motivation, interviewees divided patients into roughly two groups; those motivated and those not motivated. Expectations of the study diverged between both groups. Motivated participants were well prepared and knew that the program had a low intensity and included guidance from a distance. Interviewees felt the outcomes for those less motivated were less positive, as they did not have a goal they could or wanted to work towards. *'If patients are too unprepared…I won't say they're less motivated, but they see themselves less as a problem owner (p2)'.* Although these patients were perhaps less motivated, healthcare professionals did not see it as a significant problem, as they expected less motivated patients to drop out at the start of the program. *'The people that aren't motivated, they'll drop out, they filter themselves out of the program (p3)'.*

Preparation

Before the start of the program, healthcare professionals had to attend a two day training in order to treat patients following the protocol of PARASOL independently. Some professionals learned a lot during those days, while others felt they knew sufficient about the subject matter at hand. A downside which was expressed was the long period between the introductory training and the start of the first treatment in the program. During the training days, an instruction protocol was handed out. Healthcare professionals used this protocol in different ways, as some mentioned they followed the protocol strictly. Others stuck less to the protocol. *'I never try to just plainly follow it, because then you lose contact with what is happening on the other side (p3)'.* Furthermore, the number of patients treated was mentioned as an important factor to make the program their own. Interviewees expressed that as they treated more patients, they better mastered the program. '*You can only make it your own if you see a lot of patients in a row (p6)'.*

Experience with the program

The interviewed healthcare professionals were generally positive about the integrated blended care program. A positive point highlighted was healthcare professionals noticed that patients became more aware of their responsibility for their own health. Patients became more self-managing of their problems. '*They really become problem owner! (p2)'.* As patients started the program at home, they found that patients were better prepared. This made the healthcare professionals able to get to the core of the treatment faster. *'Part of what is told, is already told online. The patient can see and read it himself. That saves time during treatment. (p3)' 'I notice patients learn a lot when they read material at home or watched a video (p9)'.* It was a unique experience, which relieved the workload and should therefore be implemented in usual care: '*... if people return, they changed something and are enthusiastic and proud about that. That they reached goals they didn't expect to (p5)'.* Overall, there was satisfaction with the session time of 25 - 30 minutes. Only during intake this was experienced as too short. Interviewees suggested doubling the time during intake to gain a wider picture of the patient. Concerning the treatment frequency of the program, the main point put forward was the need for more evaluation moments. Interviewees wanted to know what the program had meant for their patients. *'I just give a bunch of information to the patient, but have no clue whether it sticks with them (p2)'.* In some cases, patients did not have any questions for the healthcare professionals. This made it hard for them to know if there was sufficient commitment. *'It's a bit indecipherable (p4)'.* Healthcare professionals then struggled to formulate long-term goals with their patients. In terms of

content, the information modules were perceived as well written and structured. Patients were given information in different ways (reading online, watching instruction video's) causing the information to stick better, as well as stimulating self-management among patients, which reduced healthcare professionals' workload. *'Texts were written in such a way (...) that people recognize themselves in it, they don't put off people (p7)'*. Besides, *'It is important that people get to process information in different ways, as our brain doesn't work like: 'hi, let's change something'. So that's really necessary (p2).'* There were also a number of criticisms regarding the accessibility of the e-Coaching modules. It was mentioned that there were many technical complications, such as difficulties with logging in and useless buttons. The professionals expressed doubts as to whether the e-Coaching application can offer functionality. *'... I wouldn't accept it if I couldn't log in (...) then I would really ask my money back (p2)'*. Healthcare professionals sought to deal with the technical defects as good as possible. Some printed exercises and others emailed them to the patients, enabling patients to still follow the program.

Interprofessional collaboration

One of the main added values mentioned was interprofessional collaboration between physical therapists and the mental health nurses induced by the integrated blended care program. Before the start of this program, it seemed as though healthcare professionals did not actively seek collaboration. *'I got to know the mental health nurse through this project (p8)'.* Through working together in this program, professionals better found each other. Contacts between professionals was easy to establish. Nearly all participants found the collaboration pleasant, helpful and experienced it as adding value because of the holistic approach. *'She sees things that I do not. I see things that she does not (p1)'*. *'That you seek cooperation, but stay within your own field (p6)' 'The added value is in the coordination (p4).'* After the treatment was finished, most professionals continued to collaborate. They mentioned consulting each other more often. During the program there was little support or contact with the general practitioner (GP). This was not mentioned as being problematic, yet some interviewees indicated some feedback or confirmation by the GP would have been nice for reassurance. Support of colleagues was experienced as motivating and stimulating.

DISCUSSION

This qualitative study was conducted to investigate the usability of an integrated blended care program from healthcare professionals' perspective. Semi-structured interviews were held, out of which four core themes emerged with accompanying facilitators and barriers.

The main facilitator in this integrated blended care program was the depth in treatments and the possibility to personalize the program. Patients received information in multiple ways and in different stages of the program. Prior to the face-to-face treatment, patients received information in text and saw instruction videos at home. Later, in face-to-face appointments with healthcare professionals, they could ask their questions or share their doubts. Patients were better prepared about what was going to happen next. Furthermore, repeating information made patients better prepared which saved time and allowed healthcare professionals to move on to the core of treatment faster. Repetition is a known behavioural change technique, as with repetition individuals better develop skills to actively self-regulate their behaviour [29]. Another facilitator was the presence of two different types of healthcare professionals which led to a more holistic treatment. The two professions worked from their own vision, making the treatment as thorough as possible. After the program was finished, professionals had better gotten to know each other, and were actively seeking collaboration. It is remarkable that the collaboration picked up so fast, as literature shows interprofessional collaboration between healthcare professionals is complex [30]. Professionals have their own educational background and are socialized to adopt a discipline-based vision of their patients and the services they offer. Collaboration requires making changes to this paradigm [30], which apparently succeeded in this blended treatment.

Participating healthcare professionals did not have the feeling all patients were suited to participate in the program and could be seen as an important barrier. This could be due to the condition of MUPS, which is hard to define and does not have clear criteria [31]. Healthcare professionals could quickly tell if a patient was motivated or not, which they seemed to find a predictor of succeeding with the program or not. It seems required to first invite patients to share their motivations, personal needs and preferences before starting an integrated blended care program [14]. Patients were selected through a proactive approach. An electronic screening method using data from the electronic medical record of the patients' GP was used [32]. All eligible patients who were at risk for chronicity of complaints were proactively approached by their GP via an invitation letter explaining the study. By approaching patients proactively, the chance of finding patients who may be less motivated and less clear about what they want to achieve within the intervention may increase. One should therefore take motivation and personal help-request into account in future programs.

The most frequently reported barrier in the application of the integrated blended care was dealing with the autonomy regarding decisions about when and how to stick to the

treatment protocol. For instance, professionals felt more time was needed during the intake, felt the need for an evaluation or booster session, and experienced the need for treating more patients following the protocol. Additionally, healthcare professionals struggled with the fact that their role changed into being more of a coach. They had difficulties seeking to formulate long terms goals with their patients. The feeling was patients did not have a specific help-request. This could be due to fact patients were better prepared. Furthermore, this preventative approach was new, which was hard to get used to. More insights are necessary into how to coach professionals on behavioural change techniques and how to organize healthcare around it [11,12,33]

Other perceived barriers included the lack of accessibility of the e-Coaching modules, which was also reflected in by the reported SUS scores. Eighty percent of interviewees gave SUS scores below 70, which implies a low user satisfaction [26]. Technical problems were experienced as hindering factor, and the need for user-friendly technical solutions has been repeatedly expressed in the literature [34,35,36]. The successful implementation of the integrated blended care will certainly require a more sophisticated technical setup, that is free of typical starting problems. Based on the results of the current study, a new application was developed which shows promising technical support.

Limitations and strengths

The main limitation of this study is that not all healthcare professionals who participated in the PARASOL program were included. It is possible that the professionals who were less satisfied did not participate. This gives a possible influence on the results. Another limitation is that the PARASOL program is the first program conducted at patients who suffer with moderate MUPS. A major advantage is that we can now gain insight into the first insights, but it remains difficult to make a comparison with existing literature, which focuses on chronic MUPS. Besides the fact that this study offers new insights into the end-user experience, the strengths of these studies are focused on the presence of the iterative analysis process and the triangulation in data collection and analysis. In this study, we applied two frameworks (De Bleser and TNO) to gain a broad perspective on both user experience and innovations in healthcare [22,25]. Although these framework guided on the researcher in data collection, the risk of bias was limited by triangulating in data collection and analysis.

CONCLUSION

An integrated blended care program offers the possibility to personalize treatment. This study gathered healthcare professionals' experiences with and attitudes towards integrating healthcare and offering blended care programs. Findings show attention should be given to the new responsibilities of healthcare professionals, and their role in integrated and blended care. This new approach of delivering healthcare can facilitate interprofessional collaboration. Achieving sustainable change in patients however still requires instruction and support for healthcare professionals implementing behavioural change techniques.

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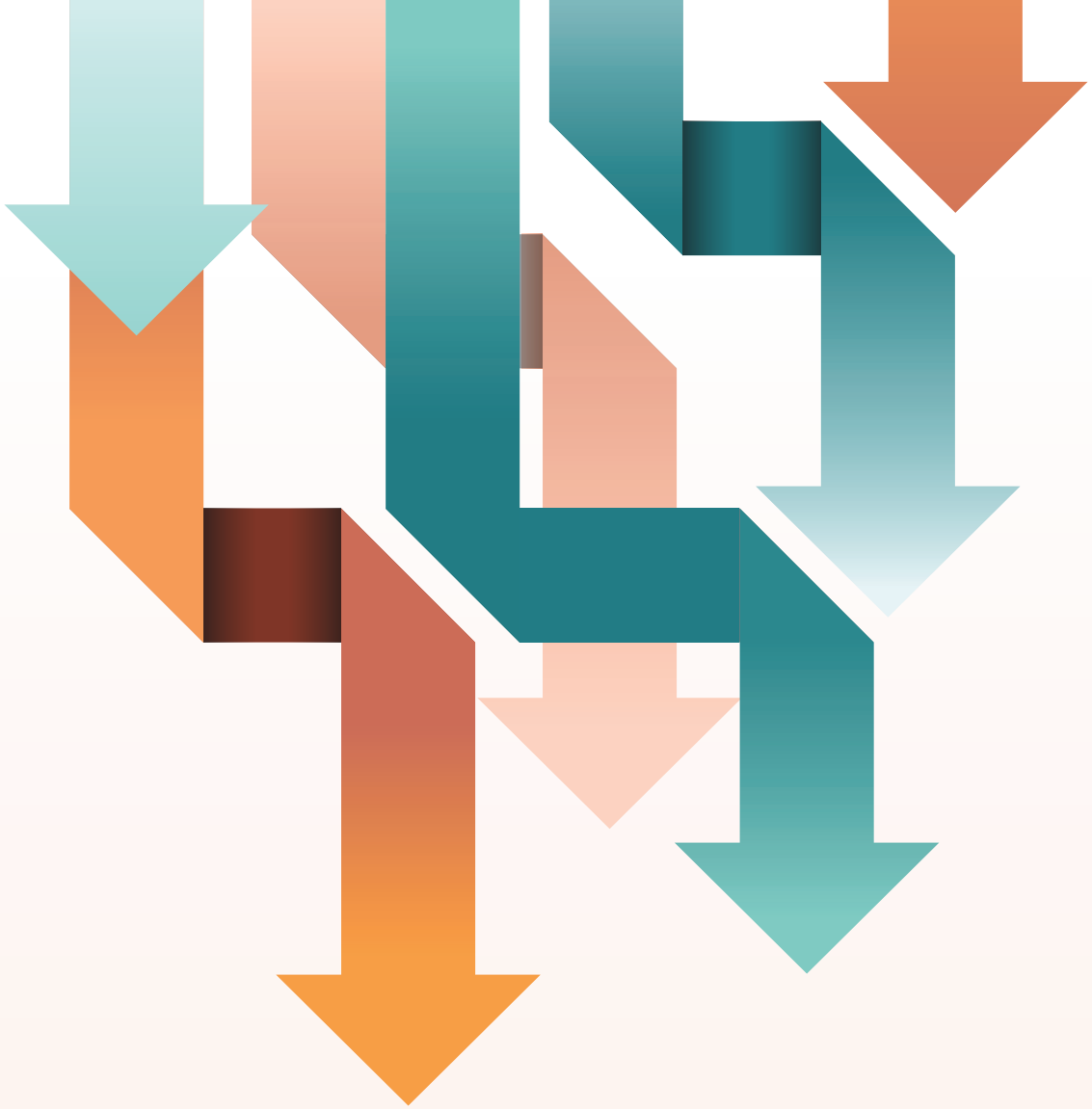

8

CHAPTER

Identifying subgroups based on self-management skills in primary care patients with moderate medically unexplained physical symptoms

Mariëlle E.C. Beems
Suze A. J. Toonders
Paula E. van Westrienen
Cindy Veenhof
Martijn F. Pisters

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ABSTRACT

Objective

Medically Unexplained Physical Symptoms (MUPS) are a major burden on both patients and society and frequently develop into chronic MUPS. Self-management interventions may prevent moderate MUPS from becoming chronic. Tailoring interventions to the patient population is strongly recommended. This can be facilitated by identifying subgroups based on self-management skills. This study aimed to identify these subgroups and their clinical profiles in primary care patients with moderate MUPS.

Methods

A cross-sectional study was performed on baseline measurements from a randomized clinical trial (PARASOL-study). To identify subgroups based on self-management skills, a hierarchical cluster analysis was conducted for adults with moderate MUPS from primary health care centers. Self-management skills were measured with the Health education impact Questionnaire. Cluster variables were seven constructs of this questionnaire. Additionally, specific patient profiles were determined by comparing the identified clusters on the clinical variables pain, fatigue and physical functioning.

Results

Four subgroups were identified: High-Self-Management Skills (SMS) (n=29), Medium-SMS (n=55), Low-SMS (n=49) and Active & Low Distress-SMS (n=20). The latter showed a distinctly different pattern on cluster variables, while the other subgroups differed significantly on means of the cluster variables ($p < .001$). On clinical variables, significant differences between subgroups were mainly found on fatigue and physical functioning.

Conclusion

This study found four specific subgroups based on self-management skills in moderate MUPS-patients. One subgroup demonstrated a distinctly different pattern on self-management skills. In other subgroups, more similar patterns on self-management skills were found that negatively correlated with pain and fatigue and positively correlated with physical functioning.

INTRODUCTION

Medically Unexplained Physical Symptoms (MUPS) are 'physical symptoms that last for more than a few weeks and where, with adequate medical examination, no somatic condition is found that sufficiently explains the complaints' [1]. These include symptoms such as pain, fatigue, physical and mental impairments and reduced quality of life [2]. A spectrum of MUPS exists along three stages: mild, moderate and chronic [3] (Appendix A). In the Netherlands, MUPS account for 25–50% of all General Practitioner (GP) visits [4]. Patients with MUPS show considerable risk of chronicity: 10–30% still experience unexplained symptoms after three months [5,6]. The condition is a major burden to patients, health care professionals and society [7] because of the impairments, the possible exposure to unnecessary and maybe harmful diagnostics and treatments, and because of the high costs patients with MUPS impose on the health care system as frequent attenders [6,8].

Self-management interventions are used as part of treatment in patients with MUPS at all three stages [9]. Rijken et al. describe the goal of self-management interventions as: 'to minimize the impact of chronic disease on physical health status and functioning, and to enable people to cope with the psychological effects of the illness' (p. 117) [10]. For chronic MUPS, self-management interventions can improve patient reported outcome measures (PROMs) like physical functioning [11,12], fatigue [13,14] and pain [15,16]. These interventions contain elements of education, training self-monitoring and symptom management, exercise and cognitive behavioral training, among others, to achieve lifestyle changes [11,13,15]. Evidence of the effectiveness of self-management interventions is still limited [17]. Furthermore, some studies find limited to no evidence that self-management interventions improve outcome measures [17–19]. Although the potential of selfmanagement interventions is widely recognized, it is argued one should not take a one-size-fits-all approach [10,20]. To show effectiveness, it is important to apply the right intervention to the right person at the right time [10,20,21].

Influencing self-management skills in the moderate stage of MUPS could prevent chronicity, due to proactive care [1,22]. Therefore, the PARASOL-intervention has been recently developed [22]. This is a blended self-management intervention conducted in a primary health care setting, which integrates face-to-face contact performed by a physiotherapist and a mental health nurse, with eHealth modules [22]. To further improve the effectiveness of self-management interventions for prevention of chronic MUPS, it is important to determine if specific subgroups, based on differences in self-management

skills, can be identified within a moderate MUPS population [1]. Once subgroups are known, it is possible to deliver better tailored care [1,10]. Self-management skills can be measured by the Health education impact Questionnaire (HeiQ) [23], which provides scores on eight different constructs of self-management, consisting of seven constructs for individual empowerment and one for partnership with health care services [23]. Cluster analysis, identifying subjects within a moderate MUPS population with similar and dissimilar patterns in self-management skills scores, can reveal specific subgroups [24].

Until now, no research has been conducted to identify subgroups based on self-management skills in primary care patients with moderate MUPS. Furthermore, even though clinical variables such as pain, fatigue, and impairment in physical functioning are frequently reported in patients with moderate MUPS [1] and have shown to be associated with self-management [11–16], it is unknown if these variables are related to specific patterns in self-management. Therefore, the aims of this study were (1) to identify subgroups based on self-management skills in primary care patients with moderate MUPS and (2) to compare these subgroups on the patient reported outcome measures of physical functioning, pain and fatigue.

METHODS

Study details and participants

A cross-sectional descriptive study design was used, which is appropriate for identifying subgroups with a cluster analysis [25,26]. Subjects were recruited between March 2017 and April 2018 at the primary health care centers Leidsche Rijn Julius Health Care Centers and Health Care Centers Foundation Eindhoven in the Netherlands. Data was collected from baseline measurements of the PARASOL-study [22], a multi-center cluster randomized clinical trial aimed at investigating the effect of the PARASOL-intervention on the impact of symptoms and quality of life in patients with moderate MUPS compared to usual care.

For the current study, adults with moderate MUPS from primary health care centers were included. They were selected (1) from the electronic medical records of the GPs, (2) by GPs from patients visiting them for consultation, and (3) from the respondents to flyers and a newsletter available to patients of the participating health care centers. For the selection of participants, the PRESUME screening method of den Boeft et al. [3,27] was applied. This method can facilitate identification of patients at risk of persistent MUPS,

enabling application of preventive interventions at the right time [3]. The screening method classifies patients with symptoms of MUPS into three groups: mild, moderate and chronic, based on severity and disease impact. Compared to a questionnaire on severity of somatic symptoms, the screening method demonstrated low sensitivity and high specificity in primary care [27]. Additionally, it showed acceptable prognostic accuracy in early identification of moderate MUPS-patients [28]. Applying this method, first a consultation rate of five or more GP consultations is used, as a high consultation rate is seen as a key characteristic of MUPS in general practice [29,30]. Second, patients with an established medical or psychiatric diagnosis were excluded [31]. Third, patients were classified as moderate MUPS, based on the presence of MUPS related symptoms and the absence of a Functional Somatic Syndrome diagnosis (Appendix A and B) [3]. Additional exclusion criteria were: command of the Dutch language, and access to the internet. Furthermore, patients were excluded by their GP if they received a medically explained diagnosis between identification for the study and inclusion. For more details, see the PARASOL-study [22].

At baseline all subjects signed an informed consent and filled in the same set of self-reported questionnaires including the HeiQ, on paper or digitally with NETQ (NETQ Healthcare, Utrecht, Netherlands). The PARASOL-study, including the analysis performed in the current study was approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht (MREC document number: NL57931.041.16).

Self-management skills

Self-management skills were assessed with the HeiQ-Dutch version, a valid, reliable and user-friendly questionnaire, consistent for a wide range of chronic conditions including MUPS [32]. Although the HeiQ was developed to evaluate self-management and patient education programs in patients with chronic conditions, it can also be used to evaluate the variation in a group of subjects by assessing different patterns in subscales of self-management [20,23]. The questionnaire consists of eight independent subscales measuring the following constructs: (1) Health Directed Activity (HDA), (2) Positive and Active Engagement in Life (PAEL), (3) Emotional Distress (ED), (4) Self-Monitoring and Insight (SMI), (5) Constructive Attitudes and Approaches (CAA), (6) Skill and Technique Acquisition (STA), (7) Social Integration and Support (SIS) and (8) Health Service Navigation (HSN). Each subscale consists of four to six questions, scored on a 4-point Likert scale (ranging from totally disagree to totally agree). Scores on the emotional distress scale were reversed. The raw data from the questions was rescaled into a construct score, ranging

from one to four. A higher score indicates a higher level of self-management [32]. There are no norm data available for HeiQ-scores in a Dutch population or in a population with moderate MUPS. The composite reliability of the subscale Self-monitoring and insight is 0.67 (95% CI 0.61–0.73). For all other subscales the composite reliability is ≥0.81 [32].

The eight constructs of the HeiQ represent two main principles, individual empowerment (construct 1–7) and partnership with health care services (construct 8) [23]. In MUPS, the partnership with health care services depends on a great number of factors (e.g. on the quality of the patient doctor relationship, which in MUPS is complicated [1]) and only partially on personal self-management skills. Therefore, as in previous research, only individual empowerment was assessed [33] and consequently only constructs one to seven were included as cluster variables.

Sample size

In cluster analysis there is no generally accepted rule for sample size calculation [34]. However, the clusters need to be filled with enough subjects to draw meaningful conclusions and to conduct further analyses. Therefore, the number of variables in cluster analysis should be proportional to the sample size [26]. The sample size was calculated following the recommendation by Formann [35] as described by Van den Berge [26], in which sample size should be equal to or greater than 2m, m being the number of clustering variables. With seven cluster variables the sample size had to be at least 27=128 subjects. Because of the explorative nature of the current study, a convenience sample with the maximum available number of subjects from the PARASOLstudy was included.

Clinical and demographic variables

The clinical variables pain, fatigue, and impairment in physical functioning were assessed. Pain was defined as self-perceived pain in the past week, and measured on an 11-point (score 0–10) numeric rating scale (NRS). Fatigue was defined as self-perceived fatigue in the past week, and measured on the same scale. The NRS is valid and reliable [36,37] with good responsiveness, ease of use, applicability and compliance rates [38]. Physical functioning (PF) was measured with the physical functioning subscale of the RAND-36 item Health Survey (RAND-36). The PF subscale is a valid and reliable self-reported generic questionnaire, with high internal consistency (Cronbach's alpha 0.92) and a test-retest reliability of 0.82 [39,40]. The subscale contains ten items measuring restrictions on daily activities due to health problems like walking stairs, washing and dressing, or carrying

groceries. The scores on a 3-point Likert scale (ranging from yes, seriously limited to no, not at all limited) were transformed to a 0–100 scale. Individuals with high scores are able to perform even the most strenuous activities such as running. Low scores on the other hand, indicate severe restrictions in performing all physical activities [39,40]. Furthermore, the demographic variables sex, age, educational level and the duration of complaints were assessed. Educational level was recoded to two categories: low education (primary school/primary education to secondary vocational education) and high education (higher general/preparatory academic education to university). Duration of complaints was recoded to three categories:<1 year, 1–5 years,>5 years.

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM, Armonk, New York, USA). Descriptive analyses were used to summarize characteristics of the study sample. Subsequently, clusters based on self-management skills were identified performing an agglomerative hierarchical cluster analysis using Ward's Linkage with Squared Euclidean distance [41,42]. In cluster analysis, subjects with homogeneous characteristics are assigned to a specific cluster and subjects with heterogeneous characteristics compared to the former group, to another cluster. Because complete datasets are required in cluster analysis [43], imputation was performed, using expectationmaximization (EM) estimation [44]. This procedure will lead to unbiased results [44], provided that the data is missing completely at random (MCAR). In hierarchical cluster analysis the number of clusters is not predefined. Determination of this number was done visually based on a dendrogram and the agglomeration schedule. Due to nonnormality of the data, a Kruskal-Wallis test with pairwise comparisons was used to determine on which self-management skills the clusters were significantly different ($p < .05$).

Additionally, to identify specific profiles in patients with moderate MUPS, the continuous clinical variables pain, fatigue and physical functioning were compared between the clusters with a Kruskal-Wallis test and pairwise comparisons with a significance level of $p < .05$. Finally, means and percentages of demographic variables were examined for differences between the clusters. Chi-square tests were conducted for the categorical variables (sex, education level and duration of complaints), and a Kruskal-Wallis test for the continuous variable (age).

Table 1: Sample characteristics (n = 153)

Sociodemographics	
Age in years, mean (SD, range)	49.2 (13.95, 22-88)
Female gender, n (%)	112 (73.2)
Type of education, n (%)	
Low education	
– primary school / primary education	5 (3.3)
– lower vocational education	15 (9.8)
– secondary general education	18 (11.8)
– secondary vocational education	40 (26.1)
High education	
– higher general / preparatory academic education	23 (15.0)
– higher professional education	23 (15.0)
– university	29 (19.0)
Duration of complaints, n (%)	
– 0 – 6 months	10 (6.5)
– 6 months – 1 year	11 (7.2)
– 1 year – 2.5 years	26 (17.0)
– 2.5 – 5 years	30 (19.6)
– ≥ 5 years	76 (49.7)
Clinical variables, mean (SD, range)	
Pain NRS (0-10)	5.04 (2.42, 0- 9)
Fatigue NRS (0-10)	5.99 (2.59, 0-10)
Physical functioning RAND-36 (0-100)	72.74 (21.87, 10-100)
HeiQ construct scores (1-4), mean (SD, range)	
– health directed activity	3.09 (.66, 1.00-4.00)
– positive and active engagement in life	3.00 (.54, 1.80-4.00)
– self-monitoring and insight	2.86 (.43, 1.67-4.00)
– constructive attitudes and approaches	3.06 (.55, 1.80-4.00)
– skill and technique acquisition	2.64 (.53, 1.00-4.00)
– social integration and support	2.80 (.62, 1.00-4.00)
– emotional distress (reversed)	2.94 (.63, 1.33-4.00)

NRS = numeric rating scale, RAND-36 = RAND-36 item Health Survey, HeiQ = Health education impact Questionnaire

RESULTS

Study population

For this study, 153 persons provided baseline data before April 2018. Sample characteristics are presented in Table 1. Of the population, most were female, middle-aged and half of the sample was highly educated. The ages widely differed, from young to elderly. On physical functioning, most restrictions are found in activities requiring considerable effort. The lowest mean HeiQ-scores were found on skill and technique acquisition and highest mean scores on health directed activity. Scale scores on emotional distress were

reversed, such that a higher score implies less self-reported negative affect. Seven cases (< 5%) had missing values, due to an error in the hardcopy HeiQ questionnaire. The missing data was marked as MCAR [45], which was confirmed by Little's MCAR test [44]: X2(103)=125.45, p=.07. Imputation could therefore be performed, applying expectation-maximization (EM) estimation.

Cluster analysis

Results from a dendrogram (Fig. 1) and the change in agglomerative coefficient showed a four cluster model, in which clusters indicated best similarities and deviations on self-management skills. The dendrogram graphically displays the distance within the cluster algorithm to join the next neighboring clusters [46]. Two larger (n=49 and 55) and two smaller (n=29 and 20) clusters emerged from the data (Fig. 2). The larger clusters represented an overall medium and an overall low score on self-management skills (SMS), compared to the mean construct scores of the complete sample of the study, as displayed in Table 1. One of the smaller clusters represented an overall high score. The final cluster represented a medium to low score on most self-management skills, combined with high health directed activity and low emotional distress. Based on these self-management characteristics, the subgroups High-SMS (H-SMS), Medium-SMS (M-SMS), Low-SMS (L-SMS), and Active & Low Distress-SMS (A&LD-SMS) were defined within the moderate MUPS population. The dendrogram shows that the L-SMS cluster is largely independent from the other clusters and the A&LD-SMS is closest to the M-SMS cluster.

All self-management skills were an important input in cluster formation. This held most for the skills of positive and active engagement in life, emotional distress and constructive attitudes and approaches (F (3,149)=65.1, 51.2, 50.7). Slightly less input came from social integration and support, and skill and technique acquisition (F (3,149)=42.4, 41.7). Least input was provided by health directed activity and self-monitoring and insight (F(3,149)=27.0, 25.7). Differences in the means of the self-management skills between the subgroups are presented in Table 2. A pattern was found for H-SMS, MSMS and L-SMS, with decreasing mean scores from H-SMS to L-SMS, on all self-management skills. Pairwise comparisons (adj. p-values<.05), found significant differences on all self-management skills, except for health directed activity between M-SMS and L-SMS. The A&LD-SMS means were comparable to H-SMS on health directed activity and emotional distress, and comparable to M-SMS and/or L-SMS on the other self-management skills.

In all four subgroups, the lowest mean scores were found on skill and technique acquisition. Furthermore, there were some specifics for each subgroup. Relatively low scores were seen in H-SMS on selfmonitoring and insight, in M-SMS on emotional distress-reversed and on health directed activity (which showed the highest standard deviation), in L-SMS on emotional distress-reversed and social integration and support, and in A&LD-SMS on social integration and support, and self-monitoring and insight.

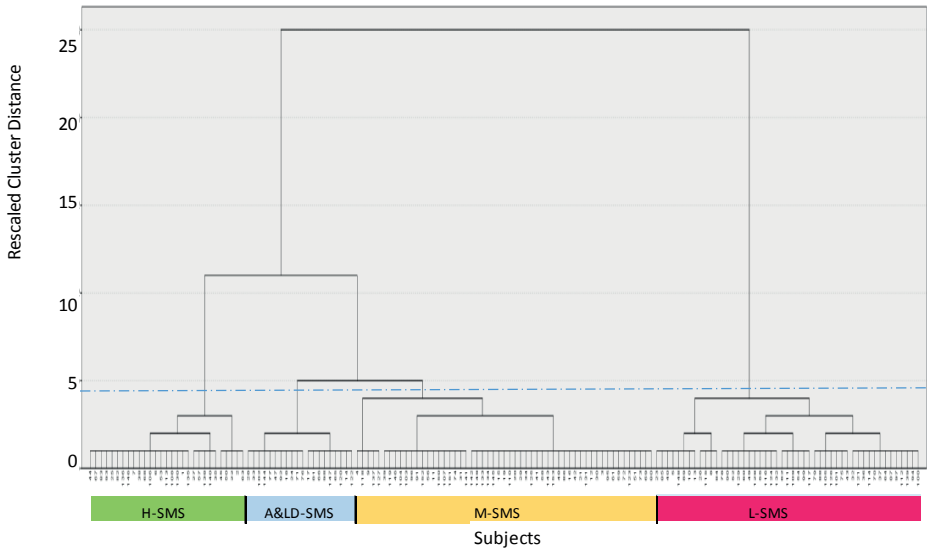

Figure 1: Dendrogram of the 4 clusters identified, from hierarchical cluster analysis using Ward's linkage method with Squared Euclidean Distance measure, SMS=self-management strategies, H-SMS=High-SMS, M-SMS= Medium-SMS, L-SMS= Low-SMS, A&LD-SMS=Active & Low Distress-SMS

Differences on demographical and clinical variables

Differences between the subgroups on demographical and clinical variables are presented in Table 3. There were significant differences in education level X2(3)=8.23, p=.04. Gender, age and duration of complaints did not differ significantly. However, when comparing the subgroups, general patterns emerged from the data. A&LD-SMS showed a high percentage of highly educated people with a duration of complaints mostly between one and five years. Similarly, the duration of complaints in H-SMS was mostly between one and five years. M-SMS showed a high percentage of women, with a duration of complaints for more than five years. L-SMS demonstrated a high percentage of men and of low educated people, with a duration of complaints for more than five years, whereas the mean age was somewhat lower compared to the other subgroups.

On the clinical variables, significant differences were found on fatigue H(3)=15.42, p=.001 and physical functioning H(3)=9.23, p=.03. The pain scores were not statistically significant H(3)=7.73, p=.05. A&LD-SMS showed the lowest score on pain and the highest score on physical functioning. H-SMS showed the lowest score on fatigue. On the other hand the L-SMS subgroup showed the highest scores on pain and fatigue, and the lowest score on physical functioning. Finally, pain and fatigue scores correlated negatively with the means of the cluster variables in the H-SMS, M-SMS and L-SMS clusters and physical functioning scores correlated positively with the means of the cluster variables in these clusters.

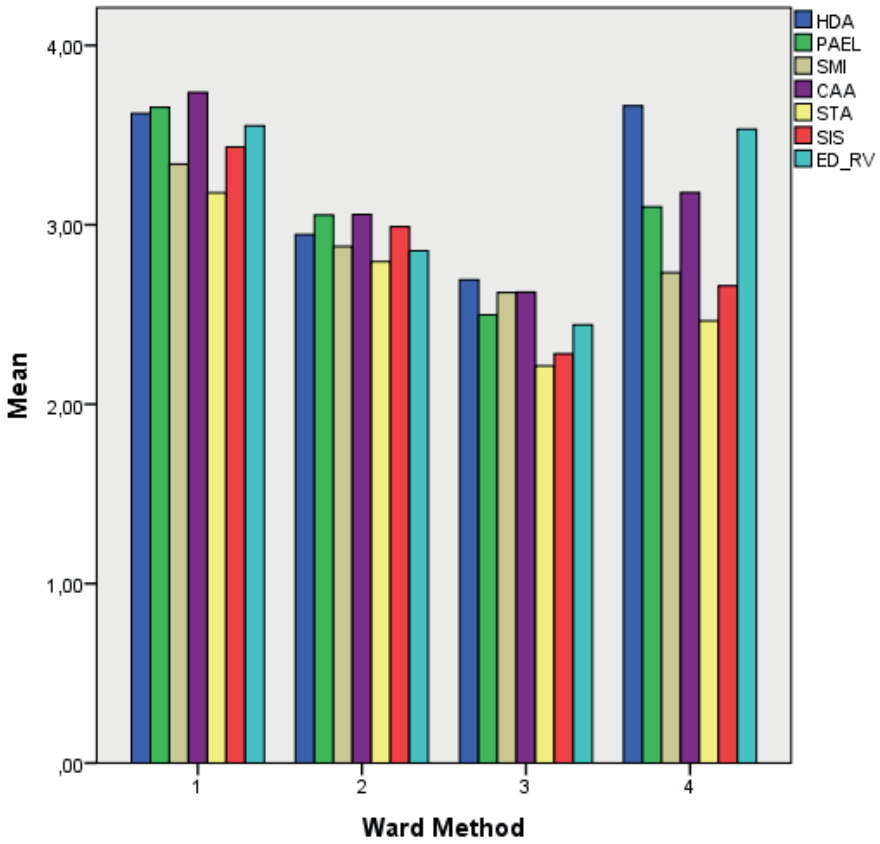

Figure 2: Construct mean differences for identified clusters. 1= H-SMS, 2=M-SMS, 3= L-SMS, 4= A&LD-SMS, HDA='health directed activity', PAEL='positive and active engagement in life', SMI='self-monitoring and insight', CAA='constructive attitudes and approaches', STA='skill and technique acquisition', SIS='social integration and support', ED_RV='emotional distress' (reversed score)

Table 2: Differences in clustering variables between phenotypes identified by Ward's cluster analysis (n=153)

Cluster variables (HeiQ constructs)	H-SMS (n = 29) Mean (SD)	M-SMS (n = 55) Mean (SD)	L-SMS (n = 49) Mean (SD)	A&LD-SMS (n = 20) Mean (SD)	Kruskal-Wallis p-values
Health Directed Activity **(HDA)**	3,62 (0,45)	2,95 (0,64)	2,69 (0,50)	3,66 (0,44)	**< .001**
Positive and Active Engagement in Life **(PAEL)**	3,66 (0,28)	3,05 (0,34)	2,50 (0,39)	3,10 (0,42)	**< .001**
Self-Monitoring and Insight **(SMI)**	3,34 (0,34)	2,88 (0,29)	2,62 (0,40)	2,73 (0,42)	**< .001**
Constructive Attitudes and Approaches **(CAA)**	3,74 (0,29)	3,06 (0,36)	2,62 (0,39)	3,18 (0,56)	**< .001**
Skill and Technique Acquisition **(STA)**	3,18 (0,42)	2,79 (0,31)	2,21 (0,46)	2,46 (0,36)	**< .001**
Social Integration and Support **(SIS)**	3,43 (0,50)	2,99 (0,32)	2,28 (0,52)	2,66 (0,57)	**< .001**
Emotional Distress (reversed) **(ED RV)**	3,55 (0,39)	2,85 (0,48)	2,44 (0,49)	3,53 (0,28)	**< .001**

HeiQ = Health education impact Questionnaire, SMS = self-management strategies, H-SMS ='High-SMS phenotype',

M-SMS ='Medium-SMS phenotype', L-SMS = 'Low-SMS phenotype' and A&LD-SMS ='Active & Low Distress-SMS phenotype'

Table 3: Differences in demographics and clinical variables between phenotypes of self-management strategies on baseline (n=153)

Demographical and Clinical variables	H-SMS (n = 29)	M-SMS (n = 55)	L-SMS (n = 49)	A&LD-SMS (n = 20)	p-value**
Gender, (%)					
Male	24,1	18,2	34,7	35,0	.219[b]
Female	75,9	81,8	65,3	65,0	
Age, mean (SD)	51,34 (13,83)	50,58 (15,95)	45,98 (11,32)	49,80 (13,71)	.227[a]
Education, (%)					
Low	51,7	45,5	65,3	30,0	.042[b]*
High	48,3	54,5	34,7	70,0	
Duration of complaints, (%)					
< 1 year	17,2	14,5	6,1	25,0	.164[b]
1-5 years	44,8	30,9	34,7	45,0	
> 5 years	37,9	54,5	59,2	30,0	
Pain NRS, mean (SD)	4,69 (2,33)	4,78 (2,40)	5,80 (2,20)	4,40 (2,84)	.052[a]
Fatigue NRS, mean (SD)	4,62 (2,76)	6,11 (2,62)	6,96 (1,79)	5,30 (2,96)	.001[a]* (H vs L p = .001)
Physical functioning RAND-36, mean (SD)	74,66 (19,08)	72,55 (24,02)	67,65 (20,72)	83,00 (19,56)	.026[a]* (L vs A&LD p = .016)

Measures in mean (SD) or percentage, * Significant p values, SMS = self-management strategies, H-SMS ='High-SMS phenotype', M-SMS ='Medium-SMS phenotype', L-SMS = 'Low-SMS phenotype' and A&LD-SMS ='Active & Low Distress-SMS phenotype', NRS = numeric rating scale, RAND-36 = RAND-36 item Health Survey, ** (statistical tests): a = Kruskal-Wallis, b = Chi-square

DISCUSSION

This is the first study identifying subgroups based on self-management skills and their characteristics on demographic and clinical variables in primary care patients with moderate MUPS. Four subgroups were identified within a moderate MUPS population using cluster analysis with seven different self-management skills (SMS) as cluster variables. The subgroups High-SMS, Medium-SMS, Low-SMS, and Active & Low Distress-SMS emerged from the data. Given that the first three subgroups showed a rather similar pattern on self-management skills, it could be possible that they represented only one group with different levels of dysfunction severity [24]. However, the dendrogram shows that the Low-SMS cluster was largely independent of the other clusters. A great distance length between Low-SMS and the other clusters confirms the heterogeneous characteristics on self-management skills [46]. Furthermore, the Active & Low Distress subgroup had a distinctly different pattern. Therefore, it is likely that there are specific subgroups in a population of moderate MUPS, with a need for different treatment strategies instead of a one-size-fits-all treatment. Whether identified subgroups in this MUPS population also apply to other patient groups is not clear. Based on the differences seen in self-management skills scores between this study and previous research in a large Australian population with chronic diseases [19], it seems possible that different subgroups can be identified in patients with other conditions.

The Active & Low Distress subgroup stood out from others. This subgroup is characterized by a high level of health directed activity and a low level of emotional distress. It could give an indication of a group known from literature to have high levels of persistence, constantly continuing activity and often ignoring pain [47,48]. As pain scores are measured as self-perceived, low scores on pain also give an indication of this. Moreover, scores on self-monitoring and insight are relatively low, and fatigue levels are higher than in High-SMS. Although this subgroup shows relatively good clinical symptom scores compared to Medium-SMS and Low-SMS, five out of the seven self-management scores are found to be significantly lower than those in High-SMS. Furthermore, in the cluster analysis, the Active & Low Distress subgroup is close to Medium-SMS. By distracting oneself and ignoring physical symptoms, the clinical picture may be distorted, masking a group at-risk [48]. Another possibility is that a strategy of more health directed activity acts as a buffer for clinical symptoms [49].

In this study all self-management skills provided an important input on the formation of the clusters which is consistent with the idea that all self-management skills are

equally important [23]. These findings correspond with the suggestion of Elsworth et al., that higher scores on all self-management skills are a desirable outcome of treatment and are associated with increased well-being [19]. Furthermore, it supports the idea of self-management as a multidimensional concept [23], in which a multifactorial self-management intervention seems useful for a positive improvement on self-management skills. Positive and active engagement in life, emotional distress and constructive attitudes and approaches gave the largest input on the cluster formation.

The demographic data in this study with moderate MUPS-patients showed differences between the subgroups. Although half of the study subjects were highly educated (49%), the Low-SMS subgroup showed a relatively high percentage of people with a lower education (65.3%). Additionally, this subgroup consisted of a high percentage of people with a duration of complaints for more than five years (59.2%). These findings in Low-SMS are consistent with the knowledge that lower selfmanagement is related to lower education and a longer duration of complaints [10]. In contrast with the Low-SMS subgroup, the Active & Low Distress-SMS subgroup showed 70% of highly educated people, which seems to support the finding that the identified subgroups are heterogeneous. Demographics further showed a high percentage of women in this study. This is consistent with the knowledge that MUPS are more common in women [4,50,51], although the Low-SMS and Active & Low Distress-SMS subgroups showed a relatively high percentage of men, for which there was no clear explanation.

A limitation of this study is the difference in cluster size between the subgroups. Although the number of participants from the sample size calculation was amply achieved, the sizes of the High-SMS and Active & Low Distress-SMS subgroups were relatively small (n=29 and 20) compared to the other clusters [52]. Ward's method is frequently used in cluster analysis but performs best with clusters of approximately the same size [53]. The cluster sizes could have influenced the clustering and therefore the results should be regarded with caution. Furthermore, the smaller groups may have impaired identifying differences in pain between the subgroups. The main strength of the study is that it provides a first insight in levels of self-management measures over a range of skills and within subgroups in a moderate MUPS population, information which was unknown to date. Because of the large implications of MUPS [6,8], further research is important. For the interpretation and generalizability of the HeiQ scores in moderate MUPS, establishing norm data is necessary, as is validation of the identified subgroups. Self-management interventions in moderate MUPS may be more effective if tailored to specific subgroups [1,22]. Interventions could be tailored by adapting the number 0f components per

subgroup or the intensity of guidance per component in subgroups. Additionally, based on subgroup characteristics the following accents could be considered: in High-SMS on self-monitoring and insight, in Medium-SMS on emotional distress and health directed activity, in Low-SMS on emotional distress and social integration and support, and in Active & Low Distress-SMS on social integration and support and self-monitoring and insight. However, results of this crosssectional study do not provide information about which adjustments will be effective. Characteristics of subgroups, combined with e.g. information about risk factors for chronicity, can inform the formulation of hypotheses which must be tested in clinical trials.

Even though further research still needs to be done, the results of this study are important for the clinical setting. MUPS are a major burden for patients and health care providers [6–8], and patients with MUPS are considered difficult patients to treat [2,4,54,55]. Information on clusters can help both health care professionals and patients. Although guidelines acknowledge the fact that interventions for MUPS patients would benefit from knowledge of specific subgroups, until now treatment is based on risk assessment of possible iatrogenic damage and development of persistent complaints [1]. Based on the results of this study, it seems important in the treatment for moderate MUPS not only to focus on symptom reduction, but also include a proactive evaluation of self-management. Knowing that various subgroups of moderate MUPS show more or less reduced self-management skills and may benefit from a self-management training tailored for different subgroups, can contribute to taking these complex patients with MUPS more seriously [56]. The level of self-management measured in individual patients can already be used to provide insight and targeted advice and interventions [20].

CONCLUSIONS

This study found four specific subgroups based on self-management skills in patients with moderate MUPS. One subgroup demonstrated a distinctly different pattern on self-management skills with relatively low scores on pain and fatigue and the highest level of physical functioning. In other subgroups, more similar patterns on self-management skills were found that negatively correlated with pain and fatigue and positively correlated with physical functioning. Tailoring self-management interventions to specific subgroups of patients with moderate MUPS could result in more effective interventions which may help prevent chronicity. Therefore, it is important to determine characteristics of specific subgroups. The results of this study are a first step in the further development of tailored interventions and may guide further longitudinal intervention studies on moderate MUPS.

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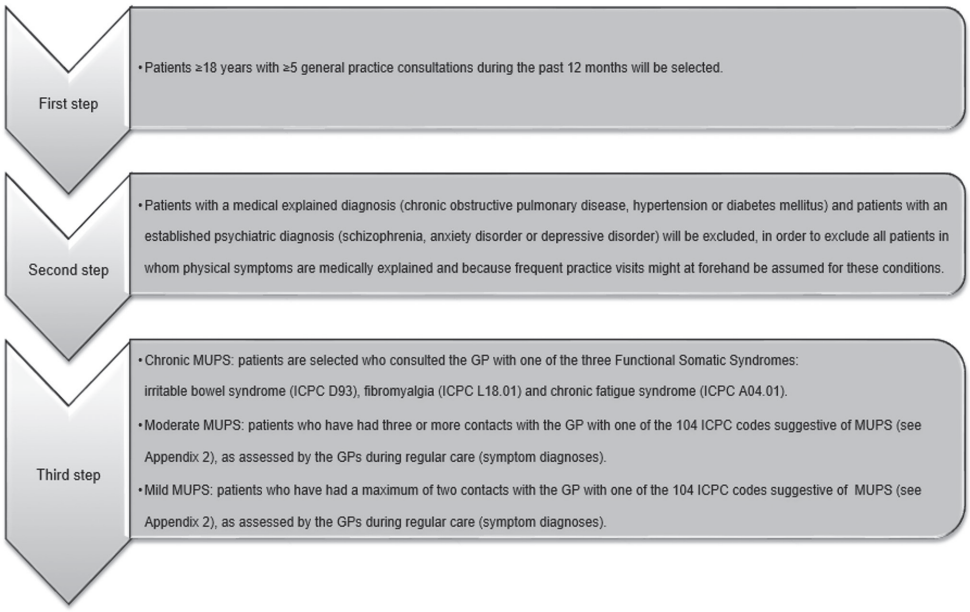
APPENDIX A: PRESUME SCREENING METHOD, WITH SPECTRUM OF MUPS (IN THIRD STEP) [3]



APPENDIX B: 104 INTERNATIONAL CLASSIFICATION OF PRIMARY CARE (ICPC) CODES [3]

Abdomen
D01 Abdominal pain/ cramps general
D02 Abdominal pain epigastric
D04 Rectal/ anal pain
D06 Abdominal pain localized other
D08 Flatulence/ gas/ belching
D09 Nausea
D11 Diarrhoea
D12 Constipation
D18 Change faeces/ bowel movements
D93 Irritable bowel syndrome
T03 Loss of appetite
T08 Weight loss

Fatigue
A04 Weakness/tiredness general
.01 Chronic fatigue syndrome

Musculoskeletal
L01 Neck symptom/ complaint
L02 Back symptom/ complaint
L03 Low back symptom/ complaint
L05 Flank symptom/ complaint
L06 Axilla symptom/ complaint
L07 Jaw symptom/ complaint
L08 Shoulder symptom/ complaint
L09 Arm symptom/ complaint
L10 Elbow symptom/ complaint
L11 Wrist symptom/ complaint
L12 Hand/ finger symptom/ complaint
L13 Hip symptom/ complaint
L14 Leg/ thigh symptom/ complaint
L15 Knee symptom/ complaint
L16 Ankle symptom/ complaint
L17 Foot/ toe symptom/ complaint
L18 Muscle pain
.01 Fibromyalgia
L79 Sprain/ strain of joint NOS
.01 Whiplash trauma cervical spine

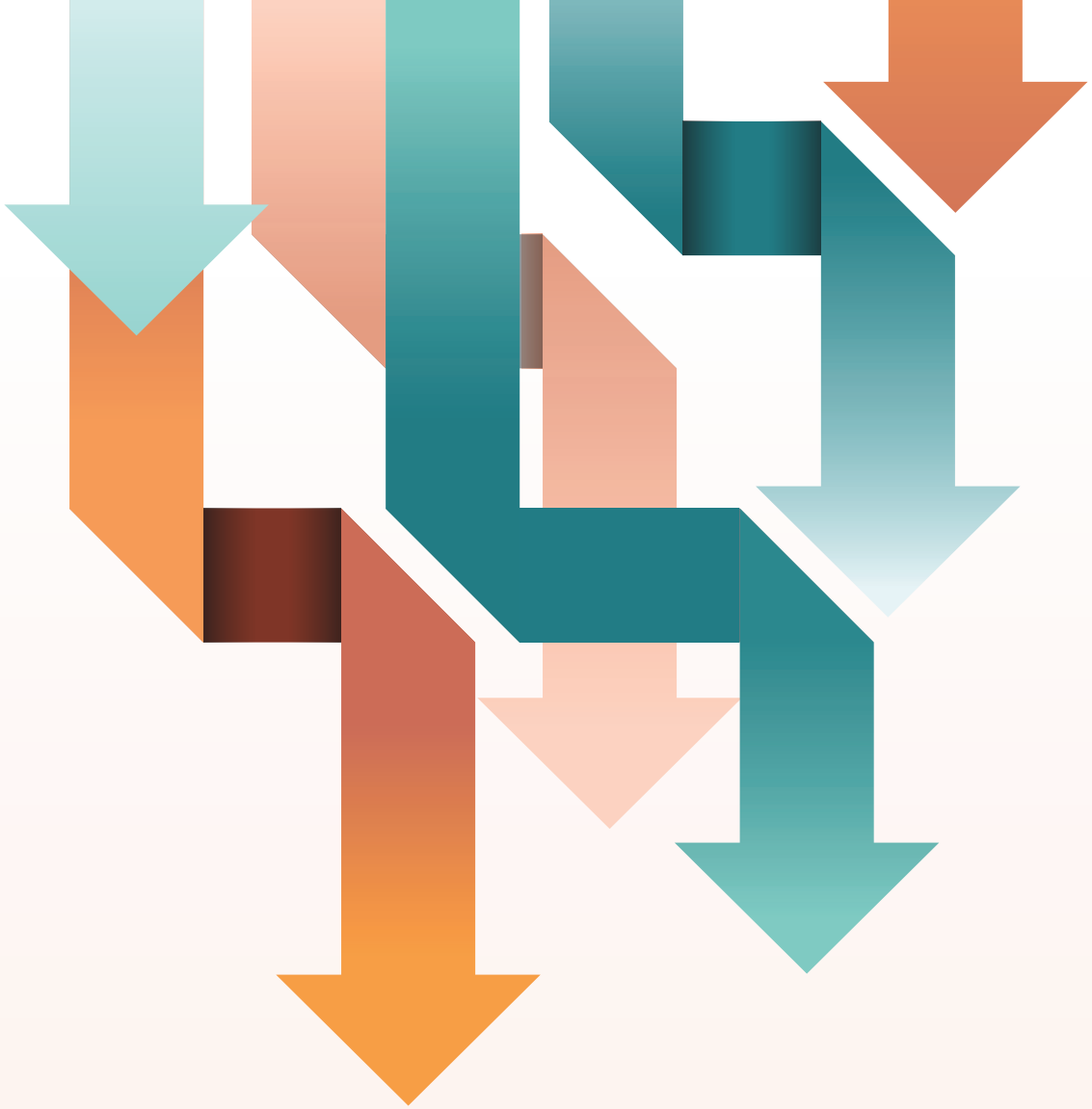
Cardiology-Respiratory
K01 Heart pain
K02 Pressure/ tightness of heart
K03 Cardiovascular pain NOS
K04 Palpitations/ awareness of heart
K05 Irregular heartbeat other
L04 Chest symptom/ complaint

(Pseudo-)Neurology and ENT
A01 Pain general/ multiple sites
F13 Eye sensation abnormal
H02 Hearing complaint
H03 Tinnitus, ringing/buzzing ear
N01 Headache
N02 Tension headache
N03 Pain face
N05 Tingling fingers/feet/toes
N17 Vertigo/dizziness
.01 Sensation of unsteadiness
.02 Lightheadedness

Other
S01 Pruritis
R98 Hyperventilation syndrome

Psychiatry
A26 Fear of cancer NOS
A27 Fear of other disease NOS
B25 Fear of aids/ HIV
B26 Fear cancer blood/ lymph
B27 Fear blood/ lymph disease other
D26 Fear of cancer of digestive system
D27 Fear of digestive disease other
F27 Fear of eye disease
H27 Fear of ear disease
K24 Fear of heart disease
K25 Fear of hypertension
K27 Fear cardiovascular disease other
L26 Fear of cancer musculoskeletal
L27 Fear musculoskeletal disease other
N26 Fear cancer neurological system
N27 Fear of neurological disease other
P01 Feeling anxious/nervous/tense
P06 Sleep disturbance
P75 Somatization disorder
R26 Fear of cancer respiratory system
R27 Fear of respiratory disease other
S26 Fear of cancer of skin
S27 Fear of skin disease other
T26 Fear of cancer of endocrine system
T27 Fear endocrine/metabolic dis other
U26 Fear of cancer of urinary system
U27 Fear of urinary disease other
X23 Fear sexually transmitted disease (f)
X24 Fear of sexual dysfunction female
X25 Fear of genital cancer female
X26 Fear of breast cancer female
Y24 Fear of sexual dysfunction male
Y25 Fear sexually transmitted dis. Male
Y26 Fear of genital cancer male
Y27 Fear of genital disease male other
Z29.01 Burnout / stress

Urological/ Genital complaints
U02 Urinary frequency/urgency
U05 Urination problems other
X01 Genital pain female
X02 Menstrual pain
X03 Intermenstrual pain
X04 Painful intercourse female
X09 Premenstrual symptom/complaint
X11 Menopausal symptom/complaint
X15 Vaginal symptom/complaint other
X16 Vulval symptom/complaint
X17 Pelvis symptom/complaint female
Y01 Pain in penis
Y02 Pain in testis/scrotum
Y04 Penis symptom/complaint other
Y08 Sexual function symptom/ complaint (m)



9

CHAPTER

Movement behavior patterns in patients with moderate Medically Unexplained Physical Symptoms (MUPS): who and how many are avoiding activity?

Suze A.J. Toonders
Paula E. van Westrienen
Roderick Wondergem
Cindy Veenhof
Martijn F. Pisters

Under review

ABSTRACT

Background

Complaints from patients with Medically Unexplained Physical Symptoms (MUPS) result from a complex interplay of biomedical, psychological and social factors. Literature shows that avoiding physical activity (PA) affects experienced pain; physical and cognitive symptoms and stimulation of PA is therefore considered an essential component in MUPS management. Insight into movement behavior patterns and associated characteristics in patients with moderate MUPS makes it possible to deploy more targeted interventions in patients with an unhealthy movement behavior pattern. Movement behavior patterns based on objectively measured data in patients with moderate MUPS are currently lacking.

Methods

This cross-sectional study was conducted using data from a multicenter randomized clinical trial. Patients were eligible to participate if there was a presence of moderate MUPS-related symptoms, aged ≥18 years with ≥ five general practitioner consultations. Movement behavior was measured on seven constructive days using an accelerometer. Movement behavior variables were calculated and compressed using Principal Component Analysis. Patterns were identified using a k-means clustering algorithm. Differences and related clinical variables between the patterns were investigated.

Results

This study identified three different patterns: 'Sedentary Movers' (n=64) spent 9.9 h/d sedentary and were mainly light physical active. 'Active Movers' (n=45) spent 7 h/d sedentary and were mainly light to moderate physical active. Sedentary Exercisers' (n=40) spent 9.5 h/d sedentary and were mainly vigorous physical active.

Conclusion

This study provides a clear and better understanding of movement behavior patterns in patients with moderate MUPS. We did not find evidence supporting the hypothesis that a class of patients avoiding PA exists.

INTRODUCTION

Given various health benefits, adhering to healthy movement behavior is receiving increased attention [1,2]. The World Health Organization (WHO) strongly recommends that all adults undertake regular physical activity and should limit sedentary time for physical health (reducing all-cause mortality, cardiovascular disease mortality, incident hypertension), mental health (reducing symptoms of anxiety and depression) and cognitive health [3]. Movement behavior patterns are defined as the daily behavior of a person in any combination of sedentary behavior (SB) (energy expenditure ≤1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture) and physical activity (PA). PA can be categorized along different intensities, ranging from light (1.5-3.0 METs), moderate (3.0-6.0 METs) to vigorous PA (>6.0 METs)[4]. Following the WHO guidelines, adults should perform moderate to vigorous PA (MVPA) for at least 150 minutes a week [3]. SB of 9.5 or more hours daily is found to lead to higher all-cause mortality [5].

To achieve healthy movement behavior, interventions aim to stimulate PA and/or reduce SB [6]. This is especially important for people with a chronic condition or those at risk of developing a chronic condition, such as those with moderate Medically Unexplained Physical Symptoms (MUPS) [7]. In patients with MUPS, complaints such as pain, fatigue, and dizziness results from the complex interplay of biomedical, psychological, and social factors and are often accompanied by complaints of stress, sleeping problems, anxiety or depression [8][9]. Based on severity and disease impact, MUPS can be classified as mild, moderate or chronic [10]. Of all patients' complaints put forward at their general practitioner, 25–50% cannot be medically explained immediately [11]. Patients with moderate MUPS experience severe unexplained symptoms, with psychological and physical distress, but without a diagnosis of a functional somatic syndrome (FSS), or a somatic symptom disorder (SSD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [12]. Literature shows stimulating physical activity has beneficial effects on experienced pain, physical and cognitive function, and sleep [13,14,15] and is therefore considered an essential component of effective MUPS management [16]. The dose-response of the amount of PA to physical or mental outcomes is currently unknown [17,18].

Patients with MUPS vary greatly in their abilities and limitations, goals, and lifestyle and therefore benefit from guidance that is tailored to their specific needs [19]. Tailoring to patients' specific needs significantly contributes to their motivation, self-efficacy, and adherence [20]. Cognitive-behavioral models of the development of chronic pain suggest

subgroups with signs of physical underuse and overuse. The cognitive-behavioral model for fear of movement is based on the assumption that for some patients, a pain experience will lead to fear of movement and consequently to avoidance of PA as a maladaptive way of coping with pain [21]. The avoidance-endurance model explains the overuse where patients overload their muscles resulting in lower activity levels [22]. In the long run, avoidance of PA can result in invalidating and psychological changes (e.g. depression, disuse and disability) that contribute to the experience of complaints for patients with moderate MUPS [23]. PA is generally safe, and side effects are typically temporary and can often be avoided by patient education [19].

The current body of knowledge on movement behavior patterns in patients with MUPS has two major limitations. Firstly, most available studies investigating associations between movement behavior and outcome measures are primarily based on self-reported PA [24]. These studies hence are complicated by recall and response bias. Such data has limitations, for instance, the inability to capture incidental, short periods of movement and light-intensity activities that are spread across the day. This leads to less accurately reported data [25]. Secondly, literature on overall time-use in movement behavior patterns in patients with moderate MUPS is currently lacking. Although the single aspects of movement behavior are independently associated with health risks, they are not self-contained and cluster in patterns. Rather than considering movement behavior in isolation, literature has therefore shown that overall time-use should be considered. This implies different movement behaviors are discernable, given how an individual distributes movement across a day [26]. Both above mentioned limitations can be overcome by measuring movement behavior with an accelerometer, distinguishing between energy expenditure and differentiating postures [27].

Insight into movement behavior patterns and associated characteristics in patients with moderate MUPS makes it possible to deploy more targeted interventions in patients with an unhealthy movement behavior pattern. This study aims to identify patterns of movement behavior in patients with moderate MUPS using an accelerometer.

METHODS

Study Design

This cross-sectional study was conducted using baseline data of a 12-month prospective, multicentre cluster randomized clinical trial in primary care [28]. The trial protocol and study material were approved by the Medical Research Ethics Committee (MREC) of the

UMC Utrecht (MREC document number: NL57931.041.16). The trial was registered in the Dutch trial register with number NL6581.

Participants

Patients were eligible to participate if there was a presence of moderate MUPS-related symptoms, aged ≥18 years with five or more GP consultations per year, based on PRESUME screening method [29]. The PRESUME screening method excluded patients with an established psychiatric and/or medical diagnosis who were part of a chronic disease management program for chronic obstructive pulmonary disease, hypertension, or diabetes mellitus. Patients were also excluded when identified with chronic MUPS, based on an established chronic MUPS diagnosis (e.g. fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome), anxiety disorders, depressive disorders and schizophrenia. All participants gave written informed consent.

Measurements

Dependent variable; movement behavior

Movement behavior was objectively measured with the Activ8, a 3-axial accelerometer (30 mm×32 mm×10 mm and 20 g). The Activ8 was worn on the thigh and can validly detect sedentary time (lying down and sitting) standing, walking, cycling, and running and yields MET values [30,31]. Participants received the Activ8 during a face-to-face visit and were instructed to wear the accelerometer in the front pocket of their trousers throughout the day during time awake and to keep a diary. The Activ8 was worn for one consecutive week, after which participants sent the devices back by mail. We offered no financial incentives to complete questionnaires or carry the accelerometer.

Time spent on activities was reported in hours per day. The frequency and length of bouts were calculated to gain insight into the distribution of PA and SB over the day. Data were converted into mean time spent sedentary (≤1.5 METs), light PA (LPA;>1.5–3.0 METs), moderate PA (MPA; 3.0 -6.0 METs), and vigorous PA (VPA; ≥ 6.0 METs). We measured mean time spent in bouts of ≥ 10 minutes of MVPA, mean time spent in a sedentary bout (uninterrupted periods of ≤1.5 MET) in ≥5 minutes per day, ≥30 minutes per day, and ≥60 minutes per day. The weighted median sedentary bout length was calculated because it gave an insight of centrality given the distribution of bout length [32]. Sedentary bouts were ordered from shortest to longest. The weighted median was represented by the length of the bout containing the 50% total sedentary time-point [32].

Finally, we measured the maximum sedentary bout length and fragmentation index. The fragmentation index is the ratio of the number of sedentary bouts ≥5 minutes divided by total sedentary time. A higher fragmentation index indicates more interrupted sedentary bouts [32]. Participants filled out diaries with a start and stop time. Non-wear time was removed from the data files by comparing start and stop time from the diaries with the device's internal clock. Valid data were considered to hold at least 4 days of at least 10 hours of movement behavior per day [33].

Demographic and clinical variables

Demographic and clinical variables were obtained through questionnaires. Demographic variables consisted of age, gender, duration of complaints, work situation, education level and marital status. Clinical variables:

- Quality of life, as assessed with the 36-Item Short Form Health Survey (RAND-36) health survey [34]. The RAND-36 consists of eight subscales, which were merged into two summary component scales: "Physical Component Scale" (PCS) and Mental Component Scale" (MCS). The norm-based score for the PCS and MCS was 50, where a score below 50 meant a less favourable physical and mental health state [35].

- Overall current health was assessed with the EuroQol visual analogue scale (EQ VAS). Scores ranged from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine") [36].

- Symptom severity on pain and fatigue was assessed using a numeric rating scale ranging from 0 (no pain/no fatigue) to 10 (worst possible pain/fatigue) [37].

- Severity of psychosocial symptoms was assessed with the Four-Dimensional Symptom Questionnaire (4DSQ) [38]. The questionnaire consists of four subscales, namely distress with a score range of 0-32, depression with a score range of 0-12, anxiety with a score range of 0-24 and the somatisation scale with a score range of 0-32. A higher score defines an increased probability of a disorder.

- Illness perceptions were assessed with the Brief Illness Perception Questionnaire [39,40]. The questionnaire consists of eight items with a score range of 0-10. Higher scores on personal control beliefs, treatment control beliefs, and coherence beliefs indicate an improvement in perception, whereas on consequences beliefs, timeline beliefs, identity beliefs, concern beliefs, and emotional response beliefs, a lower score indicates an improvement in perception.

- Self-management skills were assessed with the Health Education Impact Questionnaire (HeiQ). The questionnaire consists of eight subscales (1) Health Directed Activity, (2) Positive and Active Engagement in Life, (3) Emotional Distress, (4) Self-monitoring and Insight, (5) Constructive Attitudes and Approaches, (6) Skill and Technique Acquisition, (7) Social Integration and Support and (8) Health Service Navigation and were scored on a 4-point Likert scale ("totally disagree" to "totally agree")[41]. A higher score indicates a higher level of self-management [42].

Data analysis

Data were analyzed using SPSS version 25.0. Principal component analysis (PCA) was used, resulting in components accounting for the desired variance in 60% of the data [43]. Movement behavior variables were standardized using z-scores and contributed to one or more components. The compressed components were used to identify movement behavior patterns using the non-hierarchical k-means clustering algorithm [43]. Using repeated iteration, the k-means clustering procedure groups items together based on scores across multiple dependent variables [43]. The number of patterns were determined based on the stability of the iteration output, the silhouette coefficient, the interpretability of the patterns and the number of cases in each cluster [44]. Differences between the patterns were evaluated using ANOVA, the Kruskal-Wallis test (non-normally distributed variables), or the χ^2 test (categorical and nominal data). Bonferonni correction for post hoc analyses was performed for multiple comparisons. Statistical significance was set at $p < 0.05$.

RESULTS

The enrolment of 160 eligible patients from fifteen participating healthcare centers in the Netherlands lasted from March 2017 until April 2018. Eleven patients had invalid data on the accelerometer due to missing data. Missing data was completely at random and therefore not expected to affect the results. For the remaining 149 patients data were processed and evaluated. Participants' mean age was 48 years. A majority of the participants were female (73.8%). Almost 50 percent of the participants had experienced complaints associated with MUPS for five years or longer (Table 1). The total mean wear time of the accelerometer was 14.3 hours per day. The total mean sedentary time per day was 8.9 hours, while 2.9 hours were spent in LPA and 2.4 hours in MVPA. When counting as bouts of ≥10 minutes, on average 0.5 hours a day were spent in MVPA. The mean weighted median sedentary bout length was 14.2 minutes (Table 2).

Table 1: Participant characteristics per movement behavior pattern. N (%), Mean ± SD

Characteristics	Total group 149 (100)	Sedentary Movers 64 (43)	Active Movers 45 (30)	Sedentary Exercisers 40 (27)	P value Between Groups
Demographic characteristics					
Age, Year	48.3 ± 13.9	48.1 ± 14.8	47.3 ± 11.6	49.6 ± 14.9	0.74
Sex, Female	110 (73.8)	50 (78.1)	30 (66.7)	30 (75.0)	0.41
Duration of complaints					0.22
0-6 mo	10 (6.6)	3 (4.9)	2 (4.4)	5 (12.5)	
6 mo - 1 year	11 (7.4)	4 (6.3)	3 (6.7)	4 (10.0)	
1 year - 2.5 year	27 (18.1)	12 (18.8)	9 (20.0)	6 (15.0)	
2.5 year - 5 year	28 (18.9)	7 (10.9)	13 (28.9)	8 (20.0)	
≥5 year	73 (49.0)	38 (59.4)	18 (40.0)	17 (42.5)	
Work situation					0.44
student	2 (1.3)	0 (0)	0 (0)	2 (5.0)	
employed	97 (65.1)	37 (57.8)	32 (71.1)	28 (70.0)	
unemployed	24 (16.1)	16 (25.0)	6 (13.3)	2 (5.0)	
retired	21 (14.0)	9 (14.1)	4 (8.9)	8 (20.0)	
volunteer	5 (3.4)	2 (3.1)	3 (6.7)	0 (0)	
Highest completed education					0.76
Basic	37 (24.8)	14 (21.9)	11 (24.4)	12 (30.0)	
Intermediate	60 (40.3)	33 (51.6)	17 (37.8)	10 (25.0)	
High	52 (34.9)	17 (26.6)	17 (37.8)	18 (45.0)	
Marital status, married / cohabiting	97 (65.1)	41 (64.1)	33 (73.3)	23 (57.5)	0.37
Clinical characteristics					
Quality of Life *RAND-36 (0-100)*					
Physical scale (PCS)	42.9 ± 8.6	39.9 ± 8.4	44.4 ± 8.0	46.4 ± 7.8	0.00 [a,c]
Mental scale (MCS)	43.9 ± 12.4	42.4 ± 11.7	42.2 ± 14.2	48.5 ± 10.3	0.02 [b,c]
EQ *VAS (0-100)*					
Overall current health	64.5 ± 18.1	60.1 ± 17.3	64.5 ± 18.0	71.7 ± 17.4	0.01 [c]
Severity of symptoms *NRS (0-10)*					
Pain	4.9 ± 2.5	5.4 ± 2.4	5.2 ± 2.4	4.0 ± 2.5	0.01 [c]
Fatigue	5.9 ± 2.6	6.4 ± 2.4	6.5 ± 2.2	4.6 ± 2.9	0.00 [b,c]
Severity of psychosocial symptoms *4DSQ*					
Distress *(0-32)*	11.9 ± 8.1	13.9 ± 8.6	12.1 ± 7.2	8.8 ± 7.2	0.01 [c]
Depression *(0-12)*	1.6 ± 2.8	2.1 ± 3.2	1.8 ± 2.9	0.8 ± 1.7	0.07
Somatisation *(0-32)*	12.6 ± 6.8	13.7 ± 7.2	12.1 ± 6.0	11.3 ± 6.7	0.19
Anxiety *(0-24)*	2.7 ± 3.9	3.3 ± 4.6	2.9 ± 3.8	1.5 ± 2.7	0.07

Characteristics	Total group 149 (100)	Sedentary Movers 64 (43)	Active Movers 45 (30)	Sedentary Exercisers 40 (27)	P value Between Groups
Illness perceptions *IPQ-k (0-10)*					
Consequences	5.5 ± 2.6	6.5 ± 2.4	5.1 ± 2.5	4.4 ± 2.7	0.00 [a,c]
Timeline	7.5 ± 2.8	7.9 ± 2.4	7.4 ± 2.5	6.8 ± 3.5	0.18
Personal control	4.4 ± 2.3	4.5 ± 2.3	4.4 ± 2.3	4.3 ± 2.4	0.95
Treatment control	5.5 ± 2.4	5.7 ± 2.3	5.5 ± 2.4	5.1 ± 2.7	0.47
Identity	6.2 ± 2.1	6.7 ± 1.9	6.3 ± 1.9	5.4 ± 2.2	0.01 [c]
Concern	5.4 ± 2.7	5.9 ± 2.6	5.8 ± 2.5	4.2 ± 2.6	0.00 [b,c]
Coherence	5.7 ± 2.6	5.9 ± 2.5	5.8 ± 2.7	5.1 ± 1.9	0.31
Emotional response	5.7 ± 2.9	6.5 ± 2.7	5.9 ± 2.7	4.4 ± 3.0	0.00 [b,c]
Self-management skills *HEI-Q (1-4)*					
Health Directed activity	3.1 ± 0.7	2.9 ± 0.7	3.1 ± 0.6	3.5 ± 0.5	0.00 [b,c]
Positive and active engagement in life	3.0 ± 0.5	2.9 ± 0.6	3.0 ± 0.5	3.2 ± 0.5	0.02 [c]
Self-monitoring and insight	2.9 ± 0.4	2.8 ± 0.4	2.9 ± 0.3	2.9 ± 0.5	0.50
Constructive attitude and approaches	3.1 ± 0.5	2.9 ± 0.6	3.2 ± 0.5	3.3 ± 0.5	0.00 [a,c]
Skill and technique acquisition	2.7 ± 0.5	2.6 ± 0.5	2.7 ± 0.6	2.8 ± 0.5	0.07
Social integration and support	2.8 ± 0.6	2.7 ± 0.7	2.9 ± 0.6	2.9 ± 0.5	0.10
Emotional distress	2.9 ± 0.6	2.8 ± 0.6	2.9 ± 0.7	3.3 ± 0.5	0.00 [c]
Health Service Navigation	2.9 ± 0.5	2.9 ± 0.5	2.9 ± 0.5	3.0 ± 0.5	0.97

(a) Statistically significant differences between movement pattern 1 and 2

(b) Statistically significant differences between movement pattern 2 and 3

(c) Statistically significant differences between movement pattern 1 and 3

The PCA analysis resulted in three components identified with a total explained variance of 80.7%. The first component explained 49.5% of the total variance, while the second and third explained 17.6% and 13.6%, respectively. We identified three movement behavior patterns using the k-means clustering algorithm. The iteration history showed no change was presented in cluster centers after seven iterations. The silhouette measure of cohesion and separation was 1, meaning the clustering algorithm could partition data in well-separated clusters. Pattern 1 is renamed to 'Sedentary Movers' and included 43% (n=64) of the participants. The second pattern is renamed to 'Active Movers' and included 30% (n=45). The last pattern is renamed to 'Sedentary Exercisers' and included 27% (n=40) of the participants.

'Sedentary Movers' were found to spend on average 9.9 h/d sedentary, corresponding with 71 percent of the day based on total wear time. Participants that fit in this pattern significantly spent the highest number of hours sedentary compared to the other patterns, with a weighted median sedentary bout length of 19.5 minutes. Furthermore, they were less physical active compared to the other patterns for LPA and MVPA (resp. 17% and 13% daily).

'Active Movers' were less sedentary, with a mean of 7 h/d, corresponding to 49 percent daily based on total wear time. The weighted median sedentary bout length for this pattern was 6.7 minutes daily. They spent, compared to the other patterns, more hours in LPA and MVPA daily, respectively 30 and 20 percent. Specifically, PA of 'Active Movers' was mainly standing (4.2 h/d) and walking (2.7 h/d) and less so while cycling (0.3 h/d) and running (0.01 h/d).

'Sedentary Exercisers' were more sedentary compared to 'Active Movers', but less when compared to 'Sedentary Movers', with 9.5 hours a day, corresponding 64 percent of total wear time. The weighted median sedentary bout length was found to be 14.3 minutes daily. 'Sedentary Exercisers' spent 15% daily in LPA, and were PA on MVPA (20% daily), particularly when cycling (1.2 h/d) and running (0.04 h/d). Differences of movement behavior between the three patterns are shown in Table 2.

No significant differences were found in demographics between the three patterns (Table 1). On clinical variables however significant differences between patterns were found, especially between the patterns 'Sedentary Movers' and 'Sedentary Exercisers' concerning their quality of life, overall current health, pain, fatigue and distress. There was also a significant difference between the patterns on illness perceptions called 'consequences', 'identity', 'concern' and 'emotional response' and on the self-management skills, more specifically 'health directed activity', 'positive and active engagement', 'constructive attitude and approaches' and 'emotional distress'.

Table 2: Movement behavior outcomes per pattern. N (%), Mean ± SD

Movement behavior outcome	Total group 149 (100)	Sedentary Movers 64 (43)	Active Movers 45 (30)	Sedentary Exercisers 40 (27)	P value Between Groups
Sedentary (h/d)	8.9 ± 1.9	9.9 ± 1.4	7.0 ± 1.5	9.5 ± 1.4	0.00 [a,b]
Sedentary Bouts ≥ 5 min (h/d)	5.7 ± 1.7	6.7 ± 1.3	3.9 ± 1.2	5.9 ± 1.2	0.00 [a,b,c]
Sedentary Bouts ≥ 30 min (h/d)	3.1 ± 1.5	3.9 ± 1.3	1.6 ± 0.8	3.2 ± 1.3	0.00 [a,b,c]
Sedentary Bouts ≥ 60 min (h/d)	1.3 ± 0.9	1.7 ± 0.9	0.5 ± 0.3	1.4 ± 0.9	0.00 [a,b]
Weighted Median Sedentary Bout Length (min)	14.2 ± 9.9	19.5 ± 9.4	6.7 ± 6.0	14.3 ± 9.2	0.00 [a,b,c]
Maximum Sedentary Bout (min)	115.2 ± 40.2	125.5 ± 39.6	92.1 ± 24.3	124.9 ± 45.4	0.00 [a,b]
Fragmentation Index	2.0 ± 0.3	1.9 ± 0.2	2.2 ± 0.3	1.9 ± 0.2	0.00 [a,b]
LPA (h/d)	2.9 ± 1.4	2.3 ± 0.9	4.2 ± 1.4	2.2 ± 0.9	0.00 [a,b]
MPA (h/d)	1.9 ± 0.9	1.5 ± 0.5	2.7 ± 0.8	1.9 ± 0.9	0.00 [a,b,c]
VPA (h/d)	0.5 ± 0.5	0.3 ± 0.3	0.2 ± 0.1	1.0 ± 0.6	0.00 [b,c]
MVPA (h/d)	2.4 ± 0.8	1.8 ± 0.4	2.9 ± 0.8	2.9 ± 0.6	0.00 [a,c]
MVPA bouts ≥ 10 min (h/d)	0.5 ± 0.5	0.2 ± 0.2	0.4 ± 0.3	1.0 ± 0.5	0.00 [a,b,c]
Standing (h/d)	2.8 ± 1.4	2.3 ± 0.9	4.2 ± 1.4	2.2 ± 0.9	0.00 [a,b]
Walking (h/d)	1.9 ± 0.9	1.4 ± 0.6	2.7 ± 0.8	1.7 ± 1.0	0.00 [a,b]
Cycling (h/d)	0.6 ± 0.6	0.4 ± 0.5	0.3 ± 0.2	1.2 ± 0.8	0.00 [b,c]
Running (h/d)	0.02 ± 0.05	0.01 ± 0.05	0.01 ± 0.02	0.04 ± 0.08	0.01 [b,c]
Wear time (h/d)	14.3 ± 1.2	14.1 ± 1.1	14.2 ± 1.2	14.7 ± 1.3	0.04 [c]

(a) Statistically significant differences between movement pattern 1 and 2

(b) Statistically significant differences between movement pattern 2 and 3

(c) Statistically significant differences between movement pattern 1 and 3

'Sedentary Movers' were characterized by a significantly lower score on physical functioning and overall current health. Furthermore, they exhibit a significantly higher score on the severity of (psychosocial) symptoms pain, fatigue and distress. The results of the illness perceptions indicted a more negative perception toward complaints compared to the other patterns. Finally, 'Sedentary Movers' scored the lowest on the level of self-management skills when comparing the three patterns. In summary, 'Sedentary Movers' experienced the most limitations in physical functioning and experienced the highest amount of pain and fatigue compared to the other two patterns.

'Active Movers' were characterized by significantly lower scores on mental functioning and a significantly high score on the severity of fatigue symptoms. The other clinical variables did not differ significantly between the other two patterns.

'Sedentary Exercisers' experienced the least physical and mental limitations compared to the other patterns. In addition, they scored the significantly lowest score on the severity of (psychosocial) symptoms pain, fatigue and distress. The results of the illness perceptions indicated the most positive perception towards complaints compared to the other patterns and 'Sedentary Exercisers' scored the highest on the level of self-management skills.

DISCUSSION

This is the first study that assessed movement behavior by an accelerometer in a population with moderate MUPS. Distinguishing groups according to movement behavior patterns provides insight into the size of the respective groups and can aid more targeted interventions to offer patients additional support. Three different patterns of movement behavior were found. 'Sedentary Movers' spent relatively many hours of the day sedentary and mainly were found to be PA at the level of LPA. 'Active Movers' spent fewer hours a day sedentary and mainly were PA at the levels of both LPA and MPA. Finally, a third pattern, that of 'Sedentary Exercisers', were found spending many hours a day sedentary, and mainly PA at VPA level relative to the other patterns.

In certain other respects these three patterns were also distinguishable on clinical variables. 'Sedentary Movers' relative to the other two patterns, showed significantly low scores on physical functioning and overall current health, and the highest scores on pain, fatigue and distress. Their average score on distress suggested a presence of tension related to stress [45]. Their high score on illness perception indicated negative perceptions of complaints [39]. It is likely that due to these experienced (psycho)somatic

complaints, 'Sedentary Movers' were limited in MVPA. For 'Active Movers', the majority of clinical variables did not significantly differ, when comparing this pattern to the other two patterns. And finally, for 'Sedentary Exercisers', clinical variables showed the relatively highest scores on mental functioning and on overall current health, while also showing the lowest scores on pain, fatigue and distress. It is therefore plausible that participants in this pattern experienced fewer (psycho)somatic complaints and were consequently able to perform vigorous activities.

Based on the cognitive-behavioral models of the development of chronic pain, we hypothesized a class of patients would be found that avoid PA [21,22,46]. Although this study provides a clear and better understanding of movement behavior patterns in this population, we did not find evidence supporting this hypothesis. Moreover, regardless of the above movement behavior patterns, reported movement behavior was found to be sufficient, based on WHO guidelines on healthy movement behavior. In this WHO guideline, every minute of free-living physical activity counts [3]. Literature shows potential health benefits are realized regardless of the bout duration [47]. Other studies use the previous WHO guideline, which in its definition of healthy movement behavior only includes bouts of ten minutes of continuous MVPA or more [48,49]. Using this previous guideline, only 46% of our participants meet this standard. These two definitions used in guidelines hence can give rise to different results, and are difficult to compare [50]. Yet, even when adhering to the previous WHO guideline, as the LPA across participants remains high (with a total group mean of 2.9 h/d), no evidence could be found supporting the hypothesis that there is a class who is avoiding PA. Finally, SB among the patterns resembles the average in the general Dutch population (with 8.9 h/d on average in this study compared to 9.1 h/d for the general population) [51].

Given that there is no class of patients avoiding PA, the question arises whether the sole focus on achieving sufficient minutes of PA is a valuable direction for the treatment of patients with moderate MUPS. Meeting personal needs and preferences requires more than increasing MVPA minutes. Literature support this, arguing the relevant criterion is time spent in MVPA relative to other movement behavior that is associated with better health outcomes, rather than the absolute amount of time spent in MVPA [26,52]. To better tailor interventions on movement behavior, future research should take this into account, and additionally include the value patients attach to sedentary time and PA, as this varies from person to person [53], as do motivation, capacity, opportunities [54] and perseverance [55]. For clinical practice, movement behavior should be integrated as part of a program which involves the total lifestyle of a person [56,57]. In this sense, findings of

this study showing multiple patterns can be discerned can inform more targeted choices in treatment based on personal needs and preferences.

When interpreting the above findings, it is important to take into account two limitations in this study. Firstly, this study used cross-sectional data, and cannot make causal claims. Longitudinal research is needed to find out if there is a relationship to be found between movement behavior (patterns) and experienced complaints over time. Secondly, only waking hours were monitored, and hence data on sleep patterns is lacking. Follow-up research should include the (quality of) sleep, as quality of sleep, sedentary and movement behavior are complimentary [26].

A strength of this study is that movement behavior patterns were objectively reported, based on daily behavior of a person in any combination of SB and PA. Rather than considering movement behavior in isolation, we used overall time-use in the persons' waking hours [26]. Using outcome variables as described by Byrom et al. enabled analyzing movement behavior objectively [32]. Furthermore, the use of an accelerometer (Activ8) allowed detailed analysis and identification of movement behavior patterns. The Activ8, however does not give output based on heart rate, which means MVPA could be overestimated. The Activ8 was carried loose in the trouser pocket and this could potentially lead to acceleration [58]. Literature however found that the Activ8 accelerometer is a valid and reliable way to measure movement behavior based on body posture and time [58,59].

CONCLUSION

This study provides a clear and better understanding of movement behavior patterns in patients with moderate MUPS. Three different movement behavior patterns were identified; 'Sedentary Movers', 'Active Movers' and 'Sedentary Exercises'. We did not find evidence supporting the hypothesis that a class of patients avoiding PA exists. More research is needed into the role of movement behavior in moderate MUPS management and prognosis and the value someone attaches to sedentary time and physical activity. It seems that only stimulating additional minutes of physical activity is therefore not indicated.

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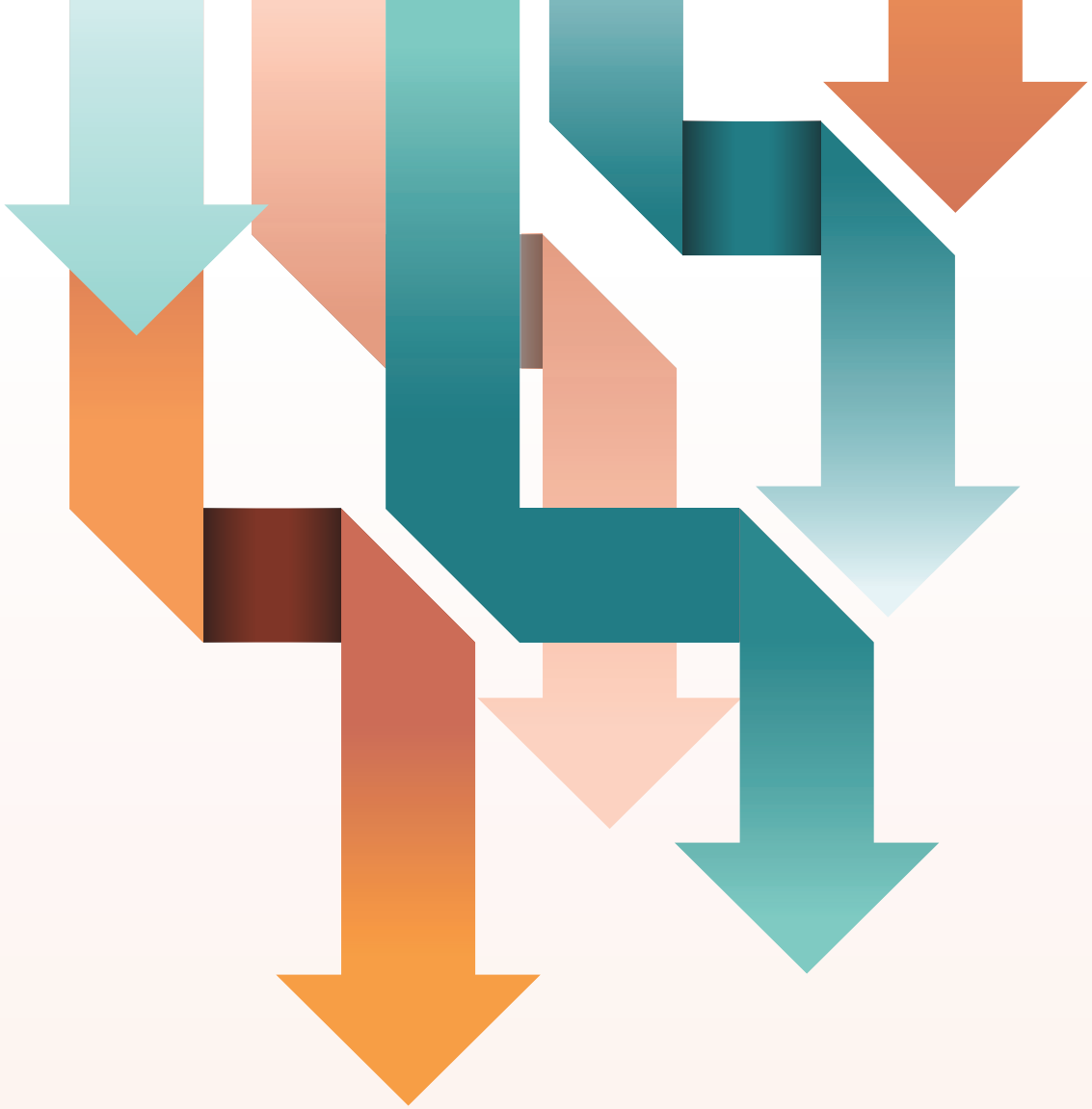

CHAPTER 10

General discussion

In order to maintain the accessibility and affordability of healthcare, policy in the Netherlands has sought to change the way in which healthcare is organized [1]. The answer has been found in what is termed 'appropriate care' [2]. Here, quality of life and the functioning of people are the main concepts, where functioning refers to both physical, psychological and social functioning [3]. Appropriate care has four guiding principles. Firstly, it is value-driven with the aim of achieving gains in health and functioning that are relevant to the patient at a reasonable price. Secondly, it is established together with the patient. Thirdly, it sets out to deliver the right care in the right place, for example by substitution or by relocating healthcare with the use of eHealth. Finally, appropriate care is concerned with health, not only illness, and focuses on one's own perceived health and functioning (positive health), and on preventing illness (prevention) [4]. Although appropriate care is a new concept in and of itself, this development towards providing health care in a different way is not new [5]. The aim to offer the right care in the right place, for instance, one of the principles now of appropriate care, came earlier, seeking to move from focus from cure and care to behavior and health [6].

Using these principles, we developed an intervention based on a proactive, integrated and blended care approach to prevent chronicity and stimulate self-management in patients with moderate Medically Unexplained Physical Symptoms (MUPS). Patients with moderate MUPS were identified in the electronic medical records of the general practitioner (GP) using the PRESUME screening method [7]. All identified patients were proactively approached with an invitation letter from their GP. Hence, in this intervention the focus of care shifted from patients consulting their GP with a health problem to GPs proactivity approaching patients at risk, whether or not these patients sought care. After identification, a proactive, integrated and blended intervention was offered. The intervention integrates face-to-face sessions with the physical therapist and mental health nurse with a web-based program of graded activity, information modules and exercises. The blended care approach provides patients with 24/7 access to an online eHealth platform, ensuring continuity of care and encouragement of self-management. The intervention further stimulates self-management by focusing on patients' perception of symptoms as well as modifiable prognostic risk factors for chronicity using therapeutic neuroscience education [8].

This dissertation aims to add knowledge to the evaluation of the effectiveness and experiences of a proactive, integrated and blended care intervention in a randomized clinical trial in primary care for patients with moderate MUPS. The second aim was to identify subgroups based on patterns in self-management skills and movement behavior.

SUMMARY OF MAIN FINDINGS

- For patients with chronic pain no evidence is found to show remote eHealth interventions without involvement of a healthcare professional to be more effective than usual care (face-to-face interventions). Strong evidence is however found suggesting remote eHealth interventions with minimal involvement of the healthcare professional are more effective than usual care in patients with chronic pain.

- A 12-week proactive, integrated and blended care intervention in primary care does improve subjective symptom impact of patients with moderate MUPS in the short-term. No further beneficial effects on the other clinical outcomes were found in the short and long-term. The cost-effectiveness of this treatment could not be demonstrated, neither from a healthcare perspective, nor from a societal perspective.

- Patients were generally positive about this intervention, specifically concerning the holistic and personal approach, the inter-professional collaboration and the integrated design of the intervention, despite technical and login problems of the web-based program used. Patients' perspectives suggest implementation of proactive, integrated blended care interventions are more successful when the intervention matches the patients' situation and motivation.

- From a healthcare professional perspective, the enrichment of the treatment and the ability to personalize the intervention were the main facilitators, aiding usability of the intervention. Another facilitator was the presence of two different types of healthcare professionals, which led to a more holistic approach. Healthcare professionals struggled with the fact that their role changed, moving towards being more of a coach. They had difficulties formulating long terms goals with their patients. Technical problems were experienced as a hindering factor. Findings show attention should be given to the new responsibilities of healthcare professionals, and their role in integrated and blended care. This new approach of delivering healthcare requires instruction and support for healthcare professionals.

- On basis of self-management skills (SMS), four subgroups of patients with moderate MUPS were identified (High-SMS, Medium-SMS, Low-SMS, and Active & Low Distress-SMS). The Active & Low Distress-SMS demonstrated a distinctly different pattern on SMS, with relatively low scores on pain and fatigue and the highest level of physical functioning. In other subgroups, patterns on self-management skills were found that negatively correlated with pain and fatigue and positively correlated with physical

functioning. Therefore, specific subgroups in a population of moderate MUPS can be distinguished with a different need for self-management support.

- Three different patterns of movement behavior were found among patients with moderate MUPS. 'Sedentary Movers' spent 9.9 h/d sedentary, and their physical activity was mainly light. 'Active Movers' spent 7 h/d sedentary, and their physical activity was mainly light to moderate. Finally, 'Sedentary Exercisers' spent 9.5 h/d sedentary, and their physical activity was mainly vigorous. No evidence was found supporting the hypothesis that a subgroup of patients with moderate MUPS avoids physical activity.

INTERPRETATIONS OF MAIN FINDINGS

Is blended care the answer to the challenge of maintaining affordability and accessibility of healthcare?

EHealth potentially enhances the affordability of healthcare by reducing healthcare costs [9]. Cost reduction can be achieved by providing patient education and counselling for disease prevention and early detection, replacing face-to-face visits with healthcare professionals, and remotely collecting patient data on medical parameters [9]. Furthermore, by using eHealth, there are more possibilities to reach people with healthcare needs, which can improve healthcare accessibility. Remote consultation or contact between healthcare professionals and patients could be useful when they are at a great distance of one another, or when scheduling an appointment is a challenge [10]. While there are thus advantages, stand-alone eHealth interventions may also see more attrition, as some patients may need more support than these interventions can provide [11]. Face-to-face meetings with patients furthermore can offer additional clinically relevant information and be used to better explain treatment [11].

In our review **(chapter 2)** we found no evidence showing remote stand-alone eHealth interventions to be more effective than usual care (face-to-face interventions). Strong evidence is however found showing remote eHealth interventions with minimal involvement of the healthcare professional (blended care) are more effective than usual care in patients with chronic pain. Combining the personal attention of a professional and the accessibility of an online tool is seen as a highly promising delivery approach, able to capitalize on both the benefits of face-to-face interventions and stand-alone eHealth [12]. These so called blended care interventions, referring to the integration of online and offline components in a treatment process, make it possible to personalize the amount

of online appointments relative to face-to-face [13]. Online and offline components, in other words, do not stand alone as treatment pathways but are interconnected [14]. Furthermore, blended care can personalize treatment, addressing patients' individual treatment goals, while also stimulating patients to take an active role in their disease management [13]. In this way, blended care can improve the quality of care with the use of self-management [15]. Implementing such eHealth initiatives in daily practice however remains a challenge [16,17,18].

Introducing blended care into the healthcare system requires careful coordination and communication among all end users [19]. It is therefore important to gather information on patients' personal preferences, motivation, capacities and opportunities at the start of a blended care process [20]. In addition, it is essential that healthcare professionals feel comfortable offering blended care. In **chapter 6** we showed that participating patients appreciated blended care, as it was experienced as more personalized because specific questions prepared at home could be addressed during the face-to-face treatment [21]. Healthcare professionals confirmed this finding in **chapter 7**, as they experienced patients were better prepared, saving them time and allowing them to move on to the core of treatment faster [22]. Repetition is a known behavioral change technique, as it helps individuals develop skills to actively self-regulate their behavior [23]. A checklist can help healthcare professionals, together with patients, to decide whether a patient is eligible for a blended care program and whether the program matches a patient's characteristics (e.g. abilities, needs, and preferences) and prior experiences with blended care [24].

In summary, blended care is a promising approach to take on the challenges of affordability and accessibility of healthcare. The intensity of face-to-face meetings and the amount of eHealth can be adjusted by the patient or healthcare professional [25] and should be personalized. Furthermore, attention should be given to implementation strategies.

Evaluation of effectiveness of a proactive, integrated and blended care intervention

We developed an intervention in primary care for patients with moderate MUPS, and put it to the test in a cluster randomized clinical trial with the involvement of a physical therapist and mental health nurse **(chapter 3).** Given the complex nature of this intervention, containing several interacting components [26], the Medical Research Council (MRC) framework for the development and evaluation of the proactive, integrated

blended care intervention was followed [26]. The resulting intervention (PARASOL) aims to prevent chronicity and stimulate self-management. In the short-term the PARASOL intervention was more effective compared to usual care in reducing the subjective impact of symptoms. For other clinical outcome measures however in both the short- and long-term no statistical differences were found between the intervention and patients receiving usual care **(chapter 4).**

Next to the effectiveness on clinical outcomes, the cost effectiveness of the intervention was studied. The total healthcare costs of the PARASOL intervention appear to be significantly higher, while total societal costs do not significantly differ compared to usual care **(chapter 5).** The results of the cost-effectiveness analysis from a social perspective, using QALY as an outcome measure, found the intervention to be less effective, yet also less costly from a societal perspective, compared to usual care. For other outcome measures (subjective symptom impact and the physical scale of the RAND-36) average societal costs seem lower, while the effectiveness of the PARASOL intervention is higher than usual care. Given these different findings, depending on the outcome measure used, overall we cannot conclude that the proactive, integrated blended care intervention is more (cost)effective than usual care in patients with moderate MUPS.

Limiting factors

Two limiting factors should be taken into account when interpreting the findings of the above studies. Firstly, the duration between baseline and follow-up could be of importance. Secondly, the sample size was smaller than calculated. Given these limiting factors, we derive three directions for future studies.

Effectiveness and cost effectiveness were studied based on data gathered 12 months after baseline. Literature suggests long term effects of interventions can show after such a period [27]. For a preventive program as ours, (cost)differences may however only appear after a longer period. Specifically for preventive interventions, literature finds a 12-month follow-up period may not be sufficient to demonstrate (cost)effectiveness [28]. Over time the severity of complaints may increase with usual care, for example, increasing its impact on daily life and utility. In the longer run, the additional costs incurred by proactively offering this preventive intervention (EUR 408) hence may be made up in lower overall societal costs.

Not achieving the pre-set sample size might be another important reason why we were not able to demonstrate the (cost)effectiveness of the intervention. The number of

eligible patients was calculated based on an intracluster correlation coefficient of 0.04, a power of 80% (alpha= .05) and a minimum of 20 patients per healthcare center [29]. At least 248 participating patients were needed with an expected drop-out rate of 20% . In total we included 160 patients with moderate MUPS. The lower number followed from a higher than expected dropout rate (32.5% in the intervention group and 25% in the control group) and less interested patients than expected. Despite the addition of a second and third recruitment strategy, the pre-set sample size was not reached. We believe that more significant differences between groups would have been found if the required sample size was achieved. However, the question remains whether these differences would have been clinically relevant.

Given these limiting factors, how should we move forward and find more opportunities for improvement to increase the effectiveness of this intervention? We set out to prevent chronicity, based on selection criteria (PRESUME) excluding patients who already had received a chronic diagnosis. Remarkably however, given the selection criteria applied, at baseline we found 86% of all participants (N=160) reported a duration of experienced symptoms for over a year. This is significantly higher than expected, as within the PRESUME method we selected patients with moderate MUPS who have experienced complaints for at least 3 months without a diagnosis of chronic MUPS [30], while patients with chronic MUPS typically experience symptoms for at least 6 months. Future trials, to demonstrate the clinical effect of preventive programs, should consider adding a selection criterion based on duration of complaints (for example complaints lasting six months or less) to better target a more homogeneous group of patients.

In both the evaluation of effectiveness and cost effectiveness, the adequate relief question was used to evaluate the subjective impact of symptoms and the RAND-36 was used to measure changes in quality of life [31,32]. Recent literature shows fluctuations in symptoms and in particular the symptom exacerbations that patients experience are an important element of symptom experience in patients with MUPS [33]. The outcome measures used may not be able to demonstrate such variability over time. A possible direction for future research is hence to supplement these primary clinical outcome measures with a Patient-Reported Outcome Measurement Information System (PROMIS) [34]. PROMIS provides advanced psychometric methods to construct, analyze and refine item banks, from which improved outcome measures can be developed [35]. Such measures can include health related quality of life (HRQOL), satisfaction with healthcare and pain interference [35][36], for instance. The use of such outcome measures may better suit the patient population, as it tailors questions to the individual.

Finally, the effectiveness of the treatment in the long term could be increased if more attention is directed towards the period after completion of the intervention. For instance, literature shows organizing booster interventions can be helpful [37], as can setting up peer support groups, in order to sustain the effects of self-management interventions [38]. Patients could furthermore be monitored by their healthcare professional at a low frequency, for example by organizing online or face-to-face (group) meetings, or providing information integrated in eHealth.

Motivation plays a key role

In self-management-based treatment, patients are expected to change their behavior. Because learning and then practicing self-management is challenging, the changes necessary for adaptive management are unlikely to occur absent patient motivation [39]. Literature also shows motivation as a key-factor of patients' adherence to eHealth [40]. The COM-B model of behavior is widely used to identify what needs to change in order for a behavior change intervention to be effective. It identifies three factors that need to be present for any behavior to occur: capability, opportunity and motivation [41]. Motivation can be increased through gaining a better understanding of the behavioral target, but requires awareness of personal beliefs, coping style and intention [20]. This especially holds true for intrinsic motivation rather than extrinsic motivation, which increases one's willingness to spend more time on assignments and results in better healthcare outcomes [42]. Intrinsic motivations can be addressed within an intervention, such as having sense of control and being able to identify with the program [43].

Proactively approach patients has implications for patients' motivation, as the chance of approaching patients who may be less motivated may increase. Patients in **chapter 6** mainly participated because of personal interest, out of curiosity, or because they saw no downsides to the treatment. Others started because of a referral from their GP. Patients mentioned there was no other treatment option available and they were glad someone was taking their complaints seriously [21]. Healthcare professionals **(chapter 7),** could quickly tell if a patient was motivated or not, which they seemed to find a predictor of succeeding with the program [22]. In the treatment protocol used, motivation was not an inclusion criterion **(chapter 3)** [8].

According to the principles of 'appropriate care', it is important that the healthcare provider determines together with the patient whether a preventive intervention meets wishes, needs and expectations [2]. The importance of informing oneself about the patient's

motivation and needs should be an integral part of a proactive, integrated blended care intervention. Future studies could make use of the Intrinsic Motivation Inventory (IMI), as a supportive questionnaire to obtain more insights into patients' motivations at the start of a program [44].

Empower healthcare professionals in their new role

As the organization of healthcare has changed, the role of healthcare professionals has also changed, moving from the role of a therapist to being more of a coach [45]. Given this tendency, the patient's needs are will increasingly be focused on prevention and less on reducing or resolving complaints. In **chapter 7,** we demonstrated healthcare professionals struggled seeking to formulate long term goals with their patients [22]. Working in preventive healthcare requires healthcare professionals with specific skills to better support patients. These new skills necessary can invoke feelings of uncertainty, time pressure and problems managing one's own expectations and those of patients [46]. General insights into how best to coach healthcare professionals to achieve behavioral change in patients (with the use of eHealth) are currently lacking. Establishing and maintaining an empathetic relationship are probably the most crucial factors for successful coaching with the use of eHealth [47]. A combination of knowledge and skills are necessary. Possible tools can be offering training through role-playing, homework assignments of gradually increasing difficulty, observational learning and feedback on (e)coaching behavior [48].

Our studies give some further direction, showing attention must be paid to the collaboration between healthcare professionals and patients. Expectations of patients described in **chapter 6** regarding the role of healthcare professionals differed. Some patients understood that healthcare professionals acted as coaches rather than as therapists. Others felt that they had to explain their complaints twice and expected that the roles of physical therapists would include more than just engaging in conversations and providing exercises [21]. It seems important to explain the new role of healthcare professionals to patients, in order to better align expectations.

One size does <u>not</u> fit all!

The group with moderate MUPS was heterogeneous, in terms of age [18-91 years], duration of complaints, number of comorbidities and educational level. Given this heterogeneity, by conducting in-depth analyses of collected data on self-management skills and movement behavior, we sought to investigate whether it was possible to distinguish subgroups with similar characteristics **(chapter 8 and 9).** More insight into

distinctive groups can give direction to stratification and personalization, shedding more light on what is the right treatment for the right patient. We chose to analyse subgroups in self-management skills as stimulating self-management was the aim of the intervention. Based on the results of **chapter 8**, it seems important to align self-management support with patient self-management skills when treating patients with moderate MUPS. Knowing that various subgroups of moderate MUPS can be distinguished, with higher or lower self-management skills, can benefit tailored self-management training in the future [49].

Next to self-management skills, also subgroups based on different movement behavior patterns were found. Insights into a movement behavior make it possible to enable healthier choices in treatment, based on personal needs and preferences. Based on the cognitive-behavioral models of the development of chronic pain, we hypothesized a subgroup of patients would be found that avoided physical activity [50,51,52]. Guidelines suggest to increase activity levels for patients with MUPS. In **chapter 9** we however show there is no such subgroup that avoids physical activity all together, and the question arises whether the sole focus on achieving sufficient minutes of physical activity is a valuable direction for the treatment of patients with moderate MUPS.

To better tailor interventions in future, the value patients attach to self-management, sedentary time and physical activity should be taken into account, as this varies from person to person [53]. Furthermore, more longitudinal research is needed to study the relationship, if any, between self-management, movement behavior (patterns) and experienced complaints over time.

METHODOLOGICAL CONSIDERATIONS

Study population

The heterogeneity of the MUPS population and the complex definition of moderate MUPS was a challenge in this dissertation. Healthcare professionals give ambiguous definitions of moderate MUPS [54] and seem to experience difficulties recognizing patients that can be identified as struggling with moderate MUPS. Previous research also recognized this problem for the MUPS population as a whole (mild, moderate and chronic) [49]. This emphasizes the importance of increasing recognition for this population in daily practice.

The term MUPS furthermore raises questions and discussion. It has been in use since the multidisciplinary guideline *MUS and Somatoform Disorders* from 2011 [55]. MUPS were defined as physical complaints that last longer than a few weeks and in which no somatic disease can be found that adequately explains the complaints after adequate medical

examination. The multidisciplinary guideline regarded MUPS as a description of a group of patients who would not benefit from further somatic interventions. In 2021, consensus was obtained in the Netherlands that Persisting Physical Symptoms (PPS) was a more appropriate term [56,57]. The concept of 'unexplained' has since been abandoned, as it gives rise to conceptual and practical problems [58]. The term PPS is in line with the international scientific literature and the DSM-5, in which also 'medically unexplained symptoms' and 'somatoform disorders' have been replaced by 'persistent physical symptoms' and 'somatic symptom disorders'. Whether or not the underlying somatic disease has been diagnosed and hence complaints can be explained is no longer at the core of the definition, but rather the consequences of the complaints and the underlying mechanisms with inhibit recovery [59].

The discussion about the term (MUPS or PPS) for this patient population is still ongoing. To avoid confusion, this dissertation still refers to MUPS, still common at the time of review and publication of included chapters. I however in the future will refer to the condition of this patient population by PPS, as I find this more appropriate. There is simply too much discussion about the 'unexplainable' aspects, while complaints *can* be explained in a bio-psycho-social sense. This discussion should however not end, in order to meet the needs of professionals and patients as best as possible.

Preventive care

Although prevention has increasingly gained the attention of healthcare providers, the effectiveness in clinical outcomes and in terms of costs (health care and societal) are difficult to demonstrate. Firstly, preventive care often involves investments at an early stage, with higher costs than usual care. This may seem to increase health care expenditures in the short term, while effects, if any, will only show in the long term. Secondly, the selection of patients for preventive care in general, and specifically selecting patients with a higher risk of developing chronicity, can be challenging. Patient themselves in some cases see no added value in preventive care when at the time of treatment no symptoms impede functioning yet.

Implementation science

The Medical Research Council (MRC) guidance characterizes the process of development, evaluation and implementation of a complex intervention [26]. Scientifically, this dissertation follows this process and includes a variety of study designs. It uses quantitative and qualitative study designs, applying a systematic review, a randomized

control trial, cost-effect analysis, interviews and cluster analyses. This enabled us to gain scientific insight into specially the development and evaluation process of the proactive, integrated and blended care intervention. Implementation, a third feature of the MRC guidance was based more on practical feasibility and less on the scientific evidence.

In addition to the systematic inventory and ordering of experiences and knowledge, there is a great need for insights into effective implementation [60]. More research on implementation is needed, requiring knowledge and experiences of different implementation strategies. This knowledge can better identify barriers and facilitators, enabling interventions to be more tailored to their context and implemented for the uptake of knowledge [61]. Context is broad, ranging from regulation, financial incentives, development within health care professions, and characteristics of patient populations.

This dissertation offers such knowledge, by identifying barriers and facilitators from both patients' and health care professionals' perspectives and thereby can aid the implementation of future interventions.

RECOMMENDATIONS FOR CLINICAL PRACTICE

A stepped care strategy is recommended in guidelines for this patient population [55]. This includes that patient are treated in accordance with their symptom severity by the right professional, in the right place at the right time. In daily practice the patients consult their GP first. In some cases MUPS recover spontaneously. When a patient is identified as having moderate MUPS, the GP could refer to our proactive, integrated blended care intervention instead of a separate intervention at the physical therapist or mental health nurse. Nowadays, healthcare insurance companies require that patients follow a primary care intervention first before they can be referred to secondary care. The PARASOL intervention fits this requirement. When symptoms deteriorate or unsatisfying results are reached, patients could be referred to secondary care.

When applying this stepped care approach in patients with moderate MUPS in clinical practice, a few recommendations for introducing a complex intervention can be given, based on our results:

- Provide blended care to increase therapy options for both patients who want to spend less money on therapy and for patients who have difficulty getting to the clinic due to scheduling problems. Tailor the amount of eHealth to the specific needs of patients.

- Carefully coordinate and communicate to all end users. At the start of the intervention, inquire into patients' motivations, capacities and opportunities.
- Organize and facilitate booster sessions.
- Support and train the involved healthcare professionals in their new role offering preventive care with the integration of eHealth, where self-management is encouraged.
- Align self-management support with patient self-management skills.
- Integrate movement behavior as part of a program, and consider the total lifestyle of a patient, not only focusing on gradually increasing a patient's physical activity.
- Take the value patients attach to self-management into account, as the value they attach to sedentary time and physical activity, as this varies from person to person.

RECOMMENDATION FOR FUTURE RESEARCH

Based on our results, several suggestions for future research can be made, some of which are given above. Four suggestions warrant highlighting. Given the heterogeneity of interventions and outcome measures used, studies on eHealth interventions are currently difficult to compare and reproduce. Future research should use the TIDieR checklist, which aims to improve the completeness of reporting of interventions [62]. Secondly, one explanation for the lack of (cost) effectiveness of the PARASOL intervention may be the duration between baseline and the follow-up, as described above. Future research should include an even longer follow-up time to better understand how chronicity evolves and can be prevented. Thirdly, as suggested above, the use of PROMIS as outcome measure would be a valuable addition to research, given this heterogeneous patient population. Finally, longitudinal research is needed to study the relationship, if any, between self-management, movement behavior (patterns) and experienced complaints over time.

RECOMMENDATION FOR EDUCATION

Three recommendations for the educational practice can be derived from this dissertation. Firstly, coaching skills and skills to support self-management in patients are important, and should be included in health care curricula. Without (formal) training, not every professional will be equipped with the right skills with are more and more

required. Secondly, attention should be given to behavioral change techniques. Thirdly, providing more blended care in the future requires knowledge and skills on behalf of health care professionals. Good examples, instruction and experience are essential for the implementation of proactive, integrated blended care interventions.

OVERALL CONCLUSION

Given the ambitions to provide the right care, for the right patient, in the right place, at the right time, we find a combination of early identification of patients with moderate MUPS and a preventive intervention integrating eHealth (blended care) a move forward. What lies ahead is to tailor such interventions, rather than offer a one-size-fits-all treatment. Increasing insights into self-management skills and movement behavior during treatment can aid the tailoring of interventions, as can early identification of patients' needs, motivation, and the requested use of eHealth. As this way of treatment differs from usual care, healthcare professionals should be coached more on their changing role from treating patients to coaching patients.

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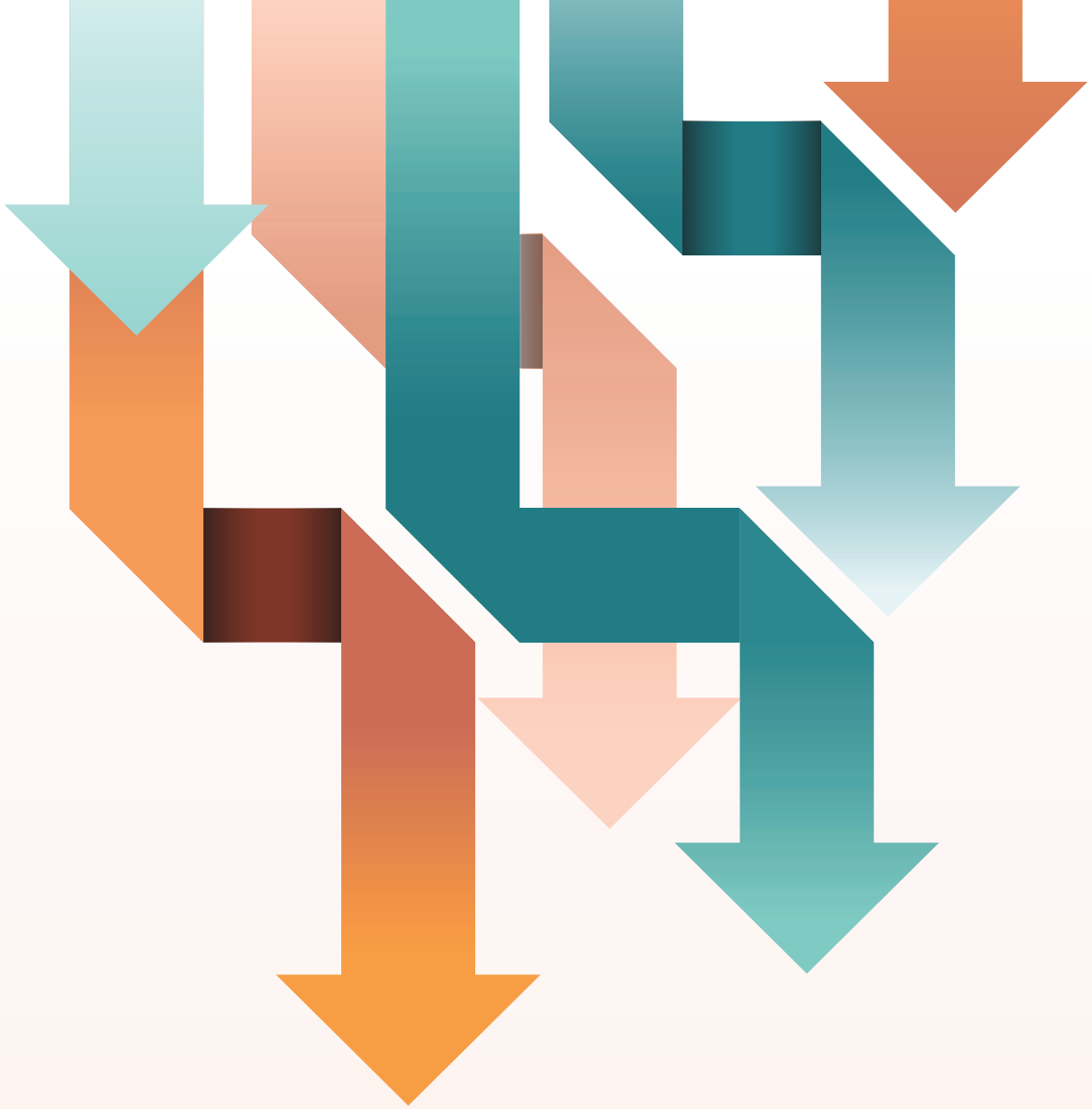

CHAPTER 11

Summary
Nederlandse samenvatting
PhD Portfolio
About the author
Authors contributions
Dankwoord

SUMMARY

Most people at times experience physical symptoms such as pain, fatigue or dizziness. Surveys show that approximately 90% of the Dutch general population experienced at least one physical symptom in the past two weeks. While in most cases symptoms disappear spontaneously, in certain cases symptoms persist for a few weeks or even months without having an identifiable underlying explanation. Such Medically Unexplained Physical Symptoms (MUPS) can have a high impact on quality of life and daily functioning, impairing social, physical and psychological functioning. Whether people visit their general practitioner with concerns about these symptoms is strongly related to the impact on daily life and ideas about these symptoms. Developing MUPS is more common when patients are concerned and develop negative catastrophizing beliefs. MUPS can be regarded on a continuum with a spectrum ranging from mild to moderate and then persisting or chronic MUPS. This dissertation focused on patients with moderate MUPS and preventing chronicity in this patient group. The moderate MUPS population has a high prevalence in primary care, yet little research has been done on preventing chronicity. Furthermore, there is not yet an appropriate treatment to reduce the burden for these patients, straining healthcare professionals and incurring high healthcare and societal costs.

Chapter 1 introduces the transition in the Dutch healthcare system: A movement from cure and care to behavior and health is required in order to meet current challenges, such as rising healthcare costs, an ageing society and technological developments offering wider opportunities. This healthcare transition requires organizational changes and the development of innovative, proactive and preventive healthcare. This especially holds for patients at risk of chronicity, such as the population of moderate MUPS. Early identification as first step in treatment is shown to be important, and the need for an innovative intervention based on proactive, integrated and preventive care is presented, using blended care. This chapter presents the main objective of this dissertation, namely adding knowledge on the evaluation of the effectiveness and experiences of a proactive, integrated and blended care intervention in a randomized clinical trial in primary care for patients with moderate MUPS. A second aim is to identify subgroups based on patterns in self-management skills and movement behavior.

Chapter 2 gives a systematic review, assessing the effectiveness of physical therapy eHealth interventions on pain in patients with musculoskeletal complaints. From 11,811 studies identified, 27 studies were included. eHealth is found to be a supportive tool for

reducing pain in some populations. For patients with lower back pain, there is limited evidence for the effectiveness of eHealth on pain intensity, regardless of the extent to which the healthcare professional was involved in the online intervention and regardless of which control group was used. In patients with chronic pain, there is no evidence that remote eHealth without involvement of healthcare professional is more effective than face-to-face interventions. There is strong evidence that remote eHealth with minimal involvement of the healthcare professional is more effective than a control intervention in patients with chronic pain. For patients after total knee surgery, there appears to be a moderate effect of an eHealth intervention with minimal involvement of the healthcare professional in the reduction of pain compared to no care. While for patients with osteoarthritis and knee pain there was no effect on the pain related outcome, regardless of the involvement of healthcare professionals.

Chapter 3 contains a protocol for the development of a proactive, integrated and blended care intervention in primary care compared to usual care for patients with moderate MUPS with the aim to prevent chronicity (PARASOL). The primary outcomes of this prospective, multicenter cluster randomized clinical trial were subjective symptom impact, as registered with the adequate relief question, and quality of life. Secondary outcomes were severity of physical and psychosocial symptoms, general health, movement behavior, illness perceptions, self-management skills and cost-effectiveness. All measurements were performed at baseline, 3 and 12 months after baseline. Retrospective cost questionnaires were also sent at 6 and 9 months after baseline. Cluster randomization was performed on healthcare level to avoid healthcare professionals within one healthcare center offering both the intervention and usual care. The twelve week intervention integrates face-to-face sessions with the physical therapist and the mental health nurse with access to a web-based program focusing on 1) graded activity, 2) exercises and 3) information modules. The intervention stimulates self-management by focusing on patients' perception of symptoms as well as modifiable prognostic risk factors for chronicity using therapeutic neuroscience education. The blended care approach provides patients 24/7 access to an online eHealth platform, ensuring continuity of care and encouragement of self-management. The aim was to include 248 participating patients with moderate MUPS (124 patients per arm).

Chapter 4 presents data on the short- and long-term effectiveness of a proactive, integrated blended care intervention compared to usual care on clinical outcomes. In total 160 participants were included, 80 participants allocated to the intervention group and 80 participants were allocated to the control group. The results showed more

patients with short-term adequate relief after treatment with the intervention (31.2%) compared to the usual care (13.7%). Unfortunately, this between group difference in favour of the intervention did not sustain in long-term. No additional beneficial effects of the intervention on quality of life and secondary outcomes were found, neither in short-term nor in long-term follow-up.

Chapter 5 demonstrates the results of the cost-effectiveness of the intervention compared to usual care from a societal and healthcare perspective. The total healthcare costs of the intervention appear to be significantly higher, with the total societal costs not being significantly different compared to usual care. When looking on relevant, but specific outcome measures (subjective symptom impact and physical health) for this population, there seems to be a positive trend of lower average costs and more effectiveness for the proactive, integrated blended care intervention compared to usual care. Overall, we could not demonstrate that the intervention was cost-effective as compared to usual care from both societal and healthcare perspective.

Chapter 6 includes a mixed-method study of the patients' perspectives on the usability of a proactive, integrated blended care intervention. Through semi structured interviews (n=13), qualitative data were gathered in order to gain an in-depth understanding. System Usability Scale (SUS) scores (low, medium, and high) enriched responses in the interviews, which allowed us to gain better insight into the relationship between identified themes from interviews and experienced usability. Of the total participants completed SUS questionnaire (N=55), 35% experienced low user satisfaction, 27% experienced medium user satisfaction and 38% experienced high user satisfaction. Participants were all generally positive about the received care. Various aspects of usability were highlighted and responses were categorized into four themes; 1) motivations and expectations prior to participating in the program, 2) the applicability of e-coaching, 3) the role of healthcare professionals, and 4) the integrated design of the blended approach. Patients appreciated the personal and holistic approach, recognizable information and the inter-professional collaboration. They experienced the face-to-face treatment as an incentive. Usability can be improved by tailoring the intervention to individual's experience and motivation, better accessibility and technical support and the possibility to ask (online) questions.

Chapter 7 describes the results of a qualitative study on the perspective of physical therapists and mental health nurses on the usability of the proactive, integrated blended care intervention. Semi-structured interviews were conducted and analyzed using thematic analysis. Ten healthcare professionals (six physical therapists and four

mental health nurses) were interviewed. Four themes on usability were identified; 1) Who fits in the program, 2) preparation, 3) experience with the program and 4) inter-professional collaboration. The main facilitator in this proactive, integrated blended care intervention was the enrichment of the treatment and the possibility to personalize the program. Repeating information made patients better prepared which saved time and allowed healthcare professionals to move on to the core of treatment faster. Another facilitator was the presence of two different types of healthcare professionals which led to a more holistic approach. Participating healthcare professionals did not have the feeling all patients were suited to participate which could be seen as an important barrier. Additionally, healthcare professionals struggled with the fact that their role changed into being more of a coach. They had difficulties seeking to formulate long terms goals with their patients. Furthermore, this preventative approach was new, which was hard to get used to. Findings however show attention should be given to the new responsibilities of healthcare professionals, and their role in preventive and blended care. Achieving sustainable change in patients requires instruction and support for healthcare professionals.

Chapter 8 shows the results on the identification of subgroups in self-management skills and compares these subgroups on the patient reported outcome measures of physical functioning, pain and fatigue. To identify subgroups based on self-management skills, a hierarchical cluster analysis was conducted. Self-management skills were measured with the Health education impact Questionnaire (HeiQ). Four subgroups were identified: High-Self-Management Skills (SMS) (n=29), Medium-SMS (n=55), Low-SMS (n=49) and Active & Low Distress-SMS (n=20). The latter showed a distinctly different pattern on cluster variables, while the other subgroups differed significantly on means of the cluster variables. On clinical variables, significant differences between subgroups were found on fatigue and physical functioning. Based on above findings, specific subgroups in a population of moderate MUPS can be distinguished with a different need for self-management support.

Chapter 9 presents data of the cluster analysis in movement behavior. Movement behavior was measured on seven constructive days using an accelerometer (Activ8). Movement behavior variables were calculated and compressed using Principal Component Analysis. Patterns were identified using a k-means clustering algorithm. This study identified three different patterns: 'Sedentary Movers' (n=64) spent 9.9 h/d sedentary and were mainly light physical active. 'Active Movers' (n=45) spent 7 h/d sedentary and were mainly light to moderate physical active. Sedentary Exercisers' (n=40) spent 9.5 h/d sedentary and

were mainly vigorous physical active. Based on the cognitive-behavioral models of the development of chronic pain, we hypothesized a subgroup of patients would be found that avoid physical activity. Although this study provides a clear and better understanding of movement behavior patterns in this population, we did not find evidence supporting this hypothesis. For clinical practice, movement behavior should be integrated as part of a program which involves the total lifestyle of a person instead of only focusing on gradually increasing someone's physical activity.

Chapter 10 discusses the implications of the main findings of this dissertation, as well as the methodological considerations and clinical implications. Recommendations for further research an education are made. This dissertation identifies a combination of early identification of patients with moderate MUPS and a preventive intervention integrating eHealth (blended care) as a move forward. What lies ahead is to tailor such interventions, rather than offer a one-size-fits-all treatment. Increasing insights into self-management skills and movement behavior during treatment can aid the tailoring of interventions, as can early identification of patients' needs, motivation, and the requested use of eHealth. As this way of treatment differs from usual care, healthcare professionals should be coached more on their changing role from treating patients to coaching patients.

NEDERLANDSE SAMENVATTING

De meeste mensen ervaren wel eens lichamelijke klachten zoals pijn, vermoeidheid of duizeligheid. Uit enquêtes blijkt dat ongeveer 90% van de Nederlandse algemene bevolking in de afgelopen twee weken ten minste één lichamelijk symptoom ervaart. Hoewel de symptomen in de meeste gevallen spontaan verdwijnen, houden de symptomen in sommige gevallen enkele weken of zelfs maanden aan zonder dat er een identificeerbare onderliggende verklaring voor is. Dergelijke somatisch onverklaarde lichamelijke klachten (SOLK) kunnen een grote impact hebben op de kwaliteit van leven en het dagelijks functioneren, waardoor het sociale, fysieke en psychologische functioneren verminderd. Of mensen met deze symptomen naar de huisarts gaan, hangt sterk samen met de impact op het dagelijks leven en de ideeën over deze symptomen. Het ontwikkelen van SOLK komt vaker voor wanneer patiënten bezorgd zijn en negatieve catastrofale overtuigingen ontwikkelen. SOLK kan worden beschouwd als een continuüm met een spectrum van lichte, tot matige en aanhoudende of chronische SOLK. Dit proefschrift richtte zich op patiënten met matige SOLK om chroniciteit van klachten te voorkomen. De matige SOLK-populatie heeft een hoge prevalentie in de eerste lijn, terwijl er weinig onderzoek is gedaan naar de preventie van chronische klachten. Bovendien is er nog geen geschikte behandeling om de belasting voor deze patiënten te verminderen, wat zorg professionals overbelast en hoge zorg- en maatschappelijke kosten met zich meebrengt.

Hoofdstuk 1 introduceert de transitie in het Nederlandse zorgstelsel. Een beweging van 'Ziekte en Zorg naar Gedrag en Gezondheid' is nodig om de huidige zorguitdagingen het hoofd te bieden, met stijgende zorgkosten, een vergrijzende samenleving en technologische ontwikkelingen. De zorgtransitie vraagt om organisatorische veranderingen en de ontwikkeling van innovatieve, proactieve en preventieve zorg. Vooral voor patiënten die risico lopen op chroniciteit, zoals de populatie van patiënten met matige SOLK klachten. De rol van vroeg signalering als eerste stap en de vraag naar innovatieve interventies gebaseerd op proactief, geïntegreerd en zorg wordt beschreven. Verder wordt de rol van 'blended care' toegelicht. Het hoofddoel van het proefschrift is om kennis toe te voegen over de evaluatie van effectiviteit en ervaringen van een proactieve, geïntegreerde en 'blended care' interventie in een gerandomiseerde klinische studie in de eerste lijn voor patiënten met matige SOLK. Het tweede doel was het identificeren van subgroepen op basis van patronen in zelfmanagementvaardigheden en beweeggedrag.

Hoofdstuk 2 betreft een systematische review, waarin de effectiviteit van fysiotherapeutische eHealth-interventies op pijn bij patiënten met musculoskeletale

klachten is beoordeeld. Van de 11.811 geïdentificeerde studies werden er 27 studies opgenomen. Deze systematische review toonde aan dat eHealth een ondersteunend instrument kan zijn voor het verminderen van pijn in sommige populaties. Voor patiënten met lage rugpijn is er beperkt bewijs voor de effectiviteit van eHealth op de pijnintensiteit, ongeacht de mate waarin de zorgverlener betrokken was bij de online interventie en ongeacht welke controlegroep werd gebruikt. Bij patiënten met chronische pijn is er geen bewijs dat eHealth zonder tussenkomst van een zorgprofessional effectiever is dan face-to-face interventies. Er is sterk bewijs dat eHealth met minimale betrokkenheid van de zorgprofessional effectiever is dan een controle-interventie bij patiënten met chronische pijn. Voor patiënten na een totale knieoperatie blijkt er een matig effect te zijn van een eHealth-interventie met minimale betrokkenheid van de zorgprofessional bij het verminderen van pijn ten opzichte van geen zorg. Terwijl er voor patiënten met artrose en kniepijn geen effect was op de pijn gerelateerde uitkomst, ongeacht de betrokkenheid van beroepsbeoefenaren in de gezondheidszorg. Deze systematische review geeft een breed inzicht in de rol van eHealth bij patiënten met chronische pijn aandoeningen, die verantwoordelijk zijn voor een groot deel van de patiënten met matige SOLK.

Hoofdstuk 3 bevat een protocol over de ontwikkeling van een proactieve, geïntegreerde en 'blended care' interventie in de eerstelijnszorg voor patiënten met matige SOLK met als doel chroniciteit te voorkomen (PARASOL). De primaire uitkomsten van deze prospectieve, multicenter cluster gerandomiseerde klinische studie waren subjectieve symptoomimpact en kwaliteit van leven. Secundaire uitkomstmaten waren ernst van lichamelijke en psychosociale symptomen, algemene gezondheid, beweeggedrag, ziekteperceptie, zelfmanagement vaardigheden en kosteneffectiviteit. Alle metingen werden uitgevoerd bij baseline, 3 en 12 maanden na baseline. Retrospectieve kostenvragenlijsten werden ook verzonden op 6 en 9 maanden na baseline. Er is clusterrandomisatie uitgevoerd op het niveau van de gezondheidscentra om te voorkomen dat zorgprofessionals binnen één gezondheidscentrum zowel de interventie als de gebruikelijke zorg aanbieden. De interventie van twaalf weken integreert face-to-face sessies met de fysiotherapeut en de praktijkondersteuner GGZ met toegang tot een online programma gericht op 1) graduele activiteit, 2) oefeningen en 3) informatiemodules. De interventie stimuleert zelfmanagement door zich te concentreren op de perceptie van ervaren symptomen van patiënten en op aanpasbare prognostische risicofactoren voor chroniciteit met behulp van therapeutische neurowetenschappelijke voorlichting. De 'blended care'-benadering geeft patiënten 24/7 toegang tot een online eHealth-platform, waardoor continuïteit van zorg wordt gegarandeerd en zelfmanagement wordt gestimuleerd. Het doel was om 248 deelnemende patiënten met matige SOLK te includeren (124 patiënten per arm).

Hoofdstuk 4 presenteert gegevens over de effectiviteit op korte en lange termijn van een proactieve, geïntegreerde en 'blended care' interventie in vergelijking met gebruikelijke zorg op klinische uitkomsten. In totaal werden 160 deelnemers geïncludeerd, 80 deelnemers werden toegewezen aan de interventiegroep en 80 deelnemers werden toegewezen aan de controlegroep. Op korte termijn, aan het einde van de behandeling, had 31,2% van de deelnemers een positief resultaat op de primaire uitkomstmaat subjectieve symptoomimpact ten opzichte van 13,7% van de deelnemers in de controle groep. Het verschil tussen de groepen ten gunste van de interventie hield geen stand op langere termijn. Er werden geen bijkomende gunstige effecten van de interventie op de kwaliteit van leven en andere secundaire uitkomsten gevonden, noch in de follow-up op korte noch in de lange termijn.

Hoofdstuk 5 toont de resultaten van de kosteneffectiviteit van de interventie in vergelijking met de gebruikelijke zorg vanuit maatschappelijk en gezondheidszorgperspectief. Retrospectieve kostenvragenlijsten werden uitgevoerd bij baseline, 3, 6, 9 en 12 maanden na baseline. In deze studie konden we niet aantonen dat de interventie kosteneffectief was in vergelijking met de gebruikelijke zorg, zowel vanuit maatschappelijk als vanuit gezondheidszorgperspectief. De totale zorgkosten van de interventie blijken beduidend hoger te zijn, waarbij de totale maatschappelijke kosten niet significant afwijken van de gebruikelijke zorg. Wanneer we kijken naar relevante, maar specifieke uitkomstmaten (subjectieve symptoomimpact en fysieke gezondheid) voor deze populatie, lijkt er een positieve trend te zijn van lagere gemiddelde kosten en meer effectiviteit voor de proactieve, geïntegreerde en 'blended care' interventie in vergelijking met de gebruikelijke zorg.

Hoofdstuk 6 bevat een 'mixed-method' onderzoek naar de perspectieven van patiënten op de bruikbaarheid van een proactieve, geïndiceerde 'blended care' interventie. Door middel van semigestructureerde interviews (n=13) werden kwalitatieve gegevens verzameld om een diepgaand inzicht te verkrijgen. System Usability Scale (SUS) scores (laag, gemiddeld en hoog) zijn vergeleken met de antwoorden in de interviews, waardoor beter inzicht werd verkregen in de relatie tussen geïdentificeerde thema's uit interviews en de ervaren bruikbaarheid. Van het totale aantal deelnemers dat de SUS-vragenlijst heeft ingevuld (N=55), ervoer 35% een lage gebruikerstevredenheid, 27% een gemiddelde gebruikerstevredenheid en 38% een hoge gebruikerstevredenheid. De deelnemers waren over het algemeen allemaal positief over de ontvangen zorg. Verschillende aspecten van gebruiksvriendelijkheid werden belicht en de reacties werden onderverdeeld in vier thema's; 1) motivaties en verwachtingen voorafgaand aan deelname aan het programma, 2) de toepasbaarheid van eCoaching, 3) de rol van zorgprofessionals, en 4) de integrale opzet van de 'blended care' aanpak. Patiënten waardeerden de persoonlijke en holistische

aanpak, de herkenbare informatie en de interprofessionele samenwerking. Zij ervaarden de face-to-face behandeling als een stimulans. De bruikbaarheid kan worden verbeterd door de interventie af te stemmen op de individuele ervaring en motivatie, toegankelijkheid en technische ondersteuning en de mogelijkheid om (online) vragen te stellen.

Hoofdstuk 7 beschrijft de resultaten van een kwalitatief onderzoek naar het perspectief van fysiotherapeuten en praktijkondersteuners GGZ op de bruikbaarheid van een proactieve, geïntegreerde 'blended care' interventie. Er zijn semigestructureerde interviews gehouden en geanalyseerd met behulp van thematische analyse. Er zijn tien zorgprofessionals (zes fysiotherapeuten en vier praktijkondersteuners GGZ) geïnterviewd. Er werden vier thema's over bruikbaarheid geïdentificeerd; 1) Wie past er in het programma, 2) voorbereiding, 3) ervaring met het programma en 4) interprofessionele samenwerking. De belangrijkste facilitator was de verkregen diepgang in behandelingen en de mogelijkheid om het programma te personaliseren. Door informatie te herhalen, waren patiënten beter voorbereid, wat tijd bespaarde en zorgprofessionals in staat stelden sneller door te gaan naar de kern van de behandeling. Een andere facilitator was de aanwezigheid van twee verschillende soorten zorgprofessionals, wat leidde tot een meer holistische behandeling. Deelnemende zorgprofessionals hadden niet het gevoel dat alle patiënten geschikt waren om aan het programma deel te nemen en dat werd als een belangrijke barrière gezien. Daarnaast worstelden zorgprofessionals met het feit dat hun rol veranderde van behandelaar naar coach. Ze hadden moeite met het formuleren van lange termijn doelen met hun patiënten. Het gevoel was dat patiënten geen specifieke hulpvraag hadden. Dit kan gerelateerd zijn aan het feit dat patiënten beter voorbereid waren. Bovendien was deze preventieve aanpak nieuw, waardoor het wennen was. Uit deze bevindingen blijkt dat er aandacht moet worden besteed aan de nieuwe verantwoordelijkheden van zorgprofessionals en hun rol in preventieve, geïntegreerde en 'blended care'. Het bereiken van duurzame verandering bij patiënten vereist instructie en ondersteuning van zorgprofessionals.

Hoofdstuk 8 laat de resultaten zien van de identificatie van subgroepen in zelfmanagementvaardigheden en vergelijkt deze subgroepen op de door de patiënt gerapporteerde uitkomstmaten van fysiek functioneren, pijn en vermoeidheid. Om subgroepen te identificeren op basis van zelfmanagementvaardigheden is een hiërarchische clusteranalyse uitgevoerd. Zelfmanagementvaardigheden werden gemeten met de 'Health education impact Questionnaire' (HeiQ). Er werden vier subgroepen geïdentificeerd: High-Self-Management Skills (SMS), Medium-SMS, Low-SMS en Active & Low Distress-SMS. Laatstgenoemde vertoonde een duidelijk verschillend

patroon op clustervariabelen, terwijl de andere subgroepen significant verschilden op gemiddelden van de clustervariabelen. Op klinische variabelen werden vooral significante verschillen tussen subgroepen gevonden op het gebied van vermoeidheid en fysiek functioneren. Op basis van bovenstaande bevindingen kunnen specifieke subgroepen in een populatie van matige SOLK worden onderscheiden met een andere behoefte aan zelfmanagementondersteuning.

Hoofdstuk 9 presenteert gegevens van de clusteranalyse in beweeggedrag. Op zeven constructieve dagen is het beweeggedrag gemeten met behulp van een accelerometer (Activ8). Variabelen in beweeggedrag werden berekend en gecomprimeerd met behulp van 'Principal Component Analysis'. Patronen werden geïdentificeerd met behulp van een k-means clustering-algoritme. Deze studie identificeerde drie verschillende patronen: 'Sedentaire Movers' (n=64) brachten gemiddeld 9,9 uur/dag sedentair door en waren voornamelijk licht lichamelijk actief. 'Active Movers' (n=45) brachten gemiddeld 7 uur per dag sedentair door en waren voornamelijk licht tot matig lichamelijk actief. 'Sedentary Exercisers' (n=40) brachten gemiddeld 9,5 uur per dag sedentair door en waren voornamelijk intensief lichamelijk actief. Op basis van de cognitief-gedragsmodellen over de ontwikkeling van chronische pijn, veronderstelden we dat er een groep patiënten zou kunnen worden onderscheiden die fysieke activiteit zou vermijden. Hoewel deze studie een duidelijk en beter begrip geeft van patronen in beweeggedrag in deze populatie, hebben we geen bewijs gevonden die deze hypothese ondersteunt. Voor de klinische praktijk zou bewegingsgedrag moeten worden geïntegreerd als onderdeel van een programma dat betrekking heeft op de totale levensstijl van een persoon in plaats van alleen gericht te zijn op het geleidelijk verhogen van iemands fysieke activiteit.

Hoofdstuk 10 bespreekt de implicaties van de belangrijkste bevindingen van dit proefschrift, evenals de methodologische overwegingen en klinische implicaties. Er worden aanbevelingen gedaan voor verder onderzoek en educatie. Dit proefschrift identificeert een combinatie van vroege identificatie van patiënten met matige SOLK en een preventieve interventie met de integratie van eHealth (blended care) als een stap voorwaarts. Wat nog voor ons ligt, is om dergelijke interventies op maat en persoonlijk te maken, in plaats van een one-size-fits-all-behandeling aan te bieden. Meer inzicht in zelfmanagementvaardigheden en bewegingsgedrag tijdens de behandeling kan helpen bij het afstemmen van interventies, evenals het vroegtijdig signaleren van behoeften, motivatie en de inzet van eHealth bij patiënten. Omdat deze manier van behandelen afwijkt van de gebruikelijke zorg, zouden zorgprofessionals meer gecoacht moeten worden op hun veranderende rol van behandelen van patiënten naar coachen van patiënten.

PHD PORTFOLIO

Name of PhD student: S.A.J. (Suze) Toonders
PhD period: 2016 - 2023
Name of PhD Supervisors: C. (Cindy) Veenhof
Name of Co-supervisors: M.F. (Martijn) Pisters
P.E. (Els) van Westrienen

	Year	Workload (ECTS)
Courses		
Motivational Interviewing and Solution-oriented coaching *Psych*Fysio	2016	1
Acceptance and Commitment Therapy for Chronic Pain PsychFysio	2017	1
Academic Writing *BABEL*	2017	2
Internship supervision *University of Applied Sciences Utrecht*	2018	0.5
Basic qualification for didactical skills (BKO) *Fontys University of Applied Sciences*	2018	6
Basic qualification for examination (BKE) *Fontys University of Applied Sciences*	2020	6
Economic evaluation *EpidM*	2020	2
Stimulation and coaching of self-regulation in teaching *Fontys University of Applied Sciences*	2020	1
Project management *Twynstra Gudde*	2022	1
Responsible Conduct of Research –Year 1 *Utrecht University*	2022	0.15
Basic course on Regulation and Organization for Clinical Investigators (BROK) *Utrecht University*	2022	1
Presentations		
'Bevorderende en belemmerende factoren voor het gebruik van het blended PARASOL interventieprogramma vanuit patiëntperspectief'. Royal Dutch Society for Physical Therapy, Den Bosch, The Netherlands (Poster)	2018	
'Sterk met pijn'. In de Kern Gezond. Utrecht, The Netherlands (Workshop)	2019 -2021	
'Demographic and health-related factors associated with reduced work functioning in people with moderate medically unexplained physical symptoms: a cross-sectional study'. World Conference for Physical Therapy, Genève, Switzerland (Poster)	2019	
'Patients' perspectives on the usability of a blended approach of an integrated intervention for patients with Medically Unexplained Physical Symptoms'. World Conference for Physical Therapy, Genève, Switzerland (Poster)	2019	
'Barriers and facilitators with regards to the usability of a blended intervention in patients with medically unexplained physical symptoms'. Pain Science in Motion, Savona, Italy (Oral presentation)	2019	

	Year	Workload (ECTS)
'De inzet van blended fysiotherapie (zowel online als face-to-face) voor mensen met Somatisch Onvoldoende verklaarde Lichamelijke Klachten'. FysioXperience, Royal Dutch Society for Physical Therapy, Eindhoven, The Netherlands (Workshop)	2019	
'Hoe kan zorgtechnologie jou en je patiënt ondersteunen?' VvOCM, Utrecht, The Netherlands (Oral presentation)	2019	
'Perspectief van zorgverleners over eHealth', eHealth week, Fontys University of Applied Sciences, Eindhoven, The Netherlands (Oral presentation)	2019	
'Use of technology to empower healthy behavior', Fontys University of Applied Sciences, Eindhoven, The Netherlands (Oral presentation)	2021	
'Aan de slag met de KNGF richtlijn Zelfmanagement!' Royal Dutch Society for Physical Therapy, Den Bosch, The Netherlands (Workshop)	2022	
'Zelfmanagement in de eerste lijn, hoe pak je dat aan?' Chronisch Zorgnet, Eindhoven (Oral presentation)	2023	
'Movement behavior in patients with Persistent Physical Symptoms; who and how many are avoiding activity?' World Conference for Physical Therapy, Dubai (Platform presentation)	2023	
(Inter)national conferences or visits		
International and Interdisciplinary Colloquium on Research Methods in Pain Sciences (Stockholm, Sweden)	2017	
Royal Dutch Society for Physical Therapy congress (Den Bosch, the Netherlands)	2018	
World Conference for Physical Therapy (Geneva, Switzerland)	2019	
International and Interdisciplinary Colloquium on Research Methods in Pain Sciences (Savona, Italy)	2019	
Royal Dutch Society for Physical Therapy congress (Den Bosch, the Netherlands)	2019	
Royal Dutch Society for Physical Therapy congress (Den Bosch, the Netherlands)	2022	
Teaching		
'Praktijk Gericht Onderzoek' Graduation phase. Fontys University of Applied Sciences, Eindhoven	2018 - 2020	
'Internship' Graduation Phase. Fontys University of Applied Sciences, Eindhoven	2018 - 2020	
'Workshops qualitative research' Graduation Phase. Fontys University of Applied Sciences, Eindhoven	2019 - 2021	
'Lifestyle coach' Post-Bachelor for higher professional education. Fontys University of Applied Sciences, Eindhoven	2019 - 2021	
'Minor Exploring Healthy Behavior' Fontys University of Applied Sciences, Eindhoven	2021 - 2022	
Supervision		
Bachelor thesis student N. Jacobs (Physical Therapy, Fontys) 'Evaluatie blended interventie bij patiënten met matige SOLK'	2017	
Bachelor thesis student A. vd Heuvel (Physical Therapy, Fontys) 'Fysiotherapeut in samenwerking met POH-GGZ bij het behandelen van patiënten met matige SOLK'	2017	
Bachelor thesis student D. van Thiel (Physical Therapy, Fontys) 'Correlatie tussen ziekteperceptie en kwaliteit van leven bij patiënten met somatisch onvoldoende verklaarde lichamelijke aandoeningen'	2017	
Bachelor thesis student L. Sietsma (Physical Therapy, Fontys) 'Bestaat er een verband tussen pijn en mentale gezondheid bij mensen met matige SOLK?'	2017	

	Year	Workload (ECTS)
Bachelor thesis student R. Camps (Physical Therapy, Fontys) 'Wat is het verband tussen de mate van somatisatie en de ernst van de pijnsymptomen bij patiënten met matige SOLK?'	2017	
Master thesis student M. Beems (master clinical health sciences, physical therapy sciences, UU) 'Phenotypes of self-management strategies in primary care patients with moderate medically unexplained physical symptoms'	2018	
Master Research Internship student E. Poolman (master clinical health sciences, physical therapy sciences, UU)	2019	
Bachelor thesis student K. Janssen (Physical Therapy, Fontys) 'Zorggebruik bij patiënten met matige SOLK'	2019	
Bachelor thesis student M. Steenbekkers (Physical Therapy, Fontys) 'Zelfstandig bewegen onder chronisch zieken: Belemmerende - & motivatiefactoren'	2019	
Bachelor thesis student W. Simons (Physical Therapy, Fontys) 'Van begeleid naar zelfstandig bewegen met een chronische aandoening gezien vanuit zorgprofessionals en sportaanbieders'	2019	
Bachelor thesis student K. Kuurstra (Physical Therapy, Fontys) 'De zienswijze van docenten fysiotherapie ten aanzien van positieve gezondheid'	2019	
Bachelor thesis student M. van Duurling (Physical Therapy, Fontys) 'Docenten op de bres voor positieve gezondheid?'	2019	
Bachelor thesis student I. Zumdick (Podiatry Fontys) 'Welke bronnen van informatievoorziening (mondeling, schriftelijk, video) houden verband met het niveau van zelfmanagement bij patiënten met DM II ter preventie van voet ulcera'	2019	
Bachelor thesis student I. Verpalen (Podiatry Fontys) 'Acceptatie van positieve gezondheid binnen de podotherapie'	2019	
Master thesis student S. Konings (master clinical health sciences, physical therapy sciences, UU) 'Who is at risk for deterioration after an integrated and blended primary care treatment in patients with moderate MUPS?'	2019	
Bachelor thesis student R. Chatelin (Physical Therapy, Fontys) 'Self-management in patients with persistent physical symptoms : a systematic review'	2021	
Bachelor thesis student P. Stauf (Physical Therapy, Fontys) 'What are the differences in emotional well-being between patients with moderate MUPS who deteriorate physically and who do not experience deterioration after treatment?'	2021	
Bachelor thesis student B. Rensen (Physical Therapy, Fontys) 'Het beweeggedrag van mensen met matige Somatische Onvoldoende verklaarde Lichamelijke Klachten voor de PARASOL interventie'	2021	
Bachelor thesis student S. de Zoete (Physical Therapy, Fontys) 'Wat is de effectiviteit van de PARASOL-interventie tussen de drie beweeg groepen ten opzichte van de huidige interventie op de uitkomst van kwaliteit van leven (component mentaal) en de ziekteperceptie van patiënten met matige ALK op korte termijn (drie maanden)'	2022	
Bachelor thesis student I. Panahi (Physical Therapy, Fontys) 'Wat is het verschil tussen de sub-groepen (A-B en C) van de PARASOL interventie na 12 maanden op de progressie van zelf-effectiviteit (sub-demensie van HeiQ-questionnaire: constructive attidude and approaches'	2022	
Master thesis student T. de Bie (master clinical health sciences, physical therapy sciences, UU) 'Movement behavior patterns in patients with non-specific lower back pain'	2023	

	Year	Workload (ECTS)
Peer reviewed publications included in this dissertation		
van Westrienen PE, Pisters MF, Toonders SAJ, Gerrits M, Veenhof C, de Wit NJ. Effectiveness of a Blended Multidisciplinary Intervention for Patients with Moderate Medically Unexplained Physical Symptoms (PARASOL): Protocol for a Cluster Randomized Clinical Trial. JMIR Res Protoc. 2018 May 8;7(5):e120. doi: 10.2196/resprot.9404. PMID: 29739735; PMCID: PMC5964304.	2018	
Beems MEC, Toonders SAJ, van Westrienen PE, Veenhof C, Pisters MF. Identifying subgroups based on self-management skills in primary care patients with moderate medically unexplained physical symptoms. J Psychosom Res. 2019 Oct;125:109785. doi: 10.1016/j.jpsychores.2019.109785. Epub 2019 Jul 22. PubMed PMID: 31421323.	2019	
Toonders, SAJ, Poolman EY, Nieboer ME, Pisters MF, Veenhof C. Healthcare professionals' perspectives on a blended care program in primary care: A qualitative study. Internet Interventions. 2021 Dec;26:1-6. 100440. https://doi.org/10.1016/j.invent.2021.100440	2021	
Toonders SAJ, van Westrienen PE, Konings S, Nieboer ME, Veenhof C, Pisters MF. Patients' Perspectives on the Usability of a Blended Approach to an Integrated Intervention for Patients With Medically Unexplained Physical Symptoms: Mixed Methods Study. J Med Internet Res. 2021 Sep 28;23(9):e19794. doi: 10.2196/19794. PMID: 34581674; PMCID: PMC8512187.	2021	
Toonders SAJ, van der Meer HA, van Bruxvoort T, Veenhof C, Speksnijder CM. Effectiveness of remote physiotherapeutic e-Health interventions on pain in patients with musculoskeletal disorders: a systematic review. Disabil Rehabil. 2022 Nov 12:1-19. doi: 10.1080/09638288.2022.2135775. PMID: 36369923.	2022	
van Westrienen PE, de Wit N, Toonders S, Veenhof C, Gerrits M, Pisters M. Effectiveness of a blended multidisciplinary intervention for patients with moderate medically unexplained physical symptoms (PARASOL): A cluster randomized clinical trial. PLoS One. 2023;18(4):e0283162. Published 2023 Apr 6. doi:10.1371/journal.pone.0283162	2023	
Peer reviewed publications outside of this dissertation		
van Westrienen PE, Pisters MF, Toonders SAJ, Gerrits M, de Wit NJ, Veenhof C. Quality of life in primary care patients with moderate medically unexplained physical symptoms. Qual Life Res. 2019 Nov 15. doi: 10.1007/s11136-019-02358-8. PubMed PMID: 31732910.	2019	
Peer reviewed publications under review		
Toonders SAJ, van Westrienen PE, de Wit NJ, van Dongen JM, Gerrits M, Pisters MF, Veenhof C. The cost-effectiveness of an indicated blended care intervention in primary care compared to usual care in patients with moderate Persistent Somatic Symptoms.		
Toonders SAJ, van Westrienen PE, Wondergem R, Veenhof C, Pisters MF. Movement behavior patterns in patients with moderate Medically Unexplained Physical Symptoms (MUPS): who and how many are avoiding activity?		
Other publications		
vd Brekel K, Toonders SAJ. Gezondheidsbewuste professionals, gezondheidsbewuste bewoners. De Eerstelijns. 18 maart 2019	2019	
Mutubuki EN, van Doormaal MCM, Conijn D, Toonders SAJ, Ostelo RWJG. Dutch guideline 'Self-management' for Royal Dutch Society for Physical Therapy	2022	

ABOUT THE AUTHOR

Suze Toonders (1989) studied physical therapy at the University of Applied Sciences Arnhem Nijmegen (HAN). Her bachelor thesis was on the therapeutic guidance of parents with children with Cerebral Palsy, written as part of her voluntary work in Nepal. She then worked as a clinical physical therapist at the St. Antonius hospital, Nieuwegein. In 2016 Suze graduated with a MSc from Utrecht University as a clinical health scientist. She then worked as physical therapist, researcher and teacher, and was employed at the Center for Physiotherapy Research and Innovation in Primary Care, a structural collaboration in innovation, education and research between Leidsche Rijn Julius Health Care Centers (LRJG), Fontys University of Applied Science, Utrecht University of Applied Sciences (HU) and the University Medical Center Utrecht (UMCU). At the LRJG, she specialized in treating patients with Medically Unexplained Physical Symptoms (MUPS). This gave her the opportunity to both better understand patients with MUPS and what is needed to improve their care. Her role as researcher-lecturer at Fontys University of Applied Science gave her the unique opportunity to match students to the research project. In 2022 she co-authored the guideline 'Self-management' for the Royal Dutch Society for Physical Therapy (KNGF). Currently, she works as senior advisor in Reinier de Graaf hospital in Delft. Here, she brings together her practical experience and academic background to improve healthcare, with a focus on the chronically ill and frail elderly.

Suze is married to Daan. They live together in Delft and are proud parents of Hein (2021).

AUTHORS' CONTRIBUTIONS

Chapter 2: Effectiveness of remote physiotherapeutic e-Health interventions on pain in patients with musculoskeletal disorders: a systematic review

Data collection	ST, HvdM
Study concept and design	ST, HvdM, TvB, CV, CS
Data analysis and interpretation	ST, HvdM
Draft of manuscript	ST, HvdM
Manuscript editing and review	ST, HvdM, TvB, CV and CS

Chapter 3: Effectiveness of a Blended Multidisciplinary Intervention for Patients with Moderate Medically Unexplained Physical Symptoms (PARASOL): Protocol for a Cluster Randomized Clinical Trial

Study concept and design	EvW, MP, CV, NdW
Draft of manuscript	EvW
Manuscript editing and review	EvW, MP, ST, MG, CV, NdW

Chapter 4: Effectiveness of a blended multidisciplinary intervention for patients with moderate medically unexplained physical symptoms (PARASOL): a cluster randomized clinical trial

Data collection	EvW, ST
Study concept and design	EvW, NdW, CV, MG, MP
Data analysis and interpretation	EvW, NdW, ST, CV, MG, MP
Draft of manuscript	EvW
Manuscript editing and review	EvW, NdW, ST, CV, MG, MP

Chapter 5: The cost-effectiveness of an indicated blended care intervention in primary care compared to usual care in patients with moderate PSS

Data collection	ST, EvW
Study concept and design	ST, EvW, JMvD, MP, CV
Data analysis and interpretation	ST, JMvD, MP
Draft of manuscript	ST
Manuscript editing and review	ST, EvW, NdW, JMvD, MG, MP and CV

Chapter 6: Patients' Perspectives on the Usability of a Blended Approach to an Integrated Intervention for Patients With Medically Unexplained Physical Symptoms: Mixed Methods Study

Data collection	ST, SK
Study concept and design	ST, EvW, CV, MP
Data analysis and interpretation	ST, SK, MN
Draft of manuscript	ST
Manuscript editing and review	ST, EvW, SK, MN, CV and MP

Chapter 7: Healthcare professionals' perspectives on a blended care program in primary care; A qualitative study

Data collection	ST, EP
Study concept and design	ST, MP, CV
Data analysis and interpretation	ST, EP, MN
Draft of manuscript	ST
Manuscript editing and review	ST, EP, MN, MP and CV

Chapter 8: Identifying subgroups based on self-management skills in primary care patients with moderate medically unexplained physical symptoms

Data collection	ST, EvW
Study concept and design	MB, ST, MP
Data analysis and interpretation	MB, ST, MP
Draft of manuscript	MB, ST
Manuscript editing and review	MB, ST, EvW, CV, MP

Chapter 9: Movement behavior patterns in patients with moderate Medically Unexplained Physical Symptoms (MUPS): who and how many are avoiding activity?

Data collection	ST, EvW
Study concept and design	ST, EvW, RW, MP
Data analysis and interpretation	ST, EvW, RW, CV, MP
Draft of manuscript	ST
Manuscript editing and review	ST, EvW, RW, CV, MP

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Fysiotherapiewetenschappen cohort [2014]. Enthousiast begonnen aan de opleiding en al snel was er zoveel verbinding! Naast heel hard studeren en werken heb ik met jullie een 2e studentenleven mogen beleven. De vrijdagen startten op het UMC en eindigden in het Utrechtse nachtleven. We hadden één doel: Samen naar het diploma, dat is gelukt! Ontzettend trots op jullie hoe ieder zijn eigen carrière heeft weten te maken en ik nu in voetsporen mag treden van Herman, Ruud, Isolde en Robbert.

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