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Summary & General Discussion
The focus of this thesis was on the role of self-regulation and physical activity in chronic fatigue management. Idiopathic Chronic Fatigue (ICF) and Chronic Fatigue Syndrome (CFS) are of unknown aetiology, but research suggests a multifactorial nature in which biological/physical, psychological and social factors interact [1, 2].

Treatment approaches target mainly perpetuating factors of fatigue chronicity, such as lack of physical activity (PA). Adopting a health behaviour change framework can thus contribute to the understanding and promotion of PA in CF(S) patients. One of the theoretical perspectives on health behaviour change is Self-regulation (SR), which postulates that behaviour is a goal driven process, in which motivational and volitional aspects interact [3]. SR based interventions have demonstrated to be effective in promoting long-lasting health behaviour change in chronic disease populations [4-7].

The main purpose of this thesis was to develop, implement and evaluate the effects of a SR-based intervention targeting PA, the “4-STEPS to control your fatigue” trial on chronic fatigue management among patients with CF(S). We also intended to examine whether changes in the intermediate targets of the intervention (self-regulation skills and physical activity) explained subsequent changes in fatigue severity.

Prior to this intervention study we conducted a series of studies that were important for the development and evaluation of the 4-STEPS Randomized Controlled Trial (RCT): (1) a validation of a measure of fatigue severity (primary endpoint) for the language and population in which we intended to implement the intervention (Portugal), (2) a comparison of clinical characteristics and behavioural and cognitive determinants of CFS in a Dutch and a Portuguese patient sample, and (3) a systematic review and meta-analysis of behavioural and psychological interventions with a graded PA component conducted with CF(S) patients.

In this chapter, we first present a summary of each empirical study. Next, we present a theoretical integration of findings and
implications for practice, followed by a number of methodological considerations with a focus on the strengths and limitations of the 4-STEPS trial. Finally, possible avenues for future research and concluding remarks are addressed.

Summary of Studies

Assessment of Fatigue
The first empirical study (Chapter 2) described the psychometric properties of the Portuguese Version of the Checklist of Individual Strength (CIS20-P; [8]). The main reason for conducting this empirical study is that fatigue severity is the primary endpoint of the 4-STEPS trial. Therefore, we intended to use a measure with adequate psychometric properties for the language and population of interest, allowing at the same time the assessment of fatigue according to international standards. The CIS20 [9, 10], a multidimensional self-report instrument incorporating both physical and mental fatigue, is a well validated measure developed for CFS patients that has been widely used within this (e.g. [11, 12]) and other populations (e.g. working population; [13]), especially in the Netherlands. For the purpose of this study, data was collected from a large sample of healthy adults (N= 430) and a sample of CF(S) patients (N=89).

Our findings were similar to what was found in previous research [14], although studies examining the factorial structure of the CIS20 are scarce. Convergent validity of the CIS20-P with the Vitality Scale and Physical and Psychological Functioning (assessed by the SF-12v2 [15]) was good. The CIS20-P was also able to adequately discriminate between matched healthy and CF(S) samples. Patients with CF(S) presented significantly higher levels of fatigue on all subscales and on total fatigue severity (Total CIS20-P). Internal consistency estimates of each subscale and total CIS20-P were satisfactory, with the exception of Motivation. Furthermore, results supported a multidimensional (four-factor) structure of the CIS20-P, but some of the adjustment indices of fit to the model were unsatisfactory, especially in the CF(S)
sample. The small sample size of the CF(S) group may explain why estimates were in general poorer within this group.

In the subsequent studies presented in this thesis, only the Subjective Experience of Fatigue subscale measuring general fatigue severity (e.g. “I feel weak”) and the total CIS20-P were considered. The choice for selecting the subscale Subjective Fatigue as the primary outcome in the 4-STEPS trial was based on the fact that most trials using the CIS20 typically use this subscale as their primary endpoint.

**From Determinants...**

**Chapter 3** focused on the cross-cultural comparison of clinical characteristics as well as on the behavioural and psychological determinants of CFS between a Portuguese and a Dutch CFS patient sample. Due to the fact that there was no published research conducted in CFS patients in Portugal, and that most trials targeting these patients are conducted in Northern European countries this comparison was important in view of culturally adapting existing CFS models and developing tailored treatment strategies.

We conducted a comparative survey based study with matched samples (female patients with CFS) from the Netherlands (N=167) and Portugal (N=85). The objective of this study was threefold. First, it compared fatigue impairment and severity, somatic distress, psychological distress (depression and anxiety) and physical and psychological Health-Related Quality of Life (HrQoL) in Portuguese and Dutch CFS samples. Second, it examined the contribution of fatigue severity and somatic complaints to HrQoL in Portuguese and Dutch CFS patients. Third, it explored differential effects of self-regulation cognitions (illness beliefs) and behaviours (physical activity and erratic behaviour regulation patterns – limiting behaviour and all-or-nothing) on fatigue severity.

As expected, there were similar levels of fatigue severity in both samples, which supports the validity of the CIS20 to assess fatigue across different CFS samples. The levels of somatic distress, the poor physical and mental HrQoL and the high rate of patients not working in both samples, reflect the disability commonly found
in CFS patients [1]. Furthermore, we found that higher levels of fatigue and additional somatic symptoms were related to poor HrQoL. In addition, the Portuguese sample demonstrated worst psychological functioning, and higher levels of depression and anxiety. In fact, more than half of the Portuguese CFS patients met clinical levels of psychological distress.

Regarding the third objective of this study, we found that both self-regulation cognitions (illness beliefs) and behavioural factors (physical activity or certain behaviour regulation patterns) were significantly associated with fatigue severity in both samples. Regarding self-regulation cognitions, which according to Leventhal’s illness cognition model [16] trigger subsequent (un-) adjusted coping behaviours, our findings are in line with previous research showing that positive illness beliefs are associated with lower fatigue severity and negative beliefs with higher fatigue severity [17]. However, there were differences in specific beliefs. For the Portuguese sample we found that attributing more symptoms to the illness (seriousness of CFS) and reporting a higher emotional impact of the experience of CFS was associated with worse fatigue severity. In relation to the behavioural determinants in the Portuguese sample, higher levels of physical activity were positively associated with fatigue improvement and, on the contrary, limiting behaviour (i.e. excessive resting and marked decrease in daily activities) [18] was associated with worst fatigue levels. This is in line with previous research and current recommendations for CFS patients [19]. In the Dutch population, in which levels of physical activity were higher, adopting an erratic all-or-nothing behaviour regulation pattern (i.e. systematic alternation between periods of over activity and excessive resting as a consequence) was significantly associated with worse fatigue severity. These findings show similarities and differences in clinical characteristics and cognitive and behavioral determinants of CFS that are important for treatment.

...to Interventions

Next, Chapter 4 presented a systematic review and meta-analysis on the efficacy of behavioral and psychological treatments for
patients with CF(S) focusing on graded PA. Physical activity is considered a key factor in chronic fatigue management, and is therefore targeted in current recommended non-pharmacological treatments for CFS, such as Graded Exercise Therapy (GET) and Cognitive-behavioral Therapy (CBT). None of the published meta-analysis [20, 21] assessed so far the efficacy of these treatment approaches upon physical activity. The first objective of this meta-analysis was to evaluate the overall effect of interventions on PA as well as on fatigue severity, physical functioning and psychological distress (anxiety and depression), among CF(S) patients. Only RCTs were included, in which intervention conditions were compared with either passive control conditions (e.g. waiting list) or active controls (e.g. flexibility/relaxation).

Overall, results showed that interventions (k=16) had beneficial medium effects on fatigue improvement, and small effects on physical functioning/impairment, physical activity/capacity and psychological distress (depression and anxiety), at post-treatment and at follow-up (up to 17 months). There was an exception for PA at post-treatment for which only a near-significant effect was found.

As treatment effects varied widely between trials, potential moderators of interventions effect were also examined in the meta-analysis. These included the type of care provided to the control condition, treatment setting, length of the intervention, provider of treatment, presence of a psychological (cognitive) component (vs. only behavioural), minimal direct contact between patient and provider (vs. more intensive interventions), and a flexible approach to physical activity (adjustment in PA levels/goals according to individual tolerance level). Although the small number of studies somewhat limit the conclusions that can be drawn from these subgroup analyses, results showed that some of the variables were moderators of interventions effect but only for Fatigue Severity and Depression. Interventions provided by psychologists/psychotherapists and interventions conducted at secondary or tertiary settings presented larger benefits. In addition, interventions providing minimal direct contact with patients had additional beneficial effects upon fatigue severity and depression. Furthermore, we found that interventions allowing
flexibility in physical activity levels and goals, presented higher effects on depression. We did not find a significant difference in effects between interventions focusing on physical activity only or also targeting psychological factors (e.g. CBT approach), though results point towards a greater effect of this last treatment modality on both fatigue and depression. These results provide valuable indications for the targets and format of future interventions for chronic fatigue management.

Informed by the previous studies, Chapter 5 presented the protocol of the “4-STEPS to control you fatigue” trial. In the study protocol we presented the theoretical and empirical rationale for developing and implementing the 4-STEPS with CF(S) patients, the aims of the RCT, and a detailed description of the methods and procedures (study design, recruitment and randomization procedures, intervention content and materials, outcomes assessed and data analysis plan).

The 4-STEPS trial was tested in several Primary care centres and in the Portuguese Patient Association. Eligible patients who were willing to participate in the RCT were randomly allocated to either the control (usual care + leaflet with PA-related information) or the intervention condition (usual care + 4-STEPS). The treatment condition received a brief intervention (12 weeks) with minimal direct contact (up to 3 hours of total contact time). The 4-STEPS consisted of a combination of Motivational Interviewing [22], with SR-skills based training. Participants set and planned a relevant PA goal, and were advised to gradually increase PA according to a personal flexible scheme [23]. Patients received manuals with information about CF(S) and physical (in-)activity and received SR based manuals which incorporated SR cognitions and skills for each phase of the goal-related process (goal selection/setting, active goal pursuit and goal attainment/maintenance). To support patients during this process, patients received additional telephone SR-based counselling, as well as a pedometer and daily activities diaries, which could be used to monitor daily activity patterns during the intervention period. Finally, participants received a leaflet
with information of CF(S) to give to their partners of significant other.

Assessments were conducted at baseline, post-treatment (3-months) and at follow-up (12-months). Primary outcome was subjective experience of fatigue (CIS20-P Subjective Experience of Fatigue subscale). Secondary outcomes analyzed in the articles presented in this thesis were fatigue severity (Total CIS20-P), fatigue impact, Health-related Quality of Life (HrQoL; dimensions of physical and psychological functioning), somatic distress and psychological distress (depression and anxiety). To capture different forms of PA in which CF(S) patients may engage in, we assessed (1) daily steps taken (pedometer), (2) Leisure-time PA (Moderate to vigorous PA), and (3) personal elicited PA goal progress and achievement. In addition, we assessed at post-treatment the use of Self-regulation (SR) skills to achieve personal elicited goals.

Post-treatment results of the 4-STEPS trial were reported in the empirical study presented in Chapter 6 and follow-up results were reported in Chapter 7.

Data from eighty-four patients who were equally randomized to treatment conditions and completed baseline assessment was analyzed. Most patients were middle-age (~48 ys.) women (97.8%), and about half of the sample was unemployed. At baseline, only a third of the participants were physically active, doing an average of ~50 minutes per week of leisure-time PA and ~6700 steps/day. Only two participants discontinued the intervention, and total attrition was 25% to post-treatment and 33% to follow-up.

In general, results are in line with what is reported in previous reviews and meta-analysis of trials conducted with CF(S) patients [20, 21, 24, 25], including the meta-analysis presented in this thesis. At post-treatment, there was a significant difference between the intervention and control group of medium magnitude. Likewise, mixed design analysis, controlling for disease duration and setting, showed a significant time by group effect on fatigue severity improvement (Subjective Experience of Fatigue and Total CIS20). In addition, patients who received the 4-STEPS program showed a significant improvement in physical and psychological
HrQoL. In contrast, we did not find significant effects of the 4-STEPS in reducing psychological distress (depression and anxiety) nor somatic distress (additional somatic complaints). Physical activity was one the main targets of the 4-STEPS trial. At post-treatment, we only found a near-significant effect of the intervention on the average number of daily steps. Regarding leisure-time PA there was a marked increase from baseline to post-treatment in the intervention group, by an average of ~80 minutes per week. In addition, there was a significantly greater number of physically active participants in the intervention group (74%; vs. 33% in the control group). Furthermore, a large effect of the 4-STEPS was found on patients’ progress in attaining a personal elicited PA goal.

At follow-up (Chapter 7), a larger difference in subjective experience of fatigue between treatment and control conditions was reached (6.6 points; $g=0.72$), and there was a marked increase by approximately 21% in the number of patients presenting non-clinical levels of fatigue in the intervention group compared to none in the control group. From post-treatment to follow-up, beneficial effects of the 4-STEPS upon fatigue severity were maintained with larger effects from baseline, and there was an additional significant effect for fatigue impact in daily life. Similarly, we found sustained beneficial effects for physical functioning and larger effects on psychological HrQoL. Treatment effects on somatic complaints and psychological distress (depression and anxiety) remained non-significant. Regarding physical activity, differences between groups on daily steps became meaningless at follow-up. Nevertheless, average of daily steps in each condition met minimal guidelines for patients with chronic diseases [26]. Regarding leisure-time PA, there was no significant time by group effect from post-treatment to follow-up. Although there was a decrease in physical activity levels in the intervention condition, it was still higher than the levels presented at baseline (+ 30 minutes/week). Similarly to what was observed at post-treatment, there was a significantly greater number of physically active participants in the intervention condition (66%; vs. 36% in the control group).
The last objective of this thesis, presented in Chapter 7, was to analyze the mechanisms by which the intervention produced sustained effects on the primary endpoint of the 4-STEPS trial (subjective experience of fatigue). For this purpose, we conducted simple mediation analyses investigating the contribution of the empirically and theoretically derived intermediate targets of the 4-STEPS - physical activity and self-regulation skills -, to fatigue improvement.

Regarding PA, we conducted mediation analysis with daily steps taken assessed by a pedometer (near-objective measure of PA) and perceived PA goal progress. Our results showed that fatigue improvement at follow-up could be partially explained by participants’ progress and achievement of personal PA goals at post-treatment. In relation to the use of SR skills in pursuing personal behavior change goals, at post-treatment, participants in the intervention group reported a greater overall use of SR-skills (action planning, self-monitoring, seeking feedback, focus attention of goal, emotion regulation, coping with problems and goal persistence) in comparison to those in the control condition. Mediation analysis revealed that increased use of SR strategies to achieve personal behavior change goals (at post-treatment) contributed to improved fatigue reported at follow-up.

The results from the 4-STEPS trial show that a brief self-regulation based intervention can have a beneficial and sustained impact in chronic fatigue management and that progress and achievement of personal PA goals and increase use of SR-skills are at least partly responsible for this sustained improvement in fatigue.
General Discussion

Theoretical Integration and Translation into Practice

In this thesis we intended to examine if a self-regulation based approach would add to the current psychological and behavioral models and treatments for chronic fatigue management.

Is a Self-regulation Framework Useful for CF(S) Management?

Central in self-regulation theories is the assumption that human actions are goal-oriented and that self-regulation concerns cognitions, emotions, and skills that guide the achievement of personally relevant goals [3, 27]. Thus, behavior change is a dynamic goal-guidance process consisting of a goal selection and setting phase, active goal pursuit and goal attainment phase, in which motivational and volitional aspects interact [3]. By using the Motivational Interviewing method and Self-regulation skills based manuals, the 4-STEPS trial targeted all phases of the goal-guidance process, based on the set of guidelines for interventions formulated by Maes & Karoly [3]. In Chapter 3, we examined how illness beliefs derived from Leventhal’s illness cognition model [16], contribute to fatigue severity in two patient samples. In line with previous research [17, 28], we found that negative illness beliefs, such as the belief that one has a severe illness with serious consequences, as well negative emotional responses, were associated with worst fatigue severity. If patients experience many symptoms, which may even be misattributed to the disease, this can lead to a hypersensitivity and hypervigilance to somatic symptoms that will confirm illness identity and perceived consequences [17]. On the other hand, positive illness beliefs such as believing that one is in control of CFS were associated with improved fatigue severity.

For this reason, providing patients with clear information on the symptoms associated with CF(S) and how self-regulation strategies can positively impact chronic fatigue was an important first step in view of intervention [3]. In the 4-STEPS intervention (Chapters 5, 6 and 7), patients were initially provided with information regarding CF(S) symptoms, perpetuating factors, and self-management of CFS, to clarify maladaptive illness perceptions in order to facilitate the formulation of more adaptive and positive goals.
Goal setting is a central component of interventions based on a self-regulation framework [3]. Several theoretical considerations should be made in this respect. First, according to self-regulation theories (e.g. Carver and Scheier’s Control Theory [27]) goals are hierarchically organized and interconnected; from lower-order concrete goals (so-called “do” goals, e.g. do physical activity) to higher-order abstract goals (so-called “be” goals, e.g. be loved). This means that the formulation of and commitment to particular health behavior goals will depend on the degree to which lower-order goals facilitate or conflict with the achievement of higher-order goals, as well as with other personal goals, at the same hierarchical level, that are valued by the individual (multiple goal pursuit). Goal conflict and goal facilitation are therefore considered to be of importance in all goal-related phases. In the 4-STEPS trial, through the use of Motivational interviewing, the link between physical activity and core values for patients was explored and established by the patients themselves, i.e. how being physically active could fulfil other important goals such as recovering from CF(S), or even more broader goals such as being cared. By doing this exercise, an increase in the personal relevance of health goals and motivation to change was expected. Likewise, during the MI sessions and in the self-regulation skills manual, patients were prompted to identify and prioritize conflicting goals with PA.

Second, choosing and setting personally salient goals (goal ownership), rather than assigned goals, increases the likelihood of goal achievement as patients will be more committed and engaged in the process of goal striving [3, 27, 29]. Moreover, research derived from Self-Determination theory [29, 30], has shown a relation between autonomous motives for goal pursuit and goal attainment [31], as well as with the adoption and maintenance of physical activity in healthy and chronic disease populations [32]. By evoking patients’ motives and strengthening confidence to change in an autonomy-supportive environment, we could prompt the formulation of personally salient and self-chosen goals. In the 4-STEPS trial we found that progress and achievement of personal physical activity goals contributed to sustained improved fatigue (Chapter 7). Third, according to a Self-regulation perspective [27], one of the
triggers of motivation to change and selection of behaviour change goals is the perceived discrepancy between an individual current state (input value) and a desired state (reference value), through a comparator (e.g. self-monitoring). By identifying discrepancy it will prompt individuals to seek a reduction in the discrepancy towards the desired state. CF(S) patients tend however to adopt a discrepancy system that reinforces their status quo as their reference value is frequently based on symptom avoidance (e.g. activity avoidance) [33]. One way in which we targeted discrepancy during MI was by eliciting the association between the current behaviour and important life goals/values (aforementioned activity) and by resolving the ambivalence that can contribute to moving from keeping the status quo to engage in behavior change, which, in turn, can lead to improved fatigue and well-being. In addition, from the first to the second MI session patients monitored their daily activity levels by means of pedometer and daily activities records, which provided the necessary feedback to trigger discrepancy reduction (i.e. behaviour change goal). By experiencing a gradual increase in physical activity without exacerbation patients are expected to adopt more positive reference values that will encourage them to formulate active and positive goals instead of avoidance behaviours [33].

To enhance the process of formulating health-related goals (e.g. physical activity) and pursuing them, several self-regulation skills are considered to play an important role [3, 34]. First, action planning (i.e. detailed plans of what, how, when, where, and with whom) is consider to promote a transition from intention to action. Research has shown the beneficial effects of action planning and implementation intentions for health behaviour change [35] and goal achievement [36]. In the 4-STEPs trial, only patients in the intervention group were supported to formulate such a detailed plan to achieve a physical activity goal, resulting in a significantly higher level of goal progress and achievement in the treatment group (Chapter 6).

Second, prompting self-monitoring of behaviour and obtaining progress-related feedback is a critical component of successful self-regulation [3, 34], as it serves to focus one’s attention on behaviour/goal progress and make the necessary adjustments in accordance.
To facilitate self-monitoring and progress-related feedback, we used several strategies: (1) patients were offered pedometers, which promoted sustained monitoring of physical activity and immediate feedback, (2) we provided daily activities records (to identify and monitor behaviour regulation patterns), (3) participants set incremental goals (goal laddering), which allowed patients to check their progress for each goal step, and (4) we provided subsequently brief telephone counselling, which was also a form of providing feedback by revisiting goals that patients had previously formulated.

Finally, participants were prompted to plan how to cope with anticipated barriers to behaviour change. A recent systematic review [37] shows that interventions combining action and coping plans were more effective than interventions targeting action planning alone, and that supporting participants in the process of forming plans to prevent relapse increases intervention effectiveness. A coping planning or problem solving activity was presented in the self-regulation skills manual and it was the main focus of the telephone counselling sessions.

The results of the 4-STEPS trial (Chapters 6 and 7) demonstrated that the strategies employed lead to a higher use of SR-skills to regulate one’s own behaviour in the treatment condition in comparison to the control condition leading to an increase in physical activity in the intervention group. Furthermore, the use of these skills significantly contributed to sustained improved fatigue. These results are in line with previous research showing the beneficial sustained effects of targeting SR-interventions in patients with chronic diseases [4, 5, 38]. Likewise, recent meta-analyses found that interventions combining SR-skills derived from Self-regulation theory (e.g. Control Theory [27]), were more effective than other interventions in the general population [34] and in patients with chronic disease [39, 40]. Unfortunately, the limited information regarding the content of the interventions included in the meta-analysis (Chapter 4), did not allow the coding and examination of potential moderation effects of specific self-regulation principles as a moderator of intervention effects (e.g. goal setting).

**Why and How to Target Physical Activity for CF(S)**
Management?
Extensive literature has demonstrated that physical inactivity and excessive resting are perpetuating factors of fatigue chronicity in CF(S) patients and that PA based on a graded activity approach can lead to improved health-related outcomes in CF(S) patients [1, 41].

In this thesis our aims regarding PA were to (1) examine physical (in-)activity behaviour in a Portuguese sample of CF(S) patients in order to inform key targets of the 4-STEPS trial, (2) to analyze whether available interventions had a positive effect on PA, (3) whether a self-regulation approach would have a beneficial impact in improving PA among CF(S) patients, and (4) whether PA was in fact related to improved outcomes in CF(S).

In Chapter 3, we found that Portuguese CFS patients were characterized by low levels of PA, and that these levels as well as limiting behaviour were associated with fatigue severity, pointing at the need to address PA in interventions for chronic fatigue management in this population.

In Chapter 4 we analyzed the effects of behavioral and psychological interventions with a graded activity component in increasing PA. Although there were few studies including PA as an outcome, our results showed that the overall effect of interventions on physical activity/capacity was either non-significant or small. None of the moderators analysed explained the heterogeneity found between studies. The fact that physical activity interventions had only limited impact on PA is worth addressing. This could be due to variability in assessment methods of PA used in the trials (walking tests, accelerometers or physiological measures) or to other potential moderators that were not included in this meta-analysis (e.g. type of PA). It also points at the need of testing other forms of interventions that may be more successful in promoting physical activity (e.g. motivational and self-regulation approaches), as we did in the 4-STEPS trial.

The fact that Portuguese patients presented with low levels of physical activity justified the adoption of an intervention combining motivational interviewing, aiming at strengthening patients own motivation and confidence to engage in personal relevant health-behaviour goals, with self-regulation skills training
to support the process of goal setting and pursuit.

Recent literature suggests that graded activity approaches rather than adopting a rigid model of gradual increases in the frequency and intensity of physical activity, independently of symptoms experienced, should promote flexibility in PA levels and goals that patients adopt on a daily basis with a personal balance between daily activities and with rest (pacing) [23]. This approach can prevent overexertion, a major symptom in CFS that contributes a boom-and-bust pattern of activity and thus to the perpetuation of fatigue, [19, 23]. In the meta-analysis presented in Chapter 4 we found that interventions incorporating a flexible approach to PA levels or goals had also beneficial effects on depression (p<.10) and a slightly larger effect on fatigue severity. In the 4-STEPS trial, we adopted this approach to PA.

Results of the 4-STEPS trial showed variability between different PA-related outcomes. Effects on increase daily steps were trivial, but moderate to large effects were found for leisure-time PA and progress towards a personal PA goal at post-treatment. The fact that the percentage of active patients in the intervention group remained stable from post-treatment to follow-up in spite of a decrease in leisure-time PA, points at the possibility that patients may have set new goals not targeting an increase in PA levels, but focusing on e.g. flexibility in PA levels or on a balance between different forms of PA or daily activities.

Furthermore, we found that progress toward a self-chosen PA goal contributed to the explanation of the effects of the 4-STEPS on fatigue improvement, contrarily to what we found for daily steps taken. Previous research analyzing the mediation effect of PA (assessed by means of accelerometer), using data from three RCTs, did not find significant mediation effects nor significant intervention effects on increasing PA [42]. In addition, a recent study found that perceived activity (assessed with a modified version of the subscale Daily Activities of the CIS20) and not objective activity (also assessed by means of accelerometer) explained the variance in fatigue during a CBT based treatment [43]. Our findings point at the benefits of setting personally meaningful PA goals on physical activity and, as a result, improved fatigue. Possible explanations for this mediation effect, are that
patients by identifying that they are progressing towards their own physical activity goal, may experience a change in other cognitive factors such as focus less on symptoms and negative consequences, get a higher sense of control over fatigue, feel more confident in their ability to continue on making the necessary efforts and changes to recover from fatigue, feel more satisfied with their progress, and/or increase their sense of goal ownership, leading to better disease management and improvement [3, 33, 44-46].

**Implications for Practice**
Findings from the studies reported in this thesis show that focusing on identifying self-regulation factors that influence CF(S) outcomes, can lead to better care for patients with CF(S). The mediation effects found for self-regulation skills and personal goal progress (Chapter 7) indicate that assessing and targeting SR mechanisms can indeed lead to disease improvement. It is however important that health care professionals have access to guidelines that best inform on how to target these mechanisms. To translate SR theory to practice, Maes and Karoly [3] developed a set of principles to guide interventions targeting illness self-regulation, from which the 4-STEPS trial was derived. By providing these guidelines, self-help materials, and adequate training, we can support health professionals in increasing patients’ skills to regulate their own behaviours and implement strategies for CF(S) management. Likewise, health care professionals can be trained on how to prompt health behaviour change by applying Motivational Interviewing principles in routine practice. In fact, there has been an increase in Motivational Interview interventions conducted in primary care [47]. Nonetheless, the results from our meta-analysis (Chapter 4) point at additional benefits of treatments provided by psychologists or psychotherapists and the 4-STEPS trial was also conducted by a health psychologist. This finding and the fact that CF(S) seems to result from a multiplicity of determinants, including cognitive, emotional and behavioural factors, reinforces the importance of a multidisciplinary approach in the treatment of CF(S) including psychologists.

The fact that the 4-STEPS is a brief intervention, consisting of a combination of minimal personal contact with health care
professionals, brief telephone counselling and self-regulation based manuals to support CF(S) patients in changing their physical (in-) activity behavior, can be seen as an advantage as it can be offered as an adjunctive treatment for CF(S) in outpatient care. In fact, interventions with minimal direct contact that also allowed for flexibility in PA, provided continuous remote contact to support patients and provided patients with self-management strategies have larger effects on fatigue severity and depression (Chapter 4). Supporting patients’ autonomy over their own process of behavior change and providing them with the resources and skills to self-regulate and achieve personal goals seems to be crucial in this respect.

Notwithstanding its potential, the 4-STEPS needs to be assessed for cost-effectiveness and standardized treatments for CF(S) patients in Portugal are yet to be implemented. Several barriers can be identified to the implementation of evidence-based treatments and standardized procedures for the diagnostic and managements of CF(S) in the Portuguese health care system. The first of which is the fact that CF(S) is not recognized as a discrete disorder by primary health care professionals and when referred to secondary-tertiary care, these patients are followed in different medical specialities based on the main symptoms presented by patients to their medical doctor (e.g. rheumatology, internal medicine, neurology or psychiatry). Second, the lack of psychologists in the Portuguese National Health care system that was recently reported by the Portuguese Association of Psychologists can be a major obstacle to the implementation of self-regulation based interventions in health care [48]. Furthermore, the implementation of psychological and self-regulation based treatments for CF(S) patients will depend on the funds available, and the financial constraints that the health care system currently face can also be an obstacle to its implementation. At the same time, due to these financial and human resources constraints the development of brief interventions with minimal direct contact can also been seen as an advantage.

The examination of self-regulation and behavioral determinants of fatigue improvement can contribute to develop predictive models that have good validity and that can be cross-culturally
applied, guiding the development of more effective interventions. Developing a diagnostic tool that explores various mechanisms of fatigue perpetuation or improvement, could lead to the development of tailored intervention strategies from which patients can benefit the most.

**Methodological Considerations**
Several methodological considerations were already made in the different chapters of the thesis. The aim of this section is to outline the main methodological issues of the 4-STEPS randomized controlled trial, and to formulate methodological considerations that should be taken into consideration in future research.

**Strengths and Limitations of the 4-STEPS Trial**
The 4-STEPS trial was based on previous studies and is characterized by (1) a randomised controlled designed, (2) inclusion of a 1-year follow-up assessment point, (3) current recommendations for CF(S) management, (4) consideration for the specificities of the Portuguese CF(S) population and context, (5) a theoretical perspective (self-regulation theory) and (6) intervention briefness with low participant burden. With this RCT we evaluated the efficacy of a complex behavior change intervention, and potential mechanisms of change (i.e. PA and SR-skills).

Notwithstanding its strengths, this trial has several limitations that were addressed in detail in Chapters 6 and 7. A first limitation is the basis for the power calculation that was used, the difference in subjective experience of fatigue between the intervention and control condition, which does not necessarily correspond to a clinically significant improvement in fatigue. At present, we believe that there are more appropriate approaches for power calculation, such as a difference of 0.5 SD in fatigue severity from baseline in the intervention group [49], the overall effect size obtained in previous meta-analysis of CBT and GET trials [21], or the change in the mean scores within the intervention group [50].

Second, patients were recruited from several Primary Care centres and from a Patient Association. Although recruitment of participants was stratified by setting, there were differences
in recruitment procedures in each setting that may have caused selection bias. While statistical analyses used to evaluate the effects of the 4-STEPS trial, controlled for potential confounding effects of the type of setting (Health care centres vs. Patient Association). On the other hand, one of the strengths of this trial is that it was a multi-centre RCT, which allowed the inclusion of a larger number of participants from different locations and targeted a more heterogeneous population, therefore contributing for the external validity and generalizability of the findings. In fact, recent reviews suggest that single-centre trials tend to overestimate effects of trials [51, 52]. Unfortunately, due to the limited sample size recruited in each health care centre, we could not control for the potential differential effects of each centre.

Third, attrition rate to the 4-STEPS trial was higher than what was initially anticipated for a brief intervention, in particular to the follow-up assessment point. The reasons for this attrition rate were not further analysed, although patients were followed and some of the patients that were lost to the post-treatment assessment were re-included at the 12-months period of assessment. Other brief and remote contact interventions have also found high dropout rates [53, 54]. It should be further explore if e.g. other forms of recruitment and contact with patients, between the end of the intervention and assessment points (e.g. booster sessions) could prevent the high attrition rate found.

Fourth, the fact that the intervention was conducted only by one therapist is a clear limitation of the 4-STEPS trial, as we could not assess the effect of the therapist on the intervention. In addition, due to constraints in available resources we could not assess treatment integrity. In clinical trials using MI it is recommended to assess therapist fidelity to the treatment, as it is the consistent use of MI principles and skills as well as the interpersonal style of the therapist that is thought to influence behaviour change and health-related outcomes [22, 47]. For this purpose, several scales such as the Motivational Interviewing Treatment Integrity [55] have been created. Likewise, we did not assess adherence to the full treatment protocol. Although all participants who completed the 4-STEPS intervention received the two MI sessions and telephone counselling, we do not know how many patients were fully adherent
to the content of the SR-skills manual.

Fifth, as the intervention combined several behavior change methods and techniques, such as the use of pedometers, motivational interviewing and SR-skills training, the effects of the different components of the 4-STEPS trial cannot be disentangled nor could we assess whether this specific combination of techniques was responsible for the intervention effects. Future research should consider using a full factorial design to determine the individual contribution of each component.

Finally, in this controlled trial the 4-STEPS program was compared against a passive control group whose participants only received general information about physical activity and formulated a personal physical activity goal without additional guidelines. Comparing the 4-STEPS with other active treatments (such as GET alone, or educational approaches), is an important target for future research.

Sample and Recruitment Considerations
One of the main limitations of the studies presented in this thesis is the small size of the Portuguese CF(S) sample. There were also large differences between samples sizes in the studies presented in Chapter 2 (Portuguese CF(S) vs. healthy sample) and in Chapter 3 (Portuguese CFS vs. Dutch samples), which limits the conclusions that can be drawn from these comparisons. Furthermore, the sample size lacks power to detect changes in secondary outcomes and mediation effects, limiting not only conclusions that can be drawn from the analysis conducted in the RCT (Chapters 6 and 7) but also the type of statistical models that could be employed.

A second limitation is that only two men with CF(S) participated in the 4-STEPS trial and only women were included in the international comparative study (Chapter 3). Studies have shown that CF(S) is more common among women [56], but report a considerable higher percentage of men suffering from CF(S). Future studies should test for differential behavioral and psychological explanatory models of CF(S) concerning gender and explore the effects of the 4-STEPS in male CF(S) patients.

Another important remark is that the empirical studies presented in this thesis targeted only adult patients with CF(S). More studies
are needed to test differential effects of interventions and the application of a self-regulation perspective on CF(S) between adolescents and adults.

The fact that samples were recruited via Health Care Centres and a Patient Association does not allow to generalize results to the general population nor to attribute differences with the Dutch population only to cross-cultural differences in the international comparative study (Chapter 3). In addition, as aforementioned, differences between settings in the recruitment strategy may have led to selection bias. To overcome this bias, not only recruitment for the RCT was stratified by setting, but also statistical analyses on the effects of the 4-STEPS trial were conducted controlling for the effects of the type of setting (Chapters 6 and 7).

The fact that inclusion/exclusion criteria were not verified by means of full laboratory examination and a structured psychiatric interview, may have led to the inclusion of patients with misdiagnosis and/or co-morbidity with other psychiatric and physical clinical conditions, such as Fibromyalgia, as there is a considerable proportion of patients presenting with both CF(S) and Fibromyalgia [1]. This possible co-morbidity with undiagnosed psychiatric disorders may in part explain the difference in psychological distress and psychological HrQoL found between the two cohorts in the cross-cultural study (Chapter 3) as well as the trivial impact of the 4-STEPS upon psychological distress (Chapters 6 and 7). Furthermore, both patients with Idiopathic Chronic Fatigue or Chronic Fatigue Syndrome were included, which means that our sample is constituted by patients presenting with different levels of disability and number of major CFS symptoms experienced. Future studies should examine the contribution of Self-regulation models and the efficacy of the 4-STEPS intervention for different levels of disease severity.

Assessment Considerations
In the studies presented in this thesis, we made extensive use of self-report measures, which are susceptible to response bias. Nevertheless, many of the questionnaires used in this thesis are well validated and reliable. In the case of physical activity, although we used a more objective measure to assess physical activity
(pedometers), it was still the individual that registered and provided written information on daily steps taken. As an alternative, future studies could use accelerometers, in which scores are stored into the internal memory of the device and afterwards fed into an external computer. In addition, accelerometers also provide information on physical activities performed at different levels of intensity and sedentary periods, which allows the assessment of daily activity patterns and fluctuations. In this respect, although we provided patients with diaries to register daily activities, we did not use them as an additional assessment measure. Future studies could use these daily records to assess behaviour regulation patterns (e.g. all-or-nothing behaviors).

Moreover, for the assessment of fatigue severity we were not able to establish normative data for the CIS20-P, as we did not have a representative sample of the Portuguese population. As such, comparisons made in the empirical studies regarding (non-)clinical levels of fatigue severity were based on cut-off scores established for the Dutch population, and should thus be interpreted with care. Future studies should examine normative scores and thresholds for clinical levels in representative samples of the general Portuguese population and populations with chronic diseases, so that the CIS20-P can be used as a complementary diagnostic tool of prolonged fatigue severity in both research and clinical practice in Portugal. Likewise, because there is no normative data for the Portuguese population of the measure used to assess depression and anxiety (Brief Symptom Inventory; BSI [57, 58]), cut-off points for (non-)clinical levels of psychological distress in the cross-cultural study (Chapter 3) were also based on normative data from the Netherlands.

Finally, some of the measures used lack a full comprehensive quality assessment for the Portuguese population (e.g. the Self-regulation Skills Battery), or validation of modified versions (e.g. the Fatigue impact scale).

**Future Directions**
The studies presented in this thesis showed promising findings indicating that a self-regulation framework can add to existing models and treatments for chronic fatigue management.
However, some questions remained unanswered while others were raised throughout the conduction of these studies. In this section we present some avenues for future research focusing on this thesis as a whole.

In the comparison study presented in Chapter 3, we found that a psychological model of CFS is common to patients from different countries, which is an important finding for the development of treatment modalities that can be internationally implemented, but we also found differences between the patient samples. While this first exploratory study has its merits, more research is needed to fully understand cross-cultural patterns of behaviour and self-regulatory factors in CFS. For example, the large difference in psychological distress found between Portuguese and the Dutch CFS patients may in part have to do with the fact that, in contrast to the situation in the Netherlands, CFS is not recognized as a discrete disorder by primary health care practitioners in Portugal. Difficulties in the diagnosis and lack of legitimization of the disease may therefore lead to higher levels of psychological distress [59]. We are currently conducting a longitudinal survey study comparing clinical characteristics, behaviours and self-regulation factors of CFS between patient samples from several European Countries (France, Italy, Netherlands, Rumania and the United Kingdom).

Our RCT (Chapters 5, 6 and 7) showed that using motivational interviewing principles and SR skills training targeting physical activity and CF(S) management leads to beneficial improvements in fatigue, but sustained effects were assessed only at one year follow-up after baseline assessment. Future studies should analyze longer-term effects of brief interventions. So far, only one study using a brief intervention targeting physical activity in CF(S), analyzed its effects at a longer period of time (2 years) [60], but there was crossover between the conditions. In the meta-analysis conducted within this thesis (Chapter 4), the average follow-up period of assessment in the trials included was 13 months. Although we found that the main effects of the 4-STEPS were maintained at follow-up, for some secondary outcomes the impact of the
intervention decreased. To increase the sustained use of self-regulation skills and to optimize long-term effects of brief interventions, other forms of remote contact using m-health and e-health are worth exploring. Using remote technology can for e.g. prompt continuous self-monitoring of behavior and provide tailored feedback.

Identifying psychological and behavioural perpetuating factors of CF(S), can contribute to the development of diagnostic tools and tailored interventions. While we identified important SR cognitions and skills as well as behaviours that are related to fatigue severity, these only explain a part of the variation in this outcome. Other potential determinants and mechanisms of change have been described in the literature that should be explored, such as social factors (e.g. social support), focusing on bodily symptoms, (in-) avoidance behaviour, or balance in daily activity patterns [1, 44, 61]. Future research should use more complex mediation models to explore how changes in physical activity impact on fatigue improvement from a psychological point of view. As previously mentioned in this chapter, from a self-regulation perspective, feeling capable to engage and progress in some form of physical activity (without exacerbating symptoms), cognitive changes (e.g. focus less on fatigue) and feelings of satisfaction with achievements, can positively impact disease management and improvement [3, 44, 45].

Likewise, examining predictive models and effects of this brief treatment for CF(S) on other important outcomes related to CF(S) is necessary, such as recovery from fatigue as well severity of disability and impairment associated with CF(S) (e.g. work, social life).

More research is clearly needed to identify moderators of explanatory models and intervention effects, so that we can better understand under which conditions (i.e. intervention design) and for whom SR based approaches are most effective. Previous moderator analyses on the effects of brief interventions for CFS found that patients with substantial depressive symptoms benefit less from these types of interventions [50, 62]. In the 4-TEPS trial we did find a lower effect than initially anticipated for psychological
distress (especially for depression). The fact that Portuguese CF(S) patients presented with high levels of psychological distress may explain this finding. At the same time, in meta-analyses that also included more intensive CBT interventions for CFS, the magnitude of treatments effect upon anxiety and depression were small ([21], Chapter), and in our meta-analysis we even found that brief interventions had a larger effect on depression improvement (Chapter 4). Although we attempted to target emotional regulation in the 4-STEPS intervention, this component was directed only to the regulation of emotions to achieve personal elicited goals. Thus, patients presenting with clinical psychological distress may need additional forms of treatments for depressive or anxiety disorders.

Other moderators are worth addressing in future research, such as severity of fatigue, co-morbidity with other Functional Somatic Syndromes (e.g. Fibromyalgia), level of physical activity (passive vs. more active patients), mastery in the use of self-regulation skills (high vs. low), combination of SR-skills, or how SR strategies are prompted (e.g. self-chosen elicited goals vs. goals assigned by practitioners; autonomy-supportive or controlled environment). Furthermore, other methodologies such as N-of-1 RCT design can be used to analyse intraindividual effects of interventions, which can be particular useful to better understand who benefits from treatment techniques and to tailor interventions to each individual [63].

Finally, although this intervention was partially conducted in primary care, a health psychologist delivered it. Due to the fact that motivational and self-regulation based interventions as well as interventions for CF(S) management in primary care are usually delivered by other health professionals (e.g. a general practitioner) in brief consultations, more research is needed to optimize existing interventions for CF(S) management in a primary care setting [21, 47, 64].
Concluding Remarks

The scope of this thesis was on the behavioral and self-regulatory factors associated with health behavior change and chronic fatigue management. Informed by preliminary investigations, we developed and implemented a self-regulation based intervention targeting physical activity for CF(S) patients, the “4-STEPS to control your Fatigue”.

The 4-STEPS program, which was tested in a multicentre randomised controlled trial, lead to significant and sustained improvements in fatigue and in patients’ functioning and quality of life. The 4-STEPS also produced significant effects on the use of self-regulation skills and physical activity, especially progress towards a personal physical activity goal, partially explaining the sustained effects of the intervention upon fatigue severity. Nonetheless, the 4-STEPS also presented limited effects for some of the outcomes assessed.

The limitations of each of the six empirical studies that were reviewed in this chapter point at the need to conduct more research on the behavioural and psychological mechanisms involved in CF(S) management. In spite of these limitations, we believe that this thesis positively contributes to the advance of disease management in CF(S) patients.
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