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A tailored psychological intervention (CoMIRA) for managing fatigue in Rheumatoid Arthritis: A protocol for a randomized controlled trial

Research Project

Scientific Area of Rheumatology

Work carried out under the guidance of

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A tailored psychological intervention (CoMIRA) for managing fatigue in Rheumatoid Arthritis: Protocol for a randomized controlled trial

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Abstract

Background: Despite remarkable medical advances in the treatment of rheumatoid arthritis (RA), a subset of patients fails to achieve complete clinical remission, as the Patient Global Assessment (PGA) of disease activity remains above 1, even after the inflammatory process is brought under control. This so-called state of 'PGA-near-remission' negatively impacts individuals' functioning and potentiates inadequate care. Fatigue is a distressing and disabling symptom frequently reported by patients in PGA-near-remission and its management remains challenging. While classic cognitive-behavioural interventions show some benefits in managing fatigue, there is potential for improvement. Recently, contextual-cognitive behavioural therapies (CCBT), like mindfulness, acceptance, and compassion-based interventions have shown promising results in fatigue-associated disorders and their determinants.

This study primarily aims to examine the efficacy of the Compassion and Mindfulness Intervention for RA (CoMIRA), a novel intervention combining different components of CCBT, compared to treatment-as-usual (TAU) in the management of RA' associated fatigue. Secondary aims involve exploring whether COMIRA produces changes in perceived impact of disease, satisfaction with disease status, levels of depression, and emotion-regulation skills. Safety will also be ascertained.

Methods: This is a multicentre, two-arm parallel randomized controlled trial. Patients will be screened for eligibility, willingness to participate, and will be assessed and randomized to the experimental (CoMIRA + TAU) or control condition (TAU) using computer-randomization. CoMIRA will be delivered by a certified psychologist and comprises eight sessions of 2 hours, followed by two booster sessions. Outcomes will be assessed via validated self-report measures and include levels of fatigue (primary outcome), perceived impact of disease, depressive symptoms, mindfulness, self-compassion, safety, and satisfaction (secondary outcomes). Assessment will take place at baseline, post-intervention, before the first and second booster session (week 12 and 20, respectively), and at 32 and 44 weeks after the interventions' beginning.

Discussion: We expect COMIRA to be effective in reducing levels of RA-associated fatigue. Secondarily, we hypothesize that the experimental group will show improvements in overall perceived impact of disease, emotional distress, and emotion regulation skills. Our findings will

contribute to determine the benefits of combining CCBT approaches for managing fatigue and associated distress in RA and to expand the existing repertoire of psychological interventions for RA.

Keywords:

Rheumatoid arthritis, Fatigue, Psychotherapy, Mindfulness, Self-Compassion, Acceptance and Commitment Therapy

Background

Rheumatoid Arthritis (RA) is a chronic condition of unknown aetiology, characterized by pain, swelling, stiffness, and progressive disability caused by the inflammation and gradual destruction of synovial joints.[1] It affects around 0.5% of the adult population worldwide, being more frequent in women,[2,3] and significantly impacts several health-related domains (e.g., fatigue, sleep), affecting the individual's functioning, well-being, and quality of life.[4–7]

Current recommendations on treatment and management of RA follow a treat-to-target (T2T) approach aimed at achieving remission of the inflammatory process, or at least, low disease activity, as soon and as consistently as possible.[8,9] The guiding principles include regular quantitative assessments of inflammatory activity and consequent adjustment of immunosuppressive medication to ensure persistent clinical and analytical remission.[10] The definitions of remission currently endorsed by the American College of Rheumatology and the European Alliance of Associations for Rheumatology,[11] are based on tender and swollen joint counts, acute phase reactants, and the patients' global assessment of disease activity (PGA), with or without the physician's global assessment.[11]

Due to advances in pharmacological treatments and the implementation of the T2T approach, remission has become a feasible and rather frequent outcome in RA.[12] However, about one-third of all patients with RA fail to achieve a complete remission status according to the Boolean definition endorsed within by ACR and EULAR, despite the absence of inflammation, solely due to the PGA score (>1), a status coined 'PGA near-remission'.[13–15] This condition entails an elevated risk of overtreatment if current recommendations are strictly followed.[16–18] These patients' condition cannot be improved by additional immunosuppression, as the disease process is already under control. Instead, they require adjunctive measures designed to address the mechanisms underlying the unabated PGA, with emphasis on fatigue.[15]

Published reports suggest that pain, functional impairment, fatigue, and comorbidities (e.g., depression and anxiety) are the major determinants of PGA,[13,15,19] especially after remission of the inflammatory process has been achieved.[15,19] In this sense, PGA is

primarily a measure of disease impact, e.g. a mirror of current somatic symptoms and functional impairment, rather than a reliable reflexion of inflammatory activity.[15,19]

These observations support the proposal for a dual target strategy in the management of RA[18] whereby a specific target focused on the patient's experience of the disease would be pursued in parallel with the current one, defined by disease remission, sharpened by the exclusion of PGA.

In RA, more than 70% of patients report levels of fatigue that are similar to those observed in chronic fatigue syndrome[20] and half of all patients report it as severe and of the highest priority in their list of persistent complaints.[21] These observations are similar among patients in PGA-near-remission despite being virtually devoid of joint inflammation.[15] Patients often consider that this symptom is unduly ignored by clinicians.[22]

Multiple factors have been associated with fatigue observed in RA,[23] reinforcing its complex and multicausal nature.[24] Depression, disability/inactivity, and sleep disturbances seem to be key drivers of fatigue,[25] whereas pain and disease activity appear to play a rather minor role.[24] This complexity underlies the major challenge faced so far in the design and implementation of effective interventions.

Adjunctive non-pharmacological interventions, including exercise, counselling, occupational therapy, cognitive behavioural therapy (CBT) and other psychological interventions have been associated with positive results.[26–28] CBT is the gold-standard intervention in many mental and physical health conditions, and a valuable intervention in RA,[29–31] with proven beneficial effects in chronic pain, sleep difficulties, fatigue, self-management, self-care, coping and well-being, both in individual and group settings.[32]

Lately, contextual CBT interventions, such as mindfulness, acceptance and compassion-focused therapies, have equally been showing promising results.[33,34] These types of interventions promote the establishment of a different relationship between internal experiences (e.g., cognitions and emotions) and the body, variables of vital importance in the experience and management of RA.[35] Preliminary evidence suggests that mindfulness-based interventions may help improve RA-related outcomes and associated psychological distress.[33,36,37] Regarding Acceptance and Commitment Therapy (ACT), studies have found it effective in enhancing the quality of life,[38] improving chronic illness-

related symptoms, such as pain, depression, and anxiety.[39–41] and decreasing fatigue levels in chronic fatigue syndrome.[42] ACT has also been shown to implicitly promote self-compassion (e.g., a warm and compassionate stance towards oneself in the face of setbacks[43]), a recognized buffer against depression and negative pain-related outcomes.[44]

The intervention and therapeutic techniques used in this study are feasible, accepted, validated in online environments, [45–47] and reveal encouraging outcomes in other chronic illnesses.[44,48] The researchers combine distinct evidence-based therapeutic components in a complementary and coherent way to target relevant processes at play in RA with the objective of alleviating fatigue and depressive symptoms in patients with this condition.

Aims and Hypothesis

The primary aim of the study is to investigate the impact of the program Compassion and Mindfulness Intervention for RA (CoMIRA) in RA-associated fatigue in comparison to treatment as usual (TAU).

Secondary aims include the effects the intervention has upon the patient's satisfaction with disease status, overall perceived impact of disease, depression and anxiety levels, and self-compassion skills.

Methods

Study design

We will perform a two-arm parallel superiority randomized controlled trial.

Participants will be randomized (1:1) into one of two conditions: the experimental condition (CoMIRA Program plus TAU]) and the control condition (TAU only).

The experimental intervention, described below, will be delivered in a group format, online, for eight consecutive weeks, followed by two booster sessions after 4 and 12 additional weeks.

Primary and secondary outcomes will be assessed at baseline (t0), post-intervention (t1, 8 weeks) and also at 12 (t2), 20 (t3) 32 (t4) and 44 weeks (t5), by means of validated self-report measures. Measures of disease activity (Joint counts and CRP) will be assessed at baseline, 20 and 44 weeks after the interventions' commencement, to take fluctuations of disease activity into account. Medication will be registered at every assessment.

CONSORT guidelines were used to design this study and will correspondingly be followed in the study's results report.

Primary Outcome and Sample size

The primary outcome of the study will be the difference in fatigue scores between the two intervention groups at week 32, controlling for baseline values.

A sample size of 91 was indicated by G*Power for an analysis of covariance (ANCOVA) [α=.05, 90% statistical power, effect size of 0.50]. Assuming a 30% attrition rate and rounding up for convenience, we plan to recruit a total of 120 participants (60 participants per arm).

Sample selection and recruitment strategy

Participants will be recruited among adult patients with RA, currently in PGA-near-remission in the Rheumatology Department at Centro Hospitalar e Universitário de Coimbra and cooperating centres. On invitation, eligible patients will be provided with a written and oral explanation of the study and its objectives. They will be informed about the voluntary nature of their participation and ensured of the anonymity and confidentiality of any data provided. Signed informed consent will be, finally, obtained before any trial procedure takes place. No compensation will be attributed to participants.

All consenting patients will undergo physical examination by the research team's rheumatologist and fill out the Rheumatoid Arthritis Impact of Disease score (RAID)[49,50] and the Patient Experienced Symptom State (PESS)[51] to ascertain eligibility. See Appendix 1.

Eligibility criteria: a) age 18-65 years b) meeting the 1987 ACR or 2010 ACR/EULAR classification criteria for RA; c) in PGA-near remission: Tender and swollen 28 joint counts and CRP (mg/dl) < 1, and PGA > 1, d) RAID – fatigue ≥ 3; e) PESS < "good" and f) under stable medication (at least 3 months).

Exclusion criteria. Participants exhibiting any of the following conditions will be excluded from the study: a) less than 6 years of formal education; b) unable to attend zoom meetings unaided; c) unable to fulfil self-report questionnaires unaided; d) pain-related comorbidities (e.g. fibromyalgia or osteoarthritis); e) presence of other comorbid medical conditions that may cause fatigue, such as anaemia (Hb<10mg/dL), uncontrolled hypothyroidism or cancer; f) presence of severe psychological symptoms or disorders (e.g. psychosis, severe depression, substance abuse); g) currently ongoing psychological interventions or formal psychiatric treatment; h) pregnant patients; i) otherwise disabled patients (advanced articular/bone erosion); j) refuse to provide informed consent.

Those who decline to participate will be inquired about the underlying reasons.

Clinical data and outcome measures will be collected via reuma.pt (www.reuma.pt), the official and ethically approved national register of rheumatic patients. All data will be encrypted, anonymized, and made accessible only to the research team.

Randomization and allocation

After baseline assessment, participants will be assigned either to the intervention or the control condition with a 1:1 allocation by means of computerised random number generator (www.random.org) stratified by depression score (above/below HADS score of 8).[52] Allocation sequence concealment will be guaranteed by using a third-party (a research member responsible only for generating the randomization schedule) and by using sealed envelopes that are opened only after patient's enrolment.

Given the nature of the study, it will be impossible to blind participants regarding their allocation. However, the following types of blinding will be implemented: blind assessment (the rheumatologist performing the examinations will be blind to the patient's allocation) and blind analysis (the researcher performing the statistical analysis will be blind to participants' allocation).

Interventions

Active Group - Compassion and Mindfulness Intervention for RA (CoMIRA)

Development

The CoMIRA program follows the Medical Research Council's (MRC) framework for the development of complex interventions, lastly updated in 2019,[53] and was developed by a multidisciplinary team with clinical and academic experience in RA, composed of rheumatologists, nurses, and psychologists. CoMIRA design was informed by existing protocols of individual and hybrid mindfulness, acceptance, and compassion-based interventions[44,54–57] and on the RAFT study.[58]

Intervention content

The CoMIRA program incorporates the following key topics during the 8 weeks of intervention (1st phase):

(i) Psychoeducation on RA, sleep hygiene, exercise, and general nutritional recommendations (promote behavioural change and self-care, boost the sense of self-worth and self-efficacy)
(ii) Activity engagement and pacing
(iii) The functioning of the mind and its problematic patterns
(iv) Focusing on the 'here and now' (mindfulness)
(v) Learning new ways of self-relating – self-compassion
(vi) Making room for suffering (acceptance); and
(vii) Moving towards what matters (identification of valued life directions and promotion of consistent values and goals-directed behaviour).

The closing session comprises a review of the main concepts and "take-home" messages, discussion of potential setbacks and strategies to deal with them, and participant's feedback on the intervention and the progress made.

The booster sessions, at 4 and 12 weeks after completion of the first phase, will focus on the revision of previously learned concepts, evaluation of potential barriers/difficulties encountered, strategies employed to deal with them, and clarification of any impending

question. They will also revisit and reinforce the continued practice of mindfulness and compassion exercises as daily practices.

A board-certified clinical psychologist with training in contextual approaches will implement the protocol, following the intervention manual. The facilitator will be provided with peer supervision during the implementation of the intervention.

An overview of the intervention is provided in Table 1.

Table 1. - Intervention overview

Session	Module	Content and learning objectives
Session 1	Psychoeducation	• Introduction to the program: goals, overview and ground rules • Participants' presentation, motivations to participate, and expectations about the intervention • Identification of current difficulties in dealing with fatigue, prior coping attempts and their costs-benefits – creative hopelessness • Psychoeducation about RA and fatigue (e.g., 'drivers' and 'feeders' of fatigue) – the importance of healthy lifestyle habits (sleep hygiene, physical activity, stress, and pacing)
Session 2	Psychoeducation & mindfulness skills development	• Psychoeducation about the body-mind link, the function of the mind, and its patterns

		• Promoting mindfulness skills and body awareness • Introducing mindfulness in daily life: informal practice
Session 3	Mindfulness skills development	• Promoting mindfulness skills and body awareness • Cognitive defusion
Session 4	Promoting acceptance	• Suffering stems from control: passengers on the bus video • Making room for discomfort – development of acceptance skills
Session 5	Self-Compassion	• Introducing the concept of self-compassion and its flows • Bringing compassion to the body • Fostering a different form of self-self and self-other relating (compassion exercises)
Session 6	Self-Compassion & loving-kindness	• Cultivating compassion and kindness towards the self and towards others • Exploring new ways of communicating effectively
Session 7	Values & Committed Action	• Reconnect with what is truly important and meaningful in life (values work, identification of 'drainers' and 'energizers') • Values-based goal setting using the SMART framework • Step-by-step action planning • Identification of barriers and facilitators to committed action

		• Reinforce the importance of pacing
Session 8	Closing Session	• Review of the key concepts and take-home-messages. • Setbacks and strategies to deal with them • Feedback on the intervention and progress made attending to the initial expectations
Follow-up after 2 and 4 Months	Booster sessions	• Refreshment of the main concepts. Evaluate difficulties in the implementation/practice of learned skills. Revisit and consolidate mindfulness, acceptance and compassion exercises from the sessions.

Implementation

The intervention will be implemented by a certified clinical psychologist with experience in ACT, mindfulness, and compassion-based interventions to groups of 10 RA patients in 8x2 hour weekly sessions, followed by 2x2 hour zoom-booster-sessions after 4 and 12 weeks post-intervention.

The sessions will be held in private Zoom conferences, allowing the participants to interact and collaborate.

Each session will employ group dynamics, visual aids, comprehensive metaphors, complementary e-books, and experiential exercises. All sessions will follow the same general structure: they will start with a soft-landing exercise, followed by the discussion of the homework assignments (feedback, difficulties, comments, and conclusions), schooling and discussion of the session's theme and underlying concepts, practice of

experiential or group exercises, discussion, and a brief closing exercise. During the duration of the intervention programme, daily practices will be recommended as a fundamental component of the process and will be used to develop and consolidate previously discussed theoretical strategies and interventions.

The implementation and consolidation of addressed strategies in daily routines will be regularly encouraged and verified. Additionally, a logbook will be used for participants to register notes, summaries, homework, exercises, goalsetting and to promote consciously driven and goal-oriented behaviour. Supporting audio materials featuring guided exercises will be provided.

To be considered an 'intervention-receiver', each participant will be required to have attended, at least, the first session of the intervention. Participants attending a minimum of 6 sessions will be considered completers. Reasons for drop-out will be assessed and registered whenever possible.

Usual care

All participants will benefit from the usual standard care in accordance with current practice at participating centres, respecting international recommendations for the management of RA. Treatment as usual consists of regular appointments with the accompanying care team, mainly involving disease assessment, treatment adjustments, and life-style recommendations. The usual care may include, according to the caring physician's orientation, treatment of comorbid conditions as, for instance, depressive or insomnia-related symptoms with use of anti-depressive medication and benzodiazepines.

Assessments

All outcome measures will be registered online. The content and timing of assessment is similar to both intervention groups.

Sociodemographic information will be collected from the patients' files. Clinical examination, including joint counts, Physician's Global Assessment of disease activity and C-reactive protein levels will be performed at screening, time 0, and after 20 and 44 weeks.

At time 0 (baseline), 8 weeks (post-intervention, 12 weeks (before the 1st booster session), 20 weeks (before the 2nd booster session) participants will complete an online assessment battery comprising a set of validated self-report measures – See Table 2. This assessment will be repeated at 32 and 44 weeks to evaluate the persistence of effects.

Table 2.

Schedule of enrolment, intervention, and assessments

	Study period							
	Enrolment	Allocation	Post-Allocation					
Timepoint	-t2	-t1	t0	t1	t2	t3	t4	t5
(Weeks)			(baseline)	(8 weeks)	(12 weeks)	(20 weeks)	(32 weeks)	(44 weeks)
Enrolment								
Informed consent	X							
Eligibility screen	X							
Randomization	X							
Allocation		X						

Interventions							
CoMIRA+TAU *		◆———	u	u			
TAU		◆———				———◆	
Assessments							
1ry outcome							
RAID-fatigue	X	X	X	X	X	X	X
2ry outcomes							
DAS28CRP3v	X	X			X		X
PGA	X						
RAID	X	X	X	X	X	X	X
PESS	X	X	X	X	X	X	X
HADS		X	X	X	X	X	X
SCS-sv		X	X	X	X	X	X
CAMS-R		X	X	X	X	X	X
Feasibility and acceptability *	X		X		X		X
Safety (adverse effects)		◆———				X	X

Note. *only for the experimental (active) condition. Booster sessions at 1 and 3-months follow-up are considered as part of the intervention; T0 = baseline; T1 =post- intervention; T2 = Before 1st booster session (u); T3 = before 2nd booster session (u); T4 = 12 weeks follow-up; T5 = 24 weeks follow-up.CoMIRA: Compassion and Mindfulness Intervention for Rheumatoid Arthritis, TAU: Treatment-as-usual, RAID: Rheumatoid Arthritis Impact of Disease, DAS28CRP3v: Disease Activity Score using 28 joints and C reactive protein and three variables, PGA: Patient Global Assessment of disease activity, PESS: Patient Experienced Symptom State, HADS - Hospital Anxiety Depression Scale, SCS-sv: Self-Compassion Scale, CAMS-R: Cognitive and Affective Mindfulness Scale-revised

Outcome Measures

Primary Outcome

- *Fatigue*

Fatigue levels will be assessed by the 0-10 numerical rating scale assessing fatigue as part of the RAID,[49] described below.

Secondary Outcomes

- *Satisfaction with disease status* ***- PESS***

The Patient Experienced Symptom State (PESS)[51], evaluates the degree of satisfaction of the patients with the status of RA during the last week, through a single item rated on a 5-level Likert scale response ('very bad', 'bad', 'acceptable', 'good' and 'very good').

- *Perceived impact of disease* ***- RAID & RAID.7***

The RAID is a 7-item patient-derived measure designed to evaluate the perceived impact of RA upon important health-related domains, namely pain, functional disability, fatigue, sleep, physical well-being, emotional well-being, and coping. The items are rated using 11-points numeric rating scales. Domains can be combined into a single score (RAID)[59] or used separately (RAID.7)[49]. Higher scores indicate greater impact of disease.

- *Anxiety and depression* ***- HADS***

Levels of emotional distress will be measured through the Hospital Anxiety Depression Scale.[52,60] This scale comprises 14 items, rated on a 4-point Likert scale, aimed at screening for the presence and severity of anxiety and depressive symptoms in the last 7 days. Higher values are indicative of more severe levels of symptoms, with a cut-off score of 11 being indicative of a probable diagnosis of depressive major episode.

- *Self-compassion -* ***SCS-sv***

Self-compassion will be assessed by the Self-Compassion Scale.[61,62] This 12-item measure is a shorter form of the original scale developed by Neff [63] and aims to assess the type of relationship one establishes with oneself in the face of setbacks or difficult

times. Items are rated on a 5-point Likert scale, with greater values indicating greater levels of self-compassion. While several factorial solutions have been proposed, in this study we will use a two-factor structure, comprising the self-compassionate attitude subscale and the self-critical attitude subscale.

- *Mindfulness – **CAMS-R***

The Cognitive and Affective Mindfulness Scale-revised (CAMS-R)[64,65] consists of a 9-items scale, rated on a 4-point Likert scale, designed to assess dispositional mindfulness in a simple and accessible way. This scale yields a unidimensional structure, with higher values reflecting greater mindfulness qualities.

- *Safety*

Safety-related outcomes will be evaluated through participants' reporting of adverse events and will include information regarding the nature/type of adverse event, duration and frequency of the event, and degree of association with the intervention ("no", "probably", "possibly", "yes").

- *Patient Global Assessment of disease activity – PGA.*

In our study, the PGA will not be used as an outcome measure, but as a tool used to define eligibility. PGA is one of the most widely used patient-reported outcomes in RA and is found in several scores, such as the 28-joint Disease Activity Score (DAS-28). The PGA is a holistic assessment of disease that goes beyond the objective measures of inflammation (acute phase reactants) and/or structural damage (radiographic).[66] Higher scores represent higher level of disease activity or a worse global health, since the proposed definition of "low global assessment" is ≤2.0 on a 0 to 10 scale.[67]

- *Feasibility and acceptability*

Feasibility will not be formally assessed in this study as they seem well established in the literature regarding similar interventions in similar conditions, namely the online delivery.[45,58] However, all aspects related to these dimensions will be proactively assessed and registered, namely through rates of attendance and drop-out and the respective underlying reasons. Aspects related to the implementation of such a program in the context of a rheumatology department will be especially scrutinized.

Analysis Plan

Descriptive analysis and test differences will be used to compare baseline demographics and participants' characteristics as well as variables of interest, such as participant's dropout-rates, reasons for dropout, and the presence/absence and severity of negative effects.

An intention-to-treat analysis will be conducted whenever possible and complemented with per-protocol analysis if needed. Missing data analysis will be performed for determining the presence and level of randomness of missing data. Multiple imputation will be used do handle the missing data. [68]

Preliminary analyses will be conducted to guarantee that the necessary assumptions for the following tests are met. Analysis of covariance (ANCOVA) will be used to assess between-group differences in fatigue scores (the primary outcome) at 3-month follow-up after the second booster session (32nd week), controlling for baseline values. The same analytic procedure will be used to examine between-group differences in perceived disease activity, depression, mindfulness, and self-compassion (secondary outcomes) at the 32nd week. All effect sizes will be reported.

Additionally, Time*Group interaction effects on fatigue levels, perceived disease activity, depression, mindfulness, and self-compassion scores across the different timepoints will be tested via repeated measures analysis of variance (ANOVA), within-between interaction (with Bonferroni correction).

Potential predictors of treatment response (e.g., sociodemographic factors, baseline levels of fatigue, disease impact, depression, and anxiety) will be explored through regression analyses.

Discussion

By combining components of contextual CBT interventions, we have designed a new psychosocial intervention aiming at the management of fatigue in RA patients. Fatigue is recognized as a frequent and important manifestation of RA which is typically very difficult to manage in practice.

Although classical CBT interventions have been found to be useful in the past, effect sizes are relatively small and considered unsatisfactory.[28,29,58,69–71]

Contextual CBT interventions hold considerable promise to address these unmet needs, but they haven't yet been fully tested or implemented in routine clinical care settings where specialized psychotherapists are rarely available.

The interventions' core comprises practices of mindfulness, acceptance, and compassion-focused therapy, designed to promote relevant changes in the bidirectional interplay between physical and psychological experiences endured by patients with RA. The key strength of the intervention is found in the emerging validity of CCBT interventions in diseases where body and mind are both potentially and interactively affected.[39,48,72,73] We therefore focused on biopsychosocial interventions, involving the creation of 'support-groups' brought together in online-sessions, considering all 3 domains impacted by disease. Benefits of group interactions in therapeutic settings are known to be a powerful component in interventions focused on coping, chronic pain, mood, and disability.[74] They also are cost-effective in nature.[75] The online intervention model is considered particularly beneficial in the current pandemic context of COVID-19, as social restrictions are still being imposed and have augmented the usage of online health services.[36]

Fatigue is elected as our primary objective but other relevant related domains, including impact of disease, depression, and anxiety, will also be addressed and, hopefully, improved.

The repeated assessment of outcome measures at different moments of the intervention will allow us to evaluate the importance of the booster sessions and the persistence of the effects up to 6 months after the end of the intervention.

Some limitations should be considered regarding online interventions, as they imply the risk of selection bias, as only participants with internet access and minimal technological aptitudes will be able to participate. Also, the patient's perception of an online intervention regarding the quality of the therapeutic relationship might be questionable, a concern frequently shared by therapists.[76] In further editions, a more inclusive approach might be employed. These factors emerge in addition with those typically recognized in all psychotherapy interventions, namely their dependence on non-specific factors and on patient's features, motivation, and adherence.[77]

Also, the age limitation of 65 years is limitative in nature, but necessary in our social setting, as older ages are associated with a high prevalence of technological and health illiteracy.

The sample size will impose the need for a multicentre study, which will add to logistical demands and background noise but also bring the benefits of diversity in management approaches.

Results obtained will be disseminated on a national and international level in the form of conference presentations and a report will be submitted to a peer-reviewed journal.

Conclusions

The CoMIRA is a tailored intervention merging contextual-cognitive behavioural components aimed at improving fatigue, depression, anxiety, impact of disease and self-regulation processes (self-compassion and mindfulness) in RA.

If positive, our findings will support the integration of the principles of the CoMIRA in clinical practices in a diversity of clinical settings, and significantly reinforce the adjuvant armamentarium available to reduce the impact of disease, even beyond remission in rheumatoid arthritis.

Declarations

Ethics

This protocol has been approved by the Ethics Committee at Centro Hospitalar e Universitário de Coimbra (Nr. UIS.CEC.OBS.SF.01/2021)

Participants will receive detailed information about the intervention protocol, and written consent will be obtained prior to any study procedures. Participation is voluntary and patients are free to withdraw and decline to continue participating at any given moment. We do not anticipate any adverse events or risk for the participants. Nevertheless, any form of unfavourable event will be reported and evaluated. Following ethical requirements, participants assigned to the control condition will be given the opportunity to receive the newly developed intervention afterwards.

Availability of data and materials

All data collected in the context of this study will be made available to external researchers upon reasonable request for cooperative investigation.

Funding

The design of the study had no external funding.

Authors' contributions

JAPS, AMP and RF produced the original concept and refinement of this study. AMP was especially involved in the design of the psychological intervention and statistical analysis. RS closely accompanied all phases of this work in cooperation with each of the other authors. He was especially involved in designing the intervention and was responsible for writing the manuscript and coordinating the rounds of consensus. All authors revised, refined, and accepted the final version of this paper.

Competing interest statement

The authors declare no conflicts of interest.

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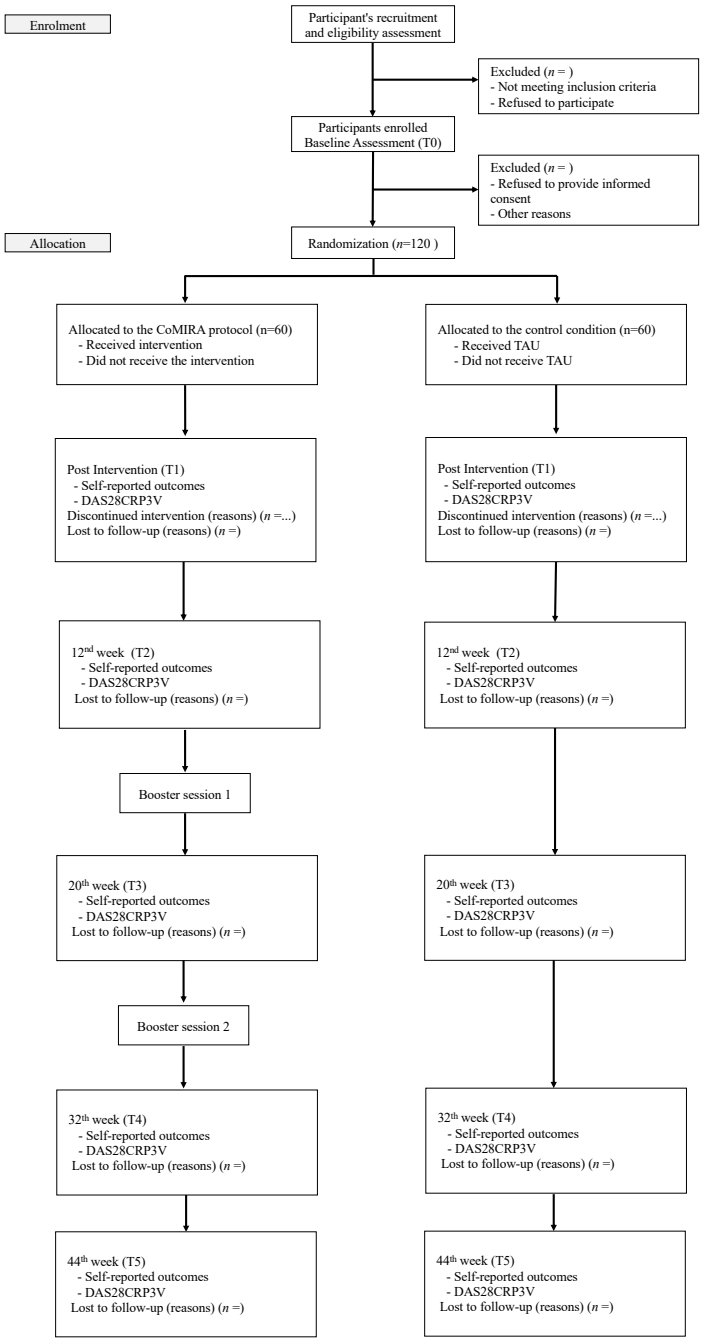
Appendix 1


Enrolment
Participant's recruitment and eligibility assessment
Excluded (n =)
- Not meeting inclusion criteria
- Refused to participate
Participants enrolled Baseline Assessment (T0)
Excluded (n =)
- Refused to provide informed consent
- Other reasons
Allocation
Randomization (n=120)
Allocated to the CoMIRA protocol (n=60)
- Received intervention
- Did not receive the intervention
Allocated to the control condition (n=60)
- Received TAU
- Did not receive TAU
Post Intervention (T1)
- Self-reported outcomes
- DAS28CRP3V
Discontinued intervention (reasons) (n =...)
Lost to follow-up (reasons) (n =)
Post Intervention (T1)
- Self-reported outcomes
- DAS28CRP3V
Discontinued intervention (reasons) (n =...)
Lost to follow-up (reasons) (n =)
12nd week (T2)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)
12nd week (T2)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)
Booster session 1
20th week (T3)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)
20th week (T3)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)
Booster session 2
32th week (T4)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)
32th week (T4)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)
44th week (T5)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)
44th week (T5)
- Self-reported outcomes
- DAS28CRP3V
Lost to follow-up (reasons) (n =)