The usefulness of an educational and goal-setting mobile app for improving self-efficacy and lifestyle factors in patients with rheumatoid arthritis.

PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL (NO IMP)

NCT05888181

Protocol Acronym/short title: AEGORA: App-based Education and Goal-setting in Rheumatoid Arthritis.

Version and date of final protocol: v6.3 (03-11-2022)

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Confidentiality Statement

The information in this document is strictly confidential and is available for review to Investigators, potential Investigators and appropriate Ethics Committees, Institutional Review Boards or Competent Authorities. No disclosure should take place without written authorization from the Sponsor.

LIST OF PARTICIPATING SITES

(as applicable)

List of Participating Sites	Principal Investigators
UZ Leuven	Prof. Dr. Patrick Verschueren
	Dr. Michaël Doumen
	Dr. Cedric Lefevre
AZ Sint-Lucas Brugge	Dr. Mieke Devinck

SIGNATURES

<u>Protocol title</u>: The usefulness of an educational and goal-setting mobile app for improving self-efficacy and lifestyle factors in patients with rheumatoid arthritis.

The undersigned confirm that the above referenced protocol has been acknowledged and accepted, and agree to conduct the Trial in compliance with the approved protocol, and will adhere to: the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in Directive 2001/20/EC and any subsequent amendments thereto, the ICH guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 related to clinical trials on medicinal products for human use (as soon as in effect), the EU General Data Protection Regulation 2016/679 (GDPR), relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

The undersigned agree not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the Trial, without prior written consent of the Sponsor.

The undersigned also commit to making the findings of the Trial publicly available through publication and/or other dissemination tools, in accordance with this protocol and applicable regulations, without any unnecessary delay and to provide an honest, accurate and transparent account of the Trial; and to explain any discrepancies or deviations from the approved Trial protocol.

Coordinating Investigator

……	……	……
Prof Dr Patrick Verschueren	Signature	Date

Principal Investigator (Participating Site) *(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)*

……	……	……
……	……	……
Name & Title	Signature	Date

LIST OF ABBREVIATIONS

Abbreviation	Definition
PI	Principal Investigator (Participating Site)
CI	Coordinating Investigator (Participating Site)
EC	Ethics Committee
ICH	International Conference on Harmonisation
GCP	Good Clinical Practice (latest version of ICH E6)
PRO	Patient-Reported Outcome
RAID	Rheumatoid Arthritis Impact of Disease
PCS	Pain Catastrophizing Scale
IPAQ-S	International Physical Activity Questionnaire short form
PSQI	Pittsburgh Sleep Quality Index
DAS28-CRP	Disease Activity Score with 28 joints, using C-reactive protein
SDAI	Simple Disease Activity Index
RA	Rheumatoid Arthritis
T2T	Treat to target
DMARD	Disease-modifying antirheumatic drug
EULAR	European League Against Rheumatism
WHO	World Health Organization
(e)CRF	(electronic) Case Report Form
AE	Adverse Event
GDPR	General Data Protection Regulation
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
REDCap	Research Electronic Data Capture
ITT	Intention-to-treat
PP	Per-protocol

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1. Funding and Support

Funder	Type of Financial or Non-Financial Support
Fonds Wetenschappelijk Onderzoek (FWO)	Co-investigator Michaël Doumen has received a Strategic Basic Research grant (grant number 1S85521N) from FWO. Funds from this grant will be used in part to support this trial.

Support in Kind

A total of 250 licenses for the unrestricted use of the mobile application Sidekick Health (Iceland) will be provided by Pfizer to the research team, to distribute among study participants. These licenses are being made available free of charge, and Pfizer's company name or logo will not be represented in any shape or form on information leaflets, study materials or in the interface of the Sidekick Health application. Sidekick Health will also make the in-app user data available, considering current GDPR rules, only for scientific purposes, without commercial purposes of any kind.

Role of study sponsor

University Hospitals Leuven, shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. University Hospitals Leuven shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Subjects or the Regulatory Authorities as sponsor of the Study.

Roles and responsibilities

The Principal Investigator (PI) is responsible for the conduct of the Trial at his/her Participating Site, and for protecting the rights, safety, and well-being of the Trial participants. As such the PI must ensure adequate supervision of the Trial conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI will ensure that adequate training is provided and documented for all Trial staff, prior to conducting assigned Trial-related activities.

It is the Coordinating investigator's (CI's) responsibility to supervise the general conduct (e.g. Trial progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Trial notification(s) and results reporting…) of the Trial. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) E6(R2) and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

2. Study Synopsis

Title of clinical trial	**The usefulness of an educational and goal-setting mobile app for improving self-efficacy and lifestyle factors in patients with rheumatoid arthritis.**
Protocol Short Title/Acronym	AEGORA: App-based Education and Goal-setting in Rheumatoid Arthritis.
Sponsor name	University Hospitals Leuven
Coordinating Investigator	Prof. Dr. Patrick Verschueren
Medical condition or disease under investigation	Rheumatoid arthritis (RA)
Purpose of clinical trial	To study the usefulness of a mobile application, developed through principles of goal-setting and gamification, to remotely monitor patient-reported outcomes (PROs) and deliver disease-specific patient education and lifestyle advice. Specifically, we aim to study the effects of this app-based intervention on self-efficacy, pain catastrophizing, physical activity, and sleep quality in patients with RA. To test the usefulness of monitoring PROs, participants in the intervention group will be asked to complete the Rheumatoid Arthritis Impact of Disease (RAID) questionnaire electronically in the app, either on a weekly or a monthly basis.
Primary objective	To investigate whether disease-specific patient education, promotion of a healthy lifestyle and remote PRO-monitoring, delivered through a mobile application based on principles of goal-setting and gamification, can improve self-efficacy in patients with RA. Self-efficacy will be assessed with the Arthritis Self-Efficacy Scale (ASES).
Secondary and exploratory objective (s)	**Secondary objectives** - To study if this app-based intervention affects pain catastrophizing (either positively or negatively), assessed with the Pain Catastrophizing Scale (PCS). Pain

	catastrophizing can be defined as an overly negative cognitive-affective orientation toward pain. **Exploratory objectives** - To study if the intervention's effects on self-efficacy and pain catastrophizing are affected by the interval at which participants are asked to report PROs (the RAID questionnaire either once per week or once per month). - To study if this app-based intervention leads to changes in physical activity or sleep quality, assessed with the International Physical Activity Questionnaire short form (IPAQ-S) and Pittsburgh Sleep Quality Index (PSQI), respectively. - To study the feasibility of delivering this intervention through a mobile application, by assessing participants' engagement with the app through the proportion of completed RAID-questionnaires and user-behavior statistics, including the proportion of days with logged activities in the app. No incentives for app-use will be provided, except those needed in the trial as built-in in the app (standard push-messages of the app), in order to provide a representative picture of participants' intrinsic and continued motivation. - To identify baseline predictors of the intervention's effect on ASES, PCS, IPAQ-S and PSQI scores. - To describe the evolution over time of scores on the RAID-questionnaire completed in the app, and its association with self-efficacy, physical activity, sleep quality, and disease activity assessed at the study visit. - To describe the evolution of the data that were actively logged by participants relating to their diet, physical activity, stress (such as minutes spent completing relaxation exercises in the application), and sleep, and study their association with (changes in) disease activity, the RAID, ASES, IPAQ-S, and PSQI.

Study population	Patients diagnosed with rheumatoid arthritis aged 18 years or older, with a disease duration of 16 weeks or more, no exclusions based on sex or therapy. Patients will be randomized (1:1) to one of the following groups: - Control group: standard of care (including referral to allied health professionals for additional education/non-pharmacological support as needed), educational leaflet, completion of the RAID questionnaire at baseline and last study visit. No access to the Sidekick Health app, and no completion of the RAID questionnaire in between study visits. - Intervention group: standard of care (including referral to allied health professionals for additional education/non-pharmacological support as needed), educational leaflet and access to the Sidekick Health app, including completion of the RAID questionnaire via the app in between study visits. Participants who are randomized to the intervention group will be re-randomized in a 1:1-ratio to one of the following arms: - Intervention arm A: intervention with the Sidekick Health app as described above, and participants will be asked to complete a RAID questionnaire in-app once a week. - Intervention arm B: intervention with the Sidekick Health app as described above, and participants will be asked to complete a RAID questionnaire in-app once a month.
Trial Design	Investigator-initiated, open-label, parallel-group, multicenter randomized controlled trial (without IMP).
Endpoints	**Primary endpoint** Difference in mean change of total ASES (Arthritis Self-Efficacy Scale) score from baseline to week 16 ± 2w in the

	intervention group when compared to the control group. The ASES is a patient-reported questionnaire consisting of 20 items to measure one's arthritis-specific self-efficacy across 2 subscales: self-efficacy for managing pain (PSE, range 5-50), and self-efficacy for controlling other symptoms (OSE, range 6-60). Both scores can be summed to derive a total ASES-score (range 11-110). **Secondary endpoints** - Difference in mean change of total PCS (Pain Catastrophizing Scale) score from baseline to week 16 ± 2w in the intervention group when compared to the control group. The PCS is a patient-reported questionnaire with 13 items scored on a 0-4 Likert scale, resulting in a total score of 0-52 with sub scores for rumination, magnification, and helplessness. Higher scores indicate more catastrophic perceptions concerning pain. **Exploratory endpoints** - Difference in mean change of total ASES score from baseline to week 16 ± 2w in the intervention arm with weekly RAID questionnaires when compared to the intervention arm with monthly RAID questionnaires. - Difference in mean change of total PCS score from baseline to week 16 ± 2w in the intervention arm with weekly RAID questionnaires when compared to the intervention arm with monthly RAID questionnaires. - Difference in mean change of total IPAQ-S score from baseline to week 16 ± 2w in the intervention group when compared to the control group. The IPAQ short form is a 7-item questionnaire enquiring about physical activities during the last 7 days. A specific activity score is obtained for different domains, each being multiplied with the accompanying mean metabolic equivalent (MET) value. This leads to a total score corresponding with low, moderate, or high physical activity. - Difference in mean change of total PSQI score from

	baseline to week 16 ± 2w in the intervention group when compared to the control group. The PSQI is a patient-reported questionnaire developed to measure sleep quality through 19 items across 7 domains. The resulting total score ranges from 0-21, with scores of 5 or higher being defined as poor sleep quality. - To describe participants' continued engagement with the app and to compare it between the weekly and monthly PRO subgroups. Engagement will be defined as: * The proportion of RAID questionnaires with at least one completed item in the Sidekick app, compared to the total number of RAID questionnaires prompted by the app for each participant during the study period. * User-behavior statistics: Sidekick Health will provide pseudonymized logged data from the app. This includes "passive" usage information such as the number of times participants logged into the app or the number of goals that were set, as well as data that were actively logged by participants relating to their physical activity, diet, stress (such as minutes spent completing relaxation exercises in the application), and sleep. - Baseline predictors of the intervention's effect on ASES, PCS, IPAQ-S and PSQI scores: candidate predictors include demographic characteristics, disease-related characteristics (autoantibody status, current and previous therapy, disease duration, …), and measures of participant engagement (as previously defined). - The evolution and fluctuation over time of scores on the RAID-questionnaire completed in the app, and its association with self-efficacy, physical activity, sleep quality, and disease activity assessed at the study visit. The RAID is a patient-reported questionnaire with 7 items scored on a 0-10 numeric rating scale, enquiring about the impact of RA on different aspects of physical and mental health. Disease activity will be assessed as in usual care, with composite scores such as the DAS28-CRP and SDAI (both are composed of the number of tender

	joints and swollen joints, patient's global assessment of disease activity on a visual analogue scale VAS, and C-reactive protein CRP; the SDAI additionally includes the physician's global assessment of disease activity). - The association of data actively logged in the app (step counts, exercise activities, diet, sleep quality, stress level, and energy level) with the validated outcome measures RAID, IPAQ-S, PSQI, ASES, and DAS28-CRP.
Sample Size	See page 27-28 for more detailed calculations. N = 120. For the primary outcome, sample size calculation was based on the minimal clinically important difference in the ASES-score, and on data from a recently published, large prospective study from our research group. Following these assumptions, 60 participants are needed in each group to detect a clinically meaningful change in ASES scores with 80% power and a significance level of 0.05, after adjusting for a 10% dropout rate and the possible need for non-parametric tests. An additional sample size calculation was made for the secondary outcome of change in PCS score from baseline between the control and intervention group, using the proposed minimal clinically important difference in the PCS score, with pooled data from the PCS development/validation studies and a French cohort of patients with RA to estimate the population distribution. Aiming to exclude any (negative) effect of the intervention on change in the PCS score, we chose a non-inferiority design for this outcome. Given that the effect of the intervention on the PCS score is unknown, we chose the aforementioned minimal clinically important difference as the non-inferiority margin. Following these assumptions and allowing for a 10% dropout rate, a total of 82 participants need to be included (41 in both the control and intervention groups) to demonstrate a non-inferior effect of the intervention on the PCS score with 80%

	power, a minimal clinically important margin and a two-sided significance level of 0.025. When 120 patients are included as per the primary outcome, and assuming a 10% drop-out rate, we should have 90.2% power to demonstrate non-inferiority for this secondary outcome. In summary, a total of 120 patients will need to be included to assess both the primary outcome of self-efficacy and the secondary outcome of pain catastrophizing with at least 80% power, with 60 participants in both the control group and the intervention group.
Summary of eligibility criteria	Consecutive participants will be assessed for eligibility at the rheumatology outpatient clinic of both participating centers. Patients enrolled in the study must meet all of the following inclusion criteria: 1. Are aged 18 years or older. 2. Have a diagnosis of RA made by a rheumatologist, with a minimal disease duration of 16 weeks or more. 3. Be able and willing to give written informed consent. 4. Are able to understand and write Dutch. 5. Have access to a smartphone with an Android (Requires Android 7.0 or later) or Apple iOS (Requires iOS 13.0 or later) operating system.
Maximum duration of intervention	16 weeks with a window of 2 weeks.
Version and date of final protocol	v6.3 (03-11-2022)
Version and date of protocol amendments	Listed at page 39, 40, 41, 42.

3. Background and rationale

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis worldwide, with an estimated prevalence of approximately 0.5-1% (1). The condition usually presents with a symmetrically distributed pain, swelling and/or redness of the small joints, such as those of the hands and feet, and significantly impacts patients' quality of life, physical functioning, and work participation (2). In recent years, shifts to a more intensive and targeted treatment paradigm, the so-called treat-to-target (T2T) strategy, along with the development of numerous novel disease-modifying antirheumatic drugs (DMARDs) have considerably improved outcomes for most patients with RA (3). Nevertheless, both international research and recent work from our research group have shown that many patients still report unmet needs despite successful treatment, such as ongoing symptoms of pain and fatigue, or suboptimal psychosocial wellbeing (4–6). Moreover, many patients with RA are confronted with comorbidities that further complicate the management of their disease (7,8).

Consequently, it is becoming increasingly clear that an adequate management of RA is only possible when pharmacological treatment is embedded within a biopsychosocial approach that additionally includes attention for aspects of the disease burden that are best addressed non-pharmacologically, for instance with lifestyle measures (9). In this regard, a crucial aspect of care is empowering patients to gain a better understanding of their disease and to assume a more active role in its management, which in turn promotes shared decision-making. An important contributor towards such self-management behavior is self-efficacy, which can be defined as patients' confidence in their ability to control disease and its consequences, and which has been shown to positively affect various aspects of living with RA (10,11). Consequently, self-efficacy was recently put forward by the European League Against Rheumatism (EULAR) as both an important facilitator and an outcome of self-management strategies for inflammatory arthritis, and several intervention studies have already shown that this is not a static personality trait but can be improved with personalised patient education and psychological support (12–14).

In addition to proposing self-efficacy as an outcome, the EULAR-taskforce also defined several recommendations for the content of self-management interventions, including patient education and lifestyle measures (12). Assuming a healthier lifestyle is not only relevant for the management of RA, but also to prevent cardiovascular events, which are known to be more prevalent in patients with RA than in the general population (15). Therefore, promoting a healthier lifestyle is crucial to improving outcomes of patients with RA and represents an often-underrecognized strategy. For instance, although being physically active is known to reduce the risk of cardiovascular events, ample research has shown that most patients with rheumatic diseases do not meet the level of physical activity recommended by the World Health Organisation (WHO) and EULAR (16,17). In addition, patients' nutritional habits are rarely assessed in clinical practice, despite a recent systematic review suggesting that some dietary approaches may improve RA symptoms (18). Finally, sleep has been identified as a key contributor to patients' wellbeing, suggesting that interventions to improve sleep quality could be an added value in RA management (19,20).

One way to deliver self-management interventions that is growing in popularity is by using mobile health (mHealth) applications, for instance employing goal-setting strategies and motivational principles such as gamification (21,22). Recent advances in the availability of mobile apps and smartphones could present an opportunity to provide patients with more personalised education and tools to guide and promote disease self-management in their everyday environment (23). However, concerns are often raised about the feasibility of using mobile apps to deliver educational or lifestyle-

promoting interventions, with large variations in patient compliance and attrition rates being reported in previous studies (24). Moreover, it remains somewhat unclear whether such app-based interventions can effectively promote self-efficacy and a healthier lifestyle or might have a negative effect by potentially inducing chronic disease behavior and increasing pain catastrophizing tendency. This study aims to mitigate these challenges.

4. Trial objectives and Design

4.1 Trial objectives

Primary objective

To investigate whether disease-specific patient education, promotion of a healthy lifestyle and remote PRO-monitoring, delivered through a mobile application based on principles of goal-setting and gamification, can improve self-efficacy in patients with RA. Self-efficacy will be assessed with the Arthritis Self-Efficacy Scale (ASES).

Secondary objectives

- To study if this app-based intervention affects pain catastrophizing (either positively or negatively), assessed with the Pain Catastrophizing Scale (PCS). Pain catastrophizing can be defined as an overly negative cognitive-affective orientation toward pain.

Exploratory objectives

- To study if the intervention's effects on self-efficacy and pain catastrophizing are affected by the interval at which participants are asked to report PROs (the RAID questionnaire either once per week or once per month).

- To study if this app-based intervention leads to changes in physical activity or sleep quality, assessed with the International Physical Activity Questionnaire short form (IPAQ-S) and Pittsburgh Sleep Quality Index (PSQI), respectively.

- To study the feasibility of delivering this intervention through a mobile application, by assessing participants' engagement with the app through the proportion of completed RAID-questionnaires and user-behavior statistics, including the proportion of days with logged activities in the app. No incentives for app-use will be provided, except those needed in the trial as built-in in the app (standard push-messages of the app), in order to provide a representative picture of participants' intrinsic and continued motivation.

- To identify baseline predictors of the intervention's effect on ASES, PCS, IPAQ-S and PSQI scores.

- To describe the evolution over time of scores on the RAID-questionnaire completed in the app, and its association with (changes in) self-efficacy, physical activity, sleep quality, and disease activity assessed at the study visits.

- To describe the evolution of the data that were actively logged by participants relating to their diet, physical activity, stress (such as minutes spent completing relaxation exercises in the application), and sleep, and study their association with disease activity, the RAID, ASES, IPAQ-S, and PSQI.

4.2 Primary endpoints

Difference in mean change of total ASES (Arthritis Self-Efficacy Scale) score from baseline to week 16 ± 2w in the intervention group when compared to the control group. The ASES is a patient-reported questionnaire consisting of 20 items to measure one's arthritis-specific self-efficacy across 2 subscales: self-efficacy for managing pain (PSE, range 5-50), and self-efficacy for controlling other symptoms (OSE, range 6-60). Both scores can be summed to derive a total ASES-score (range 11-110).

4.3 Secondary endpoints

Difference in mean change of total PCS (Pain Catastrophizing Scale) score from baseline to week 16 ± 2w in the intervention group when compared to the control group. The PCS is a patient-reported questionnaire with 13 items scored on a 0-4 Likert scale, resulting in a total score of 0-52 with sub scores for rumination, magnification, and helplessness. Higher scores indicate more catastrophic perceptions concerning pain.

4.3b Exploratory endpoints

- Difference in mean change of total ASES score from baseline to week 16 ± 2w in the intervention arm with weekly RAID questionnaires when compared to the intervention arm with monthly RAID questionnaires.

- Difference in mean change of total PCS score from baseline to week 16 ± 2w in the intervention arm with weekly RAID questionnaires when compared to the intervention arm with monthly RAID questionnaires.

- Difference in mean change of total IPAQ-S score from baseline to week 16 ± 2w in the intervention group when compared to the control group. The IPAQ short form is a 7-item questionnaire enquiring about physical activities during the last 7 days. A specific activity score is obtained for different domains, each being multiplied with the accompanying mean metabolic equivalent (MET) value. This leads to a total score corresponding with low, moderate, or high physical activity.

- Difference in mean change of total PSQI score from baseline to week 16 ± 2w in the intervention group when compared to the control group. The PSQI is a patient-reported questionnaire developed to measure sleep quality through 19 items across 7 domains. The resulting total score ranges from 0-21, with scores of 5 or higher being defined as poor sleep quality.

- To describe participants' continued engagement with the app and to compare it between the weekly and monthly PRO subgroups. Engagement will be defined as:
* The proportion of RAID questionnaires with at least one completed item in the Sidekick app, compared to the total number of RAID questionnaires prompted by the app for each participant

during the study period.
* User-behavior statistics: Sidekick Health will provide pseudonymized logged data from the app. This includes “passive” usage information such as the number of times participants logged into the app or the number of goals that were set, as well as data that were actively logged by participants relating to their physical activity, diet, stress (such as minutes spent completing relaxation exercises in the application), and sleep.

- Baseline predictors of the intervention’s effect on ASES, PCS, IPAQ-S and PSQI scores: candidate predictors include demographic characteristics, disease-related characteristics (autoantibody status, current and previous therapy, disease duration, …), and measures of participant engagement (as previously defined).

- The evolution and fluctuation over time of scores on the RAID-questionnaire completed in the app, and its association with self-efficacy, physical activity, sleep quality, and disease activity assessed at the study visit. The RAID is a patient-reported questionnaire with 7 items scored on a 0-10 numeric rating scale, enquiring about the impact of RA on different aspects of physical and mental health. Disease activity will be assessed as in usual care, with composite scores such as the DAS28-CRP and SDAI (both are composed of the number of tender joints and swollen joints, patient’s global assessment of disease activity on a visual analogue scale VAS, and C-reactive protein CRP; the SDAI additionally includes the physician’s global assessment of disease activity).

- The association of data actively logged in the app (step counts, exercise activities, diet, sleep quality, stress level, and energy level) with the validated outcome measures RAID, IPAQ-S, PSQI, ASES, and DAS28-CRP.

4.4 Trial Design

This will be an investigator-initiated, prospective, open label, parallel group, multi-center, randomized controlled trial (RCT). Participants will be randomized in a 1:1-ratio, using stratified (local) randomization by study center (UZ Leuven or AZ Sint-Lucas Brugge), to either a control group or an intervention group (n = 120 participants in total, 60 in each group). The randomization schedule will be based on center-specific, computer-generated sequences programmed in Research Electronic Data Capture (REDCap), ensuring allocation concealment.
Following randomization, the intervention group will be re-randomized (via computer-generated simple randomization in REDCap) into two arms in a 1:1 ratio (n = 30 participants in each arm). Participants in intervention arm A will be asked to complete the RAID questionnaire once a week via the Sidekick app, compared to once a month in intervention arm B.

The control group will be followed according to usual care standards. This includes informal screening for psychosocial wellbeing and illness perceptions during outpatient clinic visits, with referral to specific allied health professionals for additional education or non-pharmacological support if needed. The scores derived from questionnaires that form part of the study design can be

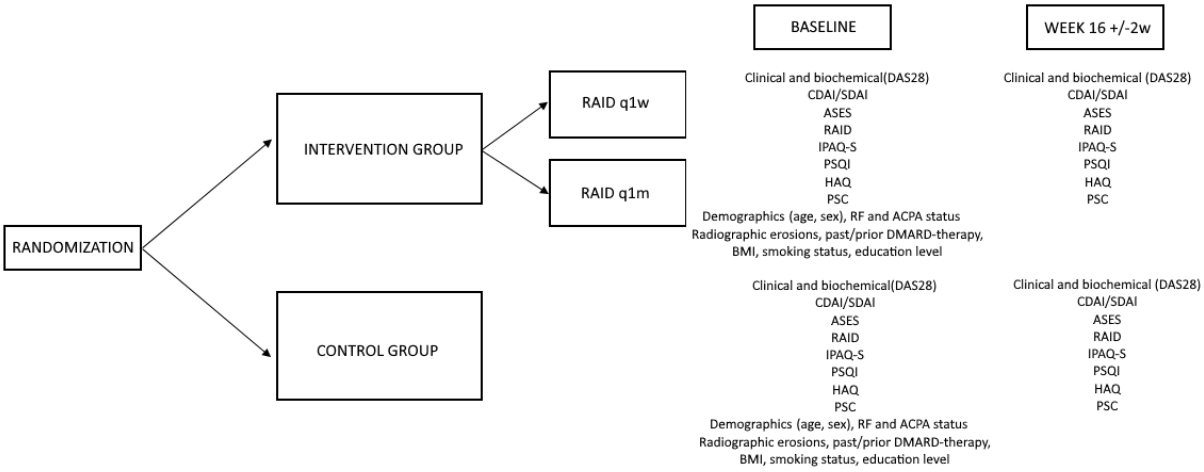
used as a guide for these discussions. As part of standard care, participants in both the control group and the intervention group will also receive a standardized educational leaflet about RA (attached as additional file), as is already available in the clinic and via the website of patient organization ReumaNet.

In addition to usual care, participants in the intervention group will receive unrestricted, free-of-charge and unincentivized access to the Sidekick Health application. The application was designed by the company Sidekick Health (Iceland) with the support of pharmaceutical company Pfizer for the adaptation of the app to the Belgian public, with a design centered particularly around promoting behavioral change and a strong focus on gamification techniques. It includes an educational module (Appendix A) that was specifically developed for patients with RA in collaboration with 10 rheumatologists. In addition, the app allows users to record nutritional diaries, subjective sleep quality and physical activity (manually or through wearable activity trackers or the smartphone's accelerometer), while also providing several physical and mindfulness-based exercises and the option to record PROs such as the RAID questionnaire. Reminders or alerts can be set up and customized by the users in the app itself, according to their personal preferences. These logs are stored in the application's designated data cloud, from which all identifiable data will be removed upon termination of the account at the end of the study (also see section on Data handling). The educational program on the app runs for a period of 16 weeks.

In all groups, an in-person visit will be scheduled at baseline and after 16 weeks, with a window of 2 weeks before and 2 weeks after this time point, taking place at the Rheumatology outpatient clinic of the participating centers. At the baseline and week 16 ± 2w visits and in all groups, we will collect routine clinical data, including clinical examination and readily available blood samples, DAS28-CRP/SDAI, and HAQ, as well as trial questionnaires in the form of the ASES, PCS, IPAQ-S, and PSQI (see 3.5 and 3.6). The following data will only be collected at baseline, also in all groups: RA phenotype (RF/ACPA/erosive), disease duration, past and current DMARD-therapy, comorbidities if present, educational level, and participants' demographic characteristics.

After the week 16 ±2w visit, the study ends, and all participants will be free to continue with the Sidekick-application at their leisure, by creating a personal account. As outlined in the section on Data Handling, the pseudonymized study account will be terminated at the end of the study, upon which all stored personal data will be removed from the application's data cloud. The aforementioned logged data and in-app data will be stored by Sidekick Health on a secure platform and provided in pseudonymized form as data for the study (also see section on Data handling), only identifiable through participants' study ID.

4.5 Study diagram



RAID = Rheumatoid Arthritis Impact of Disease ; q1w = once a week ; q1m = once a month ; DAS28 = Disease Activity Score 28 joints ; SDAI = Simple Disease Activity Index ; CDAI = Clinical Disease Activity Index ; ASES =: Arthritis Self-Efficacy Scale ; IPAQ-S = International Physical Activity Questionnaire short form ; PSQI = Pittsburgh Sleep Quality Index ; HAQ = Health Assessment Questionnaire ; RF = rheumatoid factor ; ACPA = anti-citrullinated peptide antibodies ; DMARD = disease-modifying antirheumatic drugs ; BMI = body mass index

4.6 Trial Flowchart

Procedures / Assessment	Screening and randomization	Intervention period	
Visits / Contacts	Visit 1 = Baseline	During intervention	Visit 2 = Evaluation of primary endpoint
Timing (weeks)	Week 0		Week 16 ± 2w
Informed consent	X		
Inclusion / Exclusion criteria	X		
Randomization	X		
Downloading Sidekick Health app	X		
Demographics (age, sex), RF and ACPA status, radiographic erosions, disease duration, past and current DMARD-therapy, prior DMARD-therapy, BMI, smoking status, education level	X		
Medical and Surgical history, comorbidities (if available in the patient file)	X		
Physical examination (including TJC28 and SJC28)	X		X

Patient's global assessment (VAS)	X		X
Physician's global assessment (VAS)	X		X
HAQ	X		X
Weight / Height / BMI	X		X
Blood sampling (CRP) as part of usual care (in clinic or through patient's general practitioner)	X		X
ASES	X		X
PCS	X		X
IPAQ-S	X		X
PSQI	X		X
RAID (both control- and intervention group)	X		X
RAID (via Sidekick Health app, only in intervention group): - Intervention arm A: weekly - Intervention arm B: monthly		X	
Collecting in-app logged data concerning physical activity, sleep, diet, stress management			X

RF = Rheumatoid Factor, ACPA = Anti-citrullinated peptide antibodies, DMARD = disease-modifying antirheumatic drug, BMI = body mass index, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, VAS = Visual Analogue Scale, HAQ = Health Assessment Questionnaire, CRP = C-reactive protein, ASES = Arthritis Self-Efficacy Scale, PCS = Pain Catastrophizing Scale, IPAQ-S = International Physical Activity Questionnaire short form, PSQI = Pittsburgh Sleep Quality Index, RAID = Rheumatoid Arthritis Impact of Disease

5. Selection and withdrawal of subjects

5.1 Inclusion criteria

Patients enrolled in the study must meet all of the following inclusion criteria:

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained prior to any screening procedures.
2. Are aged 18 years or older.
3. Have a diagnosis of RA, diagnosed by a rheumatologist, with a minimal disease duration of 16 weeks or more. This minimal disease duration was chosen based on conceptual reasons and previous work of our research group, suggesting that the dynamic and impactful first weeks after diagnosis are not the ideal time window to assess psychosocial outcomes (6).
4. Are able to understand and write Dutch.
5. Have access to a smartphone with an Android (requires Android 7.0 or later) or Apple iOS (requires iOS 13.0 or later) operating system.

All participants that are considered for Trial participation, per the above criteria will be documented on the Screening Log, including Screen Failures.

5.2 Exclusion criteria

Since the study intervention does not include an IMP, no strict exclusion criteria are defined other than the abovementioned inclusion criteria. However, participants will be excluded from analyses if they do not provide any questionnaire data at either of the two study visits, or, for the intervention group, if they fail to use the Sidekick Health application at least once (= dropouts).

5.3 Expected duration of trial

As stated above and illustrated in 3.5 and 3.6, the trial will end after the follow-up visit at week 16 with a window of 2 weeks before and after that timing, or if the participant requests to exit the study. The inclusion period will be covering Q3 an Q4 of 2022 (06/2022 – 12/2022) with last possible visit performed in Q1 of 2023 (end of 03/2023). Since this study does not involve an IMP, we do not expect any study-related adverse events to occur that might necessitate premature termination of the study.

6. Trial Procedures

6.1 By visit

Visit 1 (screening and baseline):

- Recruitment of eligible participants after informed consent at the Rheumatology outpatient clinic of the participating centers.

- Two-step randomization, as described above, into a control group and an intervention group (1:1), which will in turn be re-randomized in a 1:1 ratio into a weekly RAID arm and a monthly RAID arm.

- Downloading Sidekick Health app (intervention group only).

- Collection of demographic and disease-related characteristics for included patients: age, sex, RF and ACPA status, radiographic erosions, disease duration, current DMARD-therapy, prior DMARD-therapy, BMI, smoking status, education level.

- Collection of relevant medical and surgical history and comorbidities.

- Physical examination, including TJC28 and SJC28, measurement of weight and height.

- Patient’s and Physician’s global assessment (VAS).

- Participants in both the control and intervention groups will be asked to complete the following questionnaires considering self-efficacy (ASES), patient-reported outcomes (RAID), daily functioning (HAQ), pain catastrophizing (PCS), physical activity (IPAQ-S) and sleep quality (PSQI). Questionnaires will be completed in MyNexuzHealth (an online patient communication platform used by the University Hospitals Leuven Belgium) or, if not possible, in a pen-and-paper form at the outpatient clinic.

- Self-efficacy: The ASES is a patient-reported questionnaire (25) consisting of 20 items to measure one's arthritis-specific self-efficacy across 2 subscales: self-efficacy for managing pain (PSE, range 5-50), and self-efficacy for controlling other symptoms (OSE, range 6-60). Both scores can be summed to derive a total ASES-score (range 11-110).
- Patient-reported outcomes: The RAID questionnaire is a patient-derived differentially weighted 7-item tool assessing pain, functional disability, fatigue, sleep, coping, physical and emotional well-being.
- Daily functioning: The HAQ is a self-administered questionnaire, that assesses the ability in performing daily life activities and measures the functional impact of rheumatoid arthritis (26). The HAQ is routinely collected at the rheumatology outpatient clinic at University Hospitals Leuven.
- Pain catastrophizing: The PCS is a patient-reported questionnaire with 13 items scored on a 0-4 Likert scale, resulting in a total score of 0-52 with subscores for rumination, magnification, and helplessness (27). Higher scores indicate more catastrophic perceptions concerning pain.
- Physical activity: The IPAQ short form is a 7-item questionnaire enquiring about physical activities during the last 7 days (28). A specific activity score is obtained for different domains, each being multiplied with the accompanying mean metabolic equivalent (MET) value. This leads to a total score corresponding with low, moderate or high physical activity.
- Sleep quality: The PSQI is a patient-reported questionnaire developed to measure sleep quality through 19 items across 7 domains (29). The resulting total score ranges from 0-21, with scores of 5 or higher being defined as poor sleep quality.

- Disease activity will be monitored in both participant groups with the DAS28-CRP and SDAI scores, using internationally validated cut-offs. DAS28-CRP is a composite score that combines a patient's global assessment of disease activity, a clinical examination with counts of painful and swollen joints, and CRP as an inflammatory laboratory parameter (30). SDAI is an analogous composite score that additionally includes the physician's/evaluator's global assessment of disease activity and has its own validated cut-offs (31). These examinations are part of routine care.

- Results of both clinical data and the obtained questionnaires will be extracted from the electronic medical patient file used in UZ Leuven and other participating centers (KWS) or, if not possible, from the completed pen-and-paper forms.

Intervention phase (between baseline and week 16 ± 2w visit)

While using the SideKick Health app, patients in the intervention group will have the opportunity to actively log data relating to their diet, physical activity, sleep quality, stress (such as minutes spent completing relaxation exercises in the application), vital signs, and fill out short questionnaires, for example the RAID questionnaire, integrated in the application. Among these, only completion of the RAID questionnaire is actively stimulated and expected as part of the study, all other functions can be used on a voluntary basis.
As stated before, one arm of the intervention group will be asked to complete the RAID questionnaire on a weekly basis, the other one will do this on a monthly basis. During this phase of the study user behavior statistics will also be collected as described above (number of times the app was used, how often certain questions were answered, …).

Visit 2 (week 16 ± 2)

- Participants in both the control and intervention groups will be asked to again complete the previously outlined questionnaires considering self-efficacy (ASES), patient-reported outcomes (RAID), physical disability (HAQ), pain catastrophizing (PCS), physical activity (IPAQ-S), and sleep quality (PSQI). Questionnaires will be completed in MyNexuzHealth or in pen-and-paper form at the outpatient clinic if not available. In addition, disease activity will again be assessed as part of routine care by way of the DAS28-CRP and SDAI scores.

- The study will end after this visit. The participants will be free to continue with the Sidekick-application at their leisure, or alternatively, to terminate the account. Upon termination of the account, all stored personal data will be removed from the application's data cloud (also see section on Data handling).

6.2 Laboratory tests

Laboratory tests obtained for this study will be limited to those collected as part of routine care in hospital or by the patient's general practitioner, for instance the collection of CRP to calculate DAS28-CRP and SDAI scores. No additional laboratory tests will be conducted for the purposes of this study.

6.3 Other investigations

Other than any investigations required as part of routine care, no additional investigations will be carried out for this study.

7. Assessment of efficacy

Efficacy of this app-based educational, monitoring, and lifestyle intervention will be studied by assessing changes in self-efficacy (ASES), physical activity (IPAQ-S) and sleep quality (PSQI), while the intervention's effect on pain catastrophizing will be studied in a non-inferiority setting to exclude any

(negative) effects of systematic PRO-registration on pain perceptions. As stated in the sections on Trial Objectives and Design, the primary endpoint will be the difference in mean change of total ASES-score from baseline to week 16 ± 2w in the intervention group when compared to the control group, while the intervention's effect on pain catastrophizing was chosen as a secondary endpoint. Sample size calculations were based on obtaining 80% power for both the primary and the secondary endpoint, as outlined in section 9.

In addition to the information obtained from the questionnaires, we will also study participants' continued engagement with the app and its possible effects on intervention efficacy as an exploratory endpoint, as described above.

8. Assessment of Safety

8.1 Specification, timing and recording of safety parameters

Clinical examination will be conducted as prescribed in the normal procedures of standard of care. Results of blood samples to calculate the DAS28-CRP and SDAI scores, will only be used if already available, no extra blood samples will be taken for the study.

8.2 Procedures for recording and reporting adverse events (AE)

Since the study intervention does not include an IMP, recording and reporting of adverse events is not applicable for this study.

8.3 Treatment stopping rules

Not applicable for this study.

9. Statistics

9.1 Sample size

For the primary outcome, we opted for a superiority design aiming to reject the null hypothesis that there would be no difference between the intervention and control groups in the change of the total ASES-score from baseline to week 16. Sample size calculation was based on the previously proposed minimal clinically important difference in the ASES-score, corresponding with a change of 5.5 on either the pain or other symptoms subscale (13,25). Moreover, in a recently published, large prospective study from our research group, including 379 patients with RA, the mean (± SD) self-efficacy for pain (PSE) was 31.8 (± 8.9) and self-efficacy for other symptoms (OSE) was 42.6 (± 9.4) (32). Based on a minimal clinically important difference of 5.5 and population SD of 9.4, an effect size of approximately 0.59 was assumed. Additionally, based on previous research and outpatient clinic attendance experience, we expect dropout rate to be maximally 10% (13,24,33). Following these assumptions and in the setting of a superiority trial, 52 participants are needed in each group to detect a clinically meaningful difference in either PSE or OSE with 80% power and a significance level

of 0.05, while allowing for a 10% dropout rate.
It should be noted that the ASES score was not fully normally distributed in our aforementioned prospective study, implying that non-parametric tests might be needed to analyze the primary outcome. Following a general rule of thumb, sample size was thus increased by 15% to account for the loss of power these non-parametric tests would imply(34). Consequently, a total of 120 participants are needed (60 in each group) for the analysis of the primary outcome, with 80% power and a significance level of 0.05.

An additional sample size calculation was conducted for the secondary outcome of change in PCS score from baseline in the intervention group compared to the control group. Based on pooled data from the PCS development/validation studies and a French cohort of patients with RA, the population weighted mean (SD) PCS score is estimated at 20.3 (SD 12.3) (27,35,36). Thus, a clinically important difference in the PCS score, previously proposed as greater than 38% change (27,37), would correspond to a change in total PCS score of greater than 7.7/52. Aiming to exclude any (negative) effect of the intervention on change in the PCS score, we chose a non-inferiority design for this outcome. Given that the effect of the intervention on the PCS score is unknown, we chose the aforementioned minimal clinically important difference of 7.7 as the non-inferiority margin. In other words, non-inferiority will be confirmed if the upper bound of the 95% CI for the intervention's effect on PCS remains within a minimal clinically important margin(38). Following these assumptions and allowing for a 10% dropout rate, a total of 82 participants need to be included (41 in both the control and intervention groups) to demonstrate a non-inferior effect of the intervention on the PCS score with 80% power, a minimal clinically important margin and a two-sided significance level of 0.025. When 120 patients are included as per the primary outcome, and assuming a 10% drop-out rate, we should have 90.2% power to demonstrate non-inferiority for this secondary outcome.

Sample size calculations were conducted via R version 4.2.1, using the packages *pwr* and *epiR* (see Appendix B). In summary, a total of 120 patients will need to be included to assess both the primary outcome and the secondary outcome with at least 80% power, including 60 participants in both the control group and in the intervention group.

As described above, the intervention group will then again be randomized in a 1:1-ratio to assess the exploratory outcomes. The trial will thus not be powered for the exploratory analyses.

9.2 Analysis

Analyses will be carried out according to the intention-to-treat (ITT) principle, implying that participants will be analyzed based on the group they were originally assigned to.
In this study, the ITT population will consist specifically of all patients in the intervention group who effectively downloaded and installed the Sidekick application at the baseline visit, and all patients assigned to the control group. As stated above, participants in the intervention group will be re-randomized to intervention arm A or B, constituting two additional ITT populations that will only be analyzed exploratorily.

Per protocol (PP) analyses will be carried out as sensitivity analyses, including only those patients who completed the follow-up visit.

The variables described above in sections 4-6 will be extracted from the electronic medical patient file that is employed in all participating centers (KWS). Additionally, user behavior statistics and data actively logged by the patients in the app will be collected and provided for analysis in pseudonymized form by Sidekick Health. The primary and secondary outcome data of this study will be collected via questionnaires on the MyNexuzHealth app, or if not possible in pen-and-paper format at the outpatient clinic. All study-related information will be assembled and prepared for further analysis in an electronic CRF developed in REDCap. P-values <0.05 will be considered as statistically significant for all analyses. Missing data will be handled with multiple imputation by chained equations when data can be assumed to be missing at random. Descriptive statistics for baseline participant characteristics will be provided as means (± SD), medians (IQR) or proportions depending on data distribution.

Primary endpoint

The difference in mean change of total ASES (Arthritis Self-Efficacy Scale) score from baseline to week 16 ± 2w in the intervention group when compared to the control group will be evaluated with an unpaired t-test or Wilcoxon rank sum test depending on distribution of the ASES-score. As a sensitivity analysis, we will additionally assess the difference between groups in week 16 scores using ANOVA adjusted for the baseline score. Furthermore, differences in the pain and other symptoms subscales of the ASES will be presented separately.

Secondary endpoints

- The difference in mean change of total PCS score from baseline to week 16 ± 2w in the intervention group will be compared to that in the control group, using an unpaired t-test or Wilcoxon rank sum test depending on distribution of the PCS score. As a sensitivity analysis, we will additionally assess the difference between groups in week 16 scores using ANOVA adjusted for the baseline score.

Exploratory endpoints

- The difference in mean change of total ASES score from baseline to week 16 ± 2w in the intervention arm with weekly RAID questionnaires will be compared to that in the intervention arm with monthly RAID questionnaires, using an unpaired t-test or Wilcoxon rank sum test depending on distribution of the ASES-score. As a sensitivity analysis, we will additionally assess the difference between groups in week 16 scores using ANOVA adjusted for the baseline score.

- The difference in mean change of total PCS score from baseline to week 16 ± 2w in the intervention arm with weekly RAID questionnaires will be compared to that in the intervention arm with monthly RAID questionnaires, using an unpaired t-test or Wilcoxon rank sum test depending on distribution of

the PCS score. As a sensitivity analysis, we will additionally assess the difference between groups in week 16 scores using ANOVA adjusted for the baseline score.

- The difference in mean change of total IPAQ-S score from baseline to week 16 ± 2w in the intervention group when compared to the control group will be evaluated with an unpaired t-test or Wilcoxon rank sum test depending on distribution of the IPAQ-S score. As a sensitivity analysis, we will additionally assess the difference between groups in week 16 scores using ANOVA adjusted for the baseline score.

- The difference in mean change of total PSQI score from baseline to 16 ± 2w in the intervention group when compared to the control group will be evaluated with an unpaired t-test or Wilcoxon rank sum test depending on distribution of the PSQI score. As a sensitivity analysis, we will additionally assess the difference between groups in week 16 scores using ANOVA adjusted for the baseline score.

- Participant engagement with the app will be analyzed descriptively as 1) the proportion of RAID questionnaires with at least one completed item in the Sidekick app, compared to the total number of RAID questionnaires prompted by the app for each participant during the study period; and 2) several user behavior statistics as described elsewhere. Additionally, participant engagement will be compared between the weekly and monthly RAID groups with unpaired t-tests or Mann-Whitney-U tests depending on data distribution.

- Candidate predictors of a favorable effect of using the Sidekick app on self-efficacy, sleep and physical activity will be studied exploratively with (multiple) linear regression.

- The evolution over time of the RAID scores at baseline, provided in the app (intervention group only) and at week 16 ± 2w, and their association with other outcomes including ASES, IPAQ-S, PSQI and DAS28-CRP/SDAI scores, will be described with linear mixed effects regression models.

- The association of data actively logged in the app (step counts, exercise activities, sleep quality, stress level, and energy level) with (changes in) the validated outcome measures RAID, IPAQ-S, PSQI, ASES, and DAS28-CRP/SDAI collected at baseline and week 16 ± 2w will be reported as Spearman or Pearson correlation coefficients depending on data distribution.

10. Quality assurance

Data collection tools and source document identification:

Source data will be collected and recorded in the study participants' files/medical records. They will be kept on a secured location at all times. The collection and processing of source data (from subjects enrolled in this study) will be limited to those data that are necessary to fulfill the objectives

of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Personnel whose responsibilities require access to personal data agree to keep the data confidential.

Documentation of source data is necessary for the evaluation and validation of clinical findings, observations and other activities during a clinical study. Source documentation serves to substantiate the integrity of study data, confirms observations that are recorded and confirms the existence of study participants. Furthermore, source documentation must be available for the following to confirm data collected in the e-CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol and date of study completion and reason for withdrawal from the study, if applicable. Data collection is the responsibility of the clinical study staff at the site under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. All source documents will be reviewed by the clinical team to ensure that they are accurate and complete.

As defined in section 1.52 of the ICH Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes….).

11. Direct access to source data and documents

The investigator will permit trial-related audits, IEC review and regulatory inspection, providing direct access to all related source data / documents.

E-CRF's and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the data manager, auditor and inspection by health authorities (e.g. EMA, FDA). The accuracy of the data will be verified by review of the source documents sponsor's clinical trial monitor.

12. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to Ethics Committee and to the Federal Agency for medicinal products for Clinical Trial Authorization.

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed

informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws. The ICF for this study includes a dedicated section to inform participants that they will be presented with general Terms and Conditions upon downloading the application.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR") and the Belgian Law of July 30 2018 on the protection of natural persons with regard to the processing of personal data).

Any personal data shall be treated as confidential at all times including during collection, handling and use, and that the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with data protection legislation. The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access to or disclosure of or loss or destruction while in its custody.

The personal data of study participants will be encoded, which means that they can only be related to an identifiable person by means of a unique code. The unique code will only be in the possession of the members of the study team who are in direct contact with the study participants. In no event will the coded personal data include personal identifiers, including any Study participant's initials. Such coded personal data can only be traced or linked back by said study team members and said study team members shall treat these codes as strictly confidential.

13. Data Handling

Data collection tools and source document identification

The Terms and Conditions in the informed consent form (ICF) also apply to the storage and handling of personal data, specifically account registration information, user-logged data and user behavior data.

According to these general Terms and Conditions, account registration information, data logged by users in the SidekickHealth application, and user behavior data are stored in the Google Cloud SQL service on behalf of GoodlifeMe, the SidekickHealth manufacturer. Google does not have access to this information for any other reason than to store it. Account registration information includes a user's name, email and chosen password, as well as information about their height, weight, age,

gender and profile picture if app users choose to supply this. To protect the personal email address of the user, we will label the individual patient account with a unique code (coded study email address) that will also serve as the study identification code for that individual in the eCRF. This code will be matched with the unique patient identification number in the KWS (EAD number) and kept in a separate file only available to the local study team. Logged data includes only the information actively logged by the user relating to their diet, physical activity, stress (such as minutes spent completing relaxation exercises in the application), vital signs, and questionnaires entered into the application. User behavior data include specific information about how participants use the application, such as how often the app is used, to what extent the educational modules have been accessed, how often certain lifestyle information is uploaded, to what extent patients have used a wearable together with the app etc… Upon deletion of the Sidekick account, or when the user has not logged any activity in the application for a period of two years, all personally identifiable data is deleted from the Google Cloud SQL service.

Other than user behavior data and actively logged data, no data derived by or entered into the Sidekick application will be collected or stored as part of this study. Demographic, clinical and questionnaire-derived source data will be collected and recorded in the study participants' files/medical records. They will be kept on a secured location at all times. The collection and processing of source data (from subjects enrolled in this study) will be limited to those data that are necessary to fulfill the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. Personnel whose responsibilities require access to personal data agree to keep the data confidential.

Documentation of source data is necessary for the evaluation and validation of clinical findings, observations and other activities during a clinical study. Source documentation serves to substantiate the integrity of study data, confirms observations that are recorded and confirms the existence of study participants. Furthermore, source documentation will be available for the following to confirm data collected in the e-CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; and date of study completion and reason for early discontinuation of study or withdrawal from the study, if applicable. Data collection is the responsibility of the clinical study staff at the site under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. All source documents will be reviewed by the clinical team to ensure that they are accurate and complete.
As defined in section 1.52 of the ICH Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes….).

Case report forms

CRFs are provided for each subject in electronic format. The study data will be transcribed on a regular basis by study personnel from the source documents onto an e-CRF in a pseudo-anonymized manner and transmitted in a secure manner to the Chief Investigator within the timeframe agreed upon between Chief Investigator and the sites.

Worksheets may be used for the capture of some data to facilitate completion of the e-CRF. Any such worksheets (including but not limited to copies of the e-CRF) will become part of the study participant's source documentation. All data relating to the study must be recorded in e-CRFs prepared by the investigator. Data must be entered into e-CRFs in English. Designated site personnel must complete the e-CRF as soon as possible after a subject visit, and the forms should be available for review.

The investigator will ensure that data are recorded on the e-CRFs as specified in the study protocol and in accordance with the instructions provided.

All e-CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. Proper audit trails are available to demonstrate the validity of the trial data. A copy of the completed e-CRFs will be archived at the study site.

Data handling and record keeping

The investigator will maintain a certified copy of e-CRFs and all source documents that support the data collected from each study participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator will take measures to prevent accidental or premature destruction of these documents.

If data need to be transferred, this will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations. Receiving party will agree to keep the transferred data confidential at all times. Data will not be transferred outside of the EEA.

14. Data Management

The investigator will maintain a certified copy of e-CRFs and all source documents that support the data collected from each study participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator will take measures to prevent accidental or premature destruction of these documents.

If data need to be transferred, this will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations. Receiving party will agree to keep the transferred data confidential at all times. Data will not be transferred outside of the EEA.

The Sponsor is responsible for archiving study-specific documentation (such as but not limited to protocol, potential amendments, final report and database) according to ICH-GCP. Source data and Site-specific study documents (such as, but not limited to, ICF) will be archived locally on site according to local practice and guidelines for at least 20 years. Archived data may be held on electronic record,

provided that a backup exists and that hard copies can be obtained, if required. Destruction of essential documents will require authorization from the Sponsor.

Archiving at the end of the trial will be organized by the sponsor and done centrally.

15. Translational research

No biological material will be collected/shipped/stored/used for the study. Lab results obtained as part of routine care will be extracted from the electronic medical patient file (KWS) or via laboratory reports of the participants' general practitioner.

16. Publication Policy

It is anticipated that the results of the overall Study shall be published in a multi-center publication, involving the data of all clinical sites participating in the Study.
Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

Publications will be coordinated by the Investigator of Sponsor. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

17. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

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19. Amendment history

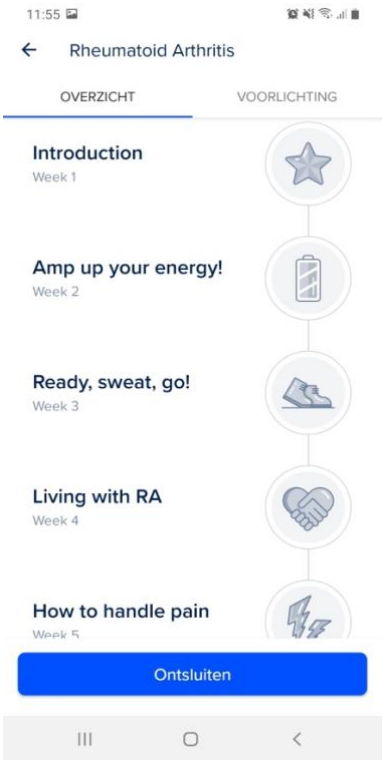
Amendment no.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	V1.0	19-09-2021	Cedric Lefevre	First draft
2	V1.1	03-10-2021	Jo Joly	New lay-out, working out of the study design, adding flow-chart to study design
3	V2.0	02-11-2021	Michaël Doumen	New, layout, new study objectives and endpoints, adding statistical methodology, data handling, ethics and regulatory approvals.
4	V2.1	18-11-2021	Delphine Bertrand, Patrick Verschueren,	Recalculating sample size, fine-tuning study

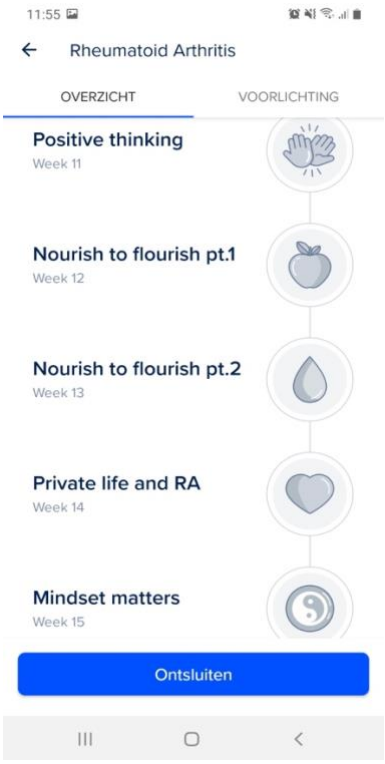
			Sofia Pazmino Lucio	design, updating study flow chart.
5	V3.0	21-11-2021	Cedric Lefevre	Implementing al considered changes in versions V2.1 and V2.2.
6	V3.1	26-11-2021	Jo Joly	Advice considering changing sample size, data handling and study flowchart.
7	V3.2	11-12-2021	Cedric Lefevre	Adaptation trial flowchart with deletion of the unscheduled visit, correction of trial periods, adaptation lay-out.
8	V4.0	17-01-2022	Cedric Lefevre, Patrick Verschueren, Jo Joly	Correcting time intervals, correcting sample size, correcting small errors, adding part about data handling, refining lay-out.
9	V4.1	23-01-2022	Cedric Lefevre, Michaël Doumen, Patrick Verschueren.	Extending trial to 32 weeks with cross-over design considering the control group, adding third visit

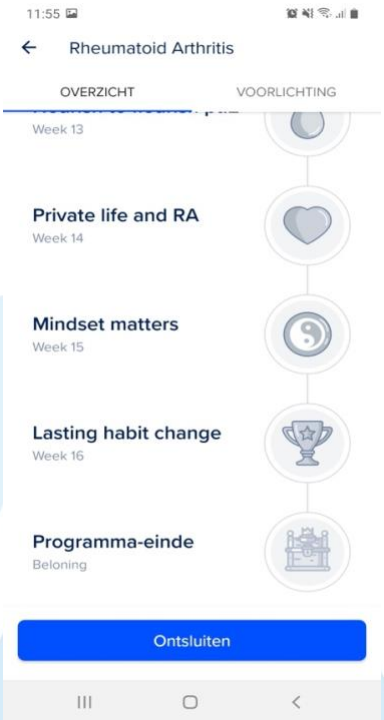
				moment, updating list of abbreviations, adapting sample size, making new study diagram, concordance between study synopsis and the whole document.
10	V5.0	20-02-2022	Cedric Lefevre, Michaël Doumen	The third evaluation moment at week 32 was dropped, the study will again end at week 16 as stated before. The intervention group will be cut in half with one group getting the RAID questionnaire weekly, the other one monthly, sample size was adjusted for this. The FFQ was dropped as it could not provide a quantitative result and was deemed too extensive to complete.
11	V6.0	24-02-2022	Michaël Doumen	Extensive formatting,

				including changes to the title. Adaptation of secondary and exploratory endpoints, including adaptation of the sample size calculations and consequent changes in the randomization procedure.
12	V6.1	12-03-2022	Patrick Verschueren, Cedric Lefevre, Michaël Doumen	Correcting minor incompatibilities, considering CDAI and SDAI for measuring disease activity, change of the protocol acronym to AEGORA: App-based Education and Goal-setting in Rheumatoid Arthritis.
13	V6.2	08-09-2022	Michaël Doumen	Fine-tuning minor incompatibilities.
14	V6.3	03-11-2022	Michaël Doumen, Patrick Verschueren, Jo Joly	Addressing comments of Ethical Committee

Appendix A. Short overview of educational content in Sidekick app







Appendix B. R script for sample size calculations

```
library(pwr)
library(epiR)

#---- Primary outcome: ASES
d <- 5.5/9.4
power <- pwr.t.test(d = d, sig.level = 0.05, power = 0.80, type = "two.sample", alternative =
"two.sided")
samplesize <- round(power$n * 2)


# Accounting for 10% drop-out
samplesize <- samplesize*1.10


# Accounting for possible need for non-parametric tests
samplesize <- round(samplesize*1.15)


#---- Secondary outcome: PCS (non-inferiority)
power <- epi.ssninfc(treat = 20.3, control = 20.3, sd = 12.3, delta = 7.7, n = NA, r = 1,

                     power = 0.80, alpha = 0.025)


# Accounting for 10% drop-out
samplesize <- power$n.total*1.10


# Calculation of power with 120 participants and 10% drop-out (= 108):
power <- epi.ssninfc(treat = 20.3, control = 20.3, sd = 12.3, delta = 7.7, n = 108, r = 1,

                     power = NA, alpha = 0.025)
```