

# BMJ Open Effectiveness and cost-effectiveness of combined asynchronous telemonitoring and patient-initiated care for spondyloarthritis: protocol for a pragmatic multicentre randomised controlled trial (TeleSpA Study)

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## ABSTRACT

**Introduction** During the COVID-19 pandemic, an accelerated uptake of remote monitoring strategies, replacing traditional face-to-face care, has been observed. However, data on the effects of remote care interventions for patients with rheumatic and musculoskeletal diseases remain scarce and interpretation is hampered by study heterogeneity and research quality concerns. High-quality evidence is required to guide future implementation in clinical practice, with health economic analyses identified as an important knowledge gap. Randomised controlled trials (RCTs) comparing telemonitoring with conventional care for patients with spondyloarthritis (SpA) are currently lacking.

**Methods and analysis** TeleSpA is a pragmatic, multicentre RCT investigating the effectiveness and cost-effectiveness of combined asynchronous telemonitoring and patient-initiated follow-up for patients with SpA, compared with conventional care. Two-hundred patients will be recruited at two hospitals and randomised (1:1) to the study intervention or standard care. The primary endpoint is a reduction in the number of follow-up visits by  $\geq 25\%$  in the intervention compared with standard care group, during a 1-year period. Secondary endpoints are (a) non-inferiority of the study intervention with regard to health outcomes, quality of care and patient-reported experience with care; and (b) cost-effectiveness of the intervention, evaluated through a prospective trial-based cost-utility analysis. In addition, experiences with the study intervention will be assessed among patients and healthcare providers, and factors associated with primary and secondary endpoints will be identified.

**Ethics and dissemination** This study was approved by the Medical Research Ethics Committee of the Academic Hospital Maastricht/Maastricht University (NL71041.068.19/METC 19-059). Results will be disseminated through publications in peer-reviewed journals and conference presentations.

**Trial registration number** NCT04673825.

## INTRODUCTION

Spondyloarthritis (SpA) represents a group of inter-related, chronic rheumatic diseases

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ To our knowledge, TeleSpA is the first randomised controlled trial to investigate the effectiveness of asynchronous telemonitoring combined with patient-initiated care in patients with spondyloarthritis.
- ⇒ Pragmatic and multicentre trial design, augmenting the reliability of inferences regarding feasibility of the study intervention in a real-life care setting.
- ⇒ A prospective trial-based cost-effectiveness analysis, using health utilities obtained through both generic and disease-specific outcome measures, will balance (savings in) costs against health outcomes and address an important knowledge gap in the field of telemedicine.
- ⇒ The follow-up period of 1 year does not allow investigating long-term effects.
- ⇒ Limited sample size for patient-reported experience with care, reducing statistical power for this secondary outcome.

comprising axial SpA (including radiographic and non-radiographic axial SpA), arthritis associated with psoriasis (psoriatic arthritis (PsA)), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis and undifferentiated SpA. Symptoms typically start in the third decade of life and can involve inflammatory back pain, arthritis, dactylitis and enthesitis as well as extramusculoskeletal manifestations that include psoriasis, IBD and uveitis. Based on clinical features and the pattern of joint involvement, patients can be classified as having ‘axial SpA’ when inflammation primarily affects the spine and/or sacroiliac joints, or ‘peripheral SpA’ in case of predominant peripheral joint involvement.<sup>1</sup>

SpA is estimated to affect 1% of the population worldwide, but prevalence varies widely in different regions and populations.<sup>23</sup> In many patients, the disease follows a chronic disabling course, leading to a lower quality of life, absenteeism and work disability. Combined with the financial cost of a lifelong need for specialised health services and antirheumatic therapies, this carries a substantial socioeconomic burden for countries across the globe.<sup>4–7</sup>

Current management guidelines emphasise the importance of individualised care and regular monitoring, ideally incorporating a specific set of evaluations including patient-reported outcome measures (PROMs) and validated measures of disease activity.<sup>8–9</sup> In particular, recommended/emerging ‘treat-to-target’ and tight disease-control strategies require more frequent monitoring and systematic assessment of composite disease activity scores.<sup>9–11</sup> Furthermore, as part of good clinical practice in general, care provided should not only be effective and safe, but also timely, efficient, equitable and patient-centred—incorporating patients’ preferences, needs and values.<sup>12</sup>

Complying with these recommendations poses important challenges in daily practice. First, many rheumatology clinics currently face capacity issues due to an increasing demand for health services and a shortage of rheumatologists, an imbalance that is expected to grow in the coming decade.<sup>13–14</sup> As a result, waiting lists and difficulties in providing timely access to care in case of fluctuating disease activity or side-effects threaten to compromise the quality of care.<sup>15–16</sup> At the same time, traditional physician-driven monitoring strategies may lead to patients repeatedly presenting for routine outpatient follow-up when they are feeling well and specialist review is unlikely to result in clinical actions. Both patients and clinicians may find such visits unnecessary or inefficient.<sup>17–19</sup> Finally, despite well-recognised benefits in terms of patient-centredness, the implementation and impact of routine registration of PROMs are limited by a lack of integrated instruments, non-disease-specific tools and time constraints.<sup>20–22</sup>

With healthcare expenditure and workforce shortages projected to increase, finding sustainable solutions for these issues is paramount but most countermeasures require years to accomplish due to regulatory barriers and the length of medical educations.<sup>16–23–24</sup> Meanwhile, improving healthcare efficiency may safeguard access to care for rheumatology outpatients, ameliorate workflow management for medical staff and potentially decrease costs. More recently, the COVID-19 pandemic abruptly necessitated rheumatologists worldwide to adopt alternative ways of care delivery to reduce or replace physical encounters in order to mitigate the risk of SARS-CoV-2 transmission among vulnerable patient populations.<sup>25</sup> This caused a surge of interest in digital health applications and telemedicine with a rapid uptake of alternative follow-up strategies, some of which can potentially contribute towards reducing patient–caregiver contacts in the long term.

Prior to the pandemic, data from several randomised controlled trials (RCTs) already indicated that telemonitoring could be a promising alternative to face-to-face care for rheumatology patients, but the evidence remains limited and validity of conclusions is uncertain due to methodological bias and study heterogeneity.<sup>26–27</sup> Specifically, ‘asynchronous’ telehealth solutions that facilitate self-monitoring for patients without relying on real-time interactions with healthcare providers may reduce the number of necessary follow-up appointments while maintaining disease control and patient safety, as demonstrated in rheumatoid arthritis (RA) and IBD.<sup>28–31</sup>

Favourable experiences with telemedicine supported by electronic PROMs (ePROMs) have since been reported for patients with rheumatic diseases during the pandemic, yet this exclusively constitutes qualitative research or retrospective observational data from provisional care interventions in times of crisis, rendering the validity of study findings uncertain beyond this context.<sup>32–34</sup> Before a more definitive shift away from traditional follow-up paradigms can be justified in a usual care setting, more high-quality RCTs comparing telemonitoring with routine care for specific disease entities in terms of disease control, equity of care and patient satisfaction are required, with a lack of economic analyses additionally identified as a specific knowledge gap.<sup>26–35–36</sup>

Multiple RCTs in RA also illustrated that regular follow-up planning by rheumatologists is not necessary, but can be at the discretion of the patient or general practitioner.<sup>18–37–39</sup> Already before the upsurge of telehealth, patient-initiated follow-up (PIFU) has been shown to reduce healthcare resource utilisation, improve self-efficacy and increase satisfaction compared with the traditional pre-booked appointment system.<sup>18–38–39</sup> In RA, PIFU resulted in similar improvements in disease activity compared with traditional appointments.<sup>37</sup> Furthermore, two RCTs in RA and one RCT among patients with RA and PsA treated with methotrexate indicated that self-monitoring combined with PIFU can reduce healthcare utilisation while maintaining clinical and psychological well-being.<sup>30–40–41</sup> Apart from the latter study, no RCTs are available on PIFU nor the effect of telemonitoring on disease activity, resource utilisation or associated costs among patients with SpA.

Since 2016, a disease-specific web-based eHealth system for patients with SpA (‘SpA-Net’) has been used in the Netherlands that allows for remote collection of ePROMs during everyday practice. The development, usability and acceptability of SpA-Net have been described elsewhere.<sup>42</sup> We hereby provide the protocol for a pragmatic multicentre RCT, in which remote care (asynchronous telemonitoring) provided through SpA-Net combined with PIFU will be compared with standard care, aiming at more efficient care. The trial will test the hypothesis that asynchronous telemonitoring, combined with PIFU, can reduce the number of outpatient consultations for patients with SpA compared with standard care without compromising health outcomes (disease activity, physical

## Box 1 Inclusion and exclusion criteria

### Inclusion criteria:

- ⇒ Age ≥18 years.
- ⇒ Diagnosis of axial and/or peripheral spondyloarthritis according to treating rheumatologist.
- ⇒ Disease duration ≥2 years, in order to be familiar with signs, symptoms and medication.
- ⇒ Stable disease, defined as being in an acceptable symptom state according to patient,<sup>46</sup> AND treating rheumatologist AND no changes to treatment expected in the next 3 months.
- ⇒ Access to a computer, tablet and/or smartphone for the entire duration of the study.

### Exclusion criteria:

- ⇒ Insufficient mastery of the Dutch language.
- ⇒ Lacking capacity to provide informed consent.
- ⇒ Limited life expectancy (eg, terminal illness).
- ⇒ Ongoing (or planned) pregnancy during the study period, as this might affect treatment, follow-up planning and healthcare resource use.
- ⇒ Patients participating in other research project(s), with an exception for strictly observational studies that do not entail additional healthcare utilisation and/or absence from paid work.

functioning, health-related quality of life), patient experience with care and quality of care. Concomitantly, a trial-based cost-utility analysis is conducted to detect between-group differences in healthcare utilisation and associated healthcare and societal costs, and to examine cost-effectiveness of the study intervention. In addition, experiences with the study intervention and SpA-Net are assessed among patients and healthcare providers.

## METHODS AND ANALYSIS

### Study design and setting

This is a multicentre, pragmatic RCT, completed with a trial-based cost-utility analysis. The study will be conducted at two participating hospitals, located in different geographical regions in the Netherlands: the Maastricht University Medical Centre+ (MUMC+), an academic hospital and referral centre for SpA care, and Medisch Spectrum Twente, a large non-academic teaching hospital.

### Population and recruitment

Patients will be recruited at the rheumatology outpatient clinics in both participating centres. All patients with a scheduled outpatient visit and considered eligible by their treating rheumatologist with respect to the inclusion and exclusion criteria (box 1) will receive an invitation letter and information brochure explaining the study, 1–4 weeks before the next visit.

Patients can communicate their willingness to participate before (by mail, email or telephone) or during the scheduled outpatient visit. Inclusion and exclusion criteria will be checked by the attending rheumatologist during the visit, after which a researcher confirms

eligibility and verifies whether information is understood before signing the informed consent form (ICF). Upon the patients' request, signing of the ICF can be postponed by 1 week to provide additional time for consideration. For patients who refuse to participate or do not respond, age, sex, diagnosis, educational level and reasons for non-participation (when disclosed) will be collected.

### Study objectives

#### Primary objective

To determine whether asynchronous telemonitoring combined with PIFU (ie, the study intervention) leads to fewer outpatient visits compared with standard care.

#### Secondary objectives

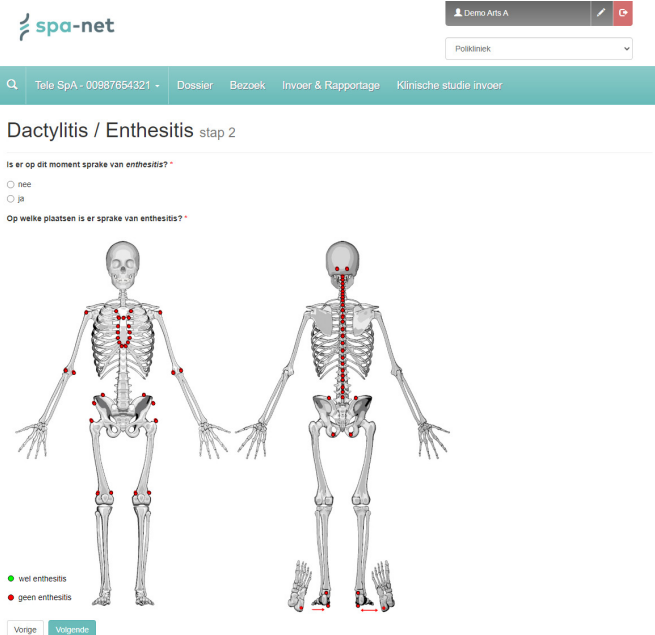
- ▶ To confirm that the study intervention does not compromise perceived quality of care and health outcomes compared with standard care.
- ▶ To evaluate how changes in healthcare and societal costs will relate to changes in overall preferences for health (health utility).
- ▶ To assess experiences with care and SpA-Net among patients and to compare these between the two study groups.
- ▶ To assess experiences with the study intervention and SpA-Net among healthcare providers.
- ▶ To determine whether self-management skills are important for successful (ie, reducing the number of outpatient visits without compromising quality of care or health outcomes) application of the study intervention.

### Randomisation

Patients are randomised after signing the ICF subsequent to their scheduled visit, which will then be considered the baseline visit. Randomisation (1:1; intervention vs standard care) is performed by the web-based software program ALEA using the minimisation method described by Pocock and Simon,<sup>43</sup> designed to minimise imbalance between treatment groups on predefined prognostic factors, while incorporating a random component to limit predictability in compliance with the International Conference on Harmonisation (ICH) E9 guidelines.<sup>44</sup> On randomisation, medical centre, SpA subtype (axial, peripheral or combined) and treatment (biological vs no biological) are taken into account. When the highest imbalance between groups for any of these factors exceeds 2, an OR of 0.9 is assigned to the group allocation resulting in the lowest imbalance. Due to the nature of the intervention, neither patients nor clinicians can be blinded to the group allocation.

### SpA-Net

SpA-Net has been described extensively elsewhere.<sup>42</sup> Briefly, it is an ongoing, disease-specific, prospective web-based registry for monitoring SpA in daily practice. Clinical characteristics, outcome measures, results of clinical examinations and laboratory investigations are collected in SpA-Net at every outpatient visit (an example



**Figure 1** Example of data entry in SpA-Net for healthcare providers. If signs of enthesitis are present, healthcare providers can specify the affected entheses in SpA-Net.

for enthesitis is shown in figure 1). Results over time are graphically visualised in a dashboard, using colour coding to aid quick interpretation (figure 2). These comprehensive up-to-date individual patient data are readily available to the healthcare provider during consultations, and an excerpt of this for patients (figure 3), facilitating informed treatment decision-making.

### Study intervention and procedures

All participants will have a scheduled outpatient visit at baseline and after 1 year. In the standard care group, additional follow-up visits are scheduled at the discretion of the treating rheumatologist. Before each visit, patients complete questionnaires in SpA-Net and routine blood tests (including C reactive protein) are obtained as per standard care at the respective study site. During the visit, clinical examination by a rheumatologist or specialised rheumatology nurse will take place.

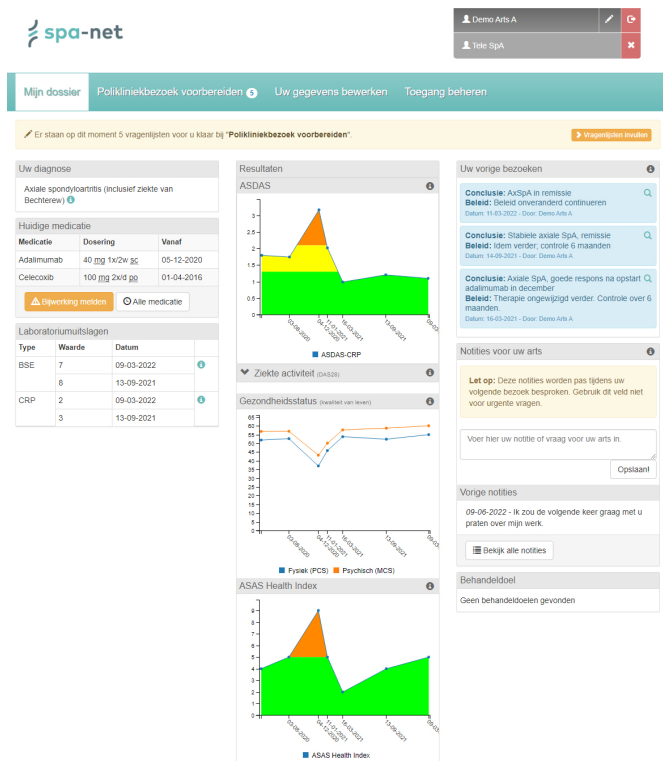
In the intervention group, no additional pre-booked appointments are provided. Instead, 'remote monitoring' will take place after 6 months. Two weeks prior to the planned remote monitoring, these patients will receive a reminder email to complete questionnaires in SpA-Net and to have routine blood tests. Rheumatologists receive an automated email notification as soon as all questionnaires have been answered. Responses to questionnaires and laboratory results are subsequently reviewed by the rheumatologist. Rheumatologists' notes are visible to patients and, at minimum, need to include a summarised interpretation of the patient's results as well as a treatment and follow-up plan. If needed, a physical visit or telephone consultation can be planned (on request via SpA-Net, telephone or email) by the patient, replacing the remote monitoring procedure, or by the rheumatologist



**Figure 2** Example of SpA-Net interface for healthcare providers. For healthcare providers, the SpA-Net dashboard environment is divided into three columns. The first column displays patients' personal information, presence or history of SpA features, current medication and history of medication-related adverse events. The second column contains graphical summaries of the following ePROMs and disease activity measures: ASDAS, SF-36, VAS Pain, VAS Fatigue (accessible in a drop-down box 'v'), ASAS Health Index. The third column contains summaries of most recent visits, complications or side-effects reported by patients and patient's notes or questions. ASDAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C reactive protein; ePROMs, electronic patient-reported outcome measures; MCS, SF-36 Mental Component Scale; PCS, SF-36 Physical Component Scale; SF-36, 36-Item Short-Form Health Survey; SpA, spondyloarthritis; VAS, Visual Analogue Scale.

when specialist review or treatment changes are indicated based on the results of ePROMs, disease activity measures and/or blood tests.

Patients in both groups will be instructed that at any time, extra 'direct access' visits (provided within 7 days) can be scheduled in case of disease flares or therapy-related side-effects as part of the study project. In this study, no investigational medicinal products are used. All patients receive treatment as indicated from their



**Figure 3** Example of SpA-Net interface from the patient's perspective. A horizontal notification bar (in yellow) allows patients to quickly access questionnaires as soon as these become available. Below, information is presented in three columns. The first column displays the patient's diagnosis, current medication (with an additional feature to report side-effects) and recent laboratory results. The second column includes multiple graphs depicting results from questionnaires. The third column displays summaries of the rheumatologist's notes regarding the most recent outpatient visits, and offers a space where patients can leave questions or notes for their healthcare provider or set personal treatment goals. Lay-term explanations for all items in these three columns are available through an information icon (lower case 'i'). ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BSE, erythrocyte sedimentation rate; CRP, C reactive protein; MCS, SF-36 Mental Component Scale; PCS, SF-36 Physical Component Scale; SF-36, 36-Item Short-Form Health Survey.

treating rheumatologists, in accordance with current management recommendations.<sup>8 9 45</sup>

### Outcome measures

Information on the number of outpatient visits in the year prior to and during the study period will be collected from the electronic medical file. In SpA-Net, multiple variables are routinely measured in regular care (table 1). Additionally for the TeleSpA Study, all included patients will complete questionnaires on whether their symptom state is acceptable,<sup>46</sup> experience with care (patient-reported experience measure (PREM)), assessing overall experience with care and specific aspects including timeliness, emotional support, patient-centredness and

safety),<sup>47</sup> a Self-Management Screening (SeMaS),<sup>48</sup> and questionnaires on health resource utilisation, work productivity, unpaid productivity loss, medication adherence, disease flares (self-reported) and experience with SpA-Net (general satisfaction, ease of use, added value) (see online supplemental file 1).

During physical visits, the rheumatologist will indicate whether the patient is in an acceptable symptom state. If patients indicate pain, swelling or skin abnormalities during a visit, an independent examination of joint (66/68 joint count), skin (body surface area affected by psoriasis) and enthesal involvement will be performed by a trained assessor, except when physical visits are replaced by a telephone or video call. At the end of the study, all rheumatology healthcare providers (ie, rheumatologists, fellows and dedicated nurses) involved in the treatment and/or follow-up of study subjects will receive a questionnaire investigating their experience with the intervention (general satisfaction, safety, effectiveness, patient-centredness, timeliness, efficiency, equitability, flexibility, time and resource-saving capacities) as well as SpA-Net (general satisfaction, ease of use, added value).

To evaluate quality of care, the dimensions 'timely care' (time to care when having a flare) and 'patient-centredness' will be operationalised by the PREM.<sup>47</sup> 'Patient safety' is evaluated through the number of complications and side-effects during follow-up. 'Effectiveness of care' is evaluated with measures of disease activity, functioning and health-related quality of life, and 'efficiency of care' through the number of rheumatology outpatient visits per year and a health economic analysis. 'Equitability of care' will be evaluated through subgroup analyses for sex, age, education level, diagnosis, disease duration and therapy.

During the study, all telephone calls will be registered per patient to detect potential shifts in the rheumatologist's workload.

### Sample size

We hypothesise that the study intervention is superior for the primary outcome. In 2016, the average number of outpatient visits for patients with SpA per year was 2.5 (SD 1.4) in the MUMC+. Based on prior research indicating that approximately one-third of routine SpA outpatient visits are considered unnecessary by rheumatologists,<sup>49</sup> we expect to reduce the number of visits by at least 25% in the intervention group. A sample size of 80 patients per group is required to detect this difference with a power of 0.80 and alpha of 0.05. Assuming a 20% drop-out during follow-up, 100 patients per group will be recruited. This sample size is also sufficient to test non-inferiority for all secondary objectives with a power of 0.80 and one-sided alpha of 0.025, except for patient-reported experience with care (table 2). Sample sizes for non-inferiority endpoints were calculated using the method described by Flight and Julious for continuous outcomes,<sup>50</sup> and the method described by Chow *et al* for

**Table 1** List of variables and questionnaires collected throughout the study

Variable	Baseline	6 months*	1 year*	Extra visits†
Demographics‡	X		X	
Lifestyle (smoking, alcohol use)‡	X		X	
Educational level‡	X			
Work status‡	X		X	
Diagnosis according to rheumatologist‡	X			
Symptom duration‡	X			
Presence or history of SpA features‡	X	X§	X	X
Comorbidities‡	X	X§	X	X
Number of outpatient visits in previous year	X		X	
Medication use (NSAID, DMARD, biological)‡	X	X	X	X
Side effects, complications‡	X	X§	X	X
Presence of tender and swollen joints, dactylitis, enthesitis‡	X	X§	X	X
Presence of psoriasis (body surface area)	X	X§	X	X
CRP‡	X	X	X	X
Disease activity (BASDAI, ASDAS)‡	X	X	X	X
Patient global assessment of disease activity (VAS)‡	X	X	X	X
Disease activity according to physician (VAS)‡	X	X§	X	X
Quality of life (SF-36, EQ-5D-5L, ASAS-HI)‡	X	X	X	X
Patient-acceptable symptom state according to patient	X	X	X	X
Patient-acceptable symptom state according to physician	X	X§	X	X
Disease flare(s) according to patient		X	X	
Patient-reported experience with care‡	X		X	
Healthcare utilisation	X	X	X	
Work productivity	X	X	X	
Experience with SpA-Net	X		X	
Self-management (SeMaS)	X			
Medication adherence (VAS)	X		X	

\*A 2-month interval before and after the 6-month and 1-year period will be accepted for this measurement.

†Extra visits can be a regular visit in the standard care group or a non-scheduled visit in either group.

‡Variables already collected in SpA-Net as part of standard care, prior to study.

§Variable not measured in intervention group, unless physical outpatient visit takes place.

ASAS-HI, Assessment of SpondyloArthritis International Society Health Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; EQ-5D-5L, EuroQol 5-dimensions 5-level; NSAID, non-steroidal anti-inflammatory drug; SeMaS, Self-Management Screening Questionnaire; SF-36, 36-Item Short-Form Health Survey; SpA, spondyloarthritis; VAS, Visual Analogue Scale (0–100 mm).

proportional outcomes.<sup>51</sup> All other sample size calculations were performed using G\*Power (V.3.1).<sup>52</sup>

## Study endpoints

### Primary endpoint

The primary endpoint is defined as at least 25% reduction in the number of rheumatology outpatient visits in the intervention group compared with the standard care group, within a 1-year period. Due to the COVID-19 pandemic, these outpatient visits may also take place through telephone or video calls.

### Secondary endpoints

- ▶ Non-inferiority of the study intervention compared with standard care with respect to health outcomes

and overall experience with rheumatology care (box 2).

- ▶ Cost-effectiveness of the study intervention compared with standard care (incremental cost-utility ratio, incremental net monetary benefit (iNMB)).
- ▶ Predictive value of screening for self-management skills with regard to attaining both the primary and secondary non-inferiority endpoints (intervention group only).

## Statistical analysis

### Patient demographics and other baseline characteristics

Descriptive statistics on prespecified demographic (age, sex, educational level, work status) and clinical (diagnosis, symptom duration, SpA features, medication use,

**Table 2** Sample size calculations for secondary objectives

Continuous	Mean	SD	$\delta_{NI}$	n
ASDAS (N=349)	2.22	1.00	0.90	20
BASDAI (N=564)	4.17	2.24	2.00	20
Pain (VAS) (N=763)	38.33	26.19	20.00	27
Patient global (VAS) (N=687)	40.26	26.07	15.00	38
Physician global (VAS) (N=711)	14.30	16.12	10.00	41
Categorical	Proportion	$\delta_{NI}$		n
Overall experience with care (N=276)	0.90	-0.10		141

All values calculated are based on data from SpA-Net retrieved on 29 October 2018. The number of patients with available data is provided in the first column. Stable values are assumed for the standard care group.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; n, sample size needed per group; VAS, Visual Analogue Scale (range: 0–100 mm);  $\delta_{NI}$ , non-inferiority limit or margin.

number of outpatient visits in previous year) parameters will be reported. In addition, baseline characteristics will be summarised for the following variables: Ankylosing Spondylitis Disease Activity Score,<sup>53</sup> Bath Ankylosing Spondylitis Disease Activity Index,<sup>54</sup> patient global assessment

## Box 2 Rationale for non-inferiority margins

- ⇒ Ankylosing Spondylitis Disease Activity Score: non-inferiority defined as an increase of  $\leq 0.9$ , based on the 2018 Assessment of SpondyloArthritis International Society (ASAS) consensus definition of clinically important worsening.<sup>69</sup>
- ⇒ Bath Ankylosing Spondylitis Disease Activity Index: non-inferiority defined as an increase of  $< 2.0$ , in accordance with the most conservative preliminary definition of clinically important worsening ('flare') based on the 2016 ASAS consensus report,<sup>70</sup> and with what is most commonly regarded as a clinically relevant change by rheumatologists in clinical practice.<sup>71</sup>
- ⇒ Patient global assessment of disease activity: non-inferiority defined as an increase of  $\leq 15$  mm on a 0–100 mm Visual Analogue Scale (VAS), which is situated between the minimally clinically important difference for patient-reported worsening for patients with psoriatic arthritis and spondyloarthritis (SpA), respectively.<sup>72,73</sup>
- ⇒ Physician global VAS: non-inferiority defined as an increase of  $\leq 10$  mm, based on what is considered a clinically relevant change by rheumatologists in clinical practice.
- ⇒ Pain VAS: non-inferiority defined as an increase of  $\leq 20$  mm, which is based on the most conservative preliminary definition of clinically important worsening ('flare') according to the 2016 ASAS consensus report,<sup>70</sup> and closely approximates findings of a study that assessed worsening of VAS-reported pain in adults with SpA, irrespective of pain levels reported at baseline.<sup>72</sup>
- ⇒ Overall experience with care: in 2018, approximately 90% of patients with SpA in the Maastricht University Medical Centre+ were satisfied with the care provided. Non-inferiority is defined as a decrease of  $\leq 10\%$ .

of disease activity (Visual Analogue Scale (VAS)), disease activity according to physician (VAS), pain (VAS), EuroQol 5-dimensions 5-level (EQ-5D-5L),<sup>55</sup> 36-Item Short-Form Health Survey,<sup>56</sup> Assessment of SpondyloArthritis International Society Health Index (ASAS-HI),<sup>57</sup> SeMaS,<sup>48</sup> experience with SpA-Net and patient-reported experience with care (PREM).<sup>47</sup> All baseline characteristics will be reported for the total population, as well as for both patient groups separately.

### Intention-to-treat and per-protocol analyses

The primary outcome will be analysed in the intention-to-treat (ITT) population. Outcomes for secondary non-inferiority and health economic analysis endpoints will be analysed in the ITT and the per-protocol population. All other analyses will be performed in the ITT population.

### Primary endpoint

The difference in number of outpatient visits after 1 year of follow-up will be compared with analysis of variance (ANOVA). Given that the population is randomised, an equal distribution of baseline characteristics is to be expected. In case differences between the two groups exist on baseline, post-hoc analyses adjusting for these differences will be done (analysis of covariance).

### Secondary endpoints

Differences in quality of care, health outcomes, experience with SpA-Net and overall care will be analysed with ANOVA. Post-hoc, subgroup analyses (male/female, young/older, peripheral/axial disease, early/long-standing disease, biological users/non-biological users) and predictive analyses with respect to self-management skills and successful application of the study intervention will be done with linear mixed-effects models with each endpoint as dependent variable and time, group and their interaction as fixed effects. P values will be adjusted for multiple testing. Descriptive statistics will be used to summarise experience with the study intervention and SpA-Net among healthcare providers.

### Economic appraisal

A trial-based health economic evaluation (incremental cost-utility and iNMB analysis) will be performed in accordance with the International Society for Pharmacoeconomics and Outcomes Research guidelines,<sup>58</sup> as well as the Dutch guidelines for economic evaluations in healthcare.<sup>59</sup> Analyses will be done from a Dutch healthcare and societal perspective.

Self-reported health resource utilisation and loss of productivity in paid and unpaid work due to any health problem will be evaluated for three separate 6-month recall periods (including at baseline, see table 1). Total resource consumption and loss of productivity in paid and unpaid work will be reported as the sum of resources used or days of lost production during the 12-month study period. In case significant differences are detected between groups in healthcare utilisation and/or productivity losses at baseline, this will be accounted for.

Total healthcare costs are calculated by multiplying volumes (resource use) with unit costs according to Dutch costing guidelines.<sup>59</sup> Costs of antirheumatic medication (non-steroidal anti-inflammatory drugs, glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), biological DMARDs) will be based on the Dutch national drug database (G-standard) accounting for type, dose and frequency of administration.

For paid productivity loss, the friction cost approach was chosen per Dutch national guidelines. Costs of paid productivity loss are calculated by dividing self-reported hours of paid work per week by the number of working days per week, multiplying the result by the reported amount of missed days at work due to illness and the cost per missed hour of paid work.<sup>59</sup> A friction period of 85 days is considered.<sup>60 61</sup> Costs of unpaid productivity loss (hours needed by housekeeping aid to complete unpaid work that remains unfinished due to illness) will be measured using questions extracted from the Institute for Medical Technology Assessment Productivity Cost Questionnaire.<sup>62</sup> Travel costs for physical visits to the rheumatology department will be valued according to Dutch costing guidelines.<sup>60</sup>

To determine incremental health effects ( $\Delta E$ ), health utility scores retrieved from both the generic standardised EQ-5D-5L and disease-specific ASAS-HI measures will be integrated over time (area under the curve method) to calculate quality-adjusted life years (QALYs),<sup>55 57</sup> using Dutch tariffs.<sup>63 64</sup> To address uncertainty and the highly skewed nature of cost data, bootstrapping will be performed to construct 95% CIs around the mean cost differences. Point estimates and bootstrap samples will be plotted on cost-effectiveness planes and cost-effectiveness acceptability curves will be constructed as a summary measure of uncertainty for cost-effectiveness estimates. The willingness-to-pay or willingness-to-accept threshold ( $\lambda$ ) will be set at €20,000 per QALY to interpret the incremental cost-utility ratios and calculate the iNMB ( $iNMB = (\Delta E \times \lambda)$ —incremental costs). Sensitivity analyses will be performed to test the robustness of the results, such as including costs of presenteeism and discounted medication prices for biological DMARDs.

#### Missing data

Data completeness will be checked at every visit and if missing, direct action (phone calls, email) will take place. Missing data will be addressed using multiple imputation.

#### Ethics and dissemination

The study will be conducted in accordance with the Declaration of Helsinki and Dutch legislation (Medical Research Involving Human Subjects Act) as well as good clinical practice. This study was approved by the Medical Research Ethics Committee of the Academic Hospital Maastricht/Maastricht University (reference

NL71041.068.19/METC 19-059). Results will be disseminated through conference presentations and publications in peer-reviewed journals.

#### Safety reporting

In this study, no investigational medicinal products are used and treatment is provided as per standard care. It is not to be expected that (serious) adverse events ((S)AEs) will occur *due to* the intervention. Side-effects and complications from treatment are registered in routine care, and reported directly to the Dutch pharmacovigilance institute through SpA-Net. Clinical and laboratory assessments performed in this study are already part of routine care. At any time, participants can contact the outpatient clinic and extra visits can be scheduled within 7 days.

#### (Serious) adverse events

Adverse events (AEs) and SAEs are defined according to Articles 2.57 and 2.58 of the European Regulation 2017/745.<sup>65</sup> All (S)AEs reported spontaneously by the subject or observed by the research team, which are suspected to be related to the study intervention, will be recorded and reported in compliance with Dutch regulations. Elective hospital admissions will not be considered SAEs.

#### Monitoring and quality assurance

Monitoring will be performed by the Clinical Trial Centre Maastricht in accordance with ICH Good Clinical Practice guidelines and local regulations.

#### Data deposition

All study data will remain available in SpA-Net for 15 years and can only be used for other (ongoing or future) research projects if permission is granted by the individual participants on the ICF. SpA-Net data storage and maintenance meet all Dutch and European legal requirements, and are in line with regulations on the protection of personal data, including the NEN7510, ISO2700 and European general data protection regulations.<sup>66</sup>

#### Patient and public involvement

In 2019, a knowledge agenda was released by the Dutch Society for Rheumatology.<sup>67</sup> This document was composed in cooperation with patient organisations, and lists the 10 most important research priorities in the field of rheumatology according to patients and healthcare providers, selected from 1077 different knowledge gaps. Of these, assessing the value of eHealth in comparison with standard care was identified as the most important research question.

Patients with rheumatic and musculoskeletal diseases (RMDs), including SpA, are often subjected to lifelong periodical follow-up at specialised outpatient clinics. Cumulatively, this incurs significant time investments and travel expenses and might entail recurring practical difficulties for patients who are functionally impaired. In our practice, multiple patients have therefore asked whether routine follow-up is truly necessary. The introduction



of SpA-Net in 2016 further stimulated some patients to propose replacing physical outpatient visits by remote monitoring through SpA-Net. On that line, patients were involved in the development of the research questions and initial conceptualisation of the study intervention. Additionally, a preliminary version of the research proposal and recruitment procedure was evaluated by two patient research partners that have been involved in previous research projects, including the development of SpA-Net. Their feedback was incorporated into the final protocol. All participants will receive a summary of results via email within 1 year after termination of the study. A separate report will be provided (in Dutch) to the Dutch Arthritis Foundation, the largest rheumatology patient organisation in the Netherlands, for dissemination.

## DISCUSSION

To our knowledge, TeleSpA will be the first RCT to investigate the effectiveness of telemonitoring combined with PIFU in patients with SpA with stable disease. This project will contribute to answering research questions that have been granted the highest priority by both rheumatology patients and healthcare providers in the Netherlands,<sup>67</sup> and will address multiple unmet needs in the field of remote care for patients with RMDs that were recently identified by a dedicated European Alliance of Associations for Rheumatology task force.<sup>36</sup>

In general, the implementation of PIFU services may however raise specific safety concerns, the most prominent of which include an inherent risk for loss to follow-up, untimely care due to patients' reluctance or inability to contact or access health services, and diagnostic delays when conditions do not immediately lead to subjective symptoms (eg, haematological or renal disorders due to medication toxicity or as a part of systemic/multiorgan manifestations of rheumatic disease) or patients fail to recognise when seeking medical review would be beneficial. Importantly, TeleSpA was specifically designed to mitigate these risks. First and foremost, by selecting patients who would theoretically be suitable for, and benefit from, PIFU in real-life care. Second, loss to follow-up will be prevented by scheduled telemonitoring (in turn supported by reminder emails, and telephone contact with the study team in case of incomplete data) and end-of-study visits, serving as safety nets and allowing for continued care planning. Finally, the availability of 'direct access' visits, which can be requested in multiple ways, aims to decrease barriers for patients and guarantees timely access to care. Both patient profiles and precautions are in line with recent guidance for implementing PIFU in adult rheumatology services published by the National Health Service in the UK.<sup>68</sup> In addition, information retrieved from TeleSpA may lead to additional insights (eg, the value of self-management screening) that could help guide the design and implementation of similar care interventions elsewhere.

This study has several strengths. The utilisation of a disease-specific eHealth platform (SpA-Net) that has been in use since 2016 and for which the usability and acceptability have previously been established,<sup>42</sup> as well as the pragmatic and multicentre trial design, will increase the reliability of inferences regarding feasibility of the study intervention in a real-life care setting. In addition, the prospective trial-based cost-utility analysis, based on utility values obtained through both generic and disease-specific outcome measures, will generate comprehensive data related to an important knowledge gap in the field of telemedicine.<sup>26 35 36</sup> The trial design is also subject to some specific limitations. The limited sample size reduces statistical power for the secondary outcome related to patient-reported experience with care as well as exploratory subgroup analyses. Due to the limited follow-up period of 1 year, this study will unfortunately not provide information about long-term effects.

If successful in reducing the amount of routine outpatient visits without compromising health outcomes, patient experience with care and quality of care, this project will not only generate evidence to support the fast-paced adoption of similar remote care interventions currently observed in rheumatology practice, but will also provide an evidence-based, pragmatic intervention that can be rapidly translated into real-life care in the Netherlands to safeguard accessibility and flexibility of care for both patients with SpA and healthcare providers.

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