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Patient-reported outcome measures collected in DANBIO reported via a smartphone app versus a touch screen solution in an outpatient clinic among patients with inflammatory arthritis: *A randomised cross-over agreement study*

AUTHORS/COLLABORATORS

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STUDY REGISTRATION

Danish Data Protection Agency

The study will be registered on Clinicaltrials.gov before enrolling patients.

STUDY SITES

The Rheumatology Department at Aalborg University Hospital

PROTOCOL VERSION 1.0

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

RA: rheumatoid arthritis

PsA: psoriatic arthritis

SpA: axial spondyloarthritis

PROM: patient-reported outcome measures

PRO: patient-reported outcome

VAS: Visual Analog Scale

HAQ: Health Assessment Questionnaire

PASS: Patient Acceptable Symptom State

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BOYD: Bring Your Own device

DANBIO: the Danish Rheumatology Database

nemID: personal ID

CPR: civil registration number

LU: Line Uhrenholt

NSK: Niels Steen Krogh

MID: Minimal Important Difference

MCID: Minimal Clinically Important Difference

DAS28crp: Disease Activity Score28crp

ASDAS: Ankylosing Spondylitis Disease Activity Score

CRP: c-reactive protein

RC: Robin Christensen

e-CRF: electronic Case Report Form

GLM: general linear model

GCP: Good Clinical Practice

3. BACKGROUND

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (SpA) are three major inflammatory arthritic diseases in Rheumatology. Since the 1980's, patient-reported outcome measures (PROM) have been used in clinical research and later on in daily clinical practice as an essential tool to evaluate the patient's perception of arthritis activity (1). PROM are important in monitoring disease activity as they capture the dynamic clinical presentation of RA, PsA and SpA with symptoms that cannot be measured objectively e.g. pain, fatigue and morning stiffness of the joints. As advised by the Food and Drug Administration in "Patient-reported outcome (PRO) Guidance for the Industry", PRO instruments should be used when measuring concepts best known by the patient or best measured from the patient's perspective (2). In Rheumatology in Denmark, patients are monitored using the following PROM: Visual Analog Scale (VAS) for pain, fatigue and global health (appendix 1), Health Assessment Questionnaire (HAQ) (appendix 2), Patient Acceptable Symptom State (PASS) (appendix 3), Anchoring question (appendix 4) and for patients with axial involvement: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (appendix 5) and Bath Ankylosing Spondylitis Functional Index (BASFI) (appendix 6).

Initially, PROM was collected in a paper form. In Denmark, PROM has been registered electronically through a touch screen solution in the outpatient clinic since 2006. It has previously been shown in a Danish rheumatic patient population, that data collecting of PROM through an electronic touch screen versus paper based forms yields comparable results (3,4). Using electronic data collection of PROM has major advantages in terms of more accurate and complete data, minimisation of errors, avoidance of secondary data entry errors, less administrative burden etc. (5). During the past years, a new approach of electronic data collection of PROM is emerging called Bring Your Own device (BOYD). In medical research, BOYD means allowing participants to use their own computer device, e.g. smartphone, tablet, laptop, to access and respond to study-related PROM (5). Thus, due to the widespread use of smartphones it is now possible to use the participants' own device for collecting PROM data via a downloaded smartphone app. The participant runs the app on his/her smartphone and completes the PROM; thereafter, the data is transmitted via the internet to a specific database. Using a smartphone app instead of the traditional touch screen solution in the outpatient clinic will eliminate problems as queue, lack of discretion and uncomfortable position during data entering etc. The major advantage to collecting PROM through a smartphone app is thus, that data can be collected when and where it suits the individual patient best, thereby possibly providing more accurate answers and minimising recall-bias (5). In addition, the smartphone app ensures that the PROM questionnaires will

be displayed in a relatively consistent manner independent of the different smartphone models and has the advantages of data entry without internet connection (i.e. data will be stored in the smartphone app and then transmitted to the database when the smartphone has internet connection) compared to a web-based BOYD data collection. One possible disadvantage to collecting PROM through a smartphone is distractions in the unsupervised setting e.g. telephone call, receiving/sending text messages, interaction on social media etc., which can interrupt the PROM data collection. Another barrier is that not all adults own or has access to a smartphone and that smartphone ownership may vary based on age, income, education etc., which means that this data collection option is not a possibility for everyone. However, it is expected, that this solution could be a preferred possibility for some patients. Thus, this study will assess the validity of PROM registration in the Danish Rheumatology Database (DANBIO) through the DANBIO app on a smartphone compared to the traditional touch screen solution in the outpatient clinic in patients with RA, PsA and SpA in standard clinical care.

4. HYPOTHESIS

Use of a smartphone app for registration of PROM in Rheumatology yields comparable results with the traditional touch screen solution in the outpatient clinic.

5. OBJECTIVE

To evaluate whether electronic reporting of PROM through a smartphone app is comparable to the traditional touch-screen solution in the rheumatology outpatient clinic among patients with RA, SpA and PsA in standard clinical care. This study will thus assess the validity of registration of PROM in DANBIO through a smartphone app.

6. METHODS

6.1. Study design

The study is a randomised, within-participants cross-over design including patients with RA, PsA and SpA. The participants will be randomised in ratio 1:1 to group AT (*App* → *Touch* i.e. data is reported through the smartphone app first and thereafter the touch screen) or group TA (*Touch* → *App* i.e. data is reported through the touch screen first and thereafter the smartphone app).

6.2. Participants

This study will include 60 participants distributed as follows: 20 participants with RA, 20 participants with PsA and 20 participants with SpA from the rheumatology outpatient clinic at Aalborg University Hospital. Eligibly participants will be recruited after submission and approval of the protocol to relevant authorities. Recruiting will start January 2018 and continue until the target population is achieved (presumably no longer than 3 months).

6.3. Eligibility criteria

6.3.1. Inclusion criteria

A participant will be eligible for study participation if he/she meets the following criteria:

- Diagnosed in DANBIO with RA, PsA or SpA
- Is currently treated and monitored at the rheumatology outpatient clinic at Aalborg University Hospital
- Have previously reported PROM in DANBIO through the touch screen solution at the rheumatology outpatient clinic ≥ 3 times

6.3.2. Exclusion criteria

A participant cannot be included in the study if he/she meets any of the following criteria:

- Inability to provide informed consent or unwilling to comply with the study protocol
- Diagnosis of RA, PsA or SpA ≤ 12 months
- Does not have access to a smartphone that can download and run the DANBIO app
- Not able to understand written Danish i.e. cannot understand the Danish version of the PROM questionnaires
- Reduced sight in such degree that the participant cannot read the questionnaire in the smartphone app/on the touch-screen with e.g. glasses

6.4. Interventions

Participants will be randomised by diagnosis to one of two groups 1:1 meaning 10 participants with RA, 10 participants with PsA and 10 participants with PsA in each of the two groups:

- Group AT (*App → Touch*): the participant reports data through the DANBIO app on a smartphone first and after a "washout period" of one day via the touch screen solution at the rheumatology outpatient clinic.

- Group TA (*Touch → App*): the participant reports data through the touch screen solution at the rheumatology outpatient clinic and after a "washout period" of one day via the DANBIO app on a smartphone.

6.5. Registration of PROM in DANBIO

The participants are informed about how to register data in DANBIO through the DANBIO app during the recruitment telephone call, see section *7.2. Recruitment procedures*. In addition, the start date of the first data registration is decided with the patient (and noted in DANBIO). Data registration through the DANBIO app can be done when the patient has logged on with his/her personal ID (nemID). Data registration through the touch screen solution in the rheumatology outpatient clinic is done with the patient's individual civil registration (CPR) number as usual. In the rheumatology outpatient clinic, the participants will as usual answer the questionnaires in DANBIO through the touch screen. For data registration through the DANBIO app, the participants must download the DANBIO app on a smartphone with internet connection. The questionnaires answered in the DANBIO app is the same as the patients answer through the touch screen solution at the rheumatology outpatient clinic. After the participant has entered data through both methods, the participant is asked which solution is preferred: touch screen solution in the rheumatology outpatient clinic or entering data in the DANBIO app on a smartphone or no preference.

Before the first data entry of PROM, the participant must be instructed about:

- Data entering through the DANBIO app must be done within a short timeframe i.e. the participant must not do anything else during the data entry, which could be a disturbing element
- Data entering through the touch screen solution in the rheumatology outpatient clinic must be during normal opening hours i.e. 8.00-15.00 Monday to Friday.
- The first and second data registration must not be done on the same day, as there shall be a "washout period" of one day between the two data registrations. It is preferred, that the data entry occurs at the same time of the day (to avoid daytime variations in arthritis symptoms)
- The participant will receive a SMS reminder about the scheduled data entry the day before and on the day of each data registrations. On the day after the scheduled data entry, the participant will receive a SMS reminder if he/she has not completed the data entry – if the registration is not done within one day PhD student Line Uhrenholt (LU) will contact the participant by telephone

- The participant will receive a link to the DANBIO app in AppStore or GooglePlay together with the SMS reminder of the scheduled data entry in the DANBIO app.

The data, which the participant register, is NOT used for treatment i.e.:

- If the patients is feeling ill, he/she must seek medical treatment
- In case of a soon scheduled visit in the rheumatology outpatient clinic, the participant must re-enter his/her data in DANBIO

The data entry must not be made in relation to a doctor or nurse visit in the rheumatology outpatient clinic as this may involve change in the patient's medical treatment or otherwise cause change in the disease activity or the patient's perception of the disease. However, data entry may be done in connection with scheduled blood sampling, scheduled X-rays or retrieval of medicine etc.
Niels Steen Krogh (NSK) creates a dedicated page in DANBIO for this project, where all study related data will be collected.

6.6. Set up

PhD student LU is responsible for patient recruitment, informing the participants about the study and collecting the informed consent. LU will also provide technical support to participants if IT problems with the smartphone app occur as explained in the participant information material.
Zitelab can be contacted by research personnel for technical support, contact person is NSK.
LU will inform staff at the Rheumatology Department at Aalborg University Hospital about the study before inclusion of patients.

6.7. Outcomes

In this study, the PROMs listed in table 1 will be collected for the different disease groups (RA, PsA and SpA). The Minimal Important Difference (MID)/Minimal Clinically Important Difference (MCID) for the different measures are consistent with data presented previously (3,6–9).
This study will also estimate Disease Activity Score28crp (DAS28crp) using a fixed level for C-reactive protein (CRP) level of 6, swollen joint count of 0.5 and tender joint count of 1 and Ankylosing Spondylitis Disease Activity Score (ASDAS) using a fixed level for CRP of 6. These data are based on DANBIO registrations of patients with RA, PsA or SpA from the rheumatology outpatient clinic at Aalborg University Hospital. In this study, DAS28crp and ASDAS are estimated from the PROM data to give the clinician an overview of PROM correlating to e.g. remission or high disease activity.

Table 1: overview of patient-reported outcome measures in this study

Variable	Disease area	Unit (range)	Aims to assess	MID/MCID	Equivalence margin
HAQ	RA/PsA/SpA	Points (0-3)	Physical function	0.22 points	± 0.11 points
VAS pain	RA/PsA/SpA	mm (0-100)	Pain intensity	10 mm	± 5 mm
VAS fatigue	RA/PsA/SpA	mm (0-100)	Fatigue severity	10 mm	± 5 mm
VAS global health	RA/PsA/SpA	mm (0-100)	Impact on global health	10 mm	± 5 mm
BASDAI	SpA	Points[1] (0-100)	Disease activity	10 points	± 5 points
BASFI	SpA	Points[1] (0-100)	Physical function	10 points	± 5 points
PASS	RA/PsA/SpA	Yes/No	Acceptable symptom state	N.A.[2]	± 15%points
Anchoring question	RA/PsA/SpA	Transition scale (much worse [-3]-much better [+3])	Change in arthritis activity	N.A.[2]	± 1 unit AND ± 15%points better
DAS28crp[3,4]	RA/PsA	Points (0.96-9.4)	Disease activity	1.2 points	± 0.6 points
ASDAS[3]	PsA[1]/SpA	Points (0.6-∞[5])	Disease activity	1.1 points	± 0.6 points

[1]: as used in the DANBIO registry

[2]: not applicable

[3]: will be estimated using a fixed level for CRP of 6

[4]: will be estimated using a fixed level for tender and swollen joint count respectively 1 tender joint and 0.5 swollen joint

[5]: no upper limit for ASDAS

6.7.1. Primary outcome

To evaluate whether electronic reporting of HAQ through a smartphone app is comparable to the traditional touch screen solution in the rheumatology outpatient clinics among patients with inflammatory arthritis.

6.7.2. Secondary outcomes

To evaluate whether electronic reporting of VAS pain, VAS fatigue, VAS global assessment, PASS, anchoring question, BASDAI and BASFI through a smartphone app is comparable to the traditional touch screen solution in the rheumatology outpatient clinic among patients with inflammatory arthritis. In addition, to evaluate whether electronic reporting of PROM through a smartphone app is comparable to the traditional touch screen solution in the rheumatology outpatient clinic stratifying by diagnosis (RA, PsA or SpA). Additionally, to evaluate whether the participants prefer reporting PROM electronically through the DANBIO app or the traditional touch screen solution in the rheumatology outpatient clinic.

6.8. Power and sample size considerations

In a two one-sided tests analysis for additive equivalence of paired means with bounds -0.11 and 0.11 for the mean difference in HAQ and a significance level of 0.05, assuming a mean difference of 0 HAQ points, a common standard deviation of 0.62 HAQ points and correlation 0.95 (between measures), a sample size of 36 pairs (12 patients with each condition) is required to obtain a power of at least 0.9. The actual power is 90.2%.

Minimal sample size: based on the same assumptions as above a sample size of 29 pairs (in total) is required to obtain a power of at least 0.8 (80.7%).

It was decided by the steering committee for this study, that in order to at least attempt to explore equivalence margins, within each disease group (i.e. RA, PsA and SpA) separately, a sample size of 20 pairs of each disease group would be feasible; i.e. enrolling 60 patients in total (corresponding to a power of 99.2%).

6.9. Randomisation and group allocation

6.9.1. Sequence generation

All participants who fulfil the eligibility criteria and who provides written informed consent for participation, will be enrolled and randomly allocated. A computer-generated randomisation sequence

will be produced before any patients are enrolled, allocating participants in permuted blocks of 2 to 4. The randomisation sequence will be prepared by a senior biostatistician with no clinical involvement in the study (Robin Christensen [RC]) and entered into the e-CRF in DANBIO by the independent data manager NSK. The sequence generation will be prepared with a 1:1 allocation ratio, stratified by diagnosis (i.e. RA, SpA or PsA). We will use SAS PROC PLAN to generate the 3 mutually independent randomisation schedules (3 diagnoses); SAS statistical software (version 9.4.).

6.9.2. Allocation concealment mechanism and implementation

After the participant is enrolled in the study (including signing informed consent), participants will be randomly allocated to the order of PROM-reporting scheduling modality after the physician "clicks" on the "randomisation button" in the electronic Case Report Form (e-CRF) in DANBIO (i.e. according to the sequence generation above). The randomisation number and assigned order will then be visible on the screen in DANBIO. Thus, the allocation will be concealed from the researcher enrolling participants and assessing study related data (LU).

6.9.3. Blinding

The interventions in this study are not blinded.

6.10. Statistical methods

This study is designed and will be carried out as a randomised cross-over agreement study. Thus, patients will be randomly assigned to one of two groups - completing either data registration on the smartphone app or the touch screen solution first. The order of questionnaires will be held constant, but patients enter the sequence at different time points starting with either the "App" or "Touch screen" version. Thus, each participant will answer the questionnaires through the app and the touch screen in randomised order at two successive periods (I or II), separated by a "washout period" of one day. In the cross-over design, each participant acts as his/her own control for questionnaire comparisons. This simple manoeuvre is attractive primarily because it increases the statistical power. Cross-over designs could suffer from a number of problems that can invalidate the results. A potential caveat related to cross-over studies concerns carryover (i.e. the residual influence of questionnaire recall in the subsequent period). We will attempt to evaluate and interpret a possible carryover effect statistically from the interaction between the main effects of questionnaire (app vs. touch screen) and

time period (I vs. II); realising, however, that the statistical test will lack power because the corresponding contrast is a 'between participant' analysis. We anticipate that a "washout period" of one day will be enough to avoid carryover (i.e. recall) bias. In addition, the arthritis conditions we include in this study are considered chronic and relatively stable, and thus it is highly unlikely that effects of their concomitant medication will interfere with the objective of this study (assessed only a couple of days apart). Another caveat to the clinical interpretation of a cross-over design could be the complications of analysis and interpretation arising from the loss of participants. We expect that losses of participants from the study will be small as the two data registration is done within one day, thus we do not anticipate that this will be an issue. A common, and generally satisfactory, use of the 2×2 cross-over design is to demonstrate the equivalence of two interventions (i.e. questionnaires) all other things being equal. We assume that an equal amount of participants will not adhere to the protocolised data collection ($n_{AT} \approx n_{TA}$).

Data will be analysed using SAS Proc Mixed. The MIXED procedure fits a variety of mixed linear models. A mixed linear model is a generalization of the general linear model (GLM); the generalization being that the data are permitted to exhibit correlation (i.e., from two measures on the same participant). Having a continuous outcome as the dependent variable (e.g. HAQ), our modelling component of SAS PROC MIXED will include both fixed (period [I or II]; questionnaire [App or Touch]; rheumatic condition [RA or PsA or SpA]) and random participant (i: 1, 2, 3, ….., n = 60) effects. In case of missing data for some of the participants, PROC MIXED handles the missing values implicitly adjusting for the missing values; unlike a GLM approach a mixed linear model uses the data for the periods where there is data and ignores the periods for which there is no data (10). Provided the data are "missing at random", the estimates from PROC MIXED are valid (e.g., the missing data cannot caused by some event happening during the first questionnaire exercise) (11). Imputations will not be used to replace missing data in the primary analyses, but will potentially be included in a sensitivity analysis to assess the impact/robustness of the conclusions.

Statistical interpretation of agreement: According to Piaggio et al. (12), equivalence is declared if the entire 2-sided 95%CI is included within the equivalence margin. Therefore, in this study a 2-sided 95% CI for the paired difference in each individual PROM (e.g HAQ) will be derived from the mixed linear model and agreement will be declared if the 95% CI of difference between PROMs is within the prespecified equivalence range (e.g., −0.11 HAQ-points to +0.11 HAQ-points). These margins (Table 1) are based on half of the effect that is usually considered a clinically relevant reduction in the individual PROMs. Thus, based on a superiority approach it was decided *a priori* that a 95% CI

excluding differences between groups of greater than half the MID/MCID units would be interpreted as indicating the absence of a clinically meaningful difference (agreement) (13). No interim analyses will be performed. All reported P values will be two-sided, based on a superiority assumption, and will not be adjusted for multiple comparisons.

6.11. Data management

Data will be collected from the two registrations in a dedicated e-CRF in the DANBIO database. Access to DANBIO is restricted by username and password and access to the study related data is restricted to research personnel. DANBIO use data logging to create an audit trail thereby registering e.g., who gains access to, is changing or entering data. In the e-CRF the following data will be entered by the patient: VAS pain, VAS fatigue, VAS global assessment, PASS and anchoring question and for patients with axial involvement BASDAI and BASMI as described in section *6.7. Outcomes*. For demographic description of the participants included in this study, the following information is collected from the DANBIO database: gender, age, diagnosis, disease duration, serological status, x-ray status, last CRP value, last joint assessment, last VAS physician, treatment with NSAID, DMARD, biologics or prednisolone and for patients with SpA last BASMI score.
In this study, data quality will be promoted through required data entry after each question. All study-related data will be destroyed 15 years after the end of this study.

7. ETHICS

7.1. Ethical consideration

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the Helsinki Declaration. The local Ethics Committee has categorised this study as a register study/questionnaire study and thus the study does not need to be approved by the Ethics Committee. As described in section *7.3. Informed consent*, the written informed consent is obtained from the participants by mail. The data collection of PROM in the rheumatology outpatient clinic at Aalborg University Hospital can be scheduled after the patient's wishes e.g. in connection to scheduled blood sampling, thus the time consumption in this study is considered acceptable. This study has no influence on the patient's current or future treatment. The participant will be informed about random findings of clinical significance if permission is given on the informed consent form.

The study is expected to contribute with information about electronic data collection of PROM through a smartphone app compared to the traditional touch screen solution in the rheumatology outpatient clinic. In light of the above, it is considered ethically justifiable to conduct the study.

7.2 Recruitment procedures

All patients with RA, PsA or SpA from the rheumatology outpatient clinic at Aalborg University hospital are requested for a telephone contact if the patient is interested in learning more about participation in this study. The request will state, that the telephone contact will be regarding participation in a small research project examine data entry through the touch screen solution versus a smartphone app. The request is made through the touch screen solution in the outpatient clinic in connection to a visit after the patients has registered their PROM data as usual. The patient must enter his/her mobile number for contact if he/she is interested in participation in the study.

7.3. Informed consent

Participants are recruited through the DANBIO touch screen solution in the outpatient clinic as described in section *7.2 Recruitment procedures.* LU will receive a list from Zitelab with telephone numbers on patients interested in participation in this study. The possible participants are contacted by telephone and informed about the study by LU. If the participant provides oral consent to receive further information about the study, the participant information is send to the patient by his/her email. The participant's email address is provided by the patient during the telephone call, where the patient also verify access to a smartphone that can download and run the DANBIO app. If the patient wishes to participate in the study, he/she is asked to sign the informed consent form and email it to LU or to give it to research personnel at the rheumatology outpatient clinic. Thereafter, LU will screen the possible participant for the inclusion criteria and exclusion criteria through DANBIO. If the possible participant fulfil the eligibility criteria, LU sign and date the informed consent form and the patient is included in the study. The participant is then randomised to group AT or group TA. For practical reasons, the participant must agree to enter data in both solutions within 1-2 weeks after the informed consent has been signed – however, there must be a "washout period" of 1 day between the two registrations.

8. APPROVAL

This study must be approved by the Danish Data protection Agency before enrolment of participants. This calibration project/agreement study is part of the ELECTOR EU project exploitation plan, thus the ELECTOR steering committee is informed about the conduct of this study and has approved it. This study is part of the Horizon 2020 ELECTOR project.
Zitelab ApS is partner in the ELECTOR consortium

9. CONFIDENTIALITY

In this study, PROM information will be passed on from the participant through a touch screen solution in the outpatient clinic and through the DANBIO app on a smartphone. The information is stored in the DANBIO database in the e-CRF. This information is used to evaluate if electronic data registration through the DANBIO app is comparable with the touch screen solution in the outpatient clinic. All study-related information will be stored securely at the study sites or in the e-CRF in DANBIO. All study-related data in the e-CRF will be identified by a coded ID number to maintain participant confidentiality, however, this does not apply for records that contain names or other personal identifiers, such as informed consent forms, which will be stored with the TMF in locked file cabinets in areas with limited access, thus away from study records identified by ID number. The code for the ID numbers is stored safely in another locked file cabinet in areas with limited access away from all other study-related data. Access to the e-CRF in DANBIO will be excluded to LU. The DANBIO database meets current data security requirements because of data logging, which create an audit trail as explained in section *6.11. Data management*. All study-related data will not be made available to a third party with the exception of authorized representatives of the relevant health or regulatory authorities, e.g. the Ethics Committee. This study will comply with The Danish laws regarding patient confidentiality (Lov om behandling af personoplysninger og Sundhedsloven) and is reported to the Danish Data Protection Agency. Data will be destroyed 15 years after the end of this study.

10. COMPENSATION

Study participants will not be financially reimbursed in this study. Research personnel including investigators will not be financially reimbursed for enrolling participants in this study.

11. DISSEMINATION POLICY

This study will be registered on Clinicaltrials.gov before enrolling patients.

All results of this study will be published e.g., in English-language peer reviewed medical journals as well as presented at international congresses. Both negative, inconclusive and positive research results will be reported. Line Uhrenholt will be first author, Niels Steen Krogh, Annette Schlemmer, Ellen-Margrethe Hauge and Robin Christensen will be co-authors and Salome Kristensen will be last author. Other authors will be dependent on the contributions. The Vancouver rules for authorship will be followed.

12. BUDGET

This study is performed without any funding; however, LU's salary is funded by the Rheumatology Department at Aalborg University Hospital, where LU is employed. The DANBIO app is developed and owned by Zitelap.

13. TIME SCHEDULE

Recruitment of participants will start after relevant authorities approve this protocol and is scheduled to start January 2018 and last until the target population is achieved (presumably no longer than 3 months).

14. LIST OF APPENDIX'

Appendix 1: VAS pain, fatigue and global health
Appendix 2: HAQ
Appendix 3: PASS
Appendix 4: Anchoring question
Appendix 5: BASDAI
Appendix 6: BASFI
Appendix 7: DAS28crp
Appendix 8: ASDAS

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Appendix 1: VAS pain, fatigue and global health

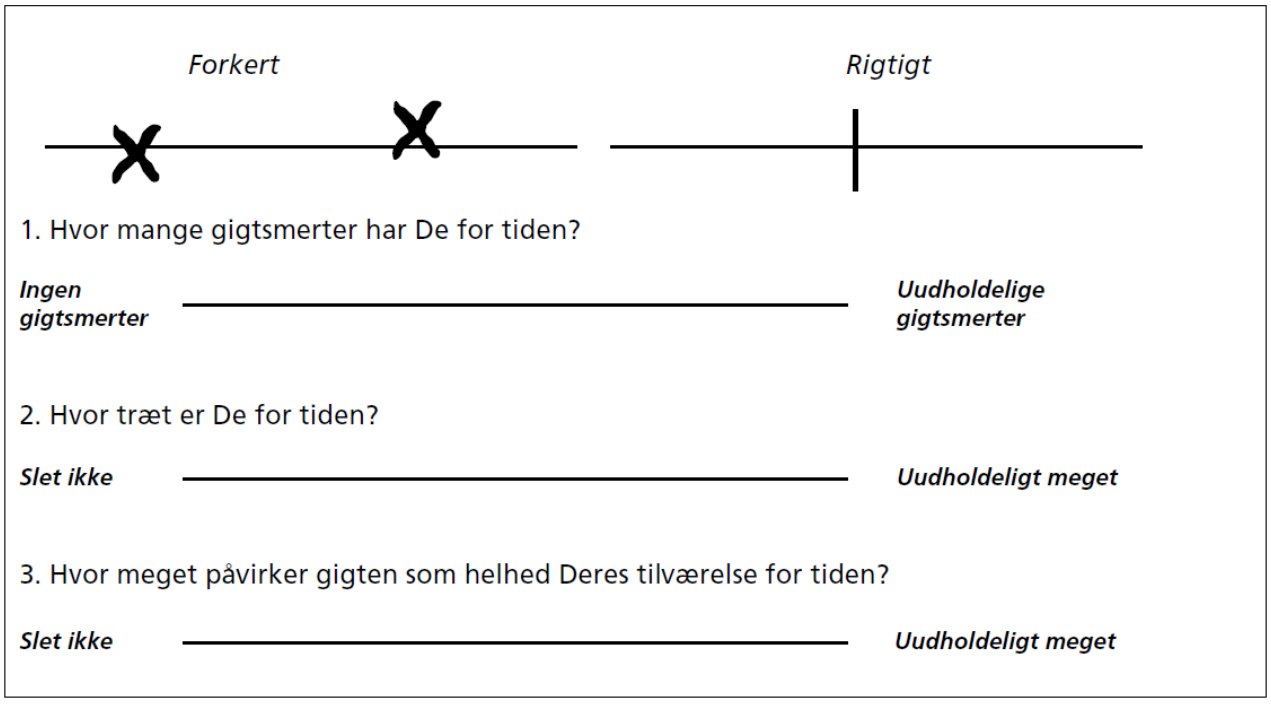
Below is the Danish version of the Patient VAS-questionnaires used DANBIO. The left of the VAS scale (0 mm) signifies the absence of symptoms and the right end (100 mm) maximum activity in terms of the parameters assessed.

Question 1 regards the patient's assessment of pain within the last week on a 100 mm horizontal VAS scale (VAS Pain)

Question 2 regards the patient's assessment of fatigue within the last week on a 100 mm horizontal VAS scale (VAS Fatigue)

Question 2 regards the patient's global assessment of disease activity (arthritis severity) within the last week on a 100 mm horizontal VAS scale (VAS Global Health)

De bedes besvare de følgende tre spørgsmål ved at sætte en kort streg gennem linien på det punkt, som De mener passer til svaret på spørgsmålet.



Appendix 2: HAQ

HAQ assess the patient's physical function and consist of 20 questions regarding eight different aspects of functional activities. Is answered by the patient on a scale from zero (no disability) to three (completely disabled).

Below is a copy of the Danish version of the HAQ used in DANBIO and in this study:

Husk kun at sætte ét kryds ved hvert spørgsmål.
Hvis De bruger hjælpemidler, skal De svare på, hvordan De klarer Dem med hjælpemidler.

	Ja, uden besvær	Ja, med noget besvær	Ja, med meget besvær	Nej, det kan jeg ikke
Kan De selv klæde Dem på? (det gælder også snørebånd og knapper)	☐	☐	☐	☐
Kan De selv vaske Deres hår?	☐	☐	☐	☐
Kan De rejse Dem fra en spisestuestol?	☐	☐	☐	☐
Kan De selv klare at komme i og ud af en seng?	☐	☐	☐	☐
Kan De selv skære et stykke stegt kød i stykker?	☐	☐	☐	☐
Kan De løfte en fyldt kop eller et fyldt glas?	☐	☐	☐	☐
Kan De selv åbne en ny mælkekarton?	☐	☐	☐	☐
Kan De selv gå rundt udendørs, hvor der er fladt?	☐	☐	☐	☐
Kan De selv gå 5 trin op ad en trappe?	☐	☐	☐	☐

	Ja, uden besvær	Ja, med noget besvær	Ja, med meget besvær	Nej, det kan jeg ikke
Kan De selv vaske og tørre Dem over det hele?	☐	☐	☐	☐
Kan De selv tage karbad?	☐	☐	☐	☐
Kan De selv klare toiletbesøg?	☐	☐	☐	☐
Kan De nå op, og hente noget tungt ned fra en hylde over hovedhøjde (f.eks. 2 kg sukker)?	☐	☐	☐	☐
Kan De selv samle f.eks. tøj op fra gulvet?	☐	☐	☐	☐
Kan De selv åbne en bildør?	☐	☐	☐	☐
Kan De skrue låget af et glas, der har været åbnet før?	☐	☐	☐	☐
Kan De åbne og lukke en almindelig vandhane?	☐	☐	☐	☐
Kan De selv klare indkøb og andre ærinder?	☐	☐	☐	☐
Kan De selv komme ind og ud af en bil?	☐	☐	☐	☐
Kan De selv klare husarbejdet f.eks. støvsugning eller lettere havearbejde?	☐	☐	☐	☐
	0	1	2	3

Appendix 3: PASS

PASS is used to access the patient's acceptable symptom state and consist of one question answered with "yes" or "no. In DANBIO the Danish PASS question states:

"Tænk på alle de måder, som din gigt har påvirket dig de seneste 48 timer. Hvis du i de kommende måneder fortsatte med at have det, som du har haft det de seneste 48 timer, ville det så være acceptabelt for dig?"

Appendix 4: Anchoring question

The anchoring question is used to access if the patient's arthritis has changed since the last visit and is answered with "much worse", "worse", "a little worse", "unchanged", "a little better", "better" and "much better". In DANBIO the Danish anchoring question states:

"Siden dit sidste besøg er din gigt blevet:"

Appendix 5: BASDAI

BASDAI is used for patients with axial arthritis. The questionnaire consist of six questions regarding essential symptoms in axial arthritis on a 100 mm horizontal VAS scale

Sygdomsaktivitet ved morbus Bechterew (MB)

(The Bath Ankylosing Spondylitis Disease Activity Index = BASDAI)

Marker på hver skala herunder dit svar til hvert punkt, der alle omhandler *den forløbne uge.*

1) Angiv sværhedsgraden af din træthed.

INGEN _____ **MEGET SVÆR**

2) Angiv sværhedsgraden af Bechterew smerter i nakke, ryg, lænd eller hofter.

INGEN _____ **MEGET SVÆR**

3) Angiv sværhedsgraden af smerter i *andre led* end nakke, ryg, lænd eller hofter.

INGEN _____ **MEGET SVÆR**

4) Angiv sværhedsgraden af ubehag i områder, som er ømme ved tryk eller berøring.

INGEN _____ **MEGET SVÆR**

5) Angiv sværhedsgraden af din morgenstivhed.

INGEN _____ **MEGET SVÆR**

6) Angiv tiden indtil din morgenstivhed begynder at aftage.

0 time _____ **2 eller flere timer**

Appendix 6: BASFI

BASFI is used for patients with axial arthritis. The questionnaire consist of ten questions regarding physical function on a 100 mm horizontal VAS scale.

Funktionsindeks ved morbus Bechterew

(The Bath Ankylosing Spondylitis Function Index = BASFI)

Hvordan bedømmer du din evne til at udføre hver af de følgende opgaver *i den forløbne uge*?

NB. Et hjælpemiddel er et redskab, som letter udførelsen af en handling eller bevægelse.

1) Kan du tage strømper på uden hjælp eller brug af hjælpemiddel (f.eks. et strømpehjælpemiddel)?

LET _____ **UMULIGT**

2) Kan du uden brug af hjælpemiddel bøje fremover i ryggen (evt. med let bøjede knæ) og samle en kuglepen op fra gulvet?

LET _____ **UMULIGT**

3) Kan du række op på en hylde over hovedhøjde uden hjælp eller brug af hjælpemiddel?

LET _____ **UMULIGT**

4) Kan du rejse dig fra en spisestuestol uden armlæn uden at bruge hænderne eller anden form for hjælp?

LET _____ **UMULIGT**

5) Kan du uden hjælp komme op fra gulvet, når du ligger på ryggen?

LET _____ **UMULIGT**

6) Kan du uden ubehag stå i 10 minutter uden støtte?

LET _____ **UMULIGT**

7) Kan du med en fod på hvert trin gå 12-15 trin på en trappe uden at bruge gelænderet eller anden hjælp?

LET _____ **UMULIGT**

8) Kan du se dig over skulderen uden at dreje kroppen?

LET _____ **UMULIGT**

9) Kan du udføre fysisk krævende opgaver (f.eks. Bechterew øvelser, havearbejde eller sport)?

LET _____ **UMULIGT**

10) Kan du gennemføre en 7½ timers arbejdsdag (hjemme eller på arbejde)?

LET _____ **UMULIGT**

Appendix 7: DAS28crp

DAS28crp are a composite score based on 28 joint count for tenderness and swelling, patient VAS global health and CRP level. The DAS28crp formula are:

$$DAS28crp = 0.56\sqrt{(TJC28)} + 0.28\sqrt{(SJC28)} + 0.36\ln(CRP + 1) + 0.014(GH) + 0.96$$

TJC28: 28 joint count for tenderness

SJC28: 28 joint count for swelling

CRP: C-reactive protein in mg/L

GH: patient global assessment of disease activity from 0-10 on the 100 mm VAS scale

The scoring range for DAS28crp are:

High disease activity: DAS28crp $\geq$ 5.1

Moderate disease activity: DAS28crp = 3.2-5.1

Low disease activity: DAS28crp = 2.6-3.1

Remission: DAS28crp < 2.6

Appendix 8: ASDAS

ASDAS are a composite score based on patient VAS back pain, patient VAS morning stiffness, patient VAS peripheral joint pain and/or swelling, patient VAS global health and CRP level. The ASDAS formula are:

ASDAS = 0.12*Back Pain + 0.06*Morning Stiffness + 0.11*Patient Global + 0.07*Peripheral Pain/Swelling + 0.58*Ln(CRP+1)

Back pain: assessed by the patient on a 100 mm VAS scale (range 0-10)

Morning Stiffness: assessed by the patient on a 100 mm VAS scale (range 0-10)

Patient Global: assessed by the patient on a 100 mm VAS scale (range 0-10)

Peripheral Pain/Swelling: assessed by the patient on a 100 mm VAS scale (range 0-10)

Ln: natural logarithm

CRP: C-reactive protein in mg/L

The scoring range for ASDAS are:

Very high disease activity: ASDAS > 3.5

High disease activity: ASDAS = 2.1-3.5

Moderate disease activity: ASDAS = 1.3-2.0

Remission: ASDAS < 1.3

Statistical Analysis Plan (SAP): Randomised Crossover Trial

Patient-reported outcome measures collected in DANBIO reported via a smartphone app *vs* a touchscreen solution in an outpatient clinic among patients with inflammatory arthritis: *A randomised, crossover, agreement study*

Short title: The DANBIO app versus touchscreen agreement trial

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Section 1: Administrative Information

Title and trial registration

Statistical analysis plan (SAP) for the DANBIO app agreement trial entitled "*Patient-reported outcome measures collected in DANBIO reported via a smartphone app vs a touchscreen solution in an outpatient clinic among patients with inflammatory arthritis: A randomised, crossover, agreement study*".

Trial registration: Clinical Trials number: NCT03486613.

SAP version

Version 1.0

November 7th 2019

Protocol version

This document has been written based on information contained in the study protocol version 1, dated December 21st 2018.

SAP revisions

None.

Roles and responsibility

LU and RC designed and wrote this SAP for "the DANBIO app versus touchscreen agreement trial" in accordance to the CONSORT statement for randomised crossover trials (1). LU and RC is responsible for analysis of the trial results according to the SAP.

Signatures

MD, PhD Student, Principal investigator Line Uhrenholt 7/11-19 Date

Professor, Senior Biostatistician, Robin Christensen, MSc, PhD Nov. 15, 2019 Date

Section 2: Introduction

Background and rationale

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) are three major inflammatory arthritic diseases in Rheumatology. Since the 1980's, patient-reported outcome measures (PROMs) have been used in clinical research and later also in daily clinical practice as an essential tool to evaluate the patient's perception of arthritis activity. Initially, PROMs was collected in a paper form; however, in Denmark, PROMs are more feasibly collected electronically through a touchscreen solution in the outpatient clinic since 2008 (2).

Today, due to the widespread use of smartphones it is now possible and feasible to use the participants' own device for collecting PROM data via a downloaded smartphone app. Using a smartphone app instead of the standard touchscreen solution in the outpatient clinic is anticipated to eliminate problems such as having to wait in a queue, lack of privacy, and uncomfortable position during data entering etc. Furthermore, data can be collected when and where it suits the individual patient best; thereby, possibly providing more accurate answers and minimising recall-bias.

In rheumatology, Health Assessment Questionnaire Disability Index (HAQ-DI) is among the most frequently used PROMs to asses patients with RA, PsA and axSpA (3–5); thus, it makes sense to consider HAQ-DI to be one of the essential PROMs to evaluate patients with these inflammatory arthritis diseases (3–5).

Aims

To evaluate whether electronic reporting of PROMs through a smartphone app is comparable to the standard touchscreen solution in the rheumatology outpatient clinic among patients with RA, PsA and axSpA in standard clinical care.

Hypothesis

Use of a smartphone app for registration of PROMs in rheumatology yields comparable results with the standard touchscreen solution in the outpatient clinic.

Objectives

Primary objective

To demonstrate a reasonably equivalent* self-reported disability status determined by the HAQ-DI score when using a smartphone app compared to the standard touchscreen solution among patients with inflammatory arthritis enrolled in a randomised, crossover, agreement study.

*Equivalence of HAQ-DI disability status will be concluded if the 95% confidence interval for monitoring difference is within ±0.11 HAQ-DI score points.

Secondary objectives

To evaluate whether electronic reporting of VAS (Visual Analog Scale) pain, VAS fatigue, VAS global assessment, Patient Acceptable Symptom State (PASS), anchoring question, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) through a smartphone app is reasonably comparable to the standard touchscreen solution in the rheumatology outpatient clinic among patients with inflammatory arthritis. In addition, to explore whether the electronic reporting of PROMs through a smartphone app is comparable to the standard touchscreen solution in the rheumatology outpatient clinic when stratifying by diagnosis (RA, PsA or axSpA). Additionally, to evaluate whether the participants prefer reporting PROMs electronically through the DANBIO app or the standard touchscreen solution in the rheumatology outpatient clinic.

Section 3: Study Methods

Trial design

The trial is a randomised, within-participant, crossover design including patients with RA, PsA and axSpA. In a crossover study, each participant acts as his/her own control for the questionnaire comparisons; thus, each patient answered the PROM questionnaires through the DANBIO app and the touchscreen in a randomised order at two consecutive time periods. The PROM questionnaires answered in the DANBIO app was exactly the same questionnaires as the participant answered on the touchscreen in the outpatient clinic.

PROM data registration through the touchscreen in the outpatient clinic was as usual done after the participant had logged on with his/her personal civil registration (CPR) number. Before PROM data registration through the DANBIO app, the participants had to download the DANBIO app on their smartphone. Thereafter, the patient logged on the app with his/her personal identification number (nemID) and gained access to the PROM questionnaires.

After inclusion, the participants was randomised in ratio 1:1 to:

- Group *App device* → *Touchscreen solution* (AD → TS) i.e. PROM data is reported through the DANBIO app first and after a "washout period" through the touchscreen
- Group *Touchscreen solution* → *App device* (TS → AD) i.e. PROM data is reported through the touchscreen first and after a "washout period" through the DANBIO app

To minimise the potential carryover (recall) effect between the two PROM registrations, it was decided that there would be a "washout period "of one day between the two registrations, whereas 2 days at the latest. We anticipated that a "washout period" of one day would be enough to avoid carryover bias i.e. the effect of questionnaire recall in the second period.

Randomisation

A computer-generated randomisation sequence was produced before any patients were enrolled, allocating the participants in permuted blocks of 2 to 4, stratified by diagnosis (i.e. RA, PsA or axSpA). The three randomisation sequences were made by the senior biostatistician with no clinical involvement in the study (RC) and entered into the electronic case report form (e-CRF) in DANBIO by the independent data manager Niels Steen Krogh (NSK). SAS PROC PLAN was used to generate the three mutually independent randomisation schedules (3 diagnoses), SAS statistical software (version 9.4.).

Power and sample size

The Minimal Important Difference (MID)/ Minimal Clinically Important Difference (MCID) for the PROMs evaluated in this trial is listed in table 2. MID/MCID describes the effect that is considered a clinically relevant reduction in the individual PROMs.

It was decided *a priori* that a difference in PROMs between groups ≤ half of the MID/MCID units would be interpreted as absence of a clinically meaningful difference (i.e. agreement) (6). Thus, for HAQ-DI the equivalence margin was set to ± 0.11 points i.e. half of the MID/MCID of 0.22 points.

The sample size was based on the following assumptions: in a two one-sided tests analysis for additive equivalence of paired means with bounds -0.11 and 0.11 for the mean difference in HAQ-DI and a significance level of 0.05, assuming a mean difference of 0 HAQ-DI points, a common standard deviation of 0.62 HAQ-DI points (7) and correlation 0.95 (between measures), a sample size of 36 pairs (12 patients with each condition) were required to obtain a power of at least 90%.

Minimal sample size: based on the same assumptions as above a sample size of 29 pairs in total (10 patients with each condition) was required to obtain a power of at least 80%. It was decided by the steering committee for this study, that in order to at least attempt to explore equivalence margins within each disease group (i.e. RA, PsA and axSpA) separately, a sample size of 20 pairs of each disease group would be feasible; i.e. enrolling 60 patients in total (corresponding to a power of 99.2%).

Framework

Although the main objective is to explore similarity between PROM devises, the precision of the estimates will be derived from a superiority analysis framework. The objective of this crossover trial is to evaluate whether electronic reporting of HAQ-DI, VAS pain, VAS fatigue, VAS global assessment, PASS, anchoring question, BASDAI and BASFI through the DANBIO app is comparable to the standard touchscreen solution in the outpatient clinics among patients with inflammatory arthritis. Furthermore, to evaluate whether electronic reporting of PROMs through the DANBIO app is comparable to the standard touchscreen solution in the outpatient clinic stratifying by diagnosis (RA, PsA or axSpA). Thus, in the outcomes listed above we will test for equivalence.

Additionally, this study will evaluate whether the participants prefer reporting PROMs electronically through the DANBIO app or the standard touchscreen solution in the outpatient clinic. Hence, this outcome will be tested for superiority.

Statistical interim analyses and stopping guidance

No interim analyses were performed during this trial; no data analyses will be done before closure of the final SAP.

Timing of final analysis

Final analysis will be performed collectively as all outcomes are short-term outcomes.

Timing of outcome assessments

The timing of outcome assessments is illustrated below in **Table 1**:

Table 1: *Overview of time points for PROM data registration in the DANBIO-App trial*

Day	**Action**
Day 1	Participant enters PROM data through the 1st device
Day 2 to 3	Washout period
Day 3 or 4	Participant enters PROM data through the 2nd device

Section 4: Statistical Principles

Confidence intervals and P values

Level of statistical significance and use of confidence intervals

All applicable statistical analyses will be 2-sided based on a superiority framework; i.e. all confidence intervals will be presented as 95% and two-sided (95%CI).

Rationale for any adjustment for multiplicity

All applicable statistical tests and 95% confidence intervals presented will be 2-sided. Even in equivalence trials (illustrating comparability), the selection of an appropriate statistical strategy for dealing with multiplicity (repeated statistical tests) is critical for performing reliable inferences and maximizing the probability of a chance finding. Multiplicity considerations play a central role in the assessment of competing clinical objectives; i.e. the more comparisons that are made, the more likely it is that a comparison that appears to be statistically important will be falsely so (i.e. that the PROM devises appear different or with too wide 95%CIs). In order to preserve the family wise error rate of the multiple analyses, the multiplicity of the analyses of the primary and selected secondary PROMs will be presented and interpreted using a gatekeeping procedure (8). The analysis interpretation will be performed in sequence until one of the analyses has failed to be within the prespecified equivalence margin (see **Table 2** below).

Adherence and protocol deviations

Acceptable compliance to the protocol is defined as participants who complete both first and second PROM data registration within the scheduled time frame.

Pre-defined major protocol violations that might occur are:

- Not completing the first and second PROM data registration
- Not completing the second PROM data registration
- No wash out period between the first and second data registration i.e. second registration performed on day 2

Pre-defined minor protocol violations are:

- Delayed second data registration i.e. PROM data registration with a washout period of > 1 days i.e. second data registration at day 4 or later

The number (*N*) and percentage of patients with major and minor protocol deviations will be summarised by randomisation group with details of the type of deviation. The participants that are included in the intention-to-treat (ITT) analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

Analysis populations

The analyses for the primary and secondary endpoints will be conducted according to the ITT principle; i.e. based on the full analysis set (all randomised individuals having at least the first outcome measures from period 1 collected, independent of subsequent protocol violations); analyses will based on maximum likelihood (mixed linear) models, where no explicit imputation techniques (data as observed). Statistical models with missing outcome data for an individual participant are valid under the 'Missing At Random' assumption when using a maximum likelihood approach (in which estimates and standard errors are based on the likelihood function given the observed data).

Per-protocol population analyses will be performed for the primary endpoint excluding participants having major protocol violations: i.e. the per-protocol population consist of participants who adhere to the eligibility criteria and complete the first and second PROM data registration within the scheduled time points.

Section 5: Agreement Trial Population

Screening data

The screening period started at March 23rd 2019 when an invitation became visible at the end of every RA, PsA and axSpA patient's PROM data registration on the touchscreen in the outpatient clinic. The following screening data will be registered and presented:

- Length of the screening period in which the invitation to participate in the study was visible on the touchscreen in the outpatient clinic
- Length of the recruiting period i.e. from start of enrolment to the last patient is enrolled
- Number of patients screened i.e. number of patients who answered "yes" or "no" to the invite on the touchscreen in the outpatient clinic
- Number of patients, who were interested in participation and send the participant information and informed consent form by e-mail but did not reply i.e. did not send the signed informed consent form back to the investigator
- Number of patients who signed the informed consent form
- Number of patients recruited i.e. patients who were randomised
- Number of screened patients not recruited
- Reason for non-recruitment

Eligibility

Inclusion criteria:

- Diagnosed and registered in DANBIO with RA, PsA or axSpA (more than a year)
- Currently treated and monitored at the rheumatology outpatient clinic at Aalborg University Hospital
- Have previously reported PROMs in DANBIO through the touchscreen solution at the outpatient clinic ≥ 3 times

Exclusion criteria:

- Inability to provide informed consent or unwilling to comply with the study protocol
- Diagnosis of RA, PsA or axSpA ≤ 12 months
- Does not have access to a smartphone that can download and run the DANBIO app

- Not able to understand written Danish i.e. cannot understand the Danish version of the PROM questionnaires
- Visual impairment to such a degree that the participant cannot read the questionnaire in the smartphone app/on the touchscreen with e.g. glasses

The number of ineligible patients randomised, if any, will be reported, with reasons for ineligibility. Furthermore, a CONSORT flow diagram (**Outline Figure 1**, presented below) will provide details on the number of screened patients who were excluded due to ineligibility.

Recruitment

Recruitment of participants began at April 24th 2019.

A CONSORT flow diagram (Outline Figure 1) will summarise the number of patients who were:

- Assessed for eligibility at screening
- Eligible at screening
- Ineligible at screening[1]
- Eligible and randomised
- Eligible but not randomised[1]
- Followed the randomised allocation
- Did not follow the randomised allocation[1]
- Lost to follow-up[1]
- Discontinued the study[1]
- Randomised and included in the primary analysis
- Randomised and excluded from the primary analysis[1]

[1]: Reasons will be provided.

Withdrawal/lost to follow-up

It is expected, that participant withdrawal of consent will be small as the two PROM data registrations are undertaken within three to four consecutive days. The level of consent withdrawal will be classified as:

- Withdraw from the trial but allow use of data collected to date
- Withdraw from the trial and withdraw consent for use of data collected to date
- Lost to follow-up

The CONSORT flow diagram (Outline Figure 1) will present withdrawals with numbers, reasons for withdrawal and/or exclusion from analysis at each stage i.e. first registration and second registration. Thus, withdrawals over the course of the trial will be presented with numbers and reasons summarised by treatment arm.

Baseline patient characteristics

Baseline participant characteristics will be presented in a table (**Outline Table 1**, presented below). Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD and range if data are normally distributed and median, IQR and range if data are skewed. Minimum and maximum values will be presented for continuous data. Tests of statistical significance for baseline characteristics will not be performed; however, the clinical importance of any imbalance will be noted.

Section 6: Analysis

Outcome measures and definitions

***Table 2**: overview of definitions of the patient-reported outcome measures in this study.*

Variable	Disease area	Unit (range)	Aims to assess	MID/MCID	Equivalence margin
HAQ-DI	RA/PsA/axSpA	Points (0-3)	Physical function	0.22 points	± 0.11 points
VAS pain	RA/PsA/axSpA	mm (0-100)	Pain intensity	10 mm	± 5 mm
VAS fatigue	RA/PsA/axSpA	mm (0-100)	Fatigue severity	10 mm	± 5 mm
VAS global health	RA/PsA/axSpA	mm (0-100)	Impact on global health	10 mm	± 5 mm
PASS	RA/PsA/axSpA	Yes/No	Acceptable symptom state	N.A.[2]	± 15%points
Anchoring question	RA/PsA/axSpA	Transition scale (much worse [-3]-much better [+3])	Change in arthritis activity	N.A.[2]	± 1 unit AND ± 15%points better
DAS28crp[3,4]	RA/PsA	Points (0.96-9.4)	Disease activity	1.2 points	± 0.6 points
ASDAS[3]	PsA[1]/axSpA	Points (0.6-∞[5])	Disease activity	1.1 points	± 0.6 points
BASDAI	axSpA	Points[1] (0-100)	Disease activity	10 points	± 5 points
BASFI	axSpA	Points[1] (0-100)	Physical function	10 points	± 5 points

[1]: as used in the DANBIO registry

[2]: not applicable

[3]: will be estimated using a fixed level for CRP of 6

[4]: will be estimated using a fixed level for tender and swollen joint count respectively 1 tender joint and 0.5 swollen joint

[5]: no upper limit for ASDAS

Analysis methods

This study is designed and will be carried out as a randomised, crossover, agreement study. Thus, patients will be randomly assigned to one of two groups; completing either the PROM data registration on the DANBIO app or the touchscreen solution first. The order of questionnaires will be held constant, but patients enter the sequence at different time points starting with either the "app device" or "touchscreen solution". Thus, each participant will answer the questionnaires through the DANBIO app and the touchscreen in a randomised order at two successive time periods (I or II) separated by a "washout period".

In the crossover design, each participant acts as his/her own control for the questionnaire comparisons. This simple manoeuvre is attractive primarily because it increases the statistical power in superiority trials. However, crossover designs can also be associated with a number of potential problems that can invalidate the results. A specific example concerns "carryover" (i.e. the residual influence of previous questionnaire responses in the subsequent period). We will attempt to evaluate and interpret a possible carryover effect statistically from the interaction between the main effects of questionnaire (app vs. touchscreen) and time period (I vs. II). We anticipate that a "washout period" of one day will be enough to avoid carryover (i.e. recall) bias. In addition, the arthritis conditions we include in this study are considered chronic and relatively stable; thus, it is highly unlikely that effects of their concomitant medication will interfere with the objective of this study (assessed only a couple of days apart).

Another caveat to the clinical interpretation of a crossover design could be the complications of analysis and interpretation arising from the loss of participants. We expect that losses of participants from the study will be small as the two data registrations are done within three days; thus, we do not anticipate that this will be an issue. A common, and generally satisfactory, use of the 2×2 crossover design is to demonstrate the equivalence of two interventions (i.e. questionnaires) all other things being equal. We assume that an equal number of participants will not adhere to the protocoled data collection ($n_{AT} \approx n_{TA}$).

Data will be analysed using SAS Proc Mixed. The MIXED procedure fits a variety of mixed linear models. A mixed linear model is a generalization of the general linear model (GLM); the generalization being that the data are permitted to exhibit correlation (i.e., from two measures on the same participant). Repeated measures from the same individuals included maximum likelihood models, analysed using mixed models enables valid inference even with missing data from individuals having only some of their outcome measures observed (9). Having a continuous outcome as the

dependent variable (e.g. HAQ-DI), our modelling component of SAS PROC MIXED will include both fixed (period [I or II]; questionnaire [App Device or Touchscreen Solution]; rheumatic condition [RA or PsA or axSpA]) and random participant (i: 1, 2, 3, ….., n = 60) effects.
All analyses will be adjusted for the PROM-level at enrolment covariate i.e. the last DANBIO registration of the outcome (e.g. HAQ-DI) prior to enrolment in this trial.

Statistical interpretation of agreement

According to Piaggio et al. (10), equivalence is declared if the entire 2-sided 95%CI is included within the equivalence margin. Therefore, in this study a 2-sided 95% CI for the paired difference in each individual PROM (e.g HAQ-DI) will be derived from the mixed linear model and agreement will be declared if the 95% CI of difference between PROMs is within the prespecified equivalence range (e.g., −0.11 HAQ-DI-points to +0.11 HAQ-DI-points). These margins (see Table 2, above) are based on half of the effect that is usually considered a clinically relevant reduction in the individual PROMs. Thus, based on a superiority approach it was decided *a priori* that a 95% CI excluding differences between groups of greater than half the MID/MCID units would be interpreted as indicating the absence of a clinically meaningful difference (agreement) (6).

Missing data

In case of missing data for some of the participants, PROC MIXED handles the missing values implicitly adjusting for the missing values; unlike a GLM approach a mixed linear model uses the data for the periods where there is data and ignores the periods for which there is no data (11). Provided the data are "missing at random" (MAR), the estimates from PROC MIXED are valid (12).
Imputations will not be used to replace missing data in the primary analyses, but will potentially be included in a sensitivity analysis to assess the impact/robustness of the conclusions.

Additional analyses

The following pre-specified subgroup analyses will be performed on HAQ-DI to identify potentially important contextual factors. Given the relatively small numbers of participants to be recruited and the gender predominance in both RA and AS, such pre-specified subgroup analyses is likely not adequately powered. Thus, the following potentially important subgroups will be explored by using stratified analyses, using a $p < 0,10$ as being potentially important:

- Female sex versus male sex

- RA versus other (i.e. PsA or axSpA)
- The younger half of the trial group versus the older half (median for each diagnosis)
- Age > 65 years versus age ≤ 65 years (e.g. participants with anticipated IT-experience)
- Duration of data registration > 30 minutes (i.e. longer than anticipated) versus duration of data registration ≤ 30 minutes

Harms and adverse events

This study only tests the DANBIO app against the touchscreen solution in the outpatient clinic among patients with inflammatory arthritis; thus, the trial has no influence on the patient's current or future arthritis treatment. Consequently, safety data will not be collected during the course of this trial.

Statistical software

Data will be analysed using SAS Proc Mixed. The MIXED procedure fits a variety of mixed linear models.

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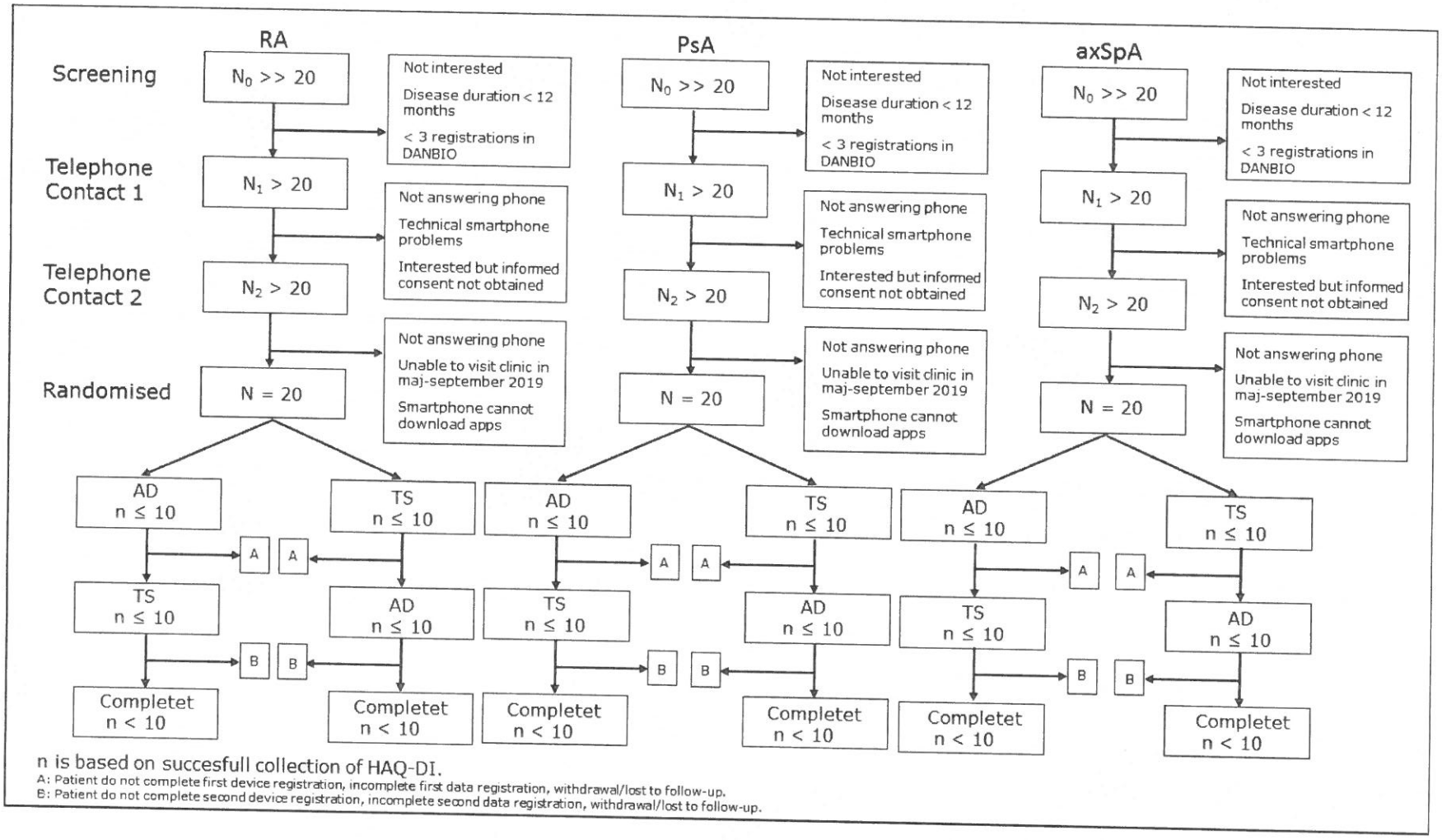
Section 7: Manuscript outline

The manuscript outline will include the following documents:

- Appendix 1: The trial protocol, version 1 (pdf)
- Appendix 2: The statistical analysis plan, version 1.0 (pdf)
- Draft Outline Figure 1: Simulated Data
- Outline Table 1: Patient demographics and clinical characteristics
- Draft Outline Figure 2: Simulated Data for Bland-Altman Plot
- Outline Table 2: Comparison between groups for all PROM and clinical outcomes
- Outline Table 3: Results of stratified (subgroup) analyses for HAQ-DI (the primary outcome)

Draft **Outline Figure 1**: Simulated Data

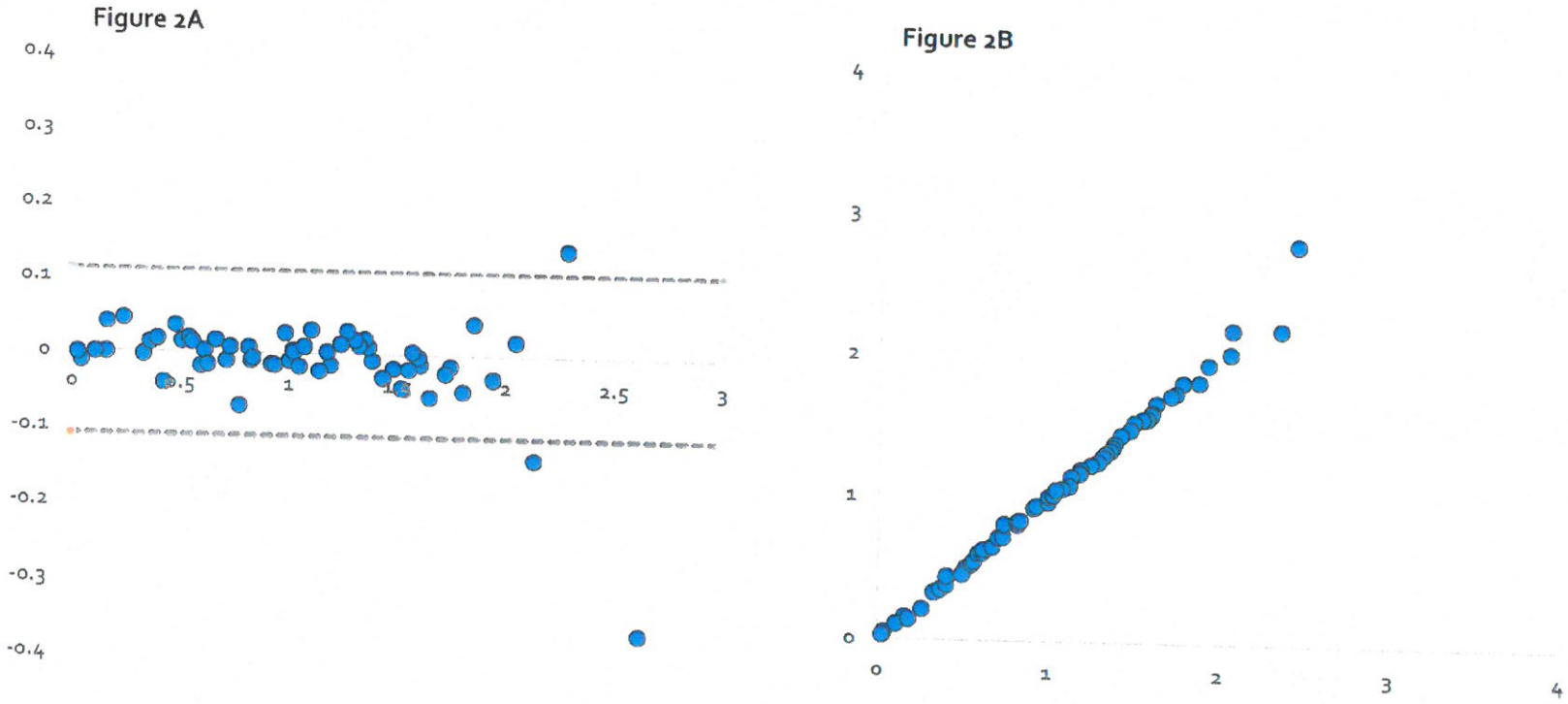


Outline Table 1: Patient demographics and clinical characteristics.

Variable	AD → TS	TS → AD	All
General characteristics			
Male, n (%)			
Age (years)			
Disease duration (years)			
Current csDMARD, n (%)			
One csDMARD, n (%)			
Two csDMARDs, n (%)			
Three csDMARDs, n (%)			
MTX, n (%)			
MTX dose (mg/week)			
Oral steroids, n (%)			
Current bDMARDs or tsDMARDs, n (%)			
Last VAS physician			
Last CRP (mg/L)			
PROM			
HAQ-DI			
VAS pain			
VAS fatigue			
VAS global			
PASS "Yes", n (%)			
Anchoring question			
Disease specifics			
Diagnosed with RA, n (%)			
IgM-RF positive, n (%)			
ACPA positive, n (%)			
Erosive, n (%)			
Last tender joint count			
Last swollen joint count			
Last Das28crp			
Diagnosed with PsA, n (%)			
Erosive, n (%)			
Last tender joint count			
Last swollen joint count			
Last Das28crp			
Diagnosed with axSpA, n (%)			
Ankylosing spondylitis, n (%)			
BASDAI			
BASFI			
HLA-B27 positive, n (%)			
Sacroiliitis on x-ray, n (%)			
Last tender joint count			
Last swollen joint count			
Last BASMI			
Last ASDAScrp			

AD: app device, TS: touchscreen solution. For continuous outcomes values will be reported as means and SDs, unless otherwise stated.

Draft **Outline Figure 2**: Simulated Data for Bland-Altman Plot



Outline Table 2: Comparison between groups for all PROM and clinical outcomes.

Outcome	**AD → TS**		**TS → AD**		**Difference (95%CI)**	**Test[1]**
	AD	***TS***	***TS***	***AD***	***AD – TS***	
General outcomes						
HAQ-DI						
VAS pain						
VAS fatigue						
VAS global						
PASS						
Anchoring question						
Device preference						
Duration of registration[2]						
RA specific outcomes						
DAS28crp						
PsA specific outcomes						
DAS28crp						
axSpA specific outcomes						
BASDAI						
BASFI						
ASDAScrp						

[1]: Generic continuous outcome measures will be analysed using the following model: $y = D + T + M + T*M + f(x_0)$; $f(x_0)$ adjusted for baseline available in DANBIO prior to study start, D: disease (RA, PsA or axSpA), T: time (first or second registration/period), M: measure device (app or touchscreen).

[2]: Duration of PROM registration through the device.

Outline Table 3: Results of stratified (subgroup) analyses for HAQ-DI (the primary outcome).

	AD – TS **Level 1**	*AD – TS* **Level 2**	**Difference (95% CI)**
Sex[1]			
Diagnosis[2]			
The younger half of the trial group versus the older half (median for each diagnosis)			
Age > 65 years versus age ≤ 65 years (e.g. participants with anticipated IT-experience)			
Duration of data registration > 30 minutes (i.e. longer than anticipated) versus duration of data registration ≤ 30 minutes Through the DANBIO app			
Duration of data registration > 30 minutes (i.e. longer than anticipated) versus duration of data registration ≤ 30 minutes Through the touchscreen solution			

[1]: Male or female

[2]: RA vs. Other (PsA or axSpA)

Supplementary Table S1: Comparison between patients invited on the outpatient touchscreen stratified by reply and diagnosis

	RA (N = 195)					PsA (N = 185)					axSpA (N = 106)				
Answer to touchscreen invitation, N (%)	**"Yes" and enrolled N = 20 (10.3%)**	**"Yes" and excluded N = 28 (14.4%)**	**P[a]**	**"No" N = 147 (75.4%)**	**P[b]**	**"Yes"and enrolled N = 20 (10.8%)**	**"Yes" and excluded N = 28 (15.1%)**	**P[a]**	**"No" N = 137 (74.0%)**	**P[b]**	**"Yes" and enrolled N = 20 (18.9%)**	**"Yes" and excluded N = 22 (20.8%)**	**P[a]**	**"No" N = 64 (60.4%)**	**P[b]**
Male[c], n (%)	9 (45.0%)	6 (21.4%)	0.08	38 (25.9%)	0.07	10 (50.0%)	13 (46.4%)	0.81	72 (52.6%)	0.83	12 (60.0%)	12 (54.6%)	0.72	43 (67.2%)	0.56
Age in years, median (IQR)	61.0 (50.5;70.5)	56.0 (49.0;69.8)	0.58	66.0 (59.0;74.0)	0.07	57.0 (44.3;59.8)	54.0 (40.0;59.0)	0.50	57.0 (43.5;67.0)	0.43	50.0 (38.0;57.8)	41.5 (29.3;47.3)	0.06	48.5 (38.3;57.0)	0.81
Disease duration in years, median (IQR)	13.5 (7.1;17.4)	8.0 (3.8;13.0)	0.06	10.3 (4,1;22,3)	0.74	12.2 (5.8;16.8)	9.9 (3.4;13.1)	0.37	9.3 (5,1;16.3)	0.65	8.0 (6.1;13.7)	6.4 (3.7;13.0)	0.30	10.8 (4,8;22,1)	0.57
HAQ-DI, median (IQR)	0.81 (0.41;1.47)	0.50 (0.25;0.75)	0.28	0.75 (0.38;1.25)	0.48	0.25 (0.03;1.19)	0.88 (0.16;1.09)	0.28	0.75 (0.13;1.25)	0.31	0.38 (1.3;0.72)	0.44 (0.00;0.88)	0.95	0.50 (0.13;0.75)	0.61
Disease activity[d], median (IQR)	3.1 (2.4;3.9)	2.5 (1.7;3.6)	0.15	2.3 (1.8;3.2)	0.02	2.6 (1.6;3.6)	2.2 (1.8;3.3)	0.99	2.2 (1.6;2.9)	0.54	2.4 (1.5;2.8)	1.8 (1.2;3.3)	0.50	2.1 (1,3;2,9)	0.51

RA: rheumatoid arthritis, N: number, n: number, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, p: p-value, IQR: interquartile range.

Unless otherwise stated, p-values are calculated using Wilcoxon rank-sum (Mann-Whitney) test.

[a]: Comparison between 1) Patients who answered "yes" to the touchscreen invitation and was enrolled and 2) Patients who answered "yes" to the touchscreen invitation and was excluded.

[b]: Comparison between 1) Patients who answered "yes" to the touchscreen invitation and was enrolled and 2) Patients who answered "no" to the touchscreen invitation.

[c]: p-value is calculated using Pearson Chi-square test.

[d]: Analysed as: 1) DAS28crp for RA and PsA and 2) ASDAS for axSpA.