

**TITLE: A Tele-health Follow-up Strategy for Tight Control of Disease Activity in Rheumatoid Arthritis: Results of the Non-inferiority Randomised Controlled Trail (the TeRA study)**

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**Abstract and keywords**

**Objective:** To test the effect of patient-reported outcome (PRO) based tele-health follow-up for tight control of disease activity in patients with rheumatoid arthritis (RA), and the differences between tele-health follow-up performed by rheumatologists or rheumatology nurses.

**Methods:** A total of 294 patients were randomized (1:1:1) to either PRO-based tele-health follow-up carried out by a nurse (PRO-TN) or a rheumatologist (PRO-TR), or conventional out-patient follow-up by physicians.

The primary outcome was change in DAS28 after week 52. Secondary outcomes were: physical function, quality of life and self-efficacy. The non-inferiority margin was a DAS28 change of 0.6. Mean differences were estimated following per-protocol (PP), intention to treat (ITT) and multivariate imputation (IMP) analysis.

**Results:** Overall patients had low disease activity at baseline and end follow-up. Demographics and baseline characteristics were similar between groups. Non-inferiority was established for DAS28. In the ITT analysis mean difference (MD) in DAS28 between PRO-TR vs. control were -0.10 (90% CI -0.30; 0.13) and -0.19 (-0.41; 0.02) between PRO-TN vs. control.

When including one yearly visit to the outpatient clinic, patients in PRO-TN had a total of 1.72 (SD 1.03) visit/year, PRO-TR 1.75 (SD 1.03) visit/year and controls 4.15 (SD 1.0) visits/year. This included extra visits due to inflammatory flare.

**Conclusion:** Among RA patients with low disease activity or remission a PRO-based tele-health follow-up for tight control of disease activity in RA can achieve similar disease control as conventional outpatient follow-up. The degree of disease control did not differ between patients seen by rheumatologists or rheumatology nurses.

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### **Significans and Innovations**

- A tele-health strategy based on Patient Reported Outcomes can achieve similar disease control among RA patients with low disease activity or remissions as conventional follow-up.
- The degree of disease control through tele-health follow-up does not differ between rheumatologists and rheumatology nurses.
- The tele-health follow-up save patient time and is likely to reduce health care costs.

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## Introduction

According to the updated European League Against Rheumatism (EULAR) treat-to-target strategy for rheumatoid arthritis (RA), monitoring of disease activity must be: “...*obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every six months) for patients in sustained low disease activity or remission.*”

(1). In recent years the prevalence of RA has risen leading to increased outpatient activity; at the same time, a general lack of rheumatologists has been described (2). This has created new demands from patients and the health care system for alternatives to conventional pre-scheduled outpatient follow-ups by rheumatologists, e.g. nurse-led follow-up (3, 4), direct access strategies (5) and tele-health interventions (2). Given the fewer appointments such tele-medicine services can ease the patients (5) and thereby fit better with patients' self-management of their condition and everyday routines, roles and responsibilities.

Tele-health can be defined as the use of communication and information technologies to deliver clinical care where the individuals involved are not at the same location (6).

In a study among patients with different rheumatic diseases, Davis found tele-health to be feasible, well received among patients and cost-effective (7, 8). In a Randomized Controlled Study from 1989, Weinberger et al found tele-consultations to improve physical health in patients with osteoarthritis (9). However, no studies have yet investigated the effect of monitoring disease activity through a tele-health follow-up strategy in patients with RA (10), and most of the evidence on the efficacy of tele-health interventions in chronic diseases is derived from studies within heart disease, obstructive lung disease, asthma, diabetes and hypertension (11-13). This indicates, however, that tele-health interventions seem to be both effective, time saving and associated with a high degree of patient satisfaction (11-13).

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Due to the lack of face-to-face contact in tele-health follow-ups it is not possible to use traditional disease activity measures based on clinical observations, i.e. the Disease Activity Score 28 (DAS28) (14).

A validation of patient-self assessment of tender and swollen joints has shown that especially swollen joint counts tends to be overestimated (15, 16), particularly in patients in low disease activity or remission (16). Therefore valid and reliable patient-reported outcome (PRO) (17) measures are essential when monitoring RA disease activity through tele-health follow-up.

In recent years disease monitoring of RA carried out by rheumatology nurses has proven both clinical effective (3, 4) and cost effective (4, 18). Thus, before replacing conventional outpatient visits with tele-health follow-up the effect of both strategies when carried out by a rheumatologist or a rheumatology nurse needs to be investigated.

The aim of the present study was to test the effect of a customized PRO-based tele-health follow-up for its ability to monitor disease activity in patients with RA, compared to a conventional pre-scheduled outpatient follow-up. A second aim was to test if the effect depended on whether the tele-health consultation was carried out by a rheumatologist or by a rheumatology nurse.

The hypothesis of the study was non-inferiority of PRO-based follow-up compared to standard care based on the expectation that the non-inferiority of a PRO-based tele-health follow-up would be sufficient to full-fill the demands for tight control both when carried out by rheumatologists or by rheumatology nurses (19).

## Methods

### Study design

The tele-health in RA study (TeRA) was a pragmatic non-inferiority randomized controlled trial (RCT) (20) carried out at two rheumatology outpatient clinics in the Central Denmark Region,

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specifically at the Aarhus University Hospital and the Silkeborg Regional Hospital. Geographically, the two departments are located in the same region with a similar patient referral structure and both are using ACR/EULAR guidelines for diagnosis and treatment of RA.

In Denmark, the majority of patients with RA are referred to specialist care for both diagnosis and treatment in hospitals (21).

### **Participations and randomization**

Between May 2014 and July 2015 all consecutive patients with a diagnosis of RA according to the American College of Rheumatology Criteria, 1987 or 2010 (22, 23) were eligible for the study if they were 18 years or older and able to speak and understand Danish.

In order to ensure that patients were familiar with signs and symptoms of disease activity and medical treatment, a disease duration of two years or more was required.

Patients were excluded if they were incapable of answering a questionnaire or unwilling to be randomized to either one of the tele-health follow-ups or conventional physician-led follow-up (control).

Patients, who fulfilled the inclusion criteria and had given written informed consent, were randomized in a ratio of 1:1:1 to either PRO-based tele-health follow-up by a rheumatologist (PRO-TR), PRO-based tele-health follow-up by a nurse (PRO-TN) or conventional rheumatologist-led follow-up (control) by using a computer-generated random number sequence. Randomization was carried out by the project nurses.

The included patients had a DAS28 assessment performed by a blind independent assessor, and were randomized to one of the three groups. A baseline questionnaire was completed electronically through open-source software in the Danish Clinical database, Danbio (24). Follow-up assessment was performed 52 weeks after randomization by a blind independent assessor.

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**Interventions**

Patients who received PRO-based tele-health follow-up were scheduled for a telephone consultation every 3-4 months. The consultation followed a predefined consultation checklist.

Prior to each consultation the patients answered a questionnaire through the generic configurable tele-PRO-system, AmbuFlex (25, 26). This system is designed to act as decision aid in deciding whether a patient is in need of an outpatient visit. The AmbuFlex concept consists of three generic elements: PRO data collection, PRO-based automated decision algorithm, and PRO-based graphical overview for clinical decision support (26). In this study, the Danish version of the Flare-RA Instrument, which was translated and validated into Danish for the purpose of this study (27, 28), served as decision support for assessing disease activity in RA during the tele-health follow-up.

Flare-RA, is an 11-item questionnaire where patients are asked to express their degree of agreement about different statements concerning disease activity on a 10-point Likert scale. Five items concerns joint symptoms (tenderness, stiffness and pain) and six items concerns general symptoms. When scoring Flare-RA it is possible to compute a Flare-RA total score (all 11 items) or a subscale for joint or general symptoms, respectively (29). Based on the Receiver Operatic Curve (ROC) (27) it was decided that patients in the tele-health follow-up groups should be called in for a consultation in the outpatient clinic if Flare-RA  $\geq 2.5$  and/or the patients C-reactive protein (CRP)  $\geq 10$  mg/L.

The tele-health follow-ups were performed by four different rheumatologists and four different rheumatology nurses with more than 4 years of experience.

Patients in the control group were seen in the outpatient clinic every 3-4 months by physicians.

According to the treat-to-target strategy, all included patients, irrespective of group allocation, were allowed access to acute outpatient visits if needed (19).

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**Outcome**

The primary outcome was DAS28 (30). The DAS28 score run from 0-9.4 and RA disease activity is defined as follow: DAS28 < 2.6: remission  $\leq$  3.2: mild disease activity, DAS28 >3.2: moderate disease activity, DAS28 >5.1: high disease activity. The Flare-RA was assessed at each tele-health consultation (i.e. every 3-4 months). Patients in the control group also filled in the Flare-RA at each contact (every 3-4 months) and in addition a DAS28 assessment was made. Patients in all three groups had both a Flare-RA assessment and a DAS28 assessment made at every acute visit.

Furthermore, all patients had X-ray taken of hands and feet at inclusion and end of follow-up.

Covariates and secondary outcomes retrieved from questionnaires included: co-morbidity, socio-demographic data, level of function (The Health Assessment Questionnaire (HAQ)) (31, 32), quality of life assessed by the EuroQol five dimensional questionnaire (EQ-5D) (33) and self-efficacy (General Self-Efficacy scale) (34). Information concerning age, gender, disease duration, rheumatoid factor, immunoglobulin M (IgM), and anti-cyclic citrullinated peptides (anti-CCP) antibody was retrieved through the medical journals. Ad-hoc questions were constructed to evaluate adherence to disease modifying anti-rheumatic drugs (DMARDs) (*“How often since your last consultation do you think you have forgotten to take your medication against RA?” Never/a few times/often*), side-effects (*“How often since your last consultation have you experienced side-effects from your medication against RA?” Never/a few times/often*) and the patient’s confidence towards the mode of consultation (*“Do you feel confident about the your present mode of consultation?” To the highest degree/to some degree/to a lesser degree/not at all*).

During the follow-up period, information about both the number and the reasons for acute visits to the outpatient clinics was retrieved from the medical records.

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### Statistical analysis

The evaluation of clinical outcomes was focused on difference of change in scores. A change in DAS28 of 1.2 or more is a clinically significant change, and a change in DAS28 of less than 0.6 is regarded as non-response (35).

For baseline data, differences between groups were evaluated by Fisher's exact test for dichotomous variables and the Kruskal-Wallis test for continuous variables. Data were reported as mean with Standard Deviation (SD) for data for which the assumption of normal distribution did not seem violated; otherwise data were reported as median and interquartile range (IQR).

Data were analyzed using both intention-to-treat (ITT) and per protocol (PP) analysis (20). In the ITT analysis, missing data were imputed using a random intercept mixed model. PP was based on evaluation of all participants who completed the follow-up visit as allocated. To investigate the effect of drop-outs, imputations (IMP) were performed on DAS28 using a multivariate chained equation approach on DAS28 (baseline and follow-up), age, gender, disease duration and randomization group.

The imputation results were robust to model specifications and imputation approach, which were varied to assess sensitivity. Four models were considered ranging from including baseline DAS28, age and gender to including all variables and the approach was varied between a univariate and a multivariate approach for a total of eight imputation analyses. All confidence intervals were obtained by bootstrapping and the bias corrected (percentile) intervals were reported. The bootstrap was performed with a 1000 replication and with 10.000 replications for the imputations results, where both the imputation and estimation step was repeated for each bootstrap sample (36, 37).

Significance was set at a 5% level. Note that the confidence interval for DAS28 is given at level  $2\alpha$  (0.90) to allow for conclusions on equivalence.

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Assuming a drop-out of 10%, sample size calculations suggested that 98 participants should be included in each group (294 in total), to have a power of 90% to reject the null-hypotheses.

Analyses were performed using Stata 14 (IC) and R version 3.3.1.

**Permission to use data**

The study was conducted in accordance with the Helsinki declaration, 2004, and approved by the local scientific committee (reference number 1-10-72-41-14). Permission to use the confidential data were granted from the Danish Data Protection Agency (reference number 1-16-02-150-14) and processing of personal data were enforced according to the Danish Health Act and the administration of personal data, Denmark. Verbal and signed written consent were obtained from each patient before enrolment.

**Results**

From May 2014 to July 2015 a total of 490 RA patients were eligible for inclusion and a total of 294 (60%) accepted the invitation, 67% from Aarhus University Hospital, and 33% from Silkeborg Regional Hospital. A total of 38 patients (12%) left the study after randomization, leaving 275 patients for analysis (Figure 1). A total of 254 patients (86%) had a full DAS28 at inclusion and at the end of follow-up. There were no statistical significant baseline differences between the three groups PRO-TN, PRO-TR or control. Table 1 shows the study baseline characteristics, and Figure 1 show the trail profile.

**Primary outcome**

Non-inferiority was established for the primary outcome, disease activity, in both tele-intervention groups when compared to conventional follow-up (Fig 2, Table 2). Figure 2 graphically depicts the change in DAS28 after one year between PRO-TR/control and PRO-TN/control based on the ITT data. Table 2 shows the mean change in each group and the mean difference between the tele-health

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and conventional follow-up. A figure and table containing the change in DAS28 based on both ITT, PP and imputed data can be found in Supplementary data 1.

### **Secondary outcomes**

No differences between tele-health interventions and conventional follow-up were found in any of the secondary outcomes HAQ, EQ-5D or self-efficacy. Results for secondary outcomes are shown in Supplementary data 2.

Overall more than 80 % of the patients in all three groups answered that they were “very satisfied” with the consultation form they received and no differences were found between the three groups.

Medication non-adherence was addressed in 31 % of the consultations in the PRO-TR group and in 33% of the PRO-TN consultations. In 53 % of the PRO-TR consultations and 40 % of the PRO-TN consultations patients reported that they had experienced side effects “a few times since the last consultation”. In approximately 10% of both the PRO-TR and PRO-TN consultations patients reported that they had experienced side-effects “often since the last consultation”.

### **Scheduled and acute visits**

During the study the mean total number of visits to the outpatient clinic was 4.15 (SD 1.00) for patients in the control group, 1.75 (SD 1.03) for patients in the the PRO-TR group and 1.72 (SD 1.03) for patients in the PRO-TN group. This number included one yearly visit for all three groups (the inclusion visit, but not the follow-up visit).

The number of acute visits due to a patient-reported flare (PRF) of disease activity are seen in Table 3. In 17% of these PRF's patients were asked to come to the out-patient clinic by HP's in connection with the tele-health consultation as they had reported a Flare-RA  $\geq 2,5$  and/or had a CRP  $\geq 10$  mg/L.

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### Non attenders and attrition analysis

When comparing attenders (n=294) with non-attenders (patients who either declined to participate or did not respond) (n=174) the attenders were found to be younger (mean age 60.8 years (SD 12.7) vs. 68.8 (SD 13.4) (p-value: 0.001). Further, non-attenders had a slightly higher baseline disease activity (median DAS28, attenders: 1.98, (IQR 1.52-2.53)) vs non-attenders (median DAS28: 2.1 (IQR 1.6-3.1) (p-value 0.02)). No statistical significant difference were found with respect to gender (% female, attenders: 68.4 vs non-attenders: 73.6 (p-value: 0.23)).

A total of 19 patients dropped out before the end of follow-up. No statistically significant difference was found with respect to age and gender. However, patients who dropped out had a higher disease activity compared to completers (median DAS28, completers 1.95 (IQR:1.52; 2.50)) vs. drop-outs 2.6 (2.02; 2.99) (p-value: 0.009).

### Discussion

This study was the first to provide evidence that tight control of disease activity in RA obtained by a PRO-based tele-health follow-up was not inferior to conventional outpatient follow-up in patients with low disease activity or in remission. We also found that the intervention was equally effective when managed by rheumatologists or rheumatology nurses. Even though patients in the tele-health follow-up groups requested more acute visits they over-all had a more than 50 per cent reduction in face-to-face consultations. Hence, the tele-health follow-up save patient time and is likely to reduce health care costs.

In a review regarding the tele-medicine influence on doctor-patient communication in different chronic diseases, the only thing that did not favor telemedicine interventions was the lack of face-to-face contact (38). Health professionals mostly worried they might lose important clinical

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information, whereas patients were more concerned they would not be able to express themselves clearly on the phone.

Alternatives to conventional follow-up offered to RA patients have been investigated by others, i.e. nurse-led follow-up (3, 39) and direct access strategies (5). Like in our study, none of these studies found any difference in disease activity between the intervention under investigation as compared to conventional outpatient follow-up.

The evidence regarding tele-health consultations in RA is sparse (10). Previously, a RCT study from the UK compared joint teleconsultations between GP's, specialists and patients (40).

However, only 8% of the consultations were related to rheumatological diseases and further, no patient outcome were provided, since the study aimed at describing the organizational impact of telemedicine (40).

In the recently published systematic review by McDougall a distinction is made between tele-health consultations used in new and established disease (10). It is pointed out that valid and reliable outcome measures are especially important when it comes to tele-health consultations dealing with diagnosis (41).

In established RA, full and sustained remission is not the rule, and often the disease fluctuates between activity and inactivity. This is also the case in our study, as approximately 20% of the included patients experienced a flare at least once during follow-up. According to the treat-to-target strategy these flares should be treated in order to prevent permanent joint damage (19), and this calls for an intervention that can handle close monitoring of disease activity, even in a cohort of patients with established and stable disease. We used the Flare-RA as decision aid in the tele-health follow-up. This instrument has been designed to reflect both the patients and the clinicians view of a flare (42), and has proven a valid tool for ruling out disease activity in RA (27-29). By having

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implemented the Flare-RA in a systematic tele-based disease monitoring strategy, we have shown that it is well-functioning as decision aid in the treat to target strategy in such an intervention (19).

One major strength of our study is the pragmatic randomized design with a high completion rate that enabled us to come up with results which are feasible in daily clinical care. It is also a strength that it includes two different outpatient clinics in two different hospitals, avoiding local systems to have influenced outcomes which thus increases the external validity of the findings.

Some limitations of the study do, however, merit further discussion. Only 60% of the patients assessed for eligibility participated in the study. Generally, attenders were younger and had less disease activity than non-attenders. The finding is in accordance with, the Bristol direct access study (5), and this means that the results observed in our study may not be representative for RA patients who are older and perceive more disease activity. Still, the differences in participation rates are moderate and we do not expect this selection bias to influence the validity of our study.

A total of 19 patients dropped out of the study, most from the PRO-TN group. Patients who dropped out in general had a higher disease activity than those who remained in the study. We do not know if the fact that patients were contacted by a nurse and not a doctor prompted some to drop out, or if some patients dropped out because they felt generally insecure about attending tele-health control. The question is, however, of great importance to future implementation and thus, studies investigating the patients perspective on tele-health interventions in RA are needed.

Blinding was not possible in our study. We tried to ensure assessor blinding of disease activity, but even though we followed a strict protocol and a consultation check-list we can not rule out the possibility of bias due to a more careful attention and obligingness towards patients in the tele-intervention groups. This could potentially have led to an overestimation of the positive effect of the primary outcome. Our study was based on RA patients with a long disease duration, and thus,

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we might have included patients with an overall long experience on self-management strategies, on i.e. adherence to medication, side effects and signs and symptoms of a flare (43).

Fewer patients than expected were IgM rheuma-factor positive. Unfortunately we were unable to retrieve data on IgM rheuma-factor for 8% of the patients, which could partially account for the unexpectedly low number. The vast majority of the patients (70 %) were, however, Anti-CCP positive and all fulfilled the ACR/EULAR criteria for RA (23).

As stated in the power calculation, we planned to have 98 patients in each group, accommodating a potential drop out of 10%, meaning that there should be sufficient power with 89 patient in each group. This number was almost reached in the PRO-TN group (n=88), and we believe to have sufficient power to draw a conclusion.

In general, patients in our cohort had low disease activity at inclusion. In recent years, the prevalence of patients with low disease activity or remission has increased markedly due to the improved early DMARD treatment and the implementation of the treat-to-target strategy (19). However, it remains unresolved whether tele-health follow-up is useful for patients with high or uncontrolled disease activity.

Finally, it is worth mentioning that our conclusion is limited to a follow-up period of one year, making us unable to evaluate the long-term impact of tele-health follow-up in RA.

In conclusion, this study shows the non-inferiority of a PRO-based tele-health follow-up in RA patients with low disease activity or remission, and thus, this mode of control could form an alternative to conventional out-patient follow-up in the future rheumatological care.

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## References

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2015.
2. Ward IM, Schmidt TW, Lappan C, Battafarano DF. How critical is tele-medicine to the rheumatology workforce?. *Arthritis Care Res (Hoboken)*. 2016.
3. Primdahl J, Sorensen J, Horn HC, Petersen R, Horslev-Petersen K. Shared care or nursing consultations as an alternative to rheumatologist follow-up for rheumatoid arthritis outpatients with low disease activity--patient outcomes from a 2-year, randomised controlled trial. *Ann Rheum Dis*. 2014; 73: 357-64.
4. Ndosu M, Lewis M, Hale C, Quinn H, Ryan S, Emery P, et al. The outcome and cost-effectiveness of nurse-led care in people with rheumatoid arthritis: A multicentre randomised controlled trial. *Ann Rheum Dis*. 2014; 73: 1975-82.
5. Hewlett S, Kirwan J, Pollock J, Mitchell K, Hehir M, Blair PS, et al. Patient initiated outpatient follow up in rheumatoid arthritis: Six year randomised controlled trial. *BMJ*. 2005; 330: 171.
6. Telemedicine: Opportunities and developments in member states: Report on the second global survey on eHealth [homepage on the Internet]. . 2009. Available from: [http://www.who.int/goe/publications/goe\\_telemedicine\\_2010.pdf](http://www.who.int/goe/publications/goe_telemedicine_2010.pdf).

## Tele-health follow-up in Rheumatoid Arthritis

7. Davis P, Howard R, Brockway P. An evaluation of telehealth in the provision of rheumatologic consults to a remote area. *J Rheumatol*. 2001; 28: 1910-3.
8. Davis P, Howard R, Brockway P. Telehealth consultations in rheumatology: Cost-effectiveness and user satisfaction. *J Telemed Telecare*. 2001; 7 Suppl 1: 10-1.
9. Weinberger M, Tierney WM, Booher P, Katz BP. Can the provision of information to patients with osteoarthritis improve functional status? A randomized, controlled trial. *Arthritis Rheum*. 1989; 32: 1577-83.
10. McDougall JA, Ferucci ED, Glover J, Fraenkel L. Telerheumatology: A systematic review. *Arthritis Care Res (Hoboken)*. 2016.
11. Pare G, Moqadem K, Pineau G, St-Hilaire C. Clinical effects of home telemonitoring in the context of diabetes, asthma, heart failure and hypertension: A systematic review. *J Med Internet Res*. 2010; 12: e21.
12. McLean S, Chandler D, Nurmatov U, Liu J, Pagliari C, Car J, et al. Telehealthcare for asthma. *Cochrane Database Syst Rev*. 2010; (10):CD007717. doi: CD007717.
13. Wootton R. Twenty years of telemedicine in chronic disease management--an evidence synthesis. *J Telemed Telecare*. 2012; 18: 211-20.
14. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 1995; 38: 44-8.

## Tele-health follow-up in Rheumatoid Arthritis

15. Barton JL, Criswell LA, Kaiser R, Chen YH, Schillinger D. Systematic review and metaanalysis of patient self-report versus trained assessor joint counts in rheumatoid arthritis. *J Rheumatol*. 2009; 36: 2635-41.

16. Janta I, Naredo E, Martinez-Estupinan L, Nieto JC, De la Torre I, Valor L, et al. Patient self-assessment and physician's assessment of rheumatoid arthritis activity: Which is more realistic in remission status? A comparison with ultrasonography. *Rheumatology (Oxford)*. 2013.

17. *Guidance for industry: Patient-reported outcome measures: Use in medical product development to support labeling claims*. [homepage on the Internet]. . 2009. Available from: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf).

18. Sorensen J, Primdahl J, Horn HC, Horslev-Petersen K. Shared care or nurse consultations as an alternative to rheumatologist follow-up for rheumatoid arthritis (RA) outpatients with stable low disease-activity RA: Cost-effectiveness based on a 2-year randomized trial. *Scand J Rheumatol*. 2015; 44: 13-21.

19. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2016; 75: 3-15.

20. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, CONSORT Group. Reporting of noninferiority and equivalence randomized trials: Extension of the CONSORT 2010 statement. *JAMA*. 2012; 308: 2594-604.

## Tele-health follow-up in Rheumatoid Arthritis

21. Pedersen JK, Kjaer NK, Svendsen AJ, Horslev-Petersen K. Incidence of rheumatoid arthritis from 1995 to 2001: Impact of ascertainment from multiple sources. *Rheumatol Int.* 2008.
22. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988; 31: 315-24.
23. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: An american college of Rheumatology/European league against rheumatism collaborative initiative. *Arthritis Rheum.* 2010; 62: 2569-81.
24. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: Results from eight years of surveillance of clinical practice in the nationwide danish DANBIO registry. *Arthritis Rheum.* 2010; 62: 22-32.
25. Hjollund NH, Larsen LP, Biering K, Johnsen SP, Riiskjaer E, Schougaard LM. Use of patient-reported outcome (PRO) measures at group and patient levels: Experiences from the generic integrated PRO system, WestChronic. *Interact J Med Res.* 2014; 3: e5.
26. Schougaard LM, Larsen LP, Jessen A, Sidenius P, Dorflinger L, de Thurah A, et al. AmbuFlex: Tele-patient-reported outcomes (telePRO) as the basis for follow-up in chronic and malignant diseases. *Qual Life Res.* 2016; 25: 525-34.
27. de Thurah A, Maribo T, Stengaard-Pedersen K. Patient self-assessment of flare in rheumatoid arthritis: Criterion and concurrent validity of the flare instrument. *Clin Rheumatol.* 2014.

## Tele-health follow-up in Rheumatoid Arthritis

28. Maribo T, de Thurah A, Stengaard-Pedersen K. Patient-self assessment of flare in rheumatoid arthritis: Translation and reliability of the flare instrument. *Clin Rheumatol*. 2015.
29. Fautrel B, Morel J, Berthelot JM, Constantin A, De Bandt M, Gaudin P, et al. Validation of flare-ra, a self-administered tool to detect recent or current rheumatoid arthritis flare. *Arthritis Rheumatol*. 2016.
30. Dougados M, Aletaha D, van Riel P. Disease activity measures for rheumatoid arthritis. *Clin Exp Rheumatol*. 2007; 25: S22-9.
31. Bruce B, Fries JF. The stanford health assessment questionnaire: A review of its history, issues, progress, and documentation. *J Rheumatol*. 2003; 30: 167-78.
32. Bruce B, Fries JF. The stanford health assessment questionnaire: Dimensions and practical applications. *Health Qual Life Outcomes*. 2003; 1: 20.
33. Sorensen J, Linde L, Ostergaard M, Hetland ML. Quality-adjusted life expectancies in patients with rheumatoid arthritis--comparison of index scores from EQ-5D, 15D, and SF-6D. *Value Health*. 2012; 15: 334-9.
34. Luszczynska A, Scholz U, Schwarzer R. The general self-efficacy scale: Multicultural validation studies. *J Psychol*. 2005; 139: 439-57.
35. van Riel PL, van Gestel AM, van de Putte LB. Development and validation of response criteria in rheumatoid arthritis: Steps towards an international consensus on prognostic markers. *Br J Rheumatol*. 1996; 35 Suppl 2: 4-7.
36. Royston P, et al. Multiple imputation of missing values updata. *Stata Journal*. 2005; 5: 188.

## Tele-health follow-up in Rheumatoid Arthritis

37. Royston P, et al. Multiple imputation of missing values. *Stata Journal*. 2004; 4: 227-41.
38. Miller EA. Telemedicine and doctor-patient communication: An analytical survey of the literature. *J Telemed Telecare*. 2001; 7: 1-17.
39. Ndosi M, Johnson D, Young T, Hardware B, Hill J, Hale C, et al. Effects of needs-based patient education on self-efficacy and health outcomes in people with rheumatoid arthritis: A multicentre, single blind, randomised controlled trial. *Ann Rheum Dis*. 2015.
40. Wallace P, Haines A, Harrison R, Barber JA, Thompson S, Roberts J, et al. Design and performance of a multi-centre randomised controlled trial and economic evaluation of joint tele-consultations [ISRCTN54264250. *BMC Fam Pract*. 2002; 3: 1.
41. Wallace CA. Developing standards of care for patients with juvenile idiopathic arthritis. *Rheumatology*. 2010; 49: 1213-4.
42. Berthelot JM, De Bandt M, Morel J, Benatig F, Constantin A, Gaudin P, et al. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: The 'FLARE' instrument. *Ann Rheum Dis*. 2012; 71: 1110-6.
43. Lorig KR, Holman H. Self-management education: History, definition, outcomes, and mechanisms. *Ann Behav Med*. 2003; 26: 1-7.

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Table 1 Baseline characteristics of 294 RA patients randomized to either PRO-based tele-health follow-up

	Control n=94	PRO-TR n=93	PRO-TN n=88	p-value
Age in years, mean (SD)	60.7 (11.1)	60.5 (13.5)	61.6 (13.5)	0.83
Female sex, n (%)	66 (70)	60 (65)	63 (72)	0.51
Rheuma-factor positive, n (%) <sup>1</sup>	44 (56)	44 (54)	32 (41)	0.14
Disease duration in years, median (IQR) <sup>2</sup>	12 [6;18]	11 [5;17]	12 [5; 17]	0.78
DAS28, mean (SD)	2.07 (0.77)	2.03 (0.78)	2.1 (0.83)	0.79
Anti-CCP positive, n (%) <sup>3</sup>	60 (71)	57 (70)	57 (70)	0.95
MTX monotherapy, n (%)	55 (59)	44 (47)	50 (57)	0.26
Two combinations of DMARD, n (%)	15 (16)	10 (11)	6 (7)	0.15
Three combinations of DMARD, n (%)	2 (2)	6 (7)	2 (2)	0.20
Anti-TNF-alpha, n (%)	6 (6)	10 (11)	14 (16)	0.12
Steroids	4 (4)	3 (3)	8 (9)	0.23
No medical treatment, n (%)	8 (9)	14 (15)	5 (6)	0.09

by rheumatologist (PRO-TR)/ rheumatology nurse (PRO-TN) or control

SD: Standard deviation; IQR: Inter Quartile Range; DAS28: Disease Activity Score 28; Anti-CCP: anti-cyclic citrullinated peptides; DMARD: Disease Modifying Anti-rheumatic Drugs; Anti-TNF-alpha: Anti-Tumor Necrosis Factor-alpha. 1: n = 239; 2: n = 272; 3: n= 248

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Table 2 Mean difference (MD) incl 95% Confidence Intervals (CI) in DAS28 in each of the three groups (PRO-TR, PRO-TN or Control), and MD incl 90 % CI between PRO-TR/PRO-TN and control, among 294 patients with rheumatoid arthritis over 12 months

	PRO-TR* (95% CI) (n=81/93)	PRO-TN* (95% CI) (n=81/88)	Control* (95% CI) (n=92/94)	PRO- TR/Control (90% CI)	p-value	PRO- TN/Control (90% CI)	p-value
ITT	-0.16 (-0.33; 0.03)	-0.26 (-0.44; -0.07)	-0.06 (-0.23; 0.12)	-0.10 (-0.30; 0.13)	0.45	-0.19 (-0.41; 0.02)	0.15

PP: Per-protocol, ITT: Intention to treat, IMP: Data imputed by multivariate chained equation approach, MD: mean-difference, CI: Confidence Interval, \*A negative estimate corresponds to a reduced symptom score from baseline to end follow-up

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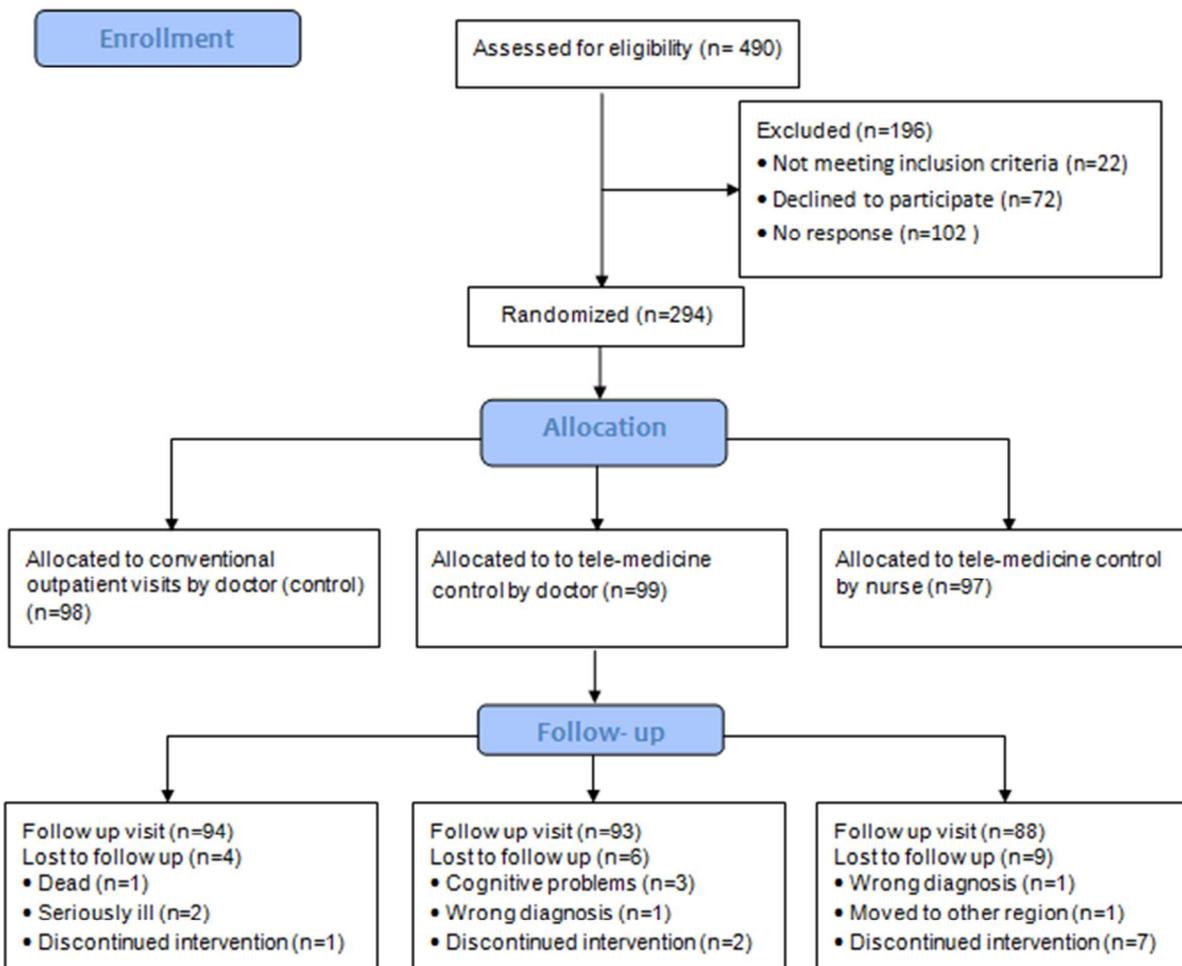
Table 3 Acute visits due to follow-up, and visits due to patient reported and clinically verified flare.

	Number of patients requiring AV's	Total number of AVs	AVs due to a PRF n (%)	Flare, verified* n (%)	DAS28, mean (SD)	CDAI, mean (SD)	Number of patients requiring at least one IA joint injection during AV's n (%) <sup>4</sup>
PRO-TR	18 <sup>1</sup>	70	66 (94)	43 (65)	3.2 (1.2)	10.8 (8.6)	33 (77)
PRO-TN	20 <sup>2</sup>	64	60 (93)	50 (83)	3.7 (1.0)	12.0 (8.5)	41 (82)
Control	14 <sup>3</sup>	37	36 (97)	29 (80)	3.8 (0.9)	13.5 (6.1)	25 (82)

AV: acute visits ; PRF: Patient Reported Flare; 1: More than one AV: 88%, 2: More than one AV: 50%; 3 More than one AV: 64%; \* By DAS28; CDAI: Clinical Disease Activity Index ; IA joint injection: Intra-articular joint injection; 4 The percentage of patients with verified flare.

Tele-health follow-up in Rheumatoid Arthritis

Figure 1 Study flow-chart



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## Tele-health follow-up in Rheumatoid Arthritis

Figure 2 Forrest plot for change in disease activity (DAS28) over 12 months based on intention to treat data.

