Study title	**Telehealth Follow-up in Patients with Rheumatoid Arthritis. A Noninferiority Randomized Control Study (v2 26.03.2020)**
Short title	**Telehealth Follow-up in RA Patients**
REK Ref No	**33172**
Clinical.trials.gov	
Study Design	**Randomized Control Study**
Study Participants	**Patients with RA in remission or low disease activity**
Planned Sample Size	**195**
Planned Study Period	**One (1) year**
Main Objective	**The main objective of the present project is to test the effect of a customized Patient-Reported-Outcome (PRO)-based telehealth follow-up compared to a conventional pre-scheduled outpatient follow-up to monitor disease activity and expenses associated with the follow-up in patients with RA**

Telehealth Follow-up in Patients With Rheumatoid Arthritis. A noninferiority randomized control trial

A collaborative project between Helse Sør-Øst, Martina Hansens Hospital and London School of Economics

Synopsis

1. Project summary:

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a high burden both for the patient and society. Outcomes for the individuals living with RA have been improved and the majority of RA patients are now in remission or low disease activity status. RA patients continue to be followed up by pre-scheduled visits, which may compromise accessibility for the sickest and thus, quality of care. The introduction of patient-initiated follow-up leads to a reduction in the use of outpatient clinic services without compromising outcomes. Self-monitoring and remote patient monitoring are facilitated by electronic innovative health tools. Among RA patients with low disease activity or remission, a Patient-Reported Outcome-based telehealth follow-up for tight control of disease activity in RA can achieve similar disease control as conventional outpatient follow-up and is likely to reduce the costs. Thus, the main objective of the present project is to test the effect of a customized PRO-based telehealth follow-up compared to a conventional pre-scheduled outpatient follow-up to monitor disease activity and expenses associated with the follow-up in Norwegian RA patients.

2. Introduction

Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease with a significant burden for the patients. Impacting roughly 1% of the world's population, RA is known for its polyarthritic involvement of the diarthrodial joints, affecting mainly the small joints of hands and feet [1]. The primary symptoms of synovitis (the inflammation of synovial membrane within joints) include pain, swelling, and stiffness of joints. Coupled with fatigue, another widely known symptom of RA, the patient's quality of life (QoL) is tremendously diminished [2]. Indirect costs to patients including reduced work performance and hours, absenteeism, changing job roles or leaving employment is calculated to be 9,300 USD per patient [3]. Globally, the estimated total Years Lost to Disability (YLD) for RA increased from

2,566,000 in 1990 to 3,776,000 in 2010, thus positioning RA as the 42nd highest disease contributor, and ranked between malaria and iodine deficiency [4].

Recently, outcomes for the individuals living with RA have been improved, due to the discovery of novel treatments, such as biological agents, and treatment strategies, which enable early aggressive therapy through treat to target (T2T) strategies [5]. RA patients in remission achieve higher QoL with improved physical functioning and higher work output compared with those who only reach low disease activity [6]. Thus, the indirect costs are lowest for RA patients attaining remission [6].

However, the direct costs for a healthcare system to deliver optimal treatments across their entire RA patient population has exponentially increased. In the United Kingdom, the estimated annual cost of treatment for the biological agents is approximately £ 9,500 (approximately USD 13,900) per patient/year [7]. During the last 30 years, the number of RA patients on medication has increased because of continuous development of innovative therapies. This presents a higher demand for closely monitoring of the patients in outpatients clinics. [8,9]. Hence, a conundrum is created: patients' RA-related morbidity has decreased leading to reduced costs for inpatient care, but with a consequently massive influx of patients into outpatient clinics [10].

As a consequence of the rising health care direct costs, there is a need to optimizing and streamline the RA patients' management. In Norway the majority of RA patients are diagnosed and initially treated in specialized hospital clinics based on the EULAR T2T strategy [11]. In one Norwegian outpatient clinic, in 2013, approximately 55% (*DAS28; disease activity score*) of the RA patients were reported to be in remission, and roughly 18% (DAS28) of the study group were in a low disease activity status [11].

Given competing demands and scarce resources that are publicly funded in the Norwegian national health care system, it is of great importance to minimize unnecessary follow-up care

which will be at the expense of patients in need for outpatient clinic resources. This could be patients with new-onset disease or with arthritis flare [10]. The already implemented follow-up method based on pre scheduled visits in outpatient clinics, doubtfully corresponds with RAs unpredictable clinical course. In addition, pre scheduled visits are compromising accessibility for the sickest and thus, quality of care [12]. Monitoring patients with chronic conditions such as RA through telemedical instruments improve healthcare while reducing costs, adding value to the provided healthcare [12]. Furthermore, the reduced utilization of healthcare at the specialist level will release resources which could be allocated to non-responders and to rapid evaluation for the newly diagnosed patients or patients with a disease flare-up, a strategy that could result in even better outcomes [12].

The introduction of patient-initiated follow-up leads to a reduction in the use of outpatient clinic services without compromising outcomes [12-14]. In other disease areas, such as diabetes, hypertension and congestive heart failure, patient self-monitoring is a well-accepted and common practice in supporting a tight control strategy and improves outcome [15]. Self-monitoring and remote patient monitoring are facilitated by electronic innovative health tools. A recent double-blind multicenter randomized controlled study of 12 months follow-up showed that monitoring IBD patients via a telemedicine system was safe and reduced outpatient visits and hospital admissions compared with standard care [12].

The use of innovative electronic tools has been recommended for close monitoring and follow up of patients with inflammatory arthritis [17]. For inflammatory arthritis, various remote monitoring tools are in use or being developed with the potential to help improve disease management [16,17]. Among RA patients with low disease activity or remission, a Patient Reported Outcome -based tele-health follow-up for tight control of disease activity in RA can achieve similar disease control as conventional outpatient follow-up and is likely to reduce the costs [16]. In patients with RA, as high as 70% were reported not to adhere to their prescribed

treatment [13]. Modern electronic tools may also improve medication compliance by reminding the patient to take their prescribed drugs. However, the beneficial effects of the telehealth follow-up are not limited to health care improvement at the patient level. It is believed that the introduction of novel follow-up strategies in chronic diseases will result in a reduction of the costs related to health care till the end of 2025 for the Norwegian Healthcare system up to 23 billion Norwegian Crowns [18].

3. Study Objectives

Study hypothesis

A customized Patient-Reported Outcome (PRO)-based telehealth follow-up to monitor disease activity in Norwegian patients with RA is noninferior to standard care (prescheduled outpatient follow-up) and reduces the use of health care resources.

Main Objective

The main objective of the present project is to compare the effect of a customized PRO-based telehealth follow-up compared to a conventional pre-scheduled outpatient follow-up to monitor disease activity and expenses associated with the follow-up in each group, in Norwegian patients with RA.

- ***Primary outcome:*** Occurrence of flare within 52 weeks, defined as a RAPID3 score of 3 or more at any measurement between randomization and 52 weeks.

Secondary objectives

- Potentially identify patients with a higher risk of flare by examining a core set of PROs (MHAQ, RAPID3, EQ-5D, Visual analog Scale (VAS) Total pain, VAS satisfaction with the follow-up) in both groups.
- Compare satisfaction rates (as measured by VAS satisfaction with the follow-up procedures) among the 2 patient groups
- CDAI for both groups at baseline and at 52 weeks.

- Correlation between RAPID 3 and CDAI at 52 weeks

4. Study design, data collection

This is a pragmatic noninferiority randomized controlled trial (RCT) in Norwegian RA patients in clinical remission (based on RAPID3 score). The RA patients will be recruited at the department of Rheumatology MHH in Bærum, Norway. Only ACPA and/or RF positive patients will be included. The patients will be allocated to 2 groups. One group will be followed up by an electronic app, while the second group will attend conventional pre-scheduled visits in the outpatient clinic of MHH. A computer-generated random number sequence will be used for randomization of the RA patients.

The primary outcome is occurrence of flare within 52 weeks, defined as a RAPID3 score of 3 or more at any measurement between randomization and 52 weeks.

RAPID3 (routine assessment of patient index data 3) is a pooled index of the 3 patient-reported American College of Rheumatology rheumatoid arthritis (RA) Core Data Set measures: function (MHAQ), pain, and patient global estimate of status. Each of the 3 individual measures is scored 0 to 10, for a total of 30 (appendix).

- At the baseline, the following data will be collected: RAPID3, MDHAQ, age, gender, disease duration, ACPA, RF, EQ-5D, Visual analog Scale Total pain, VAS satisfaction, CDAI and medications. Data will be collected every 6^{th} month for a period of 1 year.
- CDAI for both groups will be registered at 52 weeks

An electronic app (MyDigno) available both on Apple store and Android play which the patients can download for free will be used to collect data from the Telehealth follow up group. After the patient signs the informed consent, she/he will be invited to download the

app. The data which will be collected via the app will be encrypted and stored in Dignio's server. The Go Treat It program will be used to collect data of the conventional follow-up outpatient clinic group (Appendix 3). The data collected by the GTI are stored in MHH servers inside the firewall of the HSØ.

According to the treat-to-target strategy, all included patients, irrespective of group allocation, will be allowed access to extraordinary outpatient visits if needed. The patients can contact the study nurse, via the app or by phone. Extra visits will be registered, and RAPID3 score will be registered. All the patients suffering a flare during the study period will be registered in both groups. We expect that approximately 20% of the included patients will experience a flare at least once during follow up.

A cost-effectiveness analysis will also be performed. The economic evaluation will be conducted alongside the randomised controlled trial on telehealth follow-up in patients with rheumatoid arthritis (RA) to examine the difference in costs and outcomes between a telehealth patient follow-up strategy and a standard pre-scheduled follow-up strategy. The objective is to estimate the incremental cost-effectiveness ratio (ICER) of the more effective follow-up strategy (if it is associated with higher costs) or the total cost savings associated with the less expensive follow-up strategy (if it is at least as effective as the more expensive follow-up strategy). The study hypothesis is that a customised patient-reported outcome (PRO)-based telehealth follow-up strategy to monitor disease activity in patients with RA is non-inferior to standard care (Appendix 2).

5. Inclusion/exclusion criteria

Inclusion criteria

1. >18 years
2. Fulfilling EULAR/ACR 2010 classification criteria for RA
3. Being in remission (RAPID 3 score <=3)
4. Able to use the electronic app

5. Able to give informed consent

Exclusion criteria

1. <18 years
2. Severe cognitive failure

6. Statistical considerations

All statistical analyses will be detailed in a separate Statistical Analysis Plan (SAP).

6.1 Statistical Hypotheses

This study is designed to test the null hypothesis that the standard pre-scheduled outpatient follow-up scheme (RRO-OC, Rheumatologist Reported Outcome – Outpatient Clinic) is inferior to the customized PRO-based telehealth follow-up (PRO-TH, Patient Reported Outcome - TeleHealth) in monitoring disease activity in Norwegian RA patients. The alternative hypothesis is that PRO-TH is non-inferior to the RRO-OC by a pre-specified margin, on the expectation that the non-inferiority of PRO-TH is sufficient to fulfil the demands for sustained control of the disease activity in RA. Non-inferiority is established for the RAPID 3 score. In statistical terms:

$$H_0 : \pi_{RRO-OC} - \pi_{PRO-TH} \geq \delta$$
$$H_1 : \pi_{RRO-OC} - \pi_{PRO-TH} < \delta,$$

where $\pi_{\text{RRO-OC}}$ is the success proportion of the standard follow-up (patients in sustained remission at week 52), $\pi_{\text{PRO-TH}}$ is the success proportion of the telehealth follow-up, and δ is the non-inferiority margin.

6.2 Sample Size Determination

The sample size determination is based on comparing proportions for the binary outcome variable describing patients remission status at week 52 of the trial (remission: RAPID 3 < 3, increased disease activity: RAPID 3 ≥ 3) in a non-inferiority setting. Based on the literature available at the study's initiation, the proportion of the RA patients in sustained remission at week 52 after initial is assumed to be approximately 80% (equivalent to 20% increase in disease activity, ie. flare). The success proportion is assumed to be equal for both arms of the trial. A difference of 15% in the proportion of patients suffering a flare between the two follow-up groups is considered acceptable for the non-inferiority. Accordingly, a sample size of N=176

patients (n=88 per RRO-OC/PRO-TH arm) is expected to achieve a power of 80% ($p<0.05$, one sided) if the true remission rate difference at week 52 between the RRO-OC and PRO-TH groups is 15% (Table 6.1). Table 6.1 shows how deviations from these assumptions affect the sample sizes required to achieve a power of 80%. Considering a dropout rate of 10%, a total of approximately195 patients will be enrolled.

Table 6.1: Sample size required for a non-inferiority trial, with different assumptions about the non-inferiority margin and success proportion, assuming a significance level of 5% and a power of 80%. An equal number of patients in each trial arm is assumed.

Non-inferiority margin (%)	Success proportion (patients in remission at week 52) (%) 70	75	80	85
10	520	464	396	316
15	232	208	176	142
20	130	116	100	80

6.3 Randomization

After all applicable screening assessments have been performed, patients who have met all inclusion criteria and none of the exclusion criteria will be randomly allocated to one of the follow-up groups (PRO-TH or RRO-OC).

6.4 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who fulfil the study inclusion criteria and sign the informed consent form.
Randomly Assigned to Study Intervention	All enrolled patients who are randomized according to randomized intervention assignment (intervention = PRO-TH/RRO-OC). This set will be analyzed ignoring noncompliance, protocol deviations, withdrawal, and anything that happens after randomization.
Evaluable	All enrolled patients who are randomized according to the randomized intervention assignment and followed-up according to the planned randomization.
Safety	All enrolled patients who are randomly assigned to intervention according to the planned randomization. Participants will be analysed according to the intervention they actually received.

6.5 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

6.5.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Disease activity status of the patient "RAPID 3 < 3/ RAPID 3 ≥ 3", is assessed by default three times during the trial period at baseline, 6 months, and 12 months, and additionally upon patient request. The binary primary endpoint variable gets then value 1 if the RAPID 3 score has been ≥ 3 once or more at any of the time points, and 0 if RAPID 3 < 3 at all time points. To demonstrate the non-inferiority of the PRO-TH follow-up, this binary primary endpoint variable is modelled using a logistic regression model with randomized treatment group as factor, adjusted for baseline RAPID3 measurement. Patients with no (missing) RAPID3 measurements after baseline will be imputed with worst outcome (not in remission).
Secondary	Continuous secondary endpoints MHAQ, RAPID 3, EQ-5D, and Visual analog scale (VAS) total pain will be analysed using linear mixed models accounting for the correlations between repeated measurements (baseline, 6 months, 12 months) for each patient with intervention and visit as fixed factors, the respective baseline score as covariate, and allowing for an intervention by visit interaction. A patient with missing data on the remission status will be assumed to be not in remission.
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

6.5.2 Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Summary tables will be created for all safety information. All site-reported AEs will also be grouped by seriousness (SAE vs. nonserious AE), primary relationship (intervention, unrelated, and unknown) and timing of onset (pre- and post intervention).
Secondary	
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

6.5.3 Other Analyses

Secondary objective is to identify patients with higher risk of flare by examining a core set of PROs including MHAQ, RAPID3, EQ-5D, and Visual analog Scale (VAS) Total pain. Each PRO is measured repeatedly at baseline, 6 months and 12 months. The risk factors are identified by fitting a logistic regression using GEE accounting for the correlations between repeated measurements for each patient, with a dichotomous endpoint "RAPID 3 < 3/ RAPID 3 ≥ 3", all continuous PROs as predictors, and the respective continuous baseline disease activity score (RAPID 3) as covariate. The parameter space will be explored to find a combination parameter values predicting a risk of increased disease activity. A patient with missing data on the remission status will be assumed to be not in remission.

It is also of interest to compare satisfaction rates (as measured by VAS satisfaction with the follow-up procedures) among the two intervention groups. This will be assessed using ANCOVA model adjusted for baseline disease activity score (RAPID 3).

Third, the mean change in continuous CDAI disease activity index between baseline and 52 weeks is compared between the two intervention groups using an ANCOVA model adjusted for baseline CDAI. In addition, the correlation between RAPID 3 and DAS 28 scores at 52 weeks will be computed.

Finally, an economic evaluation will be performed alongside the randomised controlled trial to examine the difference in costs and outcomes between PRO-TH and RRO-OC groups. (Appendix 2)

6.6 Interim Analyses

No interim analyses involving formal statistical testing of the study hypotheses are planned.

7. Ethical considerations

Potential participants will be approached by the study nurse and provided with a participant/patient information sheet. All participants will be given the opportunity to discuss the research project before obtaining informed consent or assent.

The confidentiality will be maintained by using a study patient number for each participant. Only the project leader groupwill know the identity of the patient. Electronic information will be identified only through this non-identifiable study code. Information on study subjects will be stored in a locked electronic file in Martina Hansens Hospital server for research. All data will be managed and analyzed anonymously. All reports will be of a summary nature and no individuals could be identified.

All recruited participants will be older than 18 years. We will include every person who qualifies for inclusion regardless of race, ethnicity or socioeconomic status.

This project does not involve any experimentation on human subjects. All subjects will undergo a conversation with the study nurse before inclusion, where they will be given information about the study and that they at all time can quit the study.

8. **Risks**

We expect that approximately 20% of the included patients will experience a flare at least once during follow-up . According to the treat-to-target strategy, all included patients, irrespective of group allocation, will be allowed access to extraordinary outpatient visits if needed to evaluate disease activity and modify treatment.

In the very unusual situation in which the electronic app is not available for the patients due to technical challenges, the patients can contact the study nurse directly by telephone.

9. **Scientific competence for this project**

Andreas P Diamantopoulos: Rheumatologist with 10 years experience in treatment and follow-up of RA patients. Master in Public health from UC Berkeley and Currently studying at LSE health economics.

Anne Bull Haaversen: Rheumatologist with 8 years experience in the treatment and follow-up of RA patients.

Jannicke Karlengen: Nurse with broad experience in the follow up of patients with RA, experience with the EXODUS app.

Oslo University Unit for clinical Trials provides statistical support for the study

10. **Publications and presentation of research data**

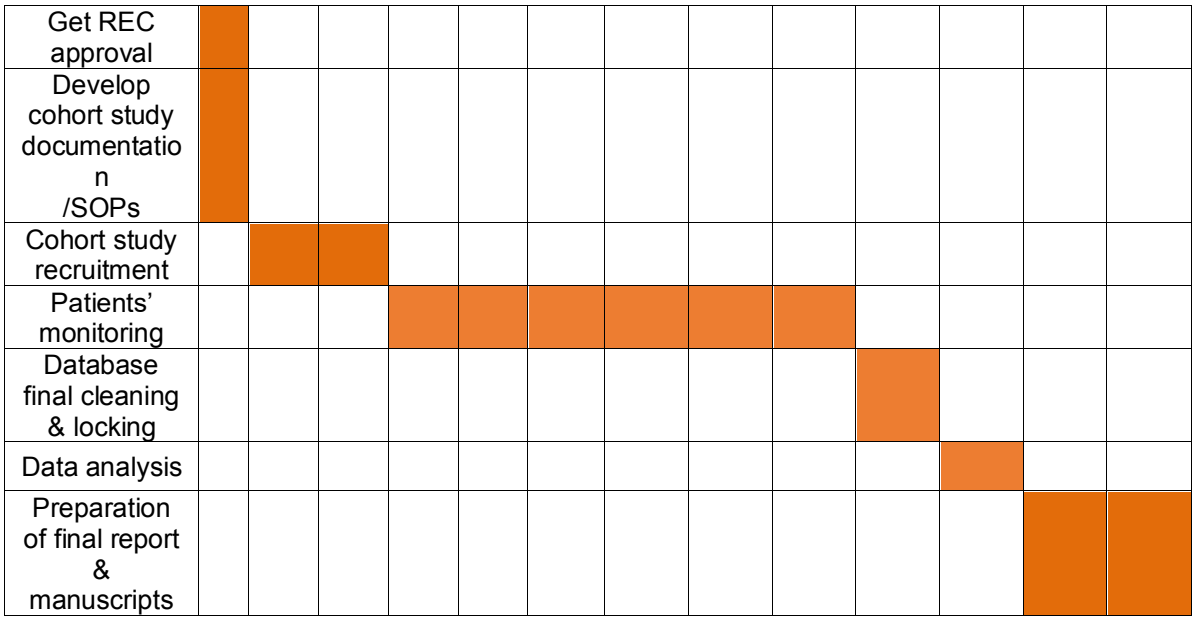
The research data will be presented to the Health Trust of South-Eastern Norway and published in peer-review journals.

11. **Budget**

Budget Telehealth follow-up study	
	Budsjett
Salary (including social costs)	
->Physician 50%	1 000 000
-> Nurse 100%	900 000
-> Clerk 20% of nurse salary	140 000
Materials	300 000
Health-economic analysis (LSE)	100 000
Visits	
-> London School of Economics (LSE)	101 000
-> Kaiser Permanente (California)	129 000
Conference HSØ	150 000
Diverse costs (15%)	300 000
Total	**3 120 000**

12. **Progress plan**

	*	Year 1						Year 2					
		month	month	month	month	month	month	month	month	month	month	month	month



13. **End of the study**

The period of recruitment and inclusion of patients is expected to last for 3 months. Written informed consent will be obtained by the project nurse and kept in a password locked

14. **References**

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14. Appendices

1. RAPID 3 score (0-30) [19]

- 0 to 3: near remission,
- 3.1 to 6: low severity
- 6.1 to 12 : moderate severity
- >12.1 : high severity

2. Telehealth follow-up in patients with rheumatoid arthritis: protocol for economic evaluation

1. Background

The economic evaluation will be conducted alongside the randomised controlled trial on telehealth follow-up in patients with rheumatoid arthritis (RA) to examine the difference in costs and outcomes between a telehealth patient follow-up strategy and a standard pre scheduled follow-up strategy. The objective is to estimate the incremental cost-effectiveness ratio (ICER) of the more effective follow-up strategy (if it is associated with higher costs) or the total cost savings associated with the cheaper follow-up strategy (if it is at least as effective as the more expensive follow-up strategy). The study hypothesis is that a customised patient reported outcome (PRO)-based telehealth follow-up strategy to monitor disease activity in patients with RA is non-inferior to standard care.

2. Methods

2.1 Population, setting and location, and comparator

The study population will comprise of RA patients in clinical remission (based on RAPID3 score). The study setting will be the Department of Rheumatology MHH in Bærum, Norway. One group of patients will be followed-up using a telehealth strategy and a second group will attend conventionally scheduled follow-up outpatient appointments at MHH.

2.2 Type of economic evaluation

Cost-utility analyses (CUA) will be used for the economic evaluation with quality-adjusted life years (QALYs) as the outcome measure.

2.3 Time horizon

Two CUAs will be considered: a within-trial economic evaluation using information collected during a 1-year follow-up period and an economic evaluation based on a long-term model.

2.4 Study perspective

This economic evaluation will adopt the Norwegian healthcare system and societal perspectives.

2.5 Discount rate

The base case analysis rate that will be used for discounting future costs and effects will be 4%.

2.6 Identification, measurements and valuation of outcomes

The EuroQol five-dimensions five level (EQ-5D-5L) will be used to assess the quality of life (QoL) for each patient. EQ-5D-5L data will be collected at baseline and followed up every 6 months for a period of 1 year. The utility weights for each health state at different periods will be obtained by using an EQ-5D index tariff appropriate for the Norwegian population. Mean differences in EQ-5D between the groups will be estimated and will be presented with statistical tests of significance for the different follow-up periods. The potential imbalances in baseline utility will be adjusted to estimate differential mean QALYs.

2.7 Identification, measurement and valuation of resource use

The primary objective of the cost analysis will be identifying, quantifying and valuing resource use accompanying the RA patient follow-up strategies. Data on the resources required to set up and run the PRO-based telehealth monitoring system will be recorded as part of the trial process. Data will be collected for the duration of the trial on participant use of healthcare services including hospital services, primary care, medicine and community care services to estimate the effect of the two follow-up strategies on resource use from the healthcare system perspective. Costs for each type of resource use unit will be calculated from sources appropriate to Norway to produce estimates of the cost of each type of resource use at the start and end of the trial for each trial arm. To estimate costs from a societal perspective, data on loss of days of work (number of working hours foregone) will be collected using questionnaires. The cost of productivity loss for the trial patients will be calculated using a human capital approach.

2.8 Modelling

A pre-trial decision model will be used for the long-term analysis. The modelling exercise will be from the Norwegian perspective and the population that will be considered in the model will be similar to the patients included in the trial. A 2-step modelling strategy will be adopted, where the model will be based on a decision tree for the first year after randomisation and then a Markov model will be used to assess the health states of the patients for their lifetime period.

2.8.1 Model parameters

The Markov model will be populated with transition probabilities and with cost and utility data conditional on health status. Values of the effectiveness parameters, transition probabilities of moving from health states and utilities will be based on the review of selected studies on clinical effectiveness and economic evaluation studies, previous reviews and expert advice from clinicians. Statistical analysis of the trial data will provide more information to generate robust values for the pre-trial model parameters. The validation of the model will be conducted by looking at the internal and external validity.

3. Analysis

3.1 Within-trial analysis

Statistical analyses and CUAs will be carried out using trial data where information on a range of resource use and outcome measures are collected at the patient level. The basis of the analysis will be intention to treat.

3.1.1 Handling missing data

Appropriate methods, such as multiple imputations, will be used to treat missing information. A descriptive analysis will be undertaken to check the nature of missing data before such a method is used. In addition, a sensitivity analysis will be conducted to examine the impact of alternative assumptions about the mechanism of missing data.

3.1.2 Base case analysis and regression

Baseline characteristics of the patients in the two different follow-up groups will be summarised. Differences in resource use and costs between the two groups will be tested using two-sample t-test (or non-parametric equivalents) and X^2 test for continuous and categorical variables, respectively. The mean costs of resource use in each trial arm and the differences in costs between the two arms will be calculated with 95% CIs. Similarly, the mean QALY score for each group will be estimated.
Regression analysis will be conducted to examine how the total cost and health outcomes may be explained by the patient characteristics and follow-up strategy. Different types of models will be explored within a generalized estimating equation framework.

3.1.3 CUA with trial data

CUA will be presented as incremental cost per QALY gained. The ICER will be calculated as:

$$ICER = \frac{Cost_{tele} - Cost_{sc}}{QALY_{tele} - QALY_{sc}}$$

where $Cost_{tele}$ is the total cost of the telehealth patient follow-up group and $Cost_{sc}$ is the total cost of the standard care group. Similarly, $QALY_{tele}$ is total QALYs for the telehealth patient follow-up group and $QALY_{sc}$ is total QALYs for the standard care patients.
Subgroup analyses (e.g., gender, age) will be considered to address potential issues of underlying heterogeneity. The results of the cost-effectiveness including the subgroup and sensitivity analysis will be presented both in terms of point estimates and cost-effectiveness planes, and cost-effectiveness acceptability curves (CEACs).
The two follow-up strategies will also be compared on the basis of incremental net monetary benefits. The net monetary benefit of the telehealth patient follow-up strategy or standard care strategy will be calculated as the mean QALYs multiplied by the acceptability threshold values for a QALY, minus the mean cost of implementing the randomized. An appropriate QALY threshold value will be chosen for Norway.

3.2 The effectiveness measure and CEA in the model-based analysis

The effectiveness measure for economic outcomes in our model-based analysis will be QALYs. Model results will provide estimates for the ICER considering long-term health outcomes and costs. The results of the economic evaluation including the subgroup and sensitivity analyses will be presented in terms of point estimates, cost-effectiveness planes and CEACs.

3.3 Handling uncertainty

To present the robustness of the estimation of cost-effectiveness, non-parametric bootstrapping techniques will be used. CEACs will illustrate the uncertainty surrounding the estimate of cost-effectiveness. Both probabilistic and deterministic sensitivity analyses will be used to explore statistical and other forms of uncertainty arising from the imprecision with which model parameters are estimated.

3. EXODUS app safety presentation

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