

**(Cost-)effectiveness of electronic drug monitoring  
feedback in order to decrease non-adherence in RA-  
patients starting with biological DMARD**

**A randomised clinical trial at Reade**

**PROTOCOL TITLE**

**(Cost-)effectiveness of electronic drug monitoring feedback in order to decrease non-adherence in RA-patients starting with biological DMARD - A randomised clinical trial at Reade**

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**LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

<b>bDMARD</b>	<b>Biological Disease Modifying Anti-Rheumatic Drugs</b>
<b>CQR</b>	<b>Compliance questionnaire on rheumatology</b>
<b>DAS28</b>	<b>Disease Activity Score (28 joints)</b>
<b>DMARDs</b>	<b>Disease Modifying Anti-Rheumatic Drugs</b>
<b>HAQ</b>	<b>Health Assessment Questionnaire</b>
<b>HR</b>	<b>Hazard Ratios</b>
<b>ICER</b>	<b>Incremental cost-effectiveness ratio</b>
<b>METC</b>	<b>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</b>
<b>MEMS</b>	<b>Medication Event Monitoring System</b>
<b>MPR</b>	<b>Medication possession ratio</b>
<b>NSAIDs</b>	<b>Non-steroidal anti-inflammatory drugs</b>
<b>QALY</b>	<b>Quality-Adjusted Life-Year</b>
<b>RA</b>	<b>Rheumatoid Arthritis</b>
<b>WMO</b>	<b>Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)</b>

## 1. SUMMARY

**Rationale:** To reduce disease activity and ultimately limit the joint damage as much as possible, DMARD-therapy (adequately taken by the patient) is warranted in the early stage of RA. As approximately 33% of the RA patients are non-adherent on their medication, interventions to improve adherence are therefore necessary to improve the efficacy of the drugs and consequently improve r health and decrease medication costs. The usage of drug monitoring devices (like Medication Event Monitoring System (MEMS™)) combined with personal feedback regarding medication behavior has proven in other diseases like HIV to be an effective strategy to improve adherence and therefore clinical outcome, decrease drug changes and drug use. Although these studies suggest that electronic drug monitor feedback might have the potential to improve adherence and possibly prevent unnecessary treatment escalation in rheumatoid arthritis patients with poor adherence, empirical evidence to prove this drug-/cost saving potential is lacking. Implementing electronic monitoring feedback in RA might result in a cost effective strategy to reach earlier low disease activity and a prolonged persistence with current biological DMARDs.

**Objective:** To determine if the implementation of electronic drug monitoring adherence feedback in standard care for patients with rheumatoid arthritis starting with a new biological DMARD is effective on medication adherence compared to a usual care group. The second objective is to examine the effect of the intervention on costs and time with high disease activity and proportion of patients with low disease activity/remission .

**Study design:** Randomised, open clinical trial comparing electronic drug monitoring feedback with standard care.

**Study population:** All consecutive patients with rheumatoid arthritis starting with or switching to a new subcutaneously administered bDMARD at Reade will be invited to participate in the study.

**Intervention:** Patients in the intervention group receive their medication during 1 year in an electronic device. Before each regular (3-monthly) consult to the rheumatologist, patient's medication adherence will be assessed by reading out the electronic device and in case of non-adherence possible barriers to medication intake will be discussed with the trained researcher/ -assistant on a semi-structured way. Patients in the control group will receive standard care (an interview with the pharmacy consultant without electronic drug monitor feedback).

**Main study parameters/endpoints:** The primary outcome measure will be the difference in proportion of non-adherence patients (less than 80% medication adherence) after 1 year between the intervention group and in the usual care control group assessed with the validated compliance questionnaire on rheumatology (CQR) and pharmacy refill data. Secondary outcomes will be time to low disease activity and remission and proportion of patients with low disease activity/remission, serum trough levels (optional) and proportion of switching patients to another biological and mean disease activity after 1 year. The use of co-medication (other DMARD's, corticosteroid's and NSAIDs) will be noted. Finally an economic evaluation of the possible added value of electronic drug monitor feedback compared with usual care will be done.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** Most patients are already invited for an interview about patient's medication use, assessment of the disease activity and blood sampling prior to their regular visit to the rheumatologist. The interview about patients medication is an excellent moment for introducing, reading out and discussing the electronic devices and their reports in this study. Electronic drug monitor feedback will be combined with the assessment of patient's actual medication use. One session takes approximately 20 minutes each and is planned before each consult to the rheumatologist (after 3,6,9 and 12 months). Participating in this study needs just a little extra effort for the patient. The intervention program does not constitute a risk for the participants.

## 2. INTRODUCTION AND RATIONALE

Pharmacotherapy is the cornerstone of treatment for inflammatory rheumatic diseases like rheumatoid arthritis (RA). In RA, both non-biological- and biological Disease Modifying Anti Rheumatic Drugs (DMARDs) reduce disease activity and radiological progression and improve long-term functional outcome. To reduce disease activity and ultimately limit the joint damage as much as possible, DMARD-therapy (adequately taken by the patient) is therefore warranted in the early stage of RA.

However, the effectiveness of pharmacological therapy may be limited by inadequate patient adherence to medication. In rheumatic arthritis it is estimated that 33% of the patients are non-adherent to medication.[1,2] Non-adherence in rheumatoid arthritis is associated with disease flares and increased disability.[3,4] Non-adherence might also lead to increased medical expenditures. Increasing medication adherence might therefore reduce disease activity (and ultimately reduce radiological damage) and decrease costs.

Interventions to improve adherence are therefore necessary to reduce undesirable effects of non-adherence on health and medication costs. Assessing medication adherence with drug monitoring devices (like Event Monitoring System (MEMS™) combined with personal feedback regarding medication behavior seems to be a possible effective strategy to improve patient adherence. [5-9] Feedback of the electronic monitoring data might encourage dialogue between patients and treating pharmacists/physicians about concerns about medication, practical barriers and the necessity of maintaining a regular medication intake, which could lead to individualized strategies to improve medication adherence.

Studies have demonstrated that monitoring of drug adherence using electronic monitors improves blood pressure (odds ratio for control of systolic blood pressure after 4 months 4.8 (95-CI:1.5-16.1), leads to fewer drug changes, less drug use and better HIV control (decreased CD4 count) [5-9] These studies suggest that electronic drug monitor feedback might therefore have the potential to prevent non-adherence in RA and furthermore unnecessary treatment escalation/switching in patients with poor adherence. However, empirical evidence to prove the efficacy of this intervention in RA on adherence and the drug-/cost saving potential is lacking. Neither a 1172-hits pubmed search (*search strategy: (((adherence) OR compliance)) AND (((drugs) OR medication) OR medicines)) AND ((electronic\*) OR MEMS)*) nor the most recent systematic review on adherence improving interventions nor a search with the same search on [www.clinicaltrials.gov](http://www.clinicaltrials.gov), retrieved a study which aims to assess the (cost-)effectiveness of electronic drug monitor feedback by preventing unnecessary treatment escalation.[10]

Biological DMARD-therapy in RA seems to be an excellent candidate to test the (cost-) effectiveness of electronic monitoring feedback embedded in usual care. Increasing adherence in RA might lead to earlier low disease activity (which can be easily objectified

with the Disease Activity Score (DAS28)) and (2) a prolonged persistence with current biological DMARDs.



### 3. OBJECTIVES

#### 3.1 Primary Objective

The primary objective is to examine the effectiveness of the electronic drug monitoring adherence feedback in standard care for patients with rheumatoid arthritis starting with or switching to a biological DMARD on medication adherence.

#### 3.2 Secondary Objectives

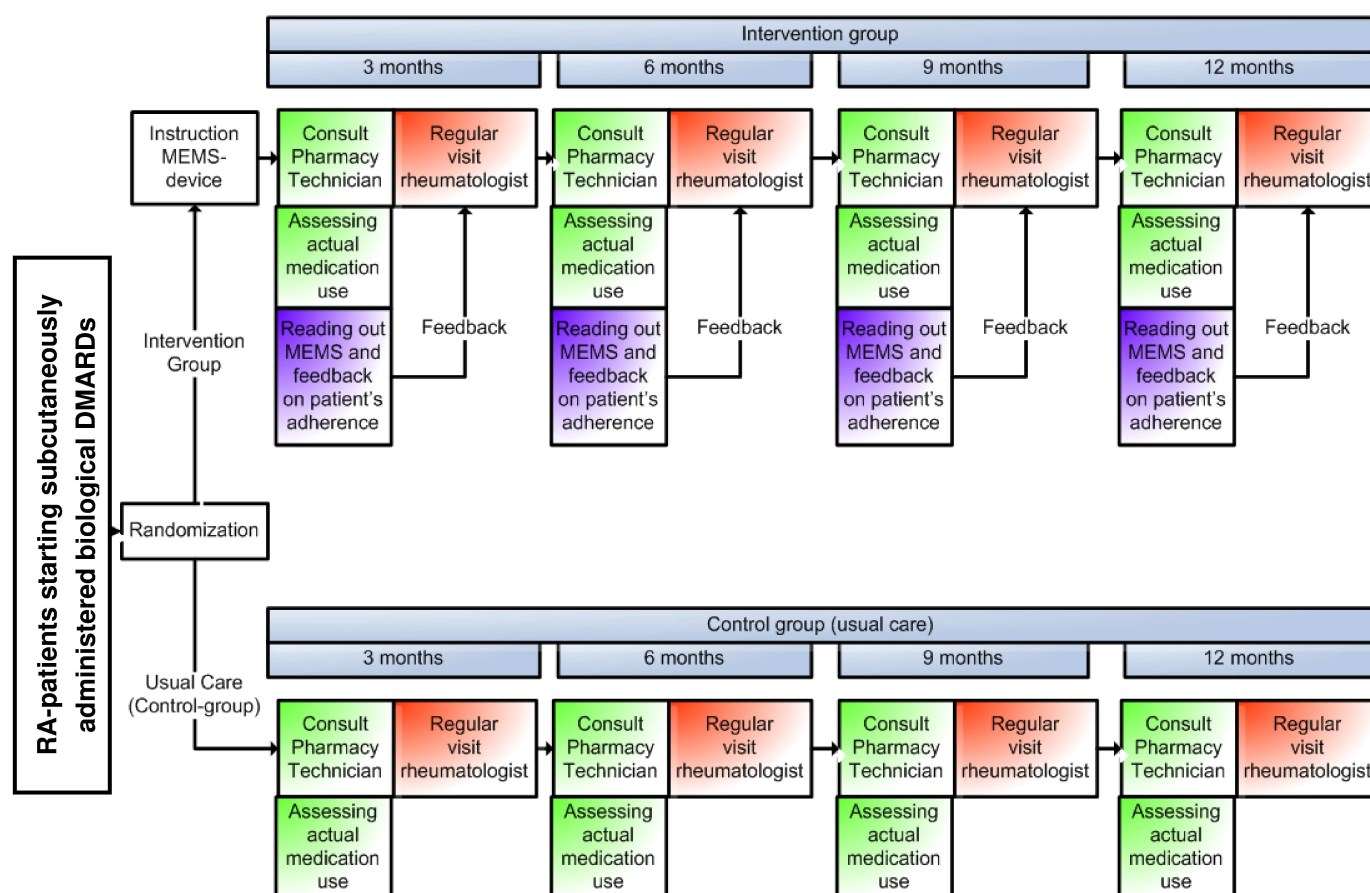
The secondary objectives of this study is to examine the effect of the intervention on time to low disease activity and remission, proportion of patients with low disease activity/remission, serum trough levels (optional) and proportion of switching patients to another biological and mean disease activity after 1 year. The use of co-medication (other DMARD's, corticosteroid's and NSAIDs) will be noted. Finally an economic evaluation of the possible added value of electronic drug monitor feedback compared with usual care will be done.

## 4. STUDY DESIGN

The assess the (cost-)effectiveness of the implementation of electronic drug monitoring feedback an open randomised clinical trial study will be performed in Reade, Amsterdam (the Netherlands).

Eligible patients will be screened during an 18 months period. The patient will be randomly assigned to the experimental or control condition, using a computer-generated randomization list. In this study, patients in the intervention group will receive their bDMARDs in an electronic monitoring device during 12 months. Within one hour before each consult to the rheumatologist (after 3, 6, 9 and 12 months) the electronic monitoring feedback is given by a researcher/ -assistant. Patients in the control group will receive standard care (an interview with the pharmacy consultant assessing patient's actual medication use and possible side-effects without using an electronic-device and electronic drug monitor feedback).

### 4.1 Flowchart



## STUDY POPULATION

### 5.1 Population (base)

As the purpose of this project is to implement electronic drug monitor feedback as standard care in RA, all consecutive patients with rheumatoid arthritis starting with or switching to a new subcutaneously administered bDMARD at Reade will be invited to participate in the study.

### 5.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Diagnosed with RA (2010 ARA criteria or clinical judgment by a rheumatologist)
- Initiating a new (subcutaneously administered) bDMARD
- >18 years
- Sufficient ability to understand Dutch
- Be able to be followed for 12 months (life expectancy).

### 5.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Large cognitive limitations
- Assistance in taking drugs (e.g. home care)
- Included in another randomised controlled trial

### 5.4 Sample size calculation

Previous studies in the Sint Maartenskliniek [2,11] demonstrated that 35% of the RA-patients with DMARDs are not adherent (< 80% adherence). Assuming that half of these non-adherent patient become adherent after electronic drug monitoring feedback, 65% of the patients in the usual care group and 83% of the patients in the control group will be adherent.

A target sample size (84 patients per arm) was computed to provide 80% power to detect a 18% difference in adherence between an expected 83% adherence rate in the intervention group after 1 year versus 65% in the usual care arm. As about 125 patients with rheumatoid arthritis are yearly starting a biological DMARD at Reade, around 168 patients can be included in this study with a 18 months inclusion period and an one year data collection period, taken into account a 10% non-inclusion and/or loss to follow up.

## 6. INTERVENTION

Before each regular (3-monthly) consult to the rheumatologist, patient's medication adherence will be assessed by reading out the electronic device and (if necessary) possible barriers to medication intake will be discussed non judgmentally by a researcher/ -assistant using a published communication typology for medication non adherence. Patients in the control group will receive standard care (an interview with the pharmacy consultant without electronic drug monitor feedback).

### 6.1 Investigational product/treatment

During the study period, patients in the intervention group will receive their bDMARDs in a tray with cavities. Each cavity will be sealed with a foil impregnated with an electronic circuit which is connected to a microchip. When a bDMARD is taken out the cavity the electronic circuit and subsequently the microchip will register medication removal.

### 6.2 Pharmacist intervention

Before each consult to the rheumatologist (after 3,6,9 and 12 months), medication intake data will be downloaded. Within one hour before each visit a pharmacist will evaluate patient's adherence and if non-adherence is present, possible barriers to medication intake will be assessed using a semi-structured interview scheme ((for example concerns about the medication, doubts about the necessity of practical barriers (forgetfulness). During this semi-structured interview communication about non-adherence will be facilitated with a communication model developed by Linn et al. [12] The way in which the feedback is given (does it follow recommended agenda?) will be assessed by audiotaping the three monthly consultations with the pharmacy consultant and analyzing these on compliance with the intended content. The pharmacists will receive a training, facilitating a patient centered efficient consult.

### 6.3 Control

Patients in the control group will receive standard care (an interview with the pharmacy consultant assessing patient's actual medication use and possible side-effects without using MEMS-devices and electronic drug monitor feedback).

## 7. METHODS

### 7.1 Study parameters/endpoints

#### 7.1.1 Main study parameter/endpoint

The primary outcome measure will be the difference in the proportion of non-adherence patients in the intervention (electronic drug monitoring adherence feedback) group compared to usual care. Non adherence will be assessed with both the validated compliance questionnaire on rheumatology (CQR), morisky scale and refill rate adherence. Refill rate adherence is defined as the number of days that bDMARDs have been dispensed to a patient in a defined period, divided by the total number of days in that time period. In this study, the dispense in a year will be used to calculate refill rates to calculate the medication possession ratio (MPR). Patients taking 80% or more of their prescribed DMARDs are defined as adherent, patients taking less than 80% of their prescribed DMARDs are defined as non-adherent.

#### 7.1.2 Secondary study parameters/endpoints

Secondary outcomes will be time to low disease activity (DAS28 < 3.2) and remission (DAS28 < 2.6), proportion of patients with LDA and remission, serum trough levels (optional) and proportion of switching patients to another biological and mean disease activity after 1 year. Finally an economic evaluation (incremental costs both QALY and 0.1 DAS28-unit gained) of the added value of electronic drug monitor feedback compared with traditional care will be performed.

#### 7.1.3 Other study parameters

At inclusion, the following data will be recorded by the researcher: demographic variables, disease related variables including date of disease onset and diagnosis, medication use and co-morbidity.

At inclusion and at each follow-up visit the type and dose of each administered (non-) biological DMARD, medication use/changes, adverse effects, refill data of the DMARD, co-medication, quality of life (HAQ) and disease activity (DAS28-score) will be registered by the trained researcher/ -assistant. The assessment of disease activity before patient's visit to the rheumatologist is already part of standard care in the Reade. Adherence and beliefs about medication will only be assessed at study start and after 1 year, in order to minimize other interventions than usual care in the usual care group.

#### Cost effectiveness

Cost effectiveness will be analyzed using the ICER incremental cost-effectiveness ratio (ICER). The ICER will be expressed as the additional costs per QALY gained for of electronic drug monitor feedback as standard care compared with traditional care from a societal perspective for a one year time-horizon. The pharmacist will register time related to the implementation of the intervention: introducing and reading the electronic device and patient counselling. Other volumes of care of all direct medical costs will be measured:(co)

medication, visits to the rheumatologist, health care professionals, general practitioners and other specialized physicians, x-rays, hospitalizations. The standard cost prices from the 'Dutch Guidelines for Cost Analyses' will be used to calculate costs. For units of care where no standard prices are available real costs prices will be determined on the basis of full cost pricing. Utilities will be measured using the EuroQol 5 dimensions (EQ5D-5L). QALY's will be calculated using the trapezium method. Uncertainty in the ICER will be presented non-parametrically using bootstrap techniques. A cost-effectiveness plane and a cost-effectiveness acceptability curve will be plotted.

### **7.2 Randomisation, blinding and treatment allocation**

After inclusion and obtaining informed consent, patients will be randomised in a conventional care group without electronic drug monitoring and an intervention group with feedback based on electronic monitoring. Patients will be randomised by the researcher using a computer-generated randomisation list. This list will be transferred to sheets of paper in sealed envelopes. When a patient is included a new envelop will be opened.

### **7.3 Withdrawal of individual subjects**

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

### **7.4 Replacement of individual subjects after withdrawal**

Individual subjects withdrawn from treatment will not be replaced.

## 8. SAFETY REPORTING

### 8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

## 9. STATISTICAL ANALYSIS

### 9.1 Descriptive statistics

Descriptive statistics will be used for demographic data, using means ( $\pm$  SD), medians (p25-p75) or percentages depending on the (non-) parametric distribution and type of measured variables. All analyses will be performed on an intention-to-treat (ITT) basis.

### 9.2 Analysis

The primary outcome measure will be the difference in the proportion of non-adherence patients in the intervention (electronic drug monitoring adherence feedback) group compared to usual care assessed with the validated Compliance Questionnaire on Rheumatology (CQR) and medication refill rates. A chi-square test will be used to evaluate differences in proportions between the intervention and control patients with respect to proportion of adherent patients (primary outcome) and the proportion switchers (secondary outcome measure). To analyze whether there is a difference in time to achievement of low disease activity and/or time to the first anti-TNF prescription, cox proportional-hazards analysis will be used to generate hazard ratios (HR) and a 95% CI. Between-group differences will be visualized by Kaplan-Meier time-to-event curves and tested with log-rank testing. The secondary continuous outcomes, disease activity, either DAS28 in RA patients, and adherence measured by the CQR are measured repeatedly and will therefore be analyzed as a repeated measure analysis (Mixed model procedures).

Cost effectiveness will be analyzed using the ICER incremental cost-effectiveness ratio (ICER). The ICER will be expressed as the additional costs per QALY gained for of electronic drug monitor feedback as standard care compared with traditional care from a societal perspective for a one year time-horizon. The pharmacist will register time related to the implementation of the intervention: introducing and reading the electronic device and patient counselling. Other volumes of care of all direct medical costs will be measured: (co) medication, visits to the rheumatologist, health care professionals, general practitioners and other specialized physicians, x-rays, hospitalizations. The standard cost prices from the 'Dutch Guidelines for Cost Analyses' will be used to calculate costs. For units of care where no standard prices are available real costs prices will be determined on the basis of full cost pricing. Utilities will be measured using the EuroQol 5 dimensions (EQ5D-5L). QALY's will be calculated using the trapezium method. Uncertainty in the ICER will be presented non-parametrically using bootstrap techniques. A cost-effectiveness plane and a cost-effectiveness acceptability curve will be plotted.



## 10. ETHICAL CONSIDERATIONS

### 10.1 Regulation statement

Local ethical approval will be sought for from the local Ethics Committee and all participants will be asked to give written informed consent before inclusion.

### 10.2 Recruitment and consent

During an 18 months period, eligible patients that are diagnosed with RA and treated in the Reade Amsterdam, will be invited by their treating physician for participation in this study. Within one week after the consult, the researcher will contact the patient and check whether the patient has any questions regarding this study and ask whether the patient is willing to cooperate in this study. If the patient would consider to participate in the study and signs the provided consent form, the patient will be included.

### 10.3 Benefits and risks assessment, group relatedness

Most patients are already invited for an interview about patient's medication use, assessment of the disease activity and blood sampling prior to their regular visit to the rheumatologist. The interview about patients medication is an excellent moment for introducing, reading out and discussing the electronic devices and their reports in this study. Electronic drug monitor feedback will be combined with the assessment of patient's actual medication use. One session takes approximately 20 minutes each and is planned before each consult to the rheumatologist (after 3,6,9 and 12 months). Participating in this study needs just a little extra effort for the patient. The intervention program does not constitute a risk for the participants.

### 10.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 9 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

€ 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;

€ 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;

€ 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

## 11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### 11.1 Handling and storage of data and documents

Data will be coded by the date of the measurement and a reference number. Data will be stored the local server and as back up on a CD. A subject identification code list will be used to link the data to the subject. An independent pharmacist is the person who will know the identification code to link the data to the subject.

The handling of personal data would comply with the Dutch Personal Data Protection Act.

### 11.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

### 11.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### 11.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

### 11.5 Public disclosure and publication policy

The criteria of the METC statement on publication policy will be used for this study. At the start of the study, this study will be registered in trial register.

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