RESEARCH PROTOCOL

GLORIA

*The **G**lucocorticoid **L**ow-dose **O**utcome in **R**heumato**I**d **A**rthritis Study*

Comparing the cost-effectiveness and safety of additional low-dose glucocorticoid in treatment strategies for elderly patients with rheumatoid arthritis

PROTOCOL TITLE

Comparing the cost-effectiveness and safety of additional low-dose glucocorticoid in treatment strategies for elderly patients with rheumatoid arthritis:
The **G**lucocorticoid **L**ow-dose **O**utcome in **R**heumato**I**d **A**rthritis Study (**GLORIA**)

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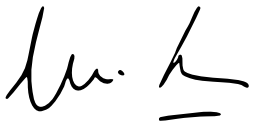
Coordinating Investigator / **Project leader:** Prof. Dr. M. Boers		12-Apr-2019

PROTOCOL SIGNATURE PAGE

The **G**lucocorticoid **L**ow-dose **O**utcome in **R**heumato**I**d **A**rthritis Study (**GLORIA**)
Comparing the cost-effectiveness and safety of additional low-dose glucocorticoid in treatment strategies for elderly patients with rheumatoid arthritis

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with this version of the protocol and all applicable local laws and regulations, Good Clinical Practice and to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality.
I will provide copies of the protocol as needed to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the study. I am aware that this protocol will need to be approved by an appropriate institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met.
I agree to conduct the clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol).

Investigator name: _____

Institution name: _____

Institution location: _____

Signature: Date:

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1. SUMMARY

Rationale: Rheumatoid arthritis (RA) is a condition with high impact both on the individual and society. In the context of comparing the effectiveness of existing healthcare interventions in the elderly, RA is a condition highly relevant to the community since it has a strongly negative impact on the quality of life of the individual, is particularly frequent in the elderly, and is associated with significant costs. RA management remains challenging: there is an urgent unmet medical and societal need for improved treatment strategies that are effective, safe and affordable. Evidence based information on the glucocorticoid (GC) harm/benefit balance will have a high impact on RA treatment strategies and on treatment strategies for the many other inflammatory disorders for which GCs are considered. The Glucocorticoid Low-dose Outcome in RheumatoId Arthritis Study (GLORIA) is a 5-year project funded by the European Commission under the Horizon 2020 Program, designed to address these needs.

Objective: The primary objectives of the GLORIA project are twofold: a) To assess the effectiveness, safety and cost-effectiveness of low-dose GC therapy (5 mg/day) compared to placebo given for two years as co-treatment for elderly RA patients (≥ 65 years) in a pragmatic randomized trial; b) To assess study medication adherence through a medication packaging solution, and test the effectiveness of smart device technology to improve adherence. Other objectives of the GLORIA project are: to deliver an outcome prediction model for individual patient outcome, to tailor treatment strategies for elderly RA patients with comorbidities; and deliver data to support: 1) better guidelines on RA treatment in the elderly; 2) more accurate information for elderly RA patients, their physicians and researchers; 3) improved strategies for trial design and conduct in the elderly.

Study design: The GLORIA study is a randomized, double-blind, placebo-controlled pragmatic multicenter clinical trial to assess the effectiveness and safety of a daily dose of 5 mg prednisolone or matching placebo in elderly RA patients. Patients will be randomized into two arms: the experimental arm (receiving prednisolone 5 mg/day) or the control arm (receiving placebo). Our design emulates the routine care setting: eligibility criteria are very liberal, assessments and procedures are tailored to represent standard of care, and concurrent antirheumatic treatment is allowed next to the trial medication with minimal limitations. Furthermore, all patients will have an adherence monitoring device loaded into the cap of the drug bottle; adherence data will be monitored throughout the trial. In addition, to test the effect of adherence reminders, a substudy (another trial) will be nested in the main GLORIA trial.

Substudy design: The substudy is limited to patients with a smartphone who have completed at least 3 months of the main study on treatment. The experimental arm of the substudy will receive an application loaded onto their smartphone that communicates with an adherence monitoring device loaded into the cap of the drug bottle and delivers reminders to improve adherence. The control arm of the substudy will not have this application and reminders. The substudy has a duration of three months.

Study population: Patients of 65 years of age and older with RA according to the 1987 or the 2010 classification criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), requiring antirheumatic therapy because of inadequate disease control, as evidenced

by a 28-joint disease activity score (DAS28) of ≥ 2.60. For eligibility, the DAS28 can be calculated with ESR or CRP, and also recalculated from the DAS of 44 joints.

Substudy population: Patients in the main study who have completed at least 3 months on treatment, in possession of and familiar with a smartphone.

Intervention: In this two-armed clinical trial, patients will be randomized to either the experimental arm or the control arm. The experimental arm will receive prednisolone 5 mg/day added to existing antirheumatic treatment. The control arm will receive matching placebo added to existing antirheumatic treatment. Treatment duration is two years per patient. Subsequently, study drug is tapered in linear fashion to zero in approximately 3 months by inserting increasing numbers of non-treatment days. Patients experiencing a flare at that time can restart open label prednisolone at the discretion of the treating rheumatologist.

Co-interventions: As part of standard of care all patients will receive Calcium 500 mg/Vitamin D3 800 IU. Besides the study medication, almost all treatment is allowed; both treatment for comorbidities, as well as antirheumatic treatment. This includes biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), short term oral and parenteral GC for flares or comorbidities (e.g. chronic obstructive pulmonary disease) and acetaminophen. However, it is advised not to start other antirheumatic therapy (DMARD, biologic) or give intra-articular or intramuscular GC injections, especially not in the first 3 months, but it is allowed if clinically judged as unavoidable. In such cases, preferred administration is at baseline.

Substudy intervention: All patients will have an adherence monitoring device loaded into the cap of the drug bottle that will be equipped with a wireless transmitter, which not only tracks adherence but can also communicate real time with the smartphone of the patient, through special software to remind patients of the time of medication. In the substudy, patients with a smartphone will receive an application loaded on their smartphone that communicates with the adherence monitoring device loaded into the cap of the drug bottle. The app sends an alert message to inform the patient he or she has forgotten to take the medication. Eligible patients will be randomized to either the experimental arm that receive reminders on their smartphone, or to the control arm that will not receive reminders, for a period of 3 months.

Main study endpoints:

- To measure benefit, primary endpoints are a) signs and symptoms: the time-averaged mean value (estimated from linear mixed models) of the DAS28; b) damage progression: change from baseline after 2-years in total Sharp/van der Heijde damage score of hands and forefeet radiographs.
- To measure safety, the primary endpoint is the total number of patients experiencing at least one serious adverse event, or one clinical event related to the disease or its therapy.
- Other major outcomes are cost-effectiveness, cost-utility, and medication adherence.

Assessment takes place at varying intervals, and includes seven clinic visits and 3 assessments by telephone.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: GLORIA is a pragmatic trial, with measurements that are almost all part of standard of care, and therefore there are no additional risks associated with these measurements. However, the intervention in this trial is that patients are randomized to either standard of care with low-dose GCs or standard of care without low-dose GCs for a duration of two years. It is known that GCs have strong favourable effects on disease activity, of which patients randomised to the control arm (placebo) cannot benefit. However, side effects of GCs are known as well, and patients in the experimental arm (prednisone 5 mg/day) might suffer from them. Although side effects predominantly occur when GC are used in high doses for long periods of time, elderly are more likely to suffer from adverse effects of the disease and its therapy than younger patients. However, elderly are underrepresented or even excluded from many clinical trials, so it is difficult to estimate their risk: this forms the rationale for the trial. To reduce risks, participants are monitored and patients with a low probability of benefit or with a high probability of harm will be excluded from participation to this trial. For the substudy to measure adherence through an innovative application, no additional risks are expected: if the application appears to be successful, patients randomised to the intervention can only benefit from it since it improves their medication adherence; in case the application is not successful, for patients not randomised to the application or for patients without a smartphone, no difference is expected with the ‘normal’ situation, in which patients do not have access to an adherence application.

2. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse event
ANCOVA	Analysis of Covariance
CI	Confidence intervals
CRP	C-reactive protein
DAS28	Disease activity score of 28 joints
DAS44	Disease activity score of 44 joints
DMARDs	Disease-modifying antirheumatic drugs
DEXA	Dual-energy X-ray Absorptiometry
eCRF	Electronic Case Report Form
EDC	Electronic data collection system
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EQ-5D	EuroQoL in 5 dimensions
EULAR	European League Against Rheumatism
GC	Glucocorticoid
GCP	Good Clinical Practice
GLORIA	Glucocorticoid Low-dose Outcome in RheumatoId Arthritis
GMP	Good Manufacturing Practice
HAQ	Health Assessment Questionnaire
ICER	incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Ethics committee
IRB	Institutional review board
IWRS	Interactive Web Response System
NSAIDs	Non-steroidal anti-inflammatory drugs
PV	Accelovance Pharmacovigilance
QALY	Quality-adjusted life year
QoL	Quality of life
RA	Rheumatoid arthritis
RAI	Ritchie Articular Index
RAID	RA Impact of Disease
SAE	Serious adverse event
SF36	Short Form 36-item Health Survey
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse drug reaction
VFA	Vertebral Fracture Assessment
WMO	Medical Research Involving Human Subjects Act

3. INTRODUCTION AND RATIONALE

Rheumatoid arthritis treatment

Rheumatoid arthritis (RA) is a systemic, inflammatory disease characterized by chronic pain, progressive disability, decreasing quality of life (QoL) and premature death. Pathological changes include periarticular cartilage and bone loss, but are not only restricted to joints. Inflammatory lesions can develop in many tissues, including the heart and pericardium, lungs, blood vessels, skin and subcutaneous tissues, eyes, and salivary and lacrimal glands. Both the disease and its treatment gives rise to multiple comorbidities such as an increased incidence of cardiovascular disease, diabetes, osteoporosis, declining organ function (especially hepatic, renal and pulmonary function) as well as osteoarthritis (Scott DL 2010). Current treatment strategies have considerably improved the prognosis, but recent treatment innovations (especially biologic drugs) have important safety issues and come at high societal cost. In addition, many patients still have a smoldering progressive disease despite treatment (Scott DL 2010).

Benefits and harm of glucocorticoid treatment

The introduction of glucocorticoids (GC) in the 1950s was a revolution in the treatment of inflammatory diseases, including RA. Enthusiasm generated by the initial results of unequalled efficacy in previously untreatable diseases led to the unrestricted use of high doses of GCs. Unfortunately, such use disclosed a spectrum of safety issues, which resulted in a still ongoing debate regarding the balance between benefit and harm of GC treatment. Whereas some clinicians are very restrictive in their application of GC treatment, most feel that GCs still have an important role in the management of inflammatory diseases such as RA. Particularly in the early phase of the disease the rapid effects of initially high dose prednisone are very useful in the “window of opportunity”. In the chronic phase of RA, many patients are treated with low-dose GC. A recent meta-analysis has proven beyond doubt that GCs at low doses slow the progression of joint damage in RA (so-called ‘disease modification’), which has renewed the debate on the benefit-risk balance of this treatment (Kirwan JR 2007). Low-dose GCs (defined as a daily dose of 7.5 mg prednisone equivalent or less) could prove an important co-treatment of RA in combination with standard of care. Apart from their clinical effects, low-dose GCs have the potential to reduce the need for expensive treatment with biologic agents: in view of an increasing RA prevalence in the elderly population such treatment may not be societally sustainable. Unfortunately, clinical studies large enough to adequately document the balance of benefit and harm of low-dose GCs in combination with standard of care are lacking.

Existing guidelines and opinions on safety and efficacy of GCs are mostly based on observational studies with high potential for bias, with a scarcity of information from controlled trials. Patients and health professionals, in rheumatology and other fields, tend to select one of two opposing strategies in GC use: either strong avoidance or strong acceptance. As the efficacy of this class of drugs in chronic use is no longer strongly questioned (Kirwan JR 2007), the opposing opinions are primarily based on safety concerns, especially in the elderly. Unfortunately, this stand-off is a reflection of the absence of definitive evidence: the limited high quality data from trials does not support strong claims of harm (as opposed to a wealth of observational studies with high potential for bias), but the generalizability of trial data is questioned. The result is a divergent landscape of RA treatment across Europe (Figure 1) (Sokka T 2007) and inappropriate treatment strategies associated with both under- and over-usage of GC, and consequently suboptimal treatment of RA. Furthermore, RA and

its associated comorbidities often lead to poly-pharmacy and high risk of negative drug interactions, especially in the elderly. According to current insights, the increased mortality is mostly due to increased incidence and lethality of cardiovascular disease caused by chronic inflammation (Kitas GD 2011).

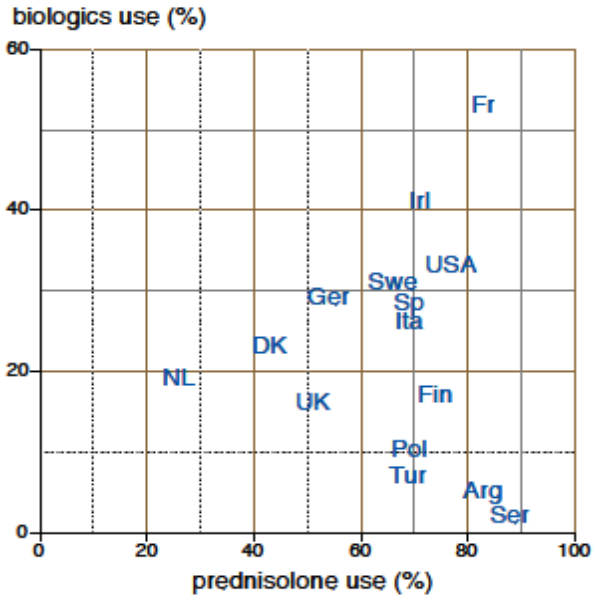

Figure 1. *RA patients (%) treated with biologics and prednisolone (GC) across Europe (graph drawn with data from Sokka et al. (Sokka T 2007).*

Elderly patients

RA is one of the most common chronic inflammatory autoimmune diseases affecting over 3 million people in Europe. RA is known to increase in incidence and prevalence with age, with a peak prevalence around age 85 (Figure 2). Approximately 1% of the world population is affected by RA with a prevalence of 2% in elderly of age 60 and older (Rasch EK 2003). In Europe the prevalence of RA is expected to increase along with the increase in the number of elderly in the population. However, although elderly patients are overrepresented in terms of patient numbers in RA, this group exemplifies the challenge of being underrepresented or even excluded from many clinical trials that generate the evidence-base for treatment of RA.

Cost-effectiveness

RA places a heavy burden on society through its social and economic cost (Kobelt G 2009). The costs of modern RA treatment are very high. Mean costs of RA treatment are currently estimated at nearly €3.000,-/patient/year, but patients starting with new biologic treatment incur costs of €15.000,-/year for the drug alone. Significant savings can be realized by improving the RA treatment strategy. It is very likely that the optimized use of GCs in RA would allow for important savings, specifically by delaying or avoiding the need for expensive biologics.

Adherence

The current treatment strategy for RA is far from ideal. A well-known phenomenon amongst all RA patients is multiple drug failure resulting in progressive disease. In addition, adherence (compliance; generally defined as the extent to which patients take medications as prescribed by their health care providers) is low, often below 50% in patients with chronic diseases such as RA (Brown MT 2011). In RA, non-adherence increases the risk of a disease flare (Muller R 2012). These problems are dramatically increased in the elderly population. The measurement of medication adherence in clinical trials is challenging (Gellad WF 2011). Self-report and patient interviews may not provide accurate and reliable assessments, and prescription refill records and pill counts

often overestimate true adherence. Computerised devices or electronic monitoring devices may assess adherence more accurately.

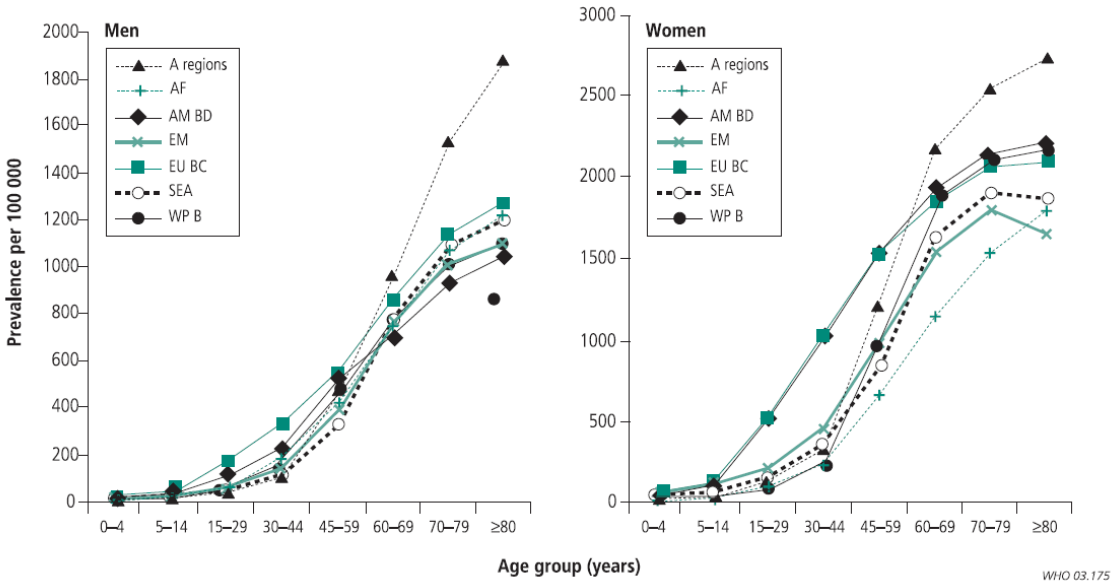

Figure 2. *Prevalence of RA by age group, sex and region. A regions = developed countries in North America, Western Europe, Japan, Australia, and New Zealand. AF = countries in sub-Saharan Africa. AM BD = developing countries in the Americas. EM = countries in the Eastern Mediterranean and North Africa regions. EU BC = developing countries in Europe. SEA = countries in South-east Asia. WP B = countries in the Western Pacific region (Woolf AD 2003)*

In brief, RA is a condition with high impact both on the individual and society. In the context of comparing the effectiveness of existing healthcare interventions in the elderly, RA is a condition highly relevant to the community since it has a strongly negative impact on the QoL of the individual, is particularly frequent in the elderly, and is associated with significant costs (Kobelt G 2009). RA management remains challenging: there is an urgent unmet medical and societal need for improved treatment strategies that are effective, safe and affordable. Evidence based information on the GC harm/benefit balance will have a high impact on RA treatment strategies and on treatment strategies for the many other inflammatory disorders for which GCs are considered.

4. OBJECTIVES

4.1 Primary objectives

Overall

The primary objectives of the GLORIA study are twofold:

a) To assess the **effectiveness, safety and cost-effectiveness** of 2 years of low-dose GC therapy (5 mg/day) compared to placebo as co-treatment for elderly RA patients in a pragmatic randomized trial
b) Study medication adherence through a medication packaging solution, and test the effectiveness of smart device technology to improve adherence

Note: the trial is part of a larger EU-Horizon 2020 project that includes the following objectives:

4.2 Other GLORIA project objectives

Overall

- Deliver an outcome prediction model for individual patient outcome, to tailor treatment strategies for elderly RA patients with comorbidities
- Deliver data to support:
  1) better guidelines on RA treatment in the elderly
  2) more accurate information for elderly RA patients, their physicians and researchers;
  3) improved strategies for trial design and conduct in the elderly.

5. STUDY DESIGN

The GLORIA study is a randomized, double-blind, placebo-controlled pragmatic multicenter clinical trial to assess the effectiveness and safety of a daily dose of 5 mg prednisolone or matching placebo in elderly RA patients.

Patients will be randomized into two arms: the experimental arm (receiving prednisolone 5 mg/day) or the control arm (receiving placebo). See chapter 7.1 for more details about the study medication. Treatment duration is two years.

Pragmatic trials are designed to evaluate the effectiveness of interventions in real-life routine practice conditions (Schwartz D 1967). Our design emulates the routine care setting: eligibility criteria are minimal, assessments and procedures are tailored to represent standard of care, and concurrent antirheumatic treatment is allowed next to the trial medication with minimal limitations. Thus we expect that almost all elderly RA patients (specifically those with comorbidities) are eligible.

The adherence of all patients in the main GLORIA trial is monitored throughout the study period by an adherence monitoring device loaded into the cap of the drug bottle. To measure the effect of smart reminders on medication adherence, a substudy (a randomized trial nested within the main study) will be performed. In this substudy, limited to patients with a smartphone, completing at least the first 3 months of the trial on treatment, the experimental arm will receive an application loaded onto their smartphone that communicates with the adherence monitoring device loaded into the cap of the drug bottle and delivers reminders to improve adherence. The control arm will not have this application and reminders. Intervention duration of the substudy is three months.

6. STUDY POPULATION

6.1 Population (base)

RA patients of 65 years of age and older requiring antirheumatic therapy.

6.2 Inclusion criteria

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

- RA according to the 1987 or 2010 classification criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (Aletaha D 2010);
- inadequate disease control, as evidenced by a 28-joint disease activity score (DAS28) of ≥ 2.60. For eligibility, the DAS28 can be calculated with ESR or CRP, and also recalculated from the DAS of 44 joints. A DAS28 may be calculated with clinical and lab assessments obtained no more than 4 weeks before the baseline visit.
- age ≥ 65 years.

6.3 Exclusion criteria

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

Lower probability of benefit:

- Change, stop or start of antirheumatic treatment in the last month prior to eligibility assessment, including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, intramuscular and oral gold, cyclosporine, biologic agents including anti-TNF, anakinra, abatacept, rituximab, tocilizumab (temporary exclusion);
- Treatment with systemic GC: oral or parenteral GC with a cumulative prednisolone equivalent dose of 200 mg or higher in the last 3 months (temporary exclusion);
- Treatment with any GC (oral, intra-articular, intravenous or intramuscular) in the last 30 days (temporary exclusion);
- Note: as this is a pragmatic trial, patients who require start of (other) antirheumatic treatment *at baseline or during the trial* can still be eligible (see 7.2).

Higher probability of harm:

- Exposure to investigational therapy in the last three months;
- Current participation in another clinical trial;
- Major surgery, donation or loss of approximately 500 ml blood within 4 weeks prior to the screening visit (temporary exclusion)
- Absolute contraindication to low-dose prednisolone, as determined by the treating physician, such as: uncontrolled chronic infections, diabetes mellitus, hypertension, osteoporosis. When these conditions are under control (e.g. with antiosteoporosis drugs, antihypertensive drugs) these patients can enter;
- Absolute contraindication to Calcium and/or Vitamin D supplement as determined by the treating physician, such as: hyperparathyroidism (when insufficiently treated);

- Uncontrolled comorbid conditions, short life span, etc. as determined by the treating physician.

Difficulty to measure harm/benefit:

- Absolute indication to start with oral or intravenous GC, according to the treating physician;
- Inability to comply with medical instructions or inability to assess major outcomes at 6-monthly visits, in the assessment of the treating physician.

Subjects/patients not capable or willing to provide informed consent.

Substudy

Additional exclusion criteria for subjects participating in the substudy to measure the effect of a reminder via smartphone on adherence:

Inability/difficulty to measure benefit:

- Not in the possession of a smartphone;
- Premature discontinuation of study medication within or at 3 months of the main trial.

6.4 Sample size calculation

In the main GLORIA trial, 225 patients per treatment group will be entered (total 450 patients).

In the chosen analysis strategy (see chapter 10), to detect differences in benefit (disease activity, radiographs) extensive RA trial experience (both for GC and other agents) has shown a sample size of 200 patients per group is amply sufficient. For example, in the CAPRA-2 study that compared modified release prednisone 5mg/d against placebo, the prednisone group had 231 patients, the placebo group 119 patients. The change in DAS28 after 3 months of treatment was –1.15 in the prednisone group, –0.63 in the placebo group; difference –0.52 (SE 0.13, p<0.001) (Buttgereit F 2013). However, the true incidence of adverse events (AEs) for GCs is currently unknown. Most relevant data to assess sample size adequacy for this study come from the reported CAMERA-2 trial (Bakker MF 2012). This trial randomized 236 early RA patients to tight-control high-dose methotrexate plus 10 mg prednisolone or placebo for two years. Interestingly, 22% of placebo patients compared to only 14% of prednisolone patients reported at least one serious AE or clinical event as defined in our protocol.

The original protocol used a base case expectation for a total of 20% of patients experiencing at least one event over two years in the placebo group and calculated a need for 400 patients in each treatment group, to have about 80% power to detect an increase of 7% (from 20% to 27% events; 90% power for an increase of 9%). However, based on our current experience the sample can be decreased to about 450 instead of 800.

Elaboration:

In Dec 2018 we had >400 patients in the trial with a mean follow up of 9 months, and we had 84 cases with at least one serious adverse event or an event of special interest (the primary harm outcome). A simple extrapolation leads to an estimated rate of about 49% over 2 years (pooled over the whole blinded trial

population, i.e. both treatment groups taken together). We have also performed life table analysis, which accounts for patients stopping prematurely; this analysis leads to an estimated rate of 40% (95% confidence interval: 30%-50%).

Given the above we can now assume with confidence that the base rate of patients with events in the placebo group will be substantially higher than originally predicted.

This adds power to the trial: we need only between 400 and 450 patients to detect the originally targeted contrast of 27,5%/20%= relative risk of 1,38 (Table 1).

At the expected pooled event rate of 40%, with 400 patients we have 80% power to detect a difference of 12% between placebo and prednisolone: i.e. placebo 34% and prednisolone 46%, a relative risk of 1,35. The results are better with 450 patients, and when the event rate is higher (Table 1).

At the moment of submission of the amendment trial recruitment has been closed on Dec 31, 2018 at a total of 452 patients.

Table 1. Sample size scenarios (one-sided alpha 5%).

expected event rate over 2 years (% unique patients with at least one event)		with power 80%, detectable rate in predn group		Relative Risk	
pooled	placebo	n=400	n=450	n=400	n=450
30%	26%	38%	37%	1,47	1,43
35%	30%	42%	41%	1,40	1,37
40%	**34%**	**46%**	**45%**	**1,35**	**1,32**
45%	39%	52%	52%	1,31	1,31
50%	43%	55%	55%	1,28	1,28

For the substudy to measure adherence, no formal sample size calculation has been done. In feasibility assessments in the centres, the proportion of elderly patients with a smartphone was about 20%. However, in our current experience this is true only in the Netherlands. All other countries have indicated none of their currently included patients has a smartphone. Assuming that patients with a smartphone are technically interested, we can expect about 80% of them to be willing to participate. This gives a total sample size of 50 patients (25 per group). No data is available on actual adherence or its variability between patients.

7. INTERVENTION/TREATMENT OF SUBJECTS

7.1 Investigational product

In this two-armed clinical trial, patients will be randomized to either the experimental arm or the control arm. The experimental arm will receive prednisolone 5 mg/day added to existing antirheumatic treatment. The control arm will receive matching placebo added to existing antirheumatic treatment. Both treatments will be given for the duration of two years.

Subsequently, study drug is slowly tapered in linear fashion to zero in 3 months by inserting increasing numbers of non-treatment days. For this purpose and to prevent unblinding, 3 months of extra study treatment will be made available. Patients experiencing a flare at that time can restart open label prednisolone at the discretion of the treating rheumatologist.

Co-medication

As part of standard of care all patients with receive Calcium 500 mg/Vitamin D3 800 IU. The supplement is beneficial in all RA patients, given the almost universally low levels of vitamin D and low intake of calcium in the diet of the target population.

Adherence

To measure adherence, an adherence medication packaging solution that combines Objective therapy Compliance Monitoring technology (OtCM) and special software is delivered. All patients will have an adherence monitoring device loaded into the cap of the drug bottle. Adherence data will be registered in the study database for all patients, and analysed at the end of the study. Furthermore, the use of RA-friendly pill bottles will avoid the difficulties many RA patients experience with blister packs (small size combined with the force required to push pills out).

For the substudy, the electronic pill bottles will be equipped with a wireless transmitter, which not only tracks adherence but can also communicate real time with a smartphone of the patient, through special software to remind patients of the time of medication. The effectiveness of this application will be tested in the substudy: patients with a smartphone will receive an application loaded on their smartphone that communicates with the adherence monitoring device loaded into the cap of the drug bottle. The app sends a reminder message to the patient when it’s time to take the medication and in case of non-adherence the app also sends an alert message to inform the patient he or she has forgotten to take the medication. Patients will be randomized to either the experimental arm that receive reminders on their smartphone, or to the control arm that will not receive reminders, for a period of 3 months. In patients without a smartphone, data on adherence will be read out from the OtCM when the patient returns for a control visit.

7.2 Use of co-interventions for the treatment of RA

Besides the study medication (prednisolone 5 mg/day or placebo), almost all treatment is allowed; both treatment for comorbidities, as well as antirheumatic treatment, at the discretion of the treating physician. This includes biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), short-term GC for comorbidities (eg, chronic obstructive pulmonary disease; see below) and acetaminophen. Patients requiring such therapy will stay in the study, continue to use study medication and will follow the normal assessment schedule. Treatment changes for worsening of disease after study start should also be coded as AE.

To further minimize intrusion in daily clinical practice, the following policy is instituted: It is advised not to start other antirheumatic therapy (DMARD, biologic, etc.) or give intra-articular or intramuscular GC injections, especially not in the first 3 months, but it is allowed if clinically judged as unavoidable. In such cases, preferred administration is at baseline. We strongly advise physicians to consider changing antirheumatic therapy if GC injections are required more than once a year. Patients receiving more than 2 intramuscular injections or more than 4 intra-articular injections after the start of the trial will also continue study drug, but be categorized as protocol violation and flagged for separate analysis, including non-responder imputation.

Treatment with oral or intravenous GC, for RA constitutes a protocol violation. All such patients will continue to be followed up at the regular study visits. Short treatments for comorbidity are not considered a protocol violation.

Regarding study medication, patients will be handled as follows:

1. Regardless of dose, patients requiring GC for a consecutive period of no more than 3 weeks, and no more than 4 of such periods in the total trial period can continue study medication and stay in the study. The use is noted, and these patients will be flagged for separate analysis.
2. Patients treated for a longer period, or more frequently will be regarded as having developed an absolute indication for chronic oral or intravenous GC therapy. Whether or not study medication is continued will be decided by the Scientific Lead in consultation with the center PI. As above, they will be retained in follow-up and handled separately in the analysis, including non-responder imputation.
3. Patients undergoing emergency or routine surgery can be unblinded if parenteral GC are needed perioperatively. In case of elective surgery, study medication can be given as oral GC perioperatively as adrenal crisis prophylaxis if local guidelines permit, thus obviating the need for unblinding.

7.3 Escape medication

There is no escape medication. See previous section.

7.4 Treatment for other medical conditions

Any medication, considered necessary for the subjects safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication will be recorded in the appropriate sections of the electronic Case Report Form (eCRF). A description of the type of drug or procedure, the amount, duration, reason for administration of drug, and the outcome of any procedures will be documented. AEs related to the administration of a concomitant medication or the performance of a procedure must also be documented in the appropriate eCRF section. When related surgical intervention is needed (in exceptional cases) this will be registered as a serious adverse event (SAE) and as a safety endpoint.

8. INVESTIGATIONAL PRODUCT

8.1 Name and description of investigational product

Prednisolone 5 mg capsules

8.2 Summary of findings from non-clinical studies

The Investigational Medicinal Product that will be manufactured by Bluepharma consists in a modification of a medicinal product which is authorised and marketed in the EU. As the Summary of Product Characteristics (SPC) of the approved medicinal product is available, information regarding the findings from non-clinical studies is mentioned in the SPC (please refer to section “5 - Pharmacological properties” of the SPC).

8.3 Summary of findings from clinical studies

The Investigational Medicinal Product that will be manufactured by Bluepharma consists in a modification of a medicinal product which is authorised and marketed in the EU. As the SPC of the approved medicinal product is available, information regarding the findings from clinical studies is mentioned in the SPC (please refer to section “5 - Pharmacological properties” of the SPC).

8.4 Summary of known and potential risks and benefits

For known and potential risks please refer to the following sections of the SPC:

- 4.3 - Contraindications
- 4.4 - Special warnings and precautions for use
- 4.5 - Interaction with other medicinal products and other forms of interaction.
- 4.6 - Fertility, pregnancy and lactation
- 4.8 - Undesirable effects

For benefits of the Investigational Medicinal Product please refer to section “4.1 - Therapeutic indications” of the SPC.

8.5 Description and justification of route of administration and dosage

The Investigational Medicinal Product has the pharmaceutical form of capsules to be taken orally. Regarding dosage, please refer to the information included in the section “4.2 - Posology and method of administration” of the SPC of the authorised product.

8.6 Dosages, dosage modifications and method of administration

Please refer to the information included in the section “4.2 - Posology and method of administration” of the SPC.

8.7 Preparation and labelling of Investigational Medicinal Product

The Investigational Medicinal Product and the matching placebo will be manufactured according to the Good Manufacturing Practice (GMP). Quality control testing will be performed to confirm that the study medication complies with all the defined quality standards for human use.

The study medication will be packed in bottles and labelled for the trial in accordance to the requirements described in EU GMP Annex 13: Investigational Medicinal Products. The label information will be in the official language(s) of the country in which the investigational medicinal product is to be used.

8.8 Drug accountability

After all the necessary regulatory approvals and upon Sponsor's request, defined quantities of study medication (investigational product and matching placebo) will be shipped to the clinical centers in appropriate conditions in order to guarantee the quality of the investigational medicinal products. Relative humidity and temperature will be controlled during shipment, if needed using a data logger.

In accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, after each study medication receipt, the research staff of each center will account for all study medication. Details of receipt, storage, dosing preparation, administration and return will be recorded. Investigational products will be provided to study subjects only. An adequate quantity of reserve samples for the investigational medicinal products and matching placebo will be retained. The packaging, storage conditions and retention period of the reserve samples shall comply with the current version of the applicable regulations.

Upon completion or premature termination of the study, both the unused and partially unused investigational products and matching placebo (except for the retention samples) will be destroyed.

9. METHODS

9.1 Study outcomes

Assessment takes place ten times during the two years of the trial. At seven timepoints the assessments are performed during a visit to the clinic, and at three timepoints the information with regard to the assessments is gathered by telephone. See Table 3 for more information.

9.1.1 Main study outcomes

a) <u>GC benefit/harm balance</u>

Benefit

Primary outcome measure

- Signs and symptoms: the time-averaged mean value of the DAS28;

Secondary outcome measures

- Damage progression: 2-year change in total Sharp/van der Heijde damage score of hands and forefeet radiographs.
- WHO-ILAR core set of RA outcome measures, including pain, patient and physician global assessment, physical disability, joint counts (swollen joints and tender joints), acute phase reactants (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), and radiographs of hands and forefeet at 0 and 2 years
    - DAS28 is calculated is calculated from 4 of these
- Severity and duration of morning stiffness
- Fatigue
- SF36 - The Short Form 36-item Health Survey, a questionnaire about QoL
- RA Impact of Disease (RAID) tool – The RAID is a validated questionnaire assessing the seven most important domains of impact of RA on the patients
- Health Assessment Questionnaire (HAQ)
- cost questionnaire, including
    - Activity limitation (part of cost questionnaire)
    - Work disability (for those holding a paid job, part of cost questionnaire)
- Utility/Quality-adjusted life years (QALY): Euro-QoL in 5 dimensions (EQ-5D)

Harm

Primary outcome measure

The total number of patients experiencing at least one AE of Special Interest. An ‘AE of Special Interest’ is defined as either a SAE according to the GCP definition (described in chapter 10.2.2), or the occurrence of one the following AEs:

- any AE (except loss of efficacy, worsening of disease) that leads to the definite cessation of one of the antirheumatic drugs, including trial medication;

- a cardiovascular event (myocardial infarction, cerebrovascular event, peripheral arterial vascular event)
- newly occurring hypertension requiring drug treatment;
- newly occurring diabetes mellitus requiring drug treatment;
- symptomatic bone fracture requiring treatment;
- infection requiring antibiotic treatment;
- newly occurring cataract or glaucoma.

AEs can be reported spontaneously by patients, on prompting at clinic visits or by telephone interviews, and by the treating physician. The AEs specified above will be recorded with special care in a separate procedure. This procedure includes adjudication through the collection of evidence. This can be a declaration of the treating physician (in case of start of treatment), or a copy of a letter confirming the event, kept on file in the center.

Secondary outcome measures

- Vital signs, height, weight, and abdominal circumference
- Bone mass assessed by Dual-energy X-ray Absorptiometry (DEXA).
- Vertebral Fracture Analysis (by DEXA OR lateral radiograph of thoracic and lumbar spine)
- Discontinuation of study drug with reason

  This includes patients in whom treatment with prednisolone becomes clinically indicated or those with unacceptable side effects attributable to study medication;
- Change of antirheumatic treatment, with reason
- Intensification of treatment for existing comorbidity, e.g. hypertension or diabetes
- Joint replacement surgery

Data collection is in agreement with industry standard (i.e. Meddra terminology etc.)

b) Cost-effectiveness and cost-utility

Estimate of costs of treatment and monitoring, including prevention and treatment of side effects; out of pocket costs. Estimate of indirect costs based on activity limitations valued at shadow price; and work disability for those still holding a paid job. Resource use data will be obtained by a cost questionnaire completed three/six-monthly, medication use data will be collected with the eCRF, and the number of hospitalization days will be extracted from the narratives of the SAE forms.

c) Medication adherence

Adherence to trial drug is measured through the e-communicative packaging solution as the count of days in which the bottle is opened on the appropriate days, as measured by the adherence tool. The tool (cap) is collected at every study visit and replaced by a new specimen. Each cap (identified by study ID only) is sent back to the provider and the data are read out centrally. At the end of the study, the adherence data is added to the study database.

9.1.2 Secondary study outcomes/endpoints

a) GC harm/benefit balance

- Collection of biological samples
- Blood samples will be collected during the study as part of the standard of care of RA patients, of which non fasting blood samples at baseline and after 3, 12, 24 and 27 months. No additional blood samples will be taken for this study. In specific cases, extra lipid analysis will be performed on the blood samples collected as part of the standard of care.
  Blood samples will not be stored for additional tests.

c) Medication adherence

- Pill count at every study visit
- For patients in the substudy:
  - Satisfaction with the application (21-point Likert scale)
  - Technical performance of the application-adherence tool dyad (to be determined)

9.2 Randomization, blinding and treatment allocation

Four hundred and fifty elderly subjects with RA, will be randomized to either prednisolone 5 mg/day or matching placebo, both added to existing anti-rheumatic treatment in a 1:1 ratio. The two groups are double-blinded.

Randomisation will be stratified for participating study site, for prior exposure to GC, and for concurrent start of other anti-rheumatic therapy.

For randomisation, an Interactive Web Response System (IWRS) will be integrated in the data management system. The minimization randomisation method based on the principles of Pocock and Simon (Pocock SJ 1975) will be used. Minimization is a method of randomization that allocates subjects to the treatment group that best maintains balance in stratifying factors. It is effective even at small sample sizes and with multiple stratification variables. Rules to calculate the amount of variation and the imbalance for each treatment, and rules to assign a probability to each treatment will be discussed with the sponsor before the implementation.

For the substudy to measure the effect of smart reminders to adherence, 50 subjects with a smartphone will be randomized, between an application loaded on their smartphone that communicates with an adherence monitoring device loaded into the cap of the drug bottle and no such application loaded on their smartphone. Randomisation will be stratified for participating country and treatment in order to have for each treatment a balance between an application and no application on the smartphone. The same method as mentioned before will be used.

9.3 Study procedures

The study procedures are described in detail below, and measurements that are included in this trial are stated in Table 2. Almost all measurements can be regarded as standard of care in the participating countries and sites.

All clinical procedures can be repeated at any time and study procedures may be performed at unscheduled time points, if deemed necessary by the investigator. Any additional tests or assessments for safety reasons may be performed if deemed necessary by the sponsor or investigator. These unscheduled assessments should be recorded in the eCRF.

9.3.1 Demographic measurements, education, medical conditions; baseline assessment of prognostic factors

Demographic data to be recorded are date of birth, sex, body weight, height, smoking, alcohol use, and the possession of a smartphone. Body weight and height will be obtained with the subject's shoes off, jacket or coat removed. Body weight will be assessed at baseline, and after 3, 6, 12, 18, 24 and 27 months, height will be measured at the baseline visit and at 24 months.

Education level (Appendix M), relevant medical history, vaccination status and current medical conditions will be obtained by the investigator or qualified designee and recorded in the eCRF. At baseline the following prognostic factors will be assessed by brief questionnaires (Appendix M): risk factors glaucoma (4 items); adherence (8 items); health literacy (3 items); arthritis helplessness index (5 items).

9.3.2 Vital signs and physical examination

Vital signs will be performed at the baseline visit, 3, 6, 12, 18, 24 and 27 months. Vital signs include heart rate and blood pressure. Any abnormalities will be recorded in the eCRF. Physical examination will be performed at the discretion of the treating physician.

9.3.3 Hand, wrist and feet X-ray

Radiographs of both hands (including wrists) (one film anteroposterior) and forefeet (one film anteroposterior) will be obtained at baseline and 24 months.

9.3.4 Laboratory measurements

Laboratory tests performed as in standard of care for hematology, biochemistry, and lipids are described in detail below (Table 2).

9.3.5 Efficacy assessments

Evaluation of joints and disease activity scores

An assessment of 44 joints for swelling and tenderness will be performed at baseline and after 24 months, assessment of 28 joints at 3, 6, 12 and 18 months. Joint swelling will be assessed as absent or present; joint

tenderness will be graded semi-quantitatively from 0-3 for the 44 joint score (Ritchie Articular Index (RAI)) (Ritchie DM 1968) and as absent or present for the 28-joint score. Appendix B.

The DAS28 is a composite index taking into account the tenderness and swelling score of 28 joints, laboratory ESR, and the global assessment of disease activity. The DAS28 has a range of 0 to 9.4, in which levels below 3.2 represent low disease activity, and levels equal or greater than 3.2 represent high disease activity. The EULAR response and ACR response are rated according to appendix C.

Damage progression of the joints in the hands and forefeet will be evaluated by the total Sharp/van der Heijde damage score (appendix D).

Global disease activity

The physician will answer a question on global assessment of disease activity on a 21-point Likert Scale (at the time points indicated in Table 2; appendix F).

The patient will answer two questions in a similar way:

1. global assessment of disease activity (appendix E).
2. pain question: this question is part of the RA Impact of Disease (RAID) questionnaire, see appendix H.

Stiffness

Morning stiffness severity is assessed using a 21-point Likert Scale. In addition, morning stiffness duration in minutes is assessed. See appendix E.

(Modified) Health Assessment Questionnaire ((M)HAQ)

The (M)HAQ index is a patient completed questionnaire specific for RA to assess physical functioning. The full HAQ consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. The MHAQ consists of 10 questions. Appendix GF.

Rheumatoid Arthritis Impact of Disease Questionnaire (RAID)

The RAID is a validated questionnaire assessing the seven most important domains of impact of RA on the patients, with a 21-point Likert Scale. See appendix H.

Cost questionnaire

Data about costs for health care and housekeeping, and sick leave in paid and unpaid work are collected with the cost questionnaire in appendix I.

Quality of life

The EQ-5D and the SF36 will be completed to assess QoL. They are added as appendix J and appendix K.

Patient symptom list

Patients will be asked to fill out the patient symptom list, a list with a number of physical complaints, as depicted in appendix L.

9.4 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 and sponsor can decide to withdraw a subject from the study for urgent medical reasons.

9.5 Replacement of individual subjects after withdrawal

For this study subjects will not be replaced after withdrawal.

9.6 Follow-up of subjects withdrawn from treatment

All patients taking study medication will be followed up for a maximum of 2 years and 3 months, when tapering of study medication is complete. When a patient prematurely discontinues study medication a full end of study visit (V9) is performed. This visit includes radiographic assessment (X-ray and DEXA) if study medication is stopped at or after 9 months from study start and if local standards permits.

Where this is not possible (because the stop of study medication lies in the past), the first visit after the event must be executed as a V9 visit.

For completeness: regulations stipulate that all adverse events (serious or nonserious) MUST be followed until resolved or stable, this also applies to situations where study medication is prematurely stopped. For all adverse events the last possible follow up will be at V10.

In addition, all patients stopping prematurely are invited to attend a follow up visit (V10) at or around 2 years after the inclusion date. Data collected at this visit is the same as those collected for a normal V10 (‘follow up/taper visit’).

For patients who stop prematurely, AE evaluation will be limited to SAE and events of special interest. At visit 10, completeness of follow up for events occurring in the first 3 months after stop of study medication will also be checked.

Completion of the data for V10 is required to receive the full fee for a patient.

9.7 Premature termination of the study

Not applicable: prednisolone at doses exceeding 5 mg/d is currently widely used as chronic therapy in the target population, so unexpected safety findings that would necessitate premature termination are extremely unlikely. One of the main objectives of the study is to provide an accurate estimate of the safety this licensed therapy.

9.8 Procedure for unblinding of study medication

The treating physician or pharmacist can request unblinding of study medication for medical reasons. Please refer to the Gloria IMP manual for unblinding instructions via the ALEA e-CRF or via telephone.
Full documentation will subsequently be collected by the Clinical Research Associate in that country.

The patient can stay in the study, but the data collected will be handled separately in the analysis (see section 7.2).

10. SAFETY REPORTING

10.1 Disadvantageous event

In accordance to applicable legislation and guidelines, the investigator will inform the subjects and the reviewing accredited ethical committee 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 ethical committee, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

10.2 AEs, SAEs and SUSARs

10.2.1 Adverse events (AEs)

An AE is any untoward medical occurrence in a subject who has received study drug, or any untoward or unintended response to an experimental intervention which does not necessarily have a causal relationship with the treatment.
An undesirable medical condition can be symptoms (e.g. dizziness, flushing), signs (e.g. local progression of swelling or hematoma), disease or the abnormal results of an investigation (e.g. laboratory findings) temporarily associated with the use of a medicinal (investigational) product. Any worsening of pre-existing condition that is temporally associated with the use of the pharmaceutical product, is also an AE.

Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions) do not represent AEs.

Subjects will be carefully monitored throughout the study for AEs. At each study visit, subjects will be asked to report any AE. All AEs are followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted. The investigator will use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

Each collected AE, regardless of the relationship to study drug, will be recorded in the AE eCRF. All entries should contain an event term, date of onset, date of resolution, severity, action taken, outcome, relationship to study drug, and a seriousness assessment. The investigator will document all AEs in the subject's source document. Reported (change in) symptoms in the "Patient symptom list" do not need to be reported in the eCRF as an AE.

Severity will be assessed by the investigator according to the following definitions:

- Mild: The event is of little concern to the subject and/or of no clinical significance. The event is not expected to have any effect on the subject's health or wellbeing.

- Moderate: The subject experienced discomfort enough to cause interference with usual activity, and/or the condition required specific treatment. The event is of some concern to the subject's health or wellbeing. The event may require medical intervention.
- Severe: The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or wellbeing. The event is likely to require medical intervention and/or close follow-up.
- Life-threatening: The subject is at risk of death due to the AE as it occurred. This does not refer to an event that hypothetically might have caused death if it were more severe.
- Death: Death related to AE.

Action taken is categorized as "none", "study drug discontinued", "dose modified", "required concomitant medication", "required procedure", or "other".

Event outcome at resolution, or time last follow-up was recorded is categorized as: "event resolved"; "resolved with sequelae"; "ongoing"; "lost to follow-up"; or "death".

The investigator will determine the relationship of the event to the study drug according to the following criteria:

- Not related: The event does not follow a plausible chronological sequence relative to trial medication administration and can be clearly assigned to other factors, such as subject's clinical condition, therapeutic procedures or administration of concomitant medications.
- Possibly related: There is sufficient information to accept the possibility of a causal relationship, although the connection is uncertain or doubtful, i.e. causal relationship is not impossible and not unlikely. The event follows a plausible chronological sequence relative to trial medication administration and/or presents the usual response to the drug tested. The event might also be caused by other factors, such as the subject's clinical condition, therapeutic procedures or administration of concomitant medications.
- Probably related: There are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely, but not necessarily highly probable. The event follows a plausible chronological sequence relative to trial medication administration and/or presents an unexpected response to the trial drug and cannot reasonably be explained by other factors, such as the subject's clinical condition, therapeutic procedures or administration of concomitant medications.
- Definitely Related: When the event cannot be attributed to the subject's underlying medical condition or other concomitant therapy and there is compelling temporal relationship between the onset of the event and the study investigational product administration that leads the PI to believe there is evidence of a reasonable causal relationship.

10.2.2 Adverse (Drug) reactions

According Directive 2001/20/EC adverse (drug) reactions (ADR) are all untoward and unintended responses to an investigational medicinal product related to any dose administered.

The definition implies a reasonable possibility of a causal relationship between the event and the investigational medicinal product (IMP). This means that there are facts (evidence) or arguments to suggest a causal relationship. The definition covers also medication errors, misuse and abuse of the product.

10.2.3 Serious adverse events (SAEs)

A SAE is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires in-subject hospitalisation or prolongation of existing inpatients' hospitalisation, unless it was a planned hospitalization, for instance for an elective surgery;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above..

Medical and scientific judgment should be exercised in deciding whether an AE is serious in other instances, such as an important medical event that may not be immediately life-threatening or resulting in death, or a hospitalisation that may jeopardize the subject or require intervention to prevent one of the above outcomes. Elective surgery for pre-existing conditions as noted in the CRF will not be included as SAE, unless the surgery is triggered by unexpected worsening of the clinical condition.

All SAEs will be reported by the investigator to the Accelovance Pharmacovigilance (PV) within 24 hours of first knowledge of the investigator or its team. All SAEs will be reported by submitting a completed SAE Report Form. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. It is critical that the information provided on the sponsor's SAE Report Form matches the information recorded in AE eCRF for the same event. In addition, the same information is to be recorded in the source documents.

PV will notify the sponsor of all SAE's within 24 hours of its initial receipt.
The CIOMS prepared by PV will be shared with sponsor for review and approval.

Pregnancy screening and handling is not applicable in this study as all subjects are 65 years or older.

10.2.4 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 10.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;

3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the SPC for an authorised medicinal product;

All serious and unexpected adverse reactions that are possibly, probably or definitely related to IMP are subject to expedited reporting to Regulatory Authorities and Ethic Committees, in accordance with ICH guidelines for GCP and the EU Directive 2001/20/EC and applicable local regulations.

SUSARs that are fatal or life-threatening must be reported as soon as possible and in any case no later than 7 calendar days after knowledge by PV/sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the IRB/IEC concerned as soon as possible but within a maximum of 15 calendar days of first knowledge by PV/sponsor.

PV will report any SUSARs on behalf of the sponsor to the IEC/CA according to local requirements. The IRB/IEC should receive the following SUSARs expeditedly:

- SUSARs that have arisen in the clinical trial that was assessed by the accredited ethical committee;

10.3 Annual safety update report

In addition to the expedited reporting of SUSARs, once a year throughout the clinical trial, a safety report will be submitted to the accredited ethical committee, competent authority and ethical committees & competent authorities of the concerned Member States.

This safety report will comprise a line listing of all SAEs, along with an aggregated summary table of all reported SAEs and other events of special interest (see 9.1.1.a), ordered by organ system.

10.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached; last potential follow up is at V10. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

10.5 Monitoring

Clinical trial management and monitoring will be performed by Curve Clinical. In order to ensure the clinical trial is managed and conducted properly Curve Clinical will:

- Set up workflows, timelines, project specific procedures and tracking tools;
- Monitor timelines and milestones on an ongoing basis and communicating the project status to the project team throughout the duration of the entire project;
- Conduct regular team meetings to discuss project status, activities, address issues, coordination of project specific trainings;
- Maintain regular contact with principal investigators;

- Provide status reports to principal investigator, regular site contacts, back-up according to agreed project structures;
- Provide weekly internal status reports to senior Curve Clinical staff;
- Maintain files according to the Standard operating procedures (SOPs);
- Supporting the site with protocol and study related questions;
- Supporting the study sites with patient visit coordination and patient follow up;
- Initiate actions to address project issues.

During the study, the monitor/clinical research associate will visit the investigational site regularly to check the completeness of patient records, the accuracy of entries in the eCRF, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. The monitor/clinical research associate is capable of reading the local language as well as being fluent in English. Key trial personnel must be available to assist the monitor during these visits. The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly in the eCRFs, which will be documented as being the source data. The investigator must also keep the original of the signed informed consent form. The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Curve Clinical monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables.

11. STATISTICAL ANALYSIS

11.1 Primary study outcome(s)

Benefit

The two primary outcomes for benefit are RA disease activity and progression of joint damage. Disease activity is operationalized as DAS28. This index comprises a formula that includes 28 tender and swollen joint counts, general health (GH; patient assessment of disease activity; Likert scale from 0-10 recoded to 0-100, with 0=best, 100=worst), plus levels of ESR (mm/h)). For calculation of DAS28, please see appendix C. Damage progression will be evaluated by the total Sharp/van der Heijde damage score of hands and forefeet (appendix D).

Primary analysis: DAS28

The DAS28 is a continuous variable. We will compute the “time averaged DAS28” based on the trajectories over time for each individual, as part of the repeated measures in the longitudinal design. Observations are included in the follow up time until end of trial or the occurrence of a protocol violation (i.e., GC co-interventions as outlined in section 7.2).

The term ‘repeated measures' refers to data with multiple observations on the same sampling unit; in this case, the multiple observations are taken over time (10 visits) in 450 RA patients. To address the issue of covariation between measures on the same unit, linear mixed models will be fitted because they permit the covariance structure to be incorporated into the statistical model. After modelling the covariance structure, inference about fixed effects proceeds essentially as when using simple Analysis of Covariance (ANCOVA); i.e., enabling estimation of group effects “averaged over time” measured in DAS28-units. Using repeated-measures mixed models we will analyse mean trajectories in continuous end points. The model will include treatment (group), and the multiple stratification variables (participating study site, prior exposure to GC, and concurrent start of other anti-rheumatic therapy) as fixed effects, with the baseline value of the relevant variable as a covariate.

Secondary analyses: DAS28

Change in DAS28 over the first 3 months of the trial (when the chance of co-intervention is least) will be compared between the treatment groups by ANCOVA, adjusting for the level at baseline. In secondary analyses, observations in patients after the protocol violation will be included in the analysis described above.

Damage progression will be evaluated by the change in total Sharp/van der Heijde damage score of hands and forefeet. It is known that this variable has a positively skewed distribution. Cumulative probability plot with the distribution of change in total Sharp/van der Heijde score from baseline to two-year follow-up will be applied as well as a non-parametric test (the Mann-Whitney test) to compare intervention and control groups.

Harm

The primary outcome variable for harm is operationalized as a binary variable with two categories (0= no adverse event, 1= at least one adverse event of special interest (see 9.1.1.a). This variable will be presented as a proportion. A chi-square test will be used to test for differences between the proportion of adverse events in intervention and control groups.

Secondary analyses:

A logistic regression model with harm as dependent variable will be fitted in order to adjust for potential factors that may alter the probability of AEs (as explained above for benefit). In addition absolute incremental risk and relative risk will be calculated for all major events, with confidence intervals.

Analysis strategy:

- One-sided significance levels (alpha=0.05); asymmetric null hypotheses: this approach increases the chance of rejecting the null hypotheses compared to standard two-sided testing. This results in a higher chance of declaring benefit (justified in view of scientific knowledge and the pragmatic trial design), but also a higher chance of declaring harm (to guard against the limited power of the study to detect harm).
    - confirmation of benefit: on the basis of the trial data we expect to reject the null hypothesis of GC (added to standard of care) yielding similar effectiveness compared to placebo (H_0); the alternative (H_1) hypothesis is that GC yields better effectiveness;
    - demonstration of absence of harm: we expect NOT to reject the null hypothesis that GC yields similar side effects; see 4.4 for considerations of the 95% non-inferiority confidence bound.
        - In case the trial detects a difference in AEs favoring the GC group, the superiority of GC will be tested in a secondary analysis.
- Handling of premature discontinuations, dropouts and missing data: for primary analysis of signs and symptoms (efficacy), after the baseline screening and the first assessment visit, each patient with at least one follow up visit (this can be an extra premature discontinuation visit) will contribute until moment of discontinuation. For harm, patients experiencing an event at or before discontinuation will be counted; patients without such an event will be included in the group numerator (weighted by total time in trial).

Different missing data pattern will be studied and Multiple Imputation will be used to handle for discontinuations and drop-out. In the imputation model all variables related with the presence of missing will be included. Then, at least 20 data-sets will be imputed and the pooled results will be reported. Sensitivity analyses will be used to assess the robustness of our results.

Prespecified interpretation rules:

The co-primary outcomes of benefit (average disease activity) and harm (occurrence of AE of special interest) will be assessed and analyzed together.

Given that GLORIA is a pragmatic trial where co-interventions are allowed, the observed effects are likely a compound of the ‘’pure’’ treatment effects and the effects of (potentially differential) co-interventions in the treatment and placebo groups. Therefore, we can distinguish benefit confounding, which can be defined as

the event that placebo patients more frequently require co-interventions because their RA is not under control, leading to subsequent improvement in disease activity.

The outcomes of benefit will be interpreted as follows (GC group compared to placebo):

1. success:
   a. lower disease activity (one-sided $p<0.05$)
      AND lower damage progression (one sided $p<0.05$)
   b. lower disease activity (one-sided $p<0.05$) OR lower damage progression (one-sided $p<0.05$)
      AND benefit confounding
2. partial success/tradeoff:
   a. lower disease activity (one-sided $p<0.05$) OR
      lower damage progression (one-sided $p<0.05$)
   b. Benefit confounding
3. failure: NO lower disease activity (one-sided $p\geq0.05$)
   AND NO lower damage progression (one sided $p\geq0.05$)
   AND NO benefit confounding

The outcomes of harm will be interpreted as follows:

1. success: NO significant increase in AEs (one sided $p\geq0.05$)
2. failure: significant increase in AEs (one-sided $p<0.05$)

For the interpretation of increases in the occurrence of AE of special interest that did not reach significance we will use the suggestions of the GRADE (Grades of Recommendations, Assessment, Development, and Evaluation) Working Group (Guyatt 2012), upper limit of one-sided 95% confidence limit (CL):

1. > 1.3: GC associated with a trend towards greater occurrence;
2. ≤ 1.2: GC appears to have little effect on the occurrence;
3. > 1.2 and ≤ 1.3: results failed to demonstrate or exclude a greater occurrence.

In the case of a numerical DECREASE in AE, a more stringent test for significance will be performed ($p<0.025$).
For the interpretation of decreases in the occurrence of AE that did not reach significance:
lower limit of one-sided 95% CL:

1. < 0.7: GC associated with a trend towards reduced occurrence;
2. ≥ 0.8: appears to have little effect on the occurrence;
3. < 0.8 and ≥ 0.7: results failed to demonstrate or exclude a reduced occurrence.

Economic evaluation

The economic evaluation will comprise a cost-effectiveness and a cost-utility study. The evaluation will be performed according to the intention-to-treat principle and from a societal perspective. All direct medical and non-medical, and indirect costs were combined to calculate the costs per patient. Costs of hospitalization days, visits to medical specialists (direct costs), and help in the household (indirect costs) are valued with standard prices according to the Dutch manual for costing studies. Dutch prices will be used for all costs to keep costs comparable between countries. The unit prices of 2017 are used because most patients were

included in this year. The Dutch consumer price index will be used to account for inflation. Production losses will be valued using the friction cost method: only sick leave during a friction period (23 weeks) needed to replace a person is taken into account (indirect costs).
Outcome measures are time-averaged disease activity (DAS28) for the cost-effectiveness analysis and Quality-Adjusted Life Year (QALY) for the cost-utility analysis.

Confidence intervals (CI) for costs will be estimated with bias-corrected accelerated bootstrapping with 1000 iterations.

All patients will be included in the cost-utility and cost-effectiveness analyses according to the intention-to-treat principle. Missing data will be imputed with multiple imputation by chained equations (with predictive mean matching). Stepwise linear and logistic regression analyses will be used to examine which variables are associated with missingness. and such variables will be included in the multiple imputation model. The data are imputed as total costs or utility score or DAS28 per time point per treatment arm (prednisolone or placebo). The imputed datasets will be bootstrapped with 5000 replications in order to estimate the uncertainty around the difference in costs and effects.

The imputed datasets will be bootstrapped with 5000 replications in order to estimate the uncertainty around the difference in costs and effects. The incremental Cost-Effectiveness and Cost-Utility Ratios (ICER and ICUR) will be calculated by dividing the difference between the mean costs per treatment group by the difference between the time-averaged disease activity per group and by the difference in QALYs per patient. The results will be graphically presented on a cost-effectiveness and cost-utility plane, and a cost-effectiveness acceptability curve will be constructed. This results in four different quadrants: two showing dominance of one treatment over the other, and two indicating a tradeoff between QALYs and costs.

Medication adherence

- Nonparametric and parametric comparisons between treatment groups where appropriate; one-sided significance levels (alpha=0.05)
- Handling of premature discontinuations, dropouts and missing data: each patient will contribute until moment of discontinuation (weighted by total time in trial)

11.2 Secondary study outcome(s)

For continuous variables, (e.g. RA core, SF36, RAID, QALY) first univariate analyses will be conducted to evaluate their distributions and the presence of outliers. If the variables are not normally distributed they will be transformed. Then mixed regression models will be used to study changes in their levels over the follow-up.

For categorical variables (e.g. ACR response, EULAR response) multiple exclusive groups will be defined and differences between the intervention and control groups will be tested by a chi-squared test for linear-by-linear association. In secondary analyses, generalized linear mixed models (GLMM) will be used to assess different

patterns of change during the follow-up. Finally, number needed to treat and number needed to harm analyses will be conducted on selected categorical variables based on the observed events in the placebo group.

12. ETHICAL CONSIDERATIONS

12.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013, see for the most recent version: www.wma.net), GCP and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and Acts.

12.2 Recruitment and consent

Subjects will be recruited from the investigational sites based on the eligibility criteria provided in the protocol. They will be informed about the study by their treating rheumatologist, where after they receive the patient information letter and the researcher or research nurse will provide extra information on request. Subjects can think about participation as long as needed.

Voluntary written Informed Consent Form (ICF) must be obtained from each subject prior to performing any study related procedures in compliance with the recommendations of the Declaration of Helsinki. Subjects should not be screened or study drug administered until the subject has signed an approved ICF written in a language that is understandable to the subject.

Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The ICF should be signed and personally dated in two originals by the subject and the person who conducted the informed consent discussion. The Investigator, or the attending health care professional will explain the nature, purpose and risks of the study. The subject will be informed that he/she has the right to withdraw at any time from the study, without giving reasons. In this condition, the subject will also be informed that he/she will not receive any indemnity. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study.

Each subject should receive one original of the signed and dated written ICF and any other information provided to the subject. The second original of the signed and dated ICF should be retained in the investigator's file. The investigator should maintain a log of all subjects who sign the ICF.

12.3 Benefits and risks assessment, group relatedness

Since GLORIA is a pragmatic trial, it is designed to evaluate the effectiveness of interventions in real-life routine practice conditions. This means almost all measurements are part of standard of care, and therefore there are no additional risks associated with these measurements.

However, the intervention in this trial is that patients are randomised to either standard of care with low-dose GCs or standard of care with matching placebo for a duration of two years. It is known that GCs have strong favourable effects on disease activity, however, side effects are known as well, predominantly when used in

high-doses and for a long period of time. Unfortunately, clinical studies large enough to adequately document the balance between benefit and harm of low-dose GCs in combination with standard of care are lacking. And although elderly patients are overrepresented in terms of patient numbers in RA, this group exemplifies the challenge that they are underrepresented or even excluded from many clinical trials that generate the evidence-base for treatment of RA. However, the limited high-quality data from trials does not support strong claims of harm, but the generalizability of trial data is questioned. Therefore, the primary objective of the GLORIA trial is to deliver evidence-based information on the GC harm/benefit balance.

For the substudy to measure adherence, no additional risks are expected. Non-adherence substantially increases the risk of a disease flare in RA. GLORIA measures adherence through a medication packaging device and tests an innovative application to improve medication adherence in elderly patients. If this application appears to be successful, patients randomised to this intervention can only benefit from it since it improves their medication adherence. In case the application is not successful, or patients are not randomised to the application, or for patients without a smartphone, no difference is expected with the 'normal' situation, in which patients do not have access to an adherence application. Furthermore, results of adherence monitoring and a positive result of the adherence intervention will have a large impact in the elderly population as a whole, and even more in the younger population where the penetration of smartphones is so much greater.

12.4 Compensation for injury

The Sponsor and/or Investigator has a liability insurance which is in accordance with relevant legislation. In the event of any suffering, deterioration in health or well-being or any harmful susceptibility or toxicity caused to subjects' participation in the trial, the subject will receive appropriate compensation irrespective of the question of legal liability.

The Sponsor and/or Investigator has an insurance which is in accordance with the legal requirements in the participating countries. This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study. Each partner will ensure proper insurance to cover their liability, and damage for subjects participating in their country.

12.5 Incentives

Patients participating in this trial will receive compensation for travelling costs if extra visits to the treating centre (outside of regular care) are necessary.

13. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

13.1 Handling and storage of data and documents

13.1.1 Data Handling

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. With the subject's permission, medical information may be given to his personal physician or other appropriate medical personnel responsible for his/her welfare.

The information required by the protocol into is entered into an electronic data collection system (EDC). The eCRF data are to be considered source data in addition to the automatic print outs as well as patient records.

The eCRF will be developed by the data manager for the study. Detailed information on the eCRF completion will be provided during the site initiation visits. Each site will also be provided with an eCRF completion manual. In general, all users who have access to the EDC system will be trained. The access to the eCRF is password controlled. Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data collection system; answers to queries or changes of the data will directly be documented in the system. After all data are entered and all queries are solved, the database will be closed.

Data generated by this study must be available for inspection by representatives of other national and local health authorities, the sponsor, and the IRB/IEC for each study site, if appropriate.

Subjects will be identified on CRFs and other documents submitted to the Sponsor or organisations working on behalf of the Sponsor by their subject number, not by name or initials. Documents not to be submitted to the Sponsor or organisations working on behalf of the Sponsor that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

13.1.2 Data Coding

All subjects who sign a study informed consent will be assigned a unique subject identification number at the time of their Screening visit (after consent). Subjects will be identified by this unique subject identification number for the duration of their participation in the study.

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and subject names to enable records to be found at a later date. Subjects will be assigned identification numbers automatically via the eCRF.

The unique subject identification number consists of a combination of numbers: the first number is the land code, followed by the site number and the patient number. For example: in the Netherlands (land code 1) in the first site (site number 01), the first patient (patient number 001) will have the unique subject identification number 101001.

13.1.3 Data Confidentiality

The Investigator is required to ensure that any documents or data given to the Sponsor or its representatives do not contain information that would affect the anonymity of the subjects. The Investigator will obtain permission for direct access to subject data from the subject as part of the written informed consent procedure. This gives permission to examine, analyse, verify, and reproduce any records and reports that are important to the evaluation of the trial. Any party (e.g., domestic and foreign regulatory authorities, Sponsor personnel or its representatives, and auditors) with direct access must take all reasonable precautions, within the constraints of the applicable regulatory requirement(s), to maintain the confidentiality of the subject's identity and Sponsor's proprietary information.

13.1.4 Data Storage

Each research site will retain copies/originals of the approved trial or study protocol, subjects' participation agreements, relevant source documents and all other supporting documentation related to the trial or study for a period of fifteen (15) years. These documents should be retained for a longer (or shorter) period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will provide each Investigator with information concerning the current status of the investigational drug as this may relate to the above stated obligation for the retention of study records. The Sponsor will inform each study site as to when these documents no longer need to be retained. Study sites should contact the Sponsor prior to disposing of or archiving any such records.

13.2 Monitoring and Quality Assurance

More information about monitoring can be found in chapter 10.5.

13.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the IEC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the IEC and to the competent authority. Non-substantial amendments will not be notified to the accredited IEC and the competent authority, but will be recorded and filed by the sponsor.

13.4 Annual progress report

The sponsor/investigator or CRO representative will submit a summary of the progress of the trial to the accredited IEC 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, SAEs/serious adverse reactions, other problems, and amendments.

13.5 End of study report

The sponsor will notify the accredited IEC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited IEC and the competent authority 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 IEC and the Competent Authority.

13.6 Public disclosure and publication policy

The final report will be written in English in a Word format and its structure will follow a template based upon the ICH E3, guidelines unless otherwise specified by the sponsor during financial agreement.
Suggested inclusions in the report are: study objectives, materials and methods (including any deviations from the study protocol), evaluation of the study results, observations by the investigator as to the value of the study drug per se, and a discussion of all adverse experiences with interpretation by the investigator as to the study drug involvement.
All information concerning the tested drug and the sponsor's operation, such as patent applications, formulae, manufacturing processes, basic scientific data and formulation information supplied by the sponsor and not previously published are considered confidential and shall remain the sole property of the sponsor. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without written consent from the sponsor.
It is understood by the investigator that the information from the clinical study will be used by the sponsor in connection with the development of the tested drug and, therefore, may be disclosed as required to other clinical Investigators or to government agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study.
The trial drug and the information in this document and in any future information supplied contain trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.
In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.
Publication rules will be consistent with local regulation and will be addressed in the study contract and should not be in contradiction with the text in the protocol.
Furthermore, a trial publication policy will be formulated by the GLORIA Study Consortium by the end of 2015.

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15. APPENDICES

Appendix A: Schedule of assessments
Appendix B: Joint counts
Appendix C: Calculation of DAS28 and DAS44; EULAR response; ACR improvement
Appendix D: Sharp/van der Heijde damage score
Appendix E: Patient global assessment and stiffness
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Appendix G: (M)HAQ – (Modified) Health Assessment Questionnaire
Appendix H: RAID – RA Impact of Disease
Appendix I: Cost Questionnaire
Appendix J: EQ-5D – EuroQoL in 5 dimensions
Appendix K: SF36 – Short Form 36-item Health Survey
Appendix L: Patient symptom list
Appendix M: Education level and Baseline prognostic factors

15.1 Appendix A: Schedule of assessments

	Base-line	2 year treatment period								Follow up / taper
Visit No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Month (visit window +/- 2 months)	*0*	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*[LV]	*27*
Location	*clinic*	*clinic*	*clinic*	*remote*	*clinic*	*remote*	*clinic*	*remote*	*clinic*	*clinic*
Written informed consent	X									
In- / exclusion criteria	X									
Demographics, education & medical history	X									
Baseline prognostic factors: adherence, health literacy, arthritis helplessness index	X*									
Randomization	X*									
Physical examination	X									
Height	X								X	
Vital signs / weight	X	X	X		X		X		X	X
AE evaluation (inc. surgery, comorbidity)		X*	X*	X*	X*	X*	X*	X*	X*	X*
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Lab (hematology[1], chemistry[2])	X	X	X		X		X		X	
Lab lipids[3]	X	X			X[3]				X	
Lab CRP, ESR	X	X	X		X		X		X	X
Joint counts (44)	X								X	
Joint counts (28)		X	X		X		X			X
DEXA either with VFA, or without VFA plus X-lat spine (thor, lumb)[4,5]	X								X	
X-rays hand and forefeet[4]	X								X	
Patient global assessment, stiffness duration, stiffness severity	X	X	X	X	X	X	X	X	X	X
Physician global assessment	X	X	X		X		X		X	X
Questionnaires:										
- RAID	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
- full HAQ-DI (24 items)	X*	X*	X*		X*		X*		X*	X*
- MHAQ-DI (10 items)				X		X		X		
- Cost questionnaire	X*	X*	X*		X*		X*		X*	X*
- EQ-5D	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
- SF36	X*								X*	
- Patient symptom list	X*								X*	X*
GC or placebo, dispense adherence	X*	X*	X*	X*	X*	X*	X*	X*	X*	

** procedures not belonging to standard of care*

lv End of study visit. This visit also needs to be completed by subjects who early terminated the trial.

Apart from CRP and ESR, the following standard of care lab tests will be done on peripheral blood samples.

Lab results of CRP and ESR no more than 4 weeks old may be used for the baseline visit.

Results of the below tests [1, 2,3] no more than 2 months old may be used for the baseline visit:

1) Hemoglobin, Mean Cell Volume, White blood cell count, White blood cell differential count, Platelet count.

2) Glucose (non-fasting), Creatinine, Alanine Aminotransferase;

3) Total cholesterol, HDL cholesterol. Optional for month 12.

4) For the baseline visit: DEXA, DEXA VFA and X-ray images with a maximum of 6 months before or until 3 months after the baseline visit may be used.

5) If possible a whole body DEXA may be performed.

15.2 Appendix B: Joint counts

	RIGHT		LEFT	
	Pain 0= not tender 1= tender on palpation 2= tender, patient winces 3= tender, patient winces, tries to withdraw	**Swelling** 0=no 1=yes	**Pain** 0= not tender 1= tender on palpation 2= tender, patient winces 3= tender, patient winces, tries to withdraw	**Swelling** 0=no 1=yes
Cervical spine		---	---	---
Jaw				
Sternoclavicular				
Acromioclavicular				
Shoulder				
Elbow				
Wrist				
MCP I				
MCP II				
MCP III				
MCP IV				
MCP V				
PIP I				
PIP II				
PIP III				
PIP IV				
PIP V				
Hip		---		---
Knee				
Ankle				
Subtalar				
Midtarsal				
MTP I				
MTP II				
MTP III				
MTP IV				
MTP V				

MCP = Metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.
Joints in grey only have to be assessed for the DAS44 joint count.

For tenderness, the examiner will exert pressure on each joint and grade the response as: not tender; tender on palpation; tender and patient winces; tender, patient winces, and patients tries to withdraw by pressure and joint manipulation on physical examination.

For the DAS44, the number of painful joints is calculated with the Ritchie Articular Index (RAI). The RAI is calculated as follows:

- For the jaw, sternoclavicular, and acromioclavicular: only the highest score of the right and left joint is counted
    - E.g. the right jaw is scored 1 and the left jaw is scored 2, then the pain score for the jaws is 2; the right sternoclavicular is scored 3 and the left sternoclavicular is scored 0, then the pain score for the sternoclaviculars is 3
- Complex joints are counted as one: of the MCP, PIP and MTP joints, only the highest score of the right joint and the highest score of left joint is counted
    - E.g. on the right hand the MCPI,II,IV are scored 1 and MCP III,V are scored 2, then the pain score for the MCPs on the right is 2 (pain score for the left hand is calculated separately); on the left foot the MTPI,II are scored 0, MTPIII is scored 3 and MTPIV,V are scored 1, then the pain score for the MTPs on the left is 3 (pain score for the right foot is calculated separately)
- For all other joints, the pain score is as indicated during assessment.

For the DAS28, no grades in tenderness will be used for the calculation of the tender joint count. All joints with a pain score of 1 or higher are counted as 1 painful joint.

Joint prosthesis, arthrodesis, or fused joints will not be taken into consideration for tenderness or swelling.

15.3 Appendix C: Calculation of DAS28 and DAS44; EULAR response; ACR improvement

CALCULATION DAS28

DAS28 is calculated as follows:

DAS28 = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR) + 0.014 * GH.

CALCULATION DAS44

DAS44 is calculated as follows:

DAS44 = 0.54 * sqrt(RAI) + 0.065 * (swollen44) + 0.33 * (ln)ESR + 0.0072 * GH

Note: for both DAS44 and DAS28, the joint factors are adjusted in case of unevaluable joints.

E.g. left knee unevaluable due to knee prosthesis:

DAS28 = (28/27)*0.56 * sqrt (tender27) + (28/27) * 0.28 * sqrt (swollen27) + etc.

EULAR RESPONSE CRITERIA FOR THE DAS28 AND DAS44

Current value of the DAS28	Current value of the DAS44	Improvement in DAS from baseline		
		>1.2	>0.6 - ≤1.2	≤0.6
≤3.2	≤2.4	good	moderate	none
>3.2 and ≤5.1	>2.4 and ≤3.7	moderate	moderate	none
>5.1	>3.7	moderate	none	none

Abbreviations: DAS28 = Disease activity score of 28 joints calculated with erythrocyte sedimentation rate; *DAS44 = Disease activity score of 44 joints.* (Van Gestel 1996; Van Gestel 1999)

ACR RESPONSE CRITERIA

American College of Rheumatology response score
≥20% improvement in tender joint count
≥20% improvement in swollen joint count
≥20% improvement in at least 3 of the following 5 measures: • Patient's global assessment of disease activity • Physician's global assessment of disease activity • Patient's assessment of pain • Disability • Acute-phase reactant

(Felson 1995)

15.4 Appendix D: Sharp/van der Heijde damage score

Hand radiographs are scored according to the method described by Sharp et al (Sharp JT 1985), as modified by Van der Heijde et al (Van der Heijde DM 1989). Foot radiographs are scored according to the method described by Van der Heijde et al (Van der Heijde DM 1989).

On each side of the upper limb (right and left), erosions are counted in the five metacarpophalangeal joints, the four proximal interphalangeal joints, the interphalangeal joints of the thumb, the first metacarpal bone, the radius and ulnar bones, the trapezium and trapezoid (as one unit; multangular), the navicular bone, and the lunate bone. On each side of the lower limb, erosions are counted in the five metatarsophalangeal joints and the hallux proximal interphalangeal joint.

Joint space narrowing is counted on each side of the upper limb, in the five metacarpophalangeal joints, the four proximal interphalangeal joints, the third, fourth, and fifth carpometacarpal joints, the multangulo-navicular joint, the capitato-naviculolunate joint, the radiocarpal joint. Joint space narrowing is counted on each side of the lower limb, in the five metatarsophalangeal joints and the hallux proximal interphalangeal joint.

Erosions are scored as 1 if there is a discrete interruption of the cortical surface; if there is a greater defect a score according to the surface of the joint involved is given (2-5). Consequently, for confluent erosions the score cannot become smaller. In the hands, the maximum score in a joint is 5; in the feet, it is 10.

Five grades of joint space narrowing are recognized: 0 = absent; 1 = doubtful or focal; 2 = general, less than 50% of the original joint space; 3 = general, more than 50% of the original joint space, or subluxation; 4 = ankylosis.

The maximum erosion score is 160 in the hands and 120 in the feet. The maximum joint space score is 120 and 48, respectively. The scores are added for the final radiologic score.

15.5 Appendix E:
Patient global assessment and stiffness

PATIENT GLOBAL ASSESSMENT OF DISEASE ACTIVITY

(Adapted from question 3 of the Routine Assessment of Patient Index Data (RAPID3))

Considering all the ways in which your rheumatoid arthritis has affected you, please indicate below how you have been doing the **last week**.

Very well ❍ Very poorly

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

STIFFNESS

(Question 6 of the Multidimensional Health Assessment Questionnaire (MDHAQ); Pincus T. Bulletin of the NYU Hospital for Joint Diseases. 2007)

When you are awakened in the morning over the **last week**, did you feel stiff?

❑ No ❑ Yes

If yes,
please indicate the number of minutes or hours until you are as limber as you will be for the day.

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
<15m	15m	30m	45m	1 hour	1hour 15m	1hour 30m	1hour 45m	2 hrs	2hrs 15m	2hrs 30m	2hrs 45m	3 hrs	>3hrs

If yes, please indicate how severe your morning stiffness was.

Not severe ❍ Very severe

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

15.6 Appendix F:
Physician global assessment

PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY

(According to ACR/EULAR remission criteria; RA added)

What is your assessment of the patient's current RA disease activity? Please indicate below.

None ❍ Very active

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

15.7 Appendix G:

(M)HAQ – (Modified) Health Assessment Questionnaire

G1. Full HAQ:

Health Assessment Questionnaire

Stanford University School of Medicine · Division of Immunology & Rheumatology

Name_____ Date_____

We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any additional comments on the back of this page.

Please check the response that best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty 0	With SOME difficulty 1	With MUCH difficulty 2	UNABLE to do 3
DRESSING & GROOMING				
Are you able to: – Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
– Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to: – Stand up from a straight chair?	☐	☐	☐	☐
– Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to: – Cut your meat?	☐	☐	☐	☐
– Lift a full cup or glass to your mouth?	☐	☐	☐	☐
– Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to: – Walk outdoors on flat ground?	☐	☐	☐	☐
– Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Cane ☐ Wheelchair ☐ Built-up or special utensils ☐ Other (Specify:)

☐ Walker ☐ Devices used for dressing (button hook, zipper pull, long shoe horn, etc.) ☐ Special or built-up chair _____

☐ Crutches

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Continued on other side

Please check the response that best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty 0	With SOME difficulty 1	With MUCH difficulty 2	UNABLE to do 3
HYGIENE				
Are you able to: – Wash and dry your body?	☐	☐	☐	☐
– Take a tub bath?	☐	☐	☐	☐
– Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to: – Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
– Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to: – Open car doors?	☐	☐	☐	☐
– Open jars which have been previously opened?	☐	☐	☐	☐
– Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to: – Run errands and shop?	☐	☐	☐	☐
– Get in and out of a car?	☐	☐	☐	☐
– Do chores such as vacuuming or yardwork?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Other (Specify):_____

☐ Bathtub seat ☐ Long-handled appliances for reach

☐ Jar opener (for jars previously opened) ☐ Long-handled appliances in bathroom

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

G2. Modified HAQ:

In the modified HAQ, only 8 questions of the full HAQ are asked, and 2 additional questions (with the same response options):

Are you able to:
- Walk two miles or three kilometers, if you wish?
- Participate in recreational activities and sports as you would like, if you wish?

Ability to function in daily life
Please check the response that best describes your usual abilities over the past week.

Are you able to:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
a. Dress yourself, including tying shoelaces and doing buttons?	❑ 0	❑ 1	❑ 2	❑ 3
b. Get in and out of bed?	❑ 0	❑ 1	❑ 2	❑ 3
c. Lift a full cup or glass to your mouth?	❑ 0	❑ 1	❑ 2	❑ 3
d. Walk outdoors on flat ground?	❑ 0	❑ 1	❑ 2	❑ 3
e. Wash and dry your body?	❑ 0	❑ 1	❑ 2	❑ 3
f. Bend down to pick up clothing from the floor?	❑ 0	❑ 1	❑ 2	❑ 3
g. Turn faucets on and off?	❑ 0	❑ 1	❑ 2	❑ 3
h. Get in and out of a car?	❑ 0	❑ 1	❑ 2	❑ 3
i. Walk two miles or three kilometers, if you wish?	❑ 0	❑ 1	❑ 2	❑ 3
j. Participate in recreational activities and sports as you would like, if you wish?	❑ 0	❑ 1	❑ 2	❑ 3

15.8 Appendix H:
RAID – RA Impact of Disease

1. PAIN

Please indicate the number that best describes the pain you felt due to your rheumatoid arthritis during the **last week**:

None ❍ Extreme

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

2. FUNCTIONAL DISABILITY ASSESSMENT

Please indicate the number that best describes the difficulty you had in doing daily physical activities due to your rheumatoid arthritis during the **last week**.

No difficulty ❍ Extreme difficulty

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

3. FATIGUE

Please indicate the number that best describes how much fatigue you felt due to your rheumatoid arthritis during the **last week**.

No fatigue ❍ Totally exhausted

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

4. SLEEP

Please indicate the number that best describes the sleep difficulties (i.e., resting at night) you felt due to your rheumatoid arthritis during the **last week**.

No difficulty ❍ Extreme difficulty

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

5. PHYSICAL WELL-BEING

Considering your arthritis overall, how would you rate your level of physical well-being during the **past week**? Please indicate the number that best describes your level of physical well-being.

Very good ❍ Very bad

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

6. EMOTIONAL WELL-BEING

Considering your arthritis overall, how would you rate your level of emotional well-being during the **past week**? Please indicate the number that best describes your level of emotional well-being.

Very good ❍ Very bad

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

7. COPING

Considering your arthritis overall, how well did you cope (manage, deal, make do) with your disease during the **last week**? Please indicate below.

Very well ❍ Very poorly

0 0,5 1 1,5 2 2,5 3 3,5 4 4,5 5 5,5 6 6,5 7 7,5 8 8,5 9 9,5 10

15.9 Appendix I: Cost Questionnaire

A. Health care

The following questions are about the use of health care. We are interested in the number of times you used health care facilities in the **past 4 weeks**.

	In the past 4 weeks, did you visit a:	**No** (0)	**Yes, how many times?**
A1.	General practitioner	☐	____ times
A2.	Physiotherapist	☐	____ times
A3.	Occupational therapist	☐	____ times
A4.	Dietician	☐	____ times
A5.	Rheumatologist (unrelated to this trial)	☐	____ times
A6.	Medical specialist (other than your rheumatologist)	☐	____ times
A7.	Psychiatrist, psychologist or psychotherapist	☐	____ times
A8.	Another health professional, namely:	☐	____ times

	In the past 4 weeks, have you been admitted to:	**No** (0)	**Yes, how many days?**
A9.	Hospital	☐	____ day(s)
A10.	Nursing home	☐	____ day(s)
A11.	Rehabilitation center	☐	____ day(s)
A12.	Another health facility, namely:	☐	____ day(s)

A13.	In the **past 4 weeks**, have you had help from a nurse for personal care? *If no, please continue with question B1.*		☐ No (0)	☐ Yes (1)
	A13.1.	How many hours have you had help from a nurse in the **past 4 weeks**?	____ hour(s)	
	A13.2.	How many of those hours were paid help?	____ hour(s)	

B. Household

The following questions are about help in housekeeping in the **past 4 weeks**.

B1.	In the **past 4 weeks**, have you had help with housekeeping? *If no, please continue with question C1.*		☐ No (0)	☐ Yes (1)
	B1.1.	How many hours have you had help with housekeeping in the **past 4 weeks**?		____ hour(s)
	B1.2.	How many of those hours were paid help in housekeeping?		____ hour(s)

C. Occupation

The following questions are about a paid job in the **past 4 weeks**.

C1.	Do you have a paid job? *If no, please continue with question D1.*		☐ No (0)	☐ Yes (1)
	C1.1.	How many hours do you work? *Count and sum (add up) the number of hours you performed paid work in the past 4 weeks.*		____ hour(s)
	C1.2.	How many hours were you on sick leave in the **past 4 weeks**? *If you were not on sick leave, please enter '0'.*		____ hour(s)

D. Voluntary work

The following questions are about an unpaid job in the **past 4 weeks**.

D1.	Do you have an unpaid job? *If no, this is the end of the questionnaire for you.*		☐ No (0)	☐ Yes (1)
	D1.1.	How many hours do you work for this unpaid job? *Count and sum (add up) the number of hours you performed unpaid work in the past 4 weeks.*		____ hour(s)
	D1.2.	How many hours were you on sick leave in the **past 4 weeks** for this unpaid job? *If you were not on sick leave, please enter '0'.*		____ hour(s)

15.10 Appendix J: EQ-5D – EuroQoL in 5 dimensions

Under each heading, please indicate the ONE box that best describes your health **today**.

MOBILITY

I have no problems in walking about ❑0
I have slight problems in walking about ❑1
I have moderate problems in walking about ❑2
I have severe problems in walking about ❑3
I am unable to walk about ❑4

SELF-CARE

I have no problems washing or dressing myself ❑0
I have slight problems washing or dressing myself ❑1
I have moderate problems washing or dressing myself ❑2
I have severe problems washing or dressing myself ❑3
I am unable to wash or dress myself ❑4

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑0
I have slight problems doing my usual activities ❑1
I have moderate problems doing my usual activities ❑2
I have severe problems doing my usual activities ❑3
I am unable to do my usual activities ❑4

PAIN / DISCOMFORT

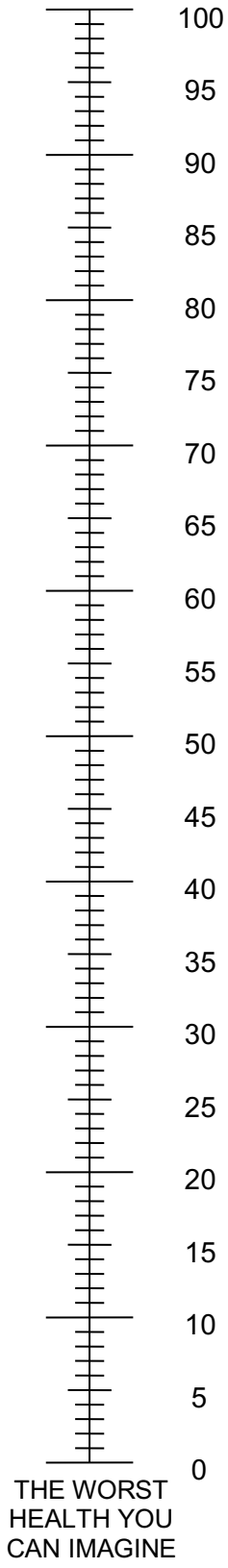
I have no pain or discomfort ❑0
I have slight pain or discomfort ❑1
I have moderate pain or discomfort ❑2
I have severe pain or discomfort ❑3
I have extreme pain or discomfort ❑4

ANXIETY / DEPRESSION

I am not anxious or depressed ❑0
I am slightly anxious or depressed ❑1
I am moderately anxious or depressed ❑2
I am severely anxious or depressed ❑3
I am extremely anxious or depressed ❑4

- We would like to know how good or bad your health is today.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **today**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.11 Appendix K:
SF36 – Short Form 36-item Health Survey

Your Health and Well-Being

HEALTH STATUS SURVEY SF-36

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐	☐	☐	☐	☐ 5
e Did you have a lot of energy?	☐	☐	☐	☐	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐	☐	☐	☐	☐ 5
h Have you been happy?	☐	☐	☐	☐	☐ 5
i Did you feel tired?	☐	☐	☐	☐	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

15.12 Appendix L:
Patient symptom list

Please indicate if you have experienced any of the following over the **last 4 weeks**:

- ❑ Fever
- ❑ Weight gain (>5 kg)
- ❑ Weight loss (> 5 kg)
- ❑ Feeling sickly
- ❑ Headaches
- ❑ Unusual fatigue
- ❑ Swollen glands
- ❑ Loss of appetite
- ❑ Skin rash or hives
- ❑ Unusual bruising or bleeding
- ❑ Other skin problems
- ❑ Loss of hair
- ❑ Dry eyes
- ❑ Other eye problems
- ❑ Problems with hearing
- ❑ Ringing in the ears
- ❑ Stuffy nose
- ❑ Sores in the mouth
- ❑ Dry mouth
- ❑ Problems with smell or taste
- ❑ Lump in your throat
- ❑ Cough
- ❑ Shortness of breath
- ❑ Wheezing
- ❑ Pain in the chest
- ❑ Heart pounding (palpitations)
- ❑ Trouble swallowing
- ❑ Heartburn or stomach gas
- ❑ Stomach pain or cramps
- ❑ Nausea
- ❑ Vomiting
- ❑ Constipation
- ❑ Diarrhoea
- ❑ Dark or bloody stools
- ❑ Problems with urination
- ❑ Gynaecological (female) problems
- ❑ Dizziness
- ❑ Losing your balance
- ❑ Muscle pain, aches, or cramps
- ❑ Muscle weakness
- ❑ Paralysis of arms or legs
- ❑ Numbness or tingling of arms or legs
- ❑ Fainting spells
- ❑ Back pain
- ❑ Neck pain
- ❑ Depression – feeling blue
- ❑ Anxiety – feeling nervous
- ❑ Problems with thinking
- ❑ Problems with memory
- ❑ Problems with sleeping
- ❑ Sexual problems
- ❑ Burning in sex organs
- ❑ Problems with social activities

15.13 Appendix M: Education level and Baseline prognostic factors: risk factors glaucoma, adherence, health literacy, and arthritis helplessness index

Education level:

- How many years did you go to school?
  Please count from the moment you started to learn to read and write, and arithmetic.
- What is the highest level of schooling you completed?
  a. primary school
  b. secondary school
  c. higher education (specify)

Risk factors glaucoma:

- Do you have a history of:
  - Increased eye pressure (glaucoma)?
  - Cataract?
  - Strong myopia (prescription glasses of -6D or more)?
- Do you have blood relatives with any of these conditions?
  If so, which conditions(s)? (specify below)

Morisky Medication Adherence Scale (MMAS-8):

Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24:67–74.

MMAS-8
1) Do you sometimes forget to take your pills?
2) People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?
3) Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?
4) When you travel or leave home, do you sometimes forget to bring along your medicine?
5) Did you take all your medicine yesterday?
6) When you feel like your symptoms are under control, do you sometimes stop taking your medicine?
7) Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?
8) How often do you have difficulty remembering to take all your medicine? ___A. Never/rarely ___B. Once in a while ___C. Sometimes ___D. Usually ___E. All the time

Health literacy index:

1. How often do you have someone help you read hospital materials?
   (for example labels on drugs)
   a. always
   b. often
   c. sometimes
   d. rarely
   e. never

2. How often do you complete medical forms by yourself?
   (for example a health insurance form)
   a. always
   b. often
   c. sometimes
   d. rarely
   e. never

3. How often do you have difficulty reading about your disease because you do not understand the written information (for example in brochures)?
   a. always
   b. often
   c. sometimes
   d. rarely
   e. never

Adapted from : Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. Fam Med 2004; 36:588-94.

RAI/AHI Helplessness subscale:

1. My arthritis is controlling my life.
    a. completely disagree
    b. disagree
    c. neither disagree nor agree
    d. agree
    e. completely agree

2. I would feel helpless if I couldn't rely on other people for help with my arthritis.
    a. completely disagree
    b. disagree
    c. neither disagree nor agree
    d. agree
    e. completely agree

3. No matter what I do, or how hard I try, I just can't seem to get relief from pain.
    a. completely disagree
    b. disagree
    c. neither disagree nor agree
    d. agree
    e. completely agree

4. I am not coping effectively with my arthritis.
    a. completely disagree
    b. disagree
    c. neither disagree nor agree
    d. agree
    e. completely agree

5. It seems as though fate and other factors beyond my control affect my arthritis completely.
    a. completely disagree
    b. disagree
    c. neither disagree nor agree
    d. agree
    e. completely agree

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