CareRA2020: Effectiveness of a combination of Methotrexate and a step down glucocorticoid regimen (COBRA-Slim) for remission induction in patients with early Rheumatoid Arthritis (RA), with or without fast access to 24 weeks of Tumor Necrosis Factor (TNF) blockade in insufficient responders, a randomized, multicenter, pragmatic trial.

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General Information

Title Page

CareRA2020: Effectiveness of a combination of methotrexate and a step down glucocorticoid regimen (COBRA-Slim) for remission induction in patients with early RA, with or without fast access to 24 weeks of TNF blockade in insufficient responders, a randomized, multicenter, pragmatic trial.

COBRA-Slim with or without fast access to TNF blockade for remission induction in early RA

Study phase: IV

EudraCT number: 2017-004054-41

Study n°: CareRA2020, version 4.1, 29/04/2020

KCE number: KCE-16002

Sponsor: This multi-center study is organized by the University Hospitals Leuven together with the investigator team of the Department of Rheumatology, Herestraat 49, 3000 Leuven in close collaboration with other academic and peripheral rheumatology practices.

It will be coordinated by Chief-Investigator:

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Signature page

Signature on behalf of the sponsor/ Chief Investigator (CI)

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the European Union (EU) as provided for in " Directive 2001/20/EC" and any subsequent amendments, Good Clinical Practice (GCP) guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's Standard Operating Procedures (SOP's), and other regulatory requirements as amended.

The undersigned agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

The undersigned also confirm that they will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Chief Investigator:

_____ _____

Signature Date
Prof. Dr. P. Verschueren

Investigator Protocol signature Page

I agree to:

- Implement and conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in " Directive 2001/20/EC" and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOP's, and other regulatory requirements as amended.
- Ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I have read this protocol in its entirety and I agree to all aspects.

_____ _____

Investigator's Signature Date

Key trial contacts

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Funder(s)	Belgian Health Care Knowledge Center (KCE) Administrative Center Botanique, Doorbuilding, Boulevard du Jardin Botanique 55, B-1000 Brussels, Belgium Telephone number: +32 2 287 33 88 E-Mail address: Trials@kce.fgov.be
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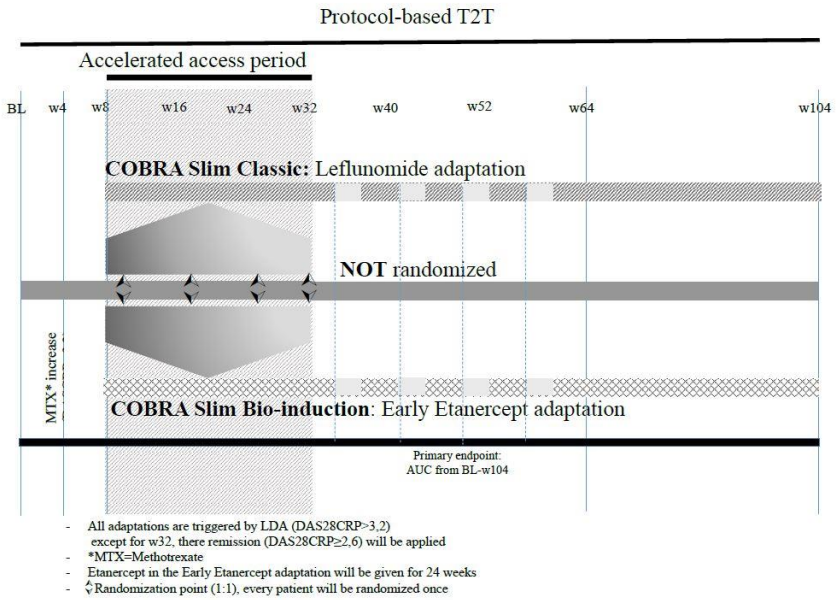
Patient representatives	ReumaNet vzw Patient Expertise Centrum Reuma (PECR) Coordinated by Ilse De Keyser and Michell Silva Imperiastraat 16, B-1930 Zaventem
Committees	**Ethics Committee and Competent Authority** Single opinion of Ethics Committee and Competent Authority (Federal Agency on Medicinal and Health Products FAMPH) will be requested with the centralized procedure (Clinical Trial Regulation (CTR) 536/2014 Pilot). **Study team and management group (STMG)** The STMG is compiled of the CI, the PM, the Clinical Research Assistant(s) (CRA's) and the DM assigned to the protocol. This group will regularly (2 weekly) meet to discuss study progress and practical implications. **Trial Steering Committee (TSC)** The core of the TSC consists of the CI, the PM, the trial statistician and the DM assigned to the protocol. This core could be broadened with a representative of KCE, representatives of the sponsor (CTC), experts, investigators participating in the trial and patient representatives/researchers on request. This committee will meet 3 times a year.

Trial Summary CareRA2020

Title of the protocol	CareRA2020: Effectiveness of a combination of methotrexate and a step down glucocorticoid regimen (COBRA-Slim) for remission induction in patients with early Rheumatoid Arthritis, with or without fast access to 24 weeks of TNF blockade in insufficient responders, a randomized, multicenter, pragmatic trial
Internal Reference	CareRA2020 COBRA-Slim with or without fast access to TNF blockade for remission induction in early RA
Clinical phase	IV
Trial design	Randomized, multicenter, pragmatic trial
Study Population and enrolment period	A total of 442 patients is planned to be included in CareRA2020. The enrolment period is estimated to be open from Q2 2018 – Q2 2020. Patients recently diagnosed with Rheumatoid Arthritis (RA) and naïve to Disease Modifying Anti Rheumatic Drug (DMARD) treatment will receive a remission induction therapy according to the COBRA-Slim regimen. Participants with an insufficient response (DAS28CRP >3.2) even after methotrexate dose optimization will be randomly assigned to 1 of 2 treatment groups (1:1 ratio) during a time window between week (w) 8 and w32, called the accelerated access period. It is expected that about 90 patients will be eligible for randomization. Patients who do not meet the criteria for randomization during the accelerated access period (DAS28CRP ≤ 3.2), will be followed and treated to target as described within the protocol.
Inclusion criteria	- Age ≥ 18 years - Diagnosis of RA as defined by the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) 2010 criteria for early RA - Early RA, defined by a diagnosis of ≤ 1 year - Use of a reliable method of contraception for women of childbearing potential to be evaluated as in daily clinical practice - Able and willing to give written informed consent and participate in the study - Understanding and able to write Dutch or French

Exclusion criteria	- Previous treatment with:
	  o Methotrexate (MTX) or leflunomide
	  o cyclophosphamide, azathioprine or cyclosporine
	  o sulphasalazine (SSZ) for more than 3 weeks
	  o hydroxychloroquine for more than 6 weeks
	  o oral glucocorticoids (GC) for more than 4 weeks within 4 months before screening
	  o oral GC at a daily dosage of more than 10 mg prednisone equivalent within 4 weeks before baseline
	  o oral GC at a daily dosage equal to or less than 10 mg prednisone equivalent within 2 weeks before baseline
	  o intra-articular, intravenous or intramuscular GC within 4 weeks before BL
	  o an investigational drug for the treatment/prevention of RA
	- History of chronic heart failure
	- History of severe infections or chronic infection
	- History of malignant neoplasm within 5 years
	- Contra indications for GC
	- Contra indications for TNF blocking agents
	- Contra indications for MTX or leflunomide
	- Psoriatic Arthritis
	- Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study
	- Pregnancy, breastfeeding or no use of a reliable method of contraception for woman of childbearing potential (as in daily clinical practice).
	- Alcohol or drug abuse
	- Active TB
	- Latent TB unless adequate prophylactic treatment is given according to local guidelines
	- No access to the Belgian Health Insurance system

Study design	**<u>Initial protocol-based treat to target period (BL until w32)</u>** In this pragmatic, prospective, multicenter, randomized, controlled trial of 2-year duration, 442 patients with early RA (≤ 1 year), previously untreated with DMARDs will be included. All participants will receive at baseline (BL) a COBRA-Slim remission induction regimen, consisting of MTX 15 mg Per Os (PO) weekly, with a step-down scheme of GC (30-20-12,5-10-7,5-5 mg prednisone PO daily, each for 7 days except for the lowest dose of 5 mg, which will be maintained until w28 and then tapered to 2.5 mg daily for 2 weeks before stopping completely). In case at any evaluation moment from w4 until w32 (not included) patients do not reach low disease activity (LDA = DAS28CRP≤3.2), the MTX dose will be increased to 20 mg PO weekly. If after this first adaptation patients still not achieve or maintain a sufficient response during the period from week 8 until 32 (the accelerated access period), they will be considered insufficient responders. Insufficient responders are defined as: - Patients not reaching LDA (DAS28CRP≤3.2) after the first adaptation (MTX increase) at any evaluation moment from week 8 until 32 - Patients not reaching remission (DAS28CRP<2.6) at the week 32 evaluation visit <u>irrespective</u> of a previous MTX increase These insufficient responders will be randomly assigned to one of two different treatment strategies: **Group 1: Standard COBRA-Slim Induction:** Addition of leflunomide 10mg PO daily as the next step in the protocol-based CareRA2020 treatment adaptation scheme. **Group 2: COBRA-Slim Bio-induction with accelerated access to anti-TNF (etanercept):** Etanercept is defined as etanercept or its biosimilars marketed and reimbursed in Belgium. Addition of etanercept 50mg Subcutaneous (SC) weekly for a period of 24 weeks in this accelerated access arm as the next treatment adaptation.



Randomization will be balanced according to time-point of randomization, baseline (BL) disease activity and Anti-Citrullinated Protein Antibody (ACPA) and Rheumatoid Factor (RF) status to ensure comparability of the treatment groups with respect to these prognostic variables.

Patients who do not meet the criteria for randomization, during the so-called accelerated access period, will all follow the same Standard COBRA-Slim treatment adaptation scheme, further detailed in the protocol.

Further protocol-based treat to target period (w32 until 104)

After w32, patients will continue on the therapy assigned to their treatment arm. Patients not maintaining or not reaching the target of LDA beyond the accelerated access time window (w8-w32), will go to the next step in the protocol-based adaptation scheme further detailed in the protocol. In accordance with the latest EULAR recommendations patients should be further treated to a target of at least LDA but this can be adapted to remission at the investigators discretion.

After completing this 2-year randomized controlled trial, all patients will be asked to give consent for roll over into a 3-year observational follow-up trial.

Treatment adjustments during study	**Treat to target adaptation steps:** If patients fail to respond (target: DAS28CRP ≤3.2), protocol-based treatment adjustments will be made from 4 weeks of treatment onwards until w104. The consecutive predefined treatment adaptation steps are summarized in Table 1 "CareRA2020 Adaptation Scheme", page 28. In the two following cases the need for treatment adaptation can be based on a different outcome instrument, still aiming for LDA: - If feet are clinically involved: DAS44 score (LDA ≤2.4) - In case of a recent infection: Clinical Disease Activity Index (CDAI) (LDA ≤10.0) No other reasons for treatment adaptations are allowed according to the protocol unless there is toxicity or discomfort due to protocol-based medication intake (detailed in paragraph "Treatment toxicity during study", page 30). **Use of GC during the protocol:** All patients will receive oral GC as part of the prescribed COBRA-Slim strategy. Only the following additional glucocorticoid use is allowed during the study: - An intramuscular depot-corticoid injection on top of the protocol-defined treatment adjustments, but not before w8 and not within 4 weeks preceding a study visit until w104. - Intra-articular GC maximally once every 8 weeks, but not before w8 and not within 4 weeks preceding a study visit until w104. **Non-Steroidal Anti Inflammatory Drug (NSAID) and analgesic use:** NSAIDs and analgesics are allowed at the discretion of the treating physician and according to local guidelines, but not encouraged, during the duration of the trial. The use of this type of medication should be documented in the source documents and e-CRF with a clear indication if it was taken for RA related symptoms or not.
Primary objective	The **primary objective** is to compare in an early RA population with insufficient response (not achieving DAS28CRP≤3.2 within 32 weeks) to COBRA-Slim remission induction, the long term effectiveness of accelerated access to a six-month course of anti-TNF therapy (etanercept) within a time window from w8 up to w32, versus further treatment adaptation according to the standard COBRA-Slim strategy.

Outcome measures	**Primary outcome:** Area under the curve of DAS28CRP over 104 weeks (long term effectiveness) in insufficient responders randomized to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction. **Main secondary outcome**: Proportion of insufficient responders achieving remission (DAS28CRP<2.6) 28 weeks after randomization (short term efficacy) to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction. **Other secondary and exploratory outcome measures:** All other secondary and exploratory outcome measures on clinical efficacy, radiographic progression, side effects, PROs and possible economic analysis are detailed further in the protocol (page 25). They will be assessed both for the insufficient responder population, as for the complete study population.

Funding and support in kind

Financial support

Financial support for this trial is provided by the **BELGIAN HEALTH CARE KNOWLEDGE CENTER**, Administrative Centre Botanique (Door building), Boulevard du Jardin Botanique 55, B-1000 Brussels, Belgium.

Support in kind

The Belgian national institute of healthcare and disability insurance (RIZIV-INAMI) is allowing participating investigators to prescribe etanercept, or its biosimilars marketed and reimbursed in Belgium, and have it reimbursed for the patient outside the current reimbursement rules via the TARDIS system. Only patients randomized in this trial, with their identifier of the trial entered into TARDIS and treated according to this protocol can benefit from this exception.

Role of study sponsor

University Hospitals Leuven, as mentioned in the Key Trial Contacts (page 9), shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. University Hospitals Leuven shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Subjects or the Regulatory Authorities as sponsor of the Study. University Hospitals Leuven acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and University Hospitals Leuven shall make no representations whatsoever in this respect.

Roles and responsibilities of trial management committees/groups & individuals

Study team and management group (STMG):

The STMG is compiled of the CI, the PM, the Clinical Research Assistant(s) (CRA's) and the DM assigned to the protocol. This group will regularly (2 weekly) meet to monitor and discuss daily progress of the trial and will act on identified issues.
All remarks and decisions of the STMG will be documented in a report and stored at the department of Rheumatology, University Hospitals Leuven and will be shared with the sponsor and KCE.

Trial Steering Committee (TSC):

The Trial Steering Committee (TSC) will overview the trial on regular meetings (3 times a year the first year and 2 to 3 times a year thereafter) based on the reports of the STMG. This committee will monitor the course of the trial logistically, but also in terms of safety, and will advise the STMG if required.
The core of the TSC consists of the chief investigator (CI), the project manager (PM), the trial statistician and Data Manager (DM) assigned to the protocol. In addition, a representative of

KCE, representatives of the CTC, experts, investigators participating in the trial and patients' representatives/researchers will be invited to attend.
All remarks and decisions of the STMG will be documented in a report that will be stored at the department of Rheumatology, University Hospitals Leuven and will be shared with the sponsor and KCE. The summary will be shared with the participating investigators.

Chief investigator (CI)

The CI is responsible for designing and implementing the protocol and, supported by the TSC, to follow-up on the conduct of the trial. CI will ensure the trial will be executed in compliance with the approved protocol and applicable regulatory requirements.
The CI has an overall medical responsibility in the trial and will follow up on safety reporting.
The CI is responsible to make the study findings publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given.

Local investigator

The local investigator is responsible to implement and conduct the trial in compliance with the approved protocol and applicable regulatory requirements, the Sponsor's SOPs, and other regulatory requirements as amended.
The local investigator is bound to confidentiality and will ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation.
Except where the investigator's signature is specifically required, it is understood that the term "investigator" as used in this protocol and protocol related documents refers to the investigators and/or appropriate study personnel that the investigators designates to perform a certain duty.
The investigator is ultimately responsible for the conduct of all aspects of the study at the site.
The organizing center, department of Rheumatology of the University Hospitals Leuven, will provide notification to the investigators of protocol and amendment approvals by regulatory authorities, if applicable.

Protocol contributors

This protocol was developed by the Trial Steering Committee (TSC), led by Chief Investigator (CI) Professor Patrick Verschueren, in close collaboration with the CTC of the University Hospital Leuven. Professor Ben Van Calster of the Department of Development and Regeneration KU Leuven acts as Statistician and Professor Steven Simoens of the Department of Clinical Pharmacology and Pharmacotherapy, as Health Economist for this trial. Wherever necessary adaptations were made after consultation of the KCE clinical trials team and in answer to questions and remarks of the KCE Trials Board.
During protocol development, feedback from patient representatives/researchers (ReumaNet vzw) was included.
Furthermore, patient researchers are engaged as scientific collaborators in the TSC, the supervision of the trial, data analyses and preparation of the study report. Patient partners were involved in the development of the informed consent form and all other information leaflets that were developed for this trial. Moreover, the study design and important endpoints of the CareRA2020 trial are inspired by the results of previous research from our research group that was looking into patient priorities concerning the management and treatment outcomes of RA.

Key words

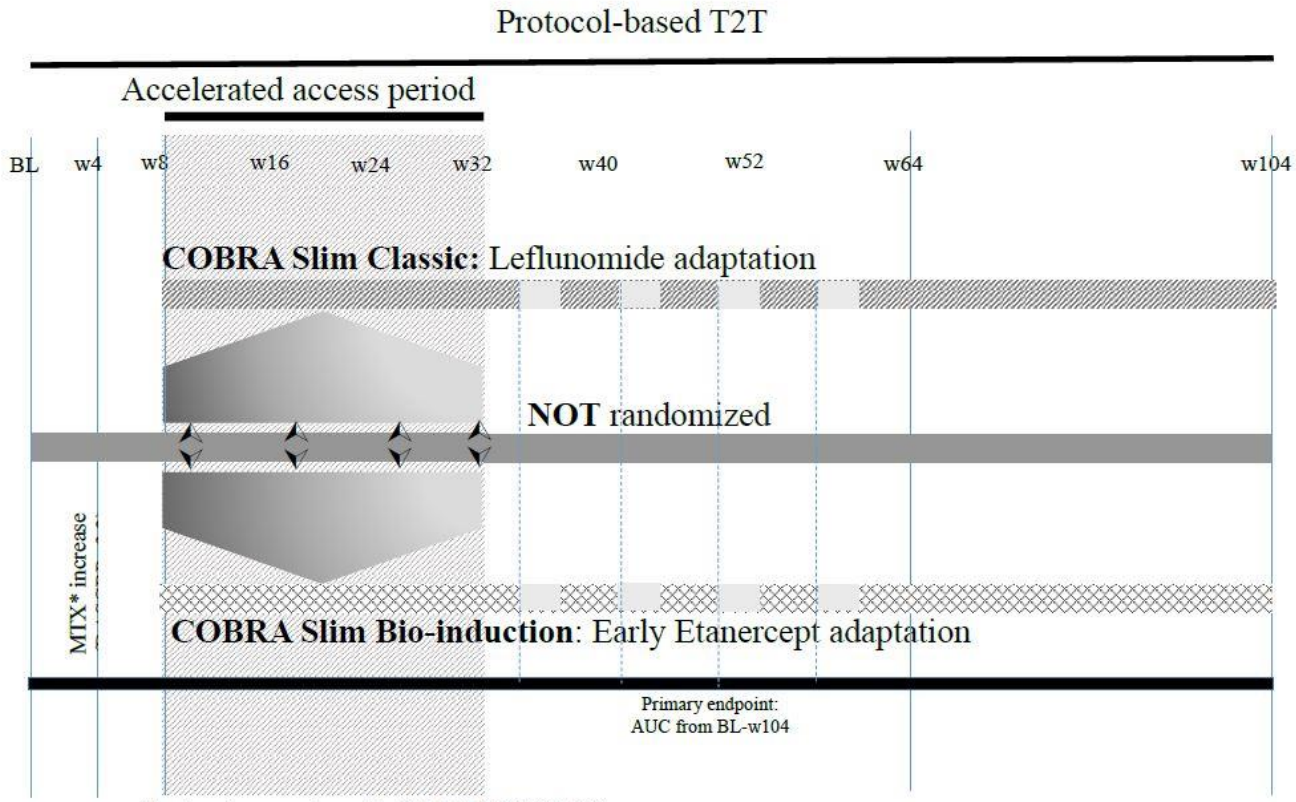
Early Rheumatoid Arthritis; Treatment strategies; Remission induction; Treat to target (T2T); COBRA; csDMARD and glucocorticoids; bDMARD

List of Abbreviations

AE	Adverse Event
ACPA	anti Citrullinated Protein antibody
ACR	American College of Rheumatology
APR	Annual Product Report
AR	Adverse Reaction
AUC	Area under the curve
BMI	Body Mass Index
BL	Baseline
CareRA	Care in early Rheumatoid Arthritis trial
CDAI	Clinical Disease Activity Index
CI	Chief Investigator
COBRA	COmbinatie therapie Bij Reumatoïde Artritis
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CRP	C-Reactive Protein
CTA	Clinical Trial Assistant
cta	Clinical Trial Agreement
CTC	Clinical Trial Center
CTR	Clinical Trial Regulation
CTU	Clinical Trial Unit
DAS28CRP	Disease Activity Score based on 28 joint count and CRP
DAS28ESR	Disease Activity Score based on 28 joint count and ESR
DM	Data Manager
DMARD	Disease Modifying Anti Rheumatic Drug
csDMARD	conventional synthetic DMARD
bDMARD	biological DMARD
DoA	Delegation of Authority
e-CRF	electronic Case Report Form
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EQ5D	EuroQuol-5-Dimensions Questionnaire
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
EULAR	European League against Rheumatism
FAMPH	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
GC	Glucocorticoids
GCP	Good Clinical Practice
GH	General Health
GOT	Glutamate Oxaloacetate Transaminase
GP	General Practitioner
GPT	Glutamate Pyruvate Transaminase
HAQ	Health Assessment Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethical Committee
IM	Intramuscular

IMP	Investigational Medicinal Product
INAMI	Institut national d'assurance maladie-invalidité
ISF	Investigator Site File
ITT	Intention To Treat analysis
IU	International Unit
IV	Intravenous
IWRS	Interactive Web Response system
KCE	Belgian Healthcare Knowledge Center
LDA	Low Disease Activity
MA	Marketing Authorization
MD	Medical Doctor
mg	Milligrams
MTX	Methotrexate
NSAID	Non-Steroidal Anti Inflammatory Drug
NIMP	Non-Investigational Medicinal Product
PASS	Patient Acceptable Symptom State
PhD	Doctor of Philosophy
PhGA	Physician Global Assessment
PI	Principal Investigator
PM	Project Manager
PO	Per Os
PP	Per Protocol analysis
PRO	Patient Reported Outcome questionnaires
Q	Quarter (of a year)
RA	Rheumatoid Arthritis
RAID	Rheumatoid Arthritis Impact of Disease questionnaire
RCT	Randomized Control Trial
RF	Rheumatoid Factor
RIZIV	Belgisch Rijksinstituut voor Ziekte- en Invaliditeitsverzekering
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SoC	Standard of Care
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious AR
SAE	Serious Adverse Event
SC	Sub Cutaneous
SIV	Site Initiation Visit
SJC	Swollen Joint Count
SSZ	Sulfasalazine
STMG	Study Team Management Group
TARDIS	Tool for Administrative Reimbursement Drug Information Sharing
TB	Tuberculosis
T2T	Treat to Target
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
TSC	Trial Steering Committee
VAS	Visual Analog Scale
w	week
WPAI	Work Productivity and Activity Impairment

Trial flow chart



- All adaptations are triggered by LDA (DAS28CRP>3,2) except for w32, there remission (DAS28CRP≥2,6) will be applied
- *MTX=Methotrexate
- Etanercept in the Early Etanercept adaptation will be given for 24 weeks
- ⇳Randomization point (1:1), every patient will be randomized once

	Screen	BL	W4	W8	(w12)	W16	(w20)	w24	(w28)	w32	(w36)	W40	(w44)	(w48)	W52	(w56)	(w60)	w64	(w68)	W78	(w82)	W91	(w95)	W104
Informed consent	X																							
Inclusion/Exclusion criteria	X																							
Demographic data	X																							
Medical history	X																							
Assessment of comorbidities	X									X					X									X
Clinical/rheumatological examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RF and ACPA status	X																							X
ESR/CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB screening*	X																							
X-Ray hands/feet	X							X							X									X
DAS28 CRP/ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO's**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Employment status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization procedure					(X)	(X)	(X)	(X)	(X)	(X)														
Relevant Concommitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
(S)AR's and (S)AE's of interest		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(X) Optional

* According to local guidelines, to be repeated in case of starting bDMARD beyond 6 months after initial testing

** PRO's: HAQ, VAS scales done in routine; RAID, EQ5D, WPAI, PASS added to evaluate disease specific activity, health economics and patient acceptance, total duration of PRO collection about 10 min.

Flowchart	Screen	BL	W4	W8	w12	W16	w20	w24	w28	w32	w36	W40	w44	w48	W52	w56	w60	w64
Randomized at W8	X	X	X	X	X	X		X		X	X	X			X			X
Randomized at W16	X	X	X	X		X	X	X		X		X	X		X			X
Randomized at W24	X	X	X	X		X		X	X	X		X		X				X
Randomized at W32	X	X	X	X		X		X		X	X	X		X		X		X
Not randomized	X	X	X	X		X		X		X		X						X

General mandatory visit
General optional visit

Mandatory visits for randomized patients

R+28w
R+24w
R+16w
R+8w

Study protocol

CareRA2020: Effectiveness of a combination of methotrexate and a step down glucocorticoid regimen (COBRA-Slim) for remission induction in patients with early Rheumatoid Arthritis, with or without accelerated access to 24 weeks of TNF blockade in insufficient responders, a randomized, multicenter, pragmatic trial.

1 Background and Rationale

Treatment for early Rheumatoid Arthritis (RA) has become much more successful over the last two decades, mainly due to the more effective use of conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) and glucocorticoids (GC). Recently, our group demonstrated that so-called “combinatietherapie bij reumatoïde artritis" (COBRA) strategies combining csDMARDs with a step-down bridge GC schedule, starting from moderate or high dosages of prednisone, resulted in remission rates of up to 70%. Moreover, combining methotrexate (MTX) monotherapy with a step down bridge GC therapy, the COBRA-Slim regimen, appeared to be equally effective as combining MTX with another DMARD and GC at higher dosages, but with less side effects. Therefore, COBRA-Slim can be considered a first-choice initial treatment for the large majority of early RA patients. Nevertheless, for about 25 to 30% of patients the desirable treatment target cannot be achieved with this approach and according to the current “treat to target” principle, the medication regimen has to be adapted until it becomes more successful. Often, this results in many months of insufficient disease control and an increased risk of side effects, unfortunately resulting in a reduced quality of life but also having unfavorable long-term consequences in terms of functionality, structural joint integrity, psychosocial wellbeing and employment. This means there is an unmet need for more effective initial treatment strategies targeting the subgroup of insufficient responders to csDMARDs and GC. Given the effectiveness of the new generation of biological (b) DMARDs in refractory RA, a short course of these compounds could prove to be more successful than GC for remission induction. Apart from being efficacious, bDMARDs should of course also prove to be cost-effective in this setting and the conditions for their cost-effectiveness should be explored further, depending on the RA subpopulation targeted.

We propose to investigate if for patients with an insufficient response to a COBRA-Slim regimen, accelerated access to a short course of anti-TNF therapy already early after treatment initiation (from w8 until w32) could improve outcomes compared to a more traditional treat to target sequence. Current practice requires first the evaluation of the effectiveness of adding or switching to another csDMARD after failure of the initial csDMARD, mostly methotrexate, before a biological can be introduced. An important additional research question would be if providing a bDMARD to insufficient responders to the COBRA-Slim remission induction regimen would be cost-effective compared to continuing treatment adaptations according to the standard COBRA-Slim strategy, taking into account direct and indirect costs.

Assessment and management of risk

This trial can be categorized as a low interventional trial according to the definition of the EU regulation n° 536/2014 for the following reasons:

- The medication (etanercept, defined as etanercept and its biosimilars marketed and reimbursed in Belgium) has a Marketing Authorization in Belgium
- According to the protocol the medication is used in accordance with the indication as mentioned in the European Marketing Authorization
- Any additional diagnostic or monitoring procedures do not deviate from routine clinical practice, with the exception of the completion of some questionnaires

2 Objectives and outcome measures/endpoints

Primary objective

To compare in an early RA population with insufficient response (not achieving DAS28CRP≤3.2) to COBRA-Slim remission induction, the long-term effectiveness of accelerated access to a 24 weeks course of anti-TNF therapy (etanercept) within a time window from w8 up to w32, versus further treatment adaptation according to the standard COBRA-Slim strategy.

For this purpose, the area under the DAS28CRP curve from BL until w104 will be assessed. This outcome parameter is considered to be clinically very relevant, since it reflects the overall evolution in disease burden over the first 2 years of treatment, taking into account the speed and stability of the response and the need for consecutive treatment adaptations.

Secondary objectives

Main secondary objective

To investigate in insufficient responders to the COBRA-Slim regimen if accelerated access to a six-month course of anti-TNF therapy (etanercept), is leading to improved remission rates when compared to conventional treatment adaptation according to the COBRA-Slim strategy, 28 weeks after randomization into one of two treatment arms.

Other secondary objectives:

1. To further determine the **clinical efficacy** of accelerated access to etanercept versus the standard COBRA-Slim strategy in terms of remission rates and functionality scales.
2. To compare **radiographic progression** between all treatment schemes.
3. To evaluate the side effects of the given treatments as evaluated according to the regulatory guidelines for marketed products.
4. To evaluate the primary outcome using the DAS28ESR instead of the DAS28CRP.

Other secondary exploratory objectives:

1. To further determine the **clinical effectiveness** of accelerated access to etanercept versus the standard COBRA-Slim strategy.
2. To evaluate treatment response based on a set of **PROs.**
3. Depending on the clinical results of the trial, **a health economic analysis** may be justified. This could be part of a health technology assessment project at KCE. Quality of life data as well as the national number of the participating patients are collected in this trial to facilitate a possible economic analysis.

All secondary and exploratory objectives will be assessed both for the insufficient responder population, as for the complete study population.

Outcome measures/endpoints

Primary outcome measure

Area under the curve of DAS28CRP over 104 weeks (long term effectiveness) in insufficient responders randomized to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction.

Main secondary outcome measure

Proportion of insufficient responders achieving remission (DAS28CRP<2.6) 28 weeks after randomization (short term efficacy) to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction.

Other secondary outcome measures

The following analyses will be performed in the randomized early insufficient responder population (w8-w32) with or without accelerated access to a six-month course of etanercept. The same analyses will also be performed including the randomized groups of insufficient responders, each completed with an early responder control population.

1. Clinical efficacy:
    - Remission (DAS28CRP<2.6) at w104.
    - EULAR response at 28 weeks after randomization and at w104
    - HAQ response at 28 weeks after randomization and at w104
2. Radiographic progression: X-ray evolution at w52 and w104 compared to BL as reviewed and evaluated by the central team.
3. Side effects: (S)ARs from BL until w104
4. To evaluate the primary outcome using the DAS28ESR instead of the DAS28CRP.

Other secondary, exploratory outcome measures:

1. Clinical effectiveness:

A) In the randomized early insufficient responder population (w8-w32) with or without accelerated access to a six-month course of etanercept.

Effectiveness:

- AUC of DAS28CRP/DAS28ESR during 28 weeks after randomization
- Time to first remission during 28 weeks after randomization
- Sustained remission = remission for at least 24 weeks (BL-w104).
- Number of treatment changes, number of patients able to follow the protocol, number of patients using biologicals and/or GC at 28 weeks after randomization and at w104.
- Cumulative doses of GC and analgesic use at 28 weeks after randomization and at w104.

B) In the complete study population, including the randomized groups of insufficient responders, each completed with an early responder control population.

Effectiveness:

- Sustained remission = remission for at least 24 weeks (BL-w64, BL-w104, w64-w104).
- Number of treatment changes, number of patients able to follow the protocol, number of patients using biologicals and/or GC throughout the entire study

- Cumulative doses of GC and analgesic use throughout the entire study

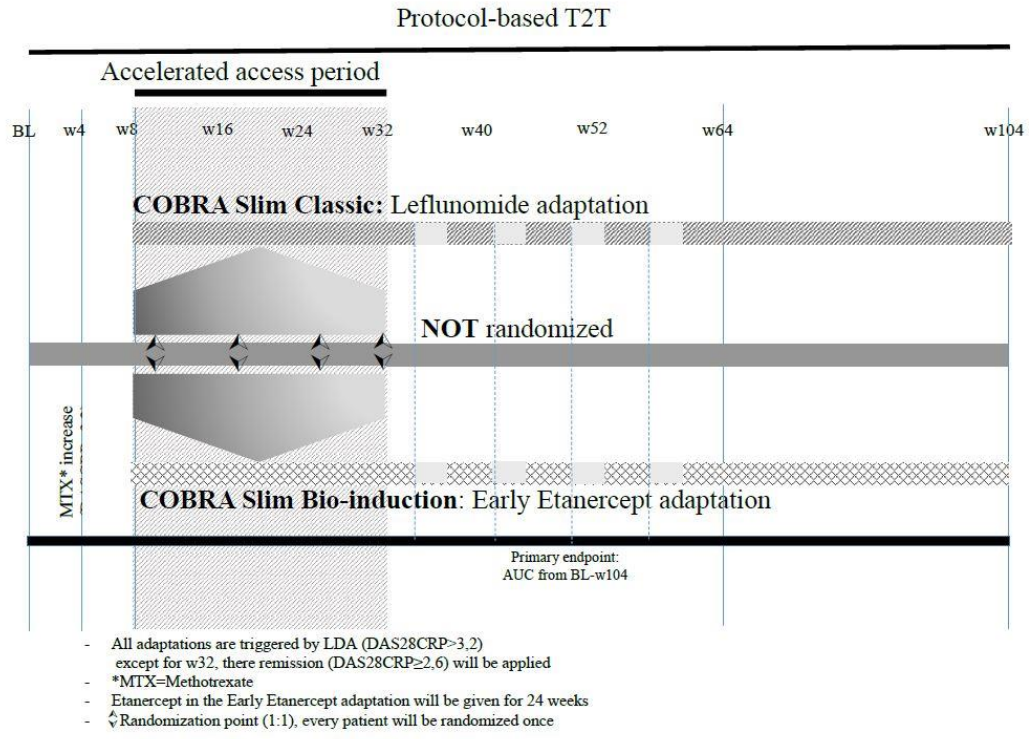
2. Treatment response in terms of PROs:
   - Patient acceptable symptom state (PASS) and RA Impact of Disease (RAID) at 28 weeks after randomization and at w104
   - PASS at w64 and w104.
   - RAID at w 64, 104.
3. Cost-effectiveness:
   - WPAI / EQ5D questionnaire at 28 weeks after randomization and at w104
   - Per-protocol and out-of-protocol medication use as well as the number of outpatient visits and occasional hospitalization

Depending on the clinical results of the trial, a health economic analysis may be justified. This could be part of a health technology assessment project at KCE. Quality of life data as well as the national number of the participating patients are collected in this trial to facilitate a possible economic analysis.

3 Study design

Overall design

In this pragmatic, prospective, multicenter, randomized, controlled trial of 2-year duration, 442 patients with early RA (≤ 1 year), previously untreated with DMARDs (disease modifying anti-rheumatic drugs), will be included. A subgroup of insufficient responders to the initial COBRA-Slim remission induction regimen will be randomly assigned, during a time window between w8 and w32, to 2 different treatment strategies.
Randomization will be balanced according to time-point of randomization, BL disease activity and RF/ACPA status using the minimization technique (see statistical plan). Patients who do not meet the criteria for randomization, during the so-called accelerated access period, will still follow the common adaptation strategy during the remaining part of the study.



Initial protocol-based treat to target period (BL until w32):

All participants will receive at BL a COBRA-Slim remission induction regimen, which includes:

- Methotrexate 15 mg PO weekly (starting from 10 mg weekly for 2 weeks)
- Step down scheme of GC: 30-20-12,5-10-7,5-5 mg prednisone PO daily, each for 7 days except for the lowest dose of 5 mg, this will be maintained until w28 and then tapered to 2.5 mg daily for two weeks before stopping completely.

In case at any evaluation moment from w4 until w32 (not included) patients do not reach low disease activity (LDA = DAS28CRP≤3.2), the MTX dose will be increased to 20 mg PO weekly.

If after this first adaptation patients still not achieve or maintain a sufficient response during the period from week 8 until 32 (the accelerated access period), they will be considered insufficient responders.

Insufficient responders are defined as:
Patients not reaching LDA (DAS28CRP≤3.2) at any evaluation moment from week 8 until 32 after the first adaptation (a previous MTX increase).
Patients not reaching remission (DAS28CRP<2.6) at the week 32 evaluation visit irrespective of a previous MTX increase.

These insufficient responders will be randomly assigned to one of two different treatment strategies:

Group 1: Standard COBRA-Slim Induction:

Addition of leflunomide 10mg PO daily as the next step in the protocol-based CareRA2020 treatment adaptation scheme.
If target of LDA is still not reached or maintained minimally 12 weeks after the initiation of Leflunomide, treatment has to be adapted according to the next step of the adaptation scheme.

Group 2: COBRA-Slim Bio-induction with accelerated access to anti TNF:

Addition of etanercept 50mg Subcutaneous (SC) weekly for a period of 24 weeks in this accelerated access arm as the next treatment adaptation.
If target of LDA is still not reached or maintained minimally 12 weeks after the initiation of etanercept, treatment has to be adapted according to the next step of the CareRA2020 adaptation scheme.

Randomization will be balanced according to time-point of randomization, baseline (BL) disease activity and Anti-Citrullinated Protein Antibody (ACPA) and/or Rheumatoid Factor (RF) status to ensure comparability of the treatment groups with respect to these prognostic variables.

Patients who do not meet the criteria for randomization, during the so-called accelerated access period, will all follow the same CareRA2020 treatment adaptation scheme, further detailed in the protocol.

Further protocol-based treat to target period (w32 until w104):

After w32, patients will continue on the therapy assigned to their treatment. In case LDA is lost or still not reached during this protocol-based treat to target phase, treatment will be adapted

according to CareRA2020 adaptation schedule (table 1 page 28). A next adaptation is only allowed after the previous treatment adaptation has reached its full strength, so minimally after the time period specified for each adaptation step (table 2 page 28).

In accordance with the latest EULAR recommendations patients should be further treated to a target of at least LDA but this can be adapted to remission at the investigators discretion.

The minimal dose of MTX required according to protocol is 15 mg PO per week except in case of documented toxicity, then 7.5 mg PO or parenteral is allowed. In case MTX has to be discontinued, Leflunomide should be given at a dose of 20 mg PO daily or 10 mg PO in case of documented toxicity (see paragraph "Treatment toxicity during study", page 30).

CareRA2020 adaptation schedule

As a first adaptation, from w4 onwards, MTX should be increased to 20mg weekly PO. The next adaptation steps are summarized in table 1.
One exception is the w32 visit, at which a MTX dose increase is not needed, and one should proceed to the second adaptation step.
After w32, adaptation of MTX or leflunomide is at the investigators discretion, but when LDA is not reached one should proceed to the next adaptation step.

Table 1: protocol defined adaptations

Adaptations	Patients randomized to Standard **COBRA-Slim** Induction	Patients randomized to **COBRA-Slim Bio-induction** with accelerated access to Etanercept		Patients **NOT** randomized
2nd	Add leflunomide 10mg/day PO	Add etanercept 50mg/week SC **for 24 weeks***		Add leflunomide 10mg/day PO
3rd	Replace leflunomide by etanercept (50mg/week SC*) (per reimbursement)	Add leflunomide 10mg/day PO and stop etanercept if it has not been already stopped		Replace leflunomide by etanercept (50mg/week SC*) (per reimbursement)
4th	Treatment at the discretion of the rheumatologist	**If previous response** to etanercept**: Replace Leflunomide by etanercept (50mg/week SC) (per reimbursement)	**If NO previous response** to etanercept:** Treatment at the discretion of the rheumatologist	Treatment at the discretion of the rheumatologist
5th	Treatment at the discretion of the rheumatologist	Treatment at the discretion of the rheumatologist	Treatment at the discretion of the rheumatologist	Treatment at the discretion of the rheumatologist

* check for latent TB if not already done within 6 months
** Previous response: If patient completed the 6 months course of etanercept and maintained LDA without toxicities during this period.

Adaptations are only allowed after the current treatment has reached its full strength, so minimally after the time period specified in table 2, or in case of toxicity.

Table 2: protocol defined time to next adaptation:

Medication	**Time to be re-evaluated**
Methotrexate dose increase	At least 4 to 8 weeks
Leflunomide initiation	At least 12 weeks
Etanercept or other bDMARD initiation	

General rules for treatment adaptations during the study from baseline until w104

If patients fail to achieve or maintain low disease activity (DAS28CRP≤3.2), protocol-based treatment adjustments will be made from 4 weeks of treatment onwards until w104.
The only exception to this rule is at w32, the end of the remission induction phase, where treatment response will not be targeted at LDA but at remission (DAS28CRP<2.6). If patients at w32 fail to reach remission, a treatment adaptation is required, unless a previous treatment adaptation has not yet reached its full strength (table 2).
In accordance with the latest EULAR recommendations patients should be further treated to a target of at least LDA but this can be adapted to remission at the investigators discretion after w32.

The need to perform treatment adjustments can only be overruled if disease activity evaluated by DAS28CRP score is not reflecting the real clinical situation according to the rheumatologist. This can only be done in 2 situations:
- In case of isolated involvement of the feet that would lead to an underestimation of disease activity by the DAS28CRP score, the original DAS44 score (LDA = score below or equal to 2.4 and remission = below 1.6) has to be used to include the feet.
- In case a recent infection would lead to an overestimation of disease activity by the DAS28CRP score the CDAI can be used, as this score is independent of elevated CRP (LDA = score below or equal to 10.0 and remission = below or equal to 2.8).
The results of these alternative scoring systems will be automatically displayed in the e-CRF when the investigator indicates this special situation by ticking the specific box.
Treatment adaptations are also allowed in the protocol in case of toxicity or discomfort due to protocol-based medication intake (detailed in paragraph "Treatment toxicity during study", stated below).
No other reasons for treatment adaptations are allowed according to the protocol.

Important points to consider:

- Investigators have to be aware that protocol specified treatment adaptations are only allowed after the current treatment has reached its full strength.
- Treatment adaptations beyond the steps defined in the CareRA2020 adaptation scheme can be made at the discretion of the investigator, according to local regulations and good clinical practice
- In all cases, patients will be followed according to the schedule of events outlined in this protocol.

Use of GC during the protocol:

All patients will receive oral GC as part of the prescribed COBRA-Slim strategy.
During the study, the following additional glucocorticoids use is allowed:
- An intramuscular depot-corticoid injection on top of these treatment adjustments, but not before w8 and not within 4 weeks preceding a study visit until week 104.
- Intra-articular GC are allowed maximally once every 8 weeks but not before week 8, and not within 4 weeks preceding a study visit until week 104.

Guidance on NSAID and analgesic use

NSAIDs and analgesics are allowed at the discretion of the treating physician and according to local guidelines, but not encouraged, during the duration of the trial. When added to the treatment they should be documented in the source documents and e-CRF with a clear indication if they were taken for RA related symptoms or not and with start and end date.

Treatment failure during study

In this trial, all included patients will be followed according to the protocol for the complete study period unless they withdraw consent, are lost to follow up or die.
Protocol violations in relation to the therapeutic strategy will not be considered a reason to interrupt follow up within the CareRA2020 study.
In case the proposed treatment schedule cannot be followed due to serious safety concerns, the patient will be kept in the study follow-up and treated at the discretion of the investigator, taking into account the interest of the patient and the feasibility of the treatment.
These patients will also be asked to roll over into the observational follow-up study.

Treatment toxicity during study

In case of toxicity, actions will be taken according to good clinical practice. Toxicities will be documented and followed up as closely as possible. If feasible and in the patients' best interest, every effort will be made to return patients to their original treatment strategy with a minimal csDMARD intake of 7.5 mg MTX weekly (either PO or parenteral) or 10mg Leflunomide PO daily.
Patients who are not able to return to their original treatment strategy will still be followed within the CareRA2020 study and will be asked to participate to the observational follow-up study.

4 Study setting

The study is a multicenter pragmatic trial sponsored by the University Hospitals Leuven, commissioned by KCE Trials and coordinated by the Chief investigator Prof. Dr. Patrick Verschueren from the department of Rheumatology, University Hospitals Leuven.
A centralized approval procedure for the independent Ethics Committee (IEC) and Competent Authority (FAMPH) will be used to get unique advice for the whole trial.
Prior to enrolment of patients into this study, the final protocol, informed consent form (ICF) and any patient recruitment materials will be submitted to, reviewed and approved by an IEC.
Any necessary amendments to the protocol and/or ICF will be prepared by the Rheumatology Department of the University Hospitals of Leuven and submitted to the IEC and FAMHP.

Four different types of sites are selected:
- University rheumatology centers with local support
- University rheumatology centers without local support
- Non-university rheumatology centers with local support (mostly group practices)
- Non-university rheumatology centers without local support

It is important to include all these types of centers in the trial in view of future generalizability of the study results, as the target population is seen as well in second as in third line centers.
Every effort will be made to ensure maximal recruitment potential in all participating centers by collaboration with their network and referring general practitioners.

Participating Centers

Approximately 20 centers will participate to this trial, consisting of rheumatology departments in a university or non-university setting.

5 Study population

Number of patients and assignment to treatment groups

A total of **442** patients are planned to be included in this study. In case patients do not achieve low disease activity (DAS28CRP ≤3.2) at any evaluation moment from w8 until 32 (not included) despite dose adjustment of MTX, or remission (DAS28CRP<2.6) at w32, they will be considered insufficient responders to COBRA-Slim induction therapy (approximately **90** patients expected) and randomly assigned to one of two treatment groups according to a 1:1 ratio and balanced according to time-point of randomization, disease activity and RF/ACPA status.

Inclusion criteria

Patients enrolled in the study must meet the following inclusion criteria:

- Age 18 years and older
- Diagnosis of RA as defined by the ACR/EULAR2010 criteria for early RA
- Early RA defined by a diagnosis made ≤ 1 year ago.
- Use a reliable method of contraception for women of childbearing potential to be evaluated as in daily clinical practice
- Able and willing to give written informed consent and to participate in the study
- Understanding and able to write Dutch or French

Exclusion criteria

Patients will be excluded from participating in the study if they meet any of the following exclusion criteria:

- Previous treatment with:
  - MTX or leflunomide
  - cyclophosphamide, azathioprine or cyclosporine
  - sulphasalazine (SSZ) for more than 3 weeks
  - hydroxychloroquine for more than 6 weeks
  - oral GC for more than 4 weeks within 4 months before screening
  - oral GC at a daily dosage of more than 10 mg prednisone equivalent within 4 weeks before baseline
  - oral GC at a daily dosage equal to or less than 10 mg prednisone equivalent within 2 weeks before baseline
  - intra-articular, intravenous or intramuscular GC within 4 weeks before BL
  - an investigational drug for the treatment/prevention of RA
- History of chronic heart failure
- History of severe infections or chronic infection
- History of malignant neoplasm within 5 years
- Contra indications for GC
- Contra indications for TNF blocking agents
- Contra indications for MTX or leflunomide
- Psoriatic Arthritis
- Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study

- Pregnancy, breastfeeding or no use of a reliable method of contraception for woman of childbearing potential (as in daily clinical practice)
- Alcohol or drug abuse
- Active TB
- Latent TB unless adequate prophylactic treatment is given according to local guidelines
- No access to the Belgian Health Insurance system

6 Trial Procedures

All procedures required in the protocol are described further; timing can be checked in the attached flow chart (Appendix1). Procedures are organized as either "Standard of Care (SoC)" or "Study Specific".
Some trial procedures can be adapted in case of restrictions in the usual outpatient care organization at the participating rheumatology centers due to governmental or local regulations. A typical example of such adaptations would be that regular outpatient visits would be replaced by telephone consultations. This measure is introduced in the context of the COVID-19 outbreak and will be valid in case of future epidemics/events as well. Details are described further under the visits header.

Recruitment

Every effort will be made to gather a representative sample of patients, reflecting a normal distribution of an early RA population in Belgium.
In order to achieve this, the purpose is to propose all newly or recently diagnosed early RA patients at the participating centers to participate in this trial.
In- and exclusion criteria are not so restrictive towards patient recruitment. This means that all csDMARD naive patients, recently diagnosed with RA, can be included unless there are contra indications to the proposed treatment strategy.
Data from patients who gave consent will be collected, if no consent is given, no data will be collected. Based on data from the CareRA trial, refusal to participate in this type of pragmatic trial is expected in less than 2% of patients.

Screening

A signed informed consent form must be obtained from each patient prior to any study-related procedure being performed. All test results and assessments required to establish eligibility of the patient must be obtained prior to enrolment and prior to dispensation of the medication.

Study specific procedures:

- Informed consent
- Assessment of inclusion/Exclusion criteria

The following information will be captured from routine clinical data (SoC):

- Demographic data (as specified on page 37)
- Relevant Medical history (co-morbidity shortlist)
- Relevant Concomitant medication
- Clinical/Rheumatologic examination
- Joint Count TJC, SJC
- Weight
- Height

- RF and ACPA status
- ESR and CRP
- X-Ray hands/feet (evaluation of erosions y/n and Sharp/van der Heijde Scoring)
- DAS28CRP/DAS28ESR
- VAS PhGA/GH/pain/fatigue
- TB screening (to be repeated in case bDMARD therapy starts beyond 6 months after initial testing).

Consent

The investigator will choose patients in accordance with eligibility criteria. The investigator will not exercise selectivity so that bias is prevented.

Prior to the study, patients will receive a comprehensive explanation of the proposed treatment including the nature and risks of the study, other possible therapies, any known side effects of the medicinal products they will receive, and any other elements that are part of properly obtaining informed consent. Patients will be allowed sufficient time to consider participation in the study and their questions will be answered.

Before entering the study, all patients must sign an informed consent form that complies with the requirements of ICH E6. By signing the informed consent form, the patient agrees to comply with all proposed evaluations required in the study, unless the patient withdraws voluntarily or is terminated from the study for any reason.
The consent will include the registration of the national number and the study code for all participating patients (even if not receiving anti-TNF) in the standard trusted third party register used for anti-TNF RA treatment approval by RIZIV-INAMI (TARDIS), which will allow for a later coupling by the trusted third party of the study data with the billing data (reimbursement).

The randomization scheme

Patients included in the trial and not achieving low disease activity (DAS28CRP≤3.2) between w8 and w32 or remission (DAS28CRP<2.6) at week 32, will be randomly assigned to one of two treatment groups (1:1 allocation):

- Group 1 stepping up to a combination of MTX with leflunomide as described in the standard COBRA-Slim strategy, or
- Group 2 receiving accelerated access to a 6 months course of etanercept (defined as etanercept or its biosimilars as marketed and reimbursed in Belgium) besides continued MTX therapy.

Randomization will be done electronically within the e-CRF whenever a patient is considered an insufficient responder within the time window from w8 until w32 included.
The randomization process will be balanced on the margins (minimization) according to time-point of randomization, BL disease activity and RF/ACPA status.

Patients who are not considered insufficient responders within the accelerated access period will be further followed in the protocol.

Method of implementing the allocation sequence

Each clinical site will be assigned a 3-digit site number, the patient numbers will start with this site number followed by a 3-digit patient number starting with 001.
At site, all study personnel (investigator and/or CTA) will be able to perform the randomization as long as this is clearly identified on the Delegation of Authority (DoA).
A patient identification and randomization list will be kept at site.

Blinding

No blinding is applicable in this trial, investigators and patients will know which medications and doses are taken.

Unblinding

Unblinding is not applicable.

Visits

In this trial two kinds of visits are defined: mandatory and optional.

Mandatory visits have to be performed for all included patients while optional visits are recommended but are not obligatory. These can be performed at the investigators discretion. The aim of these optional visits is to check if treatment adaptations have the required effect and for positive reinforcement in view of compliance.

In case patients are randomized, some optional visits are becoming mandatory (see table below) as will be shown in the patient schedule tab of the e-CRF. These visits are important for calculation of secondary outcomes.

Flowchart	Screen	BL	W4	W8	w12	W16	w20	w24	w28	w32	w36	W40	w44	w48	W52	w56	w60	w64
Randomized at W8	X	X	X	X	X	X		X		X	X	X			X			X
Randomized at W16	X	X	X	X		X	X	X		X		X	X		X			X
Randomized at W24	X	X	X	X		X		X	X	X		X		X	X			X
Randomized at W32	X	X	X	X		X		X		X	X	X		X	X	X	X	X
Not randomized	X	X	X	X		X		X		X		X			X			X

	General mandatory visit
	General optional visit

Mandatory visits for randomized patients		R+28w
		R+24w
		R+16w
		R+8w

In case of restrictions in the usual outpatient care organization at the participating rheumatology centers due to governmental or local regulations (e.g. related to the outbreak of an epidemic), regular outpatient visits can be replaced by a telephone consultation when required to reduce risks for patients and health workers .

During this telephone consultation, one should gather as much clinical data as possible with regards to the visit it is replacing. Patients should also be encouraged to continue completing their PROs. When this is done electronically, patients will be reminded of their questionnaires as usual. In case these PROs are completed on paper, the site should provide patients with a paper version of the PROs and a prepaid envelope to return them to the site.

During a telephone consultation, the rheumatologist cannot score patients' joints. Therefore, it is suggested to provide the patients with a template for self-evaluation of the joints on tenderness and swelling. Literature suggests this could be a reliable alternative. The procedure to distribute this homunculus is the same as described for the PROs: for patients with a known email address by email, for the others by regular mail.

Regular lab testing for CRP, hematology, liver- and kidney function is also a point of attention. During the telephone consultation it should be checked if blood sampling was done recently. If not, the general practitioner can be asked to take a blood sample, depending on the regulations.

If after a telephone consultation, the investigator is convinced that the disease activity is not sufficiently well controlled and there is a need for treatment adaptations, a traditional

consultation at the outpatient clinic might be justifiable. At that time the mandatory visit should be completed and a randomization procedure must be performed if required by the protocol.

In case of an epidemic like the COVID-19 outbreak, the health of patients and coworkers are the first priority. On the other hand, adequate follow-up of patients, with a chronic condition and in need of a chronic treatment, is essential. Interruption of treatment is contraindicated, not for conventional nor for biological or targeted synthetic DMARDs, except in case of active infection or other complications and preferably on the advice of the treating rheumatologist.

Data collected during telephone consultations will be transcribed by the sites at the correct visit page in the e-CRF, marking the box of the telephone visit next to the date field. This way data management can clearly discriminate between data collected by phone and during outpatient consultations.

BL data (w0)

The following information will be captured from routine clinical data (SoC) at Week 0 visit:

- Clinical/Rheumatologic examination
- Joint Count: TJC, SJC
- Weight
- ESR and CRP (in case screening blood samples were taken within 5 days, these values can be used).
- DAS28CRP/DAS28ESR (in case screening blood samples were taken within 5 days, these values can be used)
- VAS PhGA/GH/pain/fatigue
- HAQ
- Relevant concomitant medication
- Relevant side effects
- Changes in employment status

Apart from the above information following PROs will be collected from the patients specifically for the study:

- RAID
- EQ5D/WPAI

Trial assessments

(A schematic overview can be found at page 21)

At week 4, 12, 20, 28, 48, 56, 68, 82, 95 or unscheduled visit following data are captured as part of routine clinical data collection (SoC):

- Clinical/Rheumatologic examination
- Joint Count: TJC, SJC
- Weight
- ESR and CRP
- DAS28CRP/DAS28ESR
- VAS PhGA/GH/pain/fatigue
- Relevant concomitant medication
- Relevant side effects
- Changes in employment status

Randomization procedure is optional and is preferably done at the dedicated visits (w8, 16, 24 or 32). In case randomization is required in between these visits, when LDA is not reached, it is allowed at week 12, 20 and 28.

At week 8, 16, 24, 32, 40, 64, 78 and 91 following data are captured as part of routine clinical data collection (SoC):

- Clinical/Rheumatologic examination
- Changes in co-morbidities assessment (co-morbidity shortlist only at w32)
- Joint Count: TJC, SJC
- ESR and CRP
- DAS28CRP/DAS28ESR
- VAS PhGA/GH/pain/fatigue
- HAQ
- X-ray (Sharp/van der Heijde Score) only for w24 visit
- Relevant concomitant medication
- Relevant side effects
- Changes in employment status

Apart from the above information following PROs and assessments will be collected specifically for the study at these time points:

- RAID
- EQ5D/WPAI
- PASS (only w64)
- Randomization procedure in case LDA is not reached between w8 and w32, and in case remission is not reached at w32. This randomization procedure will be done preferable at the dedicated time points w8, w16, w24 or w32 but when required is also allowed in between these visits. This can be done with an optional procedure at visit w12, 20 or 28.

At yearly and endpoint visits (week 36, 44, 52, 60 and 104) following data are captured as part of routine clinical data collection (SoC):

- Clinical/Rheumatologic examination
- Joint Count TJC, SJC
- Weight
- Changes in co-morbidities assessment (co-morbidity shortlist only at w52 and 104)
- RF and ACPA status only at w104
- ESR and CRP
- X-Ray hands/feet (Sharp/van der Heijde Score) on a yearly basis
- DAS28CRP/DAS28ESR
- VAS PhGA/GH/pain/fatigue
- HAQ
- Relevant concomitant medication
- Relevant side effects
- Changes in employment status

Apart from the above information following PROs and assessments will be collected specifically for the study at these time points:

- RAID
- EQ5D/WPAI
- PASS (only w52 and 104)

Withdrawal of patients

Any patient may withdraw from the study for any reason at any time. The investigator may withdraw any patient from the study if it is not in the patient's best interest to continue.

In this trial, all included patients will be followed according to the protocol for the complete study period unless they withdraw consent, are lost to follow up or die.
Protocol violations in relation to the therapeutic strategy will not be considered a reason to interrupt follow up within the CareRA2020 study.
In case the proposed treatment schedule cannot be followed due to serious safety concerns, the patient will be kept in the study for further follow up and treated at the discretion of the investigator, taking into account the interest of the patient and the feasibility of the treatment.

When a patient withdraws consent, or is withdrawn from the study, regardless of the reason, the date of withdrawal and the reason for termination should be documented on the withdrawal/completion page of the e-CRF. To the extent possible, if follow up is refused by the patient, all evaluations as required for a yearly visit will be recorded: radiological evaluation in case no radiographs are available within the last 3 months preceding withdrawal and evaluation of RF and ACPA positivity only in case not available within the last year.

Every effort should be made to determine the reason why patients fail to return for the necessary visits or withdraw from the study. If patients cannot be reached by phone, a letter should be sent requesting that contact will be made with the investigator to confirm the reason for withdrawal from the study.

All patients followed up for 104 weeks in the CareRA2020 RCT will be asked to participate in the long-term observational follow-up.

7 Study related procedures

Laboratory tests:

A routine blood sample will be performed at each visit (if not available from the GP within 5 days of study visit). The routine laboratory tests minimally required are as follows: ESR, CRP, complete blood count, GOT, GPT and serum creatinine. Only ESR and CRP will be recorded in the e-CRF.
RF and ACPA status will be checked at screening (in case this information is not already available) and at w104.
No samples will be stored for further analysis within this protocol.

Medical history and demographic data

At screening, medical history and demographic data will be collected. This will include date of birth, gender, smoking history (never, past or current) with indication of the number of pack years (1 pack (25 cigarettes) daily for 1 year is 1 pack year), alcohol intake (yes or no) and numbers of units per week, employment status (recorded at screening, date of employment start, changes will be inquired at all other study visits), educational level and co-morbidity listing (check boxes: Cardiovascular, Respiratory, Gastrointestinal, Renal, Neurological, Cancer, Endocrine, Musculoskeletal, Psychiatric disorders, Metabolic disturbances, extra-articular manifestations of RA, other). Rheumatoid Arthritis disease characteristics including date of first symptoms, date of diagnosis, RF and ACPA status, presence of erosions (yes/no according to the rheumatologist) will be registered as well.

Clinical and Rheumatologic examination

At every visit, a routine clinical and Rheumatologic examination will be done. A complete 68/66 joint count will be done at each visit based on a simple present/absent score for pain and swelling. Nocturnal pain (present/not) and morning stiffness will be evaluated (yes/no; with specification, when present: 5, 15, 30, 45, 60, 90 min, 2-3 hours, 3-4 hours, >4 hours).
A VAS global assessment of the disease activity by the physician will be scored (VAS PhGA).

Tuberculosis (TB) screening:

As patients could have accelerated access to bDMARDs, standard TB screening should be performed at screening and the appropriate measures should be taken according to local guidelines. TB screening can be done by standard PPD, or Quantiferon test, combined with a chest X ray. In case of latent TB, patients should start prophylactic Nicotibine treatment for 6 months, at least 4 weeks before introducing the bDMARD. If a bDMARD needs to be started more than 6 months after a screening TB test is performed, TB testing should be repeated.
Active TB is an exclusion criterion.

Patient Reported Outcomes (PROs)

During the trial, Patient Reported Outcomes (PROs) will be gathered by means of self-reported patient questionnaires. Many of these PROs are collected routinely as part of good clinical practice by Belgian rheumatologists (= K55 incentive). Patients will fill-out visual analogue scales for global assessment of the disease, pain and fatigue at every visit. The HAQ will be obtained to measure patients' functional ability, while the RAID and EQ5D will be filled-out to evaluate patients' perceived impact of disease. The WPAI questionnaire will be collected to measure work productivity and activity impairment, also in view of estimating the cost-effectiveness of different treatment strategies. Lastly, Patient acceptable symptom state (PASS) will be assessed.
PROs will be collected via an app on an electronic device or via a web-application on a personal computer to minimize the risk of incompleteness and transcription errors. Therefore the email address of the patients will be recorded in the eCRF. This email will only be accessible for the site staff and stored encrypted so anonymity can be guaranteed. In case patients are not able to work with an electronic device or are not able to connect to the web-application an option will be open to fill out the questionnaires on paper.

End of trial

The maximal duration of this study will be 108 weeks (104 weeks of treatment and a maximal interval of 4 weeks between screening and BL)

The enrolment period will be 2 years estimated to start in Q2 2018, so the closure of the recruitment period is estimated at Q2 2020.

The end of the RCT is estimated at Q2 2022 (LPLV, Last patient last visit).

After completing this 2-year randomized controlled trial, all patients will be asked to give their informed consent to continue with a separate 3-year observational follow-up trial.

In case of restrictions in the usual outpatient care organization at the participating rheumatology centers due to governmental or local regulations (e.g. related to the outbreak of an epidemic), the inclusion in this trial will be temporally suspended and it will resume as soon as it is allowed. This will impact the timelines of this trial and will delay the inclusion and "end of trial" timelines for the duration of the suspension period.

Due to the COVID-19 outbreak the inclusion is suspended from 17/03/2020 until governmental and local regulations allow reopening the inclusion.

Study discontinuation

The sponsor may discontinue the study in case of safety concerns or major logistic problems.

Time schedule

The schedule of procedures is summarized at page 22 and in the appendices (page 67).
A maximum of 4 weeks is allowed between screening and BL visit (w0). In case a BL visit is done within 5 days of screening, data collected at screening and blood results can be re-used if the investigator expects no change.
Every effort will be made to see patients within a time frame of one week before and one week after the target date until week 64. With the exception of week 8, where no time window before the target date is allowed. From w64 until w104 it is aimed to see patients within two weeks of the target date.
At BL (w0), a list with target dates (+/- window) for each follow up visit will be created within the e-CRF.
In case of restrictions in the usual outpatient care organization at the participating rheumatology centers due to governmental or local regulations (e.g. related to the outbreak of an epidemic), it will not be feasible to have all visits performed within the visit window. Every effort should be made to perform mandatory visits (as outpatient visit or telephone visit) as much as possible within the defined windows. However, getting out of window will not be considered a problem.

8 Trial medication

In this trial all patients will receive a combination of MTX and prednisone at baseline (COBRA-Slim). According to the protocol and following the treat to target principle the therapeutic regimen will be adapted by adding, if necessary, another csDMARD (leflunomide) or bDMARD (etanercept first).

All medications used in this protocol have Marketing Authorization (MA) to be used in Rheumatoid Arthritis. As the IMP(s) will be prescribed on-label within this trial, they will be used within the Marketing Authorization (MA).

Etanercept, either the bio-originator etanercept or the bio-similar, is not used in conformity with current Belgian reimbursement criteria during the accelerated access period (w8-w32) and will be started in the early access group after failure of only one csDMARD instead of two.
As RIZIV-INAMI has agreed to have this reimbursed for 24 weeks, the TARDIS system will be used to receive approval for prescription, marking Methotrexate as the first DMARD and COBRA-Slim as the second DMARD.

Medications given during the trial will be prescribed as in normal daily practice and collected at the local pharmacy, including etanercept in the accelerated access phase.

Name and description of investigational medicinal product(s)

Etanercept is the IMP used in this trial, and will be prescribed generically. Etanercept is available as bio-originator (Enbrel). Currently one bio-similar (Benepali) is marketed and reimbursed in Belgium, but more may follow and can be used in this trial as etanercept.

License for the bio-originator (Enbrel) is held by Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK, filed under numbers EU/1/99/126/016, EU/1/99/126/017 and EU/1/99/126/018. First date of MA: February 3th 2000.

License for the bio-similar (Benepali) is held by Samsung UK Limited, 3000 Hillswood Drive, Chertsey, Surrey KT16 0RS, UK, filed under numbers EU/1/15/1074/001-004.

The etanercept dose used in this protocol is 50 mg subcutaneous (SC) weekly.
The bio-originator as well as the bio-similar of etanercept has been proven to be well tolerated and safe at this dose in the treatment of RA.
SmPC for both can be found at http://bijsluiters.fagg-afmps.be/ or www.ema.europa.eu.

Name and description of each Non-Investigational Medicinal Product (NIMP)

Other NIMP's used in this trial are all used within MA.
- MTX, leflunomide, prednisone, other bDMARDs.
- Calcium and vitamin D supplements as well as folic acid.
SmPC for all used NIMPs can be found at http://bijsluiters.fagg-afmps.be/ or www.ema.europa.eu.

Legal status of the drugs

All Medications used in this protocol have MA to be used in Rheumatoid Arthritis.

Summary of Product Characteristics (SmPC)

For all drugs used in the trial, SmPCs can be found at http://bijsluiters.fagg-afmps.be/ or www.ema.europa.eu.

Drug storage and supply

As this is a pragmatic trial, all drugs, IMP and NIMP's, will be prescribed by the investigators as in normal daily practice. Patients will collect prescribed drugs in their local pharmacy. The instructions for storage and use of the medication will follow the routine clinical practice.

Preparation and labelling of Investigational Medicinal Product

All medications used in this trial are ready to use or will be prepared by the patients' local pharmacist. Concerning the subcutaneous administration of etanercept, either the bio-originator or the bio-similar, this can be delivered as prefilled syringes or injection devices (pen), so no preparation is required.

Dosage schedules and modifications

Dosage schedules and modifications according to protocol are described under section "study design" (table 1 page 28).
Dosage adaptations in case of toxicity can be found in the paragraph of "treatment toxicity during study" (page 30).
Patients will be provided with a medication schedule where daily treatment schedule is visualized. This scheme will be provided and discussed on each planned study visit together with the prescriptions for the next period.

Known drug reactions and interaction with other therapies

Can be found in the SmPC's at http://bijsluiters.fagg-afmps.be/ and www.ema.europa.eu .

Relevant medication

Additional glucocorticoids, NSAIDs or analgesics are permitted according to protocol in specific circumstances described under section "Study design" on page 26.

In this trial only relevant medication has to be recorded in the e-CRF. Relevant medication is defined as medication used to treat the RA or to treat adverse reactions. A list of relevant medication such as, but not limited to, glucocorticoids, NSAIDs and analgesics will be recorded at baseline. All changes in relevant medication should be registered in the e-CRF. Also, indications for taking these products and their relation to disease and treatment strategy will be assessed.

In case NSAIDs or analgesics are used, these should be recorded for effectiveness evaluation, especially in relation to RA and RA related pain.

All study patients must receive oral folic acid supplements of minimally 1mg daily (except on day MTX is taken) as well as Calcium and vitamin D (minimal 1000 mg/800IU daily) as prophylactic treatment.

Trial restrictions

In- and exclusion criteria are clearly describing restrictions on inclusion of patients in the trial.

Assessment of compliance

Medications are prescribed according to the label and will be collected by the patients in their local pharmacy.

At each visit, patients will be questioned about medication intake. In this protocol, patients will be provided with a medication schedule/diary to follow.
In case of increased disease activity, patients will be inquired on their medication intake to pick up possible non-compliance.

9 Pharmacovigilance

Definition of an adverse event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product. The occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
The investigator and/or his study team will examine any patient experiencing an AE as soon as possible. The investigator will do whatever is medically necessary for the safety and well-being of the patient.
In this trial no adverse events have to be recorded in the e-CRF unless they are categorized as an adverse reaction, related to RA or RA treatment, or as an adverse event of interest as described further in the protocol.

Definition of an adverse reaction (AR)

All untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.

The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication or to RA qualify as adverse reactions.
This type of events needs to be recorded in the e-CRF.

Adverse event of interest

Adverse events of interest are defined by the protocol as major cardiac and cerebrovascular events, non-traumatic fractures, malignancies, severe infections, a negative outcome of a pregnancy and death.
Severe infection in the context of an epidemic (e.g.. COVID-19 infection) will also be considered an adverse event of interest and should be reported.

Laboratory Abnormalities:

Abnormal laboratory values will be evaluated by the investigator according to normal practice. Any clinically significant abnormalities should be investigated. If the abnormal value represents an adverse reaction, then this should be recorded in the e-CRF. Other abnormal values will not be recorded in the e-CRF unless considered by the investigator as an adverse event of interest.

Definition of a Serious Adverse Event or Serious Adverse Reaction

All Adverse Events or Adverse Reactions that meet one of the following criteria is considered serious:

- Is Fatal, resulting in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

In addition, important medical events that not fulfill above criteria may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.
In this trial no serious adverse events have to be recorded in the e-CRF unless they are categorized as a serious adverse reaction, related to RA or RA treatment, or as a serious adverse event of interest.

Definition of a suspected unexpected serious adverse event (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical trial is concerned, with the applicable product information (in this case the patient leaflet joined to the summary of product characteristics as it concerns the use within the label of an authorized product).
This type of events needs to be recorded in the e-CRF.

Collecting and Reporting of adverse events:

All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and evaluated for causality.

In this trial only ARs and adverse events of interest, as defined above, will be captured in the e-CRF.

Following rules apply for reporting adverse events in the e-CRF:

- **After informed consent** has been obtained **but prior to initiation of study treatment**, only SAE of interest and ARs caused by a protocol-mandated intervention should be reported
- **After initiation of study treatment**, all ARs, serious adverse reaction (SARs), SUSARs and (serious) adverse events of interest will be recorded in the e-CRF up to the patient's final study visit.

In the e-CRF all above mentioned events will be detailed with the following information:

- Full details in medical terms and case description
- Duration of the event
- The action taken regarding the event
- The outcome of the event
- *Seriousness criteria (medical judgement of the treating investigator):*
  Seriousness will be evaluated for each adverse event based on the criteria described in the paragraph on definition of a serious adverse event. In case the seriousness is answered "yes" than the event should be reported within 24h.
- *Severity Grading for Adverse Events (medical judgement of the treating investigator)*:
  Severity should be graded into one of the three classes that describe the clinical severity of the event as it occurred:
  - Mild (does not interfere with daily living)
  - Moderate (somewhat interferes with daily living or medications needed to relieve event)
  - Severe (incapacitating)
- *Causality grading (medical judgement of the treating investigator)*
  Causality should be graded, to determine to what extent the investigator thinks the adverse event is related to the proposed strategy, prescribed drugs or any other protocol-mandated intervention.
- For serious events: whether the event would be considered expected or unexpected according to the Reference Safety Information, which is the current version of the SmPc. *(medical judgement of the treating investigator)*.
- Outcome

Adverse events and reactions should be followed by the investigator until they have returned to normal or stabilized.

All events related to the normal disease course of RA, which are captured within the outcome parameters of the trial, are not considered as adverse events unless these events are considered by the investigator as adverse events of interest.

Reporting of adverse events that meet seriousness criteria:

Only SARs, SAEs of interest and deaths that occur during this study must be reported to the sponsor. No other SAEs will be reported.

After completion of the seriousness criteria in the e-CRF a SAE-form will automatically appear and should be completed by the investigator. This SAE report will then be electronically signed and automatically e-mailed to the Department of Rheumatology of the University Hospitals Leuven. In case the electronic system is unavailable, a paper copy can be used. Once the e-CRF is again available the information should be added as soon as possible.

The investigator or site must complete this form within 24 hours (immediately) after becoming aware of the SAR or SAE of interest. If the investigator is not available at the time of reporting, the report without causality and expectedness will be provided by site staff within the prescribed timeframe and must be followed-up by medical assessment as soon as possible thereafter.

Follow-up information must be submitted promptly within the electronic template available in the e-CRF.
Staff of the coordinating center will be available to provide guidance regarding SAR or SAE of interest reporting.

Contact Information:

Prof. Dr. P. Verschueren or Prof. Dr. R. Westhovens
Department of Rheumatology, University Hospitals Leuven
Herestraat 49, B-3000 Leuven, Belgium
Telephone number: +3216342541
Fax number: +3216342543
Email addresses: patrick.verschueren@uz.kuleuven.ac.be
rene.westhovens@uz.kuleuven.a.be

In case both the CI and Prof Westhovens are not available, the PM can be contacted:

Mr. Johan Joly
Department of Rheumatology, University Hospitals Leuven
Herestraat 49, B-3000 Leuven, Belgium
Telephone number: +32 16 34 02 58
Fax number: +32 16 34 63 46
E-Mail address: johan.joly@uzleuven.be

For this pragmatic strategy trial IMPs are used within the registered label, the chance of encountering a SUSAR is rather low. Nevertheless, in case this would happen, it should be reported within the given timeframe.

The department of Rheumatology of the University hospital Leuven is responsible to report SAEs of interest, SUSARs and deaths to the Competent Authority and Ethical Committees within the defined timelines:

- Immediately in case of death
- 7 days in case of fatal or life threatening SUSAR's
- 15 days in case of all other SUSAR's
- Summary report of all SAR's/SUSAR's annually or final report

Any case of death should also be reported by the investigators to their local Ethical Committee immediately on awareness.

All study-related problems will be discussed with the Trial Steering Committee (TSC), which will take appropriate measures if necessary. Safety information will also be included in trial status reports, which serve as a basis of discussion during meetings. These reports will be made available to investigators participating in the study.

Safety committees

Roles and responsibilities of Trial Steering Committee (TSC) regarding safety are described on page 17.

Pregnancy reporting

In this trial, we exclude patients to participate when pregnant or breastfeeding at screening. As in daily clinical practice the issue of pregnancy in relation to the proposed treatments (SmPC) will be discussed thoroughly and, when required, the investigator will take appropriate measures. If during the course of the trial, a female participant wants to become pregnant, this should be discussed in advance with the PI and if required with the CI so appropriate measures can be taken.
Within the first 104 weeks of the trial, planned pregnancy will however not be encouraged, and will be reported in the e-CRF as treatment adaptations are likely to be implemented. A pregnancy beyond w104 can be planned according to local guidelines.
In case of unplanned pregnancy, the participating female, should notify the investigator immediately, so appropriate advice and decisions can be made.
Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/fetus. If the outcome meets the seriousness criteria, this would be considered a SAE of interest.

Reporting urgent safety measures

If any urgent safety measures are taken, the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the Competent Authority and Ethical Committees of the measures taken and the circumstances giving rise to those measures.

10 Statistics and data analysis

Sample size calculation

Estimation of ratio insufficient responders versus responders w8-w32

To properly estimate the number of patients that will belong to this w8-w32 insufficient responder group (target of LDA: DAS28CRP≤3.2), data from the previous CareRA trial were used, in which 'COBRA-Slim' was compared with other remission induction schemes (Verschueren et al, 2015). In the CareRA trial population around 25% of patients required a second treatment adaptation because they did not reach LDA during the remission induction phase after a first adaptation of MTX dose increase to 20 mg.

Expected difference in effect

The early insufficient responders in the previous CareRA trial had a mean AUC under the DAS28CRP curve of 351.3 (SD 103) after 2 years. We estimate that patients in this insufficient responder group, when given the opportunity to have accelerated access to a short course of etanercept, will have an increase in effect size, reflected by a decrease in AUC at w104 in comparison to the reference arm. We consider a 20% decrease in AUC (from 351 to 281) to be clinically relevant and assume the same standard deviation. A 20% reduction in AUC over the first 104 weeks of treatment would reflect an important decrease of the overall disease burden. Additionally, we believe that this is the minimum effect size to consider an early access to anti-TNF to be cost-effective.

Sample size calculation of insufficient responders

For a superiority design, with a two-sided alpha of 0.05, the null and alternative hypotheses are:

- **Null hypothesis:** In early insufficient responders to COBRA-Slim induction therapy, accelerated access to anti-TNF therapy leads to the same AUC compared to treatment

adaptation according to the standard COBRA-Slim strategy after 104 weeks (there is no difference in AUC in early insufficient responders). $H0: \delta = 0$

- **Alternative hypothesis**: In early insufficient responders to COBRA-Slim induction therapy, accelerated access to anti-TNF therapy can be considered as superior to the standard COBRA-Slim strategy. $H1: \delta \neq 0$

These are the parameters taken into account for the sample size calculation, using PASS 14 software (PASS 14 Power Analysis and Sample Size Software, 2015. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass):

- Calculation of Superiority / Test for Two means (likelihood ratio test).
- Allocation of 1:1
- Power of 0.80
- α was set at 0.05.
- Primary endpoint is AUC after 104 weeks in early insufficient responders, with a mean AUC of 351 (SD 103) after 104 weeks in the reference group following the traditional COBRA-Slim adaptation strategy, as estimated based on data from the CareRA trial.
- Assumed 20% lower mean AUC after 104 weeks (281 (SD 103)) in the arm with accelerated access to etanercept.

To achieve a power of 80%, 70 insufficient responders have to be randomized. Based on the CareRA data we expect a 21% dropout rate up until week 104. Therefore, we aim to randomize 90 insufficient responders. As mentioned above, the insufficient responders are expected to represent 25% of the total population of the trial. After adjusting for the expected 6% screen/randomization failures, we expect that 383 patients have to be screened for the new CareRA2020 trial in order to randomize 90 insufficient responders. The 6% expected screen/randomization failures is based on CareRA data, showing 21 failures out of 400 patients.

Increasing the sample size would help to account for possible influence of missing data on the statistical power to detect the estimated difference in effectiveness of the remission induction schemes (Little et al, 2012) and allow us to perform a statistically more robust exploration of the secondary endpoints. Realistically, a sample size of around 440 patients is feasible in practice (see planned recruitment rate), which would lead to the randomization of 104 patients, of which 82 would not drop out. This would yield 86% power.

Table: Sample size calculation for primary endpoint

N screened	N entered (assuming 6% screening failures)	N insufficient responders (assuming 25%)	N complete insufficient responders (assuming 21% dropout)	Power
383	360	90	70	80%
442	416	104	82	86%

Planned recruitment rate

Every effort will be made to gather a representative sample of patients, reflecting a normal distribution of an early RA population in Belgium. In order to achieve this, it is aimed for to propose all early RA patients who are newly or recently diagnosed at the participating centers, to take part in this trial. In- and exclusion criteria are not too restrictive towards patient recruitment. This means that all csDMARD naive patients, recently diagnosed with RA, can be included unless there are contra indications towards the proposed treatment strategy.

There will be about twenty recruiting centers and the recruitment rate is expected to be around 18 patients per month. To obtain a total sample of 440 patients we expect the needed enrolment period to be 24 months. Therefore, we schedule the enrolment phase to be open from Q2 2018 until Q2 2020. Recruitment rate will be closely monitored and discussed on with sites in case it is lower than expected. If, however, the needed sample size is not yet reached in 24 months, the recruitment period will be extended.

Based on data from previous research, refusal to participate in this type of pragmatic trial is less than 2%. Therefore, we expect consent rate to be 98%. As stated above, screening/randomization failure rate is estimated at 6%, because there were 21 out of 400 patients eventually not randomized in the CareRA trial (2 due to not meeting inclusion/exclusion criteria, 10 due to practical reasons, 7 due to consent withdrawal and 2 due to loss of contact with patient).

Subject populations

For data analysis, we will define the insufficient responder group as 'the efficacy population' to assess efficacy of the 2 different induction schemes in this specific group.

Patients who do not meet the criteria for treatment adaptation within the accelerated access period will be followed up separately. Using the same randomization procedure as for the w8-w32 insufficient responders, at week 32 these patients will be randomized to two subgroups that will be further treated identically but will each act as a complementary responder subpopulation for one of the two insufficient responder subpopulations to reconstruct two artificial global populations, one with accelerated access to etanercept for w8-w32 insufficient responders and one without.
The entire group of patients will be called 'the effectiveness population' to investigate the effectiveness of the different schemes in a general RA population as a whole.

For both populations, an intention to treat, a per-protocol and safety analysis will be performed:

- An **intention to treat analysis** will include all patients randomized into the study. These patients will be analyzed according to the treatment they are randomized to, irrespective of whether they actually received the treatment.
- **Per protocol analysis** will include all patients randomized that did follow the initial allocated treatment scheme and had the required adaptations performed according to protocol.
- **Safety analysis** will include all treated patients, taking into account the treatment that they actually received. Any subject randomized into the study that received at least one dose of study drug will be included for safety analysis.

Statistical analysis plan

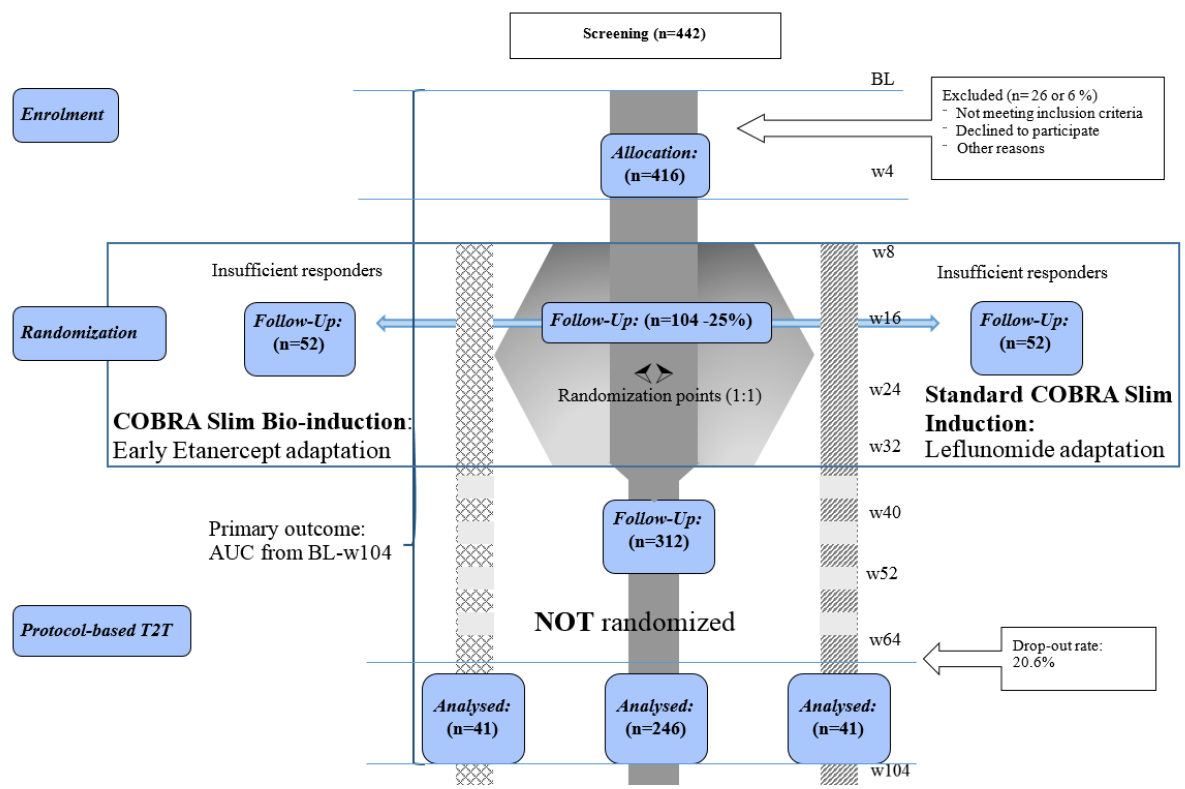
Summary of BL data and flow of patients

These BL variables, gathered at initiation of the COBRA-Slim remission induction regimen, will be used to assess comparability of the population eligible for randomization, and they will be reported as proportions or means with their standard deviations, when appropriate.

Overview of BL measurements.

Variable	**Definition**	**Measurement level**
Age		Continuous
BMI (kg/m2) at BL	body mass index	Continuous
Gender		Dichotomous
Smoking status at BL	Status never-ever-current	Categorical
Alcohol intake at BL	consumption of any form of alcohol, units per week	Ordinal
Symptom duration at BL	time elapsed between onset of symptoms and BL	Continuous
Disease duration at BL	time elapsed between diagnosis of RA and BL	Continuous
Employed before symptom onset		Categorical
Employed at screening		Categorical
Comorbidities at screening		Categorical
RF positivity at BL	rheumatoid factor	Dichotomous
ACPA positivity at BL	Anti-citrullinated protein antibody	Dichotomous
Erosions present at BL		Dichotomous
Total TJC at BL	tender joint count	Continuous
Total SJC at BL	swollen joint count	Continuous
GA (0-100) at BL	Patient global assessment	Continuous
Pain (0-100) at BL	Visual analog scale of pain	Continuous
Fatigue (0-100) at BL	Visual analog scale of fatigue	Continuous
PhGA (0-100) at BL	physician global assessment	Continuous
ESR (mm/h) at BL	erythrocyte sedimentation rate	Continuous
CRP (mg/l) at BL	C-reactive protein	Continuous
DAS28ESR at BL	28 joint disease activity score (ESR)	Continuous
DAS28CRP at BL	28 joint disease activity score (CRP)	Continuous
HAQ score (0-3) at BL	Health Assessment Questionnaire	Continuous
EQ5D at BL	5 dimensions questionnaire for health-related quality of life	Continuous
RAID at BL	RA impact of disease score	Continuous
PASS at BL	Patient Acceptable Symptom State	Dichotomous

Flow Diagram



All values are an estimation taking into account the distribution present in CareRA. There were 21 failures at screening or randomization (6%) and we expect a drop-out rate of 21%.

Primary outcome analysis

Primary endpoint

Area under the curve of DAS28CRP over 104 weeks (long term effectiveness) in insufficient responders (w8-w32) randomized to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction.

Method of analysis

Because missing data are expected, we will use the method from Bell et al to compare AUC between treatment arms based on a mixed model for repeated measures (MMRM) with DAS28CRP as the outcome (Bell et al, 2014). The model will be adjusted for the variables used in the minimization algorithm for treatment assignment (moment of randomization; between w8 and w32 but preferably at the dedicated time points w8, w16, w24, or w32 from baseline), DAS28CRP at baseline, and RF/ACPA status (see table). The effect of treatment arm is corrected for minimization factors to obtain correct P values and confidence intervals and to avoid an unnecessary loss in power (Kahan & Morris, BMJ 2012). The model will include the following mandatory visits: w4, w8, w16, w24, w32, w40, w52, w64, w78, w91, and w104.

Table: Minimization variables.

Variable	Description
Timing of randomization	Randomization is possible between w8 and w32 preferably at the dedicated time points (w8, w16, w24, w32)
Disease activity at baseline	DAS28CRP score categorized as low (≤3.2), moderate (>3.2 to ≤5.1), or high (>5.1).
RF and/or ACPA status	Positive serology of either RF or ACPA versus negative serology for both

We will report the estimated difference in AUC between study arms together with a 95% confidence interval. The confidence interval mainly helps to interpret the uncertainty around the treatment effect, but it can also reveal whether the treatment effect is statistically significant at the 5% level.

Plans for handling multiple comparisons, missing data, non-compliers, spurious data and withdrawals in analysis

Missing values for the primary endpoint may arise because not all measurements to derive the presence of remission are available, or because patients withdraw from the study. We expect around 21% dropouts based on the CareRA trial. Most will be lost to follow-up or due to patient withdrawal; occasionally patients drop out because of death or logistic reasons (Verschueren et al, 2016).

We will compare dropout between arms. More specifically, the amount of dropout, the time point of dropout, and the reason for dropout will be compared (Committee for Medicinal Products for Human Use, 2010). If this is equal, there is less concern about systematic bias (Vickers & Altman, 2013). We will also compare baseline measurements and measurements at the randomization visit between patients who do and do not drop out up until week 104.

The MMRM method assumes that data are 'missing at random' (MAR). This means that missing values are completely random conditional on other observed measurements. We believe that MAR is a plausible assumption. Last observation carried forward, although often used, is an implausible assumption and will not be considered in this trial (Mallinckrodt et al, 2001; Jansen et al, 2006; White et al, 2012; Jiang et al, 2015).

We plan two sensitivity analyses (EMA guideline):

1. An alternative analysis option under the MAR assumption of missing values involves multiple imputation of missing DAS28CRP values. After imputation, the primary endpoint (AUC of DAS28-CRP over 104 weeks) will be analyzed using linear regression. Predictor variables in the model will be treatment arm and the minimization factors, which are the timing of randomization, disease activity at baseline, and RF and/or ACPA status.
   Multiple imputation using fully conditional specification will be used to handle missing data (Sterne et al, 2009; Spratt et al 2010; van Buuren 2015; Lee et al, 2016). The multiple imputation procedure will by default include the variables in the analysis model: DAS28CRP at the timepoints used to calculate the AUC, treatment arm, time of

randomization (w8, w16, w24, or w32), DAS28CRP score at baseline, and RF/ACPA status. In addition, auxiliary variables might be included that are related to missingness of DAS28CRP or to the value of DAS28CRP (Spratt et al, 2010; Lee et al, 2016). This can increase the likelihood of the MAR assumption of missing values. Likely auxiliary variables are gender and age. However, we have to make sure that we do not make the model too large. We focus on direct imputation of DAS28CRP rather than on separate imputation of its four component variables (Lee et al 2016). In cases where maximum three of the component variables are available, we will restrict imputation of DAS28CRP to be eat least the value that is obtained when computing DAS28CRP based on the available components only. We expect DAS28CRP to have a distribution that is close to normality (Matsui et al, 2007; Castrejón et al, 2008). We use multiple imputation to generate 100 completed datasets. After multiple imputation, every completed dataset is analyzed in the same way, and results are combined using Rubin's rules.

2. Although MAR is a reasonable assumption to explain missing data, dropout may still be related to the DAS28CRP value that would have been observed. In this situation, missing values for the DAS28CRP score are said to be missing not at random (MNAR). We assume that MNAR missingness implies that the DAS28CRP score is not observed because it is poor. We plan to investigate the possible influence of MNAR missingness on the results. A simple approach can already be very informative (Rubin, 1987; Little, 2009), where we add a constant d to the imputations from the primary analysis when we assume MNAR. This number d was obtained as follows. First, a random number δ was sampled from a normal distribution with the estimated standard deviation of the distribution of DAS28CRP at 28 weeks after randomization, and standard deviation the square root of this value. Then d=max(δ, 1), such that d is restricted to imply an increase in DAS28CRP score. After the imputations under MNAR are computed, analysis proceeds as usual, using Rubin's rules to combine results. We plan to do this analysis once when assuming that MNAR is present in all dropouts, and once when assuming that MNAR is present in dropouts due to death, patient withdrawal, adverse events, or lack of efficacy. Of course, if dropout rate, timing, and reason are similar for both treatment arms, MNAR is unlikely to affect the results, and we may decide to omit this sensitivity analysis.

Statement regarding use of intention to treat (ITT) analysis

For the primary endpoint analysis, an intention to treat analysis will be performed which will include all patients randomized into the study. Patients will be analyzed according to the treatment they are randomized to, irrespective of whether they actually received the treatment. The use of LOCF or a complete case analysis in the presence of longitudinal data is inconsistent with the ITT principle (White et al, 2012).

Description of any non-statistical methods that might be used (e.g. qualitative methods)

We do not foresee any qualitative methods to be used.

Secondary outcome analysis

Main secondary outcome measure

Proportion of early insufficient responders achieving remission (DAS28CRP<2.6) 28 weeks after randomization (short term efficacy) to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction. Taking into account a screen failure rate of 6% and dropout rate of

11% at that stage in the trial, based on the CareRA data, this main secondary outcome will have sufficient power under the assumption that remission rate is 50% in the standard COBRA-Slim arm vs 80% in the experimental arm (table).

Table: Sample size calculation for main secondary endpoint

N screened	N entered (assuming 6% screening failures)	N insufficient responders (assuming 25%)	N complete insufficient responders (assuming 11% dropout)	Power
383	360	90	80	82%
442	416	104	92	87%

Assuming the MAR assumption of missing values, we plan to analyse the main secondary outcome measure with MMRM that is adapted for binary outcomes (O'Kelly & Ratitch, 2014). The model will be adjusted for the variables used in the minimization algorithm for treatment assignment (moment of randomization; i.e. w8, w16, w24, or w32 from baseline), DAS28CRP at baseline, and RF/ACPA status. For every participant, remission is measured at five visits up to week 28 after randomization: the randomization visit (RV), RV plus 4/8 weeks, RV plus 12/16 weeks, RV plus 20/24 weeks, and RV plus 28 weeks (Table 4).

Table 4.

Randomization visit (RV)	*Weeks since baseline*							
	8	*16*	*W24*	*W32*	*W36*	*W44*	*W52*	*W60*
W8	× *(RV+0w)*	× *(RV+8w)*	× *(RV+16w)*	× *(RV+24w)*	× *(RV+28w)*			
W16		× *(RV+0w)*	× *(RV+8w)*	× *(RV+16w)*	× *(RV+24w)*	× *(RV+28w)*		
W24			× *(RV+0w)*	× *(RV+8w)*	× *(RV+16w)*	× *(RV+24w)*	× *(RV+28w)*	
W32				× *(RV+0w)*	× *(RV+8w)*	× *(RV+16w)*	× *(RV+24w)*	× *(RV+28w)*

All other secondary outcomes are to be considered as explorative. We will therefore report effect sizes with 95% confidence intervals. These confidence intervals will only be used to interpret the uncertainty around the effect size, not to determine statistical significance.

All secondary outcomes measures are clearly described under section 2 objectives and outcome measures/endpoints.

Subgroup analyses

Treatment response heterogeneity could be explored by adding a possible influencing factor and its interaction term with the treatment arm into the same linear regression model made for the first sensitivity analysis of the primary endpoint (Lagakos, 2006; Gabler et al, 2009). This method of analysis could suggest the effect of this factor on the treatment response.

Adjusted analysis

Minimization will be used as allocation method to ensure balance between the insufficient responder arms with respect to predefined factors (Altman & Bland, 2005). Based on a literature search for prognostic variables of the treatment response in early RA (Cook et al 2016; Castrejón et al 2016; Hmamouchi et al 2014) and on data of CareRA, the following minimization factors were defined: timing of randomization within the 8-32 weeks accelerated access period (w8, w16, w24, or w32), disease activity at baseline based on DAS28CRP, RF and/or ACPA status. Primary analysis should be adjusted for balancing factors to obtain correct confidence intervals and to avoid an unnecessary loss in power (Kahan & Morris, 2012).

Therefore, the analysis of the primary endpoint and the main secondary endpoint will be adjusted for these minimization factors.

Interim analysis and criteria for the premature termination of the trial

The Chief Investigator and/or Steering Committee may decide to discontinue this study in case of safety concerns or major logistic problems. This trial uses marketed drugs, therefore we do not expect having to perform any interim analysis for safety or efficacy reasons. Which events are to be reported is described in paragraph "Collecting and reporting of relevant safety events" page 43.
The outcome data, before analyzing the primary endpoint will only be seen by the TSC if needed. More detailed information can be found in the Pharmacovigilance section of the protocol.

Procedure(s) to account for missing or spurious data

Several strategies will be conducted to avoid having missing data as much as possible (Little et al, 2012; White et al, 2011).

Regarding trial planning and conduct:

- Prior to initiating the trial the monitor shall ensure that the investigator understands all requirements of the protocol and his/her regulatory responsibilities as an investigator.
- There will be regular monitoring and support
    - The monitor will visit each clinical study site at appropriate intervals to ensure compliance with the protocol, to verify accuracy, completeness and correctness of data
    - Also centralized electronic monitoring will be performed
- Use of an electronic Case Report Form (CRF) with built in warnings (pop-ups) when data is incomplete or inaccurate (e.g. DAS28CRP or DAS28ESR score should always be filled out before saving, systolic blood pressure should be in a specific range, etc. …)
- Use of an Interactive Web Response System (IWRS) that will be integrated into the CRF: When a randomization procedure becomes mandatory, a pop-up will appear in the CRF and an email will be sent to the investigator of the site and the project manager of the trial. The investigator will be able to randomize the subject in the same web platform via the integrated IWRS. This should help the investigator to efficiently randomize the subject and to avoid errors or forgetfulness.

Follow-up after Treatment Discontinuation:

- When study treatment is discontinued, every effort will be made continue the follow up of the patients with their consent for collection of data on alternative treatments and outcomes. This will preserve the ability to analyze end points for all participants who underwent randomization. It also allows exploration of whether the assigned therapy affected the use and efficacy of subsequent therapies and provides the ability to monitor side effects that might occur or persist after the discontinuation of treatment. (Little et al, 2012).
- When a patient withdraws or is withdrawn from the study, regardless of the reason, the date of withdrawal and the reason for termination will be documented on a withdrawal/trial completion page.
- Every effort should be made to determine the reason why patients fail to return for the necessary visits or withdraw from the study.

Other statistical considerations.

We will focus on effect sizes and confidence intervals in the statistical analysis of this trial. Only for the analysis of the primary endpoint and the main secondary endpoint statistical significance at the 5% alpha level will be determined.

No deviations from the current statistical plan are foreseen and in case this would be needed at a later stage, an amendment to the protocol will be submitted

Economic evaluation

Depending on the clinical results of the trial, a health economic analysis may be justified. This could be part of a health technology assessment project at KCE. Quality of life (EQ5D) data, information on professional and vocational participation (Work Productivity and Activity Impairment (WPAI) questionnaire) as well as the national number of the participating patients are collected in this trial to facilitate a possible economic analysis.

11 Data handling

Data collection tools and source document identification

Source data will be collected and recorded in the study participants' files/medical records. They will be kept on a secured location at all times. The collection and processing of source data (from subjects enrolled in this study) will be limited to those data that are necessary to fulfill the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. Personnel whose responsibilities require access to personal data agree to keep the data confidential.
Documentation of source data is necessary for the evaluation and validation of clinical findings, observations and other activities during a clinical study. Source documentation serves to substantiate the integrity of study data, confirms observations that are recorded and confirms the existence of study participants. Furthermore source documentation will be available for the following to confirm data collected in the e-CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of relevant adverse events and follow-up of adverse events as required by the protocol; intake of medication as prescribed for the study and relevant concomitant medication will be documented in the source data; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. Data collection is the responsibility of the clinical study staff at the site under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. All source documents will be reviewed by the clinical team to ensure that they are accurate and complete.
As defined in section 1.52 of the ICH Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes….)
PROs will be entered electronically by the patients into the e-CRF system.

Case report forms

CRFs are provided for each subject in electronic format. The study data will be transcribed on a regular basis by study personnel from the source documents onto an e-CRF in a pseudo-

anonymized manner, and transmitted in a secure manner to the Chief Investigator within the timeframe agreed upon between Chief Investigator and the sites.
Worksheets may be used for the capture of some data to facilitate completion of the e-CRF. Any such worksheets (including but not limited to copies of the e-CRF) will become part of the study participant's source documentation. All data relating to the study must be recorded in e-CRFs prepared by the investigator. Data must be entered into e-CRFs in English. Designated site personnel must complete the e-CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.
The investigator will ensure that data are recorded on the e-CRFs as specified in the study protocol and in accordance with the instructions provided.
All e-CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. Proper audit trails are available to demonstrate the validity of the trial data. A copy of the completed e-CRFs will be archived at the study site.

Data handling and record keeping

The investigator will maintain a certified copy of e-CRFs and all source documents that support the data collected from each study participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator will take measures to prevent accidental or premature destruction of these documents.
If data need to be transferred, this will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the European Data Protection Act). Receiving party will agree to keep the transferred data confidential at all times. Data will not be transferred outside of the EEA.

12 Study monitoring, audit and inspection

Prior to the initiation of treatment in any patient, a monitoring plan will be written according to the amended ICH-GCP 5.18.7. The monitor/CRA shall ensure that the investigator understands all requirements of the protocol and his/her regulatory responsibilities as an investigator. The monitor will visit each clinical study site as described in the monitoring plan to ensure compliance with the protocol, to verify accuracy, completeness and correctness of data.
The investigator will permit trial-related monitoring, audits, IEC review and regulatory inspection, providing direct access to all related source data / documents.
E-CRF's and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. EMA, FDA). The accuracy of the data will be verified by review of the source documents.

In case of restrictions in the usual outpatient care organization at the participating rheumatology centers due to governmental or local regulations (e.g. related to the outbreak of an epidemic), monitoring at site will be suspended as long as needed. Remote e-CRF checks will be done by the monitor and data management to continuously follow-up on the trial. Findings of this remote check will be communicated with the sites.

13 Archiving of Documentation

The Sponsor is responsible for archiving study specific documentation (such as but not limited to protocol, potential amendments, final report and database) according to ICH-GCP. Source

data and Site-specific study documents (such as, but not limited to, ICF) will be archived locally on site according to local practice and guidelines for at least 20 years. Archived data may be held on electronic record, provided that a backup exists and that hard copies can be obtained, if required. Destruction of essential documents will require authorization from the Sponsor. Archiving at the end of the trial will be organized by the sponsor and done centrally.

14 Confidentiality

The study protocol and other written materials provided by the Department of Rheumatology of the University Hospitals of Leuven and documentation, data and other information generated as part of this study will be held in strict confidence by the investigator and site staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Department of Rheumatology of the University Hospitals of Leuven.

15 Ethical and regulatory considerations

Independent Ethics Committee (IEC) review& reports

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. Before the start of the study, this protocol, the informed consent forms and other related documents e.g. advertisements and GP information letters, will be submitted for review to the IEC and to the Federal Agency for Medicines and Health Products (FAMHP) for Clinical Authorization (the below mentioned obligations shall only apply to the extent applicable). The study shall not commence until such approvals have been obtained.
Any subsequent protocol amendments will be submitted to the IEC and Regulatory Authorities for approval. No substantial amendments that require review by IEC will be implemented until the IEC grants a favorable opinion for the study. The Chief Investigator acknowledges that amendments may also need to be reviewed and accepted by the FAMHP before they can be implemented in practice at sites.
The study can and will be conducted only on the basis of prior informed consent by the study participants, or their legal representatives, to participate in the study. Extensive discussion of risks and possible benefits of participation will be provided to the patients and/or their families. The participating site shall obtain a signed informed consent form (ICF) for all study participants prior to their enrolment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The participating site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.
All correspondence with the IEC/FAMHP shall be retained in the Trial Master File/Investigator Site File.
The Chief Investigator acknowledges that it is his responsibility to produce annual progress reports (APR) and he will do so by submitting to the IEC/FAMHP within 30 days of the anniversary date on which the favorable opinion was given, and annually until the study is declared ended.
The Chief Investigator shall notify the IEC/FAMHP of the end of the Study. Should the study be ended prematurely, the Chief Investigator will notify the IEC/FAMHP and include the reasons for the premature termination. The Chief Investigator will submit a final report with the results, including any publications/abstracts, to the IEC/FAMHP.

Peer review

This study protocol was peer reviewed by independent experts from the KCE Trials Board. Peer review was conducted by expert referees to the professional and scientific standards expected for clinical studies.

Public and Patient Involvement

During protocol development, feedback from patient representatives/researchers (ReumaNet vzw) was included.
Furthermore, we are planning to engage patient researchers as scientific collaborators in the TSC, participating to the further development of the protocol, the supervision of the trial, data analyses and preparation of the study report. Patient partners were involved in the development of the informed consent form and all other information leaflets that were developed for this trial. Moreover, the study design and important endpoints of the CareRA2020 trial are inspired by the results of previous research from our group that was looking into patient priorities concerning the management and treatment outcomes of RA.
Every effort will be made to distribute the results of this trial to the general public.

16 Regulatory Compliance

Before the start of the study, this protocol and other related documents will be submitted for review to the Federal Agency for Medicines and Health Products for Clinical Trial Authorization (FAMHP). The study shall not commence until such approvals have been obtained.

This study protocol and the conduct of the study in general is in compliance with applicable law, including but not limited to the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments.

Protocol compliance

The Chief Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.
It is acknowledged and agreed that prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on clinical studies and must not be used. However, should there be an accidental protocol deviation, such deviation shall be adequately documented on the source documents and on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Protocol deviations that are found to frequently recur will require immediate action. Chief Investigator acknowledges that such recurring protocol breaches could be potentially classified as a serious violation.

Notification of Serious Violation to GCP and/or the protocol

It is understood that “a serious violation” is likely to affect to a significant degree

- the safety or physical or mental integrity of the participants of the study; or
- the scientific value of the study

The Sponsor shall be notified immediately upon becoming aware of a serious violation during the study conduct phase. The Sponsor shall notify the licensing authority in writing of any serious violation of the conditions and principles of GCP in connection with that study; or the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that violation.

Data protection and patient confidentiality

The study will be conducted in compliance with the requirements of the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the European Data Protection Act. Any collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with the aforementioned personal data protection laws.
Any personal data shall be treated as confidential at all times including during collection, handling and use, and that the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with data protection legislation. The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access to or disclosure of or loss or destruction while in its custody.
The personal data of study participants will be encoded, which means that they can only be related to an identifiable person by means of a unique code. The unique code will only be in the possession of the members of the study team who are in direct contact with the study participants. In no event will the coded personal data include personal identifiers, including any Study participant's initials. Such coded personal data can only be traced or linked back by said study team members, and said study team members shall treat these codes as strictly confidential.
Only anonymized personal data will be disclosed to KCE or, where specifically requested by KCE, coded personal data. In no event shall any of the reports, documents, information disclosed to KCE include data that may be linked to the specific identity of a study participant.
The Sponsor shall make sure that the key to personal identities of all persons to whom the data relates is kept in a separate and secure place in compliance with applicable data privacy legislation and shall not be disclosed to KCE or unauthorized persons.
All study related data and documents will be stored for twenty (20) years, in accordance with Belgian legislation.
The collection of the national number and study code of all participating patients in a trusted third party database (TARDIS) under the governance of healthdata.be will allow for a later possible coupling of clinical data collected in the trial with billing data. This coupling could be of use in the context of a later health economic analysis.

Financial and other competing interests for the Chief Investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, honoraria, ownership interest that may be related to products, services or interventions considered for use in the study, or that may be significantly affected by the study, commercial ties with any pharmaceutical, behavior modification, and/or technology company, or any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.
In consideration of participation in the study, the nominated payee will receive the sums set out in the payment schedule attached to the clinical trial agreement.

Indemnity

The Sponsor shall throughout the duration of the study effect and maintain with a reputable insurance company a policy or policies of insurance providing an adequate level of cover in

respect of all risks which may be incurred by the Sponsor arising out of the Sponsor's performance of the study, including the insurance that is required to be taken out as sponsor of the study as set out in the Law of 2004.
The terms or the amount of cover of any insurance shall not relieve the Sponsor of any liabilities under the clinical trial agreement.

Amendments

In accordance with the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor may make a non-substantial amendment at any time during a study. If the Sponsor wishes to make a substantial amendment to the cta or the documents that supported the original application for the cta, the Sponsor must submit a valid notice of amendment to the licensing authority (FAMHP; if applicable) for consideration. If the Sponsor wishes to make a substantial amendment to the IEC application or the supporting documents, the Sponsor must submit a valid notice of amendment to the IEC for consideration. The FAMHP and/or the IEC will provide a response regarding the amendment within 28 days of receipt of the notice. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the FAMHP and/or IEC.

Post-trial care

Not applicable for this trial. From baseline onwards, patients receive optimal treatment, which will be continued at the end of the trial.

Access to the final trial dataset

The party who generates the study results will own them. Sponsor will have access to the study data. At the end of the study, KCE will receive from Sponsor specific study data. This will only be anonymous study data or, where requested by KCE, coded personal data are made available to KCE. The study data shall not be provided to a third party without the prior written approval of KCE, which approval KCE shall not unreasonably withhold or delay and which KCE may subject to specific conditions in order to ensure that the provision of said study data does not have a negative impact on the further performance of the study, the rights granted to KCE under the research agreement and/or the benefit of the Study for the patients and/or the public payers.

17 Dissemination policy

Dissemination policy

The results of the study shall be owned by the party who generates them.

The results of the study owned by Sponsor and/or (where applicable) any collaborator shall be disseminated as soon as possible, by disclosing them to the public by appropriate means, including in scientific publications (in any medium). Sponsor shall inform and discuss its dissemination strategy with KCE in advance.

The final Study report should be made available for review by KCE before the results are disseminated. KCE shall be notified prior to any dissemination (including publication) (whether in oral, written or other form) of the foreground IP or results or study data or of matters arising from the study. The Chief Investigator shall send one draft copy of the proposed dissemination to KCE, at least ten (10) days for an abstract and thirty (30) days for a manuscript, before the date intended for dissemination. For the avoidance of doubt, this obligation continues after the end of the study. KCE may object within thirty (30) days of receiving notification, if, in its reasonable opinion, the dissemination (or the timing thereof) is not in the public interests. In

the event Chief Investigator or (where applicable) any collaborator intends not to protect the results of the study it needs to formally notify KCE thereof before the dissemination takes place, Sponsor shall ensure that any dissemination is scientifically correct, objective and unbiased (taking into consideration the primary endpoint(s)).

In the event of a multicenter study, Sponsor nor its collaborators shall independently publish or otherwise disclose any findings resulting from the study before publication of the main multicenter publication.

Any dissemination shall acknowledge KCE's financial support and carry a disclaimer as KCE may require in accordance with the clinical trial agreement.

Open access will be ensured (free of charge, online access for any user) to all peer-reviewed scientific publications relating to the results of the study owned by it and/or the collaborators. In particular, Sponsor shall: (i) As soon as possible and at the latest on publication, deposit a machine readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications; moreover Sponsor must aim to deposit at the same time the research data needed to validate the results of the study presented in the deposited scientific publications; and; (ii) Ensure open access to the deposited publication, via the repository at the latest on publication (if an electronic version is available for free via the publisher) or, within six (6) months of publication in any other case.

Authorship eligibility guidelines and any intended use of professional writers

The results of the main study will be submitted for publication in a peer reviewed rheumatology journal. All centers will be entitled to one authorship for the publication of the primary outcome data, depending on the requirements and regulations of the journal. Authorships for all other publications will be depending on the contribution of an investigator to the manuscript and to the inclusion of patients. All investigators will be mentioned as members of the CareRA2020 study group. Additional publications concerning study data will have to be approved by the Chief Investigator and the local study team.

18 Reference List

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19 Appendices

Risk

As the IMP(s) used in this trial, are used within the license, this trial can be categorized as a low intervention trial and so no risk/benefit analysis is required

Study management / responsibilities

Patient registration/randomisation procedure

Registration and randomization of the patients will be done within the e-CRF. The study site representatives will do the registration on the day of inclusion. Randomization will be done at the specified time points in the protocol if randomization criteria are met.

Data management

As described above in the protocol a monitoring plan will be developed as well as timelines for CRF entry.
Data management will be done within the Department of Rheumatology of University Hospitals Leuven with support for data monitoring and query management of the CTC University Hospitals Leuven.

Preparation and submission of amendments

Preparation and submission of the protocol and amendments is the responsibility of the CI and PM.

Data protection/confidentiality

As described above all data collected within this protocol will be handled in a confidential manner. Patients will be assigned a unique patient number, which will be used to store the data in the database.
The database will be stored on an approved and secured data server, hosted by the vendor of the e-CRF.
Approval for the set-up of the database will be obtained from the privacy commission.
To obtain etanercept for randomized patients, some data need to be entered in the TARDIS system, which will be used for the reimbursement procedure as in standard of care.
Also, baseline data for all patients will be entered into the TARDIS system, together with their unique study number. The collection of the national number and study code of all participating patients in a trusted third party database (TARDIS) under the governance of healthdata.be will allow for a later possible coupling of clinical data collected in the trial with billing data. This coupling could be of use in the context of a later health economic analysis.
Also in the last case confidentiality of study subjects will be maintained as coupling of data bases will only be done by healthdata.be (TARDIS) as a third trusted party.

Trial documentation and archiving

Trial documentation will be provided electronically except for the site-specific logs (patient log, DoA, signature pages and signed ICF's). Source data are part of the patient medical file. Documentation will be kept for at least 20 years. Archiving at the end of the trial will be organized by the sponsor and done centrally.

Authorisation of participating sites

Centers will be selected and authorized based on a formal feasibility visit performed by the sponsor, CI and a representative of the CRO appointed by KCE (Harmony).

Required documentation

All the local documentation required prior to initiating a participating site should be collected in an Investigator Site File.
The Investigator Site File contains all essential documents held by Investigator(s) conducting a study, which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced.
For a list of all essential documents for the conduct of a clinical study, see ICH-GCP section 8.
In this trial all documentation is kept on the e-platform except for the DoA, the patients identification list and the signed ICF's. These last documents will be kept separate in a binder on site.

Procedure for initiating/opening a new site

Pre-Trial Visit

After IEC approval of a study, before the start of recruitment, monitoring starts with a preliminary meeting with the PI and /or the sub investigator(s). The study team is informed about all aspects related to the organization of the study (Investigator Site File (ISF), CRF, facilities, study medication.) in accordance with GCP. Information on how to organize an ISF as well as template log forms covering items like adverse event reporting, drug accountability, patient screening and identification, etc.…are provided

Site Initiation Visit

During the Site Initiating Visit (SIV), a first detailed review of all available documents in the ISF, essential to conduct a clinical study, will take place and study team is informed about all aspects related to the organization of the study.

Principal Investigator responsibilities

The local investigator is responsible to implement and conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in " Directive 2001/20/EC" and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended.
The local investigator is bound to confidentiality and will ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation.
Except where the investigator's signature is specifically required, it is understood that the term "investigator" as used in this protocol and protocol related documents refers to the investigators and/or appropriate study personnel that the investigators designates to perform a certain duty.
The investigator is ultimately responsible for the conduct of all aspects of the study.
The organizing center, Department of Rheumatology of the University Hospitals Leuven, will provide notification to the investigators of protocol and amendment approvals by regulatory authorities, if applicable.

Schedule of Procedures

	Screen	BL	W4	W8	(w12)	W16	(w20)	w24	(w28)	w32	(w36)	W40	(w44)	(w48)	W52	(w56)	(w60)	w64	(w68)	W78	(w82)	W91	(w95)	W104
Informed consent	x																							
Inclusion/Exclusion criteria	x																							
Demographic data	x																							
Medical history	x																							
Assessment of comorbidities	x									x					x									x
Clinical/rheumatological examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RF and ACPA status	x																							x
ESR/CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TB screening*	x																							
X-Ray hands/feet	x							x			x				x									x
DAS28 CRP/ESR	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO's**	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Employment status	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization procedure				(x)	(x)	(x)	(x)	(x)	(x)	(x)														
Relevant Concommitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
(S)AR's and (S)AE's of interest		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

(X) Optional

* According to local guidelines, to be repeated in case of starting bDMARD beyond 6 months after initial testing

** PRO's: HAQ, VAS scales done in routine; RAID, EQ5D, WPAI, PASS added to evaluate disease specific activity, health economics and patient acceptance, total duration of PRO collection about 10 min.

Flowchart	Screen	BL	W4	W8	w12	W16	w20	w24	w28	w32	w36	W40	w44	w48	W52	w56	w60	w64
Randomized at W8	X	X	X	X	X	X		X		X	X	X			X			X
Randomized at W16	X	X	X	X		X	X	X		X		X	X		X			X
Randomized at W24	X	X	X	X		X		X	X	X		X	X	X	X			X
Randomized at W32	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X
Not randomized	X	X	X	X		X		X		X		X			X			X

General mandatory visit
General optional visit

Mandatory visits for randomized patients

R+28w
R+24w
R+16w
R+8w

Safety Reporting Flow Chart

To be developed based on the final protocol and what is described previously.

Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
0	0.1	17/12/2016	JJ	First draft
0	0.2	02/01/2017	JJ	Second draft with implementation of remarks KCE and CTC
0	0.3	05/01/2017	JJ	Draft after internal discussion RW, JJ and SP
0	0.4	11/01/2017	JJ	Draft after remarks with PV VS SP JJ and AH (CTC)
0	0.5	13/01/2017	JJ	Incorporating remarks PV, VS, PS and JJ
0	0.6	19/01/2017	JJ	update
0	0.7	27/01/2017	JJ	Pre Final draft
0	0.8	31/01/2017	JJ	Final Draft
0	0.9	04/04/2017	JJ	Implementations of remarks KCE, statistical plan included (PV, VS, SP)
0	1.0	05/05/2017	SP, VS, JJ, PV, BVC	Further implementations of remarks KCE, statistical plan included (PV, VS, SP, BVC)
0	1.1	31/07/2017	JJ, SP, VS, KVE, PV	Implementation of remarks KCE
0	1.2	31/07/2017	JJ, SP, VS, KVE, PV	Internal revision Rheumatology
0	1.3	04/09/2017	JJ, PV, KCE	Implementation of remarks KCE
0	1.4	22/09/2017	JJ	Pre-final
0	1.5	30/10/2017	JJ, PV	Revision of the UZ Leuven team
0	1.6	20/11/2017	JJ, PV	Implementation of remarks KCE
0	1.7	14/12/2017	JJ, PV, CTC	Implementation of remarks on Pharmacovigilance (CTC) and economic evaluation
0	1.8	19/12/2017	JJ, PV, CTC	Review
0	1.9	02/01/2018	JJ	
0	2.0	09/01/2018	JJ, PV	Pre final review
0	2.1	11/01/2018	JJ, PV	Final review
0	2.2	25/01/2018	RW, JJ, PV	Final protocol
0	2.3	06/02/2018	JJ	Correction of typo's

0	2.4	26/04/2018	JJ	Information added on request of FAGG/EC
SM001	2.4	26/04/2018	NA	Addition of 5 sites, no adaptations made to the protocol.
SM002	2.4	26/04/2018	NA	Addition of 5 sites, no adaptations made to the protocol.
SM003	2.4	26/04/2018	NA	Addition of 1 site, no adaptation made to the protocol.
Non-SM1	3.0	16/07/2019	DB, JJ, PV	Non substantial amendment: Clarifications on the protocol and correction of typo's
SM004	4.0	18/03/2020	JJ, DB, PV, CL	Addition of procedures to be used in case of restrictions of regular outpatient visits due to governmental/local regulations (e.g. COVID-19 pandemic)
Non-SM2	4.1	29/04/2020	JJ	Clarifications on the protocol and correction of typo's

Reason for non-substantial amendment 1 (non-SM1) protocol version 3.0 16/07/2019.

The amendment is used to correct some typo's and for implementing clarifications on:

- The use of non-oral GC's before baseline: besides IA corticosteroids also IM and IV corticosteroids are not allowed within 4 weeks prior to baseline.
- The interpretation of the treat to target principle after w32
- The start-up schedule of Methotrexate
- Mandatory and optional visits
- Relevant medication
- Reportable (S)AE's

This protocol amendment does not change any procedure nor raise any possible new safety issues to patients and so only consists of clarifications to the protocol.
After discussion with our TSMC, this protocol amendment is considered as non-substantial.

Reason for substantial amendment 4 (SM004) protocol version 4.0 18/03/2020.

The amendment is used to add procedures to be used during the course of the COVID-19 outbreak, as government and hospital guidelines are limiting patient contacts when not assessed as essential.

This protocol amendment does meet the criteria to be substantial.

Reason for non-substantial amendment 2 (non-SM2) protocol version 4.1 dd 29/04/2020.

The amendment is used to correct some typo's and to add the restart of the screening of which a notification is sent to the FAGG/EC.

This protocol amendment is considered as non-substantial.