CareRA2020 LTE: a 3 year longitudinal observational, multicenter, follow-up of early RA patients after participation in the CareRA2020 RCT.

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General Information

Title Page

CareRA2020 LTE: a 3 year longitudinal observational, multicenter, follow-up of early RA patients after participation in the CareRA2020 RCT.

Long Term observational follow-up on patients started in CareRA2020 RCT (COBRA Slim with or without fast access to TNF blockade for remission induction in RA).

Study phase: IV

EudraCT number: NA

Study n°: CareRA2020 LTE, version 1.0, 25/05/2020

KCE number: CB-16002 LTE

Sponsor: This multi-centre long term observational follow up 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:

Prof. Dr. Patrick Verschueren.
Department of Rheumatology,
University Hospitals Leuven
Herestraat 49, B-3000 Leuven, Belgium
Telephone number: +32 16 34 25 41
Fax number: +32 16 34 63 46
E-Mail address: patrick.verschueren@uzleuven.be

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

Chief Investigator (CI)	Prof. Dr. Patrick Verschueren Department of Rheumatology University Hospitals Leuven Herestraat 49, B-3000 Leuven, Belgium Telephone number: +32 16 34 25 41 Fax number: +32 16 34 25 43 E-Mail address: patrick.verschueren@uzleuven.be
Project Manager (PM)	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
Sponsor	UZ Leuven University Hospitals Leuven Herestraat 49, B-3000 Leuven, Belgium
Funder(s)	Belgian Health Care Knowledge Centre (KCE) Administrative Centre 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
Clinical Trials Unit (CTU)	Clinical Trial Centre (CTC) University Hospitals Leuven Herestraat 49, B-3000 Leuven, Belgium Telephone number +32 16 34 19 98 ctc@uzleuven.be
Key Protocol Contributors	Prof. Dr. Patrick Verschueren Prof. Dr. René Westhovens Mr. Johan Joly Dr. Sofia Pazmino Mrs. Veerle Stouten Mrs. Kristien Van der Elst Mrs. Delphine Bertrand Department of Rheumatology University Hospitals Leuven Herestraat 49, B-3000 Leuven, Belgium Telephone number: +32 16 34 25 41 Fax number: +32 16 34 25 43 E-Mail address: patrick.verschueren@uzleuven.be rene.westhovens@uzleuven.be johan.joly@uzleuven.be sofia.pazmino@kuleuven.be veerle.stouten@kuleuven.be kristien.vanderelst@uzleuven.be delphine.bertrand@kuleuven.be

Statistician	Prof. Ben Van Calster Department of Development and Regeneration Herestraat 49, B-3000 Leuven E-mail address: ben.vancalster@kuleuven.be
Health Economics	Prof. Steven Simoens Department of Clinical Pharmacology and Pharmacotherapy Herestraat 49, B-3000 Leuven E-Mail address: steven.simoens@kuleuven.be
Data Manager	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
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 LTE

Title of the protocol	CareRA2020 LTE: a 3 year longitudinal observational, multicenter, follow-up of early RA patients after participation in the original CareRA2020 trial.
Internal Reference	CareRA2020 LTE Long Term observational follow-up on patients started in CareRA2020 (COBRA Slim with or without fast access to TNF blockade for remission induction in RA).
Clinical phase	IV
Trial design	Longitudinal observational follow up.
Study Population and enrolment period	368 patients are estimated to be included in this observational follow-up: CareRA2020 LTE. The enrolment period is estimated to be open from Q2 2020 – Q2 2022.
Inclusion criteria	Patients participated in the CareRA2020 RCT, who completed w104 of the RCT and are able and willing to give written informed consent, can participate in this long term observational follow up.
Study design	In this observational longitudinal trial, patients will be followed every 6 months according to the treat to target principle. Disease activity score (DAS28 CRP), need for treatment adjustment and a safety checklist will be collected. PRO's will be collected every 3 months.
Primary and main secondary objective	To evaluate the clinical disease course and safety for three years following participation of RA patients in the CareRA2020 RCT depending on the original treatment allocation.
Outcome measures	**Primary outcome:** Area under the curve of DAS28-CRP over 260 weeks (long term effectiveness) in insufficient responders randomized to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction. **Other secondary and exploratory objectives/outcomes are described on page 17.**

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.

Role of study sponsor and funder

University Hospitals Leuven, as mentioned in the Key Trial Contacts (page 8), 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 on request.

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

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 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 at the site.
The organizing centre, 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
APR	Annual Product Report
AR	Adverse Reaction
CareRA	Care in early Rheumatoid Arthritis trial
CI	Chief Investigator

COBRA	COmbinatie therapie Bij Reumatoïde Artritis
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CTA	Clinical Trial Assistant
cta	Clinical Trial Agreement
CTC	Clinical Trial Centre
CTU	Clinical Trial Unit
DAS	Disease Activity Score
DMARD	Disease Modifying Anti Rheumatic Drug
csDMARD	conventional synthetic DMARD
bDMARD	biological DMARD
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
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
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ITT	Intention To Treat analysis
KCE	Belgian Healthcare Knowledge Centre
KU	Katholieke Universiteit
LTE	Long term extension
MAR	Missing at random
min	minutes
MMRM	mixed model for repeated measures
MTX	Methotrexate
PASS	Patient acceptable symptom state
PECR	Patient expertise centrum Reuma
PhD	Doctor of Philosophy
PhGA	Physician Global Assessment
PI	Principal Investigator
PM	Project Manager
PRO	Patient Reported Outcome questionnaires
Q	Quarter (of a year)
RA	Rheumatoid Arthritis
RAID	Rheumatoid Arthritis Impact of Disease questionnaire
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
STMG	study team and management group

SUSAR	Suspected Unexpected Serious AR
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SJC	Swollen Joint Count
TB	Tuberculosis
T2T	Treat to Target
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
TSC	Trial Steering Committee
UZ	University Hospital
VAS	Visual Analog Scale
w	week
WPAI	Work Productivity and Activity Impairment

Trial flow charts

	Screen***	(W117)	W130	(W143)	W156	(W169)	W182	(W195)	W208	(W221)	W234	(W247)	W260
Informed consent	X												
Inclusion/Exclusion criteria	X												
Assessment of comorbidities					X				X				X
Clinical/rheumatological examination		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
TB screening*													
X-Ray hands/feet					X				X				X
DAS28 CRP/ESR		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
Employment status		X	X	X	X	X	X	X	X	X	X	X	X
Relevant Concommitant medication		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) optional

**PRO's are mandatory every 3 months

* According to local guidelines

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

Study protocol

CareRA2020 LTE: a 3 year longitudinal observational, multicenter, follow-up of early RA patients after participation in the original CareRA2020 RCT.

1. Background and Rationale

Treatment for early 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 perfect initial treatment choice for the large majority of early RA patients. Nevertheless, for about 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.

Starting from the overarching question, which is the optimal initial pharmacological treatment strategy for patients with early untreated rheumatoid arthritis, we propose to investigate if accelerated access to a short course of anti TNF therapy, already early (from w8 till w32) after treatment initiation, for patients with an insufficient response to a COBRA Slim regimen could improve outcomes compared to a more traditional treat to target sequence, requiring first the evaluation of the effectiveness of adding or switching to another csDMARD 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 COBRA Slim strategy, taking into account direct and indirect costs.

The present study is an observational longitudinal follow up of patients who have participated in the CareRA2020 RCT protocol. The main objective is to obtain longitudinal information on the long term effect of different intensive initial treatment strategies on the disease course in terms of safety, need for treatment adjustments, disease activity, functionality, work participation, quality of life and cost effectiveness.
During this 3 year observation period therapeutic decisions will be at the discretion of the treating rheumatologists.

Assessment and management of risk

As this is an long term observational follow-up, no IMP(s) are involved in this trial. Therefore, this trial can be categorized as non-interventional trial and so no risk/benefit analysis is required.

2. Objectives and outcome measures/endpoints

Primary objective

To evaluate the clinical disease course and safety for three years following participation of RA patients in the CareRA2020 RCT depending on the original treatment allocation.

Outcome measures/endpoints

Primary outcome measure

Area under the curve of DAS28-CRP over 260 weeks (long term effectiveness) in insufficient responders randomized to either COBRA-Slim Bio-Induction or Standard COBRA-Slim Induction.

Secondary outcome measure

1. To further determine the **clinical efficacy** of the accelerated access to Etanercept strategy versus the classic COBRA Slim strategy.
2. To evaluate the **safety** of the given treatments.

Other exploratory objectives/outcomes:

1. To evaluate treatment response in terms of **other patient reported outcomes.**
2. **Depending on the clinical results of the CareRA2020 RCT and this LTE, 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 re-assembled complete study population.

3. Study design

Overall design

In this observational longitudinal follow-up trial, patients will be followed every 6 months according to the treat to target principle. Disease activity score (DAS28 CRP), need for treatment adjustment and a safety checklist will be collected. PRO's will be collected every 3 months as much as possible by means of electronic device.

Treat to target long term observational follow up phase (week 104 until week 260):

Once patients consented for participation in this separate observational follow-up protocol, treatment adjustments will be at the discretion of the physician, according to good clinical practice. This means that there are no more restrictions concerning treatment adaptations.

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.

4. Study setting

The study is a multicenter pragmatic long term observational follow-up sponsored by the University Hospitals Leuven, commissioned by KCE and coordinated by the Chief investigator Prof. Dr. Patrick Verschueren from the department of Rheumatology, University Hospitals Leuven.
Rheumatology centers participated in the CareRA2020 RCT are invited to participate.
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.

5. Study population

Number of patients

368 patients are estimated to be included in this observational follow-up: CareRA2020 LTE.
The enrolment period is estimated to be open from Q2 2020 – Q2 2022.
Patients participated in the CareRA2020 RCT, who completed w104 of the RCT and are able and willing to give written informed consent can participate in this long term observational follow-up.

Inclusion criteria

Patients participated in the CareRA2020 RCT, who completed w104 of the RCT and are able and willing to give written informed consent can participate in this long term observational follow-up.

Exclusion criteria

No exclusion criteria are applicable.

Concomitant medication

All changes in relevant concomitant medication (corticosteroids, DMARDs, Biologicals and analgesics) should be registered.

6. Trial Procedures

All procedures required in the protocol are described further; timing can be checked in the attached flow chart. Procedures are organized as Standard of Care (SoC) and study specific.

Consent

Only data from patients who gave consent to this long term observational protocol will be collected, if no consent is given, no data will be collected.

The investigator will ask all patients who completed participation in the CareRA2020 RCT protocol to participate to this long term observational follow-up.

By signing the informed consent form, the patient agrees to comply with all proposed evaluations required in the follow-up, unless the patient withdraws voluntarily or is terminated from the study for any reason.

All patients must sign an informed consent form that complies with the requirements of ICH E6 before entering the study.

Method of implementing the allocation sequence

Numbering will be taken from the CareRA2020 RCT followed by the letters FU to indicate this patient is in the long term observational follow-up.

Blinding

No blinding is applicable in this observational follow-up.

Unblinding

Unblinding is not applicable.

Visits

In this LTE, visits will be performed at the site unless there are 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). In that case regular outpatient visits can be replaced by a telephone consultation 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.

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.

Trial assessments

Screening: (= W104 of the main CareRA2020 RCT)

- Informed consent form
- Inclusion and exclusion criteria

At Week 130,156, 182, 208, 234 and 260 following data are captured as part of routine clinical data collection (SoC):

- Clinical/Rheumatologic examination
- Joint Count: TJC, SJC
- ESR and CRP
- DAS28CRP/DAS28ESR
- VAS PhGA/GH/pain/fatigue
- HAQ
- X-ray (Sharp/van der Heijde Score) on a yearly basis (W156, W208 and W260)
- Assessment of comorbidities (W156, W208 and W260)
- Relevant concomitant medication
- Relevant side effects
- Changes in employment status
- RF and ACPA status (W260)

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

- RAID
- EQ5D/WPAI

At Week 117, 143, 169, 195, 221 and 247 following data are captured:

- PRO's (Mandatory):
  - VAS GH/pain/fatigue
  - HAQ
  - RAID
  - EQ5D/WPAI

Only in case patient has to return to the site, following can be taken optionally:

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

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.

When a patient withdraws 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.

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.

Study related procedures

Laboratory tests:

A routine safety blood sample will be performed at each visit (if not available from the GP within 5 days of study visit). The analysis will be done by an accredited laboratory. The routine laboratory tests minimally required for this trial are as follows: ESR, CRP, complet, GOT, GPT and serum creatinine. RF and ACPA status will be checked at w260.
No samples will be stored for further analysis.

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:

TB testing should be done per local guidelines whenever patients require bDMARD therapy. In case of latent TB, patients should start prophylactic Nicotibine treatment for 6 months, at least 4 weeks before introducing the bDMARD.

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.
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. 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 end of the long-term follow-up trial is estimated at Q2 2025, so the closure can be planned 90 days later, Q3 2025.

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 the RCT part of the trial will be temporally suspended and it will resume as

soon as it is allowed. This will impact the timelines of this LTE 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 in the original RCT was suspended from 17/03/2020 until 18/05/2020.

Study discontinuation

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

Time schedule

	Screen***	(W117)	W130	(W143)	W156	(W169)	W182	(W195)	W208	(W221)	W234	(W247)	W260
Informed consent	X												
Inclusion/Exclusion criteria	X												
Assessment of comorbidities					X				X				X
Clinical/rheumatological examination		X	X	X	X	X	X	X	X	X	X	X	X
RF and ACPA status													X
ESR/CRP		X	X	X	X	X	X	X	X	X	X	X	X
TB screening*													
X-Ray hands/feet					X				X				X
DAS28 CRP/ESR		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
Employment status		X	X	X	X	X	X	X	X	X	X	X	X
Relevant Concommitant medication		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) optional

* According to local guidelines

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

**PRO's are mandatory every 3 months

7. Trial medication

This is an observational longitudinal follow-up, so no medication will be prescribed as part of the protocol.

Concomitant medication

As described above, all relevant concomitant medications will be recorded in the e-CRF.

Trial restrictions

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

8. Pharmacovigilance

Definition of an adverse event (AE)

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.

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 qualify as adverse reactions.

Adverse event of interest

Adverse events of interest are defined by the protocol as reactions to RA medication given to treat patients disease, 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

The investigator must assess the clinical significance of all abnormal laboratory values as defined by the compendium of normal values for the reference laboratory. Any clinically significant abnormalities should be investigated.

Definition of a Serious Adverse Event (SAE)

The definition of a Serious Adverse Event (SAE) is any untoward medical occurrence that:

- 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 fulfil above criteria may be considered Serious Adverse Events 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.

Definition of a suspected unexpected serious adverse reaction (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 (e.g. investigator's brochure for an unauthorized investigational product or the patient leaflet joined to the summary of product characteristics for an authorized product).

Collecting and Reporting of safety 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.

As this is an observational study only adverse events of interest, as defined above, will be captured in the e-CRF.

For this pragmatic longitudinal follow-up no specific medication will be used. If a medication is used, this will be within the registered label. The chance of encountering a SUSAR is rather low. Nevertheless, in case of happening, this should be reported within the given timeframe.

- 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 safety 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 applicable timelines to report, a Serious Adverse Event or Reaction should be followed.
- *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 safety event is related to the proposed strategy or prescribed drugs.
- Whether the event would be considered expected or unexpected *(medical judgement of the treating investigator).*
- Outcome

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

Collecting and Reporting of safety events that meet seriousness criteria:

Only SUSARs, 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 SAE/SUSAR. If the investigator is not available at 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 centre will be available to provide guidance regarding SAE reporting.

Contact Information:

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

In case both the CI and Prof Westhovens is 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

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 SAE'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 11.

Pregnancy reporting

If a female participant wants to become pregnant during the study, this should be discussed in advance with the PI and if required with the CI.
A pregnancy can be planned according to local guidelines.

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 serious criteria, this would be considered a SAE of interest.

9. Statistics and data analysis

Statistical analysis

Primary outcome analysis

Primary endpoint

Area under the curve of DAS28CRP over 260 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: w130, w156, w182, w208, w234 and w260.

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 30% 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 260.

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).

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.

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 must 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 must 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 must 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 all adverse events and follow-up of adverse events; concomitant medication; study drug administration information; 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 treatment on a patient, 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 at appropriate intervals 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.

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 Clinical Trials Review Board of the KCE. Peer review was conducted by expert referees to the professional and scientific standards expected for clinical studies

Public and Patient Involvement

During protocol development, as much as possible feedback from patient representatives/researchers 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 will certainly also be involved in the development of the informed consent form and all other information leaflets that will be developed for this trial. Moreover, the study design and important endpoints of the CareRA2020 RCT 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.

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.

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19. Appendices

Risk

As this is an observational follow-up, no risk/benefit analysis is required.

Study management / responsibilities

Patient registration/randomisation procedure

Registration of the patients will be done within the e-CRF. The study site representatives will do the registration on the day of inclusion.

Data management

As described above in the protocol a monitoring plan have to be developed as well as timelines on CRF entry.
Data management will be done within the department of rheumatology of UZ Leuven with support on data monitoring and query management of the CTC UZ 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.

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

Only centers participated in the CareRA2020 RCT will be participating

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.

Procedure for initiating a site

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 centre, 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***	(W117)	W130	(W143)	W156	(W169)	W182	(W195)	W208	(W221)	W234	(W247)	W260
Informed consent	X												
Inclusion/Exclusion criteria	X												
Assessment of comorbidities					X				X				X
Clinical/rheumatological examination		X	X	X	X	X	X	X	X	X	X	X	X
RF and ACPA status													X
ESR/CRP		X	X	X	X	X	X	X	X	X	X	X	X
TB screening*													
X-Ray hands/feet					X				X				X
DAS28 CRP/ESR		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
Employment status		X	X	X	X	X	X	X	X	X	X	X	X
Relevant Concommitant medication		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) optional

* According to local guidelines

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

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	17/07/2017	JJ	First draft
0	0.2	03/01/2018	JJ	Second draft
0	0.3	09/01/2018	JJ	Prefinal draft
0	0.4	25/01/2018	JJ	Prefinal version
0	0.5	31/01/2018	JJ	Final version
0	0.6		JJ	Approved
LTE M001	1.0	25/05/2020	JJ, PV, DB, 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)

Reason for LTE Modification 1 (LTE M001) protocol version 1.0 25/05/2020.

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

This protocol modification does only affect the long term observational part of the trial and does not meet the criteria to be substantial.