Protocol Title:

A multi-center, open, randomized, 18-month, parallel-group, superiority study to compare the effect of proactive therapeutic drug monitoring versus standard of care with regards to maintenance of sustained disease control without flare in adults with rheumatoid arthritis treated with a subcutaneous tumor necrosis factor inhibitor

Protocol Version No. 1.0

Amendment No.

Date 19.04.2024

Brief Title:

Effect of proactive therapeutic drug monitoring on maintenance of sustained disease control in adults with rheumatoid arthritis on a subcutaneous TNF inhibitor:

The Rheumatoid Arthritis therapeutic DRUg Monitoring trial (RA-DRUM)

Study Phase: 4

Acronym: RA-DRUM

Sponsor name: Diakonhjemmet Hospital AS

Contact person: Professor Espen A. Haavardsholm, MD PhD
Legal Registered Address:
Box 23 Vinderen, 0319 Oslo, Norway
Telephone: 22 45 15 00
E-mail: espen.haavardsholm@diakonsyk.no

Regulatory Agency Identifier Number(s):

EU CT No: 2023-510184-35-00

Approval Date: NA

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this trial. I will submit the protocol and all other important trial-related information to the responsible investigator(s) so that they can conduct the trial correctly. I am aware that it is my responsibility to hold the staff members who work with this trial informed and trained.

Sponsor Signatory:

Professor Espen A. Haavardsholm, MD PhD **Head of Research and Innovation, Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway**	**Date**

Table of Contents

List of Abbreviations

ADAb	Anti-drug antibodies
AE	Adverse Event
ALT	Alanine aminotransferase
bDMARD	Biological Disease-Modifying Anti-Rheumatic Drug
CDAI	Clinical Disease Activity Index
CIOMS	Council for International Organizations of Medical Sciences
CRP	C-reactive protein
CSR	Clinical Study Report
DAS28-CRP	Disease Activity Score using 28 joints C-reactive protein
DMARD	Disease-Modifying Anti-Rheumatic Drug
eCRF	electronic Case Report Form
EGA	Evaluators Global Assessment of Disease Activity
ESR	Erythrocyte Sedimentation Rate
EULAR	European Alliance of Associations for Rheumatology
GCP	Good Clinical Practice
EQ-5D	European Quality of Life 5 Dimensions
HRQOL	Health Related Quality Of Life
ICF	Informed Consent Form
ICH	International Council for Harmonization
MHAQ	Modified Health Assessment Questionnaire
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Hart Association
PGA	Patient Global Assessment of Disease Activity
PROMs	Patient reported outcome Measures
RA	Rheumatoid arthritis
RA-FQ	Rheumatoid Arthritis Flare Questionnaire
RAID	Rheumatoid Arthritis Impact of Disease
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SoA	Schedule of Activities
SDAI	Simple Disease Activity Index
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
SF-36	36-Item Short-form Health Survey
SmPC	Summary of Product Characteristics
SC	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDM	Therapeutic drug monitoring
TNFi	Tumor necrosis factor inhibitor
tsDMARD	Targeted synthetic Disease-Modifying Anti-Rheumatic Drug
VAS	Visual Analogue Scale
WPAI:RA	Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis

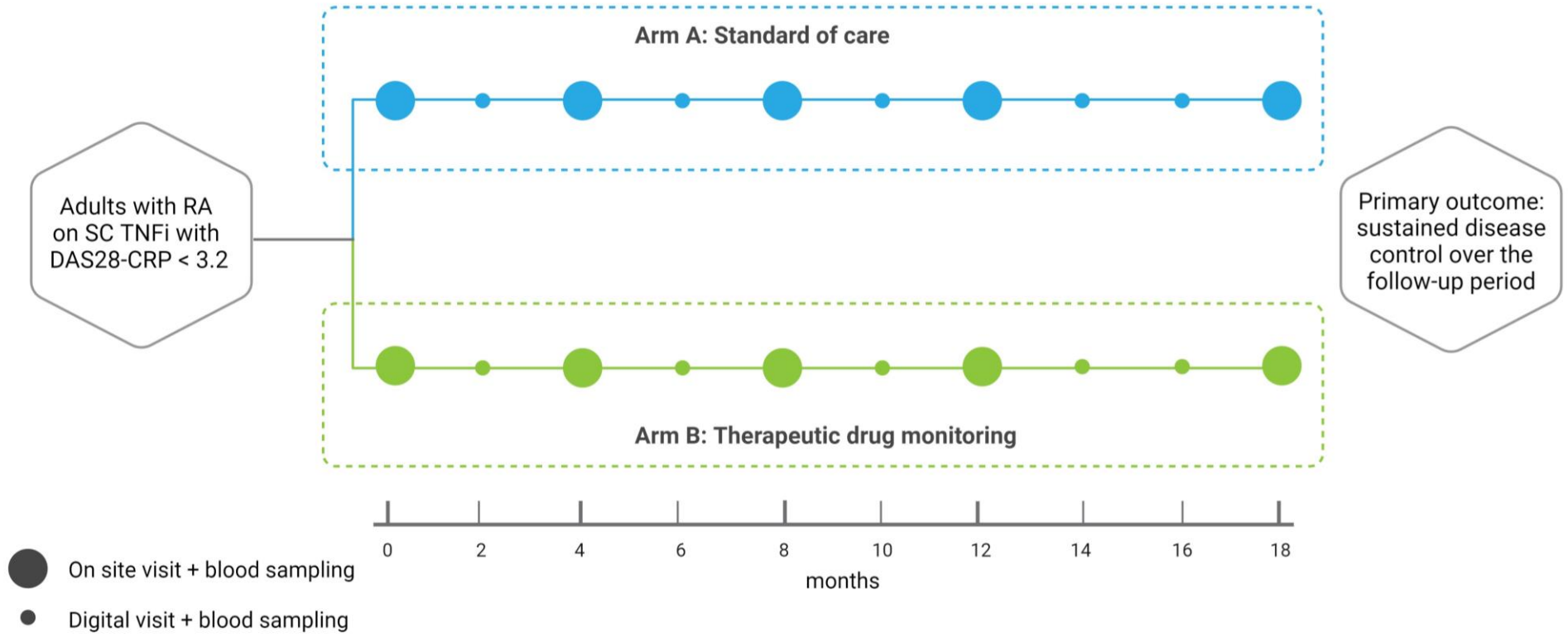
1. Protocol Summary

1.1. Synopsis

The **R**heumatoid **A**rthritis therapeutic **DRU**g **M**onitoring trial **RA-DRUM**	
Protocol Title	A multi-center, open, randomized, 18-month, parallel-group, superiority study to compare the effect of proactive therapeutic drug monitoring versus standard of care with regards to maintenance of sustained disease control without flares in adults with rheumatoid arthritis treated with a subcutaneous tumor necrosis factor inhibitor
Brief Title	Effect of proactive therapeutic drug monitoring on maintenance of sustained disease control in adults with rheumatoid arthritis on a subcutaneous TNF inhibitor: The **R**heumatoid **A**rthritis therapeutic **DRU**g **M**onitoring trial (RA-DRUM)
Rationale	There is a considerable variation in serum drug levels among rheumatoid arthritis (RA) patients on tumor necrosis factor inhibitors (TNFi), and a high number develop neutralizing anti-drug antibodies (ADAb). Sub-therapeutic drug levels and ADAb formation are major contributors to TNFi treatment failure and disease flare. Proactive therapeutic drug monitoring (TDM), i.e., individualized drug dosing based on regular assessments of serum drug levels and ADAb, has the potential to optimize the efficacy and safety of TNFi treatment. The Norwegian Drug Monitoring (NOR-DRUM) B study (JAMA 2021) showed that proactive TDM reduced the occurrence of flares in patients with immune-mediated inflammatory disease using infliximab, an intravenously administrated TNFi. Different administration routes and molecular structures limit the opportunity to extrapolate results from TDM of infliximab therapy to treatment with subcutaneous (SC) TNFi, and there is a need for trials investigating the efficacy of proactive TDM for SC TNFi.
Objectives	**Primary objective:** To assess whether TDM is superior to standard of care in order to maintain sustained disease control without flares in patients with RA treated with SC TNFi. **Secondary objectives:** • To compare effectiveness of proactive TDM to standard of care applying different outcome measures • To assess safety of proactive TDM • To assess whether proactive TDM influences drug survival, drug consumption, occurrence of ADAb and serum drug levels
Endpoints	**Primary endpoint:** Sustained disease control over the follow-up period of 18 months without flare, with flare defined as either of the following: • A combination of an increase in Disease Activity Score using 28 joints C-reactive protein (DAS28-CRP) > 1.2, or > 0.6 if DAS28-CRP ≥ 3.2, AND ≥ 2 swollen joints on examination of 44 joints

	• Consensus between patient and physician that a disease flare has occurred, leading to a major change in treatment If more than one TNFi type are included, subgroup analyses according to each TNFi type used will be performed. **Secondary endpoints:** • Disease activity at 4, 8, 12, and 18 months assessed by DAS28-CRP, Evaluators Global Assessment of Disease Activity (EGA), Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) remission criteria, Rheumatoid Arthritis Impact of Disease (RAID), Modified Health Assessment Questionnaire (MHAQ), biochemical parameters • Time to disease flare • Number and type of adverse events (AEs) • Drug survival, drug consumption, occurrence of ADAb, serum drug levels
Overall Design	A multicenter, randomized, two-arm, parallel-group, open, superiority trial where adult participants with RA in DAS28-CRP remission or low disease activity (DAS28-CRP < 3.2) on therapy with standard dose of a SC TNFi (adalimumab) for 3-24 months with indication for continuation of treatment according to the treating physician are stratified by country and allocated 1:1 to: • Administration of TNFi based on proactive TDM (TDM group) • Administration of TNFi based on standard of care without knowledge of serum drug levels or ADAb status (Standard of care group) The protocol has been developed with the aim of including RA patients on therapy with adalimumab. If sufficient evidence emerges regarding therapeutic ranges of other SC TNFi during the study period, it will be considered to amend the protocol to include RA patients on other SC TNFi.
Visit Frequency	Onsite visits will be conducted at 0, 4, 8, 12, and 18 months following randomization, with additional digital visits and blood sampling at 2, 6, 10, 14, and 16 months.
Study Duration	18 months
Number of Participants	A minimum of 350 patients will be enrolled.

1.2. Schema



Created with BioRender

DAS28-CRP = Disease Activity using 28 joints C-reactive protein; **RA** = rheumatoid arthritis; **SC** = subcutaneous; **TNFi** = Tumor Necrosis Factor Inhibitors

1.3. Schedule of Activities (SoA)

Procedure	Screening	Intervention Period (visit month/visit no) Targeted visit window: ±14days										E/D	Extra Visit	Notes
		Baseline* Visit 1	2 Visit 2	4* Visit 3	6 Visit 4	8* Visit 5	10 Visit 6	12* Visit 7	14 Visit 8	16 Visit 9	18* Visit 10			
Informed consent	X													
Inclusion and exclusion criteria	X	X												See Sections 5.1 and 5.2
Randomization		X												See Sections 6.3 and 9.3.1
Demography		X												See Section 8.1.1
Height and weight		X												See Section 8.1.1
Medical history including tobacco use		X												See Section 8.1.1
Current medical conditions		X												See Section 8.1.1
Routine laboratory tests		X		X		X		X			X	X	X	Hemoglobin, platelet count, white blood cells with differentials, ALT, creatinine, CRP, ESR. See Section 8.3.1
Biobank full blood		X												All sites See Section 8.1.2
Biobank**		X		X		X		X			X	X	X	Full blood, plasma and serum See Section 8.1.2
Assessment of disease activity		X		X		X		X			X	X	X	DAS28-CRP, EGA, 44 joint count, CDAI, SDAI See Section 8.2.1
Assessment of drug levels and ADAb***		X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.5

RA-FQ, EQ-5D, WPAI:RA		X	X	X	X	X	X	X	X	X	X	X	X	See Sections 8.2.1 and 8.8
SF-36, MHAQ, RAID		X		X		X		X			X	X	X	See Sections 8.2.1 and 8.8
Record of concomitant medication for RA		X		X		X		X			X	X	X	See Section 6.9.2
AE registration		X		X		X		X			X	X	X	See Section 10.3
Adherence		X	X	X	X	X	X	X	X	X	X	X	X	By questionnaires and digital calendar See Section 6.5
	*Onsite hospital visits ** Participants at Diakonhjemmet Hospital only ***In all participants **AE =** Adverse Events; **ALT**=Alanine Transaminase; **E/D** = Early Discontinuation; **EGA** = Evaluators Global assessment of disease activity; **ESR**= Erythrocyte sedimentation rate; **EQ-5D** = European Quality of Life 5 Dimensions; **Ex visits** = Extra visit if flare; **CDAI** = Clinical disease activity index; **CRP**= C-reactive protein; **DAS28-CRP** = Disease Activity Score using 28 joints C-reactive protein; **MHAQ** = Modified Health Assessment Questionnaire; **PGA** = Patient Global assessment of disease activity; **RAID** = Rheumatoid Arthritis Impact of Disease; **RA-FQ** = Rheumatoid Arthritis Flare Questionnaire; **SDAI** = Simple disease activity index; **SF-36**= 36-Item Short-form health survey; **WPAI:RA** = Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis													

2. Introduction

This protocol outlines the RA-DRUM (Rheumatoid Arthritis therapeutic DRUg Monitoring) trial, a randomized controlled trial that aims to optimize therapy for patients with RA using SC TNFi. RA imposes a significant burden on patients, healthcare systems, and society (1). The proposed study will assess if individualizing treatment by TDM can improve the effectiveness of SC TNFi in maintaining disease control for patients with RA.

2.1. Study Rationale

TNFi are used worldwide, with adalimumab as one of the most used medical compounds overall in 2022 (2). TNFi, including adalimumab, have revolutionized the treatment of prevalent chronic immune-mediated inflammatory diseases, including RA (2-4). However, a significant proportion of RA patients either do not respond adequately to initiated therapy or lose treatment effect over time (5, 6). Disease flares can negatively impact quality of life and can lead to irreversible joint damage, prevention of flares is thus important in management of RA (1). Observational data have shown extensive individual variation in serum drug levels among patients on standard doses of adalimumab and other SC TNFi, suggesting both under- and overtreatment of a substantial proportion of patients (7-9). Additionally, TNFi and other therapeutic antibodies can elicit an immune response in the patient. Many patients develop anti-drug antibodies (ADAb) during therapy, contributing to reduced drug levels and increasing the risk of drug reactions (10). By individualizing therapy, i.e., reducing under-and over treatment and in guiding treatment decisions, TDM is a tool that can be used to optimize the effectiveness of TNFi treatment, making it a topic of great interest to clinicians nationally and internationally (11).

The RA-DRUM study is the first trial to evaluate the effect of TDM in patients with RA treated with SC TNFi. It will provide important insights, aiming to contribute to the realization of a personalized medicine approach for TNFi therapy. The results of this study could also impact healthcare economics, as the high costs of TNFi restrict their use (12). Moreover, RA-DRUM presents unique opportunities for translational research on the poorly understood area of genetic and immunological mechanisms underlying drug immunogenicity (10). Further identification of predisposing genetic markers that could serve as predictors of loss of response is highly relevant to individualize treatment with biological drugs (13).

While a personalized medicine approach to SC TNFi by TDM seems reasonable, the effectiveness of such a treatment strategy in the management of RA with regard to sustained disease control remains to be shown in a randomized controlled trial like the RA-DRUM trial.

2.2. Background

2.2.1. Treatment of RA

RA is characterized by symmetric inflammation of the peripheral joints (14). The high burden of disease in RA is related both to symptoms of active inflammation and to the subsequent development of irreversible joint damage (15). The overarching treatment goal is early and aggressive suppression of inflammation, and maintenance of remission or low disease activity to prevent structural damage and disability (16). TNFi are widely used antibody-based drugs

.

targeting TNF and are usually added if the treatment target is not achieved with a csDMARD, such as methotrexate (16). The introduction of TNFi around year 2000 played a significant role in making remission an achievable treatment goal in RA (3). However, more than half of patients lose efficacy over time (17, 18). A failure to maintain disease control has a major negative impact on patients' quality of life and puts the individual at risk of developing serious organ damage and disability (19, 20). Loss of treatment effect can be due to underexposure to the drug (21).

2.2.2. Serum Dug Levels and ADAb

Therapy with SC TNFi and other biological drugs are not currently personalized, but prescribed in a uniform manner to all patients. Observational studies have shown associations between serum drug levels and effectiveness and also revealed considerable inter-individual variation in serum drug levels for TNFi, indicating both under- and overexposure (7-9, 22, 23). Therapeutic ranges, i.e., serum levels expected to achieve the desired therapeutic effects, have been identified for adalimumab and other TNFi (7, 22-24). A considerable proportion of patients on standard dose have serum levels above or below the therapeutic range, indicating a potential for dose-optimization. One major reason for the large variation in serum drug levels is the development of ADAb which are formed as part of immune responses to TNFi and other biological drugs, which are large, complex and allogenic proteins (10). ADAb influences the pharmacokinetics of the drug either by direct binding to the target binding site of the therapeutic antibody (neutralizing ADAb) or by forming immune complexes with the drug resulting in altered clearance (non-neutralizing ADAb). ADAb production has proved to be a significant clinical problem. Low levels of ADAb might be transient, but high levels of ADAb reduce the effect of the drug and decrease serum drug levels (25, 26). Drug holidays or low-dose regimens have been shown to predispose to ADAb formation (27). Patients with RA may be more prone to ADAb formation than patients with other immune-mediated inflammatory diseases (27). Immunosuppressive co-medication, in particular methotrexate, is protective with a reduction of ADAb formation by up to 40% (25, 26, 28, 29). Whereas the precise immunological mechanisms leading to ADAb formation remains unknown, knowledge regarding predisposing genetic factors including HLA are increasing (13, 21, 30).

2.2.3. Therapeutic Drug Monitoring

Proactive TDM, a personalized treatment strategy based on regular assessments of serum drug levels and ADAb and adjustments in drug dose to keep serum drug levels within the defined therapeutic range, has been proposed as a clinical tool to optimize efficacy, patient safety and cost-effectiveness of TNFi treatment (11). A treatment strategy based on proactive TDM may improve TNFi therapy by:

i) Minimizing drug underexposure, which might lead to loss of response
ii) Reducing drug overexposure, which predispose patients to side effects and increases costs
iii) Allowing for timely identification of ADAb development, with the possibility to prevent treatment failures prior to a clinical flare

Methods for assessment of serum drug levels and ADAb are available for use in clinical practice (21). Guidelines and recommendations for implementation of TDM in standard care of patients on treatment with biological drugs are needed as the use of therapeutic monoclonal

.

antibodies are rapidly increasing (16, 31). However, due to limited high-grade evidence with regard to clinical utility and cost-effectiveness of TDM, treatment recommendations are inconclusive, and TDM has yet to gain widespread use within rheumatology. The need for prospective studies comparing TDM with usual care, is also highlighted in the research agenda of the recent EULAR points to consider for TDM in rheumatology (31).

The NORwegian DRUg Monitoring (NOR-DRUM) trials, two randomized controlled trials across a range of IMIDs, demonstrated that TDM improved efficacy during maintenance-, but not during induction therapy with one TNFi, infliximab (32, 33). In these trials, proactive TDM resulted in a nearly 20% reduction in flare without increased infliximab consumption compared to usual care during maintenance therapy. Showing proof of principle of effectiveness of a TDM-based treatment strategy for infliximab, easily assessed due to its intravenous administration, was very important. Having established the benefit of TDM in principle, we now aim to determine if proactive TDM also is a viable, practical tool across the other TNFis, which are administered SC.

Proving a benefit of TDM for SC TNFi will be a strong point in favor of TDM implementation into treatment guidelines, and can be expected to have a particularly strong impact on the medical community treating RA patients.

As adalimumab is currently by far the most used SC TNFi and since knowledge of the therapeutic ranges is at this time most robust for adalimumab, this protocol has been developed with the aim of including RA patients on therapy with adalimumab. Should evidence regarding therapeutic ranges emerge and the clinical use of other SC TNFi increase during the study period, RA patients on other SC TNFi will be considered for inclusion following a protocol amendment.

2.3. Benefit/Risk Assessment

Participants are already on prescribed therapy with the investigational medicinal product (IMP) adalimumab, and the drug is continued in both groups. More detailed information about the known and expected benefits and risks and reasonably expected AEs of adalimumab can be found in the Summary of Product Characteristics (SmPC).

2.3.1. Risk Assessment

Investigational intervention: Patients are already on therapy with the IMP, no patients will start with a new drug as a consequence of study inclusion. During the conduct of the trial, some patients might change therapy due to findings of ADAb, but this we expect to be beneficial to the patient in that they may avoid a possible clinical flare (34). The IMP is used for an approved indication. The investigational intervention is not expected to increase the risk of AEs from the medication during the study. This includes participants with a dose decrease or increase due to the TDM strategy as treatment effectiveness and AEs are expected to be related to drug levels, i.e., the amount of pharmacologically active drug in the circulation, and not the dose.

Study design: Participants in both groups will use slightly more time at each clinical visit compared to usual clinical care due to clinical evaluation by the blinded joint assessor. They

will have to fill inn PROs every second month. Except for blood sampling, which is also performed regularly in usual clinical care, there are no invasive procedures in this study.

Mitigation Strategy

Study personnel will receive adequate training. User representatives have participated in the protocol development and will be involved in the preparations for the practical conduct of the study, to ensure the participants' interests and preferences are adequately considered. Participants will receive close follow-up from a physician and study nurse in the study and will be given the opportunity for a rapid extra assessment if a suspected disease flare occurs. If the participant does not respond to the treatment, the investigator can switch treatment regardless of study arm and without consequence for further study participation. Patients can withdraw from the study at any time.

2.3.2. Benefit Assessment

For the individual participant

Each participant will receive close follow-up. The follow-up will ensure careful and standardized assessment of treatment effects and AEs. In case of suspected disease flare, regardless of treatment group, the participant will be offered an extra assessment and necessary adjustment of treatment within a short time. The participant will contribute to knowledge within a clinically important field with current knowledge gaps.

For the group of participants

The results of RA-DRUM are expected to have significant implications for the use of adalimumab and other SC TNFi. Inadequate treatment effect and loss of effect over time is a major problem in the treatment of patients with a range of chronic immune-mediated inflammatory diseases such as RA. If RA-DRUM shows that individualized therapy based on TDM can improve treatment and/or result in fewer side effects, this study could contribute to more optimal drug treatment. This will have significant implications for patients with a range of immune-mediated inflammatory diseases.

For society

The economic burden of biological treatment is formidable. If it is possible to improve cost-effectiveness, these expensive drugs could become available to more patients. If the drugs are used more effectively, the climate footprint may also be reduced.

For science

The genetic and immunological mechanisms underlying the development of ADAb are not known but are believed to be linked to certain hereditary factors (HLA). This large, well-characterized cohort of patients will be able to contribute to translational research and generate new knowledge within this important area.

2.3.3. Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk to the participants in this study, the potential risks identified in association with proactive TDM are justified by the anticipated benefits that may be afforded to patients with RA.

.

3. Objectives and Endpoints

Objectives	Endpoints	Assessments
Primary		
To assess whether proactive TDM is superior to standard of care in order to maintain sustained disease control without flares in patients with RA treated with SC TNFi.	Sustained disease control over the follow-up period of 18 months without flare, with flare defined as either of the following: A combination of an increase in Disease Activity Score using 28 joints- C-reactive protein (DAS28-CRP) > 1.2, or > 0.6 if DAS28-CRP ≥ 3.2, AND ≥ 2 swollen joints on examination of 44 joints Consensus between participant and physician that disease flare has occurred, leading to a major change in treatment* *A major change in treatment includes switching to another biological disease-modifying anti-rheumatic drug (bDMARD) or targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD), adding a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD), increasing the dose of a concomitant csDMARD, i.e., methotrexate increased by ≥ 5 mg/week, adding or increasing systemic glucocorticoids (per orally, intravenous, or intramuscular), and receiving more than one intra articular glucocorticoid injection at one visit. If the dose of TNFi is increased for clinical reasons (Standard of care group), this should also be regarded as a major change in treatment.	• DAS28-CRP • Joint count of 44 joints

	Subgroup analyses of the primary endpoint according to each TNFi type (if more than one TNFi type will be included)	
Secondary		
To compare effectiveness of proactive TDM to standard of care on different outcome measures	Disease activity at 4, 8, 12, and 18 months Time to disease flare (as defined above)	• DAS28-CRP • Joint count of 44 joints • Patient Global assessment of disease activity (PGA) • Evaluator Global assessment of disease activity (EGA) • Clinical Disease Activity Index (CDAI) • Simple Disease Activity Index (SDAI) • Rheumatoid Arthritis Impact of disease (RAID) • Modified Health Assessment Questionnaire (MHAQ) • ACR/EULAR remission criteria • Biochemical parameters (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR))
Safety	Number and type of adverse events (AE)	• Assessments of AE
To assess whether proactive TDM influences drug survival, drug consumption, occurrence of ADAb, and serum drug levels	Drug survival, drug consumption, occurrence of ADAb, serum drug levels	• Assessments of drug consumption • Drug survival • Assessments of serum drug levels and ADAb

Explorative/Other Objectives	
• To assess cost effectiveness, utility, and impact on quality of life of proactive TDM compared to standard of care • To assess whether biomarkers (including genetic markers) and other factors can predict development of ADAb in participants on SC TNFi • To study how serum drug levels and ADAb are associated with drug efficacy and safety • To study predictors of flare and treatment response • To study differences in immunogenicity between different SC TNFi • To characterize anti-drug immune responses, including ADAb isotypes, epitopes, and association to genetic markers (e.g., HLA) • To assess how TDM influences treatment with respect to serum drug/ADAb levels and disease activity • To assess efficacy of TDM in the subgroup of participants with ADAb • To study feasibility of TDM and compliance to the treatment algorithm • To study the performance of the treatment strategy within the group of participants affected by the algorithm • To study the effect of dose escalation/decrease on serum drug levels and clinical outcomes • To study the value of TDM in the setting of switching of drug to a different bDMARD • To study effectiveness of TDM in subgroups of participants where TDM is assumed to be particularly valuable, including participants with high disease activity at baseline, participants not on immunosuppressive co-medication, and participants with previous secondary loss of effect of TNFi • To study adherence • To study corticosteroid consumption • To study different measures for assessing flares	• European Quality of Life 5 Dimensions (EQ-5D, 36-Item Short-form health survey (SF-36), Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI-GH) • Genetic markers and biomarkers • Assessments of serum drug levels and ADAb • Assessments of AE • DAS28-CRP, Joint count of 44 joints, PGA, EGA, CDAI, SDAI, RAID, MHAQ, ACR/EULAR remission criteria • Biochemical parameters (including CRP and ESR) • Drug survival • Adherence questionnaire • Drug calendar • Co-medication assessment • Rheumatoid arthritis flare questionnaire (RA-FQ

4. Study Design

4.1. Overall Design

- A multi-center, randomized, open (with partial blinding for outcome assessments), parallel-group, superiority study.
- Study intervention assignment: 1:1 by central computer randomization at the time of inclusion, stratified by country.
- Treatment strategies compared:
    - Administration of TNFi based on proactive TDM (TDM group)
    - Administration of TNFi according to standard of care without knowledge of serum drug levels or ADAb status (Standard of care group)
- Population: Adult patients with RA in DAS28-CRP remission or low disease activity (DAS28-CRP < 3.2) on therapy with a SC TNFi (adalimumab) in standard dose for 3–24 months and an indication for continuation of treatment according to the treating physician.
- Algorithm for dose adjustments: In the TDM group, adjustments of the dosing interval of the TNFi are made according to a predefined algorithm, with the aim of reaching and maintaining a serum drug level within the therapeutic range.
- Duration of study: The randomized treatment strategy will be continued for the duration of the follow-up period (18 months).
- Study visits: Onsite visits 0, 4, 8, 12, and 18 months. Additional digital visits and onsite blood sampling at 2, 6, 10, 14, and 16 months.
- Primary endpoint: sustained disease control without disease flare during the follow-up period of 18 months.
    - In order to identify the primary endpoint, each study center will have a phone number for participants to call in case of increased disease activity. If a participant is experiencing a potential flare, a visit will be arranged within one week after contacting the study center to allow for a thorough examination and documentation of disease status.
- Participants experiencing a flare (primary endpoint) will be followed according to the visit scheme. Further therapy will be at the discretion of the treating physician, but for participants in the TDM group, an increase in dose will be recommended if the drug level is low (according to the TDM algorithm).
- Participants who are switched to another treatment during the study will still be followed according to the visit scheme but without TDM.
- Biosimilars: Switching between biosimilar drugs is allowed at any time during the study.

4.2. Scientific Rationale for Study Design

Study design: A randomized superiority trial is the preferred study design to assess an intervention suggested to improve clinical outcomes.

Masking: Due to the need for communication between study personnel and participants regarding dose changes in the TDM group, blinding of study personnel and participants is not feasible. To mitigate the risk of expectation bias, joint count assessor (component of the primary outcome) will be blinded.

Primary endpoint: To maintain sustained disease control is the treatment target in RA care (3). Preventing flares may improve quality of life, delay disease progression, and avoid irreversible organ damage, which can make a great difference to a large number of patients with RA (19, 20, 35, 36). There is no consensus on the definition of flare in RA. The definition of a flare used in the present study is based on work conducted within Outcome Measures in Rheumatology (OMERACT) on the minimally clinically important difference and minimally detectable difference of DAS28-CRP, and definitions used in prior randomized controlled trials (RCTs) within this field (33, 37-40).

Eligibility: Inclusion criteria are wide in order to improve external validity.

4.2.1. Patient Input into Design

Three user representatives with RA were consulted in an early phase of planning this study and during protocol development. They gave input on the interventions, study outcomes, and study duration. Additionally, they gave specific input to the informed consent form and the patient information letter. The user representatives will continue their involvement during the continuation of the study.

4.3. Justification for the Choice of Study Drug and the TDM Strategy

As knowledge of the therapeutic ranges at this point is most robust for adalimumab, and since adalimumab is currently by far the most used SC TNFi, the study protocol has been developed with the aim of including RA patients on therapy with adalimumab. In case of evidence regarding therapeutic ranges for other SC TNFi emerge and their clinical use increase during the study period, RA patients on other SC TNFi will be considered for inclusion following a protocol amendment.

The treatment algorithm in the TDM group is based on an extensive literature review, assessment of new unpublished data, and expert opinions. It has been developed through a series of meetings in the project group including international leading experts in this field (both clinicians experienced with TDM and laboratory physicians).

There are strong indications that the lower limit of the therapeutic range of adalimumab in RA is close to 5 mg/L (7, 23, 41-44), and data indicate that an upper limit is around 12 mg/L (7, 23, 42).

The dose alterations recommended by the algorithm were based on literature review and on considerations of feasibility and expert opinion (44-47). The cut-off for ADAb leading to

.

change of therapy is based on clinical experience and is the same as the cut-off used in an equivalent assay for the TNFi infliximab in the previous NOR-DRUM trials (32, 33).

4.4. End-of-Study Definition

A participant is considered to have completed the study when the participant has completed the visit at 18 months. The end of the study is defined as the date of the last visit of the last participant in the study.

.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if *all* of the following criteria apply:

1. A clinical diagnosis of RA
2. ≥ 18 and < 75 years of age at screening
3. On stable therapy with standard dose of a SC TNFi (adalimumab) for a minimum of 3 months and a maximum of 24 months
4. In low disease activity or remission (DAS28-CRP < 3.2) and indication for continuation of treatment according to the treating physician
5. Subject capable of understanding and signing an informed consent form

5.2. Exclusion Criteria

Participants are excluded from the study if *any* of the following criteria apply:

1. Major comorbidities, such as previous malignancies within the last 5 years, uncontrolled diabetes mellitus, severe infections (including HIV), uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases, demyelinating disease, significant chronic widespread pain syndrome, significant renal or hepatic disease, and/or other diseases or conditions which either contraindicate treatment with SC TNFi or make adherence to the protocol difficult
2. Hypersensitivity to SC TNFi (adalimumab)
3. Pregnancy, or subject considering becoming pregnant during the study period
4. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers, or other factors that makes adherence to the study protocol difficult
5. Changes in csDMARD co-medication, including dose changes of csDMARD or changes in the dose of corticosteroids within the last 2 months
6. Co-medication with bDMARD, tsDMARD, or other immunosuppressive drugs (excluding csDMARD and corticosteroids ≤ 7.5 mg prednisolone (or equivalent) once daily).
7. Active participation in any other interventional study
8. In need of live vaccines during the study period

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is

.

required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trails (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened (maximally two times) under a new participant number for every screening/rescreening event.

A list of pre-screened patients not eligible for screening will be kept with the patient identification list and will describe age, gender and reason for not eligible for screening.

5.5. Criteria for Temporarily Delaying

Not applicable.

.

6. Study Intervention and Concomitant Therapy

Study interventions are all pre-specified investigational and non-investigational medicinal products, medical devices, and other interventions (e.g., surgical and behavioral interventions) intended to be administered to the study participants during the study conduct.

Participants enrolled in the RA-DRUM trial are on therapy with SC TNFi.

They are randomized 1:1 to either:

- Administration of SC TNFi based on proactive TDM (TDM group)
- Administration of SC TNFi according to standard of care without knowledge of serum drug levels or ADAb status (Standard of care group)

If the participants are using prednisolone (≤ 7.5 mg prednisolone oral dose or equivalent) or concomitant csDMARD including methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide in any dose this will be continued in an unchanged dose.

6.1. Study Intervention Administered

6.1.1. The TDM Group

In the TDM, the SC TNFi dose will be adjusted according to the algorithms outlined in Table 1 in order to keep the drug level within the therapeutic range.

Prior to a dose change, the study personnel must check by a phone call to the participant if the drug has been administered according to the treatment algorithm (as defined in Table 1) or if injections have been postponed or dropped due to medical or other reasons.

The following exceptions from the algorithm in Table 1 are recommended if the drug has not been administered according to the treatment algorithm during the last month:

- If the drug level is low with no or low ADAb and there has been a pause in medication of more than 1 week for the last month prior to the blood sampling the dose should be kept stable
- If the drug level is high and the participant has taken the injection in a higher dose or more frequent than prescribed, the dose should be kept stable.

The reason for pause in therapy should be recorded in the eCRF.

In the TDM group, results for drug levels and ADAb will be reported to the investigators via the eCRF within 10 days after receiving the sample. Results in the standard care group will be recorded in the eCRF but not accessible to study personnel, and transferred to the PI upon conclusion of the clinical trial.

.

Table 1. Study Intervention

	Adalimumab	**x**	**y**	**z**
Trade name(s)	Originator and all approved adalimumab biosimilars*			
Type	Biologic drug			
Dose Formulation	Subcutaneous (SC) injection			
Recommended Dose**	40 mg SC every 14 days, if necessary 40 mg SC every 7 days or 80 mg SC every 14 days			
IMP and NIMP	IMP			
Drug target range	5.0-12.0 mg/L			
Cut-off ADAb high levels	> 50 µg/L			
TDM strategy				
• Within target range	Keep dose			
• Low drug levels, ADAb undetectable or low levels	Decrease dosing interval by one week to a maximum of 40 mg/week			
• Low drug levels, ADAb high levels	Switch to another therapy			
• High drug levels	Increase dosing interval by one week up to a maximum of 6 weeks			

* All adalimumab biosimilars approved by the European Medicines Agency
**According to the Summary of Product Characteristics (SmPC)
ADAb = anti-drug antibodies; TDM = Therapeutic drug monitoring
X,y,z: The protocol has been developed with the aim of including RA patients on therapy with adalimumab. If sufficient evidence emerges regarding therapeutic ranges of other SC TNFi during the study period, it will be considered to amend the protocol to include RA patients on other SC TNFi.

6.1.2. The Standard of Care Group

In participants randomized to the Standard of care group, the SC TNFi will be administered according to standard of care without knowledge of serum drug levels or ADAb at all visits throughout the study. Results of serum drug levels and ADAb testing in the Standard of care group will be kept hidden from the investigators.

6.1.3. Both Groups

In order to identify the primary endpoint, each study center will have a phone number for participants to call in case of increased disease activity. If a participant is experiencing a potential flare, a visit will be arranged within one week after contacting the study center to allow for a clinical examination and documentation of disease status.

Participants with a flare (primary endpoint) will be followed according to the visit scheme. Further therapy will be at the discretion of the treating physician, but for participants in the TDM group, an increase in dose will be recommended if the drug level is low (according to the TDM algorithm).

If SC TNFi is terminated due to any reason, the participant will still be included in the study and followed with study visits according to the planned visit schedule. The reason for termination of therapy should be recorded in the eCRF. If SC TNFi is terminated due to AE, the choice of treatment should be at the discretion of the investigator. Participants who are

.

switched to another treatment during the study will still be followed according to the visit scheme. Switching between biosimilar drugs is allowed at any time during the study.

6.2. Preparation, Handling, Storage, and Accountability

Participants will be prescribed the TNFi and receive it from the pharmacy as per usual routine use. Participants will handle, store, and administer the drug according to the SmPC. This includes following the expiry date on the packaging and keeping the drug cool during storage. The IMP has already been placed on the market as an authorized medicinal product in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council, and there is no blinding of the IMP. Therefore, no additional labelling will be applied.

6.3. Assignment to Study Intervention

On the day of enrolment, participants will be assigned a unique randomization number in ascending numerical order at each study site. The randomization number encodes the participant's assignment to one of the two treatment groups of the study according to the randomization schedule. Once a randomization number has been assigned, it may not be reassigned.

Eligible participants will be allocated in a 1:1 ratio between TDM and Standard of care using a permuted block randomization procedure stratified by country (N=3), using random block sizes. Details of block size and allocation sequence generation will be kept in a separate document unavailable to those who enroll participants or assign treatment.

The computer-generated allocation sequence will be incorporated into the eCRF system and made available to site personnel. The allocation will not be available until the participant has signed the informed consent form and deemed eligible to participate in the study. That is, study personnel will only know the treatment allocation of included participants, but not of future participants.

6.4. Masking

This is an open-label study; potential bias will be reduced by the following step:

Blinded assessment of part of the primary outcome (joint count).

6.5. Study Intervention Compliance

Compliance with study intervention will be assessed at each visit including the digital visits.

- At inclusion, the participant will be instructed to keep a drug-diary, either on a paper-form provided by study personnel or optionally electronically in their own calendar or with the RheumaBuddy® app.
- At each visit (every two months), the participant will fill in the dates of the drug injections since the last visit in a calendar and fill out a questionnaire assessing compliance in into the eCRF. See Appendix 17 for wording of the questions. The questionnaire will be provided in the primary language of each country.

.

- Before adjusting the dosage according to the trial protocol, study personnel will call the participant and ask if they have taken the drug as prescribed the last four weeks. Deviations from the prescribed dosage regimen will be recorded in the eCRF, including the reason for deviation.

6.6. Other Dose and Schedule Modification

Modification of dosing regimens related to abnormal blood values and/or AEs should be performed based on the SmPC, clinical judgment and if necessary, contact with the study lead. If a TNFi dose is delayed due to non-RA related factors such as infections, surgery, vacation, subject non-compliance etc. this should be recorded and the reason given in the eCRF.

6.7. Continued Access to Study Intervention after the End of the Study

Participants will return to standard of care.

6.8. Treatment of Overdose

Not applicable.

6.9. Prior and Concomitant Therapy

6.9.1. Prior Therapy

All prior use of disease-modifying drugs/immunosuppressive therapy (excluding corticosteroids and NSAIDs) will be recorded in the eCRF with specification of both the time (month and year) of treatment start and time of termination (month and year) of biological drugs. If known, the reason for termination of prior biological therapy (i.e., lack of efficacy, loss of efficacy, side effects, development of ADAb, or other) will be recorded.

6.9.2. Concomitant Medication

All concomitant medications for any conditions and changes in concomitant medications and dosages for RA will be documented in the eCRF. Participants should continue with the same concomitant medication as prior to randomization. Any co-medication with a csDMARD should be kept stable throughout the study, but tapering and termination due to AE is permitted. Flares leading to major changes in the concomitant treatment as defined in Section 3 will lead to classification as a disease flare (primary endpoint of the study). Short courses of corticosteroids for acute medical conditions other than RA (for example asthma and allergy) are permitted and will be recorded. Participants can receive intra-articular injections in one swollen joint at each visit; more than one injection at one visit will be regarded as a major change in medication and lead to classification as flare (primary endpoint). NSAIDs are permitted for use at any time during the study. NSAID doses may be increased or tapered according to clinical response. The choice and dosage of NSAIDs will be at the discretion of the treating rheumatologist and should be recorded in the eCRF. Participants who experience a flare can receive concomitant medication or switch therapy as needed.

The following concomitant medications are prohibited:

.

- bDMARD such as other TNFi, interleukin inhibitors, B- or T cell inhibitors
- tsDMARD such as Janus Kinase Inhibitors
- Other immunosuppressants than corticosteroids including but not limited to calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for the primary outcome.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, if in accordance with local requirements and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must try to regain contact with the participant (where possible, telephone calls (maximum 2)), and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record.

.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

8.1. Administrative General, Biobank and Baseline Procedures

A screening evaluation should be performed prior to or at the same day as the inclusion visit.

The following procedures have to be completed before inclusion:

- Signing the informed consent form
- A formal assessment of the eligibility criteria

8.1.1. Baseline Procedures

Informed written consent must have been given voluntarily by each participant before any study specific procedures are initiated. In addition to the assessments and procedures performed at a regular visit described in the SoA (Section 1.3), the following assessments will be performed at baseline:

Study nurse/investigator assessments:

- Demographics (sex, birth date, and ethnic origin)
- Tobacco use
- Medical history (diagnosis, disease related previous therapy including both biological and non- biological disease modifying treatment with time for initiation and termination and reasons for discontinuation if known to the participant, duration of SC TNFi use, non-RA related medical and surgical history)
- Height and weight

8.1.2. Biobank Samples

Full blood samples (one 4 ml test tube) will be collected from all participants at the baseline visit and sent to the Department of Medical Biochemistry at Oslo University Hospital Radiumhospitalet, Norway, for biobanking. At the end of the inclusion period the samples will be transferred to a study specific biobank at Diakonhjemmet Hospital. Optionally, samples can be stored locally at the participating centers.

Participants at Diakonhjemmet Hospital only, will additionally donate samples (full blood, serum and plasma) to a study specific biobank at all onsite visits (baseline, 4, 8, 12, 18 months, early discontinuation visits and extra visits). The estimated total volume for biobank samples at each visit for these patients is 22 ml. All samples will be stored in suitable tubes and boxes designed to endure long-term storage and in a certified biobank below -70 °C. The samples will be stored until 31.12.2037 and remaining samples will thereafter be destroyed. The samples from the biobank will be used for research purposes only. Some analyses might take place in other countries than Norway including but not limited to the Netherlands, Sweden, Austria, Great Britain, Iceland, and the United States of America. These samples will be handled pseudonymised, the sample will be marked with the study ID. The laboratory receiving the samples will only have access to the study ID. The patient identification list will be stored locally at each study center.
Genetic assessments are described in Section 8.6.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. Assessment of Disease Activity

Patient Global Assessment of Disease Activity (PGA) (48)

PGA is measured on a 100 mm VAS according to the question: “Considering all the ways your arthritis affects you, rate how well you are doing on the following scale”, with 0 = best and 100 = worst (48-50). See Appendix 5. Approved versions in the primary language of each country will be used.

Evaluator Global Assessment of Disease Activity (EGA)

EGA is measured on a NRS according to the question “Please rate the patient’s overall (global) disease activity”, with 0 = best and 10 = worst (49). See Appendix 6. Approved versions in the primary language of each country will be used.

Inflammation assessment by biochemical parameters

Inflammation is measured by CRP and ESR will be recorded at all onsite visits. These tests will be analyzed at the local laboratory according to hospital procedures.

Disease Activity Score using 28 joints C-reactive protein (DAS28-CRP)

The DAS28-CRP composite score includes the 28 tender and swollen joint counts, CRP and a PGA (on a 0-100mm VAS). The DAS28-CRP is calculated as follows:

DAS28-CRP = 0.56*√ (tender joints 28) + 0.28*√ (swollen joints 28) + 0.36*ln(CRP (mg/L)+1) + 0.014*PGA + 0.96

High disease activity is defined as a DAS28-CRP value > 5.1, moderate disease activity as DAS28-CRP > 3.2 – 5.1, low disease activity as a DAS28-CRP-value of 2.6 – 3.2, and remission as DAS28-CRP < 2.6 (50). See Appendix 7.

44 joint count

44 joint count are included in the original DAS and in addition to the joints included in DAS28 it includes the MTP joints and the sternoclavicular joints for a more comprehensive valuation of the participants' joints (51). See Appendix 8.

ACR/EULAR remission criteria

The ACR/EULAR remission criteria defines a patient in remission when either a) the patient is in Boolean 2.0 remission with each of the variables TJC, SJC and CRP having a value of ≤1 and PGA having a value ≤ 2 (PGA on a VAS scale 100mm/10, CRP in mg/dl) OR b) the SDAI score is ≤ 3.3 (52).

Simple disease activity index (SDAI) and Clinical disease activity index (CDAI)

The SDAI and CDAI have been developed to provide physicians and patients with simple and more comprehensible instruments for assessment of disease activity in RA. CDAI is the only composite index that does not incorporate an acute phase response and can therefore be used to conduct a disease activity evaluation essentially anytime and anywhere (49).
The formula for SDAI is: swollen joints 28 + tender joints 28 + (PGA(VAS 0-100)/10) + EGA(NRS 0-10) + (CRP (mg/dL)/10).
The formula for CDAI is: swollen joints 28 + tender joints 28 + (PGA (VAS 0-100)/10) + EGA (NRS 0-10).
See Appendix 9 and 10. Approved versions in the primary language of each country will be used.

Patient Reported Outcome Measures (PROMs)

All PROMS will be collected by the eCRF module ViedocMe. If the patients do not respond to the questionnaires, two reminders will be sent out. Approved versions of the questionnaires in the primary language of each country will be used.

Rheumatoid Arthritis Flare Questionnaire (RA-FQ)

The RA-FQ was developed by the Omeract group to identify and measure flares in patients with RA. It encompasses pain, physical impairment, fatigue, stiffness, and participation, and

.

the score is calculated as the sum of responses for the 5 items (maximum 50) (39, 53). See Appendix 11.

Rheumatoid Arthritis Impact of Disease (RAID) score

The RAID questionnaire was developed by EULAR as a patient-derived composite score. It includes seven domains with the following relative weights: pain (0.21), functional disability (0.16), fatigue (0.15), emotional well-being (0.12), sleep (0.12), coping (0.12) and physical well-being (0.12) each rated on an NRS (0-10). The rates of each domain are weighted and summed to form a score in the range of 0-10 (54). See Appendix 12.

Modified Heath Assessment Questionnaire (MHAQ)

The Stanford Health Assessment Questionnaire (HAQ) was introduced in the 1980s and is now widely used in evaluation of physical function in patients with inflammatory joint diseases (IJD). A shortened version of the HAQ, the MHAQ reduced the number of items from 20 in the original HAQ to eight, and improved the feasibility in clinical practice. Each item is scored on a categorical 0-3 scale and the sum score is divided by 8 to form the MHAQ score 0.0 to 3.0 (55). See Appendix 13.

8.2.2. Definition of Flare

A flare is defined as a combination of an increase in DAS28-CRP of 1.2 units, or 0.6 if DAS28-CRP ≥ 3.2, AND at least 2 swollen joints on examination of 44 joints (39, 40, 53).

If a participant does not fulfil the formal definition, but experiences a clinically significant worsening, according to both the investigator and participant, that leads to a major change* in treatment, this should be considered as a flare but be recorded separately in the eCRF.

*A major change in treatment includes:

- Switching to another bDMARD or a tsDMARD
- Adding a csDMARD
- Increasing the dose of a concomitant csDMARD
- Adding or increasing systemic glucocorticoids (per orally, intravenous or intramuscular)
- Receiving more than one intra-articular glucocorticoid injection at one visit
- Shortening the interval of the SC TNFi for clinical reasons (Standard of care group)

8.3. Safety Assessment

Safety will be monitored by laboratory tests (Section 8.3.1) and the collection of AEs at every onsite visit. Significant findings that are present prior to the signing of informed consent must be included in the relevant medical history/current medical condition page of the eCRF. For details on AE collection and reporting, see Appendix 3.

Any AE encountered during the clinical study will be reported in the eCRF (see Appendix 3 for definitions). AE will be followed up as clinically indicated until they have returned to

baseline status or are stabilized. Events which are definitely due to disease progression will not be reported as an AE/SAE.

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.1. Routine Laboratory Tests

The following laboratory tests will be recorded at all visits. These tests will be analyzed at the local laboratory according to hospital procedures. If any requested testes are not available locally, samples will be referred to other laboratories according to local practice.

- Hematology: Hemoglobin, white blood cells with differentials and platelet count
- Blood chemistry: ALT, creatinine, ESR, CRP

8.4. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AE and SAEs will be collected from the start to stop of study intervention.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator is made aware of the SAE, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the SmPC and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

.

8.4.5. Pregnancy

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.
- In case of pregnancy, the participant will exit the study.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and will be reported as such.

8.5. ADAb and Serum Drug Level Assessments

Serum samples will be drawn from all participants at all visits. The samples will be sent to the Department of Medical Biochemistry at Oslo University Hospital Radiumhospitalet, Norway, by regular mail or currier with the aim of reaching the laboratory within seven days after the sampling date. Serum TNFi levels and ADAb will be measured using validated automated fluorescence assays. These assays are currently used to assess samples for clinical practice from hospitals throughout Norway and have been used in prior clinical trials (32, 33, 56).

Serum drug levels of SC TNFi are measured using recombinant TNF on the solid phase. As a result, only active TNFi (with the ability to bind TNF) will be measured. The assay for antibodies to TNFi only detects neutralizing antibodies, i.e., antibodies that block the TNF-binding capacity of the TNFi. All assays are fully automated (including dilutions) on the AutoDELFIA platform (PerkinElmer).

8.6. Genetics

A 4 ml blood sample for DNA isolation will be collected from participants who have consented to participate in the study. Analyses using DNA/RNA will assess possible associations between genes and gene expressions and response/immunogenicity. Analyses will only be conducted at a group level and participants will not receive individual feedback/genetic counseling.

Genetic analyses might take place in other countries than Norway including but not limited to the Netherlands, Sweden, Austria, Great Britain, Iceland, and the United States of America. These samples will be handled pseudonymised, the sample will be marked with a study ID. The laboratory receiving the samples will only have access to the study ID. The patient identification list will be stored locally at each site.

Biobank samples will be stored until 31.12.2037 and remaining samples will thereafter be destroyed.

See Appendix 4 for more information regarding genetic research.

.

8.7. Biomarkers

Biomarker analyses as appropriate to investigate exploratory objectives may be performed.

8.8. Health Economics

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will

- Include the reasons and duration of hospitalizations and emergency room visits and
- Exclude procedures, tests, and encounters mandated by the protocol.

The sponsor may use the collected data to conduct economic analyses.

All participants will be asked to fill in the three standard instruments (questionnaires) to capture work productivity and health related quality of life: SF-36, EQ-5D and WPAI:RA. All questionnaires will be collected by the eCRF module ViedocMe. If the patients do not respond to the questionnaires, two reminders will be sent out. Approved versions of the questionnaires in the primary language of each country will be used.

36-Item Short-form health survey (SF-36)

The SF-36 is a multi-purpose, short-form health survey with 36 questions (57). It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index (SF-6D) (58). It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments (57). See Appendix 14.

European Quality of Life 5 Dimensions (EQ-5D)

The EQ-5D is a utility instrument for measurement of health-related quality of life. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status (59, 60). See Appendix 15.

Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA)

The Work Productivity and Activity Impairment (WPAI) questionnaire is a tool that assesses impairments in both work and daily activities. It consists of six items that determine employment status and measure absenteeism caused by health issues, presenteeism, and overall health-related impairment in both paid work and regular activities over the preceding 7 days. The questionnaire yields four outcomes: i) the percentage of work time missed due to health; ii) the percentage of impairment experienced while working due to health in the past 7 days; iii) the percentage of overall work impairment; iv) activity impairment resulting from health issues. Participants will be asked to answer the Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis V2.0 (WPAI:RA) (61, 62). See Appendix 16.

.

9. Statistical Considerations

The statistical analyses are planned to be carried out when:

- The planned number of participants have been included
- Each included participant has completed their end-of-study visit, withdrawn, or been withdrawn according to protocol procedures
- All data from the study period have been entered, verified, and validated according to the data management plan

Prior to the statistical analysis, the data will be locked from further entering or editing. A SAP will be finalized prior to any analysis of treatment effects. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section gives a summary of the planned statistical analyses of the most important endpoints, including the primary endpoint and some key secondary endpoints. The SAP will be finalized, signed, and dated prior to database lock. Any deviation from the original statistical plan will be described and justified in the CSR.

9.1. Statistical Hypotheses

The primary objective is to study whether TDM is superior to standard of care in sustaining disease control during the 18-month follow-up period. To this end, we define the following hypotheses:

- Null hypothesis: The probability of sustained disease control over 18 months in the TDM group equals that in the control group
- Alternative hypothesis: The probability of sustained disease control over 18 months in the TDM group differs from that in the control group.

The null hypothesis will be tested against the alternative hypothesis. Superiority of TDM over standard of care will be claimed if the primary null hypothesis is rejected by a two-sided test using a significance level of 5% and the treatment difference is in favor of the TDM group.

9.1.1. Multiplicity Adjustment

Only a single hypothesis test will be carried out, and only the p value associated with this comparison will be reported. No other hypothesis test will be carried out or p values reported, hence adjustment for multiplicity is not needed. All other comparisons will be descriptive and, where appropriate, accompanied by confidence intervals (unadjusted for multiplicity).

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

All efficacy and safety analyses will be carried out in the full analysis set, defined as all randomized participants who have received at least one SC TNFi injection following randomization.

.

For both efficacy and safety analyses, participants will be included in the analyses according to their randomization group.

9.3. Statistical Analyses

9.3.1. General Considerations

Randomization

Allocation Sequence Generation

Eligible patients will be allocated in a 1:1 ratio between TDM and standard of care using a computer randomization procedure stratified by country. Permuted block randomization, with random block sizes of 2, 4, and 6, will be used within each stratum. Details of the allocation sequence generation will be kept in a document unavailable to those who enroll patients or assign treatment.

Allocation Procedure to Randomize Patients

The computer-generated allocation sequence will be imported into the eCRF system and made available as patients are enrolled. A particular allocation will not be unveiled until the patient has been deemed eligible to participate and signed the informed consent form.

9.3.2. Primary Endpoint Analysis

9.3.2.1. Primary Analysis

The primary endpoint is sustained disease control during follow-up. This is a binary variable, assuming the value 1 for a participant free of flare during follow-up and the value 0 for a participant experiencing one or more flares.

The hypothesis test described in Section 9.1 will be carried using logistic regression. Beyond treatment group, the analysis will be adjusted for the stratification factor used in the randomization (country). The outcome of the hypothesis test will be decided upon by the *p* value associated with the treatment group variable. Superiority of TDM over standard of care is claimed if the primary null hypothesis is rejected by a two-sided using significance level of 5% and the treatment difference is in favor of the TDM group.

Missing values of the primary endpoint will be handled using multiple imputation, accounting for both partial missingness on visits as well as visits missed completely.

Adjusted estimates of the probability of sustained disease control within randomization group and their between-group difference will be formed using average risk and risk difference estimators and presented with associated 95% confidence intervals.

9.3.2.2. Sensitivity Analysis

Sensitivity analyses will include additional approaches to dealing with missing values of the primary endpoint, possibly including, but not limited to, complete-case analysis, last-observation carried forward imputation, and worst-case imputation (i.e., imputing missing values as flare). Additional analyses may include adjustment for unbalanced baseline covariates such as age, sex, and co-medication.

.

9.3.2.3. Supplementary Analysis

The primary outcome will also be analyzed using Cox proportional-hazards regression. The time of first flare will serve as the event time, which for participants that are free of flare during follow-up will be censored at the last visit date. For this analysis, an assumption of independent censoring will be used, and adjustment for stratification factors used in the randomization will be made.

9.3.2.4. Subgroup Analyses

Subgroup analyses of the primary endpoint according to each TNFi type (if more than one TNFi type is included) will be carried out.

9.3.3. Secondary Endpoint Analyses

The between-group comparisons for secondary variables will be carried out in a manner similar to the primary endpoint where applicable and analyses will be performed based on the following methods (but not limited to):

- Continuous secondary variables will be analyzed by linear regression, using mixed effects for repeated measures, or appropriate non-parametric alternatives
- Binary response variables will be analyzed using logistic regression (possibly adjusting for within-subject dependencies by mixed model approaches)
- Time-to-event variables will be analyzed using the Kaplan-Meier method, Cox regression analysis, and/or appropriate parametric models such as the Weibull model.

9.4. Interim Analysis

No interim analysis is planned.

9.5. Sample Size Determination

A minimum of 350 participants will be randomized.

The sample size calculation is based on the primary outcome, sustained disease control throughout 18 months of follow-up, and an assumption that TDM will increase the probability of sustained control by 12.5 percentage points: from an assumed 72.5% for patients treated according to Standard of care to 85% for those whose treatment includes TDM. Requiring 80% power to reject the primary null hypothesis, this implies that at least 350 participants are needed, assuming a 10-15% drop-out rate. However, if the inclusion rate is sufficiently high, the trial steering committee could decide to increase the sample size to a maximum of 450 patients to achieve a higher power of 90% (Table 2). Sample sizes corresponding different combinations of power and effects of TDM (assuming the same 72.5% sustained remission rate in the Standard of care group, but without allowance for drop-out) are given in Table 2.

Table 2. Power Calculations

Power	Difference in sustained disease control 10%	Difference in sustained disease control 12.5%	Difference in sustained disease control 15%

.

80%	540	330	216
90%	724	440	290

The assumed rates are based on data from two prior studies, the NOR-DRUM B and ARCTIC Rewind trials (33, 38, 63). Regarding the effect of TDM versus standard of care, the first of these estimated that the hazard rate of disease flare in patients on maintenance infliximab treatment without TDM was about twice that of those whose treatment included TDM. Regarding the flare rate associated with standard care, in the NOR-DRUM B trial 22 of 40 (55%) RA patients in the standard of care group did not experience a disease flare during 12 months of follow-up, whereas in the ARCTIC Rewind trial, which also had a 12-month follow-up period, the numbers were 41 of 45 patients (91%). The disease flare definition used in the current study is similar to the one employed in the ARCTIC Rewind trial, while the one in NOR-DRUM B was more liberal. However, the present inclusion requirement of a remission duration of at least 3 months is less stringent than in the ARCTIC Rewind trial (12 months), but more so than in the NOR-DRUM B trial (none). Based on this, it seems reasonable to expect that approximately 80% of those in the standard of care group will be free of disease flare during the first 12 months of follow-up.

Assuming constant hazards (i.e., exponential survival times), this implies a daily hazard rate of flare around 0.0006 in the Standard of care group (since exp(-0.0006*365) = 0.80) and, assuming a similar hazard ratio as in the NOR-DRUM B trial, 3.0e-4 in the TDM group. With these assumptions, it follows that 72.5% in the Standard of care group are expected to be flare-free during the 18 months of follow-up compared to an expected 85% in the TDM group(*).

(*) Since, = exp(-0.0006*365*1.5) = 72.5% and exp(-0.0003*365*1.5)= 85%.

.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, SmPC, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the sponsor or investigator as applicable and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, if relevant.
- A copy of the ICF(s) must be provided to the participant.
- The informed consent will be obtained by study investigators (physicians or study nurses), not actively responsible for treatment of the patient at the time of the consent.

10.1.4. Recruitment strategy

Potential study participants with a documented diagnosis of RA on therapy with a SC TNFi (adalimumab) will be identified from the patient lists at the rheumatology outpatient clinic at each participating site either by health personnel during a clinical visit or by patient administrative tools and the electronic medical record system between planned visits. Personnel with legal access to the patient records and patient administrative tools can identify potentially eligible subjects. Names of potential participants will be forwarded to the study team (investigators and study-nurses) to be contacted for screening. In addition, participants may be identified from referral letters from other clinics or if a possible participant contact the clinic directly.

Dedicated study personnel will be used for recruiting patients. Potential participants identified as described above will receive information about the trial from study personnel not actively responsible for treatment of the patient at the time. The information will be given verbally and the informed consent form will be handed out for the patient to read. Potential participants will be offered sufficient time to meet a decision and if needed offered an additional phone consultation to discuss any further question they might have after reading the informed consent form and processed all the information given regarding the trial.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be

.

explained to the participant who will be required to give consent for their data to be used as described in the informed consent

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- In case personal data needs to be sent for analysis outside the European Union (EU) or the European Economic Area (EEA), appropriate measures to guarantee the protection of the data will be taken. Such transfer will be in accordance with the informed consent form and will follow the measures of the General Data Protection Regulation (EU) 2016/679 (GDPR). Measures will include setting up standard contractual clauses for data transfers between EU/EEA and non-EU/EEA countries.
- In case the data security has been breached for any of the participants, the sponsor must promptly but no later than 24 hours after becoming aware of the breach be notified. Prompt action to investigate the cause of the data breach must be made, and assistance to the sponsor in complying with Articles 32 to 36 of the GDPR.
- Personal data will be stored for 25 years after end of study to comply with the requirements in Regulation (EU) No 536/2014 (Clinical Trials Regulation)

10.1.6. Committees Structure

The administrative structure of the study includes the steering committee and the study group (local advisory board, SQUEEZE team, user representatives and all local PIs) as listed in Appendix 18. The steering committee and study group will meet regularly as needed. The Medical Monitor will oversee study safety data and evaluate AEs and SAEs, as described in Appendix 3.

10.1.7. Dissemination of Clinical Study Data

The clinical trial results will be uploaded in CTIS within 1 year after study end.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded in an eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

.

- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data list.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

.

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.11. Publication Policy

- Upon study completion and finalization of the study report, the results of this study will be submitted for publication and posted in a publicly assessable database of clinical study results, CTIS.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors. Authorship will be based on scientific contribution and enrolment and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.12. Funding

This trial is performed under the SQUEEZE project. This project is fully funded from the European Union's Horizon Europe research and innovation program under grant agreement No 101095052. Additional funding may be provided by the sponsor or co-sponsor.

.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in SoA (Section 1.3) and Table 3 will be performed by the local laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 3: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	• Platelet count • Hemoglobin • White blood cell (WBC) count with differential: – Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
Clinical chemistry	• C-reactive protein (CRP) • Erythrocyte sedimentation rate (ESR) • Creatinine • Alanine aminotransferase (ALT)

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

.

10.3.3. Definition of suspected unexpected serious adverse reaction (SUSAR)

If an event is not an SAE per definition above, then it cannot be a SUSAR

SUSAR Definition

Adverse Reaction: all unwanted and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction: Unexpected Adverse Reaction that:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

10.3.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

.

- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

.

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting is listed in Appendix 18.

10.3.6. Reporting of SUSAR

The investigator will report SAE to the medical monitor. The medical monitor will evaluate if the SAE also is a SUSAR, if so, the medical monitor will report the SUSAR to the Competent Authority through Eudravigilance (EV).

Sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible and in no case later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

Other SUSARs will be reported no later than 15 days after the incident.

10.3.7. Annual safety reporting

The sponsor is responsible for writing and submitting the annual safety report (ASR) for the clinical trial according to local regulations.

.

10.4. Appendix 4: Genetics

Analysis of DNA

- Genetic variation may impact a participant's response to study intervention (i.e.the risk of disease flare) and susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism (including ADAb formation), and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA analyses will only be done to answer trial specific explorative objectives/endpoints as described in section 3 related research related to study intervention or immunogenicity related to the IMP. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors related to study specific endpoints i.e. response to study intervention or immunogenicity. .
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention or study interventions of this class or indication continues but no longer than 10 years or other period as per local requirements.

10.5. Appendix 5: Patient Global Assessment of Disease Activity (PGA)

Provided in the “Not for publication” Protocol only

10.6. Appendix 6: Evaluator Global Assessment of Disease Activity (EGA)

Provided in the “Not for publication” Protocol only

10.7. Appendix 7: Disease Activity Score using 28 joints – C-reactive protein (DAS28-CRP)

Provided in the “Not for publication” Protocol only

10.8. Appendix 8: 44 joint count

Provided in the “Not for publication” Protocol only

10.9. Appendix 9: Simple Disease Activity Index (SDAI)

Provided in the “Not for publication” Protocol only

10.10. Appendix 10: Clinical Disease Activity Index (CDAI)

Provided in the “Not for publication” Protocol only

10.11. Appendix 11: Rheumatoid Arthritis Flare Questionnaire (RA-FQ)

Provided in the “Not for publication” Protocol only

10.12. Appendix 12: Rheumatoid Arthritis Impact of Disease (RAID)

Provided in the “Not for publication” Protocol only

10.13. Appendix 13: Modified Heath Assessment Questionnaire (MHAQ)

Provided in the “Not for publication” Protocol only

10.14. Appendix 14: The 36-Item Short-form Health Survey (SF-36)

Provided in the “Not for publication” Protocol only

10.15. Appendix 15: European Quality of Life 5 Dimensions (EQ-5D)

Provided in the “Not for publication” Protocol only

10.16. Appendix 16: Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA)

Provided in the “Not for publication” Protocol only

10.17. Appendix 17: Compliance Assessment

Provided in the “Not for publication” Protocol only

10.18. Appendix 18: Contact Details

Provided in the “Not for publication” Protocol only

STEERING COMMITTEE

Coordinating Investigator

Squeeze WP6 Lead and Sponsor Representative

National Coordinating Investigator

Laboratory Coordinating Investigator

Trial Statistician

Clinical Trial Methodologist

Medical Lead

Laboratory Lead

Study Coordinator

LOCAL ADVISORY BOARD

SQUEEZE LEAD

USER REPRESENTATIVES

STUDY GROUP
Steering committee
Local advisory board
SQUEEZE lead
PIs at participating study centers
User representatives

PARTICIPATING STUDY CENTERS

MEDICAL MONITOR

11. References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. The Lancet. 2016;388(10055):2023-38.

2. Urquhart L. Top companies and drugs by sales in 2022. Nat Rev Drug Discov. 2023;22(4):260.

3. Smolen JS, Landewe RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3-18.

4. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, et al. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. Int J Mol Sci. 2021;22(5).

5. Mehta P, Manson JJ. What Is the Clinical Relevance of TNF Inhibitor Immunogenicity in the Management of Patients With Rheumatoid Arthritis? Front Immunol. 2020;11:589.

6. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. Jama. 2011;305(14):1460-8.

7. Jyssum I, Gehin JE, Sexton J, Kristianslund EK, Hu Y, Warren DJ, et al. Adalimumab serum levels and anti-drug antibodies: associations to treatment response and drug survival in inflammatory joint diseases. Rheumatology (Oxford). 2023.

8. Gehin JE, Warren DJ, Syversen SW, Lie E, Sexton J, Loli L, et al. Serum golimumab concentration and anti-drug antibodies are associated with treatment response and drug survival in patients with inflammatory joint diseases: data from the NOR-DMARD study. Scand J Rheumatol. 2021;50(6):445-54.

9. Gehin JE, Goll GL, Warren DJ, Syversen SW, Sexton J, Strand EK, et al. Associations between certolizumab pegol serum levels, anti-drug antibodies and treatment response in patients with inflammatory joint diseases: data from the NOR-DMARD study. Arthritis Res Ther. 2019;21(1):256.

10. Gehin JE, Goll GL, Brun MK, Jani M, Bolstad N, Syversen SW. Assessing Immunogenicity of Biologic Drugs in Inflammatory Joint Diseases: Progress Towards Personalized Medicine. BioDrugs. 2022;36(6):731-48.

11. Syversen SW, Gehin JE, Goll GL, Bolstad N, Haavardsholm EA, Lillegraven S. Therapeutic Drug Monitoring: A Tool to Optimize Treatment of Inflammatory Joint Diseases. Arthritis & Rheumatology. 2023;n/a(n/a).

12. Bonafede M, Johnson BH, Princic N, Shah N, Harrison DJ. Cost per patient-year in response using a claims-based algorithm for the 2 years following biologic initiation in patients with rheumatoid arthritis. Journal of medical economics. 2015;18(5):376-89.

13. Brun MK, Bjørlykke KH, Viken MK, Stenvik GE, Klaasen RA, Gehin JE, et al. HLA-DQ2 is associated with anti-drug antibody formation to infliximab in patients with immune-mediated inflammatory diseases. J Intern Med. 2023;293(5):648-55.

14. Gravallese EM, Firestein GS. Rheumatoid Arthritis - Common Origins, Divergent Mechanisms. The New England journal of medicine. 2023;388(6):529-42.

15. Lillegraven S, van der Heijde D, Uhlig T, Kvien TK, Haavardsholm EA. What is the clinical relevance of erosions and joint space narrowing in RA? Nat Rev Rheumatol. 2012;8(2):117-20.

16. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the rheumatic diseases. 2020;79(6):685-99.

.

17. Movahedi M, Hepworth E, Mirza R, Cesta A, Larche M, Bombardier C. Discontinuation of biologic therapy due to lack/loss of response and adverse events is similar between TNFi and non-TNFi class: Results from a real-world rheumatoid arthritis cohort. Semin Arthritis Rheum. 2020;50(5):915-22.

18. Arora A, Mahajan A, Spurden D, Boyd H, Porter D. Long-Term Drug Survival of TNF Inhibitor Therapy in RA Patients: A Systematic Review of European National Drug Registers. Int J Rheumatol. 2013;2013:764518.

19. Markusse IM, Dirven L, Gerards AH, van Groenendael JH, Ronday HK, Kerstens PJ, et al. Disease flares in rheumatoid arthritis are associated with joint damage progression and disability: 10-year results from the BeSt study. Arthritis Res Ther. 2015;17(1):232.

20. Flurey CA, Morris M, Richards P, Hughes R, Hewlett S. It's like a juggling act: rheumatoid arthritis patient perspectives on daily life and flare while on current treatment regimes. Rheumatology (Oxford). 2014;53(4):696-703.

21. Charlotte LMK, Astrid van T, Johanna Elin G, Borja H-B, Guillaume Le M, Alejandro B, et al. EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases. Annals of the Rheumatic Diseases. 2023;82(1):65.

22. Ducourau E, Ternant D, Lequerré T, Fuzibet P, Le Loët X, Watier H, et al. Towards an individualised target concentration of adalimumab in rheumatoid arthritis. Ann Rheum Dis. 2014;73(7):1428-9.

23. Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, Rispens T, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. Ann Rheum Dis. 2015;74(3):513-8.

24. Krieckaert C, Hernández-Breijo B, Gehin JE, le Mélédo G, Balsa A, Jani M, et al. Therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal disease: a systematic literature review informing EULAR points to consider. RMD Open. 2022;8(2).

25. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis. 2013;72(12):1947-55.

26. Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. JAMA Intern Med. 2013;173(15):1416-28.

27. Brun MK, Goll GL, Jørgensen KK, Sexton J, Gehin JE, Sandanger Ø, et al. Risk factors for anti-drug antibody formation to infliximab: secondary analyses of a randomised controlled trial. Journal of internal medicine. 2022.

28. Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis. 2013;72(2):165-78.

29. Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford, England). 2014;53(2):213-22.

30. Solitano V, Facciorusso A, McGovern DPB, Nguyen T, Colman RJ, Zou L, et al. HLA-DQA1*05 Genotype and Immunogenicity to Tumor Necrosis Factor-α Antagonists: A Systematic Review and Meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2023.

31. Krieckaert CL, van Tubergen A, Gehin JE, Hernández-Breijo B, Le Mélédo G, Balsa A, et al. EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2022.

.

32. Syversen SW, Goll GL, Jørgensen KK, Sandanger Ø, Sexton J, Olsen IC, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Infliximab Induction on Disease Remission in Patients With Chronic Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. Jama. 2021;325(17):1744-54.

33. Syversen SW, Jørgensen KK, Goll GL, Brun MK, Sandanger Ø, Bjørlykke KH, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. Jama. 2021;326(23):2375-84.

34. Brun MK, Bjørlykke KH, Gehin JE, Warren DJ, Klaasen RA, Sexton J, et al. OP0060 CLINICAL CONSEQUENCES OF INFLIXIMAB IMMUNOGENICITY AND THE IMPACT OF THERAPEUTIC DRUG MONITORING: SECONDARY ANALYSES OF A RANDOMISED CLINICAL TRIAL. Annals of the Rheumatic Diseases. 2023;82(Suppl 1):40-.

35. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016;7(1):e135.

36. Berg DR, Colombel JF, Ungaro R. The Role of Early Biologic Therapy in Inflammatory Bowel Disease. Inflammatory bowel diseases. 2019;25(12):1896-905.

37. Jorgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet (London, England). 2017;389(10086):2304-16.

38. Lillegraven S, Paulshus Sundlisæter N, Aga AB, Sexton J, Olsen IC, Fremstad H, et al. Effect of Half-Dose vs Stable-Dose Conventional Synthetic Disease-Modifying Antirheumatic Drugs on Disease Flares in Patients With Rheumatoid Arthritis in Remission: The ARCTIC REWIND Randomized Clinical Trial. Jama. 2021;325(17):1755-64.

39. van der Maas A, Lie E, Christensen R, Choy E, de Man YA, van Riel P, et al. Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. Annals of the rheumatic diseases. 2013;72(11):1800-5.

40. Siri L, Nina Paulshus S, Anna-Birgitte A, Joseph S, Inge Christoffer O, Åse Stavland L, et al. Effect of tapered versus stable treatment with tumour necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: a randomised, open label, non-inferiority trial. Annals of the Rheumatic Diseases. 2023;82(11):1394.

41. Hum RM, Ho P, Nair N, Jani M, Morgan AW, Isaacs JD, et al. Non-trough adalimumab and certolizumab drug levels associated with a therapeutic EULAR response in adherent patients with rheumatoid arthritis. Rheumatology (Oxford, England). 2023;62(6):2090-7.

42. Goss SL, Klein CE, Jin Z, Locke CS, Rodila RC, Kupper H, et al. Methotrexate Dose in Patients With Early Rheumatoid Arthritis Impacts Methotrexate Polyglutamate Pharmacokinetics, Adalimumab Pharmacokinetics, and Efficacy: Pharmacokinetic and Exposure-response Analysis of the CONCERTO Trial. Clin Ther. 2018;40(2):309-19.

43. Bouman C, van Herwaarden N, van den Hoogen F, van der Maas A, van den Bemt B, den Broeder AA. Prediction of successful dose reduction or discontinuation of adalimumab, etanercept, or infliximab in rheumatoid arthritis patients using serum drug levels and antidrug antibody measurement. Expert Opin Drug Metab Toxicol. 2017;13(6):597-604.

44. Chen DY, Chen YM, Hsieh TY, Hung WT, Hsieh CW, Chen HH, et al. Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up. Rheumatology (Oxford). 2016;55(1):143-8.

45. l'Ami MJ, Krieckaert CL, Nurmohamed MT, van Vollenhoven RF, Rispens T, Boers M, et al. Successful reduction of overexposure in patients with rheumatoid arthritis with high serum adalimumab concentrations: an open-label, non-inferiority, randomised clinical trial. Ann Rheum Dis. 2018;77(4):484-7.

.

46. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Annals of the rheumatic diseases. 2007;66(7):921-6.

47. Plasencia C, Wolbink G, Krieckaert CL, Kneepkens EL, Turk S, Jurado T, et al. Comparing a tapering strategy to the standard dosing regimen of TNF inhibitors in rheumatoid arthritis patients with low disease activity. Clin Exp Rheumatol. 2016;34(4):655-62.

48. Strand V, Boers M, Idzerda L, Kirwan JR, Kvien TK, Tugwell PS, et al. It's good to feel better but it's better to feel good and even better to feel good as soon as possible for as long as possible. Response criteria and the importance of change at OMERACT 10. J Rheumatol. 2011;38(8):1720-7.

49. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005;23(5 Suppl 39):S100-8.

50. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis and rheumatism. 1995;38(1):44-8.

51. van Riel PL. The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). Clin Exp Rheumatol. 2014;32(5 Suppl 85):S-65-74.

52. Studenic P, Aletaha D, de Wit M, Stamm TA, Alasti F, Lacaille D, et al. American College of Rheumatology/EULAR Remission Criteria for Rheumatoid Arthritis: 2022 Revision. Arthritis Rheumatol. 2023;75(1):15-22.

53. Susan JB, Skye PB, Vivian PB, Ernest HC, Rieke A, Robin C, et al. Content and Construct Validity, Reliability, and Responsiveness of the Rheumatoid Arthritis Flare Questionnaire: OMERACT 2016 Workshop Report. The Journal of Rheumatology. 2017;44(10):1536.

54. Gossec L, Dougados M, Rincheval N, Balanescu A, Boumpas DT, Canadelo S, et al. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. Annals of the rheumatic diseases. 2009;68(11):1680-5.

55. Pincus T, Summey JA, Soraci SA, Jr., Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis and rheumatism. 1983;26(11):1346-53.

56. Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. The Lancet. 2017;389(10086):2304-16.

57. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

58. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Medical care. 2004;42(9):851-9.

59. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.

60. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2018;27(1):7-22.

61. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire--general health version in patients with rheumatoid arthritis. Arthritis Res Ther. 2010;12(5):R177.

62. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65.

.

63. Lillegraven S, Paulshus Sundlisæter N, Aga AB, Sexton J, Solomon DH, van der Heijde D, et al. Discontinuation of Conventional Synthetic Disease-Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis and Excellent Disease Control. Jama. 2023;329(12):1024-6.

.