Supplemental Online Content

Syversen SW, Goll GL, Jørgensen KK, 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

Protocol and Statistical Analysis Plan

This supplement contains the following items:
1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan (No updates have been made)

A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring

The NOR-DRUM study

NOR DRUM | The Norwegian drug monitoring study

Protocol Identification Number: DIA2016-1
Clinical trial registration number: NCT03074656
Regional committee for medical and health research ethics number: 2016/1231

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PROTOCOL VERSION NO. 1.3
DATE 09.12.2019

NOR DRUM

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Title: A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring

The NOR-DRUM study

Protocol ID no: DIA2016-1

I hereby declare that I will conduct the study in compliance with the protocol, the Declaration of Helsinki and applicable national regulations and laws.

Name	Title	Role	Signature	Date
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PROTOCOL SYNOPSIS

A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring **The NOR-DRUM study**	
Phase of development	Phase IV
Investigational treatment strategy	Patients are randomised 1:1 to either: 1. Administration of INX according to a treatment strategy based on therapeutic drug monitoring and assessments of ADAb (**intervention group**) 2. Administration of INX according to standard clinical care, without knowledge of drug levels or ADAb status (**control group**)
Study Centres	A national multicentre study
Study Period	Estimated date of first patient enrolled: March 1st 2017 Anticipated recruitment period: February 1st 2017 – December 31st 2019 Estimated date of last patient completed: NOR-DRUM A October 31st 2019, NOR-DRUM B January 31st 2021
Duration	NOR-DRUM A 38 weeks NOR-DRUM B 52 weeks
Main objective	To assess the effectiveness of tailoring infliximab treatment by therapeutic drug monitoring

NOR-DRUM A

Primary objective	To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in order to achieve disease control in patients with inflammatory immunological diseases starting infliximab therapy
Secondary objectives	• To compare effectiveness of a treatment strategy based on TDM to standard clinical care applying different generic and disease specific endpoints • To assess whether a treatment strategy based on TDM influences drug survival, occurrence of anti-drug antibodies serum drug levels and occurrence of adverse events • To assess cost-effectiveness of a treatment strategy based on TDM compared to standard clinical care

Endpoints	Primary endpoint: Proportion of patients in remission* at week 30 defined by disease specific composite scores **Definition of remission:* *- RA: A DAS 28 score of <2.6* *- PsA: A DAS 28 score of <2.6* *- SpA: An ASDAS score <1.3* *- UC: A Mayo score of ≤2 with no sub scores >1* *- CD: A HBI score of ≤4* *- Ps: A PASI score of ≤4* Secondary endpoints: *Generic:* • Time to sustained remission • Patient's and physician's global assessment of disease activity • Biochemical parameters of disease activity • Occurrence of anti-drug antibodies • Serum drug level • Occurrence of and reason for drug discontinuation • Safety endpoints (adverse events frequency) • Cost effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH) *Disease specific:* • Efficacy assessed by composite disease activity scores - RA: DAS28, CDAI, SDAI, RAID, MHAQ - PsA : DAS28, DAPSA, PsAID, MHAQ, DLQI - SpA: ASDAS, BASDAI,MHAQ - UC: Partial Mayo score, IBDQ - CD: HBI, IBDQ - Ps: PASI, DLQI
Study Design	A randomised, open, controlled, parallel-group, multicentre, phase IV, superiority, comparative pragmatic study. Patients will be randomised 1:1 to either infliximab with therapeutic drug monitoring by trough levels and assessments of anti-drug antibodies (ADAb) or infliximab according to standard clinical care without knowledge of trough levels and ADAb

Main Inclusion Criteria	1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis 2. Male or non-pregnant female 3. ≥18 and < 75 years of age at screening 4. A clinical indication to start INX 5. Subject not in remission according to diagnosis-specific disease activity scores (defined in 6.5.8) 6. Subject capable of understanding and signing an informed consent form * Patients with psoriatic arthritis with predominantly axial manifestations should be included and assessed as spondyloarthritis
Main exclusion criteria	1. Major co-morbidities, such as previous malignancies within the last 5 years, severe 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, laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult 2. A positive screening for TB and hepatitis 3. Inadequate birth control, 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 which makes adherence to the study protocol difficult 5. Prior use of infliximab within the last 6 months 6. For patients with UC and CD: Functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ.
Sample size	400 patients

NOR-DRUM B

Primary objective	To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in keeping disease control in patients with inflammatory immunological diseases on maintenance therapy with infliximab.
Secondary objectives	• To compare effectiveness of a treatment strategy based on TDM to standard clinical care applying different generic and disease specific endpoints • To assess whether a treatment strategy based on TDM influences drug survival, occurrence of anti-drug antibodies, serum drug levels and occurrence of adverse events • To assess cost-effectiveness of a treatment strategy based on TDM compared to standard clinical care
Endpoints	<u>Primary endpoint:</u> Sustained disease control throughout the study period without disease worsening* defined by disease specific composite scores **Definition of disease worsening:* *- RA: Increase in DAS28 of ≥1.2 and a minimum DAS28 score of 3.2* *- PsA: Increase in DAS28 of ≥1.2 and a minimum DAS28 score of 3.2* *- SpA: Increase in ASDAS-CRP of ≥1.1 and a minimum ASDAS of 2.1* *- UC: Increase in p Mayo score of ≥ 3 points and a minimum p Mayo score of 5* *- CD: Increase in HBI of ≥4 points and a minimum HBI score of 7 points* *- Ps: Increase in PASI of ≥3 points and a minimum PASI score of 5* *- Patient and investigator consensus on disease worsening* <u>Secondary endpoints:</u> *Generic:* • Time to disease worsening • Patient and physician global assessment of disease activity • Biochemical parameters of disease activity • Occurrence of anti-drug antibodies • Serum drug level • Occurrence of and reason for drug discontinuation • Safety endpoints (adverse events frequency) • Cost-effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH) *Disease specific:* • Efficacy assessed by composite disease activity scores - RA: DAS28, CDAI, SDAI, RAID, MHAQ - PsA : DAS28, DAPSA, PsAID, MHAQ, DLQI - SpA: ASDAS, BASDAI,MHAQ - UC: Partial Mayo score, IBDQ - CD: HBI, IBDQ - Ps: PASI, DLQI
Study Design	A randomised, open, controlled, parallel-group, multicentre, phase IV, superiority, comparative pragmatic study. Patients will be randomised 1:1 to either infliximab with therapeutic drug monitoring by trough levels and

	assessments of anti-drug antibodies (ADAb) or infliximab according to standard clinical care without knowledge of trough levels and ADAb
Main Inclusion Criteria	1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis 2. Male or non-pregnant female 3. ≥18 and < 75 years of age at screening 4. On maintenance therapy with infliximab for a minimum of 30 weeks and a maximum of 3 years 5. A clinical indication for further infliximab treatment 6. Subject capable of understanding and signing an informed consent form *Patients with psoriatic arthritis and predominantly axial manifestations should be included and assessed as spondyloartritis
Main exclusion criteria	1. Major co-morbidities, such as previous malignancies within the last 5 years, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases, demyelinating disease, significant chronic widespread pain syndrome, laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult 2. Inadequate birth control, pregnancy or subject considering becoming pregnant during the study period 3. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol difficult 4. For patients with UC and CD: Functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ.
Sample size	450

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ACR	American College of Rheumatology
ADAb	Anti-drug antibody(ies)
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AS	Ankylosing spondylitis
ASA	Aminosalicylate acetylsalicylic acid
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate transaminase
AU	Arbitrary units
AZA	Azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	Biological Disease-Modifying Anti-Rheumatic Drugs
bINX	Biosimilar infliximab
BME	Bone marrow edema
CD	Crohn's disease
CDAI	Clinical disease activity index
CIOMS	Council for International Organizations of Medical Sciences
COXIB	COX-2 selective inhibitor
CRF	Case Report Form (electronic/paper)
CRP	C-reactive protein
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CTCAE	Common Terminology Criteria for Adverse Events version
DAE	Discontinuation due to Adverse Event
DAS28	Disease Activity Score using 28 joints
DLQI	Dermatology Life Quality Index
DMARD	Disease-Modifying Anti-Rheumatic Drugs
DRG	Diagnosis related group
eCRF	electronic Case Report Form
EMA	European medicines agency
EPJ	Electronic patient journal
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GI	Gastrointestinal
HBI	Harvey-Bradshaw Index
HRQOL	Health related quality of life
IB	Investigator's Brochure
IBD	Inflammatory bowel diseases
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IJD	Inflammatory Joint Diseases
IL	Interleukin

IMP	Investigational Medicinal Product (includes active comparator and placebo)
IND	Investigational New Drug
INF	Interferon
INX	Innovator infliximab
ISF	Investigator Site Files
LIS	Norwegian drug procurement cooperation
MHAQ	Modified Health Assessment Questionnaire
MP	Mercaptopurine
MRI	Magnetic resonance imaging
NK	Natural killer
NorCRIN	Norwegian clinical research infrastructure network
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Hart Association
PASI	Psoriasis Area and Severity Index
PGA	Patient Global Assessment of Disease Activity
PhGA	Physician Global Assessment of Disease Activity
PMS	Partial Mayo Score
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PsAID	Psoriatic Arthritis Impact of Disease
PUVA	Photochemotherapy psoralen plus ultraviolet A phototherapy
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RAID	Rheumatoid Arthritis Impact of Disease
SAE	Serious Adverse Event
SD	Stable Disease
SDAI	Simplified disease activity index
sDMARD	Synthetic Disease-Modifying Anti-Rheumatic Drugs
SDV	Source data verification
SF-36	Short Form (36) Health Survey
SOP	Standard Operating Procedure
SpA	Spondyloarthritis
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TDM	Therapeutic drug monitoring
TMF	Trial master file
TNF	Tumor necrosis factor
TNFi	TNF inhibitor
UC	Ulcerative colitis
UVB	Ultraviolet B
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1 INTRODUCTION

1.1 Background

1.1.1 Drug and diseases of this study

Infliximab (INX) (Remicade®) was the first inhibitor of tumor necrosis factor (TNF) α registered and approved for clinical use. Efficacy and safety of INX have been demonstrated in patients with rheumatoid arthritis (RA), spondyloartritis (SpA), psoriatic arthritis (PsA), ulcerative colitis (UC), Crohn`s disease (CD) and psoriasis (Ps).(1-6) INX is a chimeric monoclonal antibody consisting of a human Fc-fragment and murine Fab-fragments. It binds TNFα with high affinity, forming a stable complex that blocks the association of TNFα with its receptor.(7) In 2013 the first biosimilar to infliximab, CT-P13, was approved by the EMA for all indications of INX based on data from two head-to-head clinical trials in RA and AS.(8, 9) The approval process of a biosimilar, a biologic medical product which is an almost identical copy of an original "innovator" product manufactured by a different company when the original product's patent expires, includes evaluation of similarity to the innovator product with regard to quality, pharmacokinetics, safety and efficacy . In Norway, CT-P13 has been preferred to innovator INX since 2014 due to the annual tender based system for prescription of biological drugs organised by the Norwegian Drug procurement cooperation (LIS).

INX is administrated as repeated intravenous infusions with a recommended starting dose of 3 mg/kg (RA) - 5 mg/kg (UC, CD, SpA, PsA and Ps). The standard regimen includes an induction phase (infusions at week 0, 2, 6) followed by maintenance therapy with infusions every 8. week. In patients with inadequate response, the dose can, according to the SPC, safely be increased either by increasing the given dose at each infusion to a maximum of 7.5 mg/kg or by shortening of the dosing interval to a minimum of 4 weeks.

The present study focus on the six diseases where infliximab has an indication in Norway; RA, SpA, PsA, UC, CD, Ps. RA is characterised by symmetric inflammation of the peripheral joints. In PsA and SpA inflammation affects both the peripheral joints and the axial skeleton, in particular the sacroiliac joints. Persistent inflammation of the joints and spine in patients with inflammatory joint diseases may subsequently lead to disabling deformations. Ps is an immune-mediated, inflammatory papulosquamous skin and nail disease. CD is a chronic, transmural inflammatory disorder which may involve any part of the gastrointestinal tract, whereas UC involves the colon only. Persistent bowel inflammation may lead to complications as strictures and fistula. These six inflammatory diseases included in the present study differ greatly in their clinical presentation, but share several common features as chronic, incurable and relapsing immune mediated inflammatory diseases with systemic symptoms and extra organ involvement. Similarities in the disease pathogenesis have been

further highlighted by the introduction of TNFi that has revolutionised the treatment of both RA, SpA, PsA, CD, UC and Ps and made remission a realistic treatment target. TNFi are considered second-line treatment after failure of conventional therapy in these autoimmune diseases, but may become first-line therapy if the current high costs are reduced.

The high burden of these immunological inflammatory diseases is related both to symptoms of active inflammation and to the subsequent development of organ damage. 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. The primary response rates to INX are high across all diseases, but 20-40% of patients do not respond to therapy.(1-6) Early identification of non- or partial responders in order to intensify or switch therapy is important to bring the patients into remission. Another major clinical problem is loss of treatment effect over time in about 50% of the patients on INX.(10, 11) Prevention of a disease flare with the possible consequence of irreversible organ damage and disability is an important clinical goal. To optimise efficacy clinicians often intensify the INX treatment by increasing the dose. Despite conflicting data regarding the effectiveness of such dose escalation and the considerable economic consequences, large cohort studies show that up to 50% of patients have had one or more dose escalations within the first year of treatment with infliximab.(12-15)

1.1.2 Anti-drug antibodies and serum drug levels

Recently it has become clear that a substantial proportion of treatment failures to INX are due to development of anti-drug antibodies (ADAb). All biological drugs, being large and complex allogenic proteins, are able to elicit a patient immune response against the drug, with production of ADAb. ADAb influences the pharmacokinetics of the drug either by direct binding to the antibody (neutralising ADAb) or by forming immune complexes with the drug resulting in increased clearance (non-neutralising ADAb). ADAb production has proved to be a significant clinical problem related to long term use of biological drugs. INX being a chimeric antibody has proven to be more immunogenic than the other humanised or human TNFi. The prevalence of ADAb in patients on INX is 10-60%.(16-18) The initial studies of the INX biosimilar CT-P13 indicate a similar immunogenicity profile to the innovator INX, and ADAb to INX is cross-reactive to CT-P13.(8,9,19) Low levels of ADAb might be transient, but high levels of ADAb influence the pharmacokinetics of the drug and decrease serum concentrations.(16-18) ADAb formation may also be associated with serious side effects of INX such as hypersensitivity reactions.(16-18) Drug holidays or low-dose regimens have been shown to predispose to ADAb formation.(20) Immunosuppressive co-medication, methotrexate in particular, is protective with a reduction of ADAb formation by up to 40%.(16,18,21,22) The predisposing genetic factors and the precise immunological mechanisms leading to ADAb formation remain unknown.

Methods for assessment of serum drug concentrations have recently become available for use in clinical practice. For drugs that are administered by regular infusions, the trough level (the lowest concentration of the drug measured just before the administration of the next dose) gives the best estimate of bioavailable drug. Advances in assay development have revealed extensive individual differences in serum drug concentrations of INX in patients on the standard dose with levels ranging from undetectable to high above the presumed therapeutic range. ADAb formation, known to considerably influence the half-life of the drug, is regarded as the most important factor responsible for this variation, but drug metabolism is also affected by other individual factors.(23) Maintaining a sufficient trough level is thought important, primarily in order to maintain treatment response, but perhaps also to decrease ADAb formation.The trough concentration of INX has been shown to be associated with clinical response parameters and sustained drug efficacy in patients with RA, UC, CD, Ps, (24-31) and a trough concentration above 3µg/ml during maintenance therapy has been associated with improved clinical outcomes in several studies and across different diseases.(26-30,32) Recent studies indicate that high serum levels after week 2 and 6 are associated with remission in patients with IBD, but the clinical role of assessments of INX concentrations during induction therapy has not been clarified.(33, 34)

1.1.3 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) aims at improving patient care by individually adjusting the dose of drugs based on regular assessments of serum drug concentrations. As assessment methods have become more available, the clinical impact of TDM in monitoring patients on treatment with INX has become a topic of great interest to clinicians both nationally and internationally.

As indicated by some observational studies, assessments of serum drug levels and ADAb could be a useful tool for guiding treatment decisions in patients on a TNFi by;(35-40)

1) Minimise undertreatment, which might lead to lack of response, loss of response, and possibly also predispose to ADAb production
2) Reduce overtreatment, which predispose patients to side effects and increases the costs of treatment
3) Allow for early identification of ADAb development, with the possibility of detecting treatment failures prior to a clinical flare and to prevent infusion reactions
4) Aid in treatment decisions if treatment fails (i.e. dose increase in patients with low levels, switch therapy to another TNFi in case of ADAb development and to another treatment mechanism in the case of treatment failure despite INX levels in the therapeutic range)

Algorithms for handling a disease flare by taking drug levels and ADAb measures into account have recently been proposed by researchers within this field, and have been implemented in clinical practice in some European centres with available methodology and

special interest in immunogenicity.(36, 41) There are currently no guidelines for the implementation of TDM in standard care of patients on INX. A small randomised controlled trial has shown lower costs of such algorithm-based management of a disease flare during treatment with TNFi.(36) Although data from observational cohorts suggests that keeping the serum INX trough level above 3 µg/ml during maintenance therapy is associated with better disease control, data assessing clinical effectiveness of systematically monitoring TNFi treatment by serum drug concentrations and ADAb is limited to two recent studies of trough level guided INX therapy in patients with inflammatory bowel diseases (IBD).(32,42) A retrospective study comparing patients treated according to TDM with patients who had been handled by standard clinical care showed better drug survival in the TDM-group.(42) A recent randomised clinical trial (TAXIT) of patients with IBD has evaluated the effect of TDM.(32) In this study all patients underwent INX dose optimisation based on trough level 3-7 µg/ml prior to randomisation, which significantly increased the percentage of CD patients in remission from 64% to 92%. After dose optimisation, continued TDM was not superior to clinically based dosing for achieving remission after 1 year, but was associated with fewer flares during the course of treatment. Dose reduction in patients with high levels did not lead to flare, but did result in significant cost savings.

1.1.4 The NOR-SWITCH study

The NOR-DRUM study will build on the infrastructure, organisation and research collaboration developed for the NOR-SWITCH study initiated and funded by South-Eastern Regional Health Authority in 2014 to assess the efficacy and safety of switching from originator INX to biosimilar INX. Norway has been among the first countries world-wide to apply biosimilars in everyday clinical use. The ongoing NOR-SWITCH study (Clinical trials registration number NCT02148640), a randomised, double blind, parallel-group study with 500 included patients is an extensive effort for Norwegian rheumatology, dermatology and gastroenterology with a total of 40 centres (16 rheumatology centres, 19 gastroenterology centres and 5 dermatology centres) participating. Diakonhjemmet Hospital is the coordinating centre. The NOR-SWITCH study includes collaboration with Oslo University Hospital for measuring serum drug levels and ADAb development in the setting of drug switching.

1.2 Purpose and rationale

The NOR-DRUM study aims to assess whether tailoring infliximab treatment by therapeutic drug monitoring improves the effectiveness of infliximab treatment in order to achieve and maintain disease control. This large randomised controlled multicenter trial of patients with rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, ulcerative colitis, Crohn's disease and psoriasis is expected to provide valuable information both clinically and in terms of health economics regarding the possible optimisation of TNF-inhibitor treatment.

INX and other TNFi have revolutionised the treatment of a range of prevalent immunological inflammatory disease with a chronic disease course. Still, a substantial proportion of patients either do not respond sufficiently to initiated therapy or loose treatment effect over time. Sustained disease activity affects the quality of life of the patients in the short term and may lead to irreversible organ damage and disability. Early identification of non-responders and partial responders after treatment initiation and prevention of a disease flare during the course of treatment are important to obtain the main therapeutic goal of rapid and sustained remission. Recent advances in assay development have revealed an extensive individual variation in serum drug concentrations in patients on standard doses of INX suggesting both under- and overtreatment of a substantial proportion of patients. Many patients develop anti-drug antibodies (ADAb) during therapy contributing to reduced drug levels and additionally predispose the patients to allergic drug reactions. The impact of therapeutic drug monitoring (TDM) as a tool optimise effectiveness of INX treatment is currently a topic of great interest to clinicians both nationally and internationally. As the first trial ever to assess the effect of TDM in patients with a wide range of inflammatory immunological diseases on treatment with a TNFi, the NOR-DRUM study will provide important information that will hopefully contribute to an implementation of a personalised medicine approach to TNF-inhibitor therapy.

The results of this study could also have impact on health care economics. The financial burden of TNF-inhibitors is significant, restricting their use.(43) Data from the Norwegian NOR-DMARD register indicates a yearly cost of a patient with RA receiving biologic DMARDs of € 60 000 (NOK 500 000), where €19 600 (NOK 160 00) are directly related to the drug.(44) The extremely high costs of these drugs put emphasis on avoiding redundant therapy. If dose tapering in patients with levels above the therapeutic range can be safely done without exposing the patients to loss of treatment effect, the savings in drug costs could be considerable.

As a large infliximab cohort, NOR-DRUM will provide unique opportunities for translational research on the poorly understood area of genetic and immunological mechanisms underlying drug immunogenicity. Identification of predisposing genetic markers that could serve as predictors of loss of response is highly relevant in order to tailor treatment with biological drugs.

A personalised medicine approach to INX therapy by TDM seems reasonable, but the effectiveness of such a treatment strategy in the management of a range of immunological inflammatory diseases with regard to rapid remission and sustained disease control still remains to be shown in a longitudinal randomised controlled trial.

2 STUDY OBJECTIVES

2.1 Main study objective

To assess the effectiveness of tailoring infliximab treatment by therapeutic drug monitoring.

2.2 Primary objectives

NOR-DRUM A

To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in order to achieve disease control in patients with inflammatory immunological diseases starting infliximab therapy.

NOR-DRUM B

To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in keeping disease control in patients with inflammatory immunological diseases on maintenance therapy with infliximab.

2.3 Secondary objectives and exploratory objectives

Secondary objectives:

- To compare effectiveness of a treatment strategy based on TDM to standard clinical care applying different generic and disease specific endpoints
- To assess whether a treatment strategy based on TDM influences drug survival, occurrence of anti-drug antibodies, serum drug levels and occurrence of adverse events
- To assess cost-effectiveness of a treatment strategy based on TDM compared to standard clinical care

Exploratory objectives:

- To assess if biomarkers (including genetic markers) or other factors (diagnosis, gender, co-medication, previous treatment with biological drugs, “drug holidays” etc) can predict development of anti-drug antibodies and drug levels in patients starting INX
- To study how serum drug levels and anti-drug antibodies are associated to drug efficacy and safety
- To study predictors of treatment response (NOR-DRUM A only)
- To study differences in efficacy, safety and immunogenicity between different diseases and disease subgroups
- To characterise anti-infliximab immune responses, including ADAb isotypes, epitopes (on infliximab) and association to genetic markers (e.g. HLA)
- To study changes in immune responses over time and the prevalence and properties of pre-existing ADAb in INX naïve patients

- To assess how TDM influences treatment with respect to serum drug/ADAb levels and disease activity
- To address efficacy of TDM in the subgroup of patients with low serum drug levels
- To study feasibility of TDM and compliance to the treatment algorithm
- To study effectiveness of TDM in the induction phase (NOR-DRUM A only)
- To study the performance of the treatment strategy within the group of patients 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 from infliximab to a different biologic agent
- To study effectiveness of TDM in subgroups of patients where TDM is assumed to be especially valuable; patients with high disease activity at baseline, patients not on immunosuppressive co-medication and patients with previous use of TNFi

3 STUDY ENROLMENT AND WITHDRAWAL

3.1 Inclusion of patients

The study population will consist of Norwegian adult male and female patients with a clinical diagnosis of rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis, ulcerative colitis, Crohn's disease or chronic plaque psoriasis who are either starting on treatment with INX (NOR-DRUM A), or have been on maintenance therapy with INX for at least 30 weeks (NOR-DRUM B). Patients will be recruited from Norwegian hospitals providing treatment with INX for the mentioned diagnoses.

3.2 Number of Patients

400 patients will be included in NOR-DRUM A.
450 patients will be included in NOR-DRUM B.
For sample size calculations see 9.5.

3.3 Inclusion Criteria

NOR-DRUM A

All of the following conditions must apply to the prospective patient at screening prior to receiving study agent (e.g.):

1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis

2. Male or non-pregnant female
3. ≥18 and < 75 years of age at screening
4. A clinical indication to start INX
5. Subject not in remission according to diagnosis-specific disease activity scores (defined in 6.5.8)
6. Subject capable of understanding and signing an informed consent form

NOR-DRUM B

All of the following conditions must apply to the prospective patient at screening prior to receiving study agent (e.g.):

1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis
2. Male or non-pregnant female
3. ≥18 and < 75 years of age at screening
4. On maintenance therapy with infliximab for a minimum of 30 weeks and a maximum of 3 years
5. A clinical indication for further infliximab treatment
6. Subject capable of understanding and signing an informed consent form

* Patients with psoriatic arthritis with predominantly axial manifestations should be included and assessed as spondyloarthritis

3.4 Exclusion Criteria

A subject will be excluded from the study if they meet any of the following criteria:

NOR-DRUM A

1. Major co-morbidities, such as previous malignancies within the last 5 years, severe 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 laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult
2. A positive screening for TB and hepatitis
3. Inadequate birth control, 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 which makes adherence to the study protocol difficult.

5. Prior use of infliximab within the last 6 months
6. For patients with UC and CD: Functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ.

NOR-DRUM B

1. Major co-morbidities, such as previous malignancies within the last 5 years, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases, demyelinating disease, significant chronic widespread pain syndrome, laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult
2. Inadequate birth control, pregnancy or subject considering becoming pregnant during the study period
3. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol difficult
4. For patients with UC and CD: Functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ.

3.5 Procedures for discontinuation

3.5.1 Patient discontinuation

Patients have the right to withdraw from the study at any time for any reason. In the case that a patient decides to prematurely withdraw from the study, he or she should be asked if he or she can still be contacted for further information, so that a final evaluation can be made with an explanation of why the patient is withdrawing from the study, including assessment of possible adverse events. Although a subject is not obliged to give his or her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.
If possible, at the last visit of the patient, all assessments of the ”End of study visit” will be done. The investigator is obliged to follow up any significant adverse events until the outcome is either recovered or resolved, recovering or resolving, not recovered or not resolved, recovered or resolved with sequelae, fatal or unknown.

3.5.2 Discontinuation from the study by the investigator

The investigator may discontinue the patient from further study participation if

- Further study participation will put the patient at risk of medical injury
- There has been a major protocol violation

3.5.3 Trial discontinuation

The study group reserves the right to terminate the study at any time. This may be due to safety reasons or if new knowledge arises that invalidates the study (including results from interim analyses). Other reasons that may have a major impact on the study, including ethical and financial aspects, and difficulties in the recruitment of patients, may also lead to termination of the study. In terminating the study, the study group and investigators will assure that adequate consideration is given to the protections of patients' interests. The sponsor and principal investigator will inform all investigators and the relevant regulatory authorities of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the relevant authorities should be informed within 15 days.

4 INVESTIGATIONAL PLAN

4.1 Overview of the study design

The NOR-DRUM study is a randomised, controlled, open, parallel-group, comparative, multi-centre, national, superiority, phase IV pragmatic study with two separate parts (NOR-DRUM A and NOR-DRUM B) aiming to assess the effectiveness of TDM of INX treatment in patients with immunological inflammatory diseases.

NOR-DRUM A (Outlined in Figure 1)
All patients with a clinical diagnosis of RA, SpA, PsA, UC, CD or Ps starting treatment with INX are potential study patients. Eligibility criteria are described in section 3.3 (inclusion criteria) and 3.4 (exclusion criteria).

Eligible patients with a signed informed consent will be randomised 1:1 according to the procedure described in section 9.1 to either:

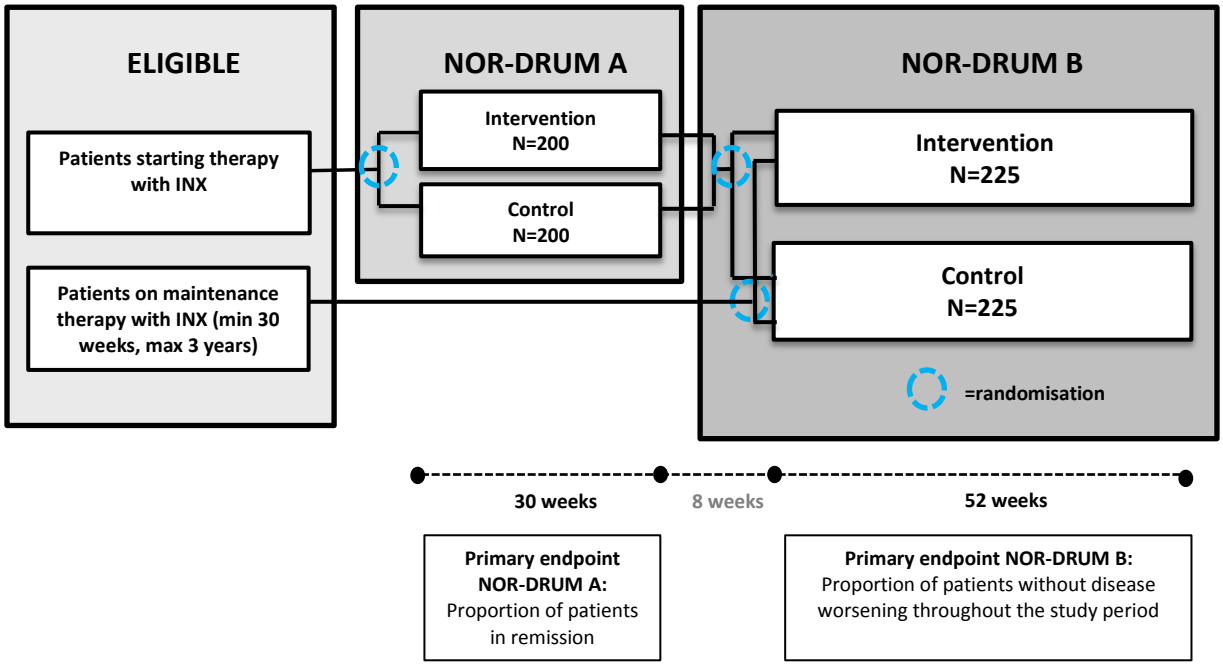
1. Administration of INX according to a treatment strategy based on therapeutic drug monitoring and assessments of ADAb (**intervention group**)
2. Administration of INX according to standard clinical care, without knowledge of drug levels or ADAb status (**control group**)

The randomised treatment strategy will be continued for the duration of the study period (38 weeks) with study visits at each scheduled INX infusion. Patients who are switched to

another treatment during the study will still be followed according to the intentional infusion scheme. Patients that are still on INX and in low disease activity or remission at week 38 will be re-randomised and included in NOR-DRUM B.

Study duration: 38 weeks +/-4 weeks

FIGURE 1 Overview of study design



NOR-DRUM B (Outlined in Figure 1)
All patients with a clinical diagnosis of RA, SpA, PsA, UC, CD or Ps on maintenance therapy with INX for at least 30 weeks and not more than 3 years with an indication for continued INX treatment are potential study patients. Patients from NOR-DRUM A who are still on treatment with INX at week 38 and are otherwise eligible according to inclusion and exclusion criteria will be included in NOR-DRUM B. Eligibility criteria are described in section 3.3 (inclusion criteria) and 3.4 (exclusion criteria).

Eligible patients with a signed informed consent will be randomised 1:1 according to the procedure described in section 9.1 to either:

3. Administration of INX according to a treatment strategy based on therapeutic drug monitoring and assessments of ADAb (**intervention group**)

4. Administration of INX according to standard clinical care, without knowledge of drug levels or ADAb status (**control group**)

The randomised treatment strategy will be continued for the duration of the study period (52 weeks) with study visits at each scheduled INX infusion. Patients who are switched to another treatment during the study will still be followed with visits every 12 weeks.

In order to identify the primary endpoint (absence of disease worsening during the study period), each study centre will have a phone number for patients to call in case of increased disease activity. If a patient is experiencing a potential disease worsening, a visit will be arranged within one week to allow for a thorough examination and documentation of disease status.

Study duration: 52 weeks+/-4 weeks

4.2 Follow-up study

In order to establish the long- term survival of ADAb, patient that develops such antibodies will be asked to participate in a follow-up study with serum samples after 6, 12, 18 and 24 months for subsequent analyses of serum levels of ADAb. There will be no clinical evaluation or other assessments, only serum sampling.

4.3 Study endpoints

4.3.1 Primary endpoints

NOR-DRUM A

<u>Primary endpoint:</u>

Proportion of patients in remission* at week 30 defined by disease specific composite scores

*Definition of remission:

- RA: A DAS 28 score of <2.6
- PsA: A DAS 28 score of <2.6
- SpA: An ASDAS score <1.3
- UC: A Mayo score of ≤2 with no sub scores >1
- CD: A HBI score of ≤4
- Ps: A PASI score of ≤4

NOR-DRUM B

Primary endpoint:

Sustained disease control throughout the study period without disease worsening* defined by disease specific composite scores

*Definition of disease worsening:

- RA and PsA: Increase in DAS28 of ≥1.2 from inclusion and a minimum DAS28 score of 3.2
- SpA: Increase in ASDAS-CRP of ≥1.1 from inclusion and a minimum ASDAS of 2.1
- UC: Increase in Partial Mayo score of ≥ 3 points from inclusion and a minimum partial Mayo score of 5 points
- CD: Increase in HBI of ≥4 points from inclusion and a minimum HBI score of 7 points
- Ps: Increase in PASI of ≥3 points from inclusion and a minimum PASI score of 5
- Patient and investigator consensus on disease worsening:
  If a patient does not fulfil the formal definition, but experiences a clinically significant worsening according to both the investigator and patient who leads to a major change* in treatment this should be considered as a disease worsening but be recorded separately in the CRF.

A major change* in treatment includes; Switching from INX to another immunosuppressant/DMARD, adding a immunosuppressant/DMARD, increasing the dose of a concomitant immunosuppressant/DMARD, adding systemic glucocorticoids (po., iv. or im.), receiving more than one i.a. glucocorticoid injection at one visit.
If the INX dose is increased for clinical reasons this should also be regarded as a major change in treatment (applies to the control arm only).

4.3.2 Secondary endpoints

NOR-DRUM A

Generic:

- Time to sustained remission. Sustained remission is defined as a status of remission on all consecutive visits following the initial obtained remission until the end of the study period (38 weeks)
- Patient's and physician's global assessment of disease activity
- Biochemical parameters of disease activity
- Occurrence of anti-drug antibodies
- Serum drug level
- Occurrence of and reason for drug discontinuation
- Safety endpoints (adverse events frequency)

- Cost effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH)

Disease specific:

- Efficacy assessed by composite disease activity scores
  - RA: DAS28, CDAI, SDAI, RAID, MHAQ
  - PsA : DAS28, PsAID, DAPSA, MHAQ, DLQI
  - SpA: ASDAS, BASDAI,MHAQ
  - UC: Partial Mayo score, IBDQ
  - CD: HBI, IBDQ
  - Ps: PASI, DLQI

NOR-DRUM B:

Generic:

- Time to disease worsening
- Patient and physician global assessment of disease activity
- Biochemical parameters of disease activity
- Occurrence of anti-drug antibodies
- Occurrence of and reason for drug discontinuation
- Safety endpoints (adverse events frequency)
- Cost-effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH)

Disease specific:

- Efficacy assessed by composite disease activity scores
  - RA: DAS28, CDAI, SDAI, RAID, MHAQ
  - PsA : DAS28, PsAID, DAPSA, MHAQ, DLQI
  - SpA: ASDAS, BASDAI,MHAQ
  - UC: Partial Mayo score, IBDQ
  - CD: HBI, IBDQ
  - Ps: PASI, DLQI

4.4 Description of the treatment strategy in NOR-DRUM A

4.4.1 The intervention group

In the patients randomised to the intervention group, the INX dose will be adjusted according to the algorithms outlined in Figure 2 and Figure 3 in order to meet the target trough level. Trough level results, drawn 0-5 days prior to each visit, will not be available at the actual visit. The investigator will receive these results some days after the infusion and must then make a decision to keep or change the dose, based on the algorithm.

At the first infusions (up to and at the week 14 visit), the dose will mainly be adjusted by decreasing the infusion interval (Figure 2). After the week 14 visit, strategies for both increasing and decreasing the INX dose to reach the target range of 3-8 µg/ml is incorporated in the algorithm (Figure 3). The former should preferably be done by increasing the dose, but decreasing the length of the infusion interval can also be performed if better suited. A dose decrease should preferably be done by increasing the infusion interval, but can also be performed by a dose-reduction if better suited. However, only one of the strategies can be performed related to each infusion (i.e. the dose interval to the next infusion and the dose at the next infusion must not be changed at the same time). Subsequent changes required according to the algorithm will be based on the adjusted dose/infusion interval.

If INX is terminated due to side effects, the choice of treatment should be at the discretion of the investigator and according to LIS. If INX is terminated due to any reason, the patient will still be included in the study and followed with study visits according to the planned infusion schedule (after 0, 2, 6, 14, 22, 30 and 38 weeks). The reason for termination of therapy should be recorded in the CRF.

Infusion 1 (Inclusion):
The patient will receive the standard weight based dose according to disease (3 mg/kg (RA) or 5 mg/kg for the other diseases). The interval to infusion 2 is 2 weeks.

Infusion 2 and 3:
Infusion 2 is scheduled after 2 weeks for all patients. Infusion 3 will be after 4 or 6 weeks from baseline depending on the infusion interval between infusion 2 and 3. The investigator (physician) will see the patients if requested by the study nurse or the patient. The algorithm for infusion 2 and 3 is depicted in Figure 2. At infusion 2 and 3 the dose will mainly be adjusted by decreasing the infusion intervals.

The week 14 visit:
This visit should be arranged between week 12 and 16 (14 +/- 2 weeks). If the 4th visit is scheduled earlier than week 12 and the 5th visit later than week 16, an extra visit must be scheduled. At this visit a formal assessment of improvement* will be performed by the investigator (physician). If the patient has not improved (defined below) the patient should be managed according to the algorithm in Figure 2.
If the patient has not improved, INX should not be given until the results of the serum drug level is ready and action can be taken accordingly.

*Improvement is defined as:

- RA and PsA: A decrease in DAS 28 of ≥1.2 from baseline
- SpA: A decrease in ASDAS of ≥1.1 from baseline
- UC: A decrease in the partial Mayo score of ≥ 3 from baseline or a partial Mayo score of 0
- CD: A decrease in the HBI of ≥ 4 from baseline
- Ps: PASI 50 (A 50% reduction in the PASI score from baseline)
- Investigator and patient consensus on improvement:
  If a patient does not fulfil the formal definition, but both the patient and the investigator agree that the patient has improved this should be considered as improvement but recorded separately in the CRF

Factors that may lead to continuation of therapy despite lack of improvement are i.e. if improvement is not expected or clinically relevant (i.e. if the patient has switched therapy due to side-effects rather than lack of efficacy) and if few/no other treatment options are available.

Visits after the week 14 visit:

The investigator (physician) will see the patients at the week 30 visit and the week 38 visit, and else if requested by the study nurse or the patient. The algorithm for INX administration is outlined in Figure 3. If the investigator considers switching therapy due to lack of efficacy at the scheduled visit or at an extra visits requested by the patient, the patient should be managed according to Figure 5.

Extra study visit:

If requested by the patient or the study nurse an extra visit will be set.

The week 30 visit:

This visit should be arranged between week 28 and 32 (30 +/- 2 weeks). Depending on the infusion interval in each individual patient this will be visit 6-9 or an extra visit. A formal assessment of remission (the primary outcome of the study) will be performed by the investigator. If the patient is not in remission and the investigator considers switching therapy, the patient should be managed according to Figure 5.

The week 38 visit:

This end of study visit should be arranged between week 34 and 42 (38 +/- 4 weeks). Depending on the infusion interval in each individual patient this will be visit 7-11. A formal assessment of remission will be performed by the investigator. If the patient is eligible for NOR-DRUM B, the patient will be re-randomised and the 38 weeks visit will also be the inclusion visit in NOR-DRUM B. If the patient is re-randomised to the control group in NOR-DRUM B, the serum level drawn at the 38 week visit will not be available to the investigator.

4.4.2 The control group

Patients randomised to the control group will be managed according to standard clinical care without knowledge of serum drug levels or ADAb. As for the intervention group, a clinical assessment by the investigator is performed routinely at baseline, at week 14 (improvement evaluation), at week 30 (end point assessment) and at week 38 (end of study visit). A decision to terminate therapy due to adverse events and the choice of any subsequent therapy should be made at the investigators preference and according to LIS. The reason for termination of therapy should be recorded in the CRF. If INX therapy is terminated during the study period, the patient should still be followed at all scheduled visits (0, 2, 6, 14, 22, 30 and 38 weeks).

Infusion 1 (Inclusion):
The patient will receive the standard weight based dose according to disease (3 mg/kg (RA) or 5 mg/kg for the other diseases). The interval to infusion 2 is 2 weeks.

Visit 2 and 3:
The investigator (physician) will see the patients if requested by the study nurse or the patient. The patient will receive standard infliximab dose according to disease. The infusion intervals are as in the SPC 4 weeks between infusion 2 and 3 and 8 weeks between infusion 3 and 4.

The week 14 visit:
This visit should be arranged between week 12 and 16 (14 +/- 2 weeks). If the 4th visit is scheduled earlier than week 12 and the 5th visit later than week 16 an extra visit must be scheduled. At this visit a formal assessment of improvement will be performed by the investigator (physician). If the patient has not improved (defined above) the investigator should consider intensifying therapy (by increasing the INX dose or by switching therapy) according to standard clinical care and LIS. Factors that may lead to continuation of therapy despite lack of improvement are i.e. if improvement is not expected or clinically relevant (i.e. if the patient has switched therapy due to side-effects rather than lack of efficacy) and if few/no other treatment options are available.

Visits after the week 14 visit:
The investigator (physician) will see the patients at week 30 and 38, and extra if requested by the study nurse or the patient.
If medically indicated (lack of improvement, adverse events or other reason) the investigator can intensify therapy by increasing the INX dose or by switching therapy according to standard clinical practice.

The week 30 visit:
This visit should be arranged between week 28 and 32 (30 +/- 2 weeks). Depending on the infusion interval in each individual patient this will be visit 6-9 or an extra visit. A formal assessment of remission (the primary outcome of the study) will be performed by the investigator. If the patient is not in the investigator should consider intensifying therapy (by increasing the INX dose or by switching therapy) according to standard clinical practice and LIS.

The week 38 visit:
This end of study visit should be arranged between week 34 and 42 (38 +/- 4 weeks). Depending on the infusion interval in each individual patient this will be visit 7-11. A formal assessment of remission will be performed by the investigator. If the patient is eligible for NOR-DRUM B, the patient will be re-randomised and the 38 weeks visit will also be the inclusion visit in NOR-DRUM B.

4.5 Description of the treatment strategy in NOR-DRUM B

4.5.1 The intervention group

In the patients randomised to the intervention group, the INX dose will be adjusted according to the algorithm outlined in Figure 4 in order to meet the target trough level range of 3-8 µg/ml. Trough level results, drawn 0-5 days prior to each visit, will not be available at the actual visit. The investigator will receive these results some days after the infusion and must then make a decision to keep or change the dose, based on the algorithm.

Strategies for both increasing and decreasing the INX dose to reach the target range are incorporated in the algorithm. The former should preferably be done by increasing the dose, but decreasing the length of the infusion interval can also be performed if better suited. A dose decrease should preferably be done by increasing the infusion interval, but can also be performed by a dose-reduction if better suited. However, only one of the strategies can be performed related to each infusion (i.e. the dose interval to the next infusion and the dose at the next infusion must not be changed at the same time). Subsequent changes required according to algorithm will be based on the adjusted dose/infusion interval.

If INX is terminated due to side effects, the patient should be managed at the discretion of the investigator. If the patient develops a disease worsening (defined in 6.5.7, primary endpoint of the study), the patient should be handled according to the algorithm in Figure 6. If INX is terminated due to any reason, the patient will still be included in the study and followed with study visits every 12 weeks. The reason for termination of therapy should be recorded in the CRF.

Infusion

1 (inclusion visit):

The patient will receive the same dose as for the previous infusion. The dose or the infusion interval may be adjusted subsequently according to the algorithm when receiving the trough level prior to visit 1.

If a high level of ADAb (>50 µg/L) is present at inclusion, therapy with INX will be stopped after infusion 1 and the investigator should either switch to another biological drug (preferably another TNFi) or if in long-term remission the investigator should consider to let the patients continue without biological therapy.

End of study visit

At week 52+/- 4 weeks there will be an end of study visit.

Extra visit if disease worsening:

The proposed strategy for managing a disease worsening is outlined in Figure 6.

4.5.2 The control group

Patients randomised to the control group will be managed according to standard clinical care without knowledge of serum drug levels or ADAb. A clinical evaluation by the investigator (physician) is performed at least every 12 (+/- 4) weeks and additionally if requested by the patient or the study nurse. The patients will keep the dose and dosing interval they had prior to randomisation. Dose adjustments are performed at the discretion of the investigator during the study period. A need to increase the dose will be regarded as a disease worsening (primary outcome of the study). A disease worsening or an adverse event will be managed at the discretion of the investigator. Both a decision to terminate therapy and the choice of any subsequent therapy should be made at the investigators preference and according to LIS. The reason for termination of therapy with INX should be recorded in the CRF. A disease worsening will be recorded according to the description in 6.5.7. If INX therapy is terminated during the study period the patient will still be included in the study and followed every 12 weeks throughout the study period.

FIGURE 2 Algorithm for INX administration in **NOR-DRUM A, intervention group** (The visits up to the week 14 visit)

	Infusions up to the week 14 visit		The week 14 visit	
Serum INX level (µg/ml)	**<20.0 at infusion 2 <15.0 at infusion 3 <3 at further infusions up to the week 14 visit**	**≥20.0 at infusion 2 ≥15.0 at infusion 3 ≥3 at further infusions up to the week 14 visit**	**<3.0**	**≥3.0**
	Increase* dose if no ADAb or low level ADAb (<50 µg/L) **or** **Switch therapy** if high levels of ADAb (>50 µg/L). If possible to another TNFi	**No action** Within target range, continue with the same dose and dosing interval	**Same strategy for improvement and no improvement:** **Increase* dose** if no ADAb or low level ADAb (<50 µg/L) **or** **Switch therapy** if high levels of ADAb (>50 µg/L) .If possible to another TNFi	**Improvement** **: No action **No improvement** **: Switch therapy ***, if possible to another treatment mechanism than TNFi

Guideline for dose increase*
Increase the dose by decreasing the dose interval by 2 weeks to a minimum of 4 weeks (except for the interval between infusion 1- 2 and 2- 3 where the interval can be minimum 2 weeks)

**Definition of improvement:
RA and PsA: A decrease in DAS 28>=1.2
SpA: A decrease in ASDAS>=1.1UC: A decrease in partial Mayo score of ≥ 3 points or a partial Mayo score of 0

CD: A decrease in HBI with ≥ 4 points
Ps: Achieved PASI 50
For all diseases: An investigator and patient consensus on improvement despite not formally fulfilling improvement definition

***Factors that may lead to continuation of therapy despite lack of improvement are i.e. if improvement is not expected or clinically relevant (i.e. if the patient has switched therapy due to side-effects rather than lack of efficacy) and if few/no other treatment options are available.

FIGURE 3 Algorithm for INX administration **NOR-DRUM A, intervention group** (all infusions after the week 14 visit)

Serum INX level (µg/ml)	≤2.0	2.1 – 2.9	3.0 – 8.0	8.1 – 10.0	>10.0
Action	**Increase dose** if no ADAb or low level ADAb (<50 µg/L) **or** **Switch therapy** if high levels of ADAb (>50 µg/L) . If possible to another TNFi	**Consider increasing dose**	**No action**	**Consider decreasing dose**	**Decrease dose**
Guideline for action	Increase the dose preferably by increasing the given dose by 2-2,5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 2 weeks to a minimum of 4 weeks	Consider (based on clinical judgement and the patients factors given below*) increasing the dose preferably by increasing the given dose by 2-2.5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 2 weeks to a minimum of 4 weeks	Within target range. Continue with the same dose and dosing interval	Consider (based on clinical judgement and the patients factors given below*) to decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2-2.5 mg/kg	Decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2-2,5 mg/kg

*Patient factors to be considered when making the treatment decisions in the yellow zones:
Disease activity and trend in disease activity, the trend of the trough level over time, previous drug interval changes, availability of alternative drug, diagnosis (RA patients are expected to have lower trough levels due to lower recommended dosing)

FIGURE 4 Algorithm for INX administration in **NOR-DRUM B, intervention group** (all visits)

Serum INX level (µg/ml)	≤2.0	2.1 – 2.9	3.0 – 8.0	8.1 – 10.0	>10.0
Action	**Increase dose** if no ADAb or low level ADAb (<50 µg/L) **or** **Switch therapy** if high levels of ADAb (>50 µg/L). If possible to another TNFi	**Consider increasing dose**	**No action**	**Consider decreasing dose**	**Decrease dose**
Guideline for action	Increase the dose preferably by increasing the given dose by 2-2,5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 2 weeks to a minimum of 4 weeks	Consider (based on clinical judgement and the patients factors given below*) increasing the dose preferably by increasing the given dose by 2-2.5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 2 weeks to a minimum of 4 weeks	Within target range. Continue with the same dose and dosing interval	Consider (based on clinical judgement and the patients factors given below*) to decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2-2.5 mg/kg	Decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2-2,5 mg/kg
*Patient factors to be considered when making the treatment decisions in the yellow zones: Disease activity and trend in disease activity, the trend of the trough level over time, previous drug interval changes, availability of alternative drug, diagnosis (RA patients are expected to have lower trough levels due to lower recommended dosing)					

FIGURE 5 Treatment algorithm **NOR-DRUM A, intervention group** (if considering intensifying treatment after the week 14 visit)

Serum INX level (µg/ml)	<3.0	≥3.0
Guideline for action	If no ADAb or ADAb in low levels (<50 µg/L) : Increase the dose preferably by increasing the dose by 2-2,5 mg/kg to a maximum of 10 mg/kg or by decreasing the infusion interval by 2 weeks to a minimum of 4 weeks If high levels of ADAb (>50 µg/L): Switch therapy, if possible to another TNFi	Consider switching therapy according to current best clinical practice and LIS. If possible another treatment mechanism than TNFi should be chosen.

FIGURE 6 Treatment algorithm **NOR-DRUM B, intervention group** (disease worsening)

Serum INX level (µg/ml)	<3.0	≥3.0
Guideline for action	If no ADAb or ADAb in low levels (<50 µg/L) : Increase the dose preferably by increasing the dose by 2- 2,5 mg/kg to a maximum of 10 mg/kg or by decreasing the infusion interval by 2 weeks to a minimum of 4 weeks If high levels of ADAb (>50 µg/L) : Switch therapy, if possible to another TNFi	Consider switching therapy according to current best clinical practice and LIS. If possible another treatment mechanism than TNFi should be chosen.

4.6 Rationale for the intervention algorithm

The treatment algorithms are based on an extensive literature review and expert opinions. They have been developed through a series of meetings in the project group consisting of national leading experts in this field (both clinicians experienced with TDM and laboratory physicians) and with additional input from international key experts in the scientific advisory board.

The therapeutic level of INX is not definitely known for all the diseases, but there are strong indications that the lower limit is close to 3µg/ml.(26-30, 32) According to the literature review and expert opinion, the upper limit has been set to 8µg/ml. The borders of the proposed therapeutic range, the yellow zones in figure 1, allow for some clinical

considerations regarding the INX dosing. In the induction phase the limits of 20µg/ml at infusion 2 and 15µg/ml at infusion 3 are based on personal observations and previous literature.(33, 34)

There is still no consensus on what is the most effective and cost effective way to increase and decrease the INX dose, by dose adjustments or interval changes. Initial pharmacokinetic modelling suggested that a higher trough level could be achieved using less INX over time by shortening the interval instead of increasing the dose by.(45) More recent studies suggest that a dose of i.e. 10mg/kg every 8 weeks are probably equal to 5 mg/kg every 4 weeks,(46) and halving the infusion intervals are not superior to increasing dose when it comes to both effect and drug costs.(47) The proposed algorithms allows for both options, but due to lower drug costs in recent years, patient convenience and high costs of running infusion units, the preferred option is dose increase by increasing each infusion dose and for decreasing the dose by increasing the infusion interval.

4.7 Study drug

Patients included in this study will either be starting treatment with INX (NOR-DRUM A) or are on maintenance treatment with INX (NOR-DRUM B). In NOR-DRUM A, the recommended INX according to the current national prescription (LIS) recommendations (Remicade, CT-P13, SB2 or others) will be used. In NOR-DRUM B eligible patients on any form of INX will be included.

4.7.1 Drug supply, preparation and storage

The supply, storage and preparation of INX will be performed according to local guidelines in each participating centre.

4.7.2 Drug administration, premedication and monitoring

The study drug will be administrated by authorised personnel according to local guidelines in each participating centre. The infusion time will vary and can be influenced by previous experience i.e. infusion reactions. Local guidelines at each participating centre will be applied regarding the indication for premedication and the type and dosage of premedication. The patients will be monitored after the infusion according to local guidelines in each participating centre.

4.7.3 Subject Compliance

Each treatment administration will be registered in the electronic case report form (eCRF) with dose and time of infusion, and if the infusion was successful. Any schedule modification due to lack of subject compliance should be registered.

4.7.4 Drug Accountability

The responsible site personnel will treat study drug according to the practice at the study site, including accountability of receipt, administration to the patient, returned and/or destruction at the site.

4.8 Prior therapy

In NOR-DRUM A and B all prior use of disease-modifying drugs/immonosupressive therapy (exl steroids and NSAIDS) will be recorded in the CRF with specification of both the time (month and year) of treatment start and time of termination (month and year) of biological drugs. The reason for termination of prior biological therapy (i.e. lack of efficacy, loss of efficacy, side effekts, development of ADAb or other) will be recorded. In NOR-DRUM B the time (day, month and year) of treatment initiation of INX will be recorded. In NOR-DRUM A patients that have previously been treated with any form of INX within the last six months will not be eligable.

4.9 Concomitant medication

All concomitant medication should be recorded in the CRF.

NOR-DRUM A

All concomitant medications and changes in concomitant medications and dosages should be documented in the CRF. Disease related synthetic concomitant medication such as 5-ASAs, systemic corticosteroids and sDMARDs/immunosuppressive therapy (i.e. methotrexate, azathioprine and 6-MP) are permitted and can be started before or during the study period. The choice and dosage of concomitant medication will be at the discretion of the investigator. Corticosteroids (oral, im., ia or iv.) should preferably not be used after week 14, and only with special consideration after week 22. Short courses of corticosteroids for acute medical conditions other than RA (for example asthma and allergy) are permitted. NSAIDs are permitted during the study. Doses may be increased or tapered according to clinical response. Analgesics may be used for pain relief as required. Patients should avoid analgesics within 12 hours prior to a visit if possible.

Patients who are switched to another treatment during the study period either due to the treatment algorithm, lack of improvement or side effects will still be included as study subjects.

NOR-DRUM B

Patients should continue with the same concomitant medication as prior to randomisation. Such medication may include 5-ASAs, systemic corticosteroids and sDMARDs like methotrexate, azathioprine and 6-MP. Any co-medication with synthetic DMARDs should be kept stable throughout the study, but tapering and termination due to side effects is

permitted. All changes in concomitant medication should be documented. Worsening in disease leading to major changes in the concomitant treatment as defined in 6.5.7 will lead to classification as worsening of disease (primary endpoint of the study). Short courses of corticosteroids for acute medical conditions other than RA (for example asthma and allergy) are permitted. Patients with RA, PsA or SpA can receive intra-articular injections in one swollen joint at each visit; more than one injection will be regarded as a major change in medication and lead to classification as disease worsening (primary endpoint). NSAIDs are permitted during the study. 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 CRF. Analgesics may be used for pain relief as required. Patients should avoid analgesics within 12 hours prior to a visit if possible.

Patients who experience a disease worsening can receive concomitant medication or switch therapy as needed.

4.10 Dose modifications and schedule modifications

Modification of dosing regimens related to abnormal blood values and/or adverse events should be performed based on the summary of product characteristics (SPC), clinical judgment and if necessary contact with the clinical coordinators. If an INX infusion is delayed due to non-disease related factors such as infections, surgery, vacation, subject non-compliance etc. this should be recorded and the reason given. In the intervention group the trough level assessed at this delayed visit cannot be used to guide the dose of the next infusion, and decisions should be based on the previous trough level assessment.

4.11 Protocol modifications

Protocol modifications must be approved by the study group, and will be submitted to the Regional Ethical committee for approval.

4.12 Linkage to other registers

In addition to the variables collected in this study, patients will be asked to give consent to collection of data from registries and databases such as; The Norwegian Prescription Database (Reseptregisteret), The Norwegian Health Economics Administration database (HELFO/KUHR), Norway's central institution for producing official statistics (Statistisk sentralbyrå i.e. FD-Trygd, IPLOS), The Norwegian Arthritis Registry (NorArthritis),The Norwegian Qualtiy Registry for Biologic Drugs (NOKBIL), The Cancer Registry of Norway (Kreftregisteret), the Norwegian Patient Registry (Norsk pasientregister – NPR), the Cause of Death Registry (Dødsårsaksregisteret), the Norwegian Myocardial Infarction Register (Norsk hjerteinfarktregister), the Norwegian Surveillance System for Communicable Diseases (Meldingssystem for smittsomme sykdommer – MSIS) and The Norwegian Labour and

Welfare Administration (NAV). This will allow certain outcomes to potentially be obtained through linkage to national medical or public registers and databases to answer research questions related to safety and health economics. Examples of such outcomes are cancer and other serious adverse events, health care utilization, work participation and social benefits. NOR-DMARD is also a potential data source for patients who have previously been enrolled in the NOR-DMARD study. The patient consent form includes information about linkage. Participation in international collaboration involving sharing of data from the NOR-DRUM study and merging of NOR-DRUM data with other (similar) studies will be based on fully de-identified data.

5 STUDY PROCEDURES AND SCHEDULE

An event flow chart is presented in appendix 15.1.

5.1 Visits

NOR-DRUM A

The study visits will be carried out according to the patient's INX treatment schedule and the number of visits will vary (between 5 and 13) depending on the infusion intervals. The assessments performed at each visit are shown in Appendix 15.1. The primary outcome will be recorded at the week 30 visit. The end of study visit is at week 38. If INX treatment is terminated, patients will still be study subjects and should be assessed at week 2, 6, 14, 22, 30 and 38. Extra study visits may be arranged at the request of the patient and/or the investigator (physician).

NOR-DRUM B

The visits will be carried out according to the patient's INX treatment schedule and the number of visits will vary depending on the infusion intervals. Over the 52±4 weeks study period the number of visits will be between 5 and 13. The assessments performed at each visit are presented in Appendix 15.1. If INX treatment is terminated, patients will still be study subjects and should be assessed at week 12, 24, 36 and 52. If the patients perceive increased disease activity, a non-scheduled visit will be arranged within one week in order to identify a disease worsening.

5.2 Screening evaluation

NOR-DRUM A

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
- Urine sample for pregnancy test in female subjects of childbearing age
- Laboratory tests including screening tests for hepatitis B and C and tuberculosis

NOR-DRUM B
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 (No prior inclusion in NOR-DRUM A)
- A formal assessment of the eligibility criteria
- Urine sample for pregnancy test in female subjects of childbearing age
- Laboratory tests

5.3 Assignment of intervention and subject numbering

Eligible patients will be assigned a unique patient identification number. Once assigned, this number cannot be reused for any other patient. The patients will be randomised 1:1 to either the intervention- or the control arm as described in 9.1. In NOR-DRUM A, patients will be stratified by disease. In NOR-DRUM B patients will be stratified by disease and prior participation NOR-DRUM A. Patients with prior participation in NOR-DRUM A will be stratified by study arm (intervention vs control). Patients with no prior participation in NOR-DRUM A will be stratified by prior or no prior TDM in the clinic (defined as one or more assessments of serum drug level during the last 3 infusions). The randomisation procedure will be performed trough the e- CRF (Viedoc).

5.4 Baseline visit

Informed written consent must have been given voluntarily by each subject before any study specific procedures are initiated. For the patients with a prior inclusion in NOR-DRUM A, the baseline visit in NOR-DRUM B is the end of study visit in NOR-DRUM A (the week 38 visit).
In addition to the assessments and procedures performed at a regular visit described in 5.5, the following assessments will be performed:

1. Full blood samples for biobank will be drawn and stored in a freezer at -70° C
2. Study nurse/investigator assessments:
   - Demographics (sex, birth date and ethnic origin)
   - Tobacco and alcohol use
   - Clinical status (physical examination)

- 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 patient, duration of INX use (NOR-DRUM B), non- RA related medical and surgical history)

3. Review of inclusion/exclusion criteria
4. Randomisation

5.5 Regular visit

The sequence of assessments and procedures is to be standardised as follows:

1. Laboratory samples for trough levels and ADAb, haematology, clinical chemistry, faecal calprotectin (IBD) and biobank storage must be drawn prior to the infusion, on the same day or not more than 5 days in advance.
2. Patient reported health outcomes assessments
    - Patient Global Assessment of disease activity (NRS)
    - EQ-5D
    - SF-36 (Except NOR-DRUM A V2 and V3)
    - WPAI-GH
    - RA: MHAQ, RAID
    - PsA: MHAQ, PsAID, DLQI
    - SpA: MHAQ, BASDAI
    - UC and CD: IBDQ
    - Chronic plaque psoriasis: DLQI
3. Study nurse/investigator assessments:
    - Investigator global assessment of disease activity (NRS)
    - Disease specific disease activity measures:
        - RA: DAS28, CDAI, SDAI
        - PsA: DAS28, DAPSA
        - SpA: ASDAS
        - UC: Partial Mayo score
        - CD: HBI
        - Psoriasis: PASI
    - Assessment of disease worsening (NOR-DRUM B, all visits)
    - Assessment of improvement (NOR-DRUM A at the week 14 visit)
    - Assessment of remission (NOR-DRUM A at the week 30 and week 38 visits)
    - Registration of concomitant medication
    - Safety assessments (AEs/SAEs)
    - Vital signs
    - Body weight

4. Treating physician:
    - Review of laboratory results
    - Decision regarding the dose and further dosing schedule of INX according to the randomised strategy of the patient. In the intervention arm, a review of trough levels and ADAb must be done with 1 week after the visit in order to schedule the next visit.
    - NOR-DRUM A: A clinical evaluation of the patient at baseline, at the week 14 visit, at the week 30 visit and at the week 38 visit and if requested by the patient or study nurse
    - NOR-DRUM B: A clinical evaluation of the patient as clinically indicated.
5. Treatment administration according to treatment strategy, registration of time and dose

5.6 Extra visits

If the patient suspects a disease worsening (NOR-DRUM B), he or she should contact the study site immediately and be seen there as soon as possible and within one week as the latest. The visit will include all assessments of a regular visit (with the exception of treatment administration). If a disease worsening is confirmed according to the definition given in 6.5.7 treatment should be modified as outlined in Figure 6. In both NOR-DRUM A and B extra visits will be scheduled on the patient's request and assessments will be performed as described in appendix 15.1.

5.7 End of Study Visit

NOR-DRUM A

The end of study visit will be performed at 38±4 weeks and will include a formal end of study assignment in the eCRF in addition to all assessments of a regular visit.

NOR-DRUM B

The end of study visit will be performed at week 52±4 and will include a formal end of study assignment in the eCRF in addition to all assessments of a regular visit.

5.8 Withdrawal Visit

A withdrawal visit will include all assessments of a regular visit (with the exception of treatment administration) in addition to an assessment of reason for withdrawal, time of withdrawal.

6 ASSESSMENTS

6.1 Ordinary laboratory Tests

The following laboratory tests will be recorded at all visits. These tests will depending on availability be analysed 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 platelets
- Blood chemistry: ALT, albumin, creatinine
- Acute phase reactants: CRP and ESR
- Fecal analyses (IBD patients only): Calprotectin

6.2 Biobank samples

Serum samples will be collected at all visits. Samples will then be aliquoted and stored in a biobank. Full blood samples will be collected at first visit only. All samples will be in a certified biobank in a freezer at -70° C. The samples from the biobank will be used for research purposes only. DNA/RNA information will be used to assess possible associations between gene expressions and response/immunogenicity. Some analyses might take place in other countries if necessary.

6.3 Immunogenicity and Serum Drug Concentration Assessments

Serum samples will be drawn from all participants at all visits. The samples will be sent to the central laboratory at Oslo University Hospital, Radiumhospitalet, where serum infliximab levels and antibodies to infliximab will be measured using the assays currently used to monitor infliximab treatment by many departments of rheumatology, gastroenterology and dermatology in Norway.

Infliximab is measured using recombinant hTNF-alpha on the solid phase. As a result, only active infliximab (with the ability to bind TNF) will be measured. The assay for antibodies to infliximab only detects neutralising antibodies, i.e. antibodies that block the TNF-binding capacity of infliximab. Both assays are fully automated (including dilutions) on the AutoDELFIA platform (PerkinElmer).

In the intervention arm results for trough levels and ADAb will be reported to the investigators within one week. Results in the standard care group will be recorded in a database on a secure server according to institutional guidelines, and transferred to the PI upon conclusion of the clinical trial. In exceptional cases, serum infliximab levels will be reported to clinicians in the standard clinical care arm during the trial upon request.

6.4 Safety and Tolerability Assessments

Safety will be monitored by vital signs, laboratory tests (paragraph 6.1) and the collection of AEs at every 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 CRF. For details on AE collection and reporting, refer to Section 7 and appendix 15.14.

6.4.1 Vital signs

Vital signs including pulse rate, systolic and diastolic blood pressure and body weight will be assessed at all visits. Height will be measured at baseline.

6.5 Assessments of efficacy

6.5.1 General efficacy assessments:

Patient Global Assessment of Disease Activity (PGA)

PGA is measured on a 100 mm visual analogue scale (VAS) according to the question: "How active was your disease on average during the last week?"

Physician Global Assessment of Disease Activity (PhGA)

PhGA is measured on a 100 mm VAS "Please rate the patient's overall (global) disease activity."

Inflammation assessment by biochemical parameters

Inflammation is measured by C-reactive protein (CRP), the Erythrocyte Sedimentation Rate (ESR) for the inflammatory joint diseases, fecal calprotectin for the inflammatory bowel diseases according to hospital/laboratory standard procedures.

6.5.2 Disease specific efficacy assessments: RA, PsA

Disease Activity Score using 28 joints (DAS28)

The DAS28 composite score includes the 28 tender and swollen joint counts, ESR and a PGA on a VAS (PGA, see above).(48) The DAS28 is calculated as follows:

DAS28 = 0.56*sqrt(tender28) + 0.28*sqrt(swollen28) + 0.70*Ln(ESR) + 0.014*PGA

High disease activity is defined as a DAS28 value >5.1, moderate disease activity as DAS28 >3.2 – 5.1, low disease activity as a DAS28-value of 2.6 – 3.2, and remission as DAS28 <2.6

Rheumatoid Arthritis Impact of Disease (RAID) score

The RAID questionnaire was developed by the European League Against Rheumatism (EULAR) as a patient-derived composite score.(49) 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). See appendix 15.2. The rates of each domain are weighted and summed to form a score in the range of 0-10. It will only be used for patients with RA.

Psoriatic Arthritis Impact of Disease (PsAID) score

The PsAID questionnaire with 9 domains of health (PsAID-9) was developed by EULAR to calculate a score for clinical trials reflecting the impact of PsA from the patient's perspective.(50) The nine domains with relative weights are: pain (0.174), fatigue (0.131), skin (0.121), work and/or leisure activities (0.110), function (0.107), discomfort (0.098), sleep (0.089), coping (0.087) and anxiety (0.085), each rated on an NRS (0-10). See appendix 15.3. The rates of each domain are weighted and summed to form a score in the range of 0-10. It will only be used for patients with PsA.

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

The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) have been developed to provide physicians and patients with simple and more comprehensible instruments for assessment of disease activity in RA.(51) 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. The formula for SDAI is SJC28 + TJC28 + PGA/10 + EGA/10 + CRP/10. The formula for CDAI is SJC28 + TJC28 + PGA/10 + EGA/10. It will only be used for patients with RA.

Disease Activity index for PSoriatic Arthritis (DAPSA)

Disease Activity index for PSoriatic Arthritis (DAPSA) has been developed using clinical trial and observational data. The DAPSA is simply calculated by summing swollen + tender joint counts + patient pain + patient global assessments + CRP, using 66/68 joint counts.

6.5.3 Disease specific efficacy assessments: SpA

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI was developed to define disease activity in patients with ankylosing spondylitis.(52) It includes six questions pertaining to the five major symptoms of ankylosing spondylitis: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness duration and morning stiffness severity. Each question is scored on an NRS (0-10). The two morning stiffness scores are averaged and added to the average of the other scores forming a total score in the range of 0-10. Se appendix 15.4.

Ankylosing Spondylitis Disease Activity Score (ASDAS)

The ASDAS composite score includes

- Total back pain: NRS 0-10 (0=none, 10=very severe) according to the BASDAI Question 2 ("How would you describe the overall level of AS neck, back or hip pain you have had during the last week")

- Patient global assessment of disease activity: NRS 0-10 (0=none, 10=Very severe) of the question ”How active was your spondylitis on average during the last week?”. The general PGA score described in section 6.5.1 will be used.
- Peripheral pain/swelling: NRS 0-10 (0=none, 10=very severe) according to the BASDAI Question 3 (“How would you describe the overall level of pain/swelling in joints other than neck, back or hip you have had during the last week”).
- Duration of morning stiffness: NRS 0-10 (0=0h, 5=1h, 10=2h or more) according to the BASDAI Question 6 (“How long does your morning stiffness last from the time you wake up during the last week?”)
- C-reactive protein (CRP) in mg/liter

The ASDAS-CRP is calculated as follows:
ASDAS=0.121*total back pain + 0.110*patient global + 0.073*peripheral pain/swelling + 0.058*duration of morning stiffness + 0579*ln(CRP+1)
Very high disease activity is defined as an ASDAS value >3.5, high disease activity as ASDAS 2.1 – 3.5, moderate disease activity as ASDAS 1.3 – 2.1 and inactive disease as ASDAS < 1.3.(53)

6.5.4 Disease specific efficacy assessments: Ulcerative colitis

Partial Mayo Score

The Mayo score is one of the most commonly used activity indices in placebo-controlled clinical trials for ulcerative colitis. It consists of four components (rectal bleeding, stool frequency, physician rating of disease activity, and mucosal appearance at endoscopy) rated from 0–3 that are summed to give a total score that ranges from 0–12. The non-invasive partial Mayo score does not require an endoscopy, and thereby ranging from 0-9.(54) Remission is defined as a partial Mayo score of ≤ 2 with no individual subscore >1.See appendix 15.5.

6.5.5 Disease specific efficacy assessments: Crohn’s disease

Harvey-Bradshaw Index (HBI)

The Harvey-Bradshaw index (55) was presented in 1980 as a simpler version of the Crohn's disease activity index (CDAI) to quantify the symptoms of Crohn’s disease. It consists of only clinical parameters. Remission is defined as a HBI score ≤ 4 points. See appendix 15.6.

6.5.6 Disease specific efficacy assessments: Psoriasis

Psoriasis Area and Severity Index (PASI)

The PASI is the most commonly used activity score in clinical trials for psoriasis. It is a measure of redness, thickness and scaliness of lesions (each graded 0-4), weighted by the area and location of involvement. It scores from 0 (no disease) to 72 (maximal disease severity). PASI examines four body regions: i) the head and neck, ii) the hands and arms, iii) the chest, abdomen and back (trunk) and iv) the buttocks, thighs and legs.

Intensity
A representative area of psoriasis is selected for each body region. The intensity of redness, thickness and scaling of the psoriasis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4). Calculation for intensity: The three intensity scores are added up for each of the four body regions to give subtotals A1, A2, A3, A4.

Each subtotal is multiplied by the body surface area represented by that region.

- A1 x 0.1 gives B1
- A2 x 0.2 gives B2
- A3 x 0.3 gives B3
- A4 x 0.4 gives B4

Area
The percentage area affected by psoriasis is evaluated in the four regions of the body. In each region, the area is expressed as nil (0), 1-9% (1), 13-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6).

- Head and neck
- Upper limbs
- Trunk
- Lower limbs

Calculations for area: Each of the body area scores is multiplied by the area affected.

- B1 x (0 to 6)= C1
- B2 x (0 to 6)= C2
- B3 x (0 to 6)= C3
- B4 x (0 to 6)= C4

Total score
The PASI score is C1 + C2 + C3 + C4

A PASI 50/75 means a 50% /75% reduction in the PASI score.

6.5.7 Definition of disease worsening

- **Disease worsening in RA and PsA**

A disease worsening in RA and PsA is defined as an increase in DAS28 of ≥ 1.2 from randomization and a minimum DAS score of 3.2.

- **Disease worsening in SpA**

A disease worsening in SpA is defined as an increase in ASDAS of ≥1.1 from randomization and a minimum ASDAS of 2.1.

- **Disease worsening in ulcerative colitis**

A disease worsening in ulcerative colitis is defined as an increase in Partial Mayo score of ≥ 3 points from randomization and a minimum partial Mayo score of ≥ 5 points.

- **Disease worsening in Crohn's disease**

A disease worsening in Crohn's disease is defined as an increase in HBI of ≥ 4 points from randomization and a minimum HBI score of 7 points.

- **Disease worsening in psoriasis**

A disease worsening in psoriasis is defined as an increase in PASI of ≥ 3 points from randomization and a minimum PASI score of 5.

- **Patient and investigator consensus on disease worsening**

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

A major change* in treatment includes; Switching from INX to another biological drug or adding either a biological drug or a a sDMARD/immunosuppressive drug, increasing the dose of a concomitant sDMARD/immunosuppressive drug, adding systemic glucocorticoids (po., iv. or im.), receiving more than one i.a. glucocorticoid injection at one visit. If the INX dose is increased for clinical reasons this should also be regarded as a major change in treatment (applies to the control arm only).

6.5.8 Definition of remission

- **Remission in RA and PsA**

Remission in RA and PsA is defined as a DAS 28 <2.6

- **Remission in SpA**

Remission in SpA is defined as a ASDAS <1.3

- **Remission in UC**

Remission in UC is defined as a Partial Mayo score ≤2 with no subscores >1

- **Remission in CD**

Remission in CD is defined as a HBI≤4

- **Remission in Ps**

Remission in Ps is defined as a PASI ≤ 4

6.5.9 Definition of improvement

- **Improvement in RA and PsA**

Improvement is defined as a decrease in DAS28 of ≥1.2 from baseline

- **Improvement in SpA**

Improvement is defined as a decrease in ASDAS of ≥1.1 from baseline

- **Improvement in UC**

Improvement in UC is defined as a decrease in the partial Mayo score of ≥ 3 points from baseline or a partial Mayo score of 0

- **Improvement in CD**

Improvement in CD is defined as a decrease in HBI of ≥ 4 points from baseline

- **Improvement in Ps**

Improvement in Ps is defined as PASI 50 (A 50% decrease in the PASI obtained at baseline)

- **Patient and investigators consensus on improvement**

If there is a consensus between the patient and the investigator that there has been an improvement, it should be considered as an improvement even if the formal definition has not been met.

6.6 Other Assessments

Modified Heath Assessment Questionnaire

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 Modified Health Assessment Questionnaire (MHAQ) reduced the number of items from 20 in the original HAQ to eight, and improved the feasibility in clinical practice.(56) 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. See appendix 15.7. The MHAQ will only be presented to patients with IJD.

Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is widely used tool to measure health-related quality of life in patients with inflammatory bowel diseases. The questionnaire consists of 32 questions scored in four domains: bowel symptoms, emotional health, systemic systems and social function.(57) The IBDQ will only be presented to patients with IBD. See appendix 15.8.

Dermatology Life Quality Index (DLQI)

The DLQI is a simple self-administered, easy and user-friendly validated questionnaire used to measure the health-related quality of life of adult patients suffering from a skin disease.(58) It consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health related quality of life over the last week. It has been validated for adult dermatology patients aged 16 years and older. The items of the DLQI encompass aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each question is scored on a 4-point Likert scale: Not at all/Not relevant=0, A little=1, A lot=2 and Very much=3. Scores of individual items (0-3) are added to yield a total score (0-30); higher scores mean greater impairment of patient's QoL. The DLQI will only be presented to patients with chronic plaque psoriasis and psoriatic arthritis. See appendix 15.9 .

SF-36

The SF-36 is a multi-purpose, short-form health survey with 36 questions.(59) 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).(60) 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. See appendix 15.10.

EQ-5D

EQ-5D is a utility instrument for measurement of health related quality of life.(61) Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. See appendix 15.11.

Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)

Worker productivity is generally subdivided into 2 components: absenteeism and presenteeism. The concept of absenteeism has been defined as productivity loss due to health-related absence from work, while presenteeism refers to reduced performance or productivity while at work due to health reasons. Absenteeism may include personal time off, sick days off work, time on short and/or long-term work disability, or time on worker's-compensated days; and presenteeism could be characterized as the time not being on the task, or decreased work quality and quantity. Patients will be asked to answer the Work

Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH).(62) See appendix 15.12.
The WPAI yields four types of scores:

1. Absenteeism (work time missed)
2. Presenteeism (impairment at work/reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment

Resource use and related data

The following types of resource use will be captured:

- Use of biologics
- Use of other pharmaceuticals (Norwegian Prescription Database)
- Use of somatic hospital services (in-patient and out-patient)(Norwegian Patient Register)
- Use of GP services and emergency room services (HELFO/KUHR database - The Norwegian Health Economics Administration database)
- Use of social benefits (NAV database)
- Use of nursing services (IPLOS database)

Drug dose

The drug dose given will be registered at each visit.

7 SAFETY MONITORING AND REPORTING

7.1 Adverse events

Any adverse event (AE) encountered during the clinical study will be reported in the eCRF (see appendix for definitions). AE should 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.

7.1.1 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.
- The intensity of the adverse event will be graded as mild, moderate, severe, life threatening and death

- The Causal relationship of the event to the study medication will be assessed as one of the following:

  Unrelated:

  There is not a temporal relationship to the administration of the study drug or there is a reasonable causal relationship between concomitant medication, concurrent disease, or circumstance and the AE.

  Unlikely:

  There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.

  Possible:

  There is reasonable causal relationship between the study drug and the AE. Dechallenge information is lacking or unclear.

  Probable:

  There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge is not required.

  Definite:

  There is a reasonable causal relationship between the study drug and the AE.

- Action taken
  The outcome of the adverse event – whether the event is resolved or still ongoing.

7.1.2 Serious adverse events

In case of a serious adverse event (defined in 15.14) the investigator should if clinically indicated send a report to RELIS.

7.2 Laboratory test abnormalities

Laboratory test results are recorded in the eCRF and abnormalities should not be recorded as AE unless there is an associated clinical condition for which the patient is given treatment or the current treatment is altered. In the event of a medically significant unexplained abnormal laboratory test value the test should be followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

7.3 Pregnancy

A female patient must be instructed to immediately inform the investigator if she becomes pregnant during the study. If clinically contraindicated to continue INX therapy the patient should be withdrawn from the study.

8 DATA MANAGEMENT

8.1 Electronic Case Report Forms (CRFs)

The designated investigator staff will enter the data required by the protocol into the electronic Case report forms (eCRF). The Principal Investigator is responsible for assuring that data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner. The electronic signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections will also be recorded. A complete list of authorised study personnel will be maintained during the study, and only study personnel authorised by the principal investigator or coordinating investigator will be allowed to sign the eCRF.
After database lock, the investigator will receive the subject data for archiving at the investigational site.
A web-based eCRF software solution will be used to collect study data (Viedoc™, Uppsala, Sweden).

8.2 Source Data

The medical records for each patient should contain information, which is important for the patient's safety and continued care, and to fulfil the requirement that critical study data should be verifiable.
To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study
- Date when Informed Consent was obtained from the patient
- Results of assessments performed during the study that will have an impact of future follow-up of the patient
- Treatments given, changes in treatments during the study and the time points for the changes;
- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, discontinuation from study treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available
- Additional information according to local regulations and practice.

Patient reported outcome (PRO) measures not recorded in an electronic patient journal (EPJ) system is recorded on paper CRFs or directly into the eCRF. If these measures are recorded

directly in the eCRF, the eCRF is source data. If they are recorded on paper and then entered into the eCRF, then the paper CRF is source data.

8.3 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc.) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Randomisation

9.1.1 Allocation- sequence generation

NOR-DRUM A:
Eligible patients will be allocated in a 1:1 ratio between intervention and control, using a computer randomisation procedure stratified by diagnosis (RA, SpA, PsA, UC, CD, Ps). The randomisation will be blocked within each stratum.
Details of block size and allocation sequence generation will be provided in a separate document unavailable to those who enrol patients or assign treatment.

NOR-DRUM B:
Eligible patients will be allocated in a 1:1 ratio between intervention and control, using a computer randomisation procedure stratified by diagnosis (RA, SpA, PsA, UC, CD, Ps) and 1) by study arm (intervention or control) if the patient originates from NOR-DRUM A or 2) by prior or no prior TDM in the clinic (defined as one or more assessments of serum drug level during the last 3 infusions) if the patient originates from NOR-DRUM B. The randomisation will be blocked within each stratum.
Details of block size and allocation sequence generation will be provided in a separate document unavailable to those who enrol patients or assign treatment.

9.1.2 Allocation- procedure to randomise a patient

The computer-generated randomised allocation sequence will be imported into the eCRF system and made available to site personnel. The allocation will not be available until the patient has signed the informed consent form and deemed eligible to participate in the

study. That is, authorized personnel will only know the allocation of included patients, but not for future patients.

9.2 Planned analyses

The statistical analysis for each part of the study is planned when

- The planned number of patients in each part have been included
- All included patients have either finalised their last assessment of the study part or has/is withdrawn according to protocol procedures
- All data from the intervention period have been entered, verified and validated according to the data management plan

Prior to the statistical analysis, the data for each respective study part will be locked for further entering or altering of data. Separate statistical analysis plans (SAP) for each study part will provide further details on the planned statistical analyses. The SAP will be finalised, signed and dated prior to data lock. There will be a planned interim analysis in NOR-DRUM A when approximately 50% of the required patients have a validated assessment of remission at week 30.
Deviation from the original statistical plan will be described and justified in the Clinical Study Report.

9.3 Populations

9.3.1 Primary population

The primary modified intention to treat (mITT) population will consist of all randomised patients who have been exposed to the allocated intervention. Exposure to the allocated intervention is defined as patients who have received infusion 2 and as well have a recorded treatment decision for infusion 3. The dose at infusion 1 and 2 and the interval between infusion 1 and 2 are not affected by the treatment algorithm (the intervention).

9.3.2 Secondary population

The secondary per-protocol (PP) population will in each of the two study parts consist of all randomised patients who sufficiently comply with the protocol. Criteria for inclusion in the PP population will be specified in the statistical analysis plan, and the final criteria will be defined prior to database lock.

9.3.3 Safety population

The safety population is identical to the primary population (defined in 9.3.1)

9.4 Statistical Analysis

9.4.1 Statistical model

This randomised clinical trial aims primarily to describe and estimate efficacy parameters and test pre-specified statistical hypotheses.
The primary variables will be analysed using logistic regression models with strategy treatment group as primary explanatory variable, adjusted for stratification factors used at randomisation. Although this is a multicentre study, study site will not be used for stratification or adjustment in the analysis due to anticipated small sample sizes within site. However, sensitivity analyses will be performed to assess the impact of site on the study conclusions. Other pre-specified covariates included in sensitivity analyses will be defined in the SAP and include age and use of disease-specific co-medication (methotrexate, azathioprine or similar The statistical analysis plan (SAP) will detail these procedures, as well as alternative and further supportive evaluations, such as analyses including unbalanced baseline predictors or modifications of the logistic regression model in case validity assumptions are not met.
The primary analysis will be performed on the primary intention to treat population.

9.4.2 Primary analyses

There will be two primary hypotheses tested in this study, one for each of the two parts (NOR-DRUM A and B). There will be no adjustments for multiplicity; each part will be regarded as answering independent research questions.

NOR-DRUM A statistical hypothesis (superiority test):

Null hypothesis: There is no difference in proportion of patients in remission at week 30 between the intervention and control group.

Alternative hypothesis: There is a difference in proportion of patients in remission at week 30 between the intervention and control group.

The primary variable will be evaluated by the p-value of the hypothesis test from the logistic regression analysis. A conclusion of superiority of any of the treatment strategies will be made if the null hypothesis is rejected on an overall significance level of 5%. If the study fails to reject the primary null hypothesis, non-inferiority of TDM vs standard care will be assessed. Non-inferiority implies that the 95% confidence limits of the estimated adjusted risk difference of disease worsening lies fully within the non-inferiority margin of 15%.

NOR-DRUM B statistical hypothesis (superiority test):

Null hypothesis: There is no difference in proportion of patients in sustained disease control throughout the study period without disease worsening between the intervention and control group.

Alternative hypothesis: There is a difference in proportion of patients in sustained disease control throughout the study period without disease worsening between the intervention and control group.

The primary variable will be evaluated by the p-value of the hypothesis test from the logistic regression analysis. A conclusion of superiority of any of the treatment strategies will be made if the null hypothesis is rejected on a significance level of 5%. If the study fails to reject the primary null hypothesis, non-inferiority of TDM vs standard care will be assessed. Non-inferiority implies that the 95% confidence limits of the estimated adjusted risk difference of disease worsening lies fully within the non-inferiority margin of 15%.

9.4.3 Secondary analyses

Between-group comparisons will be performed for the primary endpoints on secondary populations in addition to secondary efficacy endpoints on both efficacy populations.

The between-group comparisons for secondary variables will be tested as for the primary variable where applicable and additional analyses will be performed based on the following methods (but not limited to):

- Continuous secondary variables will be subject to repeated measures mixed models or appropriate non-parametric alternatives
- Binary response variables will be analysed using logistic regression (possibly adjusting for within-subject dependencies by mixed model approaches) or chi-square/Mantel-Haenszel test

- Time-to-event variables will be analysed using the Kaplan-Meier method and comparisons between the two groups will be performed using the log rank test, Cox regression analyses and/or appropriate parametric models such as the Weibull model.

Unless otherwise specified, all statistical hypotheses will be tested as the primary variable, i.e. with an assessment of superiority based on the p-value of the group differences.

Presentation of results:
All efficacy analyses will be presented with the results from the hypothesis testing with estimates and 95% confidence limits of the treatment effect. For the primary variables specifically, this will be the estimated risk differences with corresponding 95% confidence limits and p-value.

9.4.4 Safety analyses

Safety analyses will be descriptive and presented as summary tables by treatment group and (if applicable) by visit.

9.4.5 Patient reported outcome measures and disability analyses

Patient reported outcome measures (PROMs) and disability will be assessed using SF-36, EQ-5D, MHAQ (IJD), IBDQ (IBD) and DLQI (chronic plaque psoriasis). These scores will be summarised by descriptive summary tables at baseline and over time, and at the end of study. Missing data at end of study will be replaced by the last valid post-baseline assessment.

9.4.6 Other analyses/subanalyses

We will perform subgroup analyses according to diagnoses groups (RA, SpA, PsA, UC, CD, Ps) on the appropriate primary and secondary variables using methods described above.
Other exploratory subgroup analyses of primary, secondary and exploratory efficacy variables may be performed if appropriate. The decision to include such analyses will be made on basis of the collected data.

9.4.7 Health economic analyses

All patients will, with assistance from a study nurse, be asked to fill in the two standard instruments (questionnaires) to capture health related quality of life (HRQOL): SF-36 and EQ-5D. These instruments will be used at each visit.
Use of health care (costs) will be captured by the following registers: The Norwegian Patient Register (hospital services), The Norwegian Prescription Register (pharmaceuticals), The Norwegian Health Economics Administration database (emergency room and general practitioner services), Statistics Norway KOSTRA database (nursing services) and the Norwegian Welfare and Labour Administration NAV (social benefits). We will assign unit costs to each type of service by means of the DRG price list, and the price list of the Norwegian Medicines Agency. For each patient we will, based on HRQOL data, estimate the number of QALYs obtained during the study period in line with methods used previously (Bohmer et al. 717-23;Fjalestad et al. 599-605) and adjust for any baseline imbalances (Manca, Hawkins, and Sculpher 487-96). We will use EQ-5D and also translate SF-36-data into utilities according to a validated method (Brazier, Roberts, and Deverill 271-92). For each patient we will estimate one year costs based on register data for utilisation of health care and the unit costs. The mean week QALYs and cost in the two treatment arms will be used to estimate an incremental cost-effectiveness ratio (ICER), for all patients and according to diagnostic group. Not all patients in the randomised trial will have complete months data. We will therefore impute missing data (Glick and Doshi). We will use bootstrapping to estimate confidence intervals of the incremental costs and QALYs and to present uncertainty in cost-effectiveness acceptability curves.

9.4.8 Missing data

Methods to handle missing data may include mixed effect modelling, complete case analyses, last observation carried forward, worst case/best case imputation and multiple imputation techniques. Further details on missing data will be given in the SAP.

9.5 Sample size determination

Sample sizes are determined for each of the two study parts separately.

NOR-DRUM A: Under the assumption of an absolute increase in remission rate of 15% (from 40 to 55%) we need a maximum of 358 completed patients in order to reject the null hypothesis on a 5% significance level with 80% power. The sample size calculation incorporates an interim analysis when approximately 50% of the patients have a validated assessment of remission at week 30. Adjusting for possible drop-outs, we plan to randomise 400 patients.

NOR-DRUM B: Under the assumption of an absolute decrease in proportion of patients with disease worsening of 12.5% (from 30 to 17.5%) we need 414 completed patients in order to reject the null hypothesis on a 5% significance level with 85% power. Adjusting for possible drop-outs, we plan to randomise 450 patients.

9.6 Interim analyses

NOR-DRUM A:
A formal interim efficacy analysis in NOR-DRUM A will be performed after approximately 50% of the patients have a validated assessment of remission at week 30. An independent statistician can recommend to the study group whether to continue, modify or stop the clinical trial on the basis of efficacy considerations. The pre-planned interim efficacy analysis will assess the intervention effectiveness on the primary efficacy endpoint, with the intent to stop the study early if there is overwhelming evidence of intervention benefit or futility.

The Lan-DeMets alpha-spending approach will be applied with a gamma cumulative alpha spending stopping boundary (gamma=-2) for primary hypothesis test. A significance level of 0.00672 on the upper and lower boundaries will be used for the interim analysis so support early termination for efficacy. The significance level at the final analysis will depend on the exact numbers of patients at the time of the interim analysis, but is expected to be of the order of 0.0227 on each of the upper and lower tails, preserving the overall significance level at 5% (two-sided).

A decision of stopping for futility will also be made based on the interim analysis. A pre-defined beta-spending function will be applied where some of the type 2 error rate (beta) will be spent on the interim analysis according to the gamma cumulative spending function

(gamma=-2). A one-sided p-value boundary of 0.32 is defined as indicative for futility at the interim analysis. However, additional information may be addressed by the independent statistician in order to give a recommendation of stopping for futility. Such information could be the conditional power, simulation analyses in addition to analyses of secondary endpoints.

Specifications of the duties of the independent statistician will be described in a separate procedure document.

10 STUDY MANAGEMENT

10.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

10.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported as appropriate.

10.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Ethics Committee according to national regulations.

11 ETHICAL REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with applicable laws and regulations. Registration of patient data will be carried out in accordance with national personal data laws.

11.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, has been approved by the regional ethics committee before enrolment of any patients into the study.

The principle investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

11.2 Other Regulatory Approvals

The protocol will be registered in www.clinicaltrials.gov before inclusion of the first patient.

11.3 Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.
It will be emphasised that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. The patient will be given ample time to consider participation. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent. A copy will be given to the patients.
A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder.

11.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses. The patients will be identified in the eCRFs by patient number, initials and date of birth.

12 TRIAL SPONSORSHIP AND FINANCING

The medical treatment will be covered as for "usual care" by "Folketrygden/NAV". There will be no procedures/examinations that are not part of "usual care".

13 PUBLICATION POLICY

Upon study completion and finalisation of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results.
The results of this study will also be submitted to the Ethics Committee according to national regulations. 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.

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15 APPENDICES

15.1 Trial flow charts

NOR DRUM A

Visits	Screening Evaluation	Baseline visit	Other visits	Week 14 visit	Week 30 visit	Extra visit	End of study visit
Weeks		0		14 (+/-2) weeks	30 (+/-2) weeks		38 (+/-4) weeks
Informed consent	X						
Eligibility assessment	X	X					
Randomisation		X					
Demographics		X					
Medical history		X					
Comorbidities		X	X	X	X	X	X
Physical Examination[7)]		X					
Body weight		X	X	X	X		X
Pregnancy test	X						
Vital signs [1)]		X	X	X	X	X	X
Laboratory samples[2)]	X	X	X	X	X	X	X
Biobank samples		X[3)]	X[4)]	X[4)]	X	X	X[4)]

Patient reported outcomes[5)]		X	X	X	X	X	X
Assessments of disease activity[6)]		X	X	X	X	X	X
Adverse event		X	X	X	X	X	X
Record of concomitant medication		X	X	X	X	X	X
Evaluation by investigator		X		X	X	X	X
Evaluation of efficacy and treatment decision by investigator				X	X	X	X
Treatment administration according to randomised strategy		X	X	X	X		X
Establishing dose and interval to the next infusion by investigator		X	X	X	X		X

NOR DRUM B

Visits	Screening	Baseline visit	Regular visit	Extra visit if disease worsening	End of study visit
Weeks		0			52 (+/-4 weeks)
Informed consent	X				
Eligibility assessment	X	X			
Randomisation		X			
Demographics		X			
Medical history		X			
Comorbidities		X	X	X	X
Physical Examination[7)]		X			
Body weight		X	X	X	X
Vital signs [1)]		X	X	X	X
Laboratory samples[2)]	X	X	X	X	X
Biobank samples		X[3)]	X[4)]	X[4)]	X[4)]
Patient reported outcomes[5)]		X	X	X	X
Assessments of disease activity[6)]		X	X	X	X

Adverse events		X	X	X	X
Record of concomitant medication		X	X	X	X
Treatment administration according to randomised strategy		X	X		X
Establishing dose and interval to the next infusion by investigator		X	X		X

1. Blood pressure and pulse rate
2. Hemoglobin, white blood cells with differentials, platelet counts, ALT, albumin, creatinine, CRP, ESR, faecal calprotectin (IBD)
3. Serum and fullblood
4. Only serum
5. Consisting of:

   – Patient Global Assessment of disease activity (NRS)
   – EQ-5D
   – SF-36 (except for NOR-DRUM A V2 and V3)
   – WPAI-GH
   – RA: M-HAQ RAID
   – PsA: M-HAQ, PsAID, DLQI
   – SpA: M-HAQ, BASDAI
   – UC and CD: IBDQ
   – Psoriasis: DLQI
6. Consisting of:

   – Nurse/investigator global assessment of disease activity (NRS)
   – RA: DAS28, CDAI, SDAI
   – PsA : DAS28, DAPSA
   – SpA: ASDAS
   – UC: Partial Mayo score

- CD: HBI
- Psoriasis: PASI

7. Heart, lungs, lymph nodes, abdomen, peripheral oedema, height

15.2 RAID questionnaire

RAID

Smerte
Sett ring rundt det tallet som best beskriver smerten du kjente pga din leddgikt i løpet av den siste uken:

0	1	2	3	4	5	6	7	8	9	10
Ingen smerte										Ekstrem Smerte

Måling av fysisk funksjon
Sett ring rundt det tallet som best beskriver vanskeligheten du hadde med å gjøre daglige fysiske aktiviteter pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10
Ingen vanskelighet										Ekstrem vanskelighet

Fatigue/utmattelse
Sett ring rundt det tallet som best beskriver hvor mye fatigue/utmattelse du kjente pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10
Ingen fatigue										Totalt utmattet

Søvn
Sett ring rundt det tallet som best beskriver søvnvansker (hvile om natten) du følte pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10
Ingen vansker										Ekstreme *vansker*

Fysisk velvære
Tatt i betraktning din leddgikt generelt, hvordan ville du gradere nivået av fysisk velvære i løpet av den siste uken? Sett ring rundt det tallet som best beskriver nivået av fysisk velvære.

0	1	2	3	4	5	6	7	8	9	10
Veldig bra										Veldig dårlig

Følelsesmessig velvære
Tatt i betraktning din leddgikt generelt, hvordan vil du gradere nivået av følelsesmessig velvære i løpet av den siste uken. Sett ring rundt det tallet som best beskriver nivået av følelsesmessig velvære.

0	1	2	3	4	5	6	7	8	9	10
Veldig bra										Veldig dårlig

Mestring
Tatt i betraktning din leddgikt generelt, hvor bra mestret (taklet, styrte, kontrollerte) du din sykdom i løpet av den siste uken? Sett ring rundt det tallet som best beskriver din mestring.

0	1	2	3	4	5	6	7	8	9	10
Veldig bra										Veldig dårlig

15.3 PsAID Questionnaire

PSAID-9 Norwegian

Kan du vennligst beskrive for oss hvordan du har følt deg i uken som gikk.

Smerte

Sett ring rundt det tallet som best beskriver smerten du hadde som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt sterke

1. Hudproblem

Sett ring rundt det tallet som best beskriver de hudproblemene (inkludert kløe) du hadde som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

2. Utmattelse/tretthet

Sett ring rundt det tallet som best beskriver det generelle nivået av utmattelse/tretthet du hadde som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Totalt utmattet

3. Arbeid og/eller fritidsaktiviteter

Sett ring rundt det tallet som best beskriver de problemene du hadde med fullt og helt å kunne utføre arbeid og/eller fritidsaktiviteter som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

4. Fysisk funksjon

Sett ring rundt det tallet som best beskriver vanskelighetene du hadde med å utføre fysiske aktiviteter som følge av psoriasisgikt siste uke:

Ingen problem	0	1	2	3	4	5	6	7	8	9	10	Ekstremt vanskelig

5. Følelse av ubehag

Sett ring rundt det tallet som best beskriver følelsen av ubehag og irritasjon med daglige gjøremål som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

6. Søvnforstyrrelser

Sett ring rundt det tallet som best beskriver søvnproblemene (dvs. nattesøvn) du hadde som følge av psoriasisgikt siste uke:

Ingen problem	0	1	2	3	4	5	6	7	8	9	10	Ekstremt vanskelig

7. Engstelse, frykt og usikkerhet

Sett ring rundt det tallet som best beskriver nivået på engstelse, frykt og usikkerhet (f.eks. om fremtiden, behandlinger, frykt for ensomhet) som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

8. Mestring

Når du tar vurderer din psoriasisgikt generelt i løpet av siste uke, sett ring rundt det tallet som best beskriver mestringsnivået (hvordan du tilpasset deg, håndterte, klarte deg, taklet sykdommen) ditt:

Meget bra	0	1	2	3	4	5	6	7	8	9	10	Meget dårlig

15.4 BASDAI questionnaire

Fatigue

1 How would you describe the overall level of fatigue/tiredness you have experienced?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Spinal pain

2 How would you describe the overall level of AS neck, back or hip pain you have had?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Peripheral arthritis

3 How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Enthesitis

4 How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Intensity of morning stiffness

5 How would you describe the overall level of morning stiffness you have had from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Duration of morning stiffness

6 How long does your morning stiffness last from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

0 h 1 h 2 or more h

15.5 Partial Mayo Score

	Assessment Category		
Score	**Stool frequency[1]**	**Rectal bleeding[2]**	**Physician's global assessment[3]**
0	Normal number of stools	No blood seen	Normal
1	One to two stools more than normal	Streaks of blood with stool less than half the time	Mild disease
2	Three to four stools more than normal	Obvious blood with stool most of the time	Moderate disease
3	Five or more stools than normal	Blood alone passes	Severe disease
Subscore	0-3	0-3	0-3

1. Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
2. The daily bleeding score represents the most severe bleeding of the day.
3. The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well being, and other observations, such as physical findings and the patient's performance status.

15.6 Harvey-Bradshaw Index

1. General well-being (yesterday)	☐ Very well = 0 ☐ Slightly below par = 1 ☐ Poor = 2 ☐ Very poor = 3 ☐ Terrible = 4
2. Abdominal pain (yesterday)	☐ None = 0 ☐ Mild = 1 ☐ Moderate = 2 ☐ Severe = 3
3. Number of liquid or soft stools per day (yesterday) =	
4. Abdominal mass	☐ None = 0 ☐ Dubious = 1 ☐ Definite = 2 ☐ Definite and tender = 3
5. Complications (Check any that apply; score one per item except for first box)	☐ None ☐ Arthralgia ☐ Uveitis ☐ Erythema nodosum ☐ Aphthous ulcers ☐ *Pyoderma gangrenosum* ☐ Anal fissure ☐ New fistula ☐ Abcess

Add scores of questions 1 through 5 to compute the Harvey-Bradshaw Index

15.7 MHAQ

Please check the response that best describes your usual abilities OVER THE COURSE OF THE LAST WEEK

Are you able to:	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Dress yourself, including tying shoelaces and doing buttons?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of bed?	☐ 0	☐ 1	☐ 2	☐ 3
Lift a full cup or glass to your mouth?	☐ 0	☐ 1	☐ 2	☐ 3
Walk outdoors on flat ground?	☐ 0	☐ 1	☐ 2	☐ 3
Wash and dry your entire body?	☐ 0	☐ 1	☐ 2	☐ 3
Bend down to pick up clothing from the floor?	☐ 0	☐ 1	☐ 2	☐ 3
Turn regular faucets on and off?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of a bus, car, train, or airplane?	☐ 0	☐ 1	☐ 2	☐ 3

15.8 IBDQ

SPØRRESKJEMA OM LIVSKVALITET HOS PASIENTER MED INFLAMMATORISK TARMSYKDOM

1. Hvor ofte har du hatt avføring i **de siste to ukene**?:

(Sett ring rundt et tall)

Hyppigere enn eller like hyppig som på det verste	1
Ekstremt hyppig i forhold til vanlig avføringsmønster	2
Veldig hyppig i forhold til vanlig avføringsmønster	3
Moderat økning i forhold til vanlig avføringsmønster	4
Noe økning i forhold til vanlig avføringsmønster	5
Liten økning i forhold til vanlig avføringsmønster	6
Som normalt, ingen økning i forhold til vanlig avføringsmønster	7

2. Hvor stor del av tiden **de to siste ukene** har følelsen av tretthet eller det å ha vært trett og utslitt vært et problem for deg?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

3. Hvor stor del av tiden **de to siste ukene** har du følt deg frustrert, utålmodig eller rastløs?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

4. Hvor ofte i løpet av **de to siste ukene** har du vært hjemme fra skolen eller jobben eller måttet avstå fra husarbeide pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

5. Hvor stor del av tiden **de to siste ukene** har du vært plaget av løs avføring?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

6. Hvor mye arbeidslyst har du hatt i **de to siste ukene**?

(Sett en ring rundt et tall)

Ingen arbeidslyst	1
Svært liten arbeidslyst	2
Lite arbeidslyst	3
Noe arbeidslyst	4
En god del arbeidslyst	5
Mye arbeidslyst	6
Full av arbeidslyst	7

7. Hvor stor del av tiden **de to siste ukene** har du vært bekymret ved tanken på at du kanskje måtte opereres pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

8. Hvor stor del av tiden **de to siste ukene** har du måttet tilpasse eller avlyse din vanlige sosiale omgang med familie, venner, naboer eller foreninger som følge av din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

9. Hvor ofte har du hatt mageknip i løpet av **de to siste ukene**?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

10. Hvor stor del av tiden **de to siste ukene** har du følt deg i dårlig form?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

11. Hvor stor del av tiden **de to siste ukene** har du vært bekymret for ikke å finne et toalett?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

12. Hvor store vanskeligheter har din tarmsykdom medført **de to siste ukene**, med tanke på å utøve fritids- eller sportsaktiviteter som du liker å gjøre?

(Sett ring rundt et tall)

Meget store vanskeligheter, aktiviteter har vært umulig å utføre	1
Store vanskeligheter	2
En god del vanskeligheter	3
Noen vanskeligheter	4
Små vanskeligheter	5
Nesten ingen vanskeligheter	6
Ingen vanskeligheter, aktiviteter har vært utført som vanlig	7

13. Hvor stor del av tiden **de to siste ukene** har du hatt smerter i fra magen?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

14. Hvor stor del av tiden **de to siste ukene** har du hatt problemer med å få sove eller våknet om natten?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

15. Hvor stor del av tiden **de to siste ukene** har du følt deg deprimert eller motløs?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

16. Hvor stor del av tiden **de to siste ukene** har du måttet unngå å delta på møter og sammenkomster fordi du var usikker på om det var et toalett i nærheten?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

17. Hvor stort problem har luftavgang vært for deg **de to siste ukene**? (Med luftavgang menes her behov for å «slippe seg», ofte forbundet med lindring av følelse av oppblåsthet.)

(Sett ring rundt et tall)

Et meget stort problem	1
Et stort problem	2
En god del problem	3
Noe problem	4
Lite problem	5
Svært lite problem	6
Ikke noe problem	7

18. Hvor stort problem har det vært for deg å opprettholde eller oppnå den vekten du helst vil ha **de to siste ukene**?

(Sett ring rundt et tall)

Et meget stort problem	1
Et stort problem	2
En god del problem	3
Noe problem	4
Lite problem	5
Svært lite problem	6
Ikke noe problem	7

19. Mange pasienter med tarmsykdom føler ofte bekymring og engstelse i forhold til sin sykdom. Dette kan være redsel for å få kreft i tarmen, redsel for aldri å bli bedre av sin sykdom eller redsel for å få nye utbrudd av sykdommen.
Hvor stor del av tiden **de to siste ukene** har du vært bekymret eller engstelig?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

20. Hvor stor del av tiden **de to siste ukene** har du vært plaget med oppblåsthet i magen? (Med oppblåsthet menes utspiling, ofte forbundet med en følelse av luft i magen)

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

21. Hvor stor del av tiden **de to siste ukene** har du følt deg avslappet og fri for stress?

(Sett ring rundt et tall)

Ikke i det hele tatt	1
Nesten ikke i det hele tatt	2
Litt av tiden	3
Omtrent halvparten av tiden	4
En god del av tiden	5
Mesteparten av tiden	6
Hele tiden	7

22. Hvor stor del av tiden **de to siste ukene** har du hatt problemer med blødning fra endetarmen i samband med avføring?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

23. Hvor stor del av tiden **de to siste ukene** har du følt deg brydd pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

24. Hvor stor del av tiden **de to siste ukene** har du hatt følelse av å skulle på toalettet uten at det har vært noe avføring?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

25. Hvor stor del av tiden **de to siste ukene** har du følt deg nedfor eller motløs?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

26. Hvor stor del av tiden **de to siste ukene** har du vært «uheldig» og hatt avføring i underbuksene?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

27. Hvor stor del av tiden **de to siste ukene** har du vært sint pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

28. I hvilken utstrekning har din tarmsykdom begrenset din seksuelle aktivitet i løpet av **de to siste ukene**?

(Sett ring rundt et tall)

Har ikke hatt sex på grunn av sykdommen	1
Tarmsykdommen har begrenset meg svært mye	2
Tarmsykdommen har begrenset meg mye	3
Tarmsykdommen har begrenset meg noe	4
Tarmsykdommen har begrenset meg lite	5
Tarmsykdommen har begrenset meg svært lite	6
Tarmsykdommen har ikke begrenset meg	7

29. Hvor stor del av tiden **de to siste ukene** har du vært kvalm, uvel eller hatt ubehag fra magen?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

30. Hvor stor del av tiden **de to siste ukene** har du vært irritabel?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

31. Hvor stor del av tiden **de to siste ukene** har du følt en manglende forståelse fra andre?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

32. Hvor glad, fornøyd og tilfreds har du vært **de to siste ukene**?

(Sett ring rundt et tall)

Svært utilfreds, ulykkelig nesten hele tiden	1
Utilfreds og ulykkelig	2
Av og til utilfreds, noe ulykkelig	3
Stort sett tilfreds, fornøyd	4
Tilfreds nesten hele tiden, lykkelig	5
Veldig tilfreds hele tiden, lykkelig	6
Svært tilfreds, kunne ikke vært mer fornøyd	7

15.9 DLQI

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
2.	Over the last week, how embarrassed or self conscious have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from working or studying?	Yes ☐ No ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at work or studying?	A lot ☐ A little ☐ Not at all ☐	
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any sexual	Very much ☐ A lot ☐	

	difficulties?	A little	☐	
		Not at all	☐	Not relevant ☐
10.	Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐

15.10 SF-36

SPØRREUNDERSØKELSE VEDRØRENDE LIVSKVALITET VED INFLAMMATORISK TARMSYKDOM

SF-36

INSTRUKSJON FOR UTFYLLING AV SPØRRESKJEMA SF-36

Dette spørreskjemaet spør om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.

Hvert spørsmål skal besvares ved å sette et kryss i en boks eller en ring rundt det tallet som passer best for deg.
Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan. Det er viktig at du forsøker å besvare alle spørsmålene.
Når du er ferdig vil du få anledning til å gå gjennom spørsmålene med lege/sykepleier. Dette vil ikke ta lang tid.

SF-36 SPØRRESKJEMA OM HELSE

1. Stort sett, vil du si at din helse er:

(Sett kryss i en av boksene)

Utmerket	Meget god	God	Nokså god	Dårlig
☐	☐	☐	☐	☐

2. Sammenlignet med for ett år siden, hvordan vil du si helsen din stort sett er nå? *(sett ring rundt ett tall)*

Mye bedre nå enn for ett år siden..... 1
Litt bedre nå enn for ett år siden..... 2
Omtrent den samme som for ett år siden..... 3
Litt dårligere nå enn for ett år siden..... 4
Mye dårligere nå enn for ett år siden..... 5

3. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

(Sett ring rundt ett tall på hver linje)

	AKTIVITETER	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a.	Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	1	2	3
b.	Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	1	2	3
c.	Løfte eller bære en handlekurv	1	2	3
d.	Gå opp trappen flere etasjer	1	2	3
e.	Gå opp trappen en etasje	1	2	3
f.	Bøye deg eller sitte på huk	1	2	3
g.	Gå mer enn to kilometer	1	2	3
h.	Gå noen hundre meter	1	2	3
i.	Gå hundre meter	1	2	3
j.	Vaske deg eller kle på deg	1	2	3

4. I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

(sett ring rundt ett tall på hver linje)

		JA	NEI
a.	Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter?	1	2
b.	Har du utrettet mindre enn du hadde ønsket?	1	2
c.	Har du vært hindret i visse typer arbeid eller andre aktiviteter?	1	2
d.	Har du hatt vanskeligheter med å utføre arbeidet ditt eller andre aktiviteter? (f.eks fordi det krevde ekstra anstrengelser)	1	2

5. I løpet av de siste 4 ukene, har du hatt følelsesmessige problemer som har ført til vanskeligheter i ditt arbeid eller i andre av dine daglige gjøremål (f.eks. fordi du har følt deg deprimert eller engstelig)?

(sett ring rundt ett tall på hver linje)

		JA	NEI
a.	Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter?	1	2
b.	Har du utrettet mindre enn du hadde ønsket?	1	2
c.	Har du ikke arbeidet eller utført andre aktiviteter like nøye som vanlig?	1	2

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

(Sett kryss i en av boksene)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
☐	☐	☐	☐	☐

7. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 uker?

(sett ring rundt ett tall)

Ingen	1
Meget svake	2
Svake	3
Moderate	4
Sterke	5
Meget sterke	6

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

(Sett kryss i en av boksene)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
☐	☐	☐	☐	☐

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

(Sett ring rundt ett tall på hver linje)

	Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Følt deg full av tiltakslyst?	1	2	3	4	5	6
b. Følt deg veldig nervøs?	1	2	3	4	5	6
c. Vært så lang nede at ingenting har kunnet muntre deg opp?	1	2	3	4	5	6
d. Følt deg rolig og harmonisk?	1	2	3	4	5	6
e. Hatt mye overskudd?	1	2	3	4	5	6
f. Følt deg nedfor og trist?	1	2	3	4	5	6
g. Følt deg sliten?	1	2	3	4	5	6
h. Følt deg glad?	1	2	3	4	5	6
i. Følt deg trett?	1	2	3	4	5	6

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosial omgang (som det å besøke venner, slektninger osv.)?

(Sett kryss i en av boksene)

Hele tiden	Nesten hele tiden	Endel av tiden	Litt av tiden	Ikke i det hele tatt
☐	☐	☐	☐	☐

11. Hvor RIKTIG eller GAL er hver av de følgende påstander for deg?

(Sett ring rundt ett tall på hver linje)

	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
a. Det virker som om jeg blir lettere syk enn andre	1	2	3	4	5
b. Jeg er like frisk som de fleste jeg kjenner	1	2	3	4	5
c. Jeg forventer at min helse vil bli dårligere	1	2	3	4	5
d. Min helse er helt utmerket	1	2	3	4	5

15.11 EQ-5D

	NOEN SPØRSMÅL OM LIVSKVALITET **EQ-5D**	
	Vis hvilke utsagn som passer best på din helsetilstand i dag ved å sette et kryss i en av rutene utenfor hver av gruppene nedenfor.	
	Gange Jeg har ingen problemer med å gå omkring. 1☐ Jeg har litt problemer med å gå omkring. 2☐ Jeg er sengeliggende. 3☐	
	Personlig stell Jeg har ingen problemer med personlig stell. 1☐ Jeg har litt problemer med å vaske meg eller kle meg. 2☐ Jeg er ute av stand til å vaske meg eller kle meg. 3☐	
	Vanlige gjøremål *(for eksempel arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)* Jeg har ingen problemer med å utføre mine vanlige gjøremål. 1☐ Jeg har litt problemer med å utføre mine vanlige gjøremål. 2☐ Jeg er ute av stand til å utføre mine vanlige gjøremål. 3☐	
	Smerte/ubehag Jeg har verken smerte eller ubehag. 1☐ Jeg har moderat smerte eller ubehag. 2☐ Jeg har sterk smerte eller ubehag. 3☐	
	Angst/depresjon Jeg er verken engstelig eller deprimert. 1☐ Jeg er noe engstelig eller deprimert. 2☐ Jeg er svært engstelig eller deprimert. 3☐	

15.12 WPAI:GH

Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

_____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

4. During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6.)*

5.During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems _____ Health problems

had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	completely prevented me from doing my daily activities

CIRCLE A NUMBER

15.13 Joint assessed for swelling and tenderness

The following joints are assessed in the 28 joint count: Shoulders, elbows, wrists, the ten metacarpophalangeal joints, the ten proximal interphalangeal joints, the knees

The following joints are assessed in the 68/66 joint count: bilateral assessment of; temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal joints, proximal interphalangeal joints, distal interphalangeal joints (2—5.), hip (tenderness only), knee, ankle, talocalcaneal, tarsus, metatarsophalangeal joints, proximal interphalangeal joints

15.14 Adverse events

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
The term AE is used to include both serious and non-serious AEs.
If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

1. Results in death
2. Is immediately life-threatening
3. Requires in-patient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect
6. Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should

be considered as serious. Hospitalisation for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalisation.

A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring

The NOR-DRUM study

Protocol Identification Number: DIA2016-1
Clinical trial registration number:
Regional committee for medical and health research ethics number:

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PROTOCOL VERSION NO. 0.9 **DATE: 14.06.2016**
No amendments

STUDY ORGANISATION

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SIGNATURE PAGE

Title: A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring

The NOR-DRUM study

Protocol ID no:

I hereby declare that I will conduct the study in compliance with the protocol, the Declaration of Helsinki and applicable national regulations and laws.

Name	Title	Role	Signature	Date
Kåre Birger Hagen	PT,PhD,Prof	Sponsor		
Espen A. Haavardsholm	MD,PhD,Prof	Principal Investigator		
		Local Principal Investigators Center:		

PROTOCOL SYNOPSIS

A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring **The NOR-DRUM study**	
Phase of development	Phase IV
Investigational treatment strategy	Patients are randomised 1:1 to either: 1. Administration of INX according to a treatment strategy based on therapeutic drug monitoring and assessments of ADAb (**intervention group**) 2. Administration of INX according to standard clinical care, without knowledge of drug levels or ADAb status (**control group**)
Study Centres	A national multicentre study
Study Period	Estimated date of first patient enrolled: October 1st 2016 Anticipated recruitment period: October 1st 2016 – December 1st 2018 Estimated date of last patient completed: December 31st 2019
Duration	NOR-DRUM A 38 weeks NOR-DRUM B 52 weeks
Main objective	To assess the effectiveness of tailoring infliximab treatment by therapeutic drug monitoring

NOR-DRUM A

Primary objective	To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in order to achieve disease control in patients with inflammatory immunological diseases starting infliximab therapy
Secondary objectives	• To compare effectiveness of a treatment strategy based on TDM to standard clinical care applying different generic and disease specific endpoints • To assess whether a treatment strategy based on TDM influences drug survival, occurrence of anti-drug antibodies and occurrence of adverse events • To assess cost-effectiveness of a treatment strategy based on TDM compared to standard clinical care Exploratory objective: • To assess if biomarkers (including genetic markers) or other factors can predict development of anti-drug antibodies in patients starting INX

Endpoints	Primary endpoint: Proportion of patients in remission* at week 30 defined by disease specific composite scores **Definition of remission:* *- RA: A DAS 28 score of <2.6* *- PsA: A DAS 28 score of <2.6* *- SpA: An ASDAS score <1.3* *- UC: A Mayo score of ≤2 with no sub scores >1* *- CD: A HBI score of ≤4* *- Ps: A PASI score of ≤4* Secondary endpoints: *Generic:* • Time to sustained remission • Patient's and physician's global assessment of disease activity • Biochemical parameters of disease activity • Occurrence of anti-drug antibodies • Occurrence of and reason for drug discontinuation • Safety endpoints (adverse events frequency) • Cost effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH) *Disease specific:* • Efficacy assessed by composite disease activity scores - RA: DAS28, CDAI, SDAI, RAID, MHAQ - PsA : DAS28, DAPSA, PsAID, MHAQ, DLQI - SpA: ASDAS, BASDAI,MHAQ - UC: Partial Mayo score, IBDQ - CD: HBI, IBDQ - Ps: PASI, DLQI
Study Design	A randomised, open, controlled, parallel-group, multicentre, phase IV, superiority, comparative pragmatic study. Patients will be randomised 1:1 to either infliximab with therapeutic drug monitoring by trough levels and assessments of anti-drug antibodies (ADAb) or infliximab according to standard clinical care without knowledge of trough levels and ADAb

Main Inclusion Criteria	1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis diagnosed after 18 years age 2. Male or non-pregnant female 3. ≥18 and < 75 years of age at screening 4. A clinical indication to start INX 5. Subject not in remission according to diagnosis-specific disease activity scores (defined in 6.5.9) 6. Subject capable of understanding and signing an informed consent form * Patients with psoriatic arthritis with predominantly axial manifestations should be included and assessed as spondyloarthritis
Main exclusion criteria	1. Major co-morbidities, such as previous malignancies within the last 5 years, severe diabetes mellitus, severe infections (including HIV), uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases, demyelinating disease, laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult 2. A positive screening for TB and hepatitis 3. Inadequate birth control, 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 which makes adherence to the study protocol difficult 5. Prior use of infliximab within the last 6 months 6. Significant chronic widespread pain syndrome
Sample size	400 patients

NOR-DRUM B

Primary objective	To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in keeping disease control in patients with inflammatory immunological diseases on maintenance therapy with infliximab.
Secondary objectives	• To compare effectiveness of a treatment strategy based on TDM to standard clinical care applying different generic and disease specific endpoints • To assess whether a treatment strategy based on TDM influences drug survival, occurrence of anti-drug antibodies and occurrence of adverse events • To assess cost-effectiveness of a treatment strategy based on TDM compared to standard clinical care Exploratory objective: • To assess if biomarkers (including genetic markers) or other factors can predict development of anti-drug antibodies in patients starting INX
Endpoints	<u>Primary endpoint:</u> Sustained disease control throughout the study period without disease worsening* defined by disease specific composite scores **Definition of disease worsening:* *- RA: Increase in DAS28 of ≥1.2 and a minimum DAS28 score of 3.2* *- PsA: Increase in DAS28 of ≥1.2 and a minimum DAS28 score of 3.2* *- SpA: Increase in ASDAS-CRP of ≥1.1 and a minimum ASDAS of 2.1* *- UC: Increase in p Mayo score of ≥ 3 points and a minimum p Mayo score of 5* *- CD: Increase in HBI of ≥4 points and a minimum HBI score of 7 points* *- Ps: Increase in PASI of ≥3 points and a minimum PASI score of 5* *- Patient and investigator consensus on disease worsening* <u>Secondary endpoints:</u> *Generic:* • Time to disease worsening • Patient and physician global assessment of disease activity • Biochemical parameters of disease activity • Occurrence of anti-drug antibodies • Occurrence of and reason for drug discontinuation • Safety endpoints (adverse events frequency) • Cost-effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH) *Disease specific:* • Efficacy assessed by composite disease activity scores - RA: DAS28, CDAI, SDAI, RAID, MHAQ - PsA : DAS28, DAPSA, PsAID, MHAQ, DLQI - SpA: ASDAS, BASDAI,MHAQ - UC: Partial Mayo score, IBDQ - CD: HBI, IBDQ - Ps: PASI, DLQI

Study Design	A randomised, open, controlled, parallel-group, multicentre, phase IV, superiority, comparative pragmatic study. Patients will be randomised 1:1 to either infliximab with therapeutic drug monitoring by trough levels and assessments of anti-drug antibodies (ADAb) or infliximab according to standard clinical care without knowledge of trough levels and ADAb
Main Inclusion Criteria	1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis diagnosed after 18 years age 2. Male or non-pregnant female 3. ≥18 and < 75 years of age at screening 4. On maintenance therapy with infliximab for a minimum of 30 weeks and a maximum of 3 years 5. A clinical indication for further infliximab treatment 6. Subject in remission or low disease activity (defined in 6.5.8 and 6.5.9) 7. Subject capable of understanding and signing an informed consent form *Patients with psoriatic arthritis and predominantly axial manifestations should be included and assessed as spondyloartritis
Main exclusion criteria	1. Major co-morbidities, such as previous malignancies within the last 5 years, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases, demyelinating disease, laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult 2. Inadequate birth control, pregnancy or subject considering becoming pregnant during the study period 3. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol difficult 4. Significant chronic widespread pain syndrome
Sample size	450

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ACR	American College of Rheumatology
ADAb	Anti-drug antibody(ies)
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AS	Ankylosing spondylitis
ASA	Aminosalicylate acetylsalicylic acid
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate transaminase
AU	Arbitrary units
AZA	Azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	Biological Disease-Modifying Anti-Rheumatic Drugs
bINX	Biosimilar infliximab
BME	Bone marrow edema
CD	Crohn's disease
CDAI	Clinical disease activity index
CIOMS	Council for International Organizations of Medical Sciences
COXIB	COX-2 selective inhibitor
CRF	Case Report Form (electronic/paper)
CRP	C-reactive protein
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CTCAE	Common Terminology Criteria for Adverse Events version
DAE	Discontinuation due to Adverse Event
DAS28	Disease Activity Score using 28 joints
DLQI	Dermatology Life Quality Index
DMARD	Disease-Modifying Anti-Rheumatic Drugs
DRG	Diagnosis related group
eCRF	electronic Case Report Form
EMA	European medicines agency
EPJ	Electronic patient journal
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GI	Gastrointestinal
HBI	Harvey-Bradshaw Index
HRQOL	Health related quality of life
IB	Investigator's Brochure
IBD	Inflammatory bowel diseases
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IJD	Inflammatory Joint Diseases
IL	Interleukin
IMP	Investigational Medicinal Product (includes active comparator and

	placebo)
IND	Investigational New Drug
INF	Interferon
INX	Innovator infliximab
ISF	Investigator Site Files
LIS	Norwegian drug procurement cooperation
MHAQ	Modified Health Assessment Questionnaire
MP	Mercaptopurine
MRI	Magnetic resonance imaging
NK	Natural killer
NorCRIN	Norwegian clinical research infrastructure network
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Hart Association
PASI	Psoriasis Area and Severity Index
PGA	Patient Global Assessment of Disease Activity
PhGA	Physician Global Assessment of Disease Activity
PMS	Partial Mayo Score
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PsAID	Psoriatic Arthritis Impact of Disease
PUVA	Photochemotherapy psoralen plus ultraviolet A phototherapy
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RAID	Rheumatoid Arthritis Impact of Disease
SAE	Serious Adverse Event
SD	Stable Disease
SDAI	Simplified disease activity index
sDMARD	Synthetic Disease-Modifying Anti-Rheumatic Drugs
SDV	Source data verification
SF-36	Short Form (36) Health Survey
SOP	Standard Operating Procedure
SpA	Spondyloarthritis
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TDM	Therapeutic drug monitoring
TMF	Trial master file
TNF	Tumor necrosis factor
TNFi	TNF inhibitor
UC	Ulcerative colitis
UVB	Ultraviolet B
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1 INTRODUCTION

1.1 Background

1.1.1 Drug and diseases of this study

Infliximab (INX) (Remicade®) was the first inhibitor of tumor necrosis factor (TNF) α registered and approved for clinical use. Efficacy and safety of INX have been demonstrated in patients with rheumatoid arthritis (RA), spondyloartritis (SpA), psoriatic arthritis (PsA), ulcerative colitis (UC), Crohn`s disease (CD) and psoriasis (Ps).(1-6) INX is a chimeric monoclonal antibody consisting of a human Fc-fragment and murine Fab-fragments. It binds TNFα with high affinity, forming a stable complex that blocks the association of TNFα with its receptor.(7) In 2013 the first biosimilar to infliximab, CT-P13, was approved by the EMA for all indications of INX based on data from two head-to-head clinical trials in RA and AS.(8, 9) The approval process of a biosimilar, a biologic medical product which is an almost identical copy of an original "innovator" product manufactured by a different company when the original product's patent expires, includes evaluation of similarity to the innovator product with regard to quality, pharmacokinetics, safety and efficacy . In Norway, CT-P13 has been preferred to innovator INX since 2014 due to the annual tender based system for prescription of biological drugs organised by the Norwegian Drug procurement cooperation (LIS).

INX is administrated as repeated intravenous infusions with a recommended starting dose of 3 mg/kg (RA) - 5 mg/kg (UC, CD, SpA, PsA and Ps). The standard regimen includes an induction phase (infusions at week 0, 2, 6) followed by maintenance therapy with infusions every 8. week. In patients with inadequate response, the dose can, according to the SPC, safely be increased either by increasing the given dose at each infusion to a maximum of 7.5 mg/kg or by shortening of the dosing interval to a minimum of 4 weeks.

The present study focus on the six diseases where infliximab has an indication in Norway; RA, SpA, PsA, UC, CD, Ps. RA is characterised by symmetric inflammation of the peripheral joints. In PsA and SpA inflammation affects both the peripheral joints and the axial skeleton, in particular the sacroiliac joints. Persistent inflammation of the joints and spine in patients with inflammatory joint diseases may subsequently lead to disabling deformations. Ps is an immune-mediated, inflammatory papulosquamous skin and nail disease. CD is a chronic, transmural inflammatory disorder which may involve any part of the gastrointestinal tract, whereas UC involves the colon only. Persistent bowel inflammation may lead to complications as strictures and fistula. These six inflammatory diseases included in the present study differ greatly in their clinical presentation, but share several common features as chronic, incurable and relapsing immune mediated inflammatory diseases with systemic symptoms and extra organ involvement. Similarities in the disease pathogenesis have been

further highlighted by the introduction of TNFi that has revolutionised the treatment of both RA, SpA, PsA, CD, UC and Ps and made remission a realistic treatment target. TNFi are considered second-line treatment after failure of conventional therapy in these autoimmune diseases, but may become first-line therapy if the current high costs are reduced.

The high burden of these immunological inflammatory diseases is related both to symptoms of active inflammation and to the subsequent development of organ damage. 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. The primary response rates to INX are high across all diseases, but 20-40% of patients do not respond to therapy.(1-6) Early identification of non- or partial responders in order to intensify or switch therapy is important to bring the patients into remission. Another major clinical problem is loss of treatment effect over time in about 50% of the patients on INX.(10, 11) Prevention of a disease flare with the possible consequence of irreversible organ damage and disability is an important clinical goal. To optimise efficacy clinicians often intensify the INX treatment by increasing the dose. Despite conflicting data regarding the effectiveness of such dose escalation and the considerable economic consequences, large cohort studies show that up to 50% of patients have had one or more dose escalations within the first year of treatment with infliximab.(12-15)

1.1.2 Anti-drug antibodies and serum drug levels

Recently it has become clear that a substantial proportion of treatment failures to INX are due to development of anti-drug antibodies (ADAb). All biological drugs, being large, complex and allogenic proteins, are able to elicit a patient immune response against the drug, with production of ADAb. ADAb influences the pharmacokinetics of the drug either by direct binding to the antibody (neutralising ADAb) or by forming immune complexes with the drug resulting in increased clearance (non-neutralising ADAb). ADAb production has proved to be a significant clinical problem related to long term use of biological drugs. INX being a chimeric antibody has proven to be more immunogenic than the other humanised or human TNFi. The prevalence of ADAb in patients on INX is 10-60%.(16-18) The initial studies of the INX biosimilar CT-P13 indicate a similar immunogenicity profile to the innovator INX, and ADAb to INX is cross-reactive to CT-P13.(8, 9, 19) Low levels of ADAb might be transient, but high levels of ADAb influence the pharmacokinetics of the drug and decrease serum concentrations.(16-18) ADAb formation may also be associated with serious side effects of INX such as hypersensitivity reactions.(16-18) Drug holidays or low-dose regimens have been shown to predispose to ADAb formation.(20) Immunosuppressive co-medication, methotrexate in particular, is protective with a reduction of ADAb formation by up to 40%.(16,18,21,22) The predisposing genetic factors and the precise immunological mechanisms leading to ADAb formation remain unknown.

Methods for assessment of serum drug concentrations have recently become available for use in clinical practice. For drugs that are administered by regular infusions, the trough level (the lowest concentration of the drug measured just before the administration of the next dose) gives the best estimate of bioavailable drug. These advances in assay development have revealed extensive individual differences in serum drug concentrations of INX in patients on the standard dose with levels ranging from undetectable to high above the presumed therapeutic range. ADAb formation, known to considerably influence the half-life of the drug, is regarded as the most important factor responsible for this variation, but drug metabolism is also affected by other individual factors.(23) Maintaining a sufficient trough level is thought important, primarily in order to maintain treatment response, but perhaps also to decrease ADAb formation.The trough concentration of INX has been shown to be associated with clinical response parameters and sustained drug efficacy in patients with RA, UC, CD, Ps, (24-31) and a trough concentration above 3µg/ml during maintenance therapy has been associated with improved clinical outcomes in several studies and across different diseases.(26-30, 32) Recent studies indicate that high serum levels after week 2 and 6 are associated with remission in patients with IBD, but the clinical role of assessments of INX concentrations during induction therapy has not been clarified.(33, 34)

1.1.3 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) aims at improving patient care by individually adjusting the dose of drugs based on regular assessments of serum drug concentrations. As assessment methods have become more available, the clinical impact of TDM in monitoring patients on treatment with INX has become a topic of great interest to clinicians both nationally and internationally.

As indicated by some observational studies, assessments of serum drug levels and ADAb could be a useful tool for guiding treatment decisions in patients on a TNFi by;(35-40)

1) Minimise undertreatment, which might lead to lack of response, loss of response, and possibly also predispose to ADAb production
2) Reduce overtreatment, which predispose patients to side effects and increases the costs of treatment
3) Allow for early identification of ADAb development, with the possibility of detecting treatment failures prior to a clinical flare and to prevent infusion reactions
4) Aid in treatment decisions if treatment fails (i.e. dose increase in patients with low levels, switch therapy to another TNFi in case of ADAb development and to another treatment mechanism in the case of treatment failure despite INX levels in the therapeutic range)

Algorithms for handling a disease flare by taking drug levels and ADAb measures into account have recently been proposed by researchers within this field, and have been implemented in clinical practice in some European centres with available methodology and special interest in immunogenicity.(36, 41) There are currently no guidelines for the

implementation of TDM in standard care of patients on INX. A small randomised controlled trial has shown lower costs of such algorithm-based management of a disease flare during treatment with TNFi.(36) Although data from observational cohorts suggests that keeping the serum INX trough level above 3 µg/ml during maintenance therapy is associated with better disease control, data assessing clinical effectiveness of systematically monitoring TNFi treatment by serum drug concentrations and ADAb is limited to two recent studies of trough level guided INX therapy in patients with inflammatory bowel diseases (IBD).(32, 42) A retrospective study comparing patients treated according to TDM with patients who had been handled by standard clinical care showed better drug survival in the TDM-group.(42) A recent randomised clinical trial (TAXIT) of patients with IBD has evaluated the effect of TDM.(32) In this study all patients underwent INX dose optimisation based on trough level 3-7 µg/ml prior to randomizstion, which significantly increased the percentage of CD patients in remission from 64% to 92%. After dose optimisation, continued TDM was not superior to clinically based dosing for achieving remission after 1 year, but was associated with fewer flares during the course of treatment. Dose reduction in patients with high levels did not lead to flare, but did result in significant cost savings.

1.1.4 The NOR-SWITCH study

The NOR-DRUM study will build on the infrastructure, organisation and research collaboration developed for the NOR-SWITCH study initiated and funded by South-Eastern Regional Health Authority in 2014 to assess the efficacy and safety of switching from originator INX to biosimilar INX. Norway has been among the first countries world-wide to apply biosimilars in everyday clinical use. The ongoing NOR-SWITCH study (Clinical trials registration number NCT02148640), a randomised, double blind, parallel-group study with 500 included patients is an extensive effort for Norwegian rheumatology, dermatology and gastroenterology with a total of 40 centres (16 rheumatology centres, 19 gastroenterology centres and 5 dermatology centres) participating. Diakonhjemmet Hospital is the coordinating centre. The NOR-SWITCH study includes collaboration with Oslo University Hospital for measuring serum drug levels and ADAb development in the setting of drug switching.

1.2 Purpose and rationale

The NOR-DRUM study aims to assess whether tailoring infliximab treatment by therapeutic drug monitoring improves the effectiveness of infliximab treatment in order to achieve and maintain disease control. This large randomised controlled multicenter trial of patients with rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, ulcerative colitis, Crohn's disease and psoriasis is expected to provide valuable information both clinically and in terms of health economics regarding the possible optimisation of TNF-inhibitor treatment.

INX and other TNFi have revolutionised the treatment of a range of prevalent immunological inflammatory disease with a chronic disease course. Still, a substantial proportion of patients either do not respond sufficiently to initiated therapy or loose treatment effect over time. Sustained disease activity affects the quality of life of the patients in the short term and may lead to irreversible organ damage and disability. Early identification of non-responders and partial responders after treatment initiation and prevention of a disease flare during the course of treatment are important to obtain the main therapeutic goal of rapid and sustained remission. Recent advances in assay development have revealed an extensive individual variation in serum drug concentrations in patients on standard doses of INX suggesting both under- and overtreatment of a substantial proportion of patients. Many patients develop anti-drug antibodies (ADAb) during therapy contributing to reduced drug levels and additionally predispose the patients to allergic drug reactions. The impact of therapeutic drug monitoring (TDM) as a tool optimise effectiveness of INX treatment is currently a topic of great interest to clinicians both nationally and internationally. As the first trial ever to assess the effect of TDM in patients with a wide range of inflammatory immunological diseases on treatment with a TNFi, the NOR-DRUM study will provide important information that will hopefully contribute to an implementation of a personalised medicine approach to TNF-inhibitor therapy.

The results of this study could also have impact on health care economics. The financial burden of TNF-inhibitors is significant, restricting their use.(43) Data from the Norwegian NOR-DMARD register indicates a yearly cost of a patient with RA receiving biologic DMARDs of € 60 000 (NOK 500 000), where €19 600 (NOK 160 00) are directly related to the drug.(44) The extremely high costs of these drugs put emphasis on avoiding redundant therapy. If dose tapering in patients with levels above the therapeutic range can be safely done without exposing the patients to loss of treatment effect, the savings in drug costs could be considerable.

As a large infliximab cohort, NOR-DRUM will provide unique opportunities for translational research on the poorly understood area of genetic and immunological mechanisms underlying drug immunogenicity. Identification of predisposing genetic markers that could serve as predictors of loss of response is highly relevant in order to tailor treatment with biological drugs.

A personalised medicine approach to INX therapy by TDM seems reasonable, but the effectiveness of such a treatment strategy in the management of a range of immunological inflammatory diseases with regard to rapid remission and sustained disease control still remains to be shown in a longitudinal randomised controlled trial.

2 STUDY OBJECTIVES

2.1 Main study objective

To assess the effectiveness of tailoring infliximab treatment by therapeutic drug monitoring.

2.2 Primary objectives

NOR-DRUM A

To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in order to achieve disease control in patients with inflammatory immunological diseases starting infliximab therapy.

NOR-DRUM B

To assess if tailoring treatment by therapeutic drug monitoring is superior to standard clinical care in keeping disease control in patients with inflammatory immunological diseases on maintenance therapy with infliximab.

2.3 Secondary objectives and exploratory objectives

- To compare effectiveness of a treatment strategy based on TDM to standard clinical care applying different generic and disease specific endpoints
- To assess whether a treatment strategy based on TDM influences drug survival, occurrence of anti-drug antibodies and occurrence of adverse events
- To assess cost-effectiveness of a treatment strategy based on TDM compared to standard clinical care

Exploratory objectives:

- To assess if biomarkers (including genetic markers) or other factors can predict development of anti-drug antibodies in patients starting INX

3 STUDY ENROLMENT AND WITHDRAWAL

3.1 Inclusion of patients

The study population will consist of Norwegian adult male and female patients with a clinical diagnosis of rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis, ulcerative colitis, Crohn's disease or chronic plaque psoriasis who are either starting on treatment with INX (NOR-DRUM A), or have been on maintenance therapy with INX for at least 30 weeks (NOR-DRUM B). Patients will be recruited from Norwegian hospitals providing treatment with INX for the mentioned diagnoses.

3.2 Number of Patients

400 patients will be included in NOR-DRUM A.
450 patients will be included in NOR-DRUM B.
For sample size calculations see 9.5.

3.3 Inclusion Criteria

NOR-DRUM A

All of the following conditions must apply to the prospective patient at screening prior to receiving study agent (e.g.):

1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis diagnosed after 18 years age
2. Male or non-pregnant female
3. ≥18 and < 75 years of age at screening
4. A clinical indication to start INX
5. Subject not in remission according to diagnosis-specific disease activity scores (defined in 6.5.9)
6. Subject capable of understanding and signing an informed consent form

* Patients with psoriatic arthritis with predominantly axial manifestations should be included and assessed as spondyloarthritis

NOR-DRUM B

All of the following conditions must apply to the prospective patient at screening prior to receiving study agent (e.g.):

1. A clinical diagnosis of one of the following; rheumatoid arthritis, spondyloarthritis (including ankylosing spondylitis), psoriatic arthritis*, ulcerative colitis, Crohn's disease or chronic plaque psoriasis diagnosed after 18 years age
2. Male or non-pregnant female
3. ≥18 and < 75 years of age at screening
4. On maintenance therapy with infliximab for a minimum of 30 weeks and a maximum of 3 years
5. A clinical indication for further infliximab treatment
6. Subject in remission or low disease activity as defined in 6.5.8 and 6.5.9
7. Subject capable of understanding and signing an informed consent form

* Patients with psoriatic arthritis with predominantly axial manifestations should be included and assessed as spondyloarthritis

3.4 Exclusion Criteria

A subject will be excluded from the study if they meet any of the following criteria:

NOR-DRUM A

1. Major co-morbidities, such as previous malignancies within the last 5 years, severe diabetes mellitus, severe infections (including HIV), uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases, demyelinating disease, laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult
2. A positive screening for TB and hepatitis
3. Inadequate birth control, 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 which makes adherence to the study protocol difficult.
5. Prior use of infliximab within the last 6 months
6. Significant chronic widespread pain syndrome

NOR-DRUM B

1. Major co-morbidities, such as previous malignancies within the last 5 years, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4), severe respiratory diseases, demyelinating disease, laboratory abnormalities or significant renal or hepatic disease and/or other diseases or conditions where treatment with infliximab is either found contra-indicated by the clinician or which make adherence to the protocol difficult
2. Inadequate birth control, pregnancy or subject considering becoming pregnant during the study period
3. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol difficult
4. Significant chronic widespread pain syndrome

3.5 Procedures for discontinuation

3.5.1 Patient discontinuation

Patients have the right to withdraw from the study at any time for any reason. In the case that a patient decides to prematurely withdraw from the study, he or she should be asked if he or she can still be contacted for further information, so that a final evaluation can be made with an explanation of why the patient is withdrawing from the study, including assessment of possible adverse events. Although a subject is not obliged to give his or her

reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. If possible, at the last visit of the patient, all assessments of the ”End of study visit” will be done. The investigator is obliged to follow up any significant adverse events until the outcome is either recovered or resolved, recovering or resolving, not recovered or not resolved, recovered or resolved with sequelae, fatal or unknown.

3.5.2 Discontinuation from the study by the investigator

The investigator may discontinue the patient from further study participation if

- Further study participation will put the patient at risk of medical injury
- There has been a major protocol violation

3.5.3 Trial discontinuation

The study group reserves the right to terminate the study at any time. This may be due to safety reasons or if new knowledge arises that invalidates the study (including results from interim analyses). Other reasons that may have a major impact on the study, including ethical and financial aspects, and difficulties in the recruitment of patients, may also lead to termination of the study. In terminating the study, the study group and investigators will assure that adequate consideration is given to the protections of patients’ interests. The sponsor and principal investigator will inform all investigators and the relevant regulatory authorities of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the relevant authorities should be informed within 15 days.

4 INVESTIGATIONAL PLAN

4.1 Overview of the study design

The NOR-DRUM study is a randomised, controlled, parallel-group, comparative, multi-centre, national, superiority, phase IV pragmatic study with two separate parts (NOR-DRUM A and NOR-DRUM B) aiming to assess the effectiveness of TDM of INX treatment in patients with immunological inflammatory diseases.

NOR-DRUM A (Outlined in Figure 1)
All patients with a clinical diagnosis of RA, SpA, PsA, UC, CD or Ps starting treatment with INX are potential study patients. Eligibility criteria are described in section 3.3 (inclusion criteria) and 3.4 (exclusion criteria).

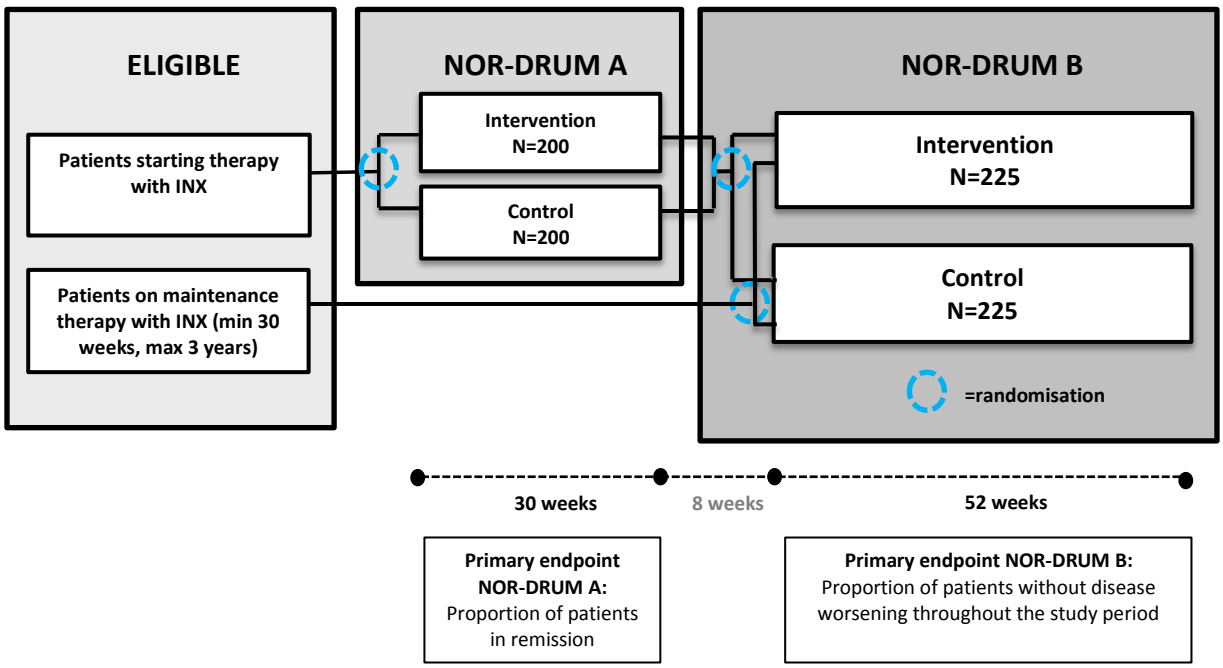
Eligible patients with a signed informed consent will be randomised 1:1 according to the procedure described in section 9.1 to either:

1. Administration of INX according to a treatment strategy based on therapeutic drug monitoring and assessments of ADAb (**intervention group**)
2. Administration of INX according to standard clinical care, without knowledge of drug levels or ADAb status (**control group**)

The randomised treatment strategy will be continued for the duration of the study period (38 weeks) with study visits at each scheduled INX infusion. Patients who are switched to another treatment during the study will still be followed according to the intentional infusion scheme. Patients that are still on INX and in low disease activity or remission at week 38 will be re-randomised and included in NOR-DRUM B.

Study Period	Estimated date of first patient enrolled: October 1st 2016
	Anticipated recruitment period: October 1st 2016 to Mars 1st 2018
	Estimated date of last patient completed: December 31st 2018
Study duration:	38 weeks +/-4 weeks

FIGURE 1 Overview of study design



NOR-DRUM B (Outlined in Figure 1)
All patients with a clinical diagnosis of RA, SpA, PsA, UC, CD or Ps on maintenance therapy with INX for at least 30 weeks and not more than 3 years in a state of remission or low disease activity and an indication for continued INX treatment are potential study patients. Patients from NOR-DRUM A who are still on treatment with INX at week 38 and are otherwise eligible according to inclusion and exclusion criteria will be included in NOR-DRUM B. Eligibility criteria are described in section 3.3 (inclusion criteria) and 3.4 (exclusion criteria).

Eligible patients with a signed informed consent will be randomised 1:1 according to the procedure described in section 9.1 to either:

3. Administration of INX according to a treatment strategy based on therapeutic drug monitoring and assessments of ADAb (**intervention group**)
4. Administration of INX according to standard clinical care, without knowledge of drug levels or ADAb status (**control group**)

The randomised treatment strategy will be continued for the duration of the study period (52 weeks) with study visits at each scheduled INX infusion. Patients who are switched to another treatment during the study will still be followed with visits every 12 weeks.

In order to identify the primary endpoint (absence of disease worsening during the study period), each study centre will have a phone number for patients to call in case of increased disease activity. If a patient is experiencing a potential disease worsening, a visit will be arranged within one week to allow for a thorough examination and documentation of disease status.

Study Period	Estimated date of first patient enrolled: October 1st 2016
	Anticipated recruitment period: October 1st 2016 to December 31st 2018
	Estimated date of last patient completed: December 31st 2019
Study duration:	52 weeks+/-4 weeks

4.2 Follow-up study

In order to establish the long- term survival of ADAb, patient that develops such antibodies will be asked to participate in a follow-up study with serum samples after 1, 2, 5 and 10 years for subsequent analyses of serum levels of ADAb. There will be no clinical evaluation or other assessments, only serum sampling.

4.3 Study endpoints

4.3.1 Primary endpoints

NOR-DRUM A

Primary endpoint:

Proportion of patients in remission* at week 30 defined by disease specific composite scores

*Definition of remission:

- RA: A DAS 28 score of <2.6
- PsA: A DAS 28 score of <2.6
- SpA: An ASDAS score <1.3
- UC: A Mayo score of ≤2 with no sub scores >1
- CD: A HBI score of ≤4
- Ps: A PASI score of ≤4

NOR-DRUM B

Primary endpoint:

Sustained disease control throughout the study period without disease worsening* defined by disease specific composite scores

*Definition of disease worsening:

- RA and PsA: Increase in DAS28 of ≥1.2 from inclusion and a minimum DAS28 score of 3.2
- SpA: Increase in ASDAS-CRP of ≥1.1 from inclusion and a minimum ASDAS of 2.1
- UC: Increase in Partial Mayo score of ≥ 3 points from inclusion and a minimum partial Mayo score of 5 points
- CD: Increase in HBI of ≥4 points from inclusion and a minimum HBI score of 7 points
- Ps: Increase in PASI of ≥3 points from inclusion and a minimum PASI score of 5
- Patient and investigator consensus on disease worsening:
  If a patient does not fulfil the formal definition, but experiences a clinically significant worsening according to both the investigator and patient who leads to a major change* in treatment this should be considered as a disease worsening but be recorded separately in the CRF.

A major change* in treatment includes; Switching from INX to another bDMARD, adding a sDMARD, increasing the dose of a concomitant sDMARD, adding systemic glucocorticoids (po., iv. or im.), receiving more than one i.a. glucocorticoid injection at one visit.
If the INX dose is increased for clinical reasons this should also be regarded as a major change in treatment (applies to the control arm only).

4.3.2 Secondary and exploratory endpoints

NOR-DRUM A

Generic:

- Time to sustained remission. Sustained remission is defined as a status of remission on all consecutive visits following the initial obtained remission until the end of the study period (38 weeks)
- Patient's and physician's global assessment of disease activity
- Biochemical parameters of disease activity
- Occurrence of anti-drug antibodies
- Occurrence of and reason for drug discontinuation
- Safety endpoints (adverse events frequency)
- Cost effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH)

Disease specific:

- Efficacy assessed by composite disease activity scores
  - RA: DAS28, CDAI, SDAI, RAID, MHAQ
  - PsA : DAS28, PsAID, DAPSA, MHAQ, DLQI
  - SpA: ASDAS, BASDAI,MHAQ
  - UC: Partial Mayo score, IBDQ
  - CD: HBI, IBDQ
  - Ps: PASI, DLQI

NOR-DRUM B:

Generic:

- Time to disease worsening
- Patient and physician global assessment of disease activity
- Biochemical parameters of disease activity
- Occurrence of anti-drug antibodies
- Occurrence of and reason for drug discontinuation
- Safety endpoints (adverse events frequency)
- Cost-effectiveness, utility and quality of life (EQ-5D, SF-36, WPAI-GH)

Disease specific:

- Efficacy assessed by composite disease activity scores
  - RA: DAS28, CDAI, SDAI, RAID, MHAQ
  - PsA : DAS28, PsAID, DAPSA, MHAQ, DLQI
  - SpA: ASDAS, BASDAI,MHAQ

- UC: Partial Mayo score, IBDQ
- CD: HBI, IBDQ
- Ps: PASI, DLQI

4.4 Description of the treatment strategy in NOR-DRUM A

4.4.1 The intervention group

In the patients randomised to the intervention group, the INX dose will be adjusted according to the algorithms outlined in Figure 2 and Figure 3 in order to meet the target trough level. Trough level results, drawn 0-5 days prior to each visit, will not be available at the actual visit. The investigator will receive these results some days after the infusion and must then make a decision to keep or change the dose, based on the algorithm.

At the first visits (up to and at the week 14 visit), the dose can only be adjusted by decreasing the infusion interval (Figure 2). After the week 14 visit, strategies for both increasing and decreasing the INX dose to reach the target range of 3-8 µg/ml is incorporated in the algorithm (Figure 3). The former should preferably be done by increasing the dose, but decreasing the length of the infusion interval can also be performed if better suited. A dose decrease should preferably be done by increasing the infusion interval, but can also be performed by a dose-reduction if better suited. However, only one of the strategies can be performed related to each infusion (i.e. the dose interval to the next infusion and the dose at the next infusion must not be changed at the same time). Subsequent changes required according to the algorithm will be based on the adjusted dose/infusion interval.

If INX is terminated due to side effects, the patient should be managed at the discretion of the investigator. If INX is terminated either due to the algorithm, side effects, lack of efficacy or any other reason, the patient will still be included in the study and followed with study visits according to the planned infusion schedule (after 0, 2, 6, 14, 22, 30 and 38 weeks). The reason for termination of therapy should be recorded in the CRF.

<u>Visit 1 (Inclusion):</u>
The patient will receive the standard weight based dose according to disease (3 mg/kg (RA) or 5 mg/kg for the other diseases). The interval to infusion 2 is 2 weeks.

<u>Visit 2 and 3:</u>
The visit 2 is scheduled after 2 weeks for all patients. The visit 3 will be after 4 or 6 weeks from baseline depending on the infusion interval between infusion 2 and 3. The investigator (physician) will see the patients if requested by the study nurse or the patient. The algorithm for visit 2 and 3 is depicted in Figure 2. At visit 2 and 3 the dose can only be adjusted by decreasing the infusion intervals.

The week 14 visit:

This visit should be arranged between week 12 and 16 (14 +/- 2 weeks). If the 4th visit is scheduled earlier than week 12 and the 5th visit later than week 16, an extra visit must be scheduled. At this visit a formal assessment of improvement* will be performed by the investigator (physician). If the patient has not improved (defined below) the patient should be managed according to the algorithm in Figure 2. If the patient has not improved, INX should not be given until the results of the serum drug level is ready and action can be taken accordingly.

*Improvement is defined as:

- RA and PsA: A decrease in DAS 28 of ≥1.2 from baseline
- SpA: A decrease in ASDAS of ≥1.1 from baseline
- UC: A decrease in the partial Mayo score of ≥ 3 from baseline
- CD: A decrease in the HBI of ≥ 4 from baseline
- Ps: PASI 50 (A 50% reduction in the PASI score from baseline)
- Investigator and patient consensus on improvement:
  If a patient does not fulfil the formal definition, but both the patient and the investigator agree that the patient has improved this should be considered as improvement but recorded separately in the CRF

Visits after the week 14 visit:

The investigator (physician) will see the patients at the week 30 visit and the week 38 visit, and else if requested by the study nurse or the patient. The algorithm for INX administration is outlined in Figure 3. If the investigator considers switching therapy due to lack of efficacy at the scheduled visit or at an extra visits requested by the patient, the patient should be managed according to Figure 5.

Extra study visit:

If requested by the patient or the study nurse an extra visit will be set.

The week 30 visit:

This visit should be arranged between week 28 and 32 (30 +/- 2 weeks). Depending on the infusion interval in each individual patient this will be visit 6-9 or an extra visit. A formal assessment of remission (the primary outcome of the study) will be performed by the investigator. If the patient is not in remission and the investigator considers switching therapy, the patient should be managed according to Figure 5.

The week 38 visit:
This end of study visit should be arranged between week 34 and 42 (38 +/- 4 weeks). Depending on the infusion interval in each individual patient this will be visit 7-11. A formal assessment of remission will be performed by the investigator. If the patient is eligible for NOR-DRUM B, the patient will be re-randomised and the 38 weeks visit will also be the inclusion visit in NOR-DRUM B. If the patient is re-randomised to the control group in NOR-DRUM B, the serum level drawn at the 38 week visit will not be available to the investigator.

4.4.2 The control group

Patients randomised to the control group will be managed according to standard clinical care without knowledge of serum drug levels or ADAb. As for the intervention group, a clinical assessment by the investigator is performed routinely at baseline, at week 14 (improvement evaluation), at week 30 (end point assessment) and at week 38 (end of study visit). A decision to terminate therapy due to adverse events and the choice of any subsequent therapy should be made at the investigators preference and according to LIS. The reason for termination of therapy should be recorded in the CRF. If INX therapy is terminated during the study period, the patient should still be followed at all scheduled visits (0, 2, 6, 14, 22, 30 and 38 weeks).

Visit 1 (Inclusion):
The patient will receive the standard weight based dose according to disease (3 mg/kg (RA) or 5 mg/kg for the other diseases). The interval to infusion 2 is 2 weeks.

Visit 2 and 3:
The investigator (physician) will see the patients if requested by the study nurse or the patient. The patient will receive standard infliximab dose according to disease. The infusion intervals are as in the SPC 4 weeks between infusion 2 and 3 and 8 weeks between infusion 3 and 4.

The week 14 visit:
This visit should be arranged between week 12 and 16 (14 +/- 2 weeks). If the 4^{th} visit is scheduled earlier than week 12 and the 5^{th} visit later than week 16 an extra visit must be scheduled. At this visit a formal assessment of improvement will be performed by the investigator (physician). If the patient has not improved (defined above) the investigator should consider intensifying therapy (by increasing the INX dose or by switching therapy) according to standard clinical care and LIS. Factors that may lead to continuation of therapy despite lack of improvement are i.e. if improvement is not expected or clinically relevant (i.e. if the patient has switched therapy due to side-effects rather than lack of efficacy) and if few/no other treatment options are available.

Visits after the week 14 visit:
The investigator (physician) will see the patients at week 30 and 38, and extra if requested by the study nurse or the patient.
If medically indicated (lack of improvement, adverse events or other reason) the investigator can intensify therapy by increasing the INX dose or by switching therapy according to standard clinical practice.

The week 30 visit:
This visit should be arranged between week 28 and 32 (30 +/- 2 weeks). Depending on the infusion interval in each individual patient this will be visit 6-9 or an extra visit. A formal assessment of remission (the primary outcome of the study) will be performed by the investigator. If the patient is not in the investigator should consider intensifying therapy (by increasing the INX dose or by switching therapy) according to standard clinical practice and LIS.

The week 38 visit:
This end of study visit should be arranged between week 34 and 42 (38 +/- 4 weeks). Depending on the infusion interval in each individual patient this will be visit 7-11. A formal assessment of remission will be performed by the investigator. If the patient is eligible for NOR-DRUM B, the patient will be re-randomised and the 38 weeks visit will also be the inclusion visit in NOR-DRUM B.

4.5 Description of the treatment strategy in NOR-DRUM B

4.5.1 The intervention group

In the patients randomised to the intervention group, the INX dose will be adjusted according to the algorithm outlined in Figure 4 in order to meet the target trough level range of 3-8 µg/ml. Trough level results, drawn 0-5 days prior to each visit, will not be available at the actual visit. The investigator will receive these results some days after the infusion and must then make a decision to keep or change the dose, based on the algorithm.

Strategies for both increasing and decreasing the INX dose to reach the target range are incorporated in the algorithm. The former should preferably be done by increasing the dose, but decreasing the length of the infusion interval can also be performed if better suited. A dose decrease should preferably be done by increasing the infusion interval, but can also be performed by a dose-reduction if better suited. However, only one of the strategies can be performed related to each infusion (i.e. the dose interval to the next infusion and the dose at the next infusion must not be changed at the same time). Subsequent changes required according to algorithm will be based on the adjusted dose/infusion interval.

If INX is terminated due to side effects, the patient should be managed at the discretion of the investigator. If the patient develops a disease worsening (defined in 6.5.7, primary endpoint of the study), the patient should be handled according to the algorithm in Figure 6. If INX is terminated either due to the algorithm, side effects, lack of efficacy or any other reason, the patient will still be included in the study and followed with study visits every 12 weeks. The reason for termination of therapy should be recorded in the CRF.

Visit 1 (inclusion visit):
The patient will receive the same dose as for the previous infusion. The dose or the infusion interval may be adjusted subsequently according to the algorithm when receiving the trough level prior to visit 1.

If a high level of ADAb (>60 AU/L) is present at inclusion, therapy with INX will be stopped after infusion 1 and the investigator should either switch to another biological drug (preferably another TNFi) or if in long-term remission the investigator should consider to let the patients continue without biological therapy.

Further visits:
An assessment by the investigator (physician) is performed every 12 (+/-4) weeks and additionally if requested by the patient or the study nurse.

End of study visit
At week 52+/- 4 weeks there will be an end of study visit.

Extra visit if disease worsening:
The proposed strategy for managing a disease worsening is outlined in Figure 6.

4.5.2 The control group

Patients randomised to the control group will be managed according to standard clinical care without knowledge of serum drug levels or ADAb. A clinical evaluation by the investigator (physician) is performed every 12 (+/- 4) weeks and additionally if requested by the patient or the study nurse. The patients will keep the dose and dosing interval they had prior to randomisation. Dose adjustments are performed at the discretion of the investigator during the study period. A need to increase the dose will be regarded as a disease worsening (primary outcome of the study). A disease worsening or an adverse event will be managed at the discretion of the investigator. Both a decision to terminate therapy and the choice of any subsequent therapy should be made at the investigators preference and according to LIS. The reason for termination of therapy with INX should be recorded in the CRF. A disease worsening will be recorded according to the description in 6.5.7. If INX therapy is terminated during the study period the patient will still be included in the study and followed every 12 weeks throughout the study period.

FIGURE 2 Algorithm for INX administration in **NOR-DRUM A, intervention group** (the visits up to the week 14 visit)

	VISIT 2 and 3		The week 14 visit	
Serum INX level (µg/ml)	**<20.0 visit 2 <15.0 visit 3**	**≥20.0 visit 2 ≥15.0 visit 3**	**<3.0**	**≥3.0**
	Increase* dose if no ADAb or low level ADAb (<60 AU/L) **or** **Switch therapy** if high levels of ADAb (>60 AU/L). If possible to another TNFi	**No action** Within target range, continue with the same dose and dosing interval	**Same strategy for improvement and no improvement:** **Increase* dose** if no ADAb or low level ADAb (<60 AU/L) **or** **Switch therapy** if high levels of ADAb (>60 AU/L). If possible to another TNFi	**Improvement** **: No action **No improvement** **: Consider ***to switch therapy, if possible to another treatment mechanism than TNFi

Guideline for dose increase*
Increase the dose by decreasing the dose interval by 2 weeks

**Definition of improvement:
RA and PsA: A decrease in DAS 28>=1.2
SpA: A decrease in ASDAS>=1.1
UC: A decrease in partial Mayo score of ≥ 3 points
CD: A decrease in HBI with ≥ 4 points
Ps: Achieved PASI 50
For all diseases: An investigator and patient consensus on improvement despite not formally fulfilling improvement definition

***Factors that may lead to continuation of therapy despite lack of improvement are i.e. if improvement is not expected or clinically relevant (i.e. if the patient has switched therapy due to side-effects rather than lack of efficacy) and if few/no other treatment options are available.

FIGURE 3 Algorithm for INX administration **NOR-DRUM A, intervention group** (all visits after the week 14 visit)

Serum INX level (µg/ml)	≤2.0	2.1 – 2.9	3.0 – 8.0	8.1 – 10.0	>10.0
Action	**Increase dose** if no ADAb or low level ADAb (<60 AU/L) **or** **Switch therapy** if high levels of ADAb (>60 AU/L). If possible to another TNFi	**Consider increasing dose**	**No action**	**Consider decreasing dose**	**Decrease dose**
Guideline for action	Increase the dose preferably by increasing the given dose by 2,5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 2 weeks to a minimum of 4 weeks	Consider (based on clinical judgement and the patients factors given below*) increasing the dose preferably by increasing the given dose by 2.5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 1 week to a minimum of 4 weeks	Within target range. Continue with the same dose and dosing interval	Consider (based on clinical judgement and the patients factors given below*) to decrease the dose preferably by increasing the dose interval by 1 week to a maximum of 10 weeks or by decreasing the given dose by 2.5 mg/kg	Decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2,5 mg/kg
*Patient factors to be considered when making the treatment decisions in the yellow zones: Disease activity and trend in disease activity, the trend of the trough level over time, previous drug interval changes, availability of alternative drug, diagnosis (RA patients are expected to have lower trough levels due to lower recommended dosing)					

FIGURE 4 Algorithm for INX administration in **NOR-DRUM B, intervention group** (all visits)

Serum INX level (µg/ml)	≤2.0	2.1 – 2.9	3.0 – 8.0	8.1 – 10.0	>10.0
Action	**Increase dose** if no ADAb or low level ADAb (<60 AU/L) **or** **Switch therapy** if high levels of ADAb (>60 AU/L). If possible to another TNFi	**Consider increasing dose**	**No action**	**Consider decreasing dose**	**Decrease dose**
Guideline for action	Increase the dose preferably by increasing the given dose by 2,5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 2 weeks to a minimum of 4 weeks	Consider (based on clinical judgement and the patients factors given below*) increasing the dose preferably by increasing the given dose by 2.5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 1 week to a minimum of 4 weeks	Within target range. Continue with the same dose and dosing interval	Consider (based on clinical judgement and the patients factors given below*) to decrease the dose preferably by increasing the dose interval by 1 week to a maximum of 10 weeks or by decreasing the given dose by 2.5 mg/kg	Decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2,5 mg/kg
*Patient factors to be considered when making the treatment decisions in the yellow zones: Disease activity and trend in disease activity, the trend of the trough level over time, previous drug interval changes, availability of alternative drug, diagnosis (RA patients are expected to have lower trough levels due to lower recommended dosing)					

FIGURE 5 Treatment algorithm **NOR-DRUM A, intervention group** (if considering intensifying treatment after the week 14 visit)

Serum INX level (µg/ml)	<3.0	≥3.0
Guideline for action	If no ADAb or ADAb in low levels (<60 AU/L): Increase the dose preferably by increasing the dose by 2,5 mg/kg to a maximum of 10 mg/kg or by decreasing the infusion interval by 2 weeks to a minimum of 4 weeks If high levels of ADAb (>60 AU/L): Switch therapy, if possible to another TNFi	Consider switching therapy according to current best clinical practice and LIS. If possible another treatment mechanism than TNFi should be chosen.

FIGURE 6 Treatment algorithm **NOR-DRUM B, intervention group** (disease worsening)

Serum INX level (µg/ml)	<3.0	≥3.0
Guideline for action	If no ADAb or ADAb in low levels (<60 AU/L): Increase the dose by 2,5 mg/kg to a maximum of 10 mg/kg or by decreasing the infusion interval by 2 weeks to a minimum of 4 weeks If high levels of ADAb (>60 AU/L): Switch therapy, if possible to another TNFi	Consider switching therapy according to current best clinical practice and LIS. If possible another treatment mechanism than TNFi should be chosen.

4.6 Rationale for the intervention algorithm

The treatment algorithms are based on an extensive literature review and expert opinions. They have been developed through a series of meetings in the project group consisting of national leading experts in this field (both clinicians experienced with TDM and laboratory physicians) and with additional input from international key experts in the scientific advisory board.

The therapeutic level of INX is not definitely known for all the diseases, but there are strong indications that the lower limit is close to 3µg/ml.(26-30, 32) According to the literature review and expert opinion, the upper limit has been set to 8µg/ml. The borders of the proposed therapeutic range, the yellow zones in figure 1, allow for some clinical

considerations regarding the INX dosing. In the induction phase the limits of 20µg/ml at infusion 2 and 15µg/ml at infusion 3 are based on personal observations and previous literature.(33, 34)

There is still no consensus on what is the most effective and cost effective way to increase and decrease the INX dose, by dose adjustments or interval changes. Initial pharmacokinetic modelling suggested that a higher trough level could be achieved using less INX over time by shortening the interval instead of increasing the dose by.(45) More recent studies suggest that a dose of i.e. 10mg/kg every 8 weeks are probably equal to 5 mg/kg every 4 weeks,(46) and halving the infusion intervals are not superior to increasing dose when it comes to both effect and drug costs.(47) The proposed algorithms allows for both options, but due to lower drug costs in recent years, patient convenience and high costs of running infusion units, the preferred option is dose increase by increasing each infusion dose and for decreasing the dose by increasing the infusion interval.

4.7 Study drug

Patients included in this study will either be starting treatment with INX (NOR-DRUM A) or are on maintenance treatment with INX (NOR-DRUM B). In NOR-DRUM A, the recommended INX according to the current national prescription (LIS) recommendations (Remicade, CT-P13, SB2 or others) will be used. In NOR-DRUM B eligible patients on any form of INX will be included.

4.7.1 Drug supply, preparation and storage

The supply, storage and preparation of INX will be performed according to local guidelines in each participating centre.

4.7.2 Drug administration, premedication and monitoring

The study drug will be administrated by authorized personnel according to local guidelines in each participating centre. The infusion time will vary and can be influenced by previous experience i.e. infusion reactions. Local guidelines at each participating centre will be applied regarding the indication for premedication and the type and dosage of premedication. The patients will be monitored after the infusion according to local guidelines in each participating centre.

4.7.3 Subject Compliance

Each treatment administration will be registered in the electronic case report form (eCRF) with dose and time of infusion, and if the infusion was successful. Any schedule modification due to lack of subject compliance should be registered.

4.7.4 Drug Accountability

The responsible site personnel will treat study drug according to the practice at the study site, including accountability of receipt, administration to the patient, returned and/or destruction at the site.

4.8 Prior therapy

In NOR-DRUM A and B all prior use of syntetic and biologic disease-modifying drugs (exl steroids and NSAIDS) will be recorded in the CRF with specification of both the time (month and year) of treatment start and time of termination (month and year) of biological DMARDS. The reason for termination of prior biological therapy (i.e. lack of efficacy, loss of efficacy, side effekts, development of ADAb or other) will be recorded. In NOR-DRUM B the time (day, month and year) of treatment initiation of INX will be recorded. In NOR-DRUM A patients that have previously been treated with any form of INX within the last six months will not be eligable.

4.9 Concomitant medication

All concomitant medication should be recorded in the CRF.

NOR-DRUM A

All concomitant medications and changes in concomitant medications and dosages should be documented in the CRF. Disease related synthetic concomitant medication such as 5-ASAs, systemic corticosteroids and sDMARDs (i.e. methotrexate, azathioprine and 6-MP) are permitted and can be started before or during the study period. The choice and dosage of concomitant medication will be at the discretion of the investigator. Corticosteroids administrated orally or as intra articular- or intra muscular injections are permitted until week 14. Intra muscular injections of corticosteroids are not permitted during the study period. Short courses of corticosteroids for acute medical conditions other than RA (for example asthma and allergy) are permitted. NSAIDs are permitted during the study. Doses may be increased or tapered according to clinical response. Analgesics may be used for pain relief as required. Patients should avoid analgesics within 12 hours prior to a visit if possible.

Patients who are switched to another treatment during the study period either due to the treatment algorithm, lack of improvement or side effects will still be included as study subjects.

NOR-DRUM B

Patients should continue with the same concomitant medication as prior to randomisation. Such medication may include 5-ASAs, systemic corticosteroids and sDMARDs like methotrexate, azathioprine and 6-MP. Any co-medication with synthetic DMARDs should be kept stable throughout the study, but tapering and termination due to side effects is

permitted. All changes in concomitant medication should be documented. Worsening in disease leading to major changes in the concomitant treatment as defined in 6.5.7 will lead to classification as worsening of disease (primary endpoint of the study). Short courses of corticosteroids for acute medical conditions other than RA (for example asthma and allergy) are permitted. Patients with RA, PsA or SpA can receive intra-articular injections in one swollen joint at each visit; more than one injection will be regarded as a major change in medication and lead to classification as disease worsening (primary endpoint). NSAIDs are permitted during the study. 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 CRF. Analgesics may be used for pain relief as required. Patients should avoid analgesics within 12 hours prior to a visit if possible.

Patients who experience a disease worsening can receive concomitant medication or switch therapy as needed.

4.10 Dose modifications and schedule modifications

Modification of dosing regimens related to abnormal blood values and/or adverse events should be performed based on the summary of product characteristics (SPC), clinical judgment and if necessary contact with the clinical coordinators. If an INX infusion is delayed due to non-disease related factors such as infections, surgery, vacation, subject non-compliance etc. this should be recorded and the reason given. In the intervention group the trough level assessed at this delayed visit cannot be used to guide the dose of the next infusion, and decisions should be based on the previous trough level assessment.

4.11 Protocol modifications

Protocol modifications must be approved by the study group, and will be submitted to the Regional Ethical committee for approval.

4.12 Linkage to other registers

In addition to the variables collected in this study, patients will be asked to give consent to collection of data from registries and databases such as; The Norwegian Prescription Database (Reseptregisteret), The Norwegian Health Economics Administration database (HELFO/KUHR), Norway's central institution for producing official statistics (Statistisk sentralbyrå i.e. FD-Trygd, IPLOS), The Norwegian Arthritis Registry (NorArthritis),The Norwegian Qualtiy Registry for Biologic Drugs (NOKBIL), The Cancer Registry of Norway (Kreftregisteret), the Norwegian Patient Registry (Norsk pasientregister – NPR), the Cause of Death Registry (Dødsårsaksregisteret), the Norwegian Myocardial Infarction Register (Norsk hjerteinfarktregister), the Norwegian Surveillance System for Communicable Diseases (Meldingssystem for smittsomme sykdommer – MSIS) and The Norwegian Labour and

Welfare Administration (NAV). This will allow certain outcomes to potentially be obtained through linkage to national medical or public registers and databases to answer research questions related to safety and health economics. Examples of such outcomes are cancer and other serious adverse events, health care utilization, work participation and social benefits. NOR-DMARD is also a potential data source for patients who have previously been enrolled in the NOR-DMARD study. The patient consent form includes information about linkage. Participation in international collaboration involving sharing of data from the NOR-DRUM study and merging of NOR-DRUM data with other (similar) studies will be based on fully de-identified data.

5 STUDY PROCEDURES AND SCHEDULE

An event flow chart is presented in appendix 15.1.

5.1 Visits

NOR-DRUM A

The study visits will be carried out according to the patient's INX treatment schedule and the number of visits will vary (between 5 and 13) depending on the infusion intervals. The assessments performed at each visit are shown in Appendix 15.1 The primary outcome will be recorded at the week 30 visit. The end of study visit is at week 38. If INX treatment is terminated, patients will still be study subjects and should be assessed at week 2, 6, 14, 22, 30 and 38. Extra study visits may be arranged at the request of the patient and/or the investigator (physician).

NOR-DRUM B

The visits will be carried out according to the patient's INX treatment schedule and the number of visits will vary depending on the infusion intervals. Over the 52±4 weeks study period the number of visits will be between 5 and 13. The assessments performed at each visit are presented in Appendix 15.1. If INX treatment is terminated, patients will still be study subjects and should be assessed at week 12, 24, 36 and 52. If the patients perceive increased disease activity, a non-scheduled visit will be arranged within one week in order to identify a disease worsening.

5.2 Screening evaluation

NOR-DRUM A

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
- Urine sample for pregnancy test
- Laboratory tests including screening tests for hepatitis B and C and tuberculosis

NOR-DRUM B
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 (No prior inclusion in NOR-DRUM A)
- A formal assessment of the eligibility criteria
- Urine sample for pregnancy test
- Laboratory tests

5.3 Assignment of intervention and subject numbering

Eligible patients will be assigned a unique patient identification number. Once assigned, this number cannot be reused for any other patient. The patients will be randomised 1:1 to either the intervention- or the control arm as described in 9.1. In NOR-DRUM A, patients will be stratified by disease. In NOR-DRUM B patients will be stratified by disease and prior participation NOR-DRUM A. Patients with prior participation in NOR-DRUM A will be stratified by study arm (intervention vs control). Patients with no prior participation in NOR-DRUM A will be stratified by prior or no prior TDM in the clinic (defined as one or more assessments of serum drug level during the last 3 infusions). The randomisation procedure will be performed trough the e- CRF (Viedoc).

5.4 Baseline visit

Informed written consent must have been given voluntarily by each subject before any study specific procedures are initiated. For the patients with a prior inclusion in NOR-DRUM A, the baseline visit in NOR-DRUM B is the end of study visit in NOR-DRUM A (the week 38 visit).
In addition to the assessments and procedures performed at a regular visit described in 5.5, the following assessments will be performed:

1. Full blood samples for biobank will be drawn and stored in a freezer at -70° C
2. Study nurse/investigator assessments:
   - Demographics (sex, birth date and ethnic origin)
   - Tobacco and alcohol use
   - Clinical status (physical examination)

- 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 patient, duration of INX use (NOR-DRUM B), non- RA related medical and surgical history)

3. Review of inclusion/exclusion criteria
4. Randomisation

5.5 Regular visit

The sequence of assessments and procedures is to be standardised as follows:

1. Laboratory samples for trough levels and ADAb, haematology, clinical chemistry, faecal calprotectin (IBD) and biobank storage must be drawn prior to the infusion, on the same day or not more than 5 days in advance.
2. Patient reported health outcomes assessments
    - Patient Global Assessment of disease activity (NRS)
    - EQ-5D
    - SF-36
    - WPAI-GH
    - RA: MHAQ, RAID
    - PsA: MHAQ, PsAID, DLQI
    - SpA: MHAQ, BASDAI
    - UC and CD: IBDQ
    - Chronic plaque psoriasis: DLQI
3. Study nurse/investigator assessments:
    - Investigator global assessment of disease activity (NRS)
    - Disease specific disease activity measures:
        - RA: DAS28, CDAI, SDAI
        - PsA: DAS28, DAPSA
        - SpA: ASDAS
        - UC: Partial Mayo score
        - CD: HBI
        - Psoriasis: PASI
    - Assessment of disease worsening (NOR-DRUM B, all visits)
    - Assessment of improvement (NOR-DRUM A at the week 14 visit)
    - Assessment of remission (NOR-DRUM A at the week 30 and week 38 visits)
    - Registration of concomitant medication
    - Safety assessments (AEs/SAEs)
    - Vital signs
    - Body weight

4. Treating physician:
    - Review of laboratory results
    - Decision regarding the dose and further dosing schedule of INX according to the randomised strategy of the patient. In the intervention arm, a review of trough levels and ADAb must be done with 1 week after the visit in order to schedule the next visit.
    - NOR-DRUM A: A clinical evaluation of the patient at baseline, at the week 14 visit, at the week 30 visit and at the week 38 visit and if requested by the patient or study nurse
    - NOR-DRUM B: A clinical evaluation of the patient every 12 (+/- 4) weeks and if requested by the patient or study nurse
5. Treatment administration according to treatment strategy, registration of time and dose

5.6 Extra visits

If the patient suspects a disease worsening (NOR-DRUM B), he or she should contact the study site immediately and be seen there as soon as possible and within one week as the latest. The visit will include all assessments of a regular visit (with the exception of treatment administration). If a disease worsening is confirmed according to the definition given in 6.5.7 treatment should be modified as outlined in Figure 6. In both NOR-DRUM A and B extra visits will be scheduled on the patient's request and assessments will be performed as described in appendix 15.1.

5.7 End of Study Visit

NOR-DRUM A

The end of study visit will be performed at 38±4 weeks and will include a formal end of study assignment in the eCRF in addition to all assessments of a regular visit.

NOR-DRUM B

The end of study visit will be performed at week 52±4 and will include a formal end of study assignment in the eCRF in addition to all assessments of a regular visit.

5.8 Withdrawal Visit

A withdrawal visit will include all assessments of a regular visit (with the exception of treatment administration) in addition to an assessment of reason for withdrawal, time of withdrawal and if the patient wishes to continue follow-up in the study.

6 ASSESSMENTS

6.1 Ordinary laboratory Tests

The following laboratory tests will be recorded at all visits. These tests will depending on availability be analysed 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 platelets
- Blood chemistry: ALT, albumin, creatinine
- Acute phase reactants: CRP and ESR
- Fecal analyses (IBD patients only): Calprotectin

6.2 Biobank samples

Serum samples will be collected at all visits. Samples will then be aliquoted and stored in a biobank. Full blood samples will be collected at first visit only. All samples will be in a certified biobank in a freezer at -70° C. The samples from the biobank will be used for research purposes only. DNA/RNA information will be used to assess possible associations between gene expressions and response/immunogenicity. Some analyses might take place in other countries if necessary.

6.3 Immunogenicity and Serum Drug Concentration Assessments

Serum samples will be drawn from all participants at all visits. The samples will be sent to the central laboratory at Oslo University Hospital, Radiumhospitalet, where serum infliximab levels and antibodies to infliximab will be measured using the assays currently used to monitor infliximab treatment by many departments of rheumatology, gastroenterology and dermatology in Norway.

Infliximab is measured using recombinant hTNF-alpha on the solid phase. As a result, only active infliximab (with the ability to bind TNF) will be measured. The assay for antibodies to infliximab only detects neutralising antibodies, i.e. antibodies that block the TNF-binding capacity of infliximab. Both assays are fully automated (including dilutions) on the AutoDELFIA platform (PerkinElmer).

In the intervention arm results for trough levels and ADAb will be reported to the investigators within one week. Results in the standard care group will be recorded in a database on a secure server according to institutional guidelines, and transferred to the PI upon conclusion of the clinical trial. In exceptional cases, serum infliximab levels will be reported to clinicians in the standard clinical care arm during the trial upon request.

6.4 Safety and Tolerability Assessments

Safety will be monitored by vital signs, laboratory tests (paragraph 6.1) and the collection of AEs at every 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 CRF. For details on AE collection and reporting, refer to Section 7 and appendix 15.14.

6.4.1 Vital signs

Vital signs including pulse rate, systolic and diastolic blood pressure and body weight will be assessed at all visits. Height will be measured at baseline.

6.5 Assessments of efficacy

6.5.1 General efficacy assessments:

Patient Global Assessment of Disease Activity (PGA)

PGA is measured on a numeric rating scale (NRS) 0-10 (0=none, 10=very severe) according to the question: “How active was your disease on average during the last week?”

Physician Global Assessment of Disease Activity (PhGA)

PhGA is measured on a numeric rating scale (NRS) 0-10 (0=none, 10=very severe) according to the question: “Please rate the patient’s overall (global) disease activity.”

Inflammation assessment by biochemical parameters

Inflammation is measured by C-reactive protein (CRP), the Erythrocyte Sedimentation Rate (ESR) for the inflammatory joint diseases, fecal calprotectin for the inflammatory bowel diseases according to hospital/laboratory standard procedures.

6.5.2 Disease specific efficacy assessments: RA, PsA

Disease Activity Score using 28 joints (DAS28)

The DAS28 composite score includes the 28 tender and swollen joint counts, ESR and a PGA on a NRS (PGA, see above).(48) The DAS28 is calculated as follows:
DAS28 = 0.56*sqrt(tender28) + 0.28*sqrt(swollen28) + 0.70*Ln(ESR) + 0.14*PGA
High disease activity is defined as a DAS28 value >5.1, moderate disease activity as DAS28 >3.2 – 5.1, low disease activity as a DAS28-value of 2.6 – 3.2, and remission as DAS28 <2.6

Rheumatoid Arthritis Impact of Disease (RAID) score

The RAID questionnaire was developed by the European League Against Rheumatism (EULAR) as a patient-derived composite score.(49) 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). See appendix 15.2. The rates of each domain are weighted and summed to form a score in the range of 0-10. It will only be used for patients with RA.

Psoriatic Arthritis Impact of Disease (PsAID) score

The PsAID questionnaire with 9 domains of health (PsAID-9) was developed by EULAR to calculate a score for clinical trials reflecting the impact of PsA from the patient's perspective.(50) The nine domains with relative weights are: pain (0.174), fatigue (0.131), skin (0.121), work and/or leisure activities (0.110), function (0.107), discomfort (0.098), sleep (0.089), coping (0.087) and anxiety (0.085), each rated on an NRS (0-10). See appendix 15.3. The rates of each domain are weighted and summed to form a score in the range of 0-10. It will only be used for patients with PsA.

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

The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) have been developed to provide physicians and patients with simple and more comprehensible instruments for assessment of disease activity in RA.(51) 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. The formula for SDAI is SJC28 + TJC28 + PGA + EGA + CRP. The formula for CDAI is SJC28 + TJC28 + PGA + EGA. It will only be used for patients with RA.

Disease Activity index for PSoriatic Arthritis (DAPSA)

Disease Activity index for PSoriatic Arthritis (DAPSA) has been developed using clinical trial and observational data. The DAPSA is simply calculated by summing swollen + tender joint counts + patient pain + patient global assessments + CRP, using 66/68 joint counts.

6.5.3 Disease specific efficacy assessments: SpA

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI was developed to define disease activity in patients with ankylosing spondylitis.(52) It includes six questions pertaining to the five major symptoms of ankylosing spondylitis: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness duration and morning stiffness severity. Each question is scored on an NRS (0-10). The two morning stiffness scores are averaged and added to the average of the other scores forming a total score in the range of 0-10. Se appendix 15.4.

Ankylosing Spondylitis Disease Activity Score (ASDAS)

The ASDAS composite score includes

- Total back pain: NRS 0-10 (0=none, 10=very severe) according to the BASDAI Question 2 ("How would you describe the overall level of AS neck, back or hip pain you have had during the last week")

- Patient global assessment of disease activity: NRS 0-10 (0=none, 10=Very severe) of the question ”How active was your spondylitis on average during the last week?”. The general PGA score described in section 6.5.1 will be used.
- Peripheral pain/swelling: NRS 0-10 (0=none, 10=very severe) according to the BASDAI Question 3 (“How would you describe the overall level of pain/swelling in joints other than neck, back or hip you have had during the last week”).
- Duration of morning stiffness: NRS 0-10 (0=0h, 5=1h, 10=2h or more) according to the BASDAI Question 6 (“How long does your morning stiffness last from the time you wake up during the last week?”)
- C-reactive protein (CRP) in mg/liter

The ASDAS-CRP is calculated as follows:
ASDAS=0.121*total back pain + 0.110*patient global + 0.073*peripheral pain/swelling + 0.058*duration of morning stiffness + 0579*ln(CRP+1)
Very high disease activity is defined as an ASDAS value >3.5, high disease activity as ASDAS 2.1 – 3.5, moderate disease activity as ASDAS 1.3 – 2.1 and inactive disease as ASDAS < 1.3.(53)

6.5.4 Disease specific efficacy assessments: Ulcerative colitis

Partial Mayo Score

The Mayo score is one of the most commonly used activity indices in placebo-controlled clinical trials for ulcerative colitis. It consists of four components (rectal bleeding, stool frequency, physician rating of disease activity, and mucosal appearance at endoscopy) rated from 0–3 that are summed to give a total score that ranges from 0–12. The non-invasive partial Mayo score does not require an endoscopy, and thereby ranging from 0-9.(54) Remission is defined as a partial Mayo score of ≤ 2 with no individual subscore >1.See appendix 15.5.

6.5.5 Disease specific efficacy assessments: Crohn’s disease

Harvey-Bradshaw Index (HBI)

The Harvey-Bradshaw index (55) was presented in 1980 as a simpler version of the Crohn's disease activity index (CDAI) to quantify the symptoms of Crohn’s disease. It consists of only clinical parameters. Remission is defined as a HBI score ≤ 4 points. See appendix 15.6.

6.5.6 Disease specific efficacy assessments: Psoriasis

Psoriasis Area and Severity Index (PASI)

The PASI is the most commonly used activity score in clinical trials for psoriasis. It is a measure of redness, thickness and scaliness of lesions (each graded 0-4), weighted by the area and location of involvement. It scores from 0 (no disease) to 72 (maximal disease severity). PASI examines four body regions: i) the head and neck, ii) the hands and arms, iii) the chest, abdomen and back (trunk) and iv) the buttocks, thighs and legs.

Intensity
A representative area of psoriasis is selected for each body region. The intensity of redness, thickness and scaling of the psoriasis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4). Calculation for intensity: The three intensity scores are added up for each of the four body regions to give subtotals A1, A2, A3, A4.

Each subtotal is multiplied by the body surface area represented by that region.

- A1 x 0.1 gives B1
- A2 x 0.2 gives B2
- A3 x 0.3 gives B3
- A4 x 0.4 gives B4

Area
The percentage area affected by psoriasis is evaluated in the four regions of the body. In each region, the area is expressed as nil (0), 1-9% (1), 13-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6).

- Head and neck
- Upper limbs
- Trunk
- Lower limbs

Calculations for area: Each of the body area scores is multiplied by the area affected.

- B1 x (0 to 6)= C1
- B2 x (0 to 6)= C2
- B3 x (0 to 6)= C3
- B4 x (0 to 6)= C4

Total score
The PASI score is C1 + C2 + C3 + C4

A PASI 50/75 means a 50% /75% reduction in the PASI score.

6.5.7 Definition of disease worsening

- **Disease worsening in RA and PsA**

A disease worsening in RA and PsA is defined as an increase in DAS28 of ≥ 1.2 from randomization and a minimum DAS score of 3.2.

- **Disease worsening in SpA**

A disease worsening in SpA is defined as an increase in ASDAS of ≥1.1 from randomization and a minimum ASDAS of 2.1.

- **Disease worsening in ulcerative colitis**

A disease worsening in ulcerative colitis is defined as an increase in Partial Mayo score of ≥ 3 points from randomization and a minimum partial Mayo score of ≥ 5 points.

- **Disease worsening in Crohn's disease**

A disease worsening in Crohn's disease is defined as an increase in HBI of ≥ 4 points from randomization and a minimum HBI score of 7 points.

- **Disease worsening in psoriasis**

A disease worsening in psoriasis is defined as an increase in PASI of ≥ 3 points from randomization and a minimum PASI score of 5.

- **Patient and investigator consensus on disease worsening**

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

A major change* in treatment includes; Switching from INX to another bDMARD, adding a sDMARD, increasing the dose of a concomitant sDMARD, adding systemic glucocorticoids (po., iv. or im.), receiving more than one i.a. glucocorticoid injection at one visit. If the INX dose is increased for clinical reasons this should also be regarded as a major change in treatment (applies to the control arm only).

6.5.8 Definition of low disease activity

- **Low disease activity in RA and PsA**

Low disease activity in RA and PsA is defined as a DAS28 score of <3.2.

- **Low disease activity in SpA**

Low disease activity in SpA is defined as an ASDAS of <2.1.

- **Low disease activity in ulcerative colitis**

Low disease activity in UC is defined as a partial Mayo score of < 5 points.

- **Low disease activity in Crohn's disease**

Low disease activity in CD is defined as a HBI score of <7 points.

- **Low disease activity in psoriasis**

Low disease activity in Ps is defined as a PASI score of <5.

6.5.9 Definition of remission

- **Remission in RA and PsA**

Remission in RA and PsA is defined as a DAS 28 <2.6

- **Remission in SpA**

Remission in SpA is defined as a ASDAS <1.3

- **Remission in UC**

Remission in UC is defined as a Partial Mayo score ≤2 with no subscores >1

- **Remission in CD**

Remission in CD is defined as a HBI≤4

- **Remission in Ps**

Remission in Ps is defined as a PASI ≤ 4

6.5.10 Definition of improvement

- **Improvement in RA and PsA**

Improvement is defined as a decrease in DAS28 of ≥1.2 from baseline

- **Improvement in SpA**

Improvement is defined as a decrease in ASDAS of ≥1.1 from baseline

- **Improvement in UC**

Improvement in UC is defined as a decrease in the partial Mayo score of ≥ 3 points from baseline

- **Improvement in CD**

Improvement in CD is defined as a decrease in HBI of ≥ 4 points from baseline

- **Improvement in Ps**

Improvement in Ps is defined as PASI 50 (A 50% decrease in the PASI obtained at baseline)

- **Patient and investigators consensus on improvement**

If there is a consensus between the patient and the investigator that there has been an improvement, it should be considered as an improvement even if the formal definition has not been met.

6.6 Other Assessments

Modified Heath Assessment Questionnaire

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 Modified Health Assessment Questionnaire (MHAQ) reduced the number of items from 20 in the original HAQ to eight, and improved the feasibility in clinical practice.(56) 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. See appendix 15.7. The MHAQ will only be presented to patients with IJD.

Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is widely used tool to measure health-related quality of life in patients with inflammatory bowel diseases. The questionnaire consists of 32 questions scored in four domains: bowel symptoms, emotional health, systemic systems and social function.(57) The IBDQ will only be presented to patients with IBD. See appendix 15.8.

Dermatology Life Quality Index (DLQI)

The DLQI is a simple self-administered, easy and user-friendly validated questionnaire used to measure the health-related quality of life of adult patients suffering from a skin disease.(58) It consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health related quality of life over the last week. It has been validated for adult dermatology patients aged 16 years and older. The items of the DLQI encompass aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each question is scored on a 4-point Likert scale: Not at all/Not relevant=0, A little=1, A lot=2 and Very much=3. Scores of individual items (0-3) are added to yield a total score (0-30); higher scores mean greater impairment of patient's QoL. The DLQI will only be presented to patients with chronic plaque psoriasis and psoriatic arthritis. See appendix 15.9 .

SF-36

The SF-36 is a multi-purpose, short-form health survey with 36 questions.(59) 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).(60) 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. See appendix 15.10.

EQ-5D

EQ-5D is a utility instrument for measurement of health related quality of life.(61) Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. See appendix 15.11.

Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)

Worker productivity is generally subdivided into 2 components: absenteeism and presenteeism. The concept of absenteeism has been defined as productivity loss due to health-related absence from work, while presenteeism refers to reduced performance or productivity while at work due to health reasons. Absenteeism may include personal time off, sick days off work, time on short and/or long-term work disability, or time on worker's-compensated days; and presenteeism could be characterized as the time not being on the task, or decreased work quality and quantity. Patients will be asked to answer the Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH).(62) See appendix 15.12.

The WPAI yields four types of scores:

1. Absenteeism (work time missed)
2. Presenteeism (impairment at work/reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment

Resource use and related data

The following types of resource use will be captured:

- Use of biologics
- Use of other pharmaceuticals (Norwegian Prescription Database)
- Use of somatic hospital services (in-patient and out-patient)(Norwegian Patient Register)
- Use of GP services and emergency room services (HELFO/KUHR database - The Norwegian Health Economics Administration database)
- Use of social benefits (NAV database)
- Use of nursing services (IPLOS database)

Drug dose

The drug dose given will be registered at each visit.

7 SAFETY MONITORING AND REPORTING

7.1 Adverse events

Any adverse event (AE) encountered during the clinical study will be reported in the eCRF (see appendix for definitions). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. AE should 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.

7.1.1 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.
- The intensity of the adverse event will be described according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE)
- The Causal relationship of the event to the study medication will be assessed as one of the following:

Unrelated:

There is not a temporal relationship to the administration of the study drug or there is a reasonable causal relationship between concomitant medication, concurrent disease, or circumstance and the AE.

Unlikely:

There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.

Possible:

There is reasonable causal relationship between the study drug and the AE. Dechallenge information is lacking or unclear.

Probable:

There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge is not required.

Definite:

There is a reasonable causal relationship between the study drug and the AE.

- Action taken
  The outcome of the adverse event – whether the event is resolved or still ongoing.

7.1.2 Serious adverse events

Any serious adverse event (defined in 15.14) must be reported immediately (within one working day) of becoming aware of the event to the study leader and a report should be sent to RELIS.

7.2 Laboratory test abnormalities

Laboratory test results are recorded in the eCRF and abnormalities should not be recorded as AE unless there is an associated clinical condition for which the patient is given treatment or the current treatment is altered. In the event of a medically significant unexplained abnormal laboratory test value the test should be followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

7.3 Pregnancy

A female patient must be instructed to immediately inform the investigator if she becomes pregnant during the study. If clinically contraindicated to continue INX therapy the patient should be withdrawn from the study.

8 DATA MANAGEMENT

8.1 Electronic Case Report Forms (CRFs)

The designated investigator staff will enter the data required by the protocol into the electronic Case report forms (eCRF). The Principal Investigator is responsible for assuring that data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner. The electronic signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections will also be recorded. A complete list of authorized study personnel will be maintained during the study, and only study personnel authorized by the principal investigator or coordinating investigator will be allowed to sign the eCRF.
After database lock, the investigator will receive the subject data for archiving at the investigational site.
A web-based eCRF software solution will be used to collect study data (Viedoc™, Uppsala, Sweden).

8.2 Source Data

The medical records for each patient should contain information, which is important for the patient's safety and continued care, and to fulfil the requirement that critical study data should be verifiable.
To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study
- Date when Informed Consent was obtained from the patient
- Results of assessments performed during the study that will have an impact of future follow-up of the patient
- Treatments given, changes in treatments during the study and the time points for the changes;
- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, discontinuation from study treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available
- Additional information according to local regulations and practice.

Patient reported outcome (PRO) measures not recorded in an electronic patient journal (EPJ) system is recorded on paper CRFs or directly into the eCRF. If these measures are recorded directly in the eCRF, the eCRF is source data. If they are recorded on paper and then entered into the eCRF, then the paper CRF is source data.

8.3 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc.) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Randomization

9.1.1 Allocation- sequence generation

NOR-DRUM A:
Eligible patients will be allocated in a 1:1 ratio between intervention and control, using a computer randomisation procedure stratified by diagnosis (RA, SpA, PsA, UC, CD, Ps). The randomisation will be blocked within each stratum.
Details of block size and allocation sequence generation will be provided in a separate document unavailable to those who enrol patients or assign treatment.

NOR-DRUM B:
Eligible patients will be allocated in a 1:1 ratio between intervention and control, using a computer randomisation procedure stratified by diagnosis (RA, SpA, PsA, UC, CD, Ps) and 1) by study arm (intervention or control) if the patient originates from NOR-DRUM A or 2) by prior or no prior TDM in the clinic (defined as one or more assessments of serum drug level during the last 3 infusions) if the patient originates from NOR-DRUM B. The randomisation will be blocked within each stratum.
Details of block size and allocation sequence generation will be provided in a separate document unavailable to those who enrol patients or assign treatment.

9.1.2 Allocation- procedure to randomise a patient

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

9.2 Planned analyses

The statistical analysis for each part of the study is planned when

- The planned number of patients in each part have been included
- All included patients have either finalised their last assessment of the study part or has/is withdrawn according to protocol procedures
- All data from the intervention period have been entered, verified and validated according to the data management plan

Prior to the statistical analysis, the data for each respective study part will be locked for further entering or altering of data. Separate statistical analysis plans (SAP) for each study part will provide further details on the planned statistical analyses. The SAP will be finalised, signed and dated prior to data lock. There will be a planned interim analysis in NOR-DRUM A when approximately 50% of the required patients have a validated assessment of remission at week 30.
Deviation from the original statistical plan will be described and justified in the Clinical Study Report.

9.3 Populations

9.3.1 Primary population

The primary intention to treat (ITT) population will in each of the two study parts will consist of all randomised patients who have received at least one dose of study medication (infliximab).

9.3.2 Secondary population

The secondary per-protocol (PP) population will in each of the two study parts consist of all randomised patients who have received at least one dose of study medication (infliximab) and who sufficiently comply with the protocol. Criteria for inclusion in the PP population will be specified in the statistical analysis plan, and the final criteria will be defined prior to database lock.

9.3.3 Safety population

The safety population consist of all randomised patients who have received at least one dose of study medication (infliximab)

9.4 Statistical Analysis

9.4.1 Statistical model

This randomised clinical trial aims primarily to describe and estimate efficacy parameters and test pre-specified statistical hypotheses.
The primary variables will be analysed using logistic regression models with strategy treatment group as primary explanatory variable, adjusted for stratification factors used at randomisation. Although this is a multicentre study, study site will not be used for stratification or adjustment in the analysis due to anticipated small sample sizes within site. However, sensitivity analyses will be performed to assess the impact of site on the study conclusions. Other pre-specified covariates included in sensitivity analyses include age, use of disease-specific co-medication (methotrexate, azathioprine or similar) and levels of neutralizing antibodies at baseline. The statistical analysis plan (SAP) will detail these

procedures, as well as alternative and further supportive evaluations, such as analyses including unbalanced baseline predictors or modifications of the logistic regression model in case validity assumptions are not met.
The primary analysis will be performed on the primary intention to treat population.

9.4.2 Primary analyses

There will be two primary hypotheses tested in this study, one for each of the two parts (NOR-DRUM A and B). There will be no adjustments for multiplicity; each part will be regarded as answering independent research questions.

NOR-DRUM A statistical hypothesis (superiority test):

Null hypothesis: There is no difference in proportion of patients in remission at week 30 between the intervention and control group.

Alternative hypothesis: There is a difference in proportion of patients in remission at week 30 between the intervention and control group.

The primary variable will be evaluated by the p-value of the hypothesis test from the logistic regression analysis. A conclusion of superiority of any of the treatment strategies will be made if the null hypothesis is rejected on an overall significance level of 5%. If the study fails to reject the primary null hypothesis, non-inferiority of TDM vs standard care will be assessed. Non-inferiority implies that the 95% confidence limits of the estimated adjusted risk difference of disease worsening lies fully within the non-inferiority margin of 15%.

NOR-DRUM B statistical hypothesis (superiority test):

Null hypothesis: There is no difference in proportion of patients in sustained disease control throughout the study period without disease worsening between the intervention and control group.

Alternative hypothesis: There is a difference in proportion of patients in sustained disease control throughout the study period without disease worsening between the intervention and control group.

The primary variable will be evaluated by the p-value of the hypothesis test from the logistic regression analysis. A conclusion of superiority of any of the treatment strategies will be made if the null hypothesis is rejected on a significance level of 5%. If the study fails to reject the primary null hypothesis, non-inferiority of TDM vs standard care will be assessed. Non-inferiority implies that the 95% confidence limits of the estimated adjusted risk difference of disease worsening lies fully within the non-inferiority margin of 15%.

9.4.3 Secondary analyses

Between-group comparisons will be performed for the primary endpoints on secondary populations in addition to secondary efficacy endpoints on both efficacy populations.

The between-group comparisons for secondary variables will be tested as for the primary variable where applicable and additional analyses will be performed based on the following methods (but not limited to):

- Continuous secondary variables will be subject to repeated measures mixed models or appropriate non-parametric alternatives
- Binary response variables will be analysed using logistic regression (possibly adjusting for within-subject dependencies by mixed model approaches) or chi-square/Mantel-Haenszel test

- Time-to-event variables will be analysed using the Kaplan-Meier method and comparisons between the two groups will be performed using the log rank test, Cox regression analyses and/or appropriate parametric models such as the Weibull model.

Unless otherwise specified, all statistical hypotheses will be tested as the primary variable, i.e. with an assessment of superiority based on the p-value of the group differences.

Presentation of results:
All efficacy analyses will be presented with the results from the hypothesis testing (by p-value) in addition to estimates and 95% confidence limits of the treatment effect. For the primary variables specifically, this will be the estimated risk differences with corresponding 95% confidence limits.

9.4.4 Safety analyses

The safety analyses population will include all patients who completed at least one follow-up visit. Safety analyses will be descriptive and presented as summary tables by treatment group and (if applicable) by visit.

9.4.5 Patient reported outcome measures and disability analyses

Patient reported outcome measures (PROMs) and disability will be assessed using SF-36, EQ-5D, MHAQ (IJD), IBDQ (IBD) and DLQI (chronic plaque psoriasis). These scores will be summarised by descriptive summary tables at baseline and over time, and at the end of study. Missing data at end of study will be replaced by the last valid post-baseline assessment.

9.4.6 Other analyses/subanalyses

We will perform subgroup analyses according to diagnoses groups (RA, SpA, PsA, UC, CD, Ps) on the appropriate primary and secondary variables using methods described above.
Other exploratory subgroup analyses of primary, secondary and exploratory efficacy variables may be performed if appropriate. The decision to include such analyses will be made on basis of the collected data.

9.4.7 Health economic analyses

All patients will, with assistance from a study nurse, be asked to fill in the two standard instruments (questionnaires) to capture health related quality of life (HRQOL): SF-36 and EQ-5D. These instruments will be used at each visit.
Use of health care (costs) will be captured by the following registers: The Norwegian Patient Register (hospital services), The Norwegian Prescription Register (pharmaceuticals), The Norwegian Health Economics Administration database (emergency room and general practitioner services), Statistics Norway KOSTRA database (nursing services) and the Norwegian Welfare and Labour Administration NAV (social benefits). We will assign unit costs to each type of service by means of the DRG price list, and the price list of the Norwegian Medicines Agency. For each patient we will, based on HRQOL data, estimate the number of QALYs obtained during the study period in line with methods used previously (Bohmer et al. 717-23;Fjalestad et al. 599-605) and adjust for any baseline imbalances (Manca, Hawkins, and Sculpher 487-96). We will use EQ-5D and also translate SF-36-data into utilities according to a validated method (Brazier, Roberts, and Deverill 271-92). For each patient we will estimate one year costs based on register data for utilisation of health care and the unit costs. The mean week QALYs and cost in the two treatment arms will be used to estimate an incremental cost-effectiveness ratio (ICER), for all patients and according to diagnostic group. Not all patients in the randomised trial will have complete months data. We will therefore impute missing data (Glick and Doshi). We will use bootstrapping to estimate confidence intervals of the incremental costs and QALYs and to present uncertainty in cost-effectiveness acceptability curves.

9.4.8 Missing data

Methods to handle missing data may include complete case analyses, last observation carried forward, worst case/best case imputation and multiple imputation techniques. For the primary analyses, worst case imputation will be used for missing observations. Further details on missing data will be given in the SAP.

9.5 Sample size determination

Sample sizes are determined for each of the two study parts separately.

NOR-DRUM A: Under the assumption of an absolute increase in remission rate of 15% (from 40 to 65%) we need a maximum of 358 completed patients in order to reject the null hypothesis on a 5% significance level with 80% power. The sample size calculation incorporates an interim analysis when approximately 50% of the patients have a validated assessment of remission at week 30. Adjusting for possible drop-outs, we plan to randomise 400 patients.

NOR-DRUM B: Under the assumption of an absolute decrease in proportion of patients with disease worsening of 12.5% (from 30 to 17.5%) we need 414 completed patients in order to reject the null hypothesis on a 5% significance level with 85% power. Adjusting for possible drop-outs, we plan to randomise 450 patients.

9.6 Interim analyses

NOR-DRUM A:
A formal interim efficacy analysis in NOR-DRUM A will be performed after approximately 50% of the patients have a validated assessment of remission at week 30. An independent statistician can recommend to the study group whether to continue, modify or stop the clinical trial on the basis of efficacy considerations. The pre-planned interim efficacy analysis will assess the intervention effectiveness on the primary efficacy endpoint, with the intent to stop the study early if there is overwhelming evidence of intervention benefit or futility.

The Lan-DeMets alpha-spending approach will be applied with a gamma cumulative alpha spending stopping boundary (gamma=-2) for primary hypothesis test. A significance level of 0.00672 on the upper and lower boundaries will be used for the interim analysis so support early termination for efficacy. The significance level at the final analysis will depend on the exact numbers of patients at the time of the interim analysis, but is expected to be of the order of 0.0227 on each of the upper and lower tails, preserving the overall significance level at 5% (two-sided).

A decision of stopping for futility will also be made based on the interim analysis. A pre-defined beta-spending function will be applied where some of the type 2 error rate (beta) will be spent on the interim analysis according to the gamma cumulative spending function (gamma=-2). A one-sided p-value boundary of 0.32 is defined as indicative for futility at the interim analysis. However, additional information may be addressed by the independent statistician in order to give a recommendation of stopping for futility. Such information could be the conditional power, simulation analyses in addition to analyses of secondary endpoints.

Specifications of the duties of the independent statistician will be described in a separate procedure document.

10 STUDY MANAGEMENT

10.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

10.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported as appropriate.

10.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Ethics Committee according to national regulations.

11 ETHICAL REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with applicable laws and regulations. Registration of patient data will be carried out in accordance with national personal data laws.

11.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, will be approved by the regional ethics committee before enrolment of any patients into the study.
The principle investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

11.2 Other Regulatory Approvals

The protocol will be registered in www.clinicaltrials.gov before inclusion of the first patient.

11.3 Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.
It will be emphasised that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. The patient will be given ample time to consider participation. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent. A copy will be given to the patients.
A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder.

11.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses. The patients will be identified in the eCRFs by patient number, initials and date of birth.

12 TRIAL SPONSORSHIP AND FINANCING

The medical treatment will be covered as for "usual care" by "Folketrygden/NAV". There will be no procedures/examinations that are not part of "usual care".

13 PUBLICATION POLICY

Upon study completion and finalisation of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results.
The results of this study will also be submitted to the Ethics Committee according to national regulations. 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.

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15 APPENDICES

15.1 Trial flow charts

NOR DRUM A

Visits	Screening Evaluation	Baseline visit	Other visits	Week 14 visit	Week 30 visit	Extra visit	End of study visit
Weeks		0		14 (+/-2) weeks	30 (+/-2) weeks		38 (+/-4) weeks
Informed consent	X						
Eligibility assessment	X	X					
Randomisation		X					
Demographics		X					
Medical history		X					
Comorbidities		X	X	X	X	X	X
Physical Examination[7)]		X					
Body weight		X	X	X	X		X
Pregnancy test	X						
Vital signs [1)]		X	X	X	X	X	X
Laboratory samples[2)]	X	X	X	X	X	X	X
Biobank samples		X[3)]	X[4)]	X[4)]	X	X	X[4)]

Patient reported outcomes[5)]		X	X	X	X	X	X
Assessments of disease activity[6)]		X	X	X	X	X	X
Adverse event		X	X	X	X	X	X
Record of concomitant medication		X	X	X	X	X	X
Evaluation by investigator		X		X	X	X	X
Evaluation of efficacy and treatment decision by investigator				X	X	X	X
Treatment administration according to randomised strategy		X	X	X	X		X
Establishing dose and interval to the next infusion by investigator		X	X	X	X		X

NOR DRUM B

Visits	**Screening**	**Baseline visit**	**Regular visit**	**Extra visit if disease worsening**	**End of study visit**
Weeks		0			52 (+/-4 weeks)
Informed consent	X				
Eligibility assessment	X	X			
Randomisation		X			
Demographics		X			
Medical history		X			
Comorbidities		X	X	X	X
Physical Examination[7)]		X			
Body weight		X	X	X	X
Vital signs [1)]		X	X	X	X
Laboratory samples[2)]	X	X	X	X	X
Biobank samples		X[3)]	X[4)]	X[4)]	X[4)]
Patient reported outcomes[5)]		X	X	X	X
Assessments of disease activity[6)]		X	X	X	X
Adverse events		X	X	X	X
Record of concomitant		X	X	X	X

medication					
Treatment administration according to randomised strategy		X	X		X
Establishing dose and interval to the next infusion by investigator		X	X		X

1. Blood pressure and pulse rate
2. Hemoglobin, white blood cells with differentials, platelet counts, ALT, ALP, albumin, creatinine, CRP, ESR, faecal calprotectin (IBD)
3. Serum and fullblood
4. Only serum
5. Consisting of:

   – Patient Global Assessment of disease activity (NRS)
   – EQ-5D
   – SF-36
   – WPAI-GH
   – RA: M-HAQ RAID
   – PsA: M-HAQ, PsAID, DLQI
   – SpA: M-HAQ, BASDAI
   – UC and CD: IBDQ
   – Psoriasis: DLQI

6. Consisting of:

   – Nurse/investigator global assessment of disease activity (NRS)
   – RA: DAS28, CDAI, SDAI
   – PsA : DAS28, DAPSA
   – SpA: ASDAS
   – UC: Partial Mayo score
   – CD: HBI
   – Psoriasis: PASI

7. Heart, lungs, lymph nodes, abdomen, peripheral oedema, height

15.2 RAID questionnaire

RAID

Smerte
Sett ring rundt det tallet som best beskriver smerten du kjente pga din leddgikt i løpet av den siste uken:

0	1	2	3	4	5	6	7	8	9	10

Ingen smerte — Ekstrem Smerte

Måling av fysisk funksjon
Sett ring rundt det tallet som best beskriver vanskeligheten du hadde med å gjøre daglige fysiske aktiviteter pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10

Ingen vanskelighet — Ekstrem vanskelighet

Fatigue/utmattelse
Sett ring rundt det tallet som best beskriver hvor mye fatigue/utmattelse du kjente pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10

Ingen fatigue — Totalt utmattet

Søvn
Sett ring rundt det tallet som best beskriver søvnvansker (hvile om natten) du følte pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10

Ingen vansker — Ekstreme *vansker*

Fysisk velvære
Tatt i betraktning din leddgikt generelt, hvordan ville du gradere nivået av fysisk velvære i løpet av den siste uken? Sett ring rundt det tallet som best beskriver nivået av fysisk velvære.

0	1	2	3	4	5	6	7	8	9	10

Veldig bra — Veldig dårlig

Følelsesmessig velvære
Tatt i betraktning din leddgikt generelt, hvordan vil du gradere nivået av følelsesmessig velvære i løpet av den siste uken. Sett ring rundt det tallet som best beskriver nivået av følelsesmessig velvære.

0	1	2	3	4	5	6	7	8	9	10

Veldig bra — Veldig dårlig

Mestring
Tatt i betraktning din leddgikt generelt, hvor bra mestret (taklet, styrte, kontrollerte) du din sykdom i løpet av den siste uken? Sett ring rundt det tallet som best beskriver din mestring.

0	1	2	3	4	5	6	7	8	9	10

Veldig bra — Veldig dårlig

15.3 PsAID Questionnaire

PSAID-9 Norwegian

Kan du vennligst beskrive for oss hvordan du har følt deg i uken som gikk.

Smerte

Sett ring rundt det tallet som best beskriver smerten du hadde som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt sterke

1. Hudproblem

Sett ring rundt det tallet som best beskriver de hudproblemene (inkludert kløe) du hadde som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

2. Utmattelse/tretthet

Sett ring rundt det tallet som best beskriver det generelle nivået av utmattelse/tretthet du hadde som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Totalt utmattet

3. Arbeid og/eller fritidsaktiviteter

Sett ring rundt det tallet som best beskriver de problemene du hadde med fullt og helt å kunne utføre arbeid og/eller fritidsaktiviteter som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

4. Fysisk funksjon

Sett ring rundt det tallet som best beskriver vanskelighetene du hadde med å utføre fysiske aktiviteter som følge av psoriasisgikt siste uke:

Ingen problem	0	1	2	3	4	5	6	7	8	9	10	Ekstremt vanskelig

5. Følelse av ubehag

Sett ring rundt det tallet som best beskriver følelsen av ubehag og irritasjon med daglige gjøremål som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

6. Søvnforstyrrelser

Sett ring rundt det tallet som best beskriver søvnproblemene (dvs. nattesøvn) du hadde som følge av psoriasisgikt siste uke:

Ingen problem	0	1	2	3	4	5	6	7	8	9	10	Ekstremt vanskelig

7. Engstelse, frykt og usikkerhet

Sett ring rundt det tallet som best beskriver nivået på engstelse, frykt og usikkerhet (f.eks. om fremtiden, behandlinger, frykt for ensomhet) som følge av psoriasisgikt siste uke:

Ingen	0	1	2	3	4	5	6	7	8	9	10	Ekstremt

8. Mestring

Når du tar vurderer din psoriasisgikt generelt i løpet av siste uke, sett ring rundt det tallet som best beskriver mestringsnivået (hvordan du tilpasset deg, håndterte, klarte deg, taklet sykdommen) ditt:

Meget bra	0	1	2	3	4	5	6	7	8	9	10	Meget dårlig

15.4 BASDAI questionnaire

Fatigue

1 How would you describe the overall level of fatigue/tiredness you have experienced?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Spinal pain

2 How would you describe the overall level of AS neck, back or hip pain you have had?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Peripheral arthritis

3 How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Enthesitis

4 How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Intensity of morning stiffness

5 How would you describe the overall level of morning stiffness you have had from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

Duration of morning stiffness

6 How long does your morning stiffness last from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

0 h 1 h 2 or more h

15.5 Partial Mayo Score

	Assessment Category		
Score	**Stool frequency[1]**	**Rectal bleeding[2]**	**Physician's global assessment[3]**
0	Normal number of stools	No blood seen	Normal
1	One to two stools more than normal	Streaks of blood with stool less than half the time	Mild disease
2	Three to four stools more than normal	Obvious blood with stool most of the time	Moderate disease
3	Five or more stools than normal	Blood alone passes	Severe disease
Subscore	0-3	0-3	0-3

1. Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
2. The daily bleeding score represents the most severe bleeding of the day.
3. The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well being, and other observations, such as physical findings and the patient's performance status.

15.6 Harvey-Bradshaw Index

1. General well-being (yesterday)	☐ Very well = 0 ☐ Slightly below par = 1 ☐ Poor = 2 ☐ Very poor = 3 ☐ Terrible = 4
2. Abdominal pain (yesterday)	☐ None = 0 ☐ Mild = 1 ☐ Moderate = 2 ☐ Severe = 3
3. Number of liquid or soft stools per day (yesterday) =	
4. Abdominal mass	☐ None = 0 ☐ Dubious = 1 ☐ Definite = 2 ☐ Definite and tender = 3
5. Complications (Check any that apply; score one per item except for first box)	☐ None ☐ Arthralgia ☐ Uveitis ☐ Erythema nodosum ☐ Aphthous ulcers ☐ *Pyoderma gangrenosum* ☐ Anal fissure ☐ New fistula ☐ Abcess

Add scores of questions 1 through 5 to compute the Harvey-Bradshaw Index

15.7 MHAQ

Please check the response that best describes your usual abilities OVER THE COURSE OF THE LAST WEEK

Are you able to:	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Dress yourself, including tying shoelaces and doing buttons?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of bed?	☐ 0	☐ 1	☐ 2	☐ 3
Lift a full cup or glass to your mouth?	☐ 0	☐ 1	☐ 2	☐ 3
Walk outdoors on flat ground?	☐ 0	☐ 1	☐ 2	☐ 3
Wash and dry your entire body?	☐ 0	☐ 1	☐ 2	☐ 3
Bend down to pick up clothing from the floor?	☐ 0	☐ 1	☐ 2	☐ 3
Turn regular faucets on and off?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of a bus, car, train, or airplane?	☐ 0	☐ 1	☐ 2	☐ 3

15.8 IBDQ

SPØRRESKJEMA OM LIVSKVALITET HOS PASIENTER MED INFLAMMATORISK TARMSYKDOM

1. Hvor ofte har du hatt avføring i **de siste to ukene**?:

(Sett ring rundt et tall)

Hyppigere enn eller like hyppig som på det verste	1
Ekstremt hyppig i forhold til vanlig avføringsmønster	2
Veldig hyppig i forhold til vanlig avføringsmønster	3
Moderat økning i forhold til vanlig avføringsmønster	4
Noe økning i forhold til vanlig avføringsmønster	5
Liten økning i forhold til vanlig avføringsmønster	6
Som normalt, ingen økning i forhold til vanlig avføringsmønster	7

2. Hvor stor del av tiden **de to siste ukene** har følelsen av tretthet eller det å ha vært trett og utslitt vært et problem for deg?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

3. Hvor stor del av tiden **de to siste ukene** har du følt deg frustrert, utålmodig eller rastløs?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

4. Hvor ofte i løpet av **de to siste ukene** har du vært hjemme fra skolen eller jobben eller måttet avstå fra husarbeide pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

5. Hvor stor del av tiden **de to siste ukene** har du vært plaget av løs avføring?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

6. Hvor mye arbeidslyst har du hatt i **de to siste ukene**?

(Sett en ring rundt et tall)

Ingen arbeidslyst	1
Svært liten arbeidslyst	2
Lite arbeidslyst	3
Noe arbeidslyst	4
En god del arbeidslyst	5
Mye arbeidslyst	6
Full av arbeidslyst	7

7. Hvor stor del av tiden **de to siste ukene** har du vært bekymret ved tanken på at du kanskje måtte opereres pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

8. Hvor stor del av tiden **de to siste ukene** har du måttet tilpasse eller avlyse din vanlige sosiale omgang med familie, venner, naboer eller foreninger som følge av din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

9. Hvor ofte har du hatt mageknip i løpet av **de to siste ukene**?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

10. Hvor stor del av tiden **de to siste ukene** har du følt deg i dårlig form?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

11. Hvor stor del av tiden **de to siste ukene** har du vært bekymret for ikke å finne et toalett?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

12. Hvor store vanskeligheter har din tarmsykdom medført **de to siste ukene**, med tanke på å utøve fritids- eller sportsaktiviteter som du liker å gjøre?

(Sett ring rundt et tall)

Meget store vanskeligheter, aktiviteter har vært umulig å utføre	1
Store vanskeligheter	2
En god del vanskeligheter	3
Noen vanskeligheter	4
Små vanskeligheter	5
Nesten ingen vanskeligheter	6
Ingen vanskeligheter, aktiviteter har vært utført som vanlig	7

13. Hvor stor del av tiden **de to siste ukene** har du hatt smerter i fra magen?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

14. Hvor stor del av tiden **de to siste ukene** har du hatt problemer med å få sove eller våknet om natten?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

15. Hvor stor del av tiden **de to siste ukene** har du følt deg deprimert eller motløs?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

16. Hvor stor del av tiden **de to siste ukene** har du måttet unngå å delta på møter og sammenkomster fordi du var usikker på om det var et toalett i nærheten?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

17. Hvor stort problem har luftavgang vært for deg **de to siste ukene**? (Med luftavgang menes her behov for å «slippe seg», ofte forbundet med lindring av følelse av oppblåsthet.)

(Sett ring rundt et tall)

Et meget stort problem	1
Et stort problem	2
En god del problem	3
Noe problem	4
Lite problem	5
Svært lite problem	6
Ikke noe problem	7

18. Hvor stort problem har det vært for deg å opprettholde eller oppnå den vekten du helst vil ha **de to siste ukene**?

(Sett ring rundt et tall)

Et meget stort problem	1
Et stort problem	2
En god del problem	3
Noe problem	4
Lite problem	5
Svært lite problem	6
Ikke noe problem	7

19. Mange pasienter med tarmsykdom føler ofte bekymring og engstelse i forhold til sin sykdom. Dette kan være redsel for å få kreft i tarmen, redsel for aldri å bli bedre av sin sykdom eller redsel for å få nye utbrudd av sykdommen.
Hvor stor del av tiden **de to siste ukene** har du vært bekymret eller engstelig?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

20. Hvor stor del av tiden **de to siste ukene** har du vært plaget med oppblåsthet i magen? (Med oppblåsthet menes utspiling, ofte forbundet med en følelse av luft i magen)

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

21. Hvor stor del av tiden **de to siste ukene** har du følt deg avslappet og fri for stress?

(Sett ring rundt et tall)

Ikke i det hele tatt	1
Nesten ikke i det hele tatt	2
Litt av tiden	3
Omtrent halvparten av tiden	4
En god del av tiden	5
Mesteparten av tiden	6
Hele tiden	7

22. Hvor stor del av tiden **de to siste ukene** har du hatt problemer med blødning fra endetarmen i samband med avføring?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

23. Hvor stor del av tiden **de to siste ukene** har du følt deg brydd pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

24. Hvor stor del av tiden **de to siste ukene** har du hatt følelse av å skulle på toalettet uten at det har vært noe avføring?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

25. Hvor stor del av tiden **de to siste ukene** har du følt deg nedfor eller motløs?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

26. Hvor stor del av tiden **de to siste ukene** har du vært «uheldig» og hatt avføring i underbuksene?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

27. Hvor stor del av tiden **de to siste ukene** har du vært sint pga din tarmsykdom?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

28. I hvilken utstrekning har din tarmsykdom begrenset din seksuelle aktivitet i løpet av **de to siste ukene**?

(Sett ring rundt et tall)

Har ikke hatt sex på grunn av sykdommen	1
Tarmsykdommen har begrenset meg svært mye	2
Tarmsykdommen har begrenset meg mye	3
Tarmsykdommen har begrenset meg noe	4
Tarmsykdommen har begrenset meg lite	5
Tarmsykdommen har begrenset meg svært lite	6
Tarmsykdommen har ikke begrenset meg	7

29. Hvor stor del av tiden **de to siste ukene** har du vært kvalm, uvel eller hatt ubehag fra magen?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

30. Hvor stor del av tiden **de to siste ukene** har du vært irritabel?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

31. Hvor stor del av tiden **de to siste ukene** har du følt en manglende forståelse fra andre?

(Sett ring rundt et tall)

Hele tiden	1
Mesteparten av tiden	2
En god del av tiden	3
Omtrent halvparten av tiden	4
Litt av tiden	5
Nesten ikke i det hele tatt	6
Ikke i det hele tatt	7

32. Hvor glad, fornøyd og tilfreds har du vært **de to siste ukene**?

(Sett ring rundt et tall)

Svært utilfreds, ulykkelig nesten hele tiden	1
Utilfreds og ulykkelig	2
Av og til utilfreds, noe ulykkelig	3
Stort sett tilfreds, fornøyd	4
Tilfreds nesten hele tiden, lykkelig	5
Veldig tilfreds hele tiden, lykkelig	6
Svært tilfreds, kunne ikke vært mer fornøyd	7

15.9 DLQI

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		
2.	Over the last week, how embarrassed or self conscious have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		Not relevant ☐
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		Not relevant ☐
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		Not relevant ☐
7.	Over the last week, has your skin prevented you from working or studying?	Yes ☐ No ☐		Not relevant ☐
	If "No", over the last week how much has your skin been a problem at work or studying?	A lot ☐ A little ☐ Not at all ☐		
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		Not relevant ☐
9.	Over the last week, how much has your skin caused any sexual difficulties?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		Not relevant ☐
10.	Over the last week, how much of a	Very much ☐		

problem has the treatment for your	A lot	☐	
skin been, for example by making	A little	☐	
your home messy, or by taking up time?	Not at all	☐	Not relevant ☐

15.10 SF-36

SPØRREUNDERSØKELSE VEDRØRENDE LIVSKVALITET VED INFLAMMATORISK TARMSYKDOM

SF-36

INSTRUKSJON FOR UTFYLLING AV SPØRRESKJEMA SF-36

Dette spørreskjemaet spør om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.

Hvert spørsmål skal besvares ved å sette et kryss i en boks eller en ring rundt det tallet som passer best for deg.
Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan. Det er viktig at du forsøker å besvare alle spørsmålene.
Når du er ferdig vil du få anledning til å gå gjennom spørsmålene med lege/sykepleier. Dette vil ikke ta lang tid.

SF-36 SPØRRESKJEMA OM HELSE

1. Stort sett, vil du si at din helse er:

(Sett kryss i en av boksene)

Utmerket	Meget god	God	Nokså god	Dårlig
☐	☐	☐	☐	☐

2. Sammenlignet med for ett år siden, hvordan vil du si helsen din stort sett er nå? *(sett ring rundt ett tall)*

Mye bedre nå enn for ett år siden..... 1
Litt bedre nå enn for ett år siden..... 2
Omtrent den samme som for ett år siden..... 3
Litt dårligere nå enn for ett år siden..... 4
Mye dårligere nå enn for ett år siden..... 5

3. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

(Sett ring rundt ett tall på hver linje)

	AKTIVITETER	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a.	Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	1	2	3
b.	Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	1	2	3
c.	Løfte eller bære en handlekurv	1	2	3
d.	Gå opp trappen flere etasjer	1	2	3
e.	Gå opp trappen en etasje	1	2	3
f.	Bøye deg eller sitte på huk	1	2	3
g.	Gå mer enn to kilometer	1	2	3
h.	Gå noen hundre meter	1	2	3
i.	Gå hundre meter	1	2	3
j.	Vaske deg eller kle på deg	1	2	3

4. I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

(sett ring rundt ett tall på hver linje)

		JA	NEI
a.	Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter?	1	2
b.	Har du utrettet mindre enn du hadde ønsket?	1	2
c.	Har du vært hindret i visse typer arbeid eller andre aktiviteter?	1	2
d.	Har du hatt vanskeligheter med å utføre arbeidet ditt eller andre aktiviteter? (f.eks fordi det krevde ekstra anstrengelser)	1	2

5. I løpet av de siste 4 ukene, har du hatt følelsesmessige problemer som har ført til vanskeligheter i ditt arbeid eller i andre av dine daglige gjøremål (f.eks. fordi du har følt deg deprimert eller engstelig)?

(sett ring rundt ett tall på hver linje)

		JA	NEI
a.	Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter?	1	2
b.	Har du utrettet mindre enn du hadde ønsket?	1	2
c.	Har du ikke arbeidet eller utført andre aktiviteter like nøye som vanlig?	1	2

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

(Sett kryss i en av boksene)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
☐	☐	☐	☐	☐

7. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 uker?

(sett ring rundt ett tall)

Ingen..... 1
Meget svake 2
Svake 3
Moderate 4
Sterke 5
Meget sterke 6

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

(Sett kryss i en av boksene)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
☐	☐	☐	☐	☐

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

(Sett ring rundt ett tall på hver linje)

	Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Følt deg full av tiltakslyst?	1	2	3	4	5	6
b. Følt deg veldig nervøs?	1	2	3	4	5	6
c. Vært så lang nede at ingenting har kunnet muntre deg opp?	1	2	3	4	5	6
d. Følt deg rolig og harmonisk?	1	2	3	4	5	6
e. Hatt mye overskudd?	1	2	3	4	5	6
f. Følt deg nedfor og trist?	1	2	3	4	5	6
g. Følt deg sliten?	1	2	3	4	5	6
h. Følt deg glad?	1	2	3	4	5	6
i. Følt deg trett?	1	2	3	4	5	6

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosial omgang (som det å besøke venner, slektninger osv.)?

(Sett kryss i en av boksene)

Hele tiden ☐ Nesten hele tiden ☐ Endel av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt ☐

11. Hvor RIKTIG eller GAL er hver av de følgende påstander for deg?

(Sett ring rundt ett tall på hver linje)

	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
a. Det virker som om jeg blir lettere syk enn andre	1	2	3	4	5
b. Jeg er like frisk som de fleste jeg kjenner	1	2	3	4	5
c. Jeg forventer at min helse vil bli dårligere	1	2	3	4	5
d. Min helse er helt utmerket	1	2	3	4	5

15.11 EQ-5D

	NOEN SPØRSMÅL OM LIVSKVALITET **EQ-5D**	
	Vis hvilke utsagn som passer best på din helsetilstand i dag ved å sette et kryss i en av rutene utenfor hver av gruppene nedenfor.	
	Gange Jeg har ingen problemer med å gå omkring. 1☐ Jeg har litt problemer med å gå omkring. 2☐ Jeg er sengeliggende. 3☐	
	Personlig stell Jeg har ingen problemer med personlig stell. 1☐ Jeg har litt problemer med å vaske meg eller kle meg. 2☐ Jeg er ute av stand til å vaske meg eller kle meg. 3☐	
	Vanlige gjøremål *(for eksempel arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)* Jeg har ingen problemer med å utføre mine vanlige gjøremål. 1☐ Jeg har litt problemer med å utføre mine vanlige gjøremål. 2☐ Jeg er ute av stand til å utføre mine vanlige gjøremål. 3☐	
	Smerte/ubehag Jeg har verken smerte eller ubehag. 1☐ Jeg har moderat smerte eller ubehag. 2☐ Jeg har sterk smerte eller ubehag. 3☐	
	Angst/depresjon Jeg er verken engstelig eller deprimert. 1☐ Jeg er noe engstelig eller deprimert. 2☐ Jeg er svært engstelig eller deprimert. 3☐	

15.12 WPAI:GH

Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

_____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

4. During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6.)*

5.During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

15.13 Joint assessed for swelling and tenderness

The following joints are assessed in the 28 joint count: Shoulders, elbows, wrists, the ten metacarpophalangeal joints, the ten proximal interphalangeal joints, the knees

The following joints are assessed in the 68/66 joint count: bilateral assessment of; temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal joints, proximal interphalangeal joints, distal interphalangeal joints (2—5.), hip (tenderness only), knee, ankle, talocalcaneal, tarsus, metatarsophalangeal joints, proximal interphalangeal joints

15.14 Adverse events

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
The term AE is used to include both serious and non-serious AEs.
If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

1. Results in death
2. Is immediately life-threatening
3. Requires in-patient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect
6. Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalisation for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalisation.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse Reaction: all untoward 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: SAE that is unexpected and possibly related to the investigational medicinal product(s).

Expected Adverse Events

Expected AEs/SAEs for the IMPs according to the IMPs Summary of Product Characteristics (SmPC) will be recorded in the eCRF.

SUMMARY OF CHANGES IN THE PROTOCOL FROM THE FIRST TO THE FINAL VERSION

Version 0_9 – Initial protocol submitted to the Regional Ethics Committee *June 14 2016*.

Version 1_0 – Updated protocol submitted to the Regional Ethics Committee *Feb 06 2017*. Change made: Change in inclusion criteria for NOR-DRUM B; Inclusion criteria 6 "Subject in remission or low disease activity" removed (Section 3.4).

No changes made for NOR-DRUM A.

Version 1_1 – Protocol version at inclusion of first patient. Updated protocol submitted to the Regional Ethics Committee *Feb 13 2017*. Change made: New exclusion criteria for NOR-DRUM B and NOR-DRUM A: "For patients with UC and CD: Functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ" (Section 3.3).

Version 1_2 –Updated protocol submitted to the Regional Ethics Committee *Feb 13 2017*. Change made: Paragraph in appendix defining SUSAR removed as not relevant for this trial (Section 15.14).

Version 1_3 – Final version. Submitted to the Regional Ethics Committee *Dec 09 2019*. Main changes made; Explorative endpoints defined (Section 2.3). Mixed effect modelling was added as one possible strategy to handle missing data (Section 9.4.8).

Statistical Analysis Plan for NOR-DRUM A

A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring

The NOR-DRUM study

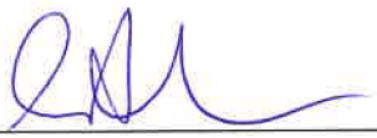
Protocol DIA2016-1
Final Protocol Version 1.3: 09.12.2019

SAP Version 1.0
Date: 11.12.19

SIGNATURE PAGE

PRINCIPAL INVESTIGATOR:

Espen A. Haavardsholm, MD PhD



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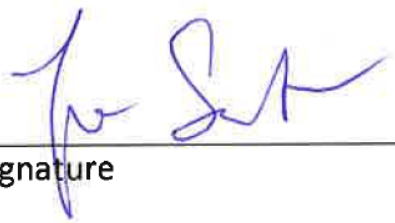
11/12-19

Date

TRIAL STATISTICIAN:

Joseph Sexton, PhD



Signature

11/12 - 2019

Date

PROJECT LEADER:

Silje W. Syversen, MD PhD

Signature

11.12.19

Date

ABBREVIATIONS

ACR	American College of Rheumatology
ADAb	Anti-drug antibodies
AE	Adverse Event
ARD	Adjusted Risk Difference
ARR	Adjusted Relative Risk
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ATC	Anatomical/Therapeutic/Chemical
AU	Arbitrary units
AZA	Azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	Biological Disease-Modifying Anti-Rheumatic Drugs
BMI	Body Mass Index
CD	Crohn's disease
CDAI	Clinical Disease Activity Index / Crohn's Disease Activity Index
CI	Confidence Interval
CRF	Case Report Form (electronic/paper)
CRP	C-reactive protein
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
DAS28	Disease Activity Score using 28 joints
DLQI	Dermatology Life Quality Index
DMARD	Disease-Modifying Anti-Rheumatic Drugs
DRG	Diagnosis related group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
EPJ	Electronic patient journal
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FAS	Full analysis Set
GCP	Good Clinical Practice
GI	Gastrointestinal
HBI	Harvey-Bradshaw Index
HR	Hazard Ratio
HRQOL	Health related quality of life
IBD	Inflammatory bowel diseases
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IJD	Inflammatory Joint Diseases
INX	infliximab
ISF	Investigator Site Files

KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
MHAQ	Modified Health Assessment Questionnaire
MP	Mercaptopurine
MRI	Magnetic resonance imaging
MTX	Methotrexate
NorCRIN	Norwegian clinical research infrastructure network
NOR-DRUM	A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PGA	Patient Global Assessment of Disease Activity
PH	Proportional Hazards
PhGA	Physician Global Assessment of Disease Activity
PMS	Partial Mayo Score
PP	Per Protocol
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PsAID	Psoriatic Arthritis Impact of Disease
QALY	Quality-adjusted life year
QoL	Quality of Life
RA	Rheumatoid arthritis
RAID	Rheumatoid Arthritis Impact of Disease
SAE	Serious Adverse Event
SD	Stable Disease / Standard deviation
SDAI	Simplified Disease Activity Index
sDMARD	Synthetic Disease-Modifying Anti-Rheumatic Drugs
SE	Standard Error
SF-36	Short Form (36) Health Survey
SOC	System Organ Class
SOP	Standard Operating Procedure
SpA	Spondyloarthritis
TDM	Therapeutic drug monitoring
TNF	Tumor necrosis factor
TNFi	TNF-inhibitors
UC	Ulcerative colitis
VAS	Visual Analogue Scale
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1. TABLE OF CONTENTS

2. AMENDMENTS FROM PREVIOUS VERSION

Not applicable

3. INTRODUCTION

This document describes the planned data summaries and statistical analyses to be performed for study part A of the NOR-DRUM trial (A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUg Monitoring, Clinical Trial Protocol DIA 2016-1). It will supplement the study protocol, which contains details regarding the objectives and design of the study.

3.1 Background and rationale

Infliximab (INX) and other TNF-inhibitors (TNFi) have revolutionised the treatment of several immune mediated inflammatory diseases. Still, many patients do not respond sufficiently to therapy or lose efficacy over time. The large inter-individual variation in serum drug concentrations on standard doses and the development of anti-drug antibodies are among the reasons for treatment failures. Therapeutic drug monitoring (TDM), individualised drug dosing based on the serum drug concentration of the drug, has the potential to optimise efficacy of INX treatment. TDM seems reasonable from both a clinical and an economical point of view, but the effectiveness of this treatment strategy for biological drugs used in the treatment of immune mediated inflammatory diseases has yet to be demonstrated in clinical trials. The NORwegian DRUg Monitoring study (NOR-DRUM) aims to assess the effectiveness of TDM, both in in achieving remission in patients starting INX treatment (study part A) as well as in maintaining disease control in patients on INX treatment (study part B).

3.2 Study Objectives

3.2.1 Primary Objective

The primary objective of NOR-DRUM A is to assess if tailoring treatment by TDM is superior to standard clinical care in order to achieve disease control in patients with immune mediated inflammatory diseases starting infliximab therapy.

3.2.2 Secondary Objectives

- To compare effectiveness of a treatment strategy based on TDM to standard clinical care applying different generic and disease specific endpoints
- To assess whether a treatment strategy based on TDM influences; drug survival, occurrence of anti-drug antibodies, serum drug levels and occurrence of adverse events
- To assess cost-effectiveness of a treatment strategy based on TDM compared to standard clinical care (Detailed analysis plan not given here)

3.2.3 Exploratory Objectives

- To assess if biomarkers (including genetic markers) or other factors (diagnosis, gender, co-medication, previous treatment with biological drugs, “drug holidays” etc) can predict development of anti-drug antibodies and drug levels in patients starting INX
- To study how serum drug levels and anti-drug antibodies are associated to drug efficacy and safety
- To study predictors of treatment response
- To study differences in efficacy, safety and immunogenicity between different diseases and disease subgroups

- To characterise anti-infliximab immune responses, including ADAb isotypes, epitopes (on infliximab) and association to genetic markers (e.g. HLA)
- To study changes in immune responses over time and the prevalence and properties of pre-existing ADAb in INX naïve patients
- To assess how TDM influences treatment with respect to serum drug/ADAb levels and disease activity
- To address efficacy of TDM in the subgroup of patients with low serum drug levels
- To study feasibility of TDM and compliance to the treatment algorithm
- To study effectiveness of TDM in the induction phase
- To study the performance of the treatment strategy within the group of patients 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 from infliximab to a different biologic agent
- To study effectiveness of TDM in subgroups of patients where TDM is assumed to be especially valuable; patients with high disease activity at baseline, patients not on immunosuppressive co-medication and patients with previous use of TNFi

The statistical analyses of explorative objectives will not be described in the SAP.

3.3 Study Design

NOR-DRUM is a randomised, open, controlled, parallel group, multicentre, phase IV, superiority, comparative study to evaluate the effectiveness, safety and cost-effectiveness of TDM in patients with immune mediated inflammatory diseases treated with INX.

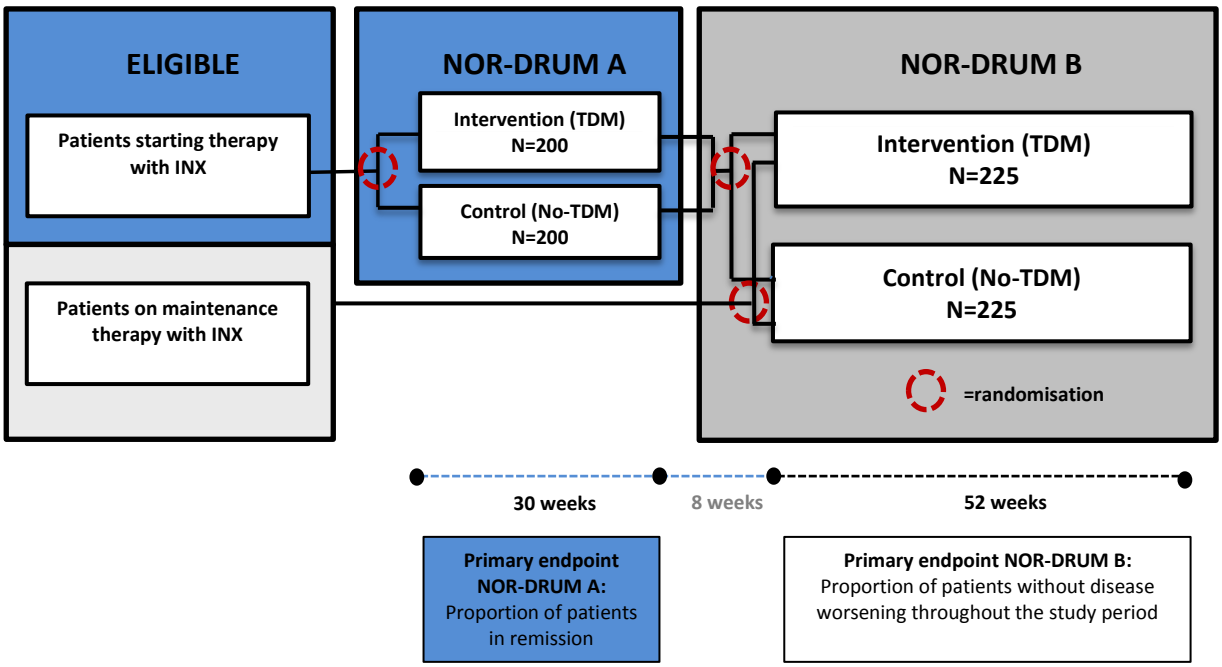
NOR-DRUM includes two separate randomised clinical trials. Study part A (NOR-DRUM A) addresses the effectiveness of TDM in regard to achieve remission in patients starting INX treatment. Study part B (NOR-DRUM B) addresses the effectiveness of TDM in maintenance treatment with INX. The current SAP describes the planned analyses of the primary endpoint and main secondary endpoints in NOR-DRUM A. A separate SAP will outline the analyses in NOR-DRUM B.

Figure 1 depicts the design of the NOR-DRUM trial. Patients with a diagnosis of rheumatoid arthritis (RA), psoriatic arthritis (PsA), spondyloarthritis (SpA), ulcerative colitis (UC), Crohn's disease (CD) or psoriasis (Ps) starting INX treatment are potential study patients n NOR-DRUM A. Eligible patients are allocated in a 1:1 ratio to either:

1. Administration of INX according to a treatment strategy based on TDM (**intervention group**)
2. Administration of INX according to standard clinical care without TDM (**control group**)

NOR-DRUM A has been designed to include 400 patients. In order to balance the patient characteristics in the two study arms, stratification is applied according to diagnosis (RA, SpA, PsA, UC, CD, Ps). The randomised treatment strategy is kept for the duration of the study period (38 weeks) with study visits at each scheduled INX infusion (every 4-10 week). Patients who are switched to another treatment during the study are followed according to the intentional infusion scheme. The primary endpoint, remission, is assessed at the 30-week visit. Patients who are still on INX at week 38 are re-randomised and included in NOR-DRUM B.

FIGURE 1 Overview of study design



3.3.1 Treatment algorithm

The treatment strategy for the intervention group is outlined in Figure 2 and 3. The dose and infusion interval is adjusted according to the strategy (Figure 2 and 3). During the first infusions (up to and including week 14), the dose is adjusted by decreasing the infusion interval only (Figure 1). After week 14, the algorithm permits both increasing and decreasing the INX dose/ intervals to reach the target range of 3-8 µg/ml (Figure 2).

In NOR-DRUM A, improvement is assessed after 3 months (Week 14 visit), for which a separate algorithm is used (Figure 2). Improvement is defined in 6.10.

Figure 2 Algorithm for INX administration in **NOR-DRUM A, intervention group** (The visits up to week 14 visit)

<table>
<tr><th></th><th colspan="2">Infusions up to week 14</th><th colspan="2">week 14 visit</th></tr>
<tr><td>Serum INX level (µg/ml)</td><td><20.0 at infusion 2
<15.0 at infusion 3
<3 at following infusions up to the week 14 visit</td><td>≥20.0 at infusion 2
≥15.0 at infusion 3
≥3 at further infusions up to the week 14 visit</td><td><3.0</td><td>≥3.0</td></tr>
<tr><td></td><td>Increase* dose
if no ADAb or low level ADAb (<50 µg/L)

or

Switch therapy
if high levels of ADAb (>50 µg/L)
If possible to another TNFi</td><td>No action

Within target range, continue with the same dose and dosing interval</td><td>Same strategy for improvement and no improvement:

Increase* dose
if no ADAb or low level ADAb (<50 µg/L)

or
Switch therapy
if high levels of ADAb (>50 µg/L)
If possible to another TNFi</td><td>Improvement **:
No action

No improvement **:
Switch therapy, if possible to other mode of action than than TNFi</td></tr>
</table>

Guideline for dose increase*
Increase the dose by decreasing the dose interval by 2 weeks to a minimum of 4 weeks (except for the interval between infusion 1- 2 and 2- 3 where the interval can be minimum 2 weeks)

**Definition of improvement:
RA and PsA: A decrease in DAS 28>=1.2
SpA: A decrease in ASDAS>=1.1
UC: A decrease in partial Mayo score of ≥ 3 points or a partial Mayo score of 0
CD: A decrease in HBI with ≥ 4 points
Ps: Achieved PASI 50
For all diseases: An investigator and patient consensus on improvement despite not formally fulfilling improvement definition

FIGURE 3 Algorithm for INX administration **NOR-DRUM A, intervention group** (all infusions after the week 14 visit)

Serum INX level (µg/ml)	≤2.0	2.1 – 2.9	3.0 – 8.0	8.1 – 10.0	>10.0
Action	**Increase dose** if no ADAb or low level ADAb (<50 µg/L) **or** **Switch therapy** if high levels of ADAb (>50 µg/L) If possible to another TNFi	**Consider increasing dose**	**No action**	**Consider decreasing dose**	**Decrease dose**
Guideline for action	Increase the dose preferably by increasing the given dose by 2-2,5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the dose interval by 2 weeks to a minimum of 4 weeks	Consider (based on clinical judgement and the patients factors given below*) increasing the dose preferably by increasing the given dose by 2-2.5 mg/kg to a maximum dose of 10 mg/kg or by decreasing the interval by 2 weeks to a minimum of 4 weeks	Within target range. Continue with the same dose and dosing interval	Consider (based on clinical judgement and the patients factors given below*) to decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2-2.5 mg/kg	Decrease the dose preferably by increasing the dose interval by 2 weeks to a maximum of 10 weeks or by decreasing the given dose by 2-2,5 mg/kg

*Patient factors to be considered when making the treatment decisions in the yellow zones:
Disease activity and trend in disease activity, the trend of the trough level over time, previous drug interval changes, availability of alternative drug, diagnosis (RA patients are expected to have lower trough levels due to lower recommended dosing)

4. HYPOTHESES AND DECISION RULES

4.1 Statistical Hypotheses

For the remainder of the statistical analysis plan, the term "study" is used to refer to NOR-DRUM A.

The study is designed to establish the superiority of TDM (intervention group) compared to standard drug administration without TDM (control group) with regard to remission in patients with immune mediated inflammatory diseases starting INX therapy.

The null hypothesis is that there is no difference in the probability of remission at week 30 between patients allocated to the intervention versus the control arm. The alternative hypothesis is that such a difference exists. Letting Δ denote the treatment difference, defined as the probability of remission at week 30 for a patient receiving the control therapy minus that of patients receiving the intervention, the hypothesis is:

H_0: Δ=0
vs
H_1: Δ≠0

If H_0 is rejected, the treatment strategy with the highest estimated probability of week 30 remission will be deemed superior to the other treatment. If the study fails to reject H_0, the non-inferiority of TDM vs standard care will be assessed using a non-inferiority margin of 15%. Formally, this entails testing

N_0: Δ≥15%
vs
N_1: Δ<15%

4.2 Statistical Decision Rule

The main hypothesis, H_0, will be tested at the 0.05 level.

In case H_0 is not rejected, the non-inferiority null hypothesis, N_0, will be assessed at the 0.025 level. Letting ($\boldsymbol{\Delta}_L$, $\boldsymbol{\Delta}_U$) denote the 95% confidence interval for the treatment difference Δ, N_0 is rejected if $\boldsymbol{\Delta}_U$<15%.

Note that while formally two hypothesis tests are (potentially) carried out, this does not require adjustment for multiple testing due to the closed testing principle, since both tests are performed using the same population.

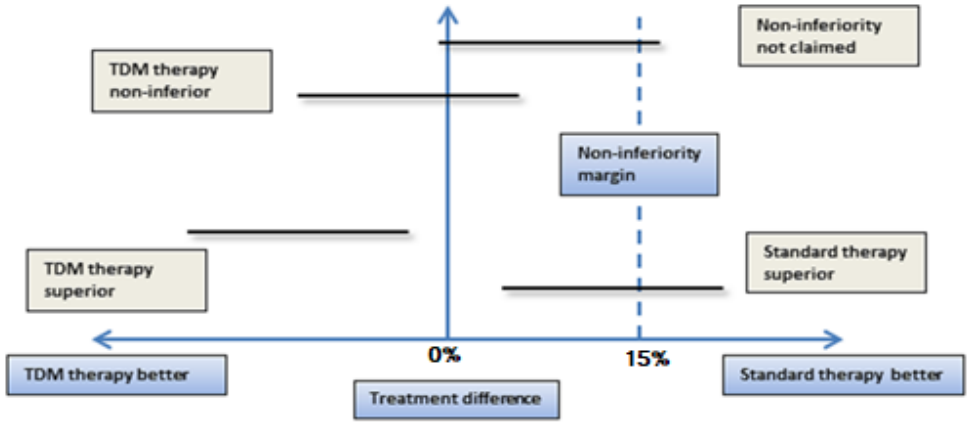


FIGURE 4 Illustration of Statistical Decision Rule (bars indicate 95% confidence limits)

5. ANALYSIS SETS

5.1 Enrolled

The Enrolled set will include all patients who have provided informed consent and have been included into the study data base.

5.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomised patients who have been exposed to the allocated intervention. Exposure to the allocated intervention is defined as patients who have received infusion 2 and as well have a recorded treatment decision for infusion 3. The dose at infusion 1 and 2 and the interval between infusion 1 and 2 are not affected by the treatment algorithm (the intervention).

5.3 Safety Analysis Set

The Safety Set will include all randomised patients who have been exposed to the allocated intervention (defined identical to FAS).

5.4 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPS) will include all randomised patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy (see SAP section 5.5).

5.5 Protocol Deviation

The following protocol deviations lead to exclusion from the PPS:

5.5.1 Deviations to inclusion and/or exclusion criteria

Not fulfilling inclusion and exclusion criteria will be considered a protocol deviation.

5.5.2 Deviations assessed Post-randomisation

Only protocol deviations thought to affect the efficacy of the treatment strategy will be considered in the SAP. Patients will be considered to have a protocol deviation if there is a(n):

- Early withdrawal from study before the week 30 visit
- Delay in scheduled infusion with an infusion interval >12 weeks
- Non-compliance to study algorithm defined as discrepancies between recommended and actual ordination at >1 visit, excluding ordinations at week 30 and onwards

6. DEFINITIONS AND DERIVED VARIABLES

In this section we outline the variables used in the study, including variables that will be used in subsequent analyses of secondary objectives not covered in the primary publication.

Visits follow the treatment frequency. For analysis and tabulation purposes, we define study time points as shown in the table 1.

TABLE 1 Definition of study time points

Time Point Label	Target Day	Definition
TP1. Baseline	Day 0	Information up to randomisation
TP2. Visit 2	Day 14	Visit for planned 2nd infusion
TP3. Visit 3	Day 42	Visit for planned 3nd infusion
TP4. Visits between visit 3 and week 14 visit		
TP5. Week 14 visit	Day 98	Week 14 visit
TP6. Visits between week 14 and week 30 visit		
TP7. Week 30 visit	Day 210	Week 30 visit

6.1 Change from baseline

Change from baseline (Δ) = time-point value - baseline value.
% change from baseline (%Δ) = [(time-point value – baseline value) / baseline value] *100%

6.2 Inflammation parameters

Inflammation is measured by C-reactive protein (CRP) mg/L, the Erythrocyte Sedimentation Rate (ESR) in mm/hg and fecal calprotectin in mg/kg (IBD only) according to hospital/laboratory standard procedures. The faecal calprotectin values are divided into four groups: normal ≤ 200 mg/kg, slightly elevated < 200 to ≤ 500 mg/kg, and moderately elevated > 500 to ≤ 1000 mg/kg, high > 1000 mg/kg.

6.3 Patient's and Physician's global assessment of disease activity

Patient Global Assessment of Disease Activity (PGA) is measured on a 100 mm visual analogue scale (VAS) according to the question: “How active was your disease on average during the last week?” Physician Global Assessment of Disease Activity (PhGA) is measured on a 100 mm VAS “Please rate the patient’s overall (global) disease activity.”

6.4 Disease activity in RA and PsA patients

6.4.1 Joint Counts

For RA tender and swollen joint counts are performed on 28 joints, with total joint count ranging from 0 to 28. This is denoted the 28 swollen and tender joint count (SJC28 and TJC28). For PsA tender and swollen joint counts are performed on 66/68 joints, with total joint count ranging from 0 to 66/68. This is denoted the 66/68 swollen and tender joint count (SJC 66 and TJC 68). See Table 2 for an overview of joints and their count.

TABLE 2 Overview of Joint Counts

Joints	TJC68 left	TJC68 right	TJC28 left	TJC28 right	SJC66 left	SJC66 right	SJC28 left	SJC28 right
Temporomandibular (Jaws)	0-1	0-1	NA	NA	0-1	0-1	NA	NA
Sternoclavicular (SC)	0-1	0-1	NA	NA	0-1	0-1	NA	NA
Acromioclavicular (AC)	0-1	0-1	NA	NA	0-1	0-1	NA	NA
Shoulder*	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
Elbow*	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
Wrist*	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
Metacarpophalangeal (MCP)*								
- First (MCP1)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Second (MCP2)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Third (MCP3)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Fourth (MCP4)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Fifth (MCP5)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
Proximal interphalangeal (IP/PIP)*								
- First (IP1)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Second (PIP2)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Third (PIP3)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Fourth (PIP4)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
- Fifth (PIP5)	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
Hip	0-1	0-1	NA	NA	NA	NA	NA	NA
Knee*	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
Ankle	0-1	0-1	NA	NA	0-1	0-1	NA	NA
Talocalcaneal	NA	NA	NA	NA	NA	NA	NA	NA
Tarsus	NA	NA	NA	NA	NA	NA	NA	NA
Metatarsophalangeal (MTP)								
- First (MTP1)	0-1	0-1	NA	NA	0-1	0-1	NA	NA
- Second (MTP2)	0-1	0-1	NA	NA	0-1	0-1	NA	NA
- Third (MTP3)	0-1	0-1	NA	NA	0-1	0-1	NA	NA
- Fourth (MTP4)	0-1	0-1	NA	NA	0-1	0-1	NA	NA
- Fifth (MTP5)	0-1	0-1	NA	NA	0-1	0-1	NA	NA

6.4.2 DAS28

The 28-joint Disease Activity Score (DAS28) includes TJC28, SJC28, ESR and PGA (VAS 0-100). The DAS28 is calculated as follows:
DAS28 = 0.56*sqrt(tender28) + 0.28*sqrt(swollen28) + 0.70*Ln(ESR) + 0.014*PGA

If values of ESR and/or PGA are missing, the following formulas are used:
DAS28 = [0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70*Ln(ESR)]*1.08 + 0.016
DAS28 = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*Ln(CRP+1) + 0.014*PGA + 0.96
DAS28 = [0.56*sqrt(TJC288) + 0.28*sqrt(SJC28) + 0.36*Ln(CRP+1)]*1.10 + 1.15
CRP is measured in mg/L.

According to DAS28, the following cut-points are used:
High disease activity: DAS28 > 5.1
Moderate disease activity: 5.1 ≥ DAS28>3.2
Low disease activity: 3.2 ≥ DAS28 ≥ 2.6
In remission: DAS28 < 2.6

6.4.3 SDAI

The Simplified Disease Activity Index (SDAI) includes TCJ28, SJC28, PGA, PhGA and CRP.

The SDAI is calculated as follows:
SDAI=TCJ28 + SJC28 + PGA/10 + PhGA/10 + CRP/10

According to SDAI, the following cut-points are used:
High disease activity: SDAI> 26.0
Moderate disease activity: 26.0 ≥ SDAI>11.0
Low disease activity: 11.0 ≥ SDAI > 3.3
In remission: SDAI ≤ 3.3

6.4.4 EULAR response

The European League Against Rheumatism (EULAR) response rates will be calculated. A EULAR response is defined by the state and change in DAS28, and categorized into good, moderate and none using the following definitions:

TABLE 3 EULAR DAS28 response

	Change from baseline		
DAS28 at time-point	ΔDAS28 ≤ - 1.2	-1.2 < ΔDAS28 < -0.6	ΔDAS28 ≥ 0.6
DAS28 ≤ 3.2	Good	Moderate	None
3.2 < DAS28 ≤ 5.1	Moderate	Moderate	None
DAS28 > 5.1	Moderate	None	None

6.4.5 ACR/EULAR remission

The patient must satisfy all of the following in order to achieve ACR/EULAR remission:

- TJC28 ≤ 1
- SJC28 ≤ 1
- CRP ≤ 10 (mg/l)
- PGA ≤ 14

6.4.6 ACR response

The ACR response rates ACR20, ACR50, ACR70 and will be calculated.

An ACR20 response is defined if the following criteria are fulfilled:

- 20% improvement in tender joint count 28
  AND
- 20% improvement in swollen joint count 28
  AND
- 20% improvement in at least 3 of 5 other core set items

The other core set items consist of:

- Investigator global assessment of disease activity
- Patient global assessment of disease activity
- Patient pain
- Disability
- ESR/CRP

ACR50, ACR70 and ACR90 are defined in a similar manner with 50%, 70% and 90% improvement, respectively. In the NOR-DRUM study, VAS will be used to assess pain and patient/investigator global assessment of disease activity and MHAQ will be used to assess disability. High sensitivity CRP will be used as primary measure of inflammation, while ESR will be used if CRP is not available. All improvements will be % change from baseline.

6.4.7 DAPSA

Disease Activity index for PSoriatic Arthritis (DAPSA) is calculated as follows:
TJC68 + SJC66 + CRP (mg/L)/10 + PGA (0-100)/10+VAS Pain (0-100)/10

6.5 Disease Activity in SpA patients

6.5.1 BASDAI

The Bath Ankylosing Spondylitits Disease Activity Index (BASDAI) includes six questions pertaining to the five major symptoms of ankylosing spondylitis: fatigue (Q1), spinal pain (Q2), joint pain/swelling (Q3), areas of localized tenderness (Q4), morning stiffness duration (Q5) and morning stiffness severity (Q6). Each question is scored on an NRS (0-10). The two morning stiffness scores are averaged and added to the average of the other scores forming a total score in the range of 0-10.

The BASDAI is calculated as follows:

$$\text{BASDAI} = \frac{Q1+Q2+Q3+Q4+\frac{Q5+Q6}{2}}{5}$$

6.5.2 ASDAS

The Ankylosing Spondylitis Disease Activity Score (ASDAS) includes

- Total back pain: NRS 0-10 (0=none, 10=very severe) according to the BASDAI Question 2 (“How would you describe the overall level of AS neck, back or hip pain you have had during the last week”)

- Patient global assessment of disease activity: VAS 0-100 of the question ”How active was your spondylitis on average during the last week?”.

- Peripheral pain/swelling: NRS 0-10 (0=none, 10=very severe) according to the BASDAI Question 3 (“How would you describe the overall level of pain/swelling in joints other than neck, back or hip you have had during the last week”).

- Duration of morning stiffness: NRS 0-10 (0=0h, 5=1h, 10=2h or more) according to the BASDAI Question 6 (“How long does your morning stiffness last from the time you wake up during the last week?”)

- C-reactive protein (CRP) in mg/litre

The ASDAS-CRP is calculated as follows:
ASDAS-CRP=0.121*total back pain + 0.0110*patient global + 0.073*peripheral pain/swelling + 0.058*duration of morning stiffness + 0.579*ln(CRP+1)

If CRP is not available, the ASDAS-ESR is calculated and used instead:
ASDAS-ESR=0.079*total back pain + 0.0113*patient global + 0.086*peripheral pain/swelling + 0.069*duration of morning stiffness + 0.293*sqrt(ESR)

Very high disease activity is defined as an ASDAS value >3.5, high disease activity as ASDAS 2.1 – 3.5, moderate disease activity as ASDAS 1.3 – 2.1 and inactive disease as ASDAS < 1.3

Cut-offs for improvement scores were: a change ≥1.1 units for "clinically important improvement" and a change ≥2.0 units for "major improvement".

6.6 Disease activity in UC patients

6.6.1 Partial Mayo Score

The Mayo score consists of four components (rectal bleeding, stool frequency, physician rating of disease activity, and mucosal appearance at endoscopy) rated from 0–3 that are summed to give a total score that ranges from 0–12. The non-invasive partial Mayo score (PMS) does not require an endoscopy, and thereby ranging from 0-9.

Remission is defined as a partial Mayo score of ≤ 2 with no individual subscore >1.

6.7 Disease activity in CD patients

6.7.1 Harvey-Bradshaw Index

The Harvey-Bradshaw index (HBI) consists of five domains, general well-being (0-4), abdominal pain (0-3), number of liquid soft stools per day, abdominal mass (0-3) and number of predefined complications. The scores of each sub-domain is summed up to compute the HBI.

Remission is defined as a HBI score ≤ 4 points.

6.8 Disease activity in Ps patients

6.8.1 Psoriasis Area and Severity Index (PASI)

PASI is a measure of redness, thickness and desquamation of lesions (each graded 0-4), weighted by the area and location of involvement. PASI scores from 0 (no disease) to 72 (maximal disease severity). PASI examines four body regions: i) the head and neck, ii) the upper limb iii) the trunk and iv) the lower limb including the buttocks.

Intensity
A representative area of psoriasis is selected for each body region. The intensity of redness, thickness and scaling of the psoriasis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4). Calculation for intensity: The three intensity scores are added up for each of the four body regions to give subtotals A1, A2, A3, A4.

Each subtotal is multiplied by the body surface area represented by that region.

- A1 x 0.1 gives B1 (head and neck)
- A2 x 0.2 gives B2 (upper limb)
- A3 x 0.3 gives B3 (trunk)
- A4 x 0.4 gives B4 (lower limb)

Area
The percentage area affected by psoriasis is evaluated in the four regions of the body. In each region, the area is expressed as nil (0), 1-9% (1), 13-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6).

Calculations for area: Each of the body area scores is multiplied by the area affected.

- B1 x (0 to 6)= C1
- B2 x (0 to 6)= C2
- B3 x (0 to 6)= C3
- B4 x (0 to 6)= C4

Total score
The PASI score is C1 + C2 + C3 + C4

A PASI 50/75 means a 50% /75% reduction in the PASI score.
Complete clearance is defined as PASI=0, mild to moderate psoriasis is defined as PASI < 10, moderate to severe psoriasis between 10 and 20 and severe psoriasis above 20.

Remission is defined as PASI $\leq$4

6.9 Definition of remission

- **Remission in RA and PsA**

Remission in RA and PsA is defined as a DAS 28 <2.6

- **Remission in SpA**

Remission in SpA is defined as a ASDAS <1.3

- **Remission in UC**

Remission in UC is defined as a Partial Mayo score ≤2 with no subscores >1

- **Remission in CD**

Remission in CD is defined as a HBI≤4

- **Remission in Ps**

Remission in Ps is defined as a PASI ≤ 4

6.10 Definition of improvement

Improvement is assessed at the week 14 visit.

- **Improvement in RA and PsA**

Improvement is defined as a decrease in DAS28 of ≥1.2 from baseline

- **Improvement in SpA**

Improvement is defined as a decrease in ASDAS of ≥1.1 from baseline

- **Improvement in UC**

Improvement in UC is defined as a decrease in the partial Mayo score of ≥ 3 points from baseline or a partial Mayo score of 0

- **Improvement in CD**

Improvement in CD is defined as a decrease in HBI of ≥ 4 points from baseline

- **Improvement in Ps**

Improvement in Ps is defined as PASI 50 (A 50% decrease in the PASI obtained at baseline)

- **Patient and investigators consensus on improvement**

If there is a consensus between the patient and the investigator that there has been an improvement, it should be considered as an improvement even if the formal definition has not been met.

6.11 Definition of sustained remission

A status of remission on all consecutive visits following the initial obtained remission until the week 30 visit.

6.12 Patient reported outcomes

6.12.1 SF-36

The SF-36 is a multi-purpose, short-form health survey with 36 questions. The SF-36 will be scored according to RAND 36-Item Health Survey 1.0 (http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html) to form eight measures scores 0-100: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. In addition, composite scores for physical and mental health summary measures are calculated according to the New England Medical Centre scoring instructions.(Ware, Kosinski, & Keller, 1994) The composite scores are computed according to both the 1998 US and 1996 Norwegian general population means and standard deviations.

6.12.2 EQ-5D 5L

EQ-5D 5L is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D index values are calculated according to the EQ-5D UK Time Trade-Off (TTO) value set. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

6.12.3 WPAI

Worker productivity is generally subdivided into 2 components: absenteeism and presenteeism. The worker productivity in this study is based on the Work Productivity and Activity Impairment Questionnaire: General health V2.0 (WPAI:GH).

The WPAI yields four types of scores:
1. Absenteeism (work time missed)
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment

The scores are based on the following questions:

Q1= currently employed
Q2 = hours missed due to specified problem
Q3 = hours missed other reasons
Q4 = hours actually worked
Q5 = degree problem affected productivity while working
Q6 = degree problem affected regular activities

Scores:
Multiply scores by 100 to express in percentages.

Percent work time missed due to specified problem (Absenteeism): $\frac{Q2}{Q2+Q4}$

Percent impairment while working due to specified problem (Presenteeism): $\frac{Q5}{10}$

Percent overall work impairment due to specified problem (Work productivity loss):

$$\frac{Q2}{(Q2+Q4)} + \left[1 - \frac{Q2}{Q2+Q4}\right] \cdot \frac{Q5}{10}$$

Percent activity impairment due to specified problem: $\frac{Q6}{10}$

6.12.4 Modified Health Assessment Questionnaire

Each item of the Modified Health Assessment Questionnaire (MHAQ) 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. The MHAQ will only be calculated in patients with IJD.

6.12.5 Rheumatoid Arthritis Impact of Disease

The Rheumatoid Arthritis Impact of Disease (RAID) score is calculated based on seven numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10. The seven NRS correspond to pain, function, fatigue, sleep, emotional wellbeing, physical wellbeing and coping/self-efficacy.

1. Calculation

RAID final value = (pain NRS value (range 0–10) × 0.21) + (function NRS value (range 0–10) × 0.16) + (fatigue NRS value (range 0–10) × 0.15) + (physical wellbeing NRS value (range 0–10) × 0.12) + (sleep NRS value (range 0–10) × 0.12) + (emotional wellbeing NRS value (range 0–10) × 0.12) + (coping NRS value (range 0–10) × 0.12).
Thus, the range of the final RAID value is 0–10 where higher figures indicate worse status.

2. Missing data imputation

If one of the seven NRS values composing the RAID is missing, the imputation is as follows:

a Calculate the mean value of the six other (non-missing) NRS (range 0–10)
b Impute this value for the missing NRS
c Then, calculate the RAID as explained above.

If two or more of the NRS are missing, the RAID is considered as missing value (no imputation).

The RAID will only be calculated in patients with RA.

6.12.6 Psoriatic Arthritis Impact of Disease (PsAID) score

The PsAID questionnaire with 9 domains of health (PsAID-9) was developed by EULAR to calculate a score for clinical trials reflecting the impact of PsA from the patient's perspective. [52] The nine domains with relative weights are: pain (0.174), fatigue (0.131), skin (0.121), work and/or leisure activities (0.110), function (0.107), discomfort (0.098), sleep (0.089), coping (0.087) and anxiety (0.085), 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. The PsAID will only be calculated for patients with PsA. Higher score indicate worse status. Missing data are imputed as follows:
If one of the nine NRS values composing the PsAID is missing, the imputation is as follows:

a Calculate the mean value of the eight other (non-missing) NRS (range 0–10)
b Impute this value for the missing NRS
c Then, calculate the PsAID as explained above.

If two or more of the NRS are missing, the PsAID is considered as missing value (no imputation).

6.12.7 Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is a widely used tool to measure health-related quality of life in patients with inflammatory bowel diseases. The questionnaire consists of 32 questions scored in four domains: bowel symptoms, emotional health, systemic systems and social function. The response for each question ranges from one to seven with one corresponding to significant impairment and seven corresponding to no impairment. The total IBDQ score is the sum of all the question scores, ranging 32 to 224. The IBDQ will only be calculated in patients with IBD.

6.12.8 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health related quality of life over the last week. It has been validated for adult dermatology patients aged 16 years and older. The items of the DLQI encompass aspects of symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each question is scored on a 4-point Likert scale: Not at all/Not relevant=0, A little=1, A lot=2 and Very much=3. Scores of individual items (0-3) are added to yield a total score (0-30); higher scores mean greater impairment of patient's QoL. The DLQI will only be presented to patients with chronic plaque psoriasis.

6.12.9 Other calculations

Age (years) = [(date of baseline – date of birth)/365.25].

BMI = weight in kilograms / (height in metres x height in metres)
BMI will be categorised according to the WHO definitions for underweight, normal, overweight and obese.

Time of event = date of event – date of randomisation

Total drug consumption in the maintenance period* is calculated as mg/kg/ week on medication
*The maintenance period is defined as infusion 3 and onwards

Total drug consumption in induction period* is calculated as mg/kg/week on medication
*The induction period is defined as infusion 1 to infusion 3

6.13 Safety definitions

6.13.1 Treatment emerging adverse events

Treatment emerging adverse events (TEAEs) are defined as AEs with a start date on or after the first randomised treatment infusion.

6.13.2 Past disease and concomitant disease

Past disease/condition
A disease/condition is considered as past disease/condition if it is not ongoing at randomisation.

Concomitant disease
A disease/condition is considered as concomitant disease/condition if it is ongoing at randomisation.

6.13.3 Previous and Concomitant medications

- previous medication (stop date < date of randomisation);
- concomitant medication (stop date ≥ date of randomisation or ongoing at study end)

In case of missing or incomplete dates/times not directly allowing allocation to any of the two categories of medications, a worst-case allocation will be performed according to the available parts of the start and the end dates. The medication will be allocated to the first category allowed by the available data, according to the following order:

- concomitant medication
- previous medication

7. ENDPOINTS

7.1 Primary endpoint

The primary endpoint is the proportion of patients in remission at week 30.

Remission is defined by disease specific composite scores (6.9) *; DAS 28 score <2.6 in patients with RA and PsA, ASDAS score <1.3 in patients with SpA, Mayo score of ≤2 with no sub scores >1 in patients with UC, HBI score of ≤4 in CD and PASI score of ≤4 in patients with Ps.*

7.2 Secondary endpoints

7.2.1 Efficacy endpoints

Diagnosis	Endpoint	Assessment time	Type
All*	Remission	All	Time to
	Sustained remission	All	Time to
	Remission	Week 14	Dichotomous
	Improvement	Week 14	Dichotomous
	PhGA	Week 30,all	Continuous
	PGA	Week 30,all	Continuous
	ESR	Week 30,all	Continuous
	CRP	Week 30,all	Continuous
RA/PsA	DAS28 remission	All Week 14,30	Time to Dichotomous
	SDAI remission	Week 14,30	Dichotomous
	ACR/EULAR remission	Week 14,30	Dichotomous
	ACR 20/50/70	Week 14,30	Ordinal
	EULAR response	Week 14,30	Ordinal
	DAS28	Week 30,all	Continuous
	SDAI	Week 30,all	Continuous
	MHAQ	Week 30,all	Continuous
	DAPSA (PsA only)	Week 30,all	Continuous
SpA	ASDAS inactive disease (remission)	All Week 14,30	Time to Dichotomous
	ASDAS	Week 30,all	Continuous
	BASDAI	Week 30,all	Continuous
	MHAQ	Week 30,all	Continuous
UC	PMS remission	All Week 14,30	Time to Dichotomous
	PMS	Week 30,all	Continuous
	Calprotectin	Week 30,all	Continuous

CD	HBI remission	All Week 14,30	Time to Dichotomous
	HBI	Week 30,all	Continuous
	Calprotectin	Week 30,all	Continuous
Ps	PASI remission	All Week 14,30	Time to Dichotomous
	PASI Complete clearance	Week 14,30	Dichotomous
	PASI mild to moderate	Week 14,30	Dichotomous
	PASI	Week 30,all	Continuous

*Analyses are also performed separately in the different diagnostic groups

7.2.2 Quality of life and utility endpoints

Diagnosis	Group	Endpoint	Assessment time	Type
All*	**SF-36**	Physical functioning	Week 30,all	Continuous
		Bodily pain	Week 30,all	Continuous
		Role limitations due to physical health problems	Week 30,all	Continuous
		Role limitations due to personal or emotional problems	Week 30,all	Continuous
		Emotional well-being	Week 30,all	Continuous
		Social functioning	Week 30,all	Continuous
		Energy/fatigue	Week 30,all	Continuous
		General health perception	Week 30,all	Continuous
		Physical health composite score	Week 30,all	Continuous
		Mental health composite score	Week 30,all	Continuous
	EQ5D	EQ5D index value	Week 30,all	Continuous
		EQ5D VAS	Week 30,all	Continuous
	WPAI	Absenteeism	Week 30,all	Continuous
		Presenteeism	Week 30,all	Continuous
		Work productivity loss	Week 30,all	Continuous
		Activity impairment	Week 30,all	Continuous
	Fatigue	VAS fatigue	Week 30,all	Continuous
RA	**RAID**	RAID total score	Week 30,all	Continuous
	Pain	VAS pain	Week 30,all	Continuous
PsA	**PsAID**	PsAID total score	Week 30,all	Continuous
	Pain	VAS pain	Week 30,all	Continuous
SpA	**Pain**	VAS pain	Week 30,all	Continuous
UC/CD	**IBDQ**	IBDQ total score	Week 30,all	Continuous
Ps	**DLQI**	DLQI total score	Week 30,all	Continuous

*Analyses are also performed separately in the different diagnostic groups

7.2.3 Drug survival, drug levels, immunogenicity, drug consumption and compliance

Group	Type
Drug survival	
INX discontinuation - Due to lack of improvement at week 14 (according to algorithm) - Due to lack of response - Due to AE - Due to intercurrent disease - Due to ADAb (according to algorithm, intervention only) - Other reason	Ordinal, time to event
Drug levels (trough*)	
Serum drug level	Continuous
Serum drug level low at one or more visits (<20 µg/ml inf2, <15 µg/ml inf3, <3 µg/ml later infusions)	Dichotomous, time to event
Serum drug level high at one or more infusions (>8 µg/ml after week 14)	Dichotomous, time to event
Serum drug level in therapeutic range at all time points (≥20 µg/ml inf2, ≥15 µg/ml inf3, ≥3 to w14, 3-8 µg/ml at infusions after w14)	Dichotomous
Serum drug level at week 14	Continuous
Low (<3 µg/ml)	Dichotomous
Therapeutic range (>3 µg/ml)	Dichotomous
Serum drug level at week 30	Continuous
High (>8 µg/ml)	Dichotomous
Low (<3 µg/ml)	Dichotomous
Therapeutic range (3-8 µg/ml)	Dichotomous
Immunogenicity	
ADAb (≥15 µg/L) while on medication**	Dichotomous, time to event
ADAb low (≥15 µg/L <50 µg/L) while on medication**	Dichotomous, time to event
ADAb high (≥50 µg/L) while on medication**	Dichotomous, time to event
ADAb (≥15 µg/L), all study period	Dichotomous, time to event
ADAb high (≥50 µg/L), all study period	Dichotomous, time to event
Drug consumption, dose and interval	
INX consumption in induction period (mg/kg/week)	Continuous
INX consumption in maintenance period (mg/kg/week)	Continuous
Dose (mg/kg)	Continuous
Infusion interval in maintenance period(weeks)	Continuous
Number of infusions	Continuous
Compliance	
Compliance to algorithm	Dichotomous
Change in dose/interval - Increase due to low level (intervention only) - Increase due to clinical reason - Decrease due to high level (intervention only) - Decrease due to clinical reason - No change	Ordinal

* Trough defined as: Sample taken ≤ 7 days prior to planned infusion and ≤14 days past planed (delayed) infusion.

**While on medication defined as: Sample taken ≤ 8 weeks from last INX infusion

All analyses also performed separately in the different diagnostic groups

7.3 Safety

Measures of safety will include the following:

- Clinical and laboratory adverse events (AEs) and coding of AEs performed (using the [Medical Dictionary for Regulatory Activities] MedDRA, version 20.0E
- Clinical laboratory data

8. STATISTICAL METHODOLOGY

8.1 Statistical and Analytical Issues

8.1.1 Statistical Methods

The primary and secondary efficacy analyses will be performed in the Full Analysis Set (FAS). Analyses performed in the Per Protocol Analysis Set (PPS) will be considered sensitivity analyses or robustness analyses. Analysis of the primary endpoint (remission at week 30) does not require adjustment for multiple testing, and no such adjustments will be made for the secondary analyses.

All categorical (including binary) data will be summarised using frequency counts and percentages of patient incidence. Percentages will be calculated using the study population (FAS); any exceptions to this will be highlighted in the table footnote. The continuous variables will be summarised using number of patients (N), mean, standard deviation (SD), median, 25/75 percentile and range (minimum/maximum), as appropriate

All efficacy analyses will be presented by the size (point estimate) of the difference between the treatments and the associated 95% confidence interval. For the test of the primary hypothesis, H_0 vs H_1 (section 4.1), the associated p-value will also be given.

All statistical analyses will be done in Stata v14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX, USA).

8.1.2 Analysis of primary endpoint

The primary endpoint (remission at the week 30 visit) will be analysed using mixed effect logistic regression. The visits will be categorized as: baseline, visit 2, visit 3, between visit 3 and the week 14 visits, week 14 visit, between week 14 and week 30 visits, and the week 30 visit. The fixed effects of the model will be treatment, diagnosis and visit, and will include interactions between visit and treatment, and between visit and diagnosis. The random effects will be patient level random intercepts.

The p-value for testing the primary hypothesis will correspond that of the treatment difference at the week 30 visit from the model.

In case the primary null hypothesis, H_0, is not rejected, the non-inferiority of TDM vs standard care will be assessed. The treatment difference (Δ) will be estimated using the marginal probability of remission in the control group minus that of the intervention group at the week 30 visit. The 95% confidence interval for this difference, and upon which the non-inferiority test will be assessed, will be based on a normal-approximation estimating the standard error using the delta-method.

Sensitivity analyses with adjustments for age, gender, use of prior TNFi, use of immunomodulation medication at baseline (methotrexate, azathioprine, sulfasalazine, leflunomide, prednisolone ≥ 15 mg) and disease activity at baseline will be performed, as will sensitivity analyses in the PP analysis set. Adjustment for baseline disease activity will be done using an interaction term with diagnosis, to account for the different scaling of the diagnosis specific measures.

8.1.3 Analysis of secondary endpoints

Analyses of dichotomous endpoints
Secondary dichotomous endpoints will be analysed using the same approach applied to the primary endpoint.

Analyses of continuous endpoints
Continuous endpoints will be analysed using the linear mixed effect model. Each analysis will include as fixed factors an adjustment for the baseline value of the endpoint, and further include treatment, visit, diagnosis and interactions between visit and treatment as well as between visit and diagnosis. Patient specific intercepts will be treated as random effects. The difference between the treatment groups at a given visit will be estimated using marginal means with normal-based confidence intervals with standard errors estimated using the delta method.

Analyses of time to event endpoints
Time to event endpoints will be analysed using Cox regression and Kaplan-Meier product-limit analysis. Estimates of the hazard ratio will be presented in addition to Kaplan-Meier plots.

Analysis of per-protocol effect
The per-protocol analysis will be done in two ways. The first will run the same analyses as in the FAS population, but with the protocol-violators removed (i.e. only using the per-protocol patients). The second will include all FAS patients, but censor patients at the time of protocol violation.

8.1.4 Handling of Dropouts and Missing Data

In general, missing values will not be imputed for descriptive statistics.

Primary endpoint
Under the assumption that missing values of the outcome are 'Missing at Random', the mixed effect model provides unbiased effect estimates (under no other model misspecification). The analysis here will make this assumption, and consequently no imputation for missing values of the primary endpoint will be made. Robustness analyses using complete case analyses, last observation carried forward and worst case/best case imputation will be performed.

Other dichotomous endpoints
Other dichotomous endpoints will be analysed using the logistic regression model and no imputation will be performed. Missing values will be assumed missing at random.

Continuous endpoints
All continuous endpoints will be analysed using the linear mixed model and no imputation will be performed. Missing values will be assumed missing at random.

Time to event endpoints
For the time to event analysis, all patients that withdraw from follow-up prior to experiencing the event will be censored at the withdrawal date.

8.1.5 Determination of Sample Size

NOR-DRUM A: Under the assumption of an absolute increase in remission rate of 15% (from 40 to 55%) we needed a maximum of 358 completed patients in order to reject the null hypothesis on a 5% significance level with 80% power. Adjusting for possible drop-outs, we randomised 400 patients.

8.1.6 Timing of Main Analysis

The main analysis is planned when all patients have concluded 38 ± 4 weeks, all data up to 38 weeks have been entered, verified and validated and the primary database has been locked.

8.2 Patient Characteristics

8.2.1 Patient Disposition

The disposition of all patients will be listed and summarised by study arm. The number and percentage of patients who are randomised, received allocated intervention and prematurely discontinued from the study will be summarised.

The number and percentage of patients will be categorised by the reason(s) for study discontinuation: Patients withdrawal of consent, investigator decision (unable to follow protocol or prevent harm), death and other.

8.2.2 Protocol Deviations

Protocol deviations resulting in exclusion from the PPS will be determined and summarised by treatment group. See section 5.5 for protocol deviation categories.

8.2.3 Background and Demographic Characteristics

Patient demographics and baseline characteristics will be summarised for the FAS population.

Patient demographics and baseline characteristics will be summarised by randomised treatment arm and overall using descriptive statistics (N, mean, standard deviation, median, 25/75 percentiles, minimum, and maximum) for continuous variables, and number and percentages of patients for categorical variables. The patient demographics and baseline characteristics to be summarised include (but are not restricted to) age in years, gender, disease duration, CRP, ESR, use of concomitant immunosuppressive medication, use of concomitant prednisolone, previous use of biological immunosuppressive drugs and diagnosis specific disease activity measures.

Medical history will be coded using the MedDRA dictionary (v20.0E). Concomitant medication will be coded using the Anatomical Therapeutic Chemica (ATC) coding system.

8.2.4 Concomitant Medications and Other Therapies

Concomitant medication information collected will be coded by the ATC classification system. Concomitant medications taken during the study will be summarised by generic name. The number and percentage of patients who took at least one drug within each specific preferred term will be presented. Patients will only be counted once if they are taking more than one medication (within the same code) or take the same generic medication in more than one period within the study. If it cannot be determined whether a medication is concomitant (based on stop date or, if the stop date is missing, start date), then the medication will be considered to be concomitant.

8.2.5 Patient reported outcome measure data

Analyses of patient reported outcome measure (PROM) data will be done using the procedures described above for continuous endpoints (section 8.1.3).

8.2.6 Exploratory Analysis

Analyses to address the explorative objectives described in 3.2.3 will be performed, but are not described in the SAP.

9. SAFETY ANALYSIS

Safety evaluations will be based on the incidence, intensity, and type of AEs.Safety variables will be tabulated and presented for all patients in the safety set.

9.1.1 Adverse Events

Adverse events will be coded using MedDRA, version 20.0E. The investigator records the maximum intensity of each AE using the levels mild, moderate and severe. Adverse events with missing intensity will be considered to be severe.

The number (%) of subjects with any AE, with 1, 2 or $\geq$ 3 AEs, with treatment emerging serious AEs (SAE), with AEs of special interest (infusion reactions and infections) and AEs leading to study drug withdrawal will be summarised by treatment group. The number of events and number (%) of subjects with adverse events by system organ class (SOC) and preferred term (PT) will be summarised by treatment group. In addition, a summary table of AEs reported by >= 10% of all patients might be presented by SOC and PT. A detailed patient narrative will be given for any death or cancer.

9.1.2 Clinical Laboratory Parameters

Safety clinical laboratory parameters were collected and assessed, but only used to identify adverse events.

9.1.3 Software implementation

All analysis will be done using Stata v14. Estimation of the logistic mixed effect models will be done using the *melogit* function, the linear mixed effect models via the *mixed* function, time-to-event end-points by *stcox* and fixed effect logistic regression via the function *logit*

The primary end-point treatment difference will be assessed using that average marginal effect, estimated by the *margins* function. Combined with *melogit*, this estimates the marginal effect, integrating over the unconditional distribution of random effects.

The stata margins command fails if a variance component is estimated too close to zero. For this reason, if this occurs, the model is re-estimated with the corresponding random effect removed, and the margins command run on the reduced model.

10. DATA ANALYSES FOLDER PLAN

All programs and datasets will be organized according to the following plan.

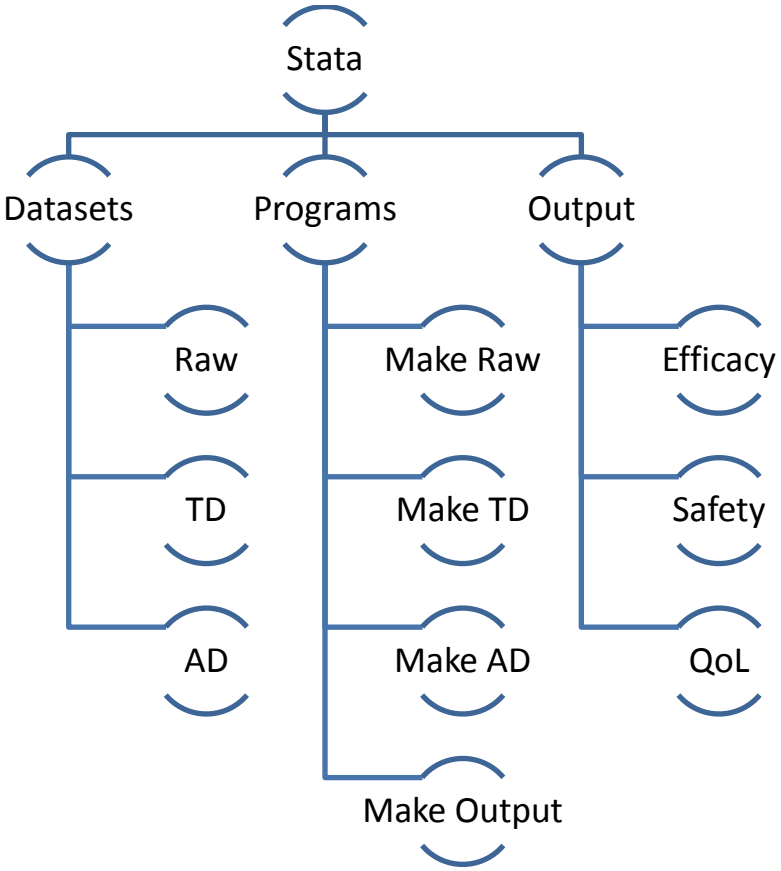


Figure 10.1 Data analysis folder plan

- Datasets
  - Raw; all raw datasets, exported from the study database in a flat file and converted to Stata files
  - TD; Tabulation Datasets, compiled from the raw datasets to form tabulations of study observations. Derived variables are computed, but no imputation will be made
  - AD; Analysis Datasets, compiled from the td datasets to form basis for analyses. Observations may be imputed according to the SAP, and visits and timepoints are defined.
- Programs
  - Make Raw: Programs to import, format and prettify the raw datasets into Stata datasets. Results in datasets stored in the Raw folder
  - Make TD: Programs to combine and compile raw datasets and make calculated variables. Results in datasets stored in the TD folder
  - Make AD: Programs to prepare datasets for analyses. Results stored in AD folder.
  - Make Output: Programs to perform analyses and produce tables and figures.
- Output
  - Analysis output according to this SAP.

11. LIST OF PLANNED TABLES, FIGURES AND LISTINGS

This section contains lists of all the summary tables, figures and patient data listings for this study.

11.1 Data Tables

Data tables will be configured according to publication requirements.

11.2 Data Listings

Data listings will be provided as needed.

11.3 Data Figures

Data figures will be configured according to publication requirements.