

# Fra ide til protokoll – hvordan komme i gang?

Siri Lillegraven MD MPH PhD

Nestleder, Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY)

Leder, Enhet for klinisk forskning

Diakonhjemmet sykehus

# Innhold

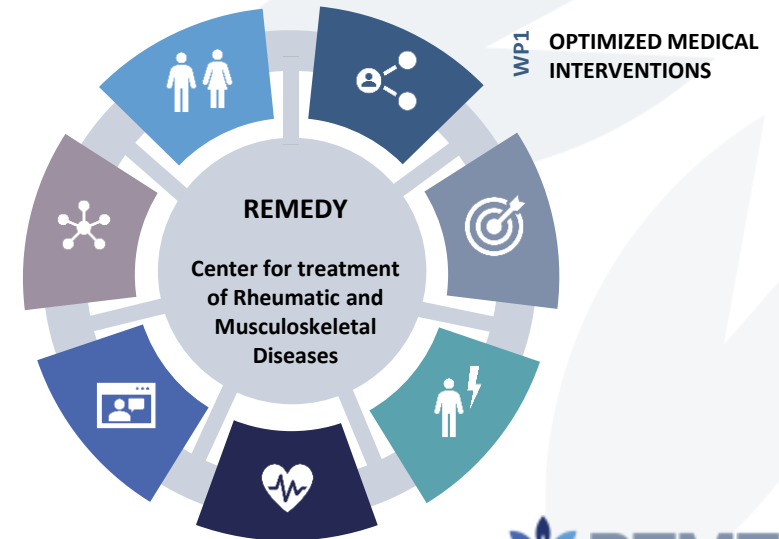
- Eksempler – fra ide til protokoll
- Problemstilling
  - Klinisk relevans
  - Pasientgrunnlag
  - Nytteverdi
- Praktisk ved prosjektstart
  - Forankring i sykehuset og i klinisk drift
  - Ressurser (personale, tid)
  - Forfatterskap/vitenskapelig samarbeid
- Prosjektskisse

# Innhold

- **Eksempler – fra ide til protokoll**
- Problemstilling
  - Klinisk relevans
  - Pasientgrunnlag
  - Nytteverdi
- Praktisk ved prosjektstart
  - Forankring i sykehuset og i klinisk drift
  - Ressurser (personale, tid)
  - Forfatterskap/vitenskapelig samarbeid
- Prosjektskisse

# Forskningsmiljø

- Diakonhjemmet sykehus
- Klinikk for revmatologi, poliklinikk og forskning
  - Ansvar for artritt-sykdommer i Oslo
  - Regionale og nasjonale funksjoner
- REMEDY senteret
  - Hovedfokus på klinisk forskning



# Forskerinitierte studier



Randomized clinical trial in early rheumatoid arthritis assessing management with and without ultrasound



Randomized clinical trial of switch from innovator infliximab to biosimilar infliximab



Nordic randomized clinical trial in early rheumatoid arthritis comparing conventional therapy versus three biologic treatments



Randomized clinical trial in rheumatoid arthritis assessing withdrawal of disease-modifying drugs

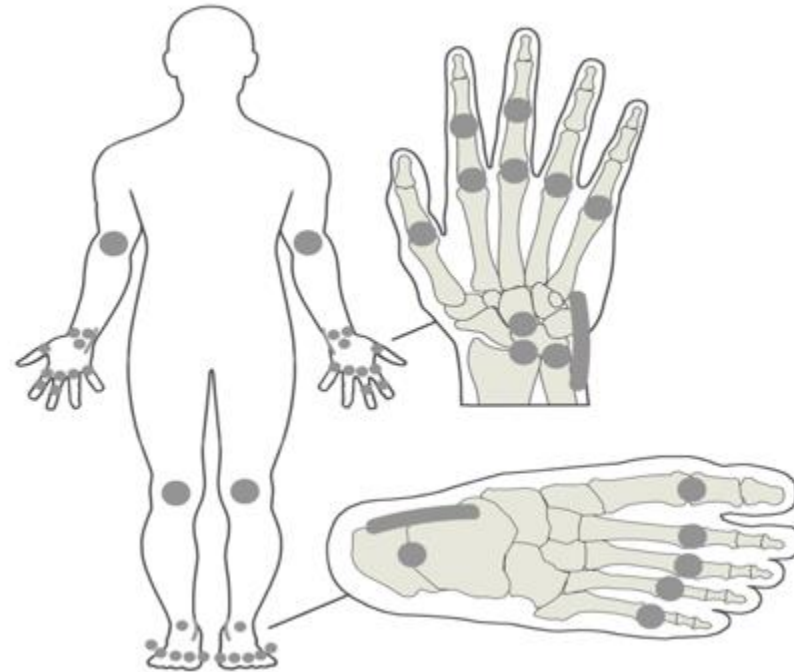
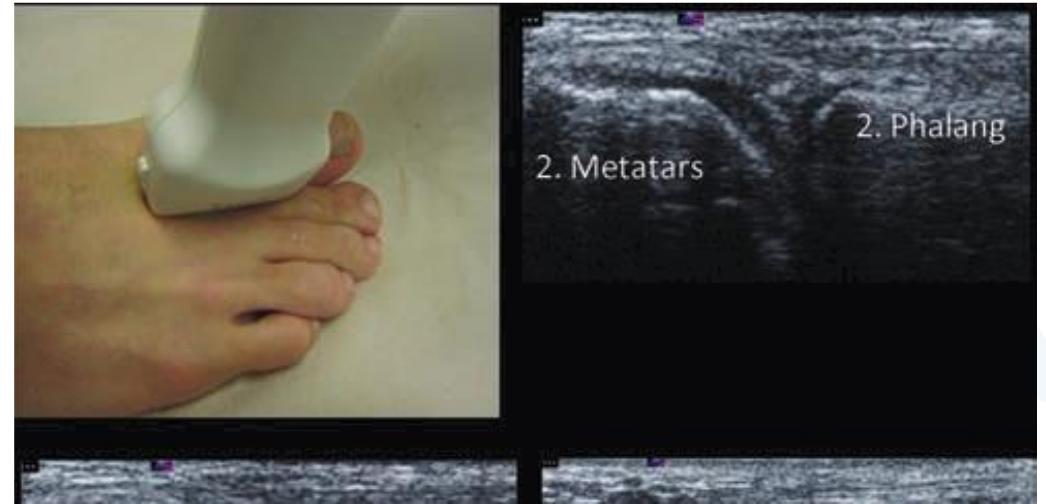


Randomized clinical trial assessing the effectiveness of targeting infliximab treatment by therapeutic drug monitoring versus routine care



# Eksempel: Ide

- **2000-tallet:** Ultralyd øker i bruk i revmatologisk praksis
- Studier viser sammenheng mellom subklinisk inflammasjon påvist med ultralyd og leddskade samt sykdomsoppbluss ved RA
- Økt fokus på definerte behandlingsmål



# ARCTIC-studien

- Aiming for Remission in rheumatoid arthritis: a randomised trial examining the benefit of ultrasonography in a Clinical Tight Control regimen<sup>1</sup>
  - N=230
  - Inklusjon 2010-2013
- Pasientert randomisert til en av to behandlingsstrategier:
  - Målstyrt behandlingen med ultralydinformasjon
  - Målstyrt behandling basert på konvensjonelle sykdomsaktivitetsmål
- **Strategistudie = sammenligner to behandlingsstrategier, ikke to medikamenter**

# ARCTIC studiegruppe

## Local PIs

**Hallvard Fremstad MD**

**Tor Magne Madland MD PhD**

**Åse Stavland Lexberg MD**

**Hilde Haukeland MD**

**Erik Rødevand MD**

**Christian Høili MD**

**Hilde Stray MD**

**Anne Noraas Bendvold MD**

**Inger Johanne Hansen MD**

**Gunnstein Bakland MD PhD**

**Espen A. Haavardsholm MD PhD** Diakonhjemmet Hospital (coordinating center)

## Study center

Ålesund Hospital

Haukeland University Hospital

Vestre Viken Hospital Drammen

Martina Hansens Hospital

St. Olavs Hospital Trondheim University Hospital

Østfold Hospital Moss

Haugesund Sanitetsforening Rheumatism Hospital

Specialist practice Bendvold/Dovland Kristiansand

Sørlandet Hospital Kristiansand

University Hospital of Northern Norway Tromsø





# ARCTIC-studien

thebmj

Research ▾

Education ▾

News & Views ▾

Campaigns

Archive

For authors

Jobs

Hosted

Search

RESEARCH



OPEN ACCESS



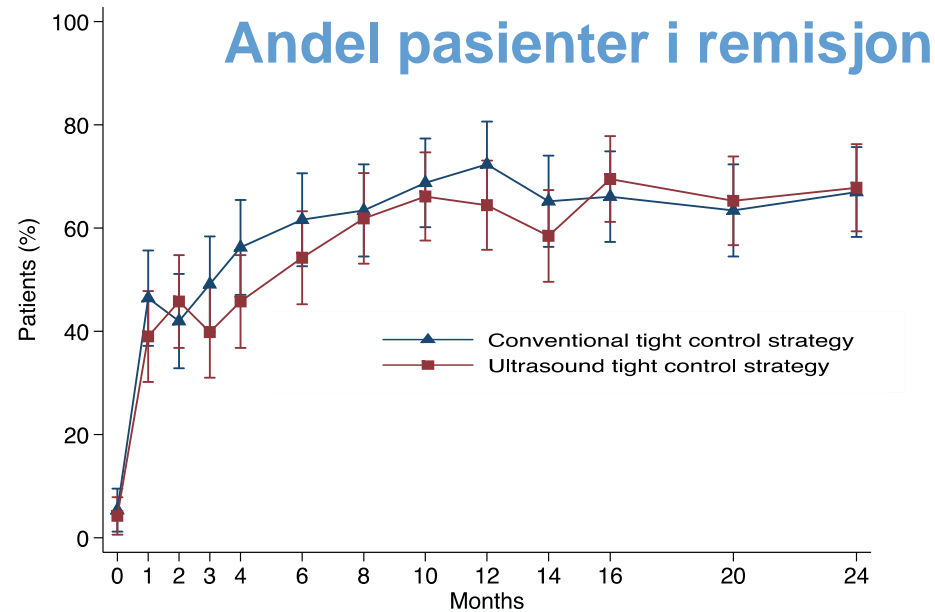
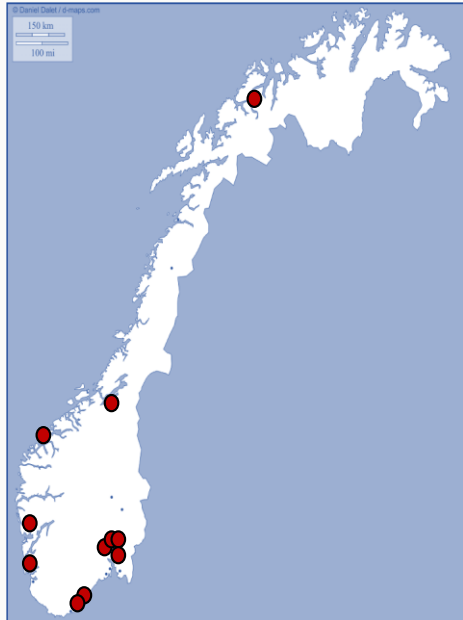
CrossMark  
click for updates

## Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial

Espen A Haavardsholm,<sup>1</sup> Anna-Birgitte Aga,<sup>1</sup> Inge Christoffer Olsen,<sup>1</sup> Siri Lillegraven,<sup>1</sup> Hilde B Hammer,<sup>1</sup> Till Uhlig,<sup>1</sup> Hallvard Fremstad,<sup>2</sup> Tor Magne Madland,<sup>3</sup> Åse Stavland Lexberg,<sup>4</sup> Hilde Haukeland,<sup>5</sup> Erik Rødevand,<sup>6</sup> Christian Høili,<sup>7</sup> Hilde Stray,<sup>8</sup> Anne Noraas,<sup>9</sup> Inger Johanne Widding Hansen,<sup>10</sup> Gunnstein Bakland,<sup>11,12</sup> Lena Bugge Nordberg,<sup>1</sup> Désirée van der Heijde,<sup>1,13</sup> Tore K Kvien<sup>1</sup>

thebmj | *BMJ* 2016;354:i4205 | doi: 10.1136/bmj.i4205

# Erfaringer fra gjennomført klinisk studie



thebmj Research - Education - News & Views - Campaigns Archive For authors Jobs Hosted Search

RESEARCH

OPEN ACCESS



## Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial

Espen A Haavardsholm,<sup>1</sup> Anna-Birgitte Aga,<sup>1</sup> Inge Christoffer Olsen,<sup>1</sup> Siri Lillegraven,<sup>1</sup> Hilde B Hammer,<sup>2</sup> Tull Uhlig,<sup>1</sup> Hallvard Fremstad,<sup>2</sup> Tor Magne Madland,<sup>3</sup> Åse Stavland Lexberg,<sup>4</sup> Hilde Haukeland,<sup>5</sup> Erik Rødevand,<sup>6</sup> Christian Hølli,<sup>7</sup> Hilde Stray,<sup>8</sup> Anne Noraas,<sup>9</sup> Inger Johanne Widding Hansen,<sup>10</sup> Gunnstein Bakland,<sup>11,12</sup> Lena Bugge Nordberg,<sup>1</sup> Désirée van der Heijde,<sup>1,13</sup> Tore K Kvien<sup>1</sup>

thebmj | BMJ 2016;354:i4205 | doi: 10.1136/bmj.i4205



## Nasjonal veileder i revmatologi

### Revmatoid artritt

Forfattere: Anna-Birgitte Aga og Espen A. Haavardsholm

Dato publisert: 19.06.2020

Versjon: 0.11

# Konklusjoner

- Tilsvarende resultater med konvensjonell oppfølging vs. ultralydoppfølging
- Negativ studie – men like viktig
- Illustrerer behovet for studier før innføring av nye behandlingsstrategier og undersøkelsesmetoder, ikke bare medikamenter

# Forskerinitierte studier



Randomized clinical trial in early rheumatoid arthritis assessing management with and without ultrasound



Randomized clinical trial of switch from innovator infliximab to biosimilar infliximab



Nordic randomized clinical trial in early rheumatoid arthritis comparing conventional therapy versus three biologic treatments



Randomized clinical trial in rheumatoid arthritis assessing withdrawal of disease-modifying drugs

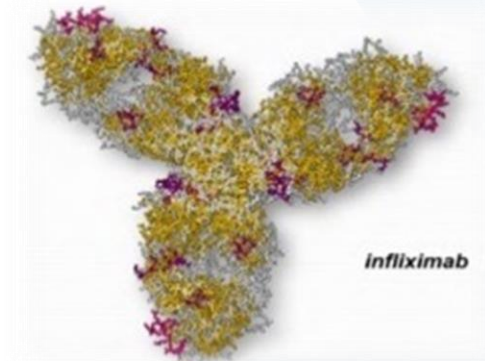


Randomized clinical trial assessing the effectiveness of targeting infliximab treatment by therapeutic drug monitoring versus routine care



# Eksempel Ide 2: Kan vi bytte til biotilsvarende legemidler?

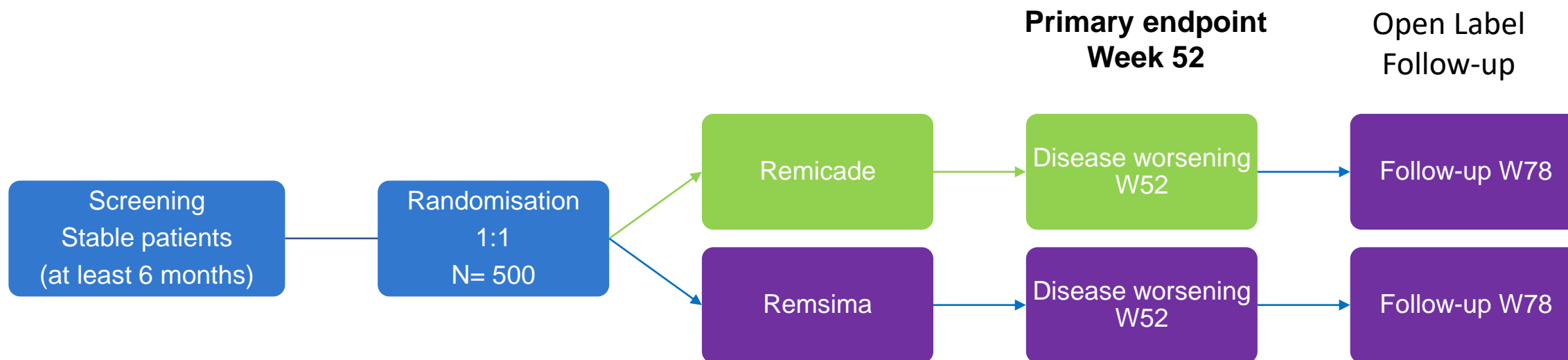
- 2015: Patentet utløper på infliximab og biotilsvarende infliximab blir tilgjengelig
- Biotilsvarende:
  - Lignende det originale produktet
    - Ikke bedre
    - Ikke verre
  - Billigere
  - Kan gi økt tilgang på effektiv behandling for pasienter med immunmedierte inflammatoriske sykdommer



# Hovedmål

- Å undersøke om CT-P13 var non-inferior (ikke underlegen) sammenlignet med original infliximab (INX) med tanke på sykdomsforverring hos pasienter som har vært behandlet med stabil INX behandling i minst 6 måneder
- Sekundærmål:
  - Safety
  - Immunogenisitet

# NOR- SWITCH Study design



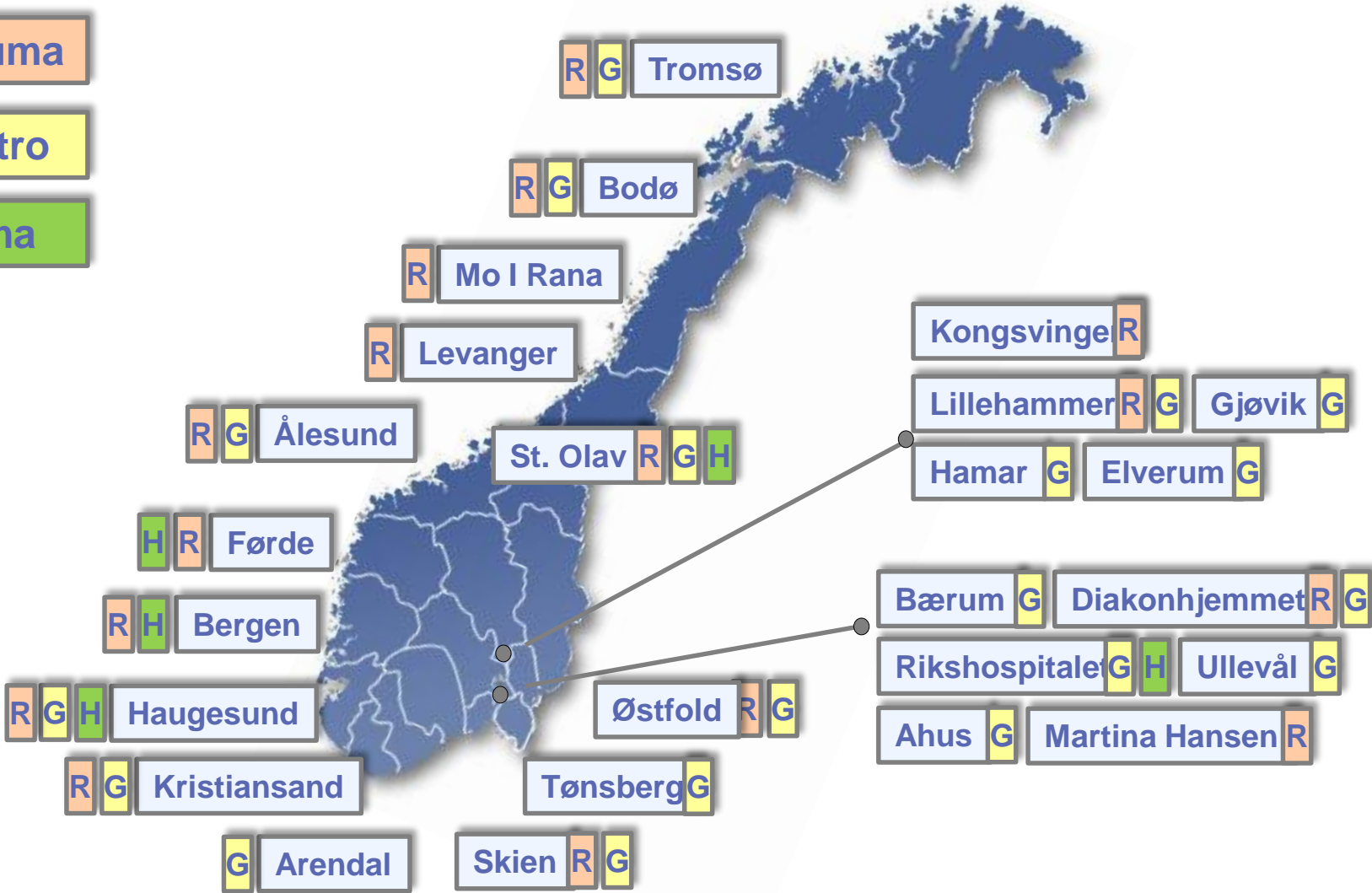
**Primary endpoint:** Disease worsening  
**Non-inferiority margin:** 15%

# Studiesentre

16 Rheuma

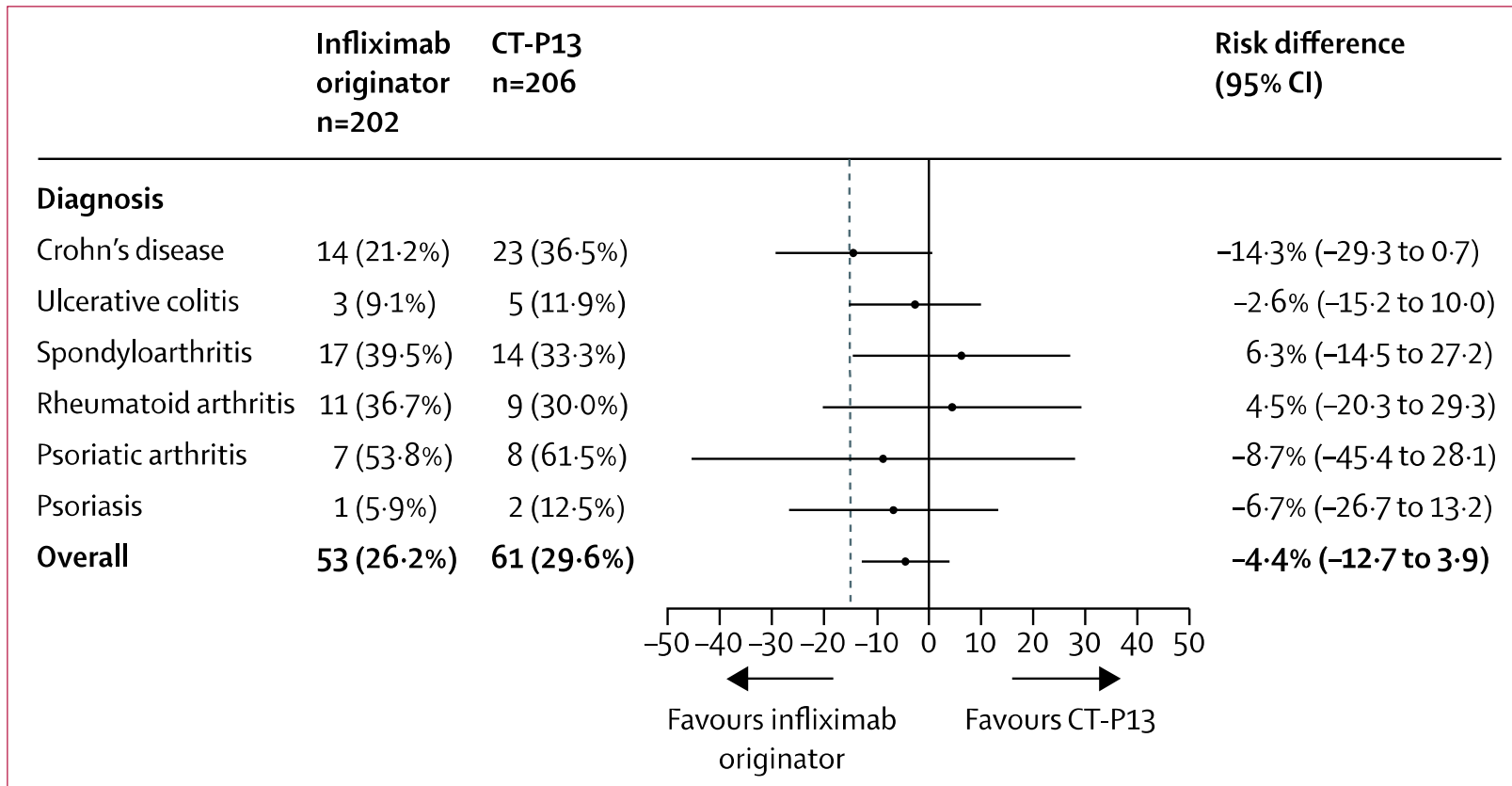
19 Gastro

5 Derma





# Resultater: Sykdomsforverring



**Figure 2: Forest plot of risk difference according to disease**

Figure shows data for the per-protocol set. Risk difference is adjusted for treatment duration of infliximab originator at baseline.

# THE LANCET

Volume 389 - Number 10086 - Pages 2263-2348 - June 10-16, 2017

[www.thelancet.com](http://www.thelancet.com)

"NOR-SWITCH is, to our knowledge, the first randomised study to show that switching from an originator to a biosimilar TNF inhibitor is not inferior to continued treatment with the originator drug, according to a prespecified non-inferiority margin of 15%."

See Articles page 2304

## Comment

Renewed push to strengthen vector control globally  
See page 2270

## Articles

Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids  
See page 2282

## Articles

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab  
See page 2304

## Articles

Ipilimumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors  
See page 2317

## Series

Targeted treatments for rheumatoid arthritis  
See pages 2318 and 2318

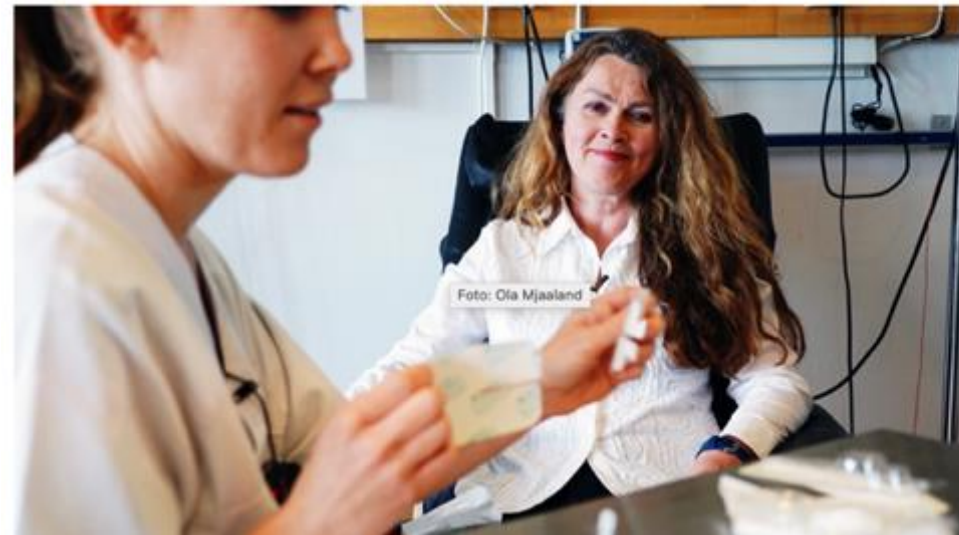
£5.00 Registered as a newspaper - ISSN 0140-6736  
Founded 1821 - Published weekly

# Tolkning NOR-SWITCH

- Bytte fra original infliximab til biotilsvarende infliximab var ikke underlegent sammenlignet med fortsatt original infliximabbehandling
- Resultatene støtter bytte fra original infliximab til biotilsvarende infliximab på ikke-medisinsk indikasjon

## Banebrytende norsk studie åpner for viktige kopimedisiner

Biologiske medisiner har revolusjonert revmatiske sykdommer som leddgikt og tarmsykdommer som Chrons og Ulcerøs kolitt. Medisinene er svært kostbare, men en ny norsk studie åpner for langt billigere kopimedisiner.



Ola Mjaaland  
@olamjaaland  
Journalist

Publisert 12. mai 2017 kl. 21:34



Artikkelen er mer enn to år gammel.



**NOR  
SWITCH**



VARSKOM MED GENERALISERING – Etter vårt skjønn, må vi være forsiktede med å generalisere til alle andre biologiske legemidler og deres biotilsvarende, sier Tore K. Kvien ved Diakonhjemmet sykehus. Han presenterer resultatene på gastroenterologisk kongress i Wien tirsdag 18. oktober. Arkivfoto: Vidar Sandnes.

RESULTATENE KLARE FRA DEN NORSKE BYTTESTUDIEN

## – Trygt å bytte til biotilsvarende

Verden over har ventet i spenning på resultatene fra Nor-Switch, som nå viser at det ikke er forskjell på Remicade og biotilsvarende. – Byttestudien gir tre streker under svaret, sier leder av studien, Tore K. Kvien.

Publisert: 2016-10-17 01:23  
Lisbeth Nilsen

## – Nordmenn har grunn til å være stolte

Den tyske gastroenterologen Stefan Schreiber berømmer de norske forskerne. Han føler seg trygg på å bytte slik det er gjort i Nor-Switch-studien, men vil ha mer data på bytte med andre biotilsvarende.

Publisert: 2016-10-18 11:03 Skrevet av: Lisbeth Nilsen/Lasse Moe

## Britisk ekspert: – Nor-Switch er et vendepunkt

– Nor-Switch-studien vil øke bruken av biotilsvarende, og gir oss den real world evidence vi trenger, mener den britiske rådgiveren Michael Sobanja.

Publisert: 2016-10-18 09:40 Skrevet av: Lisbeth Nilsen/Lasse Moe  
redaksjonen@dagensmedisin.no

Blogger

Debatt og kronikk

Leder

## – Vi trenger mer dokumentasjon enn én studie

Legemiddelindustrien (LMI) er positive til studier som kan føre til store besparelser for samfunnet. De peker på at det må gjøres flere studier som Nor-Switch for å skaffe mer kunnskap om biotilsvarende legemidler.

Publisert: 2016-10-17 12:18 Skrevet av: Lasse Moe

# Forskerinitierte studier



Randomized clinical trial in early rheumatoid arthritis assessing management with and without ultrasound



Randomized clinical trial of switch from innovator infliximab to biosimilar infliximab



Nordic randomized clinical trial in early rheumatoid arthritis comparing conventional therapy versus three biologic treatments



Randomized clinical trial in rheumatoid arthritis assessing withdrawal of disease-modifying drugs



Randomized clinical trial assessing the effectiveness of targeting infliximab treatment by therapeutic drug monitoring versus routine care



## Eksempel 3

# Nedtrapping av medisiner

- Hva gjør vi med pasienter med revmatoid artritt (RA, leddgikt) som er i langvarig remisjon?
- Grunner til å vurdere å trappe ned eller seponere behandling:
  - Pasientene foretrekker å stå på færrest mulig medikamenter
  - Bivirkninger – betydelig immunsuppresjon, ukjente langtidsbivirkninger
  - Helseøkonomi

# Status RA-behandling ved studiestart



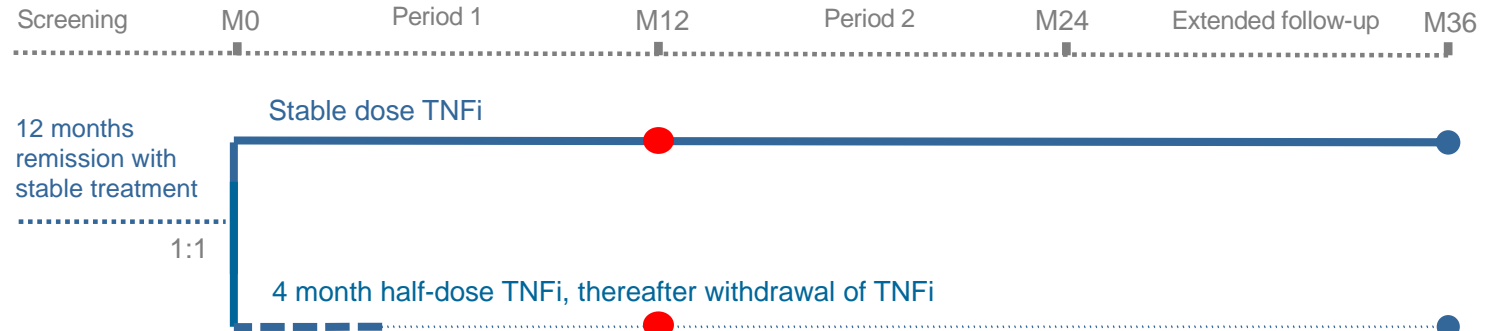
# Studiedesign ARCTIC REWIND

- To randomisert kontrollerte, fase 4 non-inferiority multistudier
  - Fullfinansiert av Helse Sør-Øst og Forskningsrådet
- RA diagnose
  - I henhold til etablerte kriterier
- Remisjon (ingen eller svært få tegn til sykdomsaktivitet)
  - I minst 12 måneder
  - Ved inklusjon ingen artritt i 44 undersøkte ledd
- Stabil behandling i minst 12 måneder

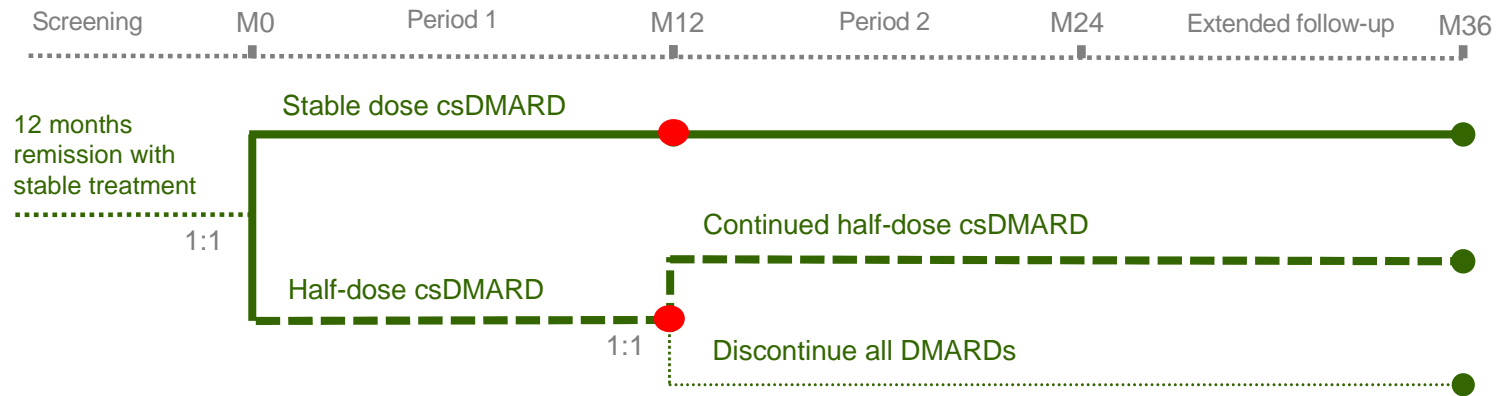


# ARCTIC REWIND

## ARCTIC REWIND TNFi



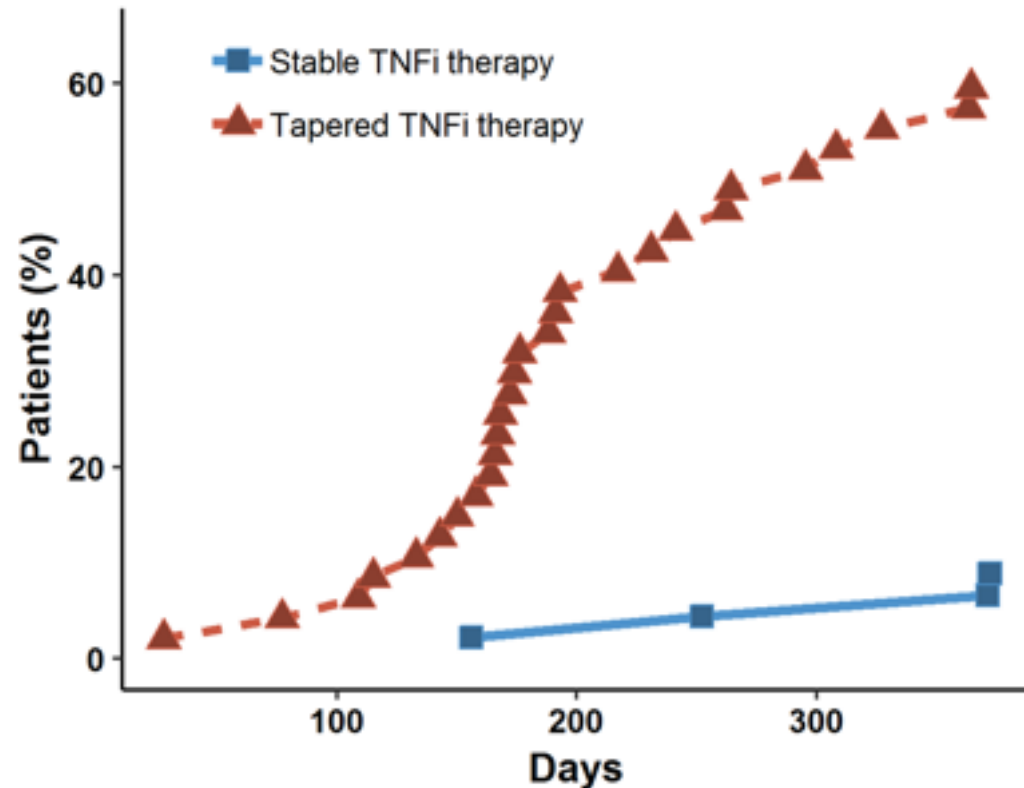
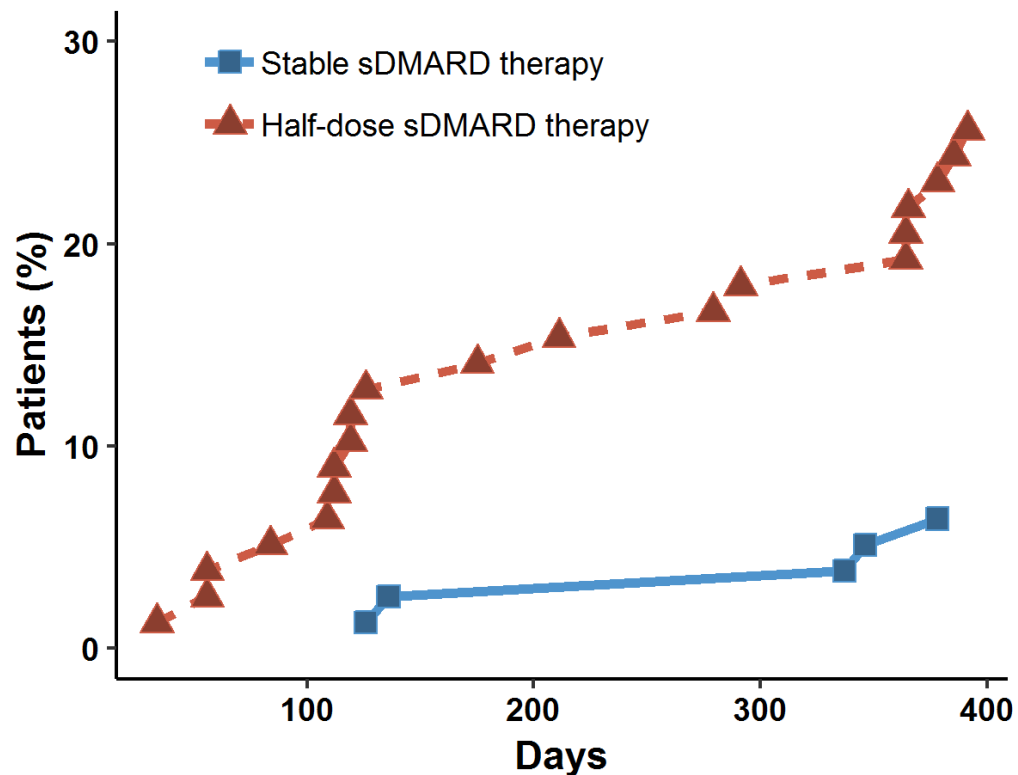
## ARCTIC REWIND csDMARD



● Primary endpoint

# Hovedresultater

- Halv dose ikke non-inferior til stabil behandling
- Stabil dose superior – gir mindre flare



Research

JAMA | Original Investigation

# Effect of Half-Dose vs Stable-Dose Conventional Synthetic Disease-Modifying Antirheumatic Drugs on Disease Flares in Patients With Rheumatoid Arthritis in Remission

## The ARCTIC REWIND Randomized Clinical Trial







Siri Lillegraven, MD, MPH, PhD; Nina Paulshus Sundlisæter, MD, PhD; Anna-Birgitte Aga, MD, PhD; Joseph Sexton, PhD; Inge C. Olsen, PhD; Hallvard Fremstad, MD; Cristina Spada, MD; Tor Magne Madland, MD, PhD; Christian A. Høili, MD; Gunnstein Bakland, MD, PhD; Åse Lexberg, MD; Inger Johanne Widding Hansen, MD; Inger Myrnes Hansen, MD; Hilde Haukeland, MD; Maud-Kristine Aga Ljoså, MD; Ellen Moholt, RN, Msc; Till Uhlig, MD, PhD; Daniel H. Solomon, MD, MPH; Désirée van der Heijde, MD, PhD; Tore K. Kvien, MD, PhD; Espen A. Haavardsholm, MD, PhD



OPEN ACCESS

CLINICAL SCIENCE

## Effect of tapered versus stable treatment with tumour necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: a randomised, open label, non-inferiority trial

Siri Lillegraven <sup>1</sup>, Nina Paulshus Sundlisæter <sup>1</sup>, Anna-Birgitte Aga <sup>1</sup>, Joseph Sexton,<sup>1</sup> Inge Christoffer Olsen,<sup>2</sup> Åse Stavland Lexberg,<sup>3</sup> Tor Magne Madland,<sup>4</sup> Hallvard Fremstad,<sup>5</sup> Christian A. Høili,<sup>6</sup> Gunnstein Bakland,<sup>7</sup> Cristina Spada,<sup>8</sup> Hilde Haukeland,<sup>9</sup> Inger Myrnes Hansen,<sup>10</sup> Ellen Moholt,<sup>1</sup> Till Uhlig <sup>1,11</sup>, Daniel H Solomon,<sup>12,13</sup> Désirée van der Heijde <sup>1,14</sup>, Tore K Kvien <sup>1,11</sup>, Espen A Haavardsholm<sup>1,11</sup>

Annals of the  
**Rheumatic Diseases**

Home / Online First

JAMA<sup>\*</sup> Search All Enter Search Term

[View Correction](#)

**This Issue** Views **2,675** | Citations **0** | Altmetric **33**

[Download PDF](#) [More](#) [Cite This](#) [Permissions](#)

**Research Letter** FREE

March 28, 2023

## Discontinuation of Conventional Synthetic Disease-Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis and Excellent Disease Control

Siri Lillegraven, MD, MPH, PhD<sup>1</sup>; Nina Paulshus Sundlisæter, MD, PhD<sup>1</sup>; Anna-Birgitte Aga, MD, PhD<sup>1</sup>; Joseph Sexton, PhD<sup>1</sup>; Daniel H. Solomon, MD, MPH<sup>2</sup>; Désirée van der Heijde, MD, PhD<sup>3</sup>; Espen A. Haavardsholm, MD, PhD<sup>1</sup>

[> Author Affiliations](#) | [Article Information](#)

JAMA. 2023;329(12):1024-1026. doi:10.1001/jama.2023.0492



## Vekker oppsikt med publisering: Forskerne tok en dobbel JAMA



**LEDDGIKTFORSKERE:** Seks av syv forfattere samlet, fra venstre: Anna-Birgitte Aga, Nina Paulshus Sundliæter, Siri Lillegraven, Daniel H. Solomon, Joe Sexton og Espen A. Haavardsholm. Foto: Nicolas Tourrenc

### Studie indikerer at enkelte leddgiktspasienter kan klare seg uten medisin

Forskergruppen bak den norske ARCTIC REWIND-studien melder om positive funn for leddgiktspasienter. - Studiefunnene gir klare indikasjoner på at pasienter som først har vært i langvarig remisjon kan klare seg helt uten medisiner, uttaler Siri Lillegraven, lege, førsteamanuensis og forsker ved Diakonhjemmet sykehus.

# Oppsummering - eksempler

- Viktig at begge utfall av studien er av interesse
- Studier som svarer på kliniske spørsmål → innvirkning på klinisk praksis
- Gjennomføring av studier er krevende, krever årelang innsats og betydelig finansiering
  - Men er mulig på ikke-universitetssykehus!

# Innhold

- Eksempler – fra ide til protokoll
- **Problemstilling**
  - Klinisk relevans
  - Pasientgrunnlag
  - Nytteverdi
- Praktisk ved prosjektstart
  - Forankring i sykehuset og i klinisk drift
  - Ressurser (personale, tid)
  - Forfatterskap/vitenskapelig samarbeid
- Prosjektskisse

# Forskningsspørsmål

- Forskningsspørsmålet bør/skal besvare en viktig problemstilling og påvirke klinisk praksis
- Forskningsspørsmålet bør være så viktig at du ikke er i tvil om:
  - At du bør få innvilget støtte
  - At du vil bruke mange av dine (beste?) år i arbeidslivet på studien
- Hvis du er i tvil, vanskeligere å overbevise andre

# VIKTIG AVKLARING!! Søknadspliktig CTIS?

The screenshot shows the European Medicines Agency (EMA) website. At the top, there is a navigation bar with the EMA logo and the text "EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH". Below this is a search bar with a "Search" button. The main navigation menu includes "Medicines", "Human regulatory", "Veterinary regulatory", "Committees", "News & events", "Partners & networks", and "About us". The "Human regulatory" section is expanded, showing sub-sections: "Overview", "Research and development", "Marketing authorisation", and "Post-authorisation". The "Research and development" sub-section is highlighted. Below this, there is a sidebar with a menu containing "Adaptive pathways", "Advanced therapies", "Clinical trials", "Accelerating Clinical Trials in the EU (ACT EU)", and "Data submission: guidance". The main content area is titled "Clinical Trials Information System" with a "Share" button. Below the title is a "Table of contents" section with a list of items: "Secure workspaces", "Sponsor workspace", "Authority workspace", "Searching for clinical trials", and "Processing of personal data".

Clinical Trials Information System | European Medicines Agency

An official website of the European Union How do you know? ▾

EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

Search

Medicines ▾ Human regulatory Veterinary regulatory ▾ Committees ▾ News & events ▾ Partners & networks ▾ About us ▾

## Human regulatory

Overview Research and development Marketing authorisation

Post-authorisation Herbal products

Adaptive pathways

Advanced therapies

Clinical trials ▾

Accelerating Clinical Trials in the EU (ACT EU)

Data submission: guidance

## Clinical Trials Information System [Share](#)

### Table of contents

- [Secure workspaces](#)
- [Sponsor workspace](#)
- [Authority workspace](#)
- [Searching for clinical trials](#)
- [Processing of personal data](#)



# Clinical Trials Information System (CTIS)

Publisert: 21.05.2023 | Oppdatert: 21.06.2023

## Innhold på siden

- ↳ [Hva er CTIS?](#)
- ↳ [Saksbehandling i CTIS](#)
- ↳ [Hvordan kan jeg få tilgang til CTIS?](#)
- ↳ [Opplæringsmoduler og -materiell](#)



To document overview

## Procedures for clinical trials applied to the authorities through CTIS

### CT procedures

These procedures are valid from 31 January 2022 when Regulation 536/2014 is implemented.

The procedures with accompanying appendices have been prepared to meet the mandatory requirements described in National and International laws, regulations and guidelines for good clinical research practice "Good Clinical Practice" (GCP).

A [flowchart](#) of how to use the LM procedures and appendices has been prepared. You can [watch a video](#) about the use of the flowchart.

The appendices are practical aids / guiding documents that can be adapted for use in individual clinical trials.

Course material for handling adverse [reactions](#) / [safety reporting](#) can be found under the tab 'courses and activities'.

**For monitors:** Additional relevant documents for monitors can [be found here](#).

**Corona adaptations:** Special adaptations in some documents can [be found here](#).

If you find errors or omissions in any of the documents, please give us feedback via [post@norcrin.no](mailto:post@norcrin.no) so we can correct them as soon as possible.

# Pasientgrunnlag

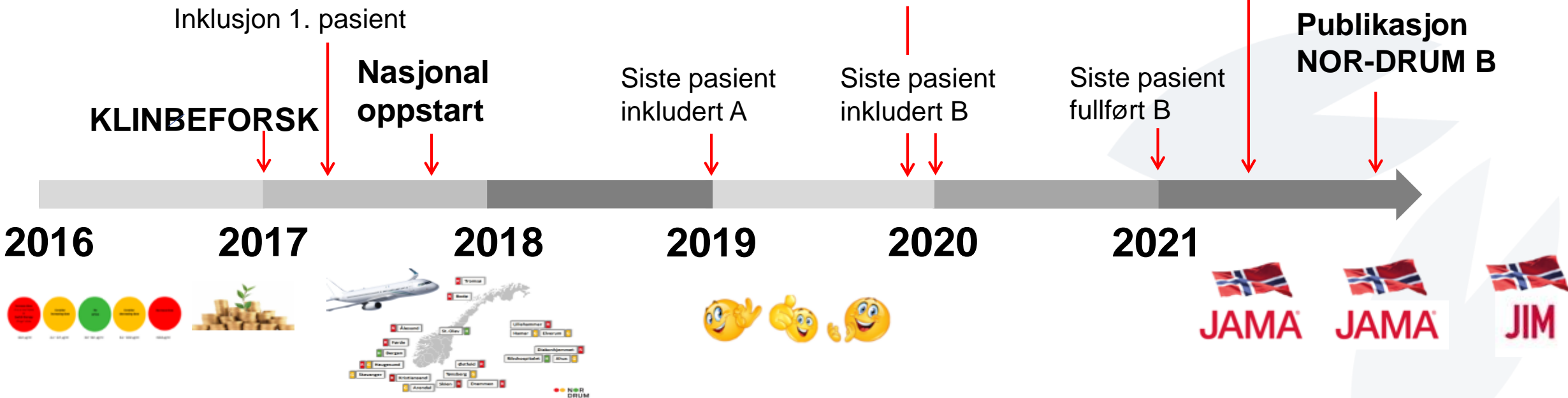
- Inklusjons- og eksklusjonskriterier
- Eksisterer disse pasientene?
- **VIKTIG! Avgjørende del av studieplanleggingen**



# Tidslinje

- **Tidlig fase**
    - Definere forskningsspørsmål/hypotese
    - Synopsis
    - Finansiering
  - **Studie besluttet igangsatt**
    - Utvikle protokoll
    - Regional etisk komite / Statens legemiddelverk
  - **Aktiv fase**
    - Pasientinkludering
    - Datainnsamling
    - Datasjekker
  - **Resultater**
    - Koding
    - Analyser inkl. analyseplan
    - Publisering
  - **Forlengelse, publisering sekundære mål**
- 1-2 år
- 1-5 år
- 6-12 mnd.

- **Tidlig fase**
  - Definere forskningsspørsmål/hypotese
  - Synopsis
  - Finansiering
- **Studie besluttet igangsatt**
  - Utvikle protokoll
  - Regional etisk komite / Statens legemiddelverk
- **Aktiv fase**
  - Pasientinkludering
  - Datainnsamling
  - Datasjekker
- **Resultater**
  - Koding
  - Analyser inkl. analyseplan
  - Publisering
- **Forlengelse, publisering sekundære mål**



# Dedikasjon

- Kliniske studier er kompliserte!
- Krever betydelig dedikasjon og utholdenhet, særlig av hovedutprøver/prosjektleder
- Krever støtte fra koordinerende senter

# Innhold

- Eksempler – fra ide til protokoll
- Problemstilling
  - Klinisk relevans
  - Pasientgrunnlag
  - Nytteverdi
- **Praktisk ved prosjektstart**
  - Forankring i sykehuset og i klinisk drift
  - Ressurser (personale, tid)
  - Forfatterskap/vitenskapelig samarbeid
- Prosjektskisse

# Synopsis

## PROTOCOL SYNOPSIS

	TITLE
Phase of development	
Investigational treatment strategy	
Study Centres	
Study organisation	
Study Period	
Duration	
Primary objective	
Secondary objectives	
Endpoints	
Study Design	
Main Inclusion Criteria	
Main exclusion criteria	
Sample size	
Hypothesis and statistical model	



# Prosjektbeskrivelse

## Modern treatment of rheumatoid arthritis

**Applicant** Siri Lillegraven, MD MPH PhD  
Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo

### 2) INTRODUCTION

This application for a career fellowship outlines five work packages (WPs) to improve modern treatment of rheumatoid arthritis (RA) (figure 1). The proposed work aims to increase the knowledge of how early RA and RA remission should be treated, considering both patients and society. The project uses data from three studies and includes the main analyses of the Norwegian multi-center randomized clinical trial ARCTIC REWIND, which assesses the effects of tapering and withdrawal of disease-modifying antirheumatic drugs (DMARDs) in sustained RA remission.

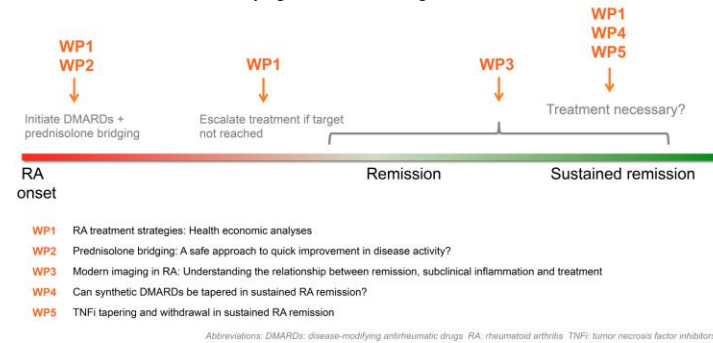


Figure 1: Conceptual illustration of the project

### An introduction to RA

RA is a chronic inflammatory disease predominantly affecting women [3]. The main feature is joint inflammation with subsequent joint destruction, but the disease can also have extra-articular manifestations and be associated with increased risk of cardiovascular disease and reduced life-expectancy [4]. In early disease, disability is driven by disease activity, and thus reversible with successful medical treatment (figure 2). RA is treated with DMARDs, which are classified as synthetic (e.g. methotrexate, sulfasalazine), biologic (e.g. tumor necrosis factor inhibitors (TNFi), rituximab) [3, 5, 6] or targeted synthetic (e.g. janus kinase inhibitors) [3].

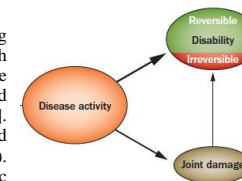


Figure 2: Disease activity, disability and joint damage in early RA [2]

### Modern RA treatment and remission

The introduction of biologic DMARDs has changed the outcome of RA, and the goal in modern RA treatment has become to reach and sustain remission, with prevention of structural joint damage and disability [5, 6]. Synthetic DMARD treatment is started when a patient is diagnosed, with initial corticosteroid bridging according to current treatment recommendations [3, 5]. Although the use of corticosteroids when initiating synthetic DMARDs is supported by considerable evidence, the dosing, administration route and duration is debated and experts struggle to agree on a definite recommendation [5]. RA treatment strategies now implement tight control of RA care, with a

A NORwegian randomized Strategy trial in Psoriatic arthritis: ImagiNg Treat-to-target vs conventional treat-to-target

## The NOR-SPRINT study

### 2) INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous inflammatory disease which may affect several musculoskeletal structures and skin. Treatment should be tailored based on presentation in the individual patient as some of the potential drugs have limited or no effect on certain features. However, inflammatory involvement may be difficult to assess clinically in PsA. This application outlines a Norwegian multi-center study comparing a novel treatment strategy actively assessing the patient with modern imaging techniques to tailor the treatment based on imaging findings, to a conventional treatment strategy. The results will potentially make significant changes in the treatment of this patient group.

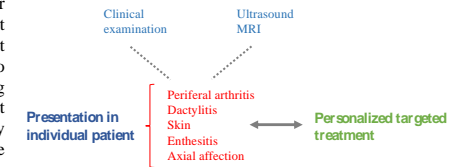


Figure 1: Conceptual illustration of the project

### An introduction to psoriatic arthritis

PsA occurs in about 30% of psoriasis patients, and is characterized by diverse clinical features, often resulting in delayed diagnosis and treatment<sup>1</sup>. Disease manifestations include arthritis, tenosynovitis, enthesitis, axial inflammation, skin- and nail changes. Norwegian data have yielded prevalence estimates of 2.0 (Bergen) and 6.7 (Nord-Trøndelag) cases per 1000 inhabitants in the adult population<sup>2,3</sup>. Persistent disease activity will, in addition to the immediate symptoms of inflammation, result in joint damage in a significant proportion of patients<sup>4,5</sup> with associated permanent loss of function<sup>5,6</sup>, reduced quality of life<sup>7</sup> and decreased work participation<sup>8</sup>. PsA is also associated with increased risk of cardiovascular disease<sup>9</sup>.

### Assessment of inflammation in psoriatic arthritis

All pharmacological treatments of PsA are targeted at reducing inflammation, thus the detection of inflammation is crucial to make appropriate treatment decisions. The overarching goal of PsA treatment is to ensure symptom control and prevention of structural damage, while avoiding unnecessary exposure to treatments with risk of adverse events. Because of the heterogeneous nature of PsA, it has been difficult to define how to best record disease activity at clinical visits. Current disease activity measures are based a combination of patient reported outcomes (PROs) and clinical assessment. Patients reported symptoms and functional assessments partially reflects inflammation, but is also influenced by factors that should not be treated by anti-inflammatory medication, such as established joint damage and comorbid conditions, including fibromyalgia and widespread pain syndromes. Clinical assessment of joints and entheses are core measures of disease activity, but there are concerns regarding both their validity and their reliability in a clinical setting<sup>10</sup>.

Modern imaging techniques, such as ultrasound and magnetic resonance imaging (MRI), is widely used in rheumatology. Ultrasound can be a useful tool to examine joints, tendons and entheses<sup>11</sup> bedside, with direct visualization of subclinical inflammation such as by the finding of power Doppler activity. Subclinical ultrasound synovitis has been found in three of four newly diagnosed PsA patients<sup>12</sup> and subclinical inflammation of joints, tendons and entheses has also been detected in a large proportion of patients found to be in clinical remission<sup>13</sup>. MRI is the only reliable method to assess inflammation of the sacroiliac joints and the spine, and is an established part of axial spondyloarthritis classification criteria<sup>14,15</sup>. However, although axial affection is a feature of PsA, data on imaging of the column in PsA are scarce and there is no consensus on to what extent it would be beneficial to perform axial MRIs routinely in this patient group<sup>16</sup>.

## 1. PROJECT TITLE

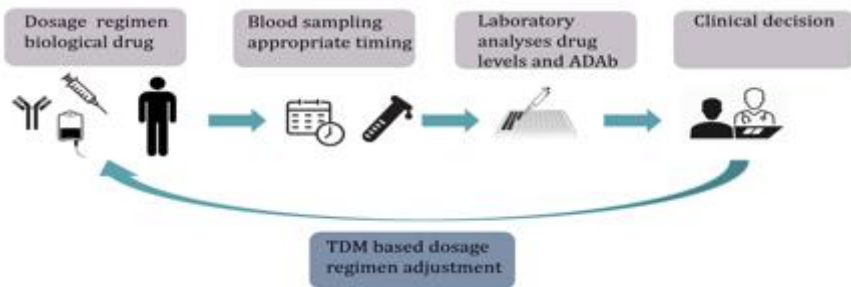
### Assessing the efficacy of proactive therapeutic drug monitoring of Adalimumab therapy: The AURORA trial

## 2. INTRODUCTION

This application outlines the AURORA trial, a multicentre randomised controlled trial, aiming at optimising therapy with subcutaneous (SC) tumour necrosis factor alpha inhibitors (TNFi) in patients with immune-mediated inflammatory diseases (IMiDs). IMiDs such as inflammatory bowel- and joint diseases constitute a significant burden for the patient, health-care systems and society. The proposed study will assess whether a personalised treatment strategy based on therapeutic drug monitoring (TDM) improves efficacy of adalimumab therapy, the most frequently used TNFi both globally and nationally. The study will include patients with rheumatoid arthritis (RA), spondyloarthritis (SpA), ulcerative colitis (UC) or Crohn's disease (CD) on adalimumab therapy and is expected to provide clinically valuable information that will hopefully contribute to reduce the disease burden in these common chronic inflammatory diseases with a potentially disabling disease course, as well as a to reduce expenses related to biological therapy.

The steering group of this proposal consisting of major clinical rheumatological and gastroenterological centres within the Eastern Norway Regional Health Authority possesses the expertise, network and infrastructure necessary to fill current knowledge gaps within this field. The AURORA trial will build on the infrastructure, organisation and research collaboration already established for the successful NOR-SWITCH and NOR-DRUM studies<sup>1-4</sup>, previous extensive efforts within Norwegian rheumatology and gastroenterology. As outlined in the budget, a recent EU grant (Horizon-HLTH-2022) to the project "Maximising Impact of Prescription Drugs in Rheumatoid Arthritis" with Diakonhjemmet Hospital and Oslo University Hospital as partners, has secured funding for operating costs and personnel related to the RA patients in the proposed study. The current grant proposal will enable AURORA as a multi-disciplinary study that includes patients both from gastroenterology and rheumatology. The experience with NOR-DRUM has highlighted the importance of multicentre, multi-disciplinary research collaborations within this field, and by the AURORA trial we hope to take further advantage of the rewarding research alliance between clinical rheumatology and gastroenterology and leading research communities within laboratory medicine, clinical immunology and genetics.

Development and implementation of personalised medicine in the healthcare services is a national and regional strategic research goal<sup>5</sup>. The impact of TDM of biological therapy is currently a topic of great interest to clinicians both nationally and internationally.



## Personalised management of early inflammatory arthritis

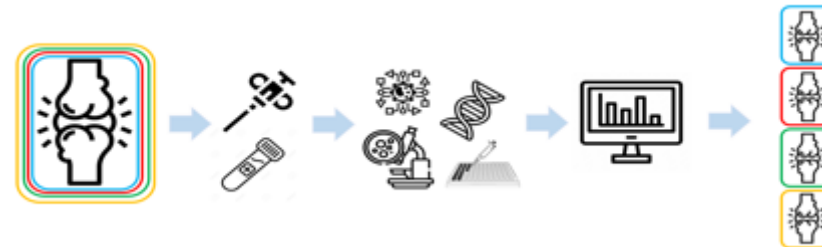
### APPLICANT

Silje Watterdal Syversen, MD PhD  
 Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY)  
 Division of Rheumatology and Research  
 Diakonhjemmet Hospital, Oslo, Norway

### 1 INTRODUCTION

This application outlines the prospective observational study "Early Stratification of acute inflammatory ARthritis" (START) which aims at building a platform for development of stratification tools for personalised management of patients with early stage inflammatory arthritis (IA). The heterogeneity of disease presentation, progression and response to therapies in patients with IA makes it difficult for clinicians to successfully treat patients, predict treatment outcome and provide optimal care. Development and implementation of personalised medicine in the healthcare services are strategic goals both nationally and regionally.<sup>1</sup> The current project proposal outlines a project where the applicant and the project group have the expertise, network and infrastructure necessary to fill current knowledge gaps, and to improve management and care for a large group of patients with a potentially disabling disease course.

Figure 1: Conceptual figure- Stratification of early inflammatory arthritis





### 1.1 Background, state of knowledge and description of needs

#### 1.1.1 Inflammatory arthritis

Arthritis is characterised by inflammation of the joint leading to swelling, pain and loss of function. Several conditions may cause IA, such as intraarticular infections, reactive arthritis, crystal disposition and early stage of chronic inflammatory joint diseases such as rheumatoid arthritis (RA), spondyloarthritis (SpA) or psoriatic arthritis (PsA). A significant proportion of both acute and chronic IA remains "undifferentiated" according to current classification criteria.

# Protokoll – et lagarbeid

- **Dedikert hovedutprøver/prosjektleder**
- **Styringsgruppe**
  - Nasjonale meningsbærere, forskere med erfaring fra kliniske studier, hovedutprøvere, statistikere, klinikere
  - Internasjonalt advisory board
  - Internasjonalt ledende forskere
- Brukerrepresentanter
- Studieleger og studiesykepleiere
- **Forankring klinikk**

<b>A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUG Monitoring</b>	
<b>The NOR-DRUM study</b>	
	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	
<b>SPONSOR:</b>	<b>Diakonhjemmet Hospital AS</b> Contact person: Karin Hesseberg, PhD Box 23 Vinderen, 0319 Oslo Tel : 22 45 15 00 E-mail: karin.hesseberg@diakonsyk.no
<b>PRINCIPAL INVESTIGATOR:</b>	<b>Professor Espen A. Haavardsholm, MD PhD</b> Dept. of Rheumatology Diakonhjemmet Hospital Box 23 Vinderen, 0319 Oslo Tel: 22 45 15 00 E-mail: e.a.haavardsholm@medisin.uio.no
PROTOCOL VERSION NO. 1.3 DATE 09.12.2019	
	
1	

## TABLE OF CONTENTS

STUDY ORGANISATION.....	2
STEERING COMMITTEE.....	2
METHODOLOGY ADVISORS.....	2
CONTACT INFORMATION.....	3
SIGNATURE PAGE.....	4
PROTOCOL SYNOPSIS.....	5
TABLE OF CONTENTS.....	10
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	15
<b>1 INTRODUCTION.....</b>	<b>17</b>
1.1 Background.....	17
1.1.1 Drug and diseases of this study.....	17
1.1.2 Anti-drug antibodies and serum drug levels.....	18
1.1.3 Therapeutic drug monitoring.....	19
1.1.4 The NOR-SWITCH study.....	20
1.2 Purpose and rationale.....	20
<b>2 STUDY OBJECTIVES.....</b>	<b>22</b>
2.1 Main study objective.....	22
2.2 Primary objectives.....	22
2.3 Secondary objectives and exploratory objectives.....	22
<b>3 STUDY ENROLMENT AND WITHDRAWAL.....</b>	<b>23</b>
3.1 Inclusion of patients.....	23
3.2 Number of Patients.....	23
3.3 Inclusion Criteria.....	23
3.4 Exclusion Criteria.....	24
3.5 Procedures for discontinuation.....	25
3.5.1 Patient discontinuation.....	25
3.5.2 Discontinuation from the study by the investigator.....	25
3.5.3 Trial discontinuation.....	26
<b>4 INVESTIGATIONAL PLAN.....</b>	<b>26</b>
4.1 Overview of the study design.....	26

4.2 Follow-up study.....	28
4.3 Study endpoints.....	28
4.3.1 Primary endpoints.....	28
4.3.2 Secondary and exploratory endpoints.....	29
4.4 Description of the treatment strategy in NOR-DRUM A.....	30
4.4.1 The intervention group.....	30
4.4.2 The control group.....	33
4.5 Description of the treatment strategy in NOR-DRUM B.....	34
4.5.1 The intervention group.....	34
4.5.2 The control group.....	35
4.6 Rationale for the intervention algorithm.....	39
4.7 Study drug.....	40
4.7.1 Drug supply, preparation and storage.....	40
4.7.2 Drug administration, premedication and monitoring.....	40
4.7.3 Subject Compliance.....	40
4.7.4 Drug Accountability.....	41
4.8 Prior therapy.....	41
4.9 Concomitant medication.....	41
4.10 Dose modifications and schedule modifications.....	42
4.11 Protocol modifications.....	42
4.12 Linkage to other registers.....	42
<b>5 STUDY PROCEDURES AND SCHEDULE.....</b>	<b>43</b>
5.1 Visits.....	43
5.2 Screening evaluation.....	43
5.3 Assignment of intervention and subject numbering.....	44
5.4 Baseline visit.....	44
5.5 Regular visit.....	45
5.6 Extra visits.....	46
5.7 End of Study Visit.....	46
5.8 Withdrawal Visit.....	46
<b>6 ASSESSMENTS.....</b>	<b>47</b>
6.1 Ordinary laboratory Tests.....	47
6.2 Biobank samples.....	47
6.3 Immunogenicity and Serum Drug Concentration Assessments.....	47

6.4 Safety and Tolerability Assessments.....	48
6.4.1 Vital signs.....	48
6.5 Assessments of efficacy.....	48
6.5.1 General efficacy assessments.....	48
6.5.2 Disease specific efficacy assessments: RA, PsA.....	48
6.5.3 Disease specific efficacy assessments: SpA.....	49
6.5.4 Disease specific efficacy assessments: Ulcerative colitis.....	50
6.5.5 Disease specific efficacy assessments: Crohn's disease.....	50
6.5.6 Disease specific efficacy assessments: Psoriasis.....	50
Calculations for area: Each of the body area scores is multiplied by the area affected.....	51
6.5.7 Definition of disease worsening.....	51
6.5.8 Definition of remission.....	52
6.5.9 Definition of improvement.....	53
6.6 Other Assessments.....	53
<b>7 SAFETY MONITORING AND REPORTING.....</b>	<b>55</b>
7.1 Adverse events.....	55
7.1.1 Recording of Adverse Events.....	55
7.1.2 Serious adverse events.....	56
7.2 Laboratory test abnormalities.....	56
7.3 Pregnancy.....	56
<b>8 DATA MANAGEMENT.....</b>	<b>57</b>
8.1 Electronic Case Report Forms (CRFs).....	57
8.2 Source Data.....	57
8.3 Confidentiality.....	58
<b>9 STATISTICAL METHODS AND DATA ANALYSIS.....</b>	<b>58</b>
9.1 Randomisation.....	58
9.1.1 Allocation- sequence generation.....	58
9.1.2 Allocation- procedure to randomise a patient.....	58
9.2 Planned analyses.....	59
9.3 Populations.....	59
9.3.1 Primary population.....	59
9.3.2 Secondary population.....	59
9.3.3 Safety population.....	59
9.4 Statistical Analysis.....	60

9.4.1 Statistical model.....	60
9.4.2 Primary analyses.....	60
9.4.3 Secondary analyses.....	61
9.4.4 Safety analyses.....	62
9.4.5 Patient reported outcome measures and disability analyses.....	62
9.4.6 Other analyses/subanalyses.....	62
9.4.7 Health economic analyses.....	62
9.4.8 Missing data.....	63
9.5 Sample size determination.....	63
9.6 Interim analyses.....	63
<b>10 STUDY MANAGEMENT.....</b>	<b>64</b>
10.1 Investigator Delegation Procedure.....	64
10.2 Protocol Adherence.....	64
10.3 Study Amendments.....	64
<b>11 ETHICAL REQUIREMENTS.....</b>	<b>64</b>
11.1 Ethics Committee Approval.....	64
11.2 Other Regulatory Approvals.....	65
11.3 Informed Consent Procedure.....	65
11.4 Subject Identification.....	65
<b>12 TRIAL SPONSORSHIP AND FINANCING.....</b>	<b>65</b>
<b>13 PUBLICATION POLICY.....</b>	<b>66</b>
<b>14 REFERENCES.....</b>	<b>66</b>
<b>15 APPENDICES.....</b>	<b>70</b>



# Ressurser

- Kliniske studier er kostbart!
- **Adekvat finansiering avgjørende**
- Nødvendig for å rekruttere studiesentra
  - Studiepersonell
  - Legemiddel
  - Prosedyrer (radiologi, biobanking)
  - Forsikring
  - Monitorering

# Økende krav

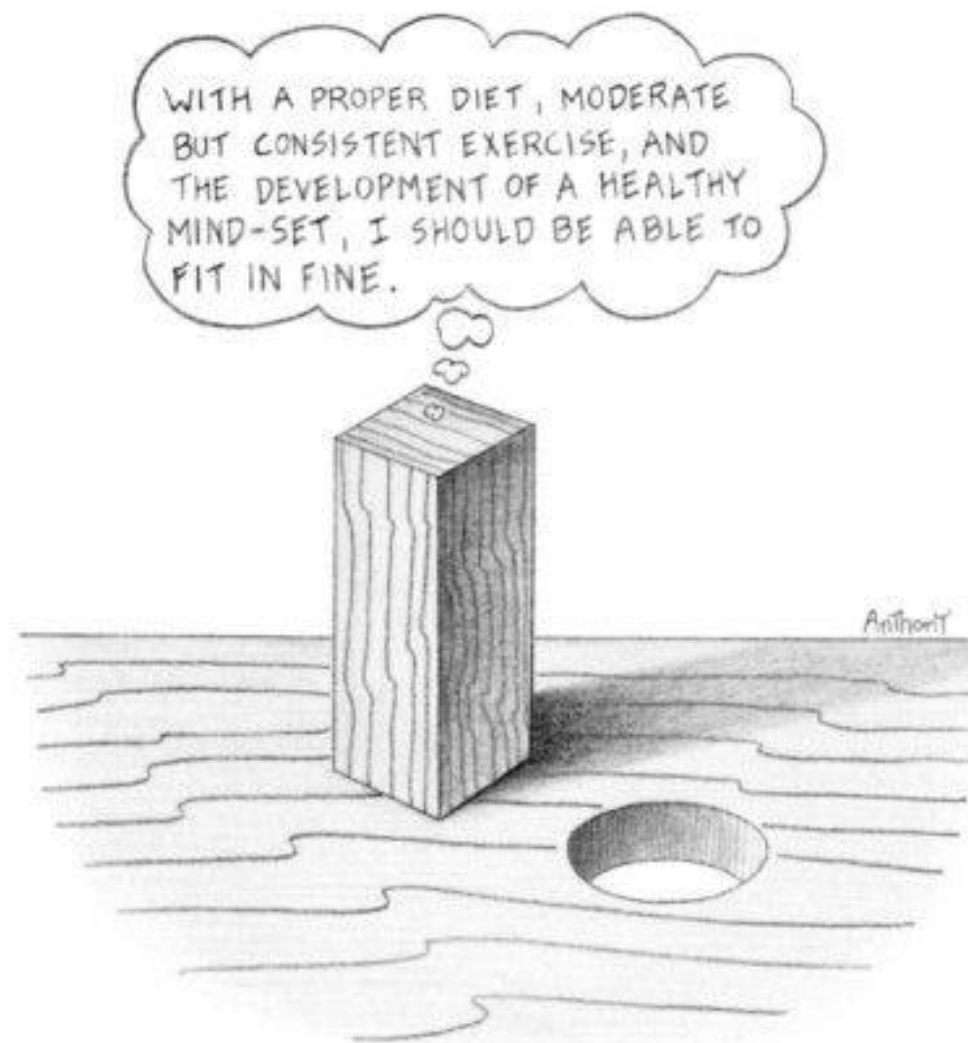
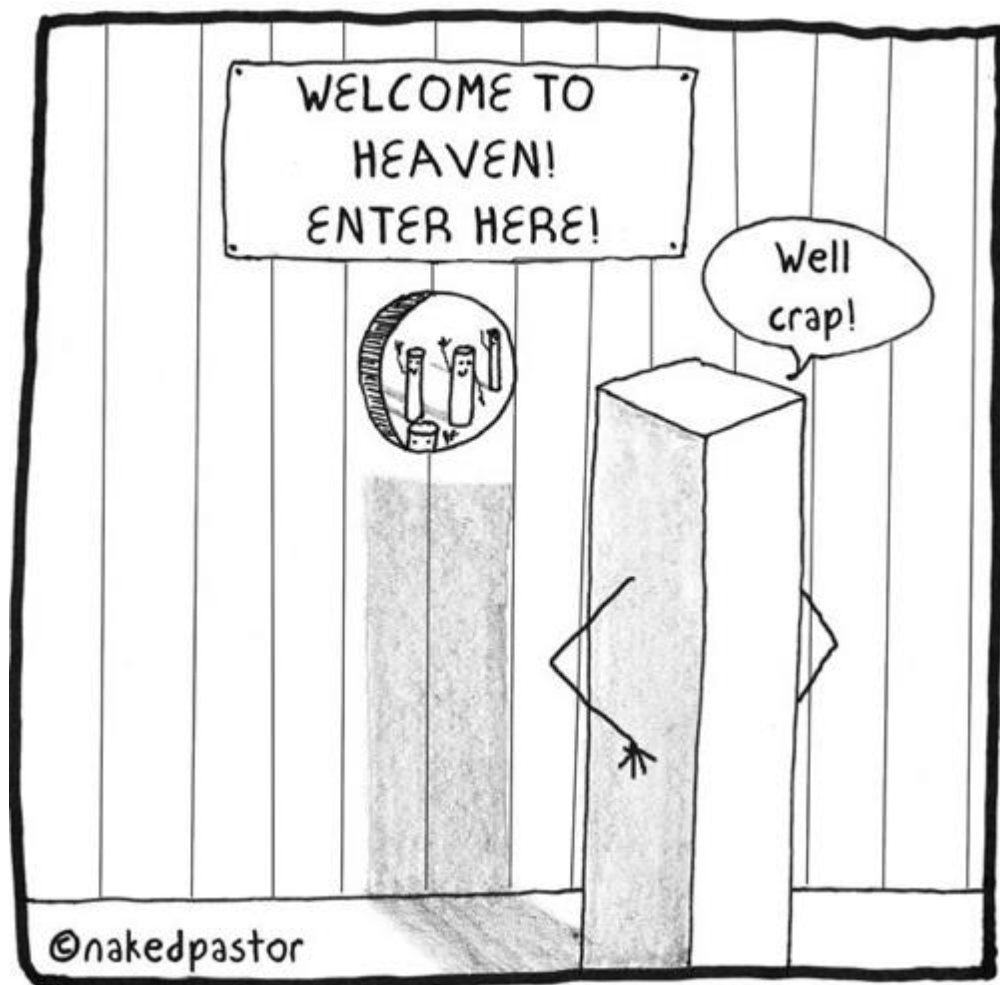


*“Is it just me or are these review panels getting a lot tougher?”*

# Søkeåret



# Hvor skal man prøve å søke penger?





# Helse Sør-Øst 2020

Tabell 3. Antall søknader innstilt til støtte per søknadskategori.

Søknadskategori	Antall vurderte søknader	Antall innstilte søknader	Beløp (tusen kroner)	
Doktorgradsstipend	268	44	43 322	16%
Postdoktorstipend	115	32	31 596	28%
Karrierestipend	37	7	13 437	19%
Åpen prosjektstøtte	106	16	42 689	15%
Prosjektmidler til klinisk forskning *	11	5	2 875	45%
<b>Totalt</b>	<b>537</b>	<b>104</b>	<b>133 919</b>	

\*) Prosjektmidler til klinisk forskning er beregnet for avgrensede, mindre kliniske forskningsprosjekter, for eksempel oppstarts- eller pilotprosjekter. Kategorien har søknadsadgang begrenset til to søknader per helseforetak eller klinikk ved universitetssykehusene. Det vises her til føringer i utlysningsteksten.

# Forskningsrådet 2018

- FRIMEDBIO fikk 503 søknader om til sammen 4,25 milliarder kroner

	FRIMEDBIO
Forskerprosjekt	31
Unge forskertalenter	12
FRIPRO mobilitetsstipend	5
<b>Totalt</b>	<b>48 (9,5%)</b>

# Prosjektbeskrivelse: Metodeavsnitt

- **Hvordan besvares forskningsspørsmålet best?**
  - RCT? Mulig bruke allerede innsamlede data?
- **Hva er realistisk å gjennomføre innenfor gitte rammer?**
  - Styrkeberegning
  - NB! Viktigheten av riktig utfallsmål for å optimalisere hvor mange pasienter man må inkludere
  - Multisenter? Fordel og ulemper
- **Hvordan planlegge for god datakvalitet?**
  - Vise forståelse for krav om søknad til REK, CTIS
  - Plan for monitorering dersom legemiddelstudie
  - Ta stilling til CRF-løsning?

# Evalueringsskriterier

	Project quality	Impact
1	<b>Originality:</b> <ul style="list-style-type: none"> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation; does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>	<b>Needs justification:</b> <ul style="list-style-type: none"> <li>Target group(s), i.e. patient group(s), carers, other identified users</li> <li>Needs in the specialist health services</li> <li>Filling knowledge gaps</li> <li>Meeting other needs of society</li> </ul>
2	<b>Design of the application:</b> <ul style="list-style-type: none"> <li>Scientific background of the project</li> <li>Overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important for PhD grants) and roles</li> </ul>	<b>Importance of generating new knowledge:</b> <ul style="list-style-type: none"> <li>Realistic importance for the health services, possible improvements of existing offers/practices</li> <li>Importance of new knowledge / filling knowledge gaps, academic impact</li> <li>Impact on society, potential for generalisation / broad use of new knowledge</li> </ul>
3	<b>Feasibility:</b> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistics etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>	<b>Potential for implementation:</b> <ul style="list-style-type: none"> <li>Realistic plans for implementation / translation of research into improved practice</li> <li>Realistic time line for implementation (short/long term)</li> <li>Identified dependencies on development in other areas</li> </ul>
4	<b>Quality of the applicant (relative to career stage):</b> <ul style="list-style-type: none"> <li>Expertise and qualifications</li> <li>Productivity</li> <li>Skills related to project management and supervision</li> <li>Independency relative to career stage (particularly important for career fellowship proposals)</li> </ul>	<b>Competence building:</b> <ul style="list-style-type: none"> <li>Gain of knowledge/skills required in the health services</li> <li>Development of methods, techniques</li> <li>Strengthening of the research area</li> </ul>
5	<b>Research environment:</b> <ul style="list-style-type: none"> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators</li> <li>Educational environment, capacity and ability to supervise</li> <li>Cross-disciplinarity if relevant</li> </ul>	<b>Dissemination and visibility:</b> <ul style="list-style-type: none"> <li>Plan for dissemination; publications, articles, web sites etc.</li> <li>Plan for user involvement when relevant</li> <li>Other relevant plans for disseminating new knowledge, nationally and internationally</li> </ul>

Scientific quality
<b>Project design and originality:</b> <ul style="list-style-type: none"> <li>Scientific background of the project, overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important if including PhD grants) and roles</li> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation. Does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>
<b>Feasibility:</b> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistic strength etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>
<b>Quality of the applicant and the research environment:</b> <ul style="list-style-type: none"> <li>Expertise, productivity and qualifications</li> <li>Skills related to project management and supervision</li> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators creating a research environment of capacity</li> <li>Cross-disciplinarity if relevant</li> </ul>
<b>Impact</b>
<b>Needs justification:</b> <ul style="list-style-type: none"> <li>Needs in the specialist health services</li> <li>Target group(s), i.e. patient group(s), carers, other identified users</li> <li>Filling knowledge gaps</li> </ul>
<b>Potential for implementation:</b> <ul style="list-style-type: none"> <li>Realistic plans for implementation / translation of research into improved practice</li> <li>Realistic time line for implementation (short/long term)</li> <li>Identified dependencies on development in other areas, alternative strategies</li> </ul>
<b>Importance of generating new knowledge and competence building:</b> <ul style="list-style-type: none"> <li>Realistic importance for the health services, possible improvements of existing offers/practices</li> <li>Importance of new knowledge / filling knowledge gaps, academic impact</li> <li>Impact on society, potential for generalisation / broad use of new knowledge/methods/procedures</li> </ul>
<b>Mandatory items of the application</b>
<b>Dissemination and visibility:</b> <ul style="list-style-type: none"> <li>Plan for dissemination; publications, articles, web sites etc.</li> <li>Other relevant plans for disseminating new knowledge, nationally and internationally</li> </ul>
<b>Plan for user involvement</b>

## Excellence

**The extent to which the proposed work is ambitious, novel, and goes beyond the state of the art**

- Scientific creativity and originality.
- Novelty and boldness of hypotheses or research questions.
- Potential for development of new knowledge beyond the current state-of-the-art, including significant theoretical, methodological, experimental or empirical advancement.

## The quality of the proposed R&D activities

- Quality of the research questions, hypotheses and project objectives, and the extent to which they are clearly and adequately specified.
- Credibility and appropriateness of the theoretical approach, research design and use of scientific methods. Appropriate consideration of interdisciplinary approaches.
- Where relevant, the extent to which appropriate consideration has been given to ethical issues, safety issues, gender dimension in research content, and appropriate use of stakeholder/user knowledge.

## Impact

### Potential impact of the proposed research

- The extent to which the planned outputs of the project address important present and/or future scientific challenges.
- If relevant with respect to the project objectives, the extent to which the planned outputs will address UN Sustainable Development Goals or other important present and/or future societal challenges.
- The extent to which the potential impacts are clearly formulated and plausible.

### Communication and exploitation

Quality and scope of communication and engagement activities with different target audiences, including relevant stakeholders/users.

### Implementation

#### The quality of the project manager and project group

- The extent to which the project manager has relevant expertise and experience, and has demonstrated the ability to perform high-quality research (as appropriate to the career stage).
- The degree of complementarity of the participants and the extent to which the project group as a whole encompasses the expertise needed to undertake the research effectively, and provides added value.

#### The quality of the project organisation and management

- Effectiveness of the work plan, including the extent to which resources assigned to work packages are aligned with project objectives and deliverables.
- Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role.
- Appropriateness of the proposed management structures and governance.

Helse Sør-Øst

KLINBEFORSK

Forskningsrådet

# Evalueringsskriterier

## Originalitet/novelty

Project quality	
1	<p><b>Originality:</b></p> <ul style="list-style-type: none"> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation; does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>
2	<p><b>Design of the application:</b></p> <ul style="list-style-type: none"> <li>Scientific background of the project</li> <li>Overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important for PhD grants) and roles</li> </ul>
3	<p><b>Feasibility:</b></p> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistics etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>
4	<p><b>Quality of the applicant (relative to career stage):</b></p> <ul style="list-style-type: none"> <li>Expertise and qualifications</li> <li>Productivity</li> <li>Skills related to project management and supervision</li> <li>Interdependency relative to career stage (particularly important for career fellowship proposals)</li> </ul>
5	<p><b>Research environment:</b></p> <ul style="list-style-type: none"> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators</li> <li>Educational environment, capacity and ability to supervise</li> <li>Cross-disciplinarity if relevant</li> </ul>

Scientific quality
<p><b>Project design and originality</b></p> <ul style="list-style-type: none"> <li>Scientific background of the project, overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important if including PhD grants) and roles</li> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation. Does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>
<p><b>Feasibility:</b></p> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistic strength etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>
<p><b>Quality of the applicant and the research environment:</b></p> <ul style="list-style-type: none"> <li>Expertise, productivity and qualifications</li> <li>Skills related to project management and supervision</li> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators creating a research environment of capacity</li> <li>Cross-disciplinarity if relevant</li> </ul>
<p><b>Impact</b></p>
<p><b>Needs justification:</b></p> <ul style="list-style-type: none"> <li>Needs in the specialist health services</li> <li>Target group(s), i.e. patient group(s), carers, other identified users</li> <li>Filling knowledge gaps</li> </ul>
<p><b>Potential for implementation:</b></p> <ul style="list-style-type: none"> <li>Realistic plans for implementation / translation of research into improved practice</li> <li>Realistic time line for implementation (short/long term)</li> <li>Identified dependencies on development in other areas, alternative strategies</li> </ul>
<p><b>Importance of generating new knowledge and competence building:</b></p> <ul style="list-style-type: none"> <li>Realistic importance for the health services, possible improvements of existing offers/practices</li> <li>Importance of new knowledge / filling knowledge gaps, academic impact</li> <li>Impact on society, potential for generalisation / broad use of new knowledge/methods/procedures</li> </ul>
<p><b>Mandatory items of the application</b></p>
<p><b>Dissemination and visibility:</b></p> <ul style="list-style-type: none"> <li>Plan for dissemination; publications, articles, web sites etc.</li> <li>Other relevant plans for disseminating new knowledge, nationally and internationally</li> </ul>
<p><b>Plan for user involvement</b></p>

### Excellence

**The extent to which the proposed work is ambitious, novel, and goes beyond the state of the art**

- Scientific creativity and originality.
- Novelty and boldness of hypotheses or research questions.
- Potential for development of new knowledge beyond the current state-of-the-art, including significant theoretical, methodological, experimental or empirical advancement.

### The quality of the proposed R&D activities

- Quality of the research questions, hypotheses and project objectives, and the extent to which they are clearly and adequately specified.
- Credibility and appropriateness of the theoretical approach, research design and use of scientific methods. Appropriate consideration of interdisciplinary approaches.
- Where relevant, the extent to which appropriate consideration has been given to ethical issues, safety issues, gender dimension in research content, and appropriate use of stakeholder/user knowledge.

### Impact

#### Potential impact of the proposed research

- The extent to which the planned outputs of the project address important present and/or future scientific challenges.
- If relevant with respect to the project objectives, the extent to which the planned outputs will address UN Sustainable Development Goals or other important present and/or future societal challenges.
- The extent to which the potential impacts are clearly formulated and plausible.

### Communication and exploitation

Quality and scope of communication and engagement activities with different target audiences, including relevant stakeholders/users.

### Implementation

#### The quality of the project manager and project group

- The extent to which the project manager has relevant expertise and experience, and has demonstrated the ability to perform high-quality research (as appropriate to the career stage).
- The degree of complementarity of the participants and the extent to which the project group as a whole encompasses the expertise needed to undertake the research effectively, and provides added value.

### The quality of the project organisation and management

- Effectiveness of the work plan, including the extent to which resources assigned to work packages are aligned with project objectives and deliverables.
- Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role.
- Appropriateness of the proposed management structures and governance.

# Evalueringsskriterier

## Quality of project manager / project group

	Project quality	Impact
1	<b>Originality:</b> <ul style="list-style-type: none"> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation; does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>	<b>Needs justification:</b> <ul style="list-style-type: none"> <li>Target group(s), i.e. patient group(s), carers, other identified users</li> <li>Needs in the specialist health services</li> <li>Filling knowledge gaps</li> <li>Meeting other needs of society</li> </ul>
2	<b>Design of the application:</b> <ul style="list-style-type: none"> <li>Scientific background of the project</li> <li>Overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important for PhD grants) and roles</li> </ul>	<b>Importance of generating new knowledge:</b> <ul style="list-style-type: none"> <li>Realistic importance for the health services, possible improvements of existing offers/practices</li> <li>Importance of new knowledge / filling knowledge gaps, academic impact</li> <li>Impact on society, potential for generalisation / broad use of new knowledge</li> </ul>
3	<b>Feasibility:</b> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistics etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>	<b>Potential for implementation:</b> <ul style="list-style-type: none"> <li>Realistic plans for implementation / translation of research into improved practice</li> <li>Realistic time line for implementation (short/long term)</li> <li>Identified dependencies on development in other areas</li> </ul>
4	<b>Quality of the applicant (relative to career stage):</b> <ul style="list-style-type: none"> <li>Expertise and qualifications</li> <li>Productivity</li> <li>Skills related to project management and supervision</li> <li>Interdependency relative to career stage (particularly important for career fellowship proposals)</li> </ul>	<b>Competence building:</b> <ul style="list-style-type: none"> <li>Gain of knowledge/skills required in the health services</li> <li>Development of methods, techniques</li> <li>Strengthening of the research area</li> </ul>
5	<b>Research environment:</b> <ul style="list-style-type: none"> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators</li> <li>Educational environment, capacity and ability to supervise</li> <li>Cross-disciplinarity if relevant</li> </ul>	<b>Dissemination and visibility:</b> <ul style="list-style-type: none"> <li>Plan for dissemination; publications, articles, web sites etc.</li> <li>Plan for user involvement when relevant knowledge, nationally and internationally</li> <li>Other relevant plans for disseminating new knowledge, nationally and internationally</li> </ul>

Scientific quality
<b>Project design and originality:</b> <ul style="list-style-type: none"> <li>Scientific background of the project, overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important if including PhD grants) and roles</li> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation. Does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>
<b>Feasibility:</b> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistic strength etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>
<b>Quality of the applicant and the research environment:</b> <ul style="list-style-type: none"> <li>Expertise, productivity and qualifications</li> <li>Skills related to project management and supervision</li> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators creating a research environment of capacity</li> <li>Cross-disciplinarity if relevant</li> </ul>
<b>Impact</b>
<b>Needs justification:</b> <ul style="list-style-type: none"> <li>Needs in the specialist health services</li> <li>Target group(s), i.e. patient group(s), carers, other identified users</li> <li>Filling knowledge gaps</li> </ul>
<b>Potential for implementation:</b> <ul style="list-style-type: none"> <li>Realistic plans for implementation / translation of research into improved practice</li> <li>Realistic time line for implementation (short/long term)</li> <li>Identified dependencies on development in other areas, alternative strategies</li> </ul>
<b>Importance of generating new knowledge and competence building:</b> <ul style="list-style-type: none"> <li>Realistic importance for the health services, possible improvements of existing offers/practices</li> <li>Importance of new knowledge / filling knowledge gaps, academic impact</li> <li>Impact on society, potential for generalisation / broad use of new knowledge/methods/procedures</li> </ul>
<b>Mandatory items of the application</b>
<b>Dissemination and visibility:</b> <ul style="list-style-type: none"> <li>Plan for dissemination; publications, articles, web sites etc.</li> <li>Other relevant plans for disseminating new knowledge, nationally and internationally</li> </ul>
<b>Plan for user involvement</b>

### Excellence

**The extent to which the proposed work is ambitious, novel, and goes beyond the state of the art**

- Scientific creativity and originality.
- Novelty and boldness of hypotheses or research questions.
- Potential for development of new knowledge beyond the current state-of-the-art, including significant theoretical, methodological, experimental or empirical advancement.

### The quality of the proposed R&D activities

- Quality of the research questions, hypotheses and project objectives, and the extent to which they are clearly and adequately specified.
- Credibility and appropriateness of the theoretical approach, research design and use of scientific methods. Appropriate consideration of interdisciplinary approaches.
- Where relevant, the extent to which appropriate consideration has been given to ethical issues, safety issues, gender dimension in research content, and appropriate use of stakeholder/user knowledge.

### Impact

**Potential impact of the proposed research**

- The extent to which the planned outputs of the project address important present and/or future scientific challenges.
- If relevant with respect to the project objectives, the extent to which the planned outputs will address UN Sustainable Development Goals or other important present and/or future societal challenges.
- The extent to which the potential impacts are clearly formulated and plausible.

### Communication and exploitation

Quality and scope of communication and engagement activities with different target audiences, including relevant stakeholders/users.

### Implementation

**The quality of the project manager and project group**

- The extent to which the project manager has relevant expertise and experience, and has demonstrated the ability to perform high-quality research (as appropriate to the career stage).
- The degree of complementarity of the participants and the extent to which the project group as a whole encompasses the expertise needed to undertake the research effectively, and provides added value.

### The quality of the project organisation and management

- Effectiveness of the work plan, including the extent to which resources assigned to work packages are aligned with project objectives and deliverables.
- Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role.
- Appropriateness of the proposed management structures and governance.

# Evalueringsskriterier

## Quality of research questions, methodology

	Project quality	Impact
1	<b>Originality:</b> <ul style="list-style-type: none"> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation; does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>	<b>Needs justification:</b> <ul style="list-style-type: none"> <li>Target group(s), i.e. patient group(s), carers, other identified users</li> <li>Needs in the specialist health services</li> <li>Filling knowledge gaps</li> <li>Meeting other needs in society</li> </ul>
2	<b>Design of the application:</b> <ul style="list-style-type: none"> <li>Scientific background of the project</li> <li>Overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important for PhD grants) and roles</li> </ul>	<b>Importance of generating new knowledge:</b> <ul style="list-style-type: none"> <li>Realistic importance for the health services, possible improvements of existing offers/practices</li> <li>Importance of new knowledge / filling knowledge gaps, academic impact</li> <li>Impact on society, potential for generalisation / broad use of new knowledge</li> </ul>
3	<b>Feasibility:</b> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistics etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>	<b>Potential for implementation:</b> <ul style="list-style-type: none"> <li>Realistic plans for implementation / translation of research into improved practice</li> <li>Realistic time line for implementation (short/long term)</li> <li>Identified dependencies on development in other areas</li> </ul>
4	<b>Quality of the applicant (relative to career stage):</b> <ul style="list-style-type: none"> <li>Expertise and qualifications</li> <li>Productivity</li> <li>Skills related to project management and supervision</li> <li>Interdependency relative to career stage (particularly important for career fellowship proposals)</li> </ul>	<b>Competence building:</b> <ul style="list-style-type: none"> <li>Gain of knowledge/skills required in the health services</li> <li>Development of methods, techniques</li> <li>Strengthening of the research area</li> </ul>
5	<b>Research environment:</b> <ul style="list-style-type: none"> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators</li> <li>Educational environment, capacity and ability to supervise</li> <li>Cross-disciplinarity if relevant</li> </ul>	<b>Dissemination and visibility:</b> <ul style="list-style-type: none"> <li>Plan for dissemination; publications, articles, web sites etc.</li> <li>Plan for user involvement when relevant knowledge, nationally and internationally</li> <li>Other relevant plans for disseminating new knowledge, nationally and internationally</li> </ul>

Scientific quality
<b>Project design and originality:</b> <ul style="list-style-type: none"> <li>Scientific background of the project, overview of the research front, state-of-the-art, relevant references / literature</li> <li>Description of hypotheses, objectives and milestones</li> <li>Description of positions (particularly important if including PhD grants) and roles</li> <li>Scientific novelty /originality relative to the research front of the subject area</li> <li>Degree of innovation. Does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?</li> </ul>
<b>Feasibility:</b> <ul style="list-style-type: none"> <li>Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistic strength etc.)</li> <li>Identified risks, alternative strategies for conducting the project</li> <li>Data available from pilot projects or other preliminary data where relevant</li> <li>Realistic budgets</li> </ul>
<b>Quality of the applicant and the research environment:</b> <ul style="list-style-type: none"> <li>Expertise, productivity and qualifications</li> <li>Skills related to project management and supervision</li> <li>Infrastructure, access to equipment and resources, necessary/relevant scientific networks</li> <li>Relevant collaborators creating a research environment of capacity</li> <li>Cross-disciplinarity if relevant</li> </ul>
<b>Impact</b>
<b>Needs justification:</b> <ul style="list-style-type: none"> <li>Needs in the specialist health services</li> <li>Target group(s), i.e. patient group(s), carers, other identified users</li> <li>Filling knowledge gaps</li> </ul>
<b>Potential for implementation:</b> <ul style="list-style-type: none"> <li>Realistic plans for implementation / translation of research into improved practice</li> <li>Realistic time line for implementation (short/long term)</li> <li>Identified dependencies on development in other areas, alternative strategies</li> </ul>
<b>Importance of generating new knowledge and competence building:</b> <ul style="list-style-type: none"> <li>Realistic importance for the health services, possible improvements of existing offers/practices</li> <li>Importance of new knowledge / filling knowledge gaps, academic impact</li> <li>Impact on society, potential for generalisation / broad use of new knowledge/methods/procedures</li> </ul>
<b>Mandatory items of the application</b>
<b>Dissemination and visibility:</b> <ul style="list-style-type: none"> <li>Plan for dissemination; publications, articles, web sites etc.</li> <li>Other relevant plans for disseminating new knowledge, nationally and internationally</li> </ul>
<b>Plan for user involvement</b>

### Excellence

**The extent to which the proposed work is ambitious, novel, and goes beyond the state of the art**

- Scientific creativity and originality.
- Novelty and boldness of hypotheses or research questions.
- Potential for development of new knowledge beyond the current state-of-the-art, including significant theoretical, methodological, experimental or empirical advancement.

### The quality of the proposed R&D activities

- Quality of the research questions, hypotheses and project objectives, and the extent to which they are clearly and adequately specified.
- Credibility and appropriateness of the theoretical approach, research design and use of scientific methods. Appropriate consideration of interdisciplinary approaches.
- Where relevant, the extent to which appropriate consideration has been given to ethical issues, safety issues, gender dimension in research content, and appropriate use of stakeholder/user knowledge.

### Impact

#### Potential impact of the proposed research

- The extent to which the planned outputs of the project address important present and/or future scientific challenges.
- If relevant with respect to the project objectives, the extent to which the planned outputs will address UN Sustainable Development Goals or other important present and/or future societal challenges.
- The extent to which the potential impacts are clearly formulated and plausible.

#### Communication and exploitation

Quality and scope of communication and engagement activities with different target audiences, including relevant stakeholders/users.

#### Implementation

##### The quality of the project manager and project group

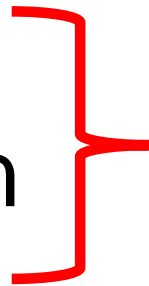
- The extent to which the project manager has relevant expertise and experience, and has demonstrated the ability to perform high-quality research (as appropriate to the career stage).
- The degree of complementarity of the participants and the extent to which the project group as a whole encompasses the expertise needed to undertake the research effectively, and provides added value.

##### The quality of the project organisation and management

- Effectiveness of the work plan, including the extent to which resources assigned to work packages are aligned with project objectives and deliverables.
- Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role.
- Appropriateness of the proposed management structures and governance.

# Nytte

- Pasient
- Samfunn



Sørg for å beskrive begge deler i søknaden!



# Formelle godkjenninger

- Clinical Trials Information System (CTIS)
- Regional Etisk Komite, REK
- Personvernombud
- Lokale forskningsutvalg
- Registrering
  - Eks: [clinicaltrials.gov](http://clinicaltrials.gov)



# Lokale forskningsutvalg

 <b>Diakonhjemmet Sykehus</b> Administrerende Direktør - Forskningsutvalget - Forskning, kvalitet og registre		Dok.id.: EK.13.6.1.3
<b>Forskningsprosjekter - planlegging og gjennomføring</b>		Versjon:5.00
Dokumenttype: Rutine	Fagansvarlig: Forskningsutvalg	Godkjent av: Administrerende direktør Anders Mohn Frafjord
		Gyldig fra: 27.02.2019

Utskrift kun gyldig på utskriftstidspunktet: 26.11.2019

## Endringer siden forrige versjon

**Flere endringer - bl.a. i tråd med registreringssystem for kvalitet og forskningsprosjekter, innføring av personvernombud på sykehuset og trinnvis fremstilling av fremgangsmåte.**

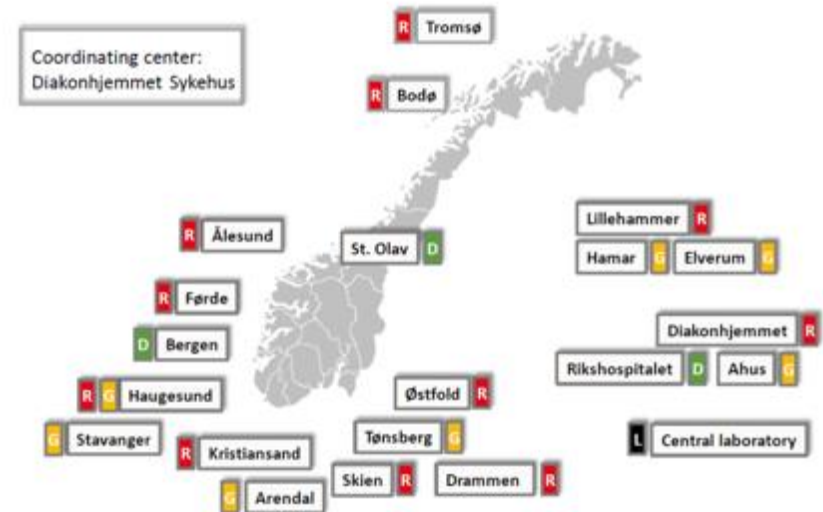
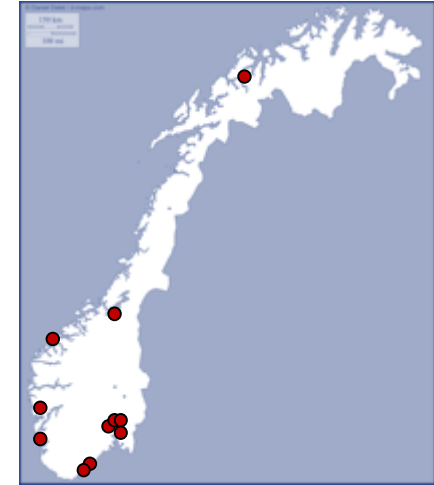
### 1. HENSIKT

Sikre at planlegging, godkjenning og gjennomføring av medisinsk og helsefaglig forskning ved sykehuset skjer i samsvar med krav i lov og forskrifter.

- På koordinerende senter
- På andre studiesentra

# Rekruttering av studiesentre

- **Viktige personer**
  - Avdelingsleder – må være positiv!
  - **Lokal hovedutprøver**
  - Studiesykepleier(e) og studieleger
- **Ressurser og forskningsinfrastruktur**
  - Bildediagnostikk, lab, biobank, apotek, CTU-enhet, monitorer etc
- **Lokale møter for rekruttering av studiesentra**
  - Informasjon
  - Vurdere senteret (motivasjon, personell, ressurser)
  - Mulighet for vitenskapelig samarbeid



# Rekruttering av studiesentre



- Bidra til økt kunnskap
- Meritterende
- Nettverk
- Krydre hverdagen
- Dugnadsånd
- Pasientene
- Penger

- Kapasitet
- Egen forskning på feltet
- Prosjektets relevans

# Vellykket rekruttering av studiesentra

- Vær innstilt på reising. Besøk alle studiesentra
- Sørg for finansiering
- Vitenskapelig samarbeid – medforfatterskap, tilgang til data



# Studiedrift



- Motivasjon
- Senterkontakt
  - Tilgjengelighet
- Nyhetsbrev
- Utprøvermøter
- Datasjekker/regelmessige kontroller av datainnsamlingen
- Samarbeid med monitor/forskningsstøtte
  - Egne monitor-møter

Hvis dere står fast  
«Ring en venn»

Klinisk koordinator REV Guro 90885859  
Klinisk koordinator GASTRO Kristin 99745657  
Klinisk koordinator HUD Øystein 99625945  
Prosjektleder Silje 92040315  
Studiesykepleiere Diakonhjemmet eller AHUS



NOR  
DRUM

## Nyhetsbrev Desember 2019

Vi er stolte og glade over at NOR-DRUM nå har inkludert alle 450 pasienter i NOR-DRUM B. Vi stenger nå inkluderingen. Totalt er 635 pasienter inkludert i NOR-DRUM (I). Tusen takk for strålende innsats, mange av dere har virkelig stått på for å få inn de aller siste!



### Studiestatus

Inkluderte i NOR-DRUM A: 400  
Inkluderte i NOR-DRUM B: 450

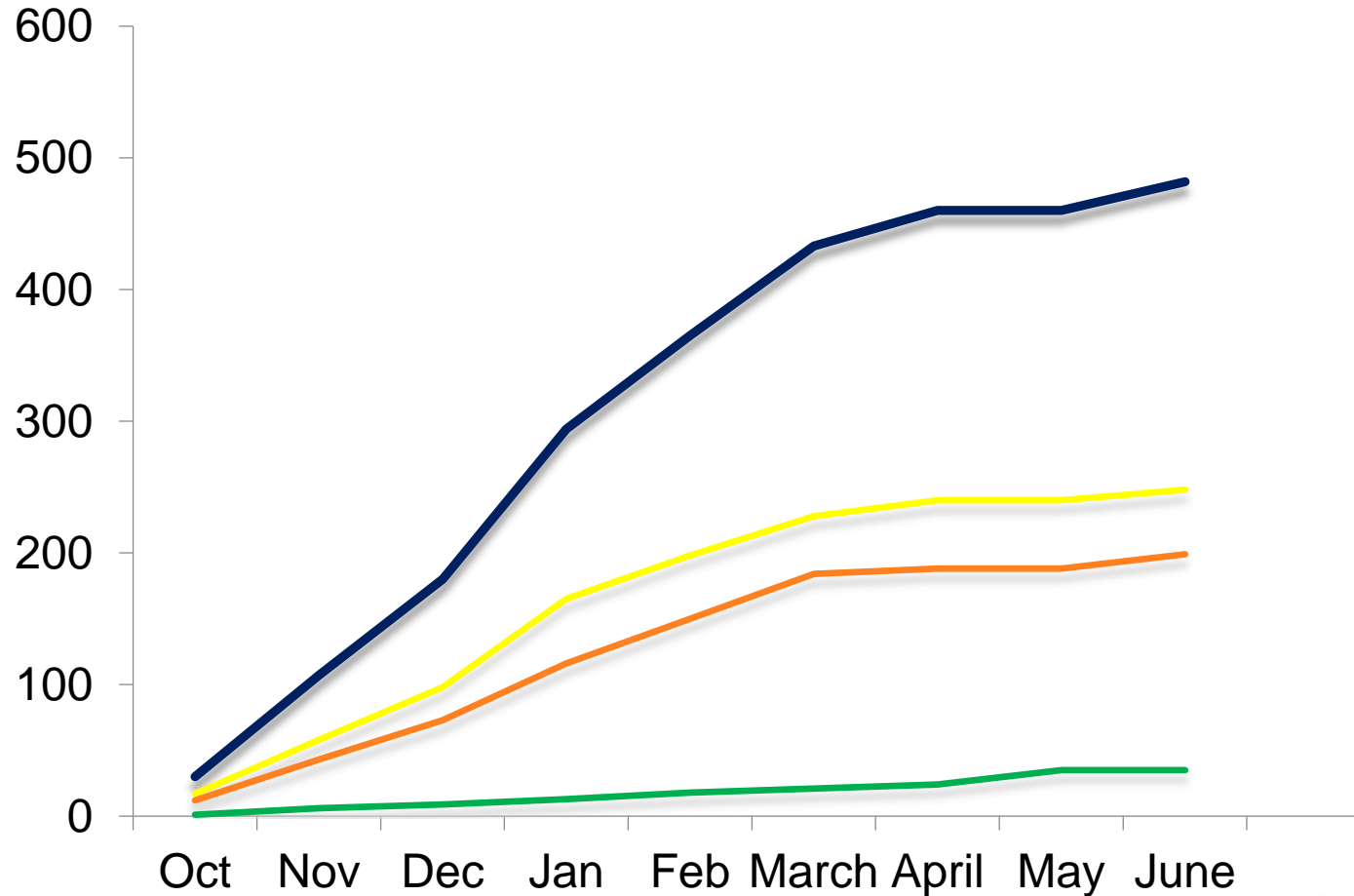
Totalt inkluderte enkeltpasienter i NOR-DRUM: 635

NOR-DRUM B forventes ferdig gjennomført januar 2021. Vi planlegger nå analyser fra A-delen og submittering av abstract til EULAR. Hovedutprøver fra hvert senter vil få informasjon om dette fra januar 2020.

# Rekruttering av deltakere

- Inklusjons- og eksklusjonskriterier
  - Eksisterer disse pasientene ved studiesenteret?
- Skriftlig og muntlig informasjon om studien
  - Muntlig viktigst – avgjørende å informere, motivere og inkludere pasienter, få frem positive sider ved studien, informere om potensiell risiko og skade
  - Finansiering
  - Ingen egenandel for studiespesifikke prosedyrer
  - Kompensasjon for reisekostnader/tid?

# NOR-SWITCH : 2014-2015



482 in total

248 Gastro

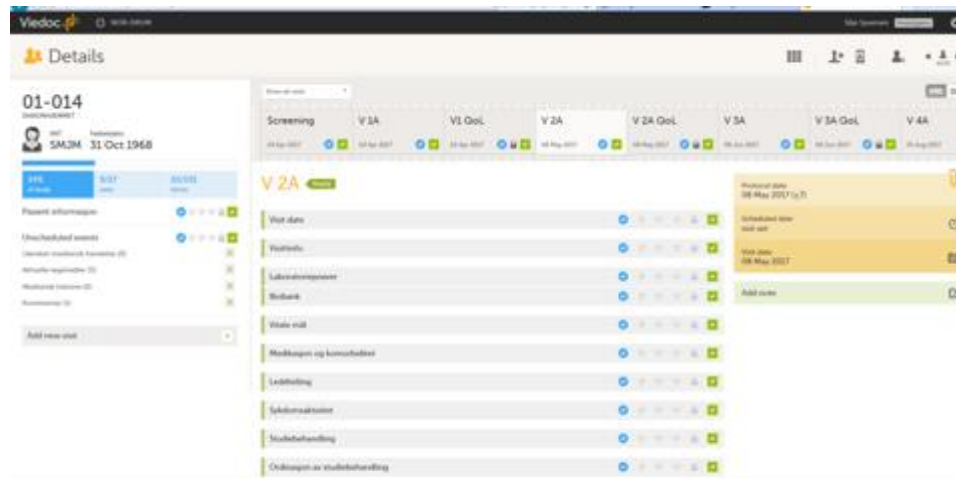
199 Rheuma

35 Derma



# Elektronisk datainnsamling

- Avgjørende for vellykket studie
- God erfaring med Viedoc



© POC Software AS 2017. Terms of Use. Privacy Policy.  
Version 5.24.1430.2016.2017.08.27.19.17.02.11

The screenshot shows the Viedoc ARCTIC interface. The top navigation bar includes "Start page", "Links/Documents", and "Contact". The main header displays "ARCTIC REWIND/prototype" and "Siri Lillegraven, Diakonhjemmet Sykehus AS". The interface features a search bar for patient ID and birth date, with a "Search" button. Below the search bar is a table of patient data.

Patient ID	Patient ID	Fødselsdato	Initialer	Randomisering	Studiearm	Study status	Locked
01-0031*	01-0031	04 Jun 1954	wer	Stabil	TNFI	Ongoing	<no>
01-0032*	01-0032	02 Feb 1955	dd	Nedtrapping	TNFI	Ongoing	<no>
01-0033*	01-0033	04 Mar 1943	dd	Stabil	sDMARD	Withdrawn	<no>
01-0034*	01-0034	23 May 1954	sdf	Nedtrapping	sDMARD	Ongoing	<no>
01-0035*		26 Jul 1961	nl			Withdrawn	<no>
01-0036*	01-0036	02 Feb 1933	dd	Nedtrapping	sDMARD	Ongoing	<no>
01-0037*	01-0037	26 Aug 1960	AKK	Nedtrapping	sDMARD	Ongoing	<no>
01-0038	01-0038	11 Jan 1957	dd	Nedtrapping	sDMARD	Withdrawn	<no>
01-0039*	01-0039	02 Mar 1959	C-G	Stabil	TNFI	Ongoing	<no>
01-0040*	01-0040	01 Jan 1952	TKK	Nedtrapping	sDMARD	Ongoing	<no>

\* the patient is not signed

# Good Clinical Practice (GCP)

- «Internasjonal, etisk, vitenskapelig kvalitetsstandard for design, utførelse, innsamling, dokumentasjon, lagring og rapportering av data i kliniske studier på mennesker»
- Bruk sertifisert elektronisk datainnsamlingsverktøy som legger til rette for GCP
  - Monitorering (pragmatisk)
- GCP-kursing for alt studiepersonell
  - Oppstartsmøte, NorCRIN, onlinekurs



*“Here—go make Daddy’s Fitbit think he’s exercising.”*

# Analyser

- Flink biostatistiker
- Statistisk analyseplan (SAP)
  - Utvikle og signere før databasen «låses»
  - **Predefiner** alle analyser
  - SAP og protokoll submitteres med studiens hovedresultater
  - Prespesifiserte sekundæranalyser
- Oppdater underveis
  - SAP, protokoll og studieregistrering – med samme opplysninger



Statistical Analysis Plan for ARCTIC REWIND, Protocol No. DIA2012-1 / ver 4\_1 Page 1 of 43

ARCTIC REWIND  
REmission in rheumatoid arthritis– assessing Withdrawal of disease-  
modifying antirheumatic drugs in a Non-inferiority Design

Statistical Analysis Plan Final Version 1.1, 18.06.2019  
Analyses of patients who receive synthetic disease modifying antirheumatic drugs

Protocol Identification Number: DIA2012-1 / ver 4\_1  
EudraCT Number: 2012-005275-14



# Publisering: Hovedresultater



- NEJM:
  - Ultrasound in the management of Rheumatoid Arthritis
- Lancet:
  - Ultrasound in the management of rheumatoid arthritis: results from the randomized controlled ARCTIC trial
- BMJ:
  - Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial

<p>1. Einleitung</p> <p>2. Zielsetzung</p> <p>3. Methodik</p> <p>4. Ergebnisse</p> <p>5. Diskussion</p> <p>6. Schlussfolgerungen</p>	<p>7. Literaturverzeichnis</p> <p>8. Anhang</p> <p>9. Zusammenfassung</p> <p>10. Danksagung</p>	<p>11. Einleitung</p> <p>12. Zielsetzung</p> <p>13. Methodik</p> <p>14. Ergebnisse</p> <p>15. Diskussion</p> <p>16. Schlussfolgerungen</p>	<p>17. Einleitung</p> <p>18. Zielsetzung</p> <p>19. Methodik</p> <p>20. Ergebnisse</p> <p>21. Diskussion</p> <p>22. Schlussfolgerungen</p>	<p>23. Einleitung</p> <p>24. Zielsetzung</p> <p>25. Methodik</p> <p>26. Ergebnisse</p> <p>27. Diskussion</p> <p>28. Schlussfolgerungen</p>	<p>29. Einleitung</p> <p>30. Zielsetzung</p> <p>31. Methodik</p> <p>32. Ergebnisse</p> <p>33. Diskussion</p> <p>34. Schlussfolgerungen</p>	<p>35. Einleitung</p> <p>36. Zielsetzung</p> <p>37. Methodik</p> <p>38. Ergebnisse</p> <p>39. Diskussion</p> <p>40. Schlussfolgerungen</p>
<p>41. Einleitung</p> <p>42. Zielsetzung</p> <p>43. Methodik</p> <p>44. Ergebnisse</p> <p>45. Diskussion</p> <p>46. Schlussfolgerungen</p>	<p>47. Einleitung</p> <p>48. Zielsetzung</p> <p>49. Methodik</p> <p>50. Ergebnisse</p> <p>51. Diskussion</p> <p>52. Schlussfolgerungen</p>	<p>53. Einleitung</p> <p>54. Zielsetzung</p> <p>55. Methodik</p> <p>56. Ergebnisse</p> <p>57. Diskussion</p> <p>58. Schlussfolgerungen</p>	<p>59. Einleitung</p> <p>60. Zielsetzung</p> <p>61. Methodik</p> <p>62. Ergebnisse</p> <p>63. Diskussion</p> <p>64. Schlussfolgerungen</p>	<p>65. Einleitung</p> <p>66. Zielsetzung</p> <p>67. Methodik</p> <p>68. Ergebnisse</p> <p>69. Diskussion</p> <p>70. Schlussfolgerungen</p>	<p>71. Einleitung</p> <p>72. Zielsetzung</p> <p>73. Methodik</p> <p>74. Ergebnisse</p> <p>75. Diskussion</p> <p>76. Schlussfolgerungen</p>	<p>77. Einleitung</p> <p>78. Zielsetzung</p> <p>79. Methodik</p> <p>80. Ergebnisse</p> <p>81. Diskussion</p> <p>82. Schlussfolgerungen</p>
<p>83. Einleitung</p> <p>84. Zielsetzung</p> <p>85. Methodik</p> <p>86. Ergebnisse</p> <p>87. Diskussion</p> <p>88. Schlussfolgerungen</p>	<p>89. Einleitung</p> <p>90. Zielsetzung</p> <p>91. Methodik</p> <p>92. Ergebnisse</p> <p>93. Diskussion</p> <p>94. Schlussfolgerungen</p>	<p>95. Einleitung</p> <p>96. Zielsetzung</p> <p>97. Methodik</p> <p>98. Ergebnisse</p> <p>99. Diskussion</p> <p>100. Schlussfolgerungen</p>	<p>101. Einleitung</p> <p>102. Zielsetzung</p> <p>103. Methodik</p> <p>104. Ergebnisse</p> <p>105. Diskussion</p> <p>106. Schlussfolgerungen</p>	<p>107. Einleitung</p> <p>108. Zielsetzung</p> <p>109. Methodik</p> <p>110. Ergebnisse</p> <p>111. Diskussion</p> <p>112. Schlussfolgerungen</p>	<p>113. Einleitung</p> <p>114. Zielsetzung</p> <p>115. Methodik</p> <p>116. Ergebnisse</p> <p>117. Diskussion</p> <p>118. Schlussfolgerungen</p>	<p>119. Einleitung</p> <p>120. Zielsetzung</p> <p>121. Methodik</p> <p>122. Ergebnisse</p> <p>123. Diskussion</p> <p>124. Schlussfolgerungen</p>
<p>125. Einleitung</p> <p>126. Zielsetzung</p> <p>127. Methodik</p> <p>128. Ergebnisse</p> <p>129. Diskussion</p> <p>130. Schlussfolgerungen</p>	<p>131. Einleitung</p> <p>132. Zielsetzung</p> <p>133. Methodik</p> <p>134. Ergebnisse</p> <p>135. Diskussion</p> <p>136. Schlussfolgerungen</p>	<p>137. Einleitung</p> <p>138. Zielsetzung</p> <p>139. Methodik</p> <p>140. Ergebnisse</p> <p>141. Diskussion</p> <p>142. Schlussfolgerungen</p>	<p>143. Einleitung</p> <p>144. Zielsetzung</p> <p>145. Methodik</p> <p>146. Ergebnisse</p> <p>147. Diskussion</p> <p>148. Schlussfolgerungen</p>	<p>149. Einleitung</p> <p>150. Zielsetzung</p> <p>151. Methodik</p> <p>152. Ergebnisse</p> <p>153. Diskussion</p> <p>154. Schlussfolgerungen</p>	<p>155. Einleitung</p> <p>156. Zielsetzung</p> <p>157. Methodik</p> <p>158. Ergebnisse</p> <p>159. Diskussion</p> <p>160. Schlussfolgerungen</p>	



# Viktig å tenke på: Sekundære analyser

EXTENDED REPORT

**First step in the development of an ultrasound joint inflammation score for rheumatoid arthritis using a data-driven approach**

ARD

Anna-Birgitte Aga,<sup>1</sup> Hilde Berner Hammer,<sup>1</sup> Inge Christoffer Olsen,<sup>1</sup> Till Uhlig,<sup>1</sup> Tore K Kvien,<sup>1</sup> Désirée van der Heijde,<sup>1,2</sup> Hallvard Fremstad,<sup>3</sup> Tor Magne Madland,<sup>4</sup> Åse Stavland Lexberg,<sup>5</sup> Hilde Haukeland,<sup>6</sup> Erik Rodevand,<sup>7</sup> Christian Hoitl,<sup>8</sup> Hilde Stray,<sup>9</sup> Anne Noraas Bendvold,<sup>10</sup> Dag Magnar Soldal,<sup>11</sup> Gunnstein Bakland,<sup>12,13</sup> Elisabeth Lie,<sup>1</sup> Espen A Haavardsholm<sup>1</sup>

*Ann Rheum Dis* 2016;**75**:1444–1451.

Concise report

**Development of a feasible and responsive ultrasound inflammation score for rheumatoid arthritis through a data-driven approach**

RMD Open

Anna-Birgitte Aga,<sup>1</sup> Hilde Berner Hammer,<sup>1</sup> Inge Christoffer Olsen,<sup>1</sup> Till Uhlig,<sup>1</sup> Tore K Kvien,<sup>1</sup> Désirée van der Heijde,<sup>1</sup> Hallvard Fremstad,<sup>3</sup> Tor Magne Madland,<sup>4</sup> Åse Stavland Lexberg,<sup>5</sup> Hilde Haukeland,<sup>6</sup> Erik Rodevand,<sup>7</sup> Christian Hoitl,<sup>8</sup> Hilde Stray,<sup>9</sup> Anne Lindner Noraas,<sup>10</sup> Inger Johanne Widding Hansen,<sup>11</sup> Gunnstein Bakland,<sup>12,13</sup> Siri Lillegraven,<sup>1</sup> Elisabeth Lie,<sup>1</sup> and Espen A Haavardsholm<sup>1</sup>

BMJ | *RMD Open* 2016;**2**:e000325. doi:10.1136/rmdopen-2016-000325 | eular

## RHEUMATOLOGY

### Original article

doi:10.1093/rheumatology/key202

#### Predictors of sustained remission in patients with early rheumatoid arthritis treated according to an aggressive treat-to-target protocol

Nina Paulshus Sundlisæter<sup>1,2</sup>, Inge C. Olsen<sup>3</sup>, Anna-Birgitte Aga<sup>1</sup>, Hilde B. Hammer<sup>1</sup>, Till Uhlig<sup>1</sup>, Désirée van der Heijde<sup>1,4</sup>, Tore K. Kvien<sup>1</sup>, Siri Lillegraven<sup>1,5\*</sup> and Espen A. Haavardsholm<sup>1,2,6\*</sup>; the ARCTIC study group<sup>†</sup>

## RMD Open

Rheumatic & Musculoskeletal Diseases

### ORIGINAL ARTICLE

#### Comparing the disease course of patients with seronegative and seropositive rheumatoid arthritis fulfilling the 2010 ACR/EULAR classification criteria in a treat-to-target setting: 2-year data from the ARCTIC trial

Lena Bugge Nordberg,<sup>1,2</sup> Siri Lillegraven,<sup>1</sup> Anna-Birgitte Aga,<sup>1</sup> Joseph Sexton,<sup>1</sup> Inge Christoffer Olsen,<sup>1,3</sup> Elisabeth Lie,<sup>1</sup> Hilde Berner Hammer,<sup>1</sup> Till Uhlig,<sup>1</sup> Désirée van der Heijde,<sup>1,4</sup> Tore K Kvien,<sup>1</sup> Espen A Haavardsholm<sup>1,2</sup>

To cite: Nordberg LB.

### CONCISE REPORT

#### Clinical and ultrasound remission after 6 months of treat-to-target therapy in early rheumatoid arthritis: associations to future good radiographic and physical outcomes

Nina Paulshus Sundlisæter,<sup>1,2</sup> Anna-Birgitte Aga,<sup>1</sup> Inge Christoffer Olsen,<sup>3</sup> Hilde Berner Hammer,<sup>1</sup> Till Uhlig,<sup>1</sup> Désirée van der Heijde,<sup>1,4</sup> Tore K Kvien,<sup>1</sup> Siri Lillegraven,<sup>1</sup> Espen A Haavardsholm,<sup>1,2</sup> the ARCTIC study group



Full Length | Full Access

#### The impact of ultrasound on the use and efficacy of intra-articular glucocorticoid injections in early rheumatoid arthritis: Secondary analyses from the randomised ARCTIC trial

Lena B. Nordberg, Siri Lillegraven, Anna-Birgitte Aga, Joe Sexton, Elisabeth Lie, Hilde B. Hammer, Inge C. Olsen, Till Uhlig, Désirée van der Heijde, Tore K. Kvien, Espen A. Haavardsholm

First published: 25 March 2018 | <https://doi.org/10.1002/art.40494>

### CONCISE REPORT

#### Patients with seronegative RA have more inflammatory activity compared with patients with seropositive RA in an inception cohort of DMARD-naïve patients classified according to the 2010 ACR/EULAR criteria

Lena Bugge Nordberg,<sup>1</sup> Siri Lillegraven,<sup>1</sup> Elisabeth Lie,<sup>1</sup> Anna-Birgitte Aga,<sup>1</sup> Inge Christoffer Olsen,<sup>1</sup> Hilde Berner Hammer,<sup>1</sup> Till Uhlig,<sup>1</sup> Maria Karolina Jonsson,<sup>1,2</sup> Désirée van der Heijde,<sup>1,3</sup> Tore K Kvien,<sup>1</sup> Espen Andre Haavardsholm,<sup>1</sup> and the ARCTIC working group

## RMD Open

Rheumatic & Musculoskeletal Diseases

### ORIGINAL ARTICLE

#### Comparative analyses of responsiveness between the Rheumatoid Arthritis Impact of Disease score, other patient-reported outcomes and disease activity measures: secondary analyses from the ARCTIC study

Karen Hotten,<sup>1,2</sup> Joseph Sexton,<sup>1</sup> Tore K Kvien,<sup>1,2</sup> Anna-Birgitte Aga,<sup>1</sup> Espen A Haavardsholm<sup>1,2</sup>

#### Conventional versus ultrasound treat to target: no difference in magnetic resonance imaging inflammation or joint damage over 2 years in early rheumatoid arthritis

Ulf Sundin, Anna-Birgitte Aga, Øivind Skare, Lena B Nordberg, Till Uhlig, Hilde B Hammer, Désirée van der Heijde, Tore K Kvien, Siri Lillegraven, Espen A Haavardsholm ... Show more

*Rheumatology*, kez674, <https://doi.org/10.1093/rheumatology/kez674>

Published: 30 January 2020 | Article history ▼

Research Article | OMERACT 2018: International Consensus Conference on Outcome Measures in Rheumatology, Terrasil, Australia, May 2018 Special Interest Groups, Part 1

#### Validity and Responsiveness of Combined Inflammation and Combined Joint Damage Scores Based on the OMERACT Rheumatoid Arthritis MRI Scoring System (RAMRIS)

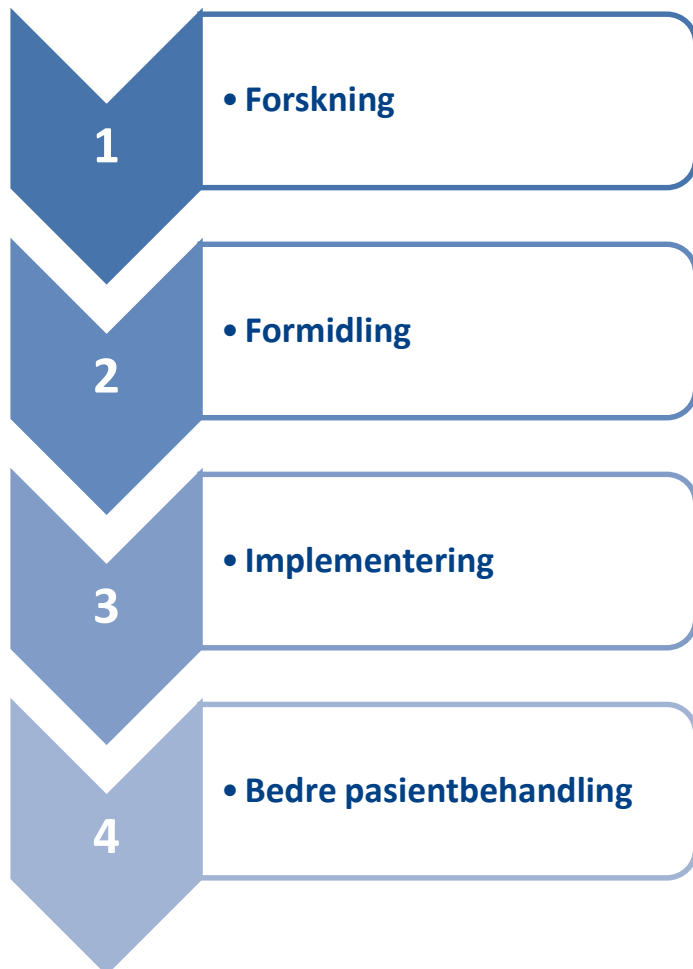
Ulf Sundin, Mikkel Ostergaard, Daniel Glinatsi, Anna-Birgitte Aga, Kim Hørslev-Petersen, Merete L. Hetland, Kristian Stengard-Pedersen, Peter Junker, Bo J. Eijbjerg, Paul Bird, Philip G. Conaghan, Siri Lillegraven and Espen A. Haavardsholm

*The Journal of Rheumatology* September 2019, 46 (9): 1222-1227; DOI: <https://doi.org/10.3899/jrheum.181064>

# Forfatterskap/vitenskapelig samarbeid

- Hovedpublikasjon vs sekundære publikasjoner
  - Legge til rette for at lokale hovedutprøvere har naturlig rolle som medforfattere
- Studiegruppe med PubMed-kreditering
- Nytt av internasjonale medforfattere
  - Både i tidlig og sen fase av studien
  - Fortolkning resultater
  - Implementering

# Vellykket klinisk studie



- Egenfinansiering (EU/NORDFORSK/NFR etc)
- Forskerutdanning (PhD/Post.doc)
- Internasjonal forskningsfront - flaggskip
- Mobilitet av forskere/nettverk
- Innovasjon/patenter

- Publikasjoner på høyt nivå/riktig målgruppe
- Delta i samfunnsdebatt
- Kunnskapsgrunnlag for politiske beslutninger
- Formidling på internasjonale kongresser
- Pasienttidsskrifter/møter/web/sosiale medier

- Samhandling med pasienter/brukere
- Prosedyrer (lokale/nasjonale)
- Retningslinjer (nasjonale/internasjonale)
- Kommersialisering/verdiskapning

- Burden-of-disease
- Mortalitet/morbiditet
- Livskvalitet
- Fysisk funksjon
- Arbeidslivsdeltakelse
- Sosial fungering



# Er kliniske studier verdt innsatsen?

Kliniske studier skal besvare spørsmål som:

- Virker en behandling?
- Virker behandlingen bedre enn andre behandlinger?
- Har den bivirkninger?
- Er behandlingen kostnadseffektiv?

**Resultatene fra en vellykket klinisk studie bør endre klinisk praksis – da er det verdt innsatsen å gjennomføre studien!**



# Oppsummering

- Problemstilling
  - **Må være klart definert**
- Klinisk relevans/pasientgrunnlag/nytteverdi
  - **Endre klinisk praksis**
- Forankring i sykehuset
  - **Følge lokale prosedyrer**
- Ressurser (personale, tid)
  - **Planlegg nøye**
- Forankring i klinikken
  - **Involver klinikere, sykepleiere, sekretærer, lab, rtg etc.**
- Forfatterskap/vitenskapelig samarbeid
  - **Avklare tidlig vs. sent**
  - **Krav fra finansieringskilde?**
- Prosjektskisse
  - **Synopsis – fint utgangspunkt**
  - **Skille mellom prosjektsøknad og full protokoll**

# Takk for oppmerksomheten!

