

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

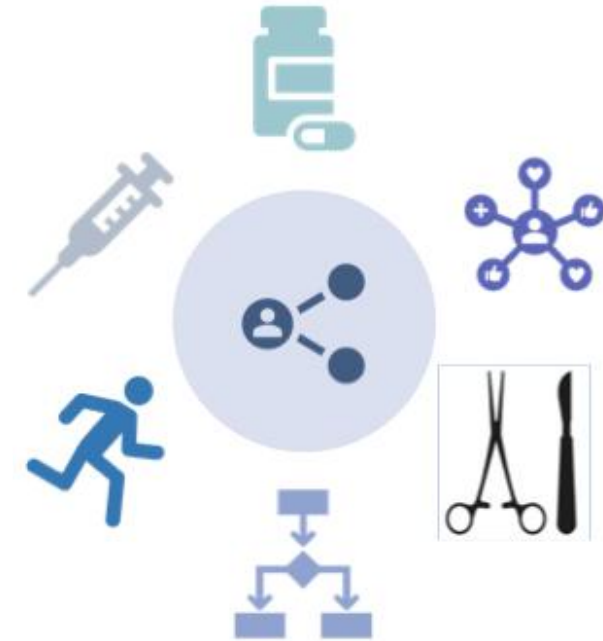
- Eksempler – fra ide til protokoll
- Problemstilling
 - Klinisk relevans
 - Pasientgrunnlag
 - Nytteverdi
- Praktisk ved prosjektstart
 - Forankring i sykehuset og i klinisk drift
 - Ressurser (personale, tid)
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Forskningsmiljø

- 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

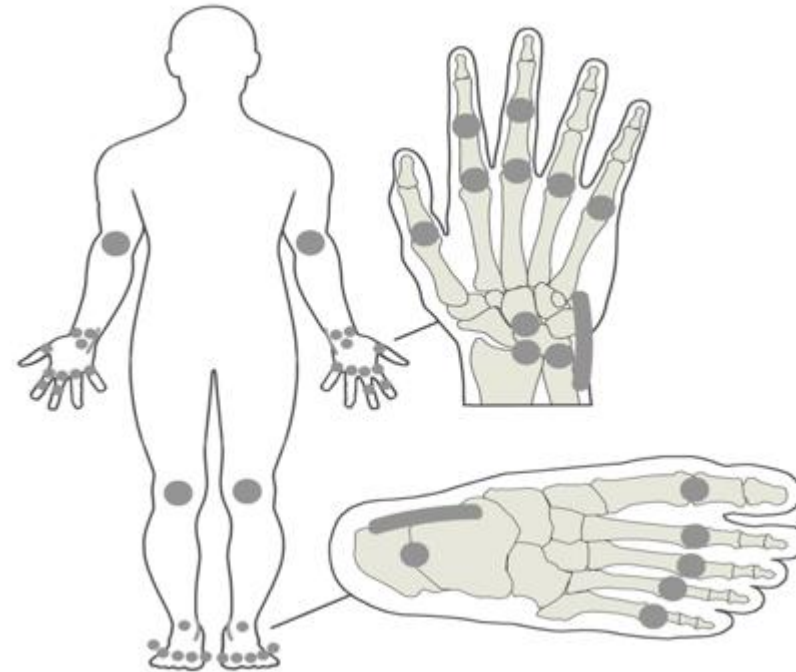


Randomized clinical trial assessing the effectiveness of targeting infliximab treatment by therapeutic drug monitoring versus routine care



Eksempel: Ide

- **2000-tallet:** Ultralyd øker i bruk i revmatologisk praksis
- Studier viser sammenheng mellomsubklinisk 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 regimen¹
 - N=230
 - Inklusjon 2010-2013
- Pasientert randomisert til en av to behandlingsstrategier:
 - Målstyre behandlingen med ultralydinformasjon
 - Målstyre behandling basert på konvensjonelle sykdomsaktivitetsmål
- Strategistudie = sammenligner to behandlingsstrategier, ikke to medikamenter

ARCTIC studiegruppe

Local Pls

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

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

Diakonhjemmet Hospital (coordinating center)

ARCTIC-studien

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

Espen A Haavardsholm,¹ Anna-Birgitte Aga,¹ Inge Christoffer Olsen,¹ Siri Lillegraven,¹ Hilde B Hammer,¹ Till Uhlig,¹ Hallvard Fremstad,² Tor Magne Madland,³ Åse Stavland Lexberg,⁴ Hilde Haukeland,⁵ Erik Rødevand,⁶ Christian Høili,⁷ Hilde Stray,⁸ Anne Noraas,⁹ Inger Johanne Widding Hansen,¹⁰ Gunnstein Bakland,^{11,12} Lena Bugge Nordberg,¹ Désirée van der Heijde,^{1,13} Tore K Kvien¹

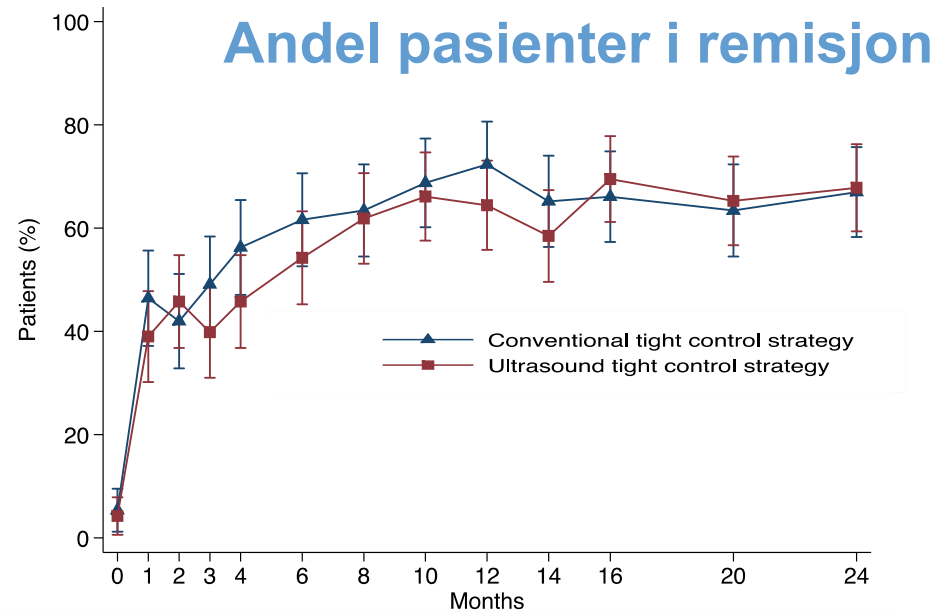
thebmj | BMJ 2016;354:i4205 | doi: 10.1136/bmj.i4205



Diakonhjemmet Hospital



Erfaringer fra gjennomført klinisk studie



– Resultatene er helt oppsiktsvekkende

Aggressiv medisinerer endrer behandling av leddgikt.

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RESEARCH

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

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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



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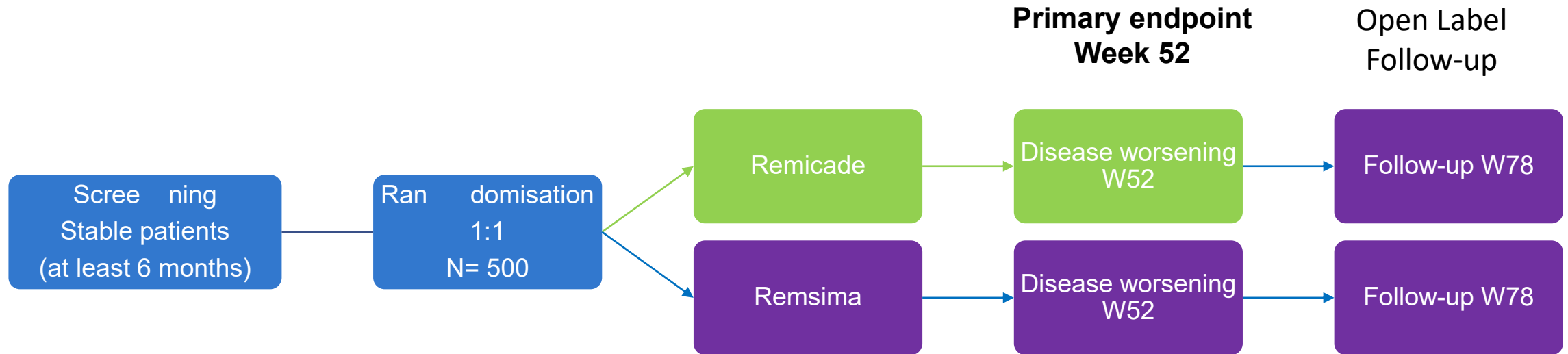
Eksempel Ide 2: Kan vi bytte til biotilsvarende legemidler?

- **2015**
 - Patentet utløper på infliximab
 - Biotilsvarende infliximab blir tilgjengelig
- Hva er biotilsvarende legemidler?
 - 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 infliximab-behandling i minst 6 måneder
- Sekundærmål:
 - Safety
 - Immunogenisitet

NOR- SWITCH Study design



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

Studiesentre



Resultater: Sykdomsforverring

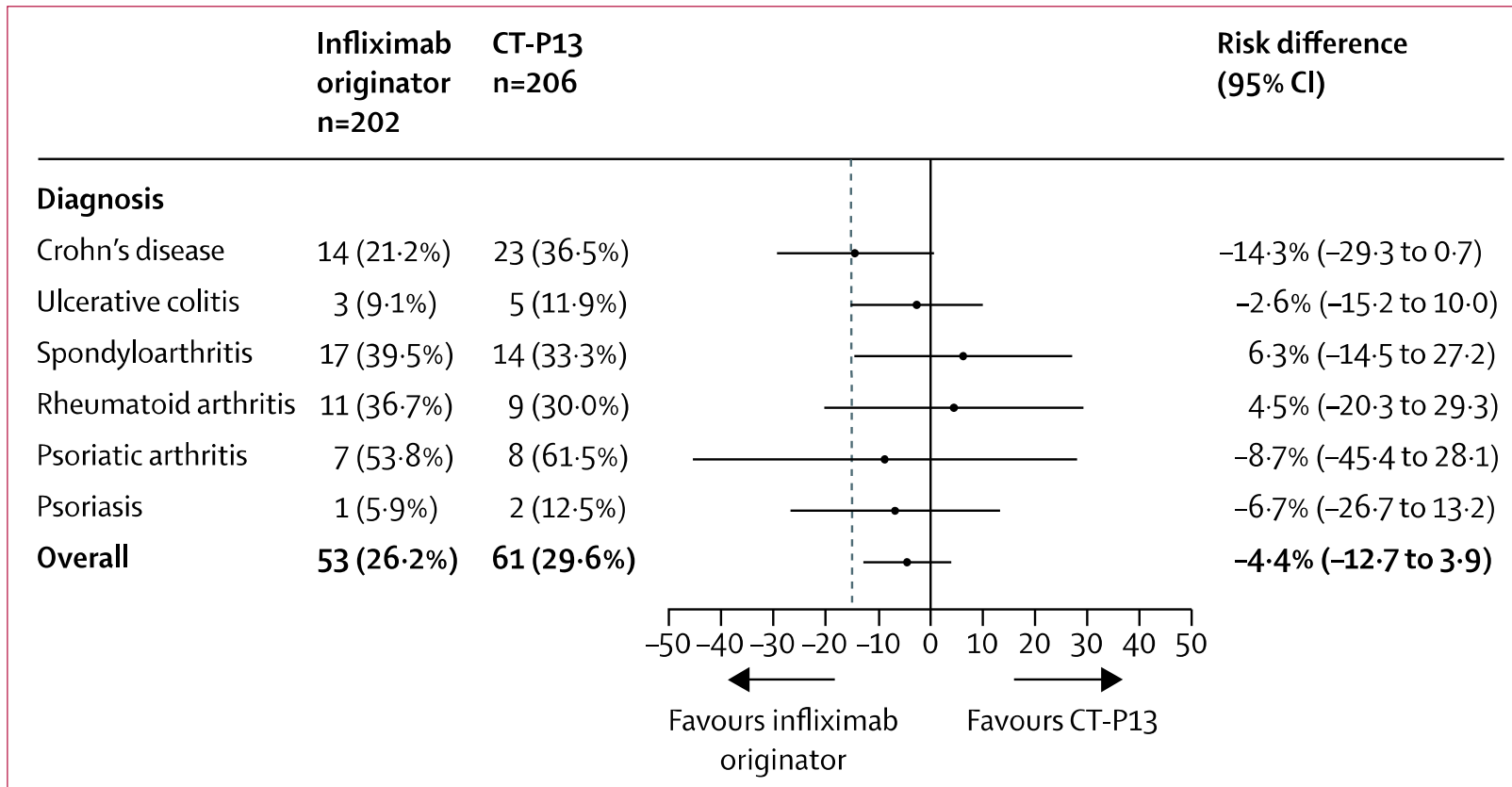


Figure 2: Forest plot of risk difference according to disease

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

"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 1282

Articles

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

Articles

Isakzumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors
See page 2312

Series

Targeted treatments for rheumatoid arthritis
See pages 1318 and 1319

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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



VARSLUM MED GENERALISERING – Etter vårt skjønn, må vi være forsiktige 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 BYTTSTUDIEN

– 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. – Byttstudien 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

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Eksempel 3

Nedtrapppping 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

Studiedesign ARCTIC REWIND

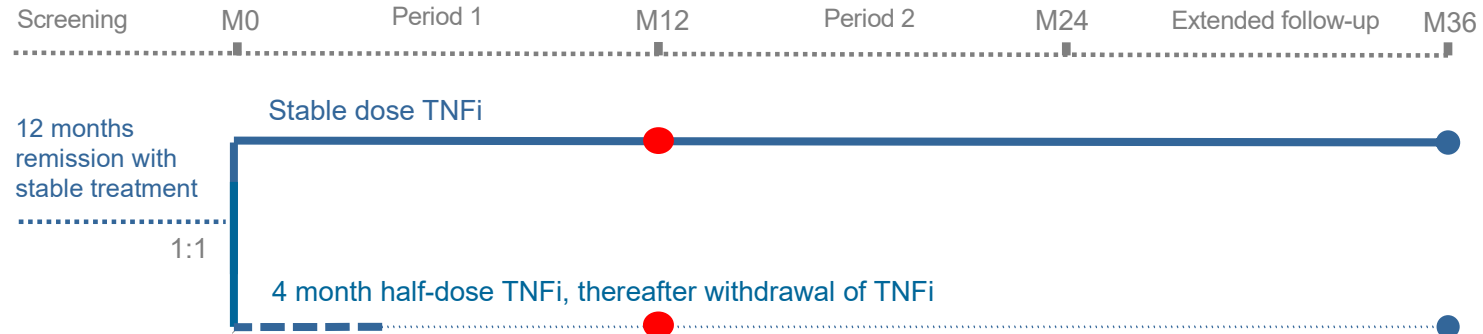
- To randomisert kontrollerte non-inferiority multistudier
 - Fullfinansiert av Helse Sør-Øst og Forskningsrådet
- RA diagnose
 - I henhold til etablerte kriterier
- Remisjon (ingen eller svært få tegn til sykdomsaktivitet)
 - I minst 12 måneder
 - Ved inklusjon ingen artritt i 44 undersøkte ledd
- Stabil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

ARCTIC REWIND csDMARD RCT

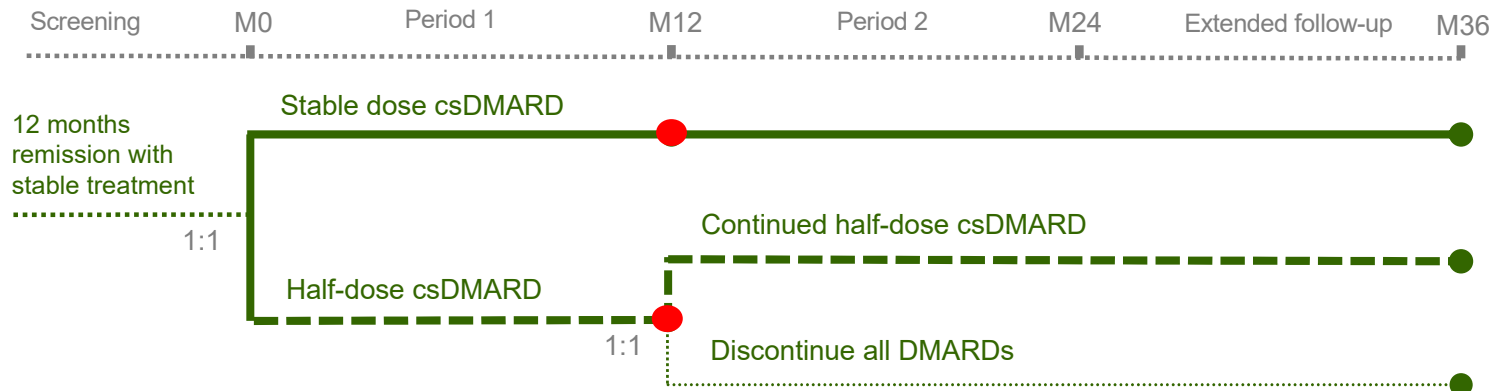
ARCTIC REWIND TNFi RCT

ARCTIC REWIND

ARCTIC REWIND TNFi



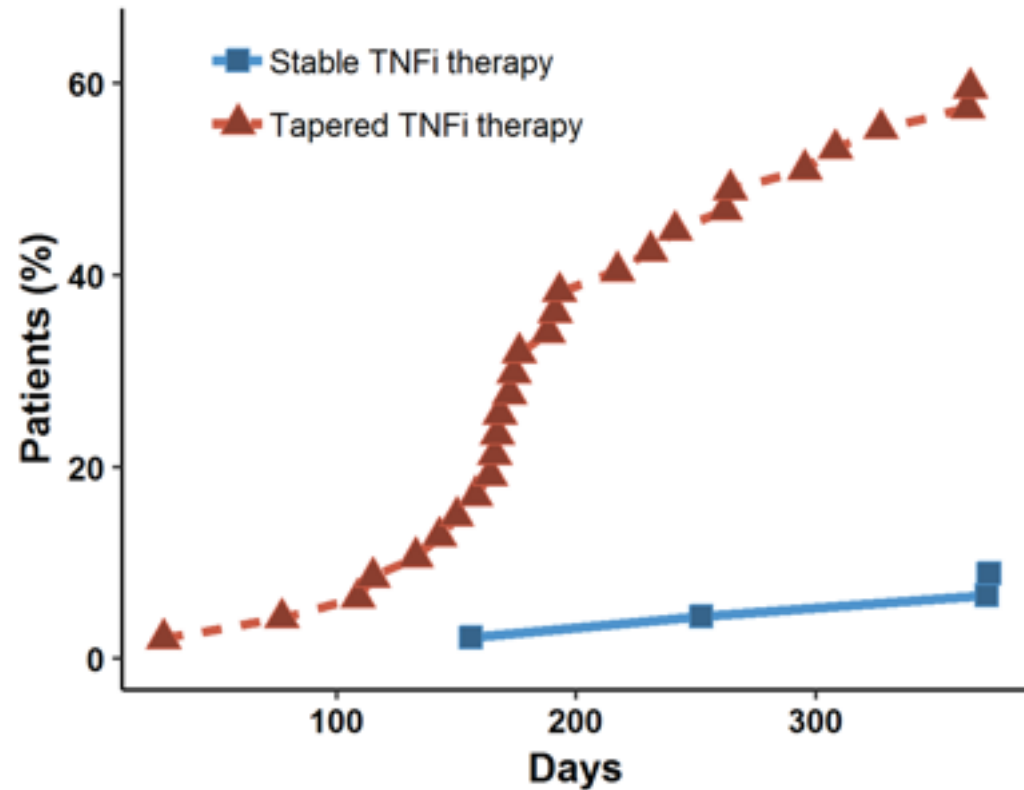
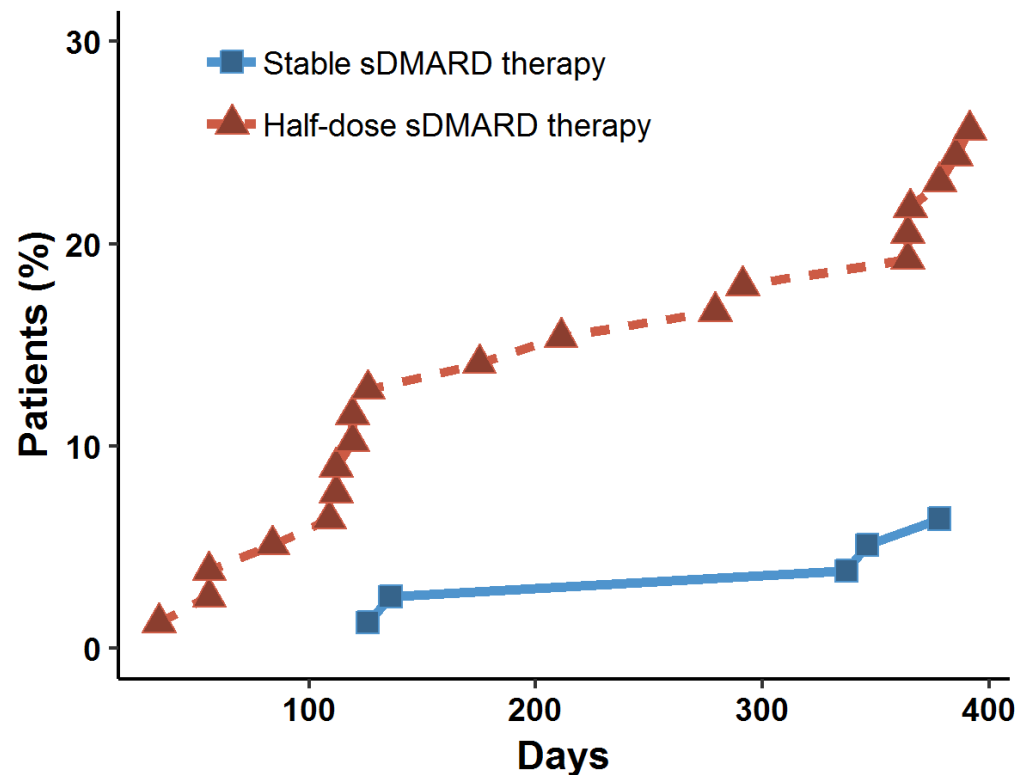
ARCTIC REWIND csDMARD



● Primary endpoint

Hovedresultater

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



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



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

Annals of the
Rheumatic Diseases

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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, PhD¹; Nina Paulshus Sundlisæter, MD, PhD¹; Anna-Birgitte Aga, MD, PhD¹; Joseph Sexton, PhD¹; Daniel H. Solomon, MD, MPH²; Désirée van der Heijde, MD, PhD³; Espen A. Haavardsholm, MD, PhD¹

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

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

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!

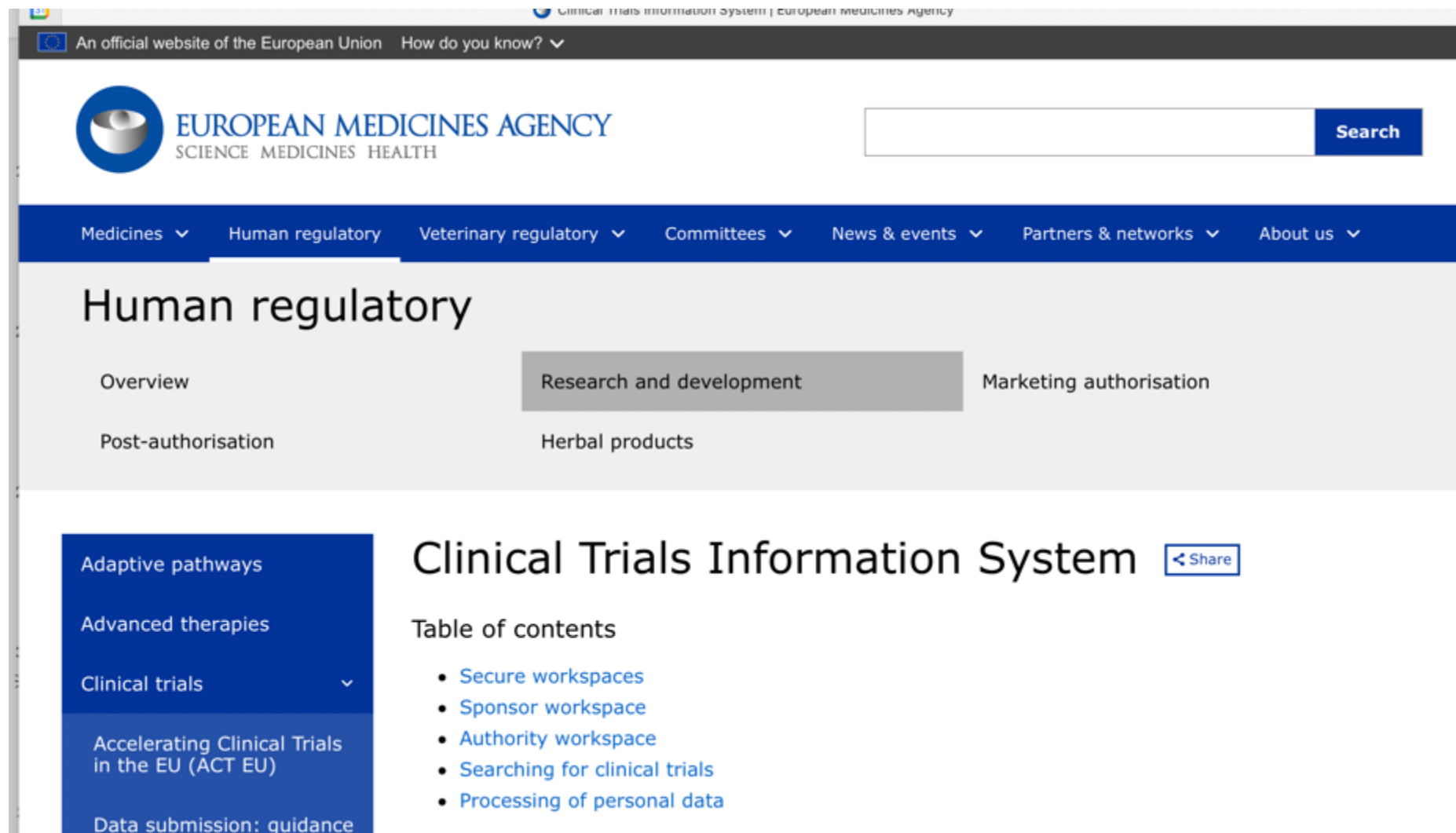
Innhold

- Eksempler – fra ide til protokoll
- **Problemstilling**
 - Klinisk relevans
 - Pasientgrunnlag
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- 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 EMA website with the following elements:

- Header:** "An official website of the European Union" and "How do you know?" dropdown.
- Logo:** European Medicines Agency (EMA) logo with the tagline "SCIENCE MEDICINES HEALTH".
- Search:** A search bar with a "Search" button.
- Navigation Menu:** Medicines, Human regulatory, Veterinary regulatory, Committees, News & events, Partners & networks, About us.
- Human regulatory section:** Overview, Research and development (highlighted), Marketing authorisation, Post-authorisation, Herbal products.
- Clinical Trials Information System:** A section with a "Share" button and a "Table of contents" list.
- Left sidebar:** Adaptive pathways, Advanced therapies, Clinical trials (selected), 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 so we can correct them as soon as possible.

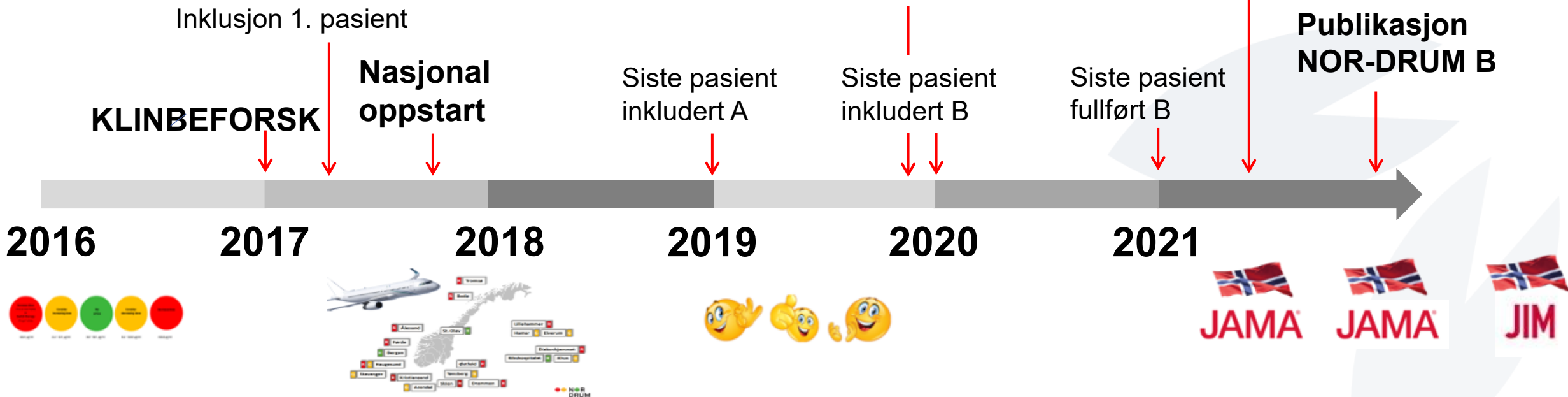
Pasientgrunnlag

- 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**
-
- The diagram uses blue curly braces to group tasks and indicate their duration. The first two phases (Early phase and Study decided and started) are grouped together with a duration of 1-2 years. The third phase (Active phase) has a duration of 1-5 years. The fourth phase (Results) has a duration of 6-12 months. The final phase (Extension, publication of secondary goals) is listed without a specific duration.
- 1-2 år
- 1-5 år
- 6-12 mnd.

- **Tidlig fase**
 - Definere forskningsspørsmål/hypotese
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- **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

Career fellowship - Lillegraven

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.

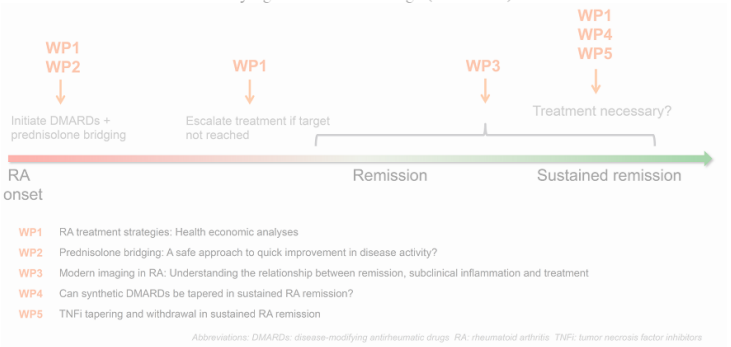


Figure 1: Conceptual illustration of the project

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].

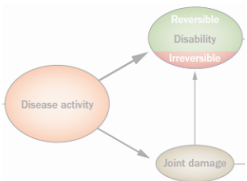


Figure 2: Disease activity, disability and joint damage in early RA [2]

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

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

A NORwegian multicentre randomised controlled trial assessing the effectiveness of tailoring infliximab treatment by therapeutic DRUG Monitoring	
The NOR-DRUM study	
	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	
SPONSOR:	Diakonhjemmet Hospital AS Contact person: Karin Hesseberg, PhD Box 23 Vinderen, 0319 Oslo Tel : 22 45 15 00 E-mail: karin.hesseberg@diakonsyk.no
PRINCIPAL INVESTIGATOR:	Professor Espen A. Haavardsholm, MD PhD 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	
	

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
1 INTRODUCTION.....	17
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
2 STUDY OBJECTIVES.....	22
2.1 Main study objective.....	22
2.2 Primary objectives.....	22
2.3 Secondary objectives and exploratory objectives.....	22
3 STUDY ENROLMENT AND WITHDRAWAL.....	23
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
4 INVESTIGATIONAL PLAN.....	26
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
5 STUDY PROCEDURES AND SCHEDULE.....	43
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
6 ASSESSMENTS.....	47
6.1 Ordinary laboratory Tests.....	47
6.2 Biobank samples.....	47
6.3 Immunogenicity and Serum Drug Concentration Assessments.....	47

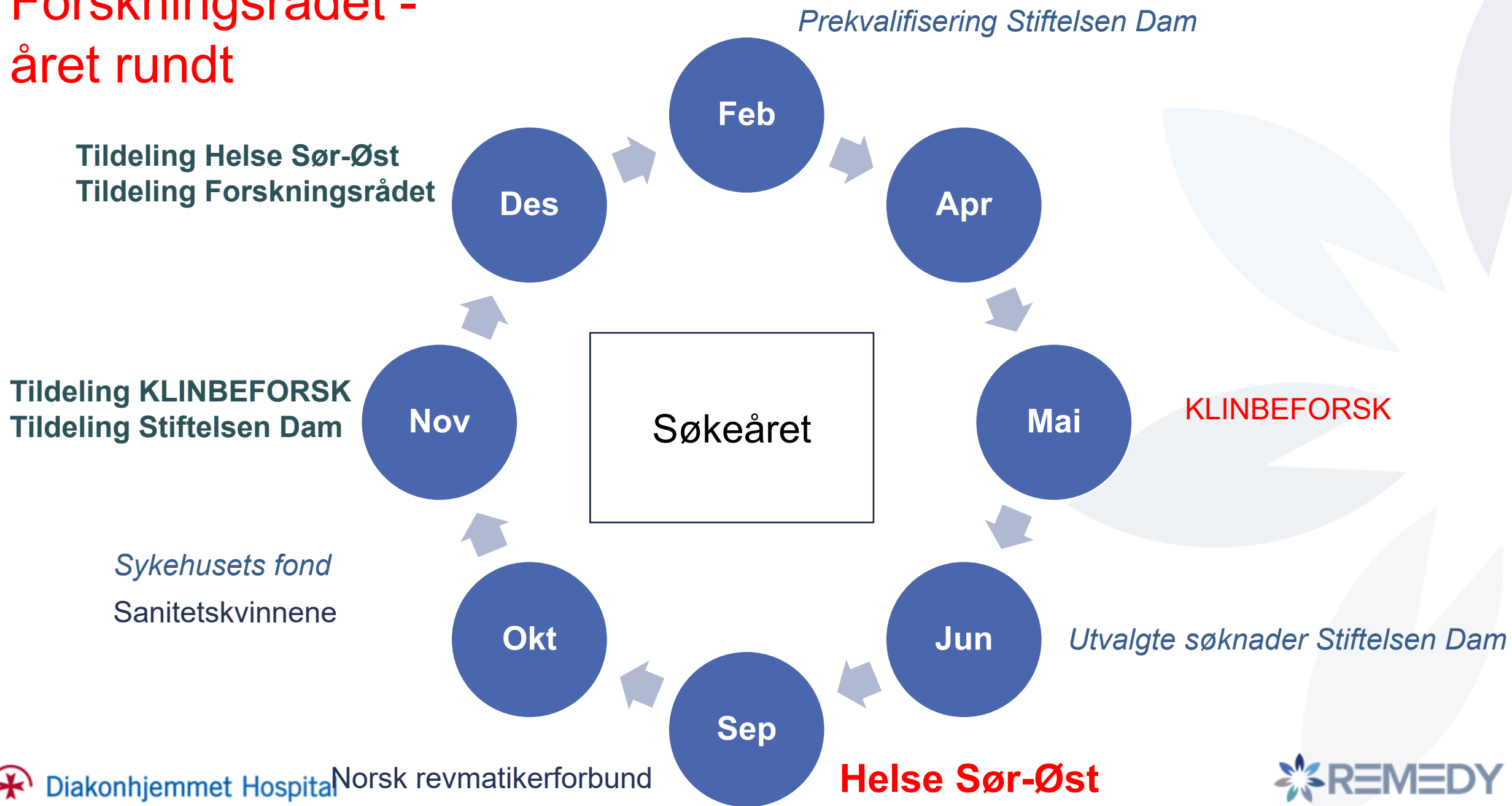
6.4 Safety and Tolerability Assessments.....	48
6.4.1 Vital signs.....	48
6.5 Assessments of efficacy.....	48
6.5.1 General efficacy assessments.....	48
6.5.2 Disease specific efficacy assessments: RA, PsA.....	48
6.5.3 Disease specific efficacy assessments: SpA.....	49
6.5.4 Disease specific efficacy 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
7 SAFETY MONITORING AND REPORTING.....	55
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
8 DATA MANAGEMENT.....	57
8.1 Electronic Case Report Forms (CRFs).....	57
8.2 Source Data.....	57
8.3 Confidentiality.....	58
9 STATISTICAL METHODS AND DATA ANALYSIS.....	58
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
10 STUDY MANAGEMENT.....	64
10.1 Investigator Delegation Procedure.....	64
10.2 Protocol Adherence.....	64
10.3 Study Amendments.....	64
11 ETHICAL REQUIREMENTS.....	64
11.1 Ethics Committee Approval.....	64
11.2 Other Regulatory Approvals.....	65
11.3 Informed Consent Procedure.....	65
11.4 Subject Identification.....	65
12 TRIAL SPONSORSHIP AND FINANCING.....	65
13 PUBLICATION POLICY.....	66
14 REFERENCES.....	66
15 APPENDICES.....	70

Ressurser

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

Forskningsrådet - året rundt



Helse Sør-Øst 2024

Tabell 3. Antall søknader innstilt til støtte per søknadskategori – åpen tematisk utlysning, prioriterte områder og midler til ikke-universitetssykehus.

Søknadskategori	Antall vurderte søknader	Antall innstilte søknader	Beløp - tusen kroner
Doktorgradsstipend	205	31	34 081
Postdoktorstipend	101	18	20 109
Åpen prosjektstøtte	159	37	94 986
Totalt	465	86	149 176

15,1%

17,8%

23,3%

KLINBEFORSK

Antall pågående studier koordinert i hver helseregion og totalt antall vurderte søknader per helseregion i perioden 2016–2023

Helseregion	Antall regionalt koordinerte studier	Totalt antall vurderte søknader etter åpen utlysning	Tildelingsandel
Sør-Øst	40 (57%)	180 (62%)	22%
Vest	19 (27%)	63 (22%)	30%
Midt-Norge	9 (13%)	38 (13%)	24%
Nord	2 (3%)	10 (3%)	20%
Totalt	70 (100%)	291 (100%)	24%

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	Originality: - Scientific novelty /originality relative to the research front of the subject area - Degree of innovation; does the project challenge current practices (clinical and research), e.g. through innovative use of theory/methods?	Needs justification: - Target group(s), i.e. patient group(s), carers, other identified users - Needs in the specialist health services - Filling knowledge gaps - Meeting other needs of society
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3	Feasibility: - Realistic, well-reasoned and appropriate project plans (data collection, methods, analyses, statistics etc.) - Identified risks, alternative strategies for conducting the project - Data available from pilot projects or other preliminary data where relevant - Realistic budgets	Potential for implementation: - Realistic plans for implementation / translation of research into improved practice - Realistic time line for implementation (short/long term) - Identified dependencies on development in other areas
4	Quality of the applicant (relative to career stage): - Expertise and qualifications - Productivity - Skills related to project management and supervision - Independency relative to career stage (particularly important for career fellowship proposals)	Competence building: - Gain of knowledge/skills required in the health services - Development of methods, techniques - Strengthening of the research area
5	Research environment: - Infrastructure, access to equipment and resources, necessary/relevant scientific networks - Relevant collaborators - Educational environment, capacity and ability to supervise - Cross-disciplinarity if relevant	Dissemination and visibility: - Plan for dissemination; publications, articles, web sites etc. - Plan for user involvement when relevant - Other relevant plans for disseminating new knowledge, nationally and internationally

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Excellence

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

- Scientific creativity and originality.
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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

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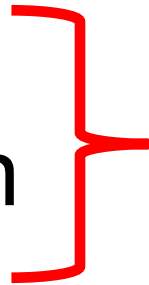
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Nytte

- 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

Lokale forskningsutvalg

 Diakonhjemmet Sykehus Administrerende Direktør - Forskningsutvalget - Forskning, kvalitet og registre			Dok.id.: EK.13.6.1.3
Forskningsprosjekter - planlegging og gjennomføring			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.

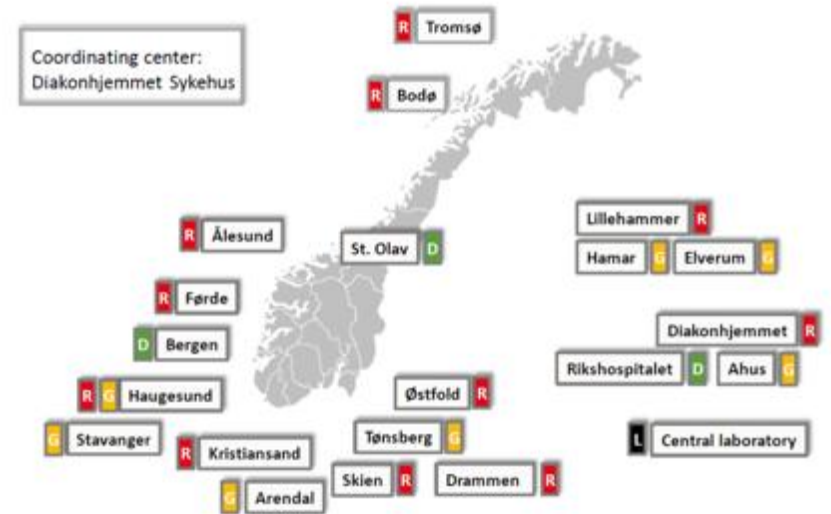
1. HENSIKT

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



Nyhetsbrev Desember 2019

Vi er stolte og glade over at NOR-DRUM nå har inkludert alle 450 pasienter i NOR-DRUM B. Vi trenger nå inklusjonen. 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!

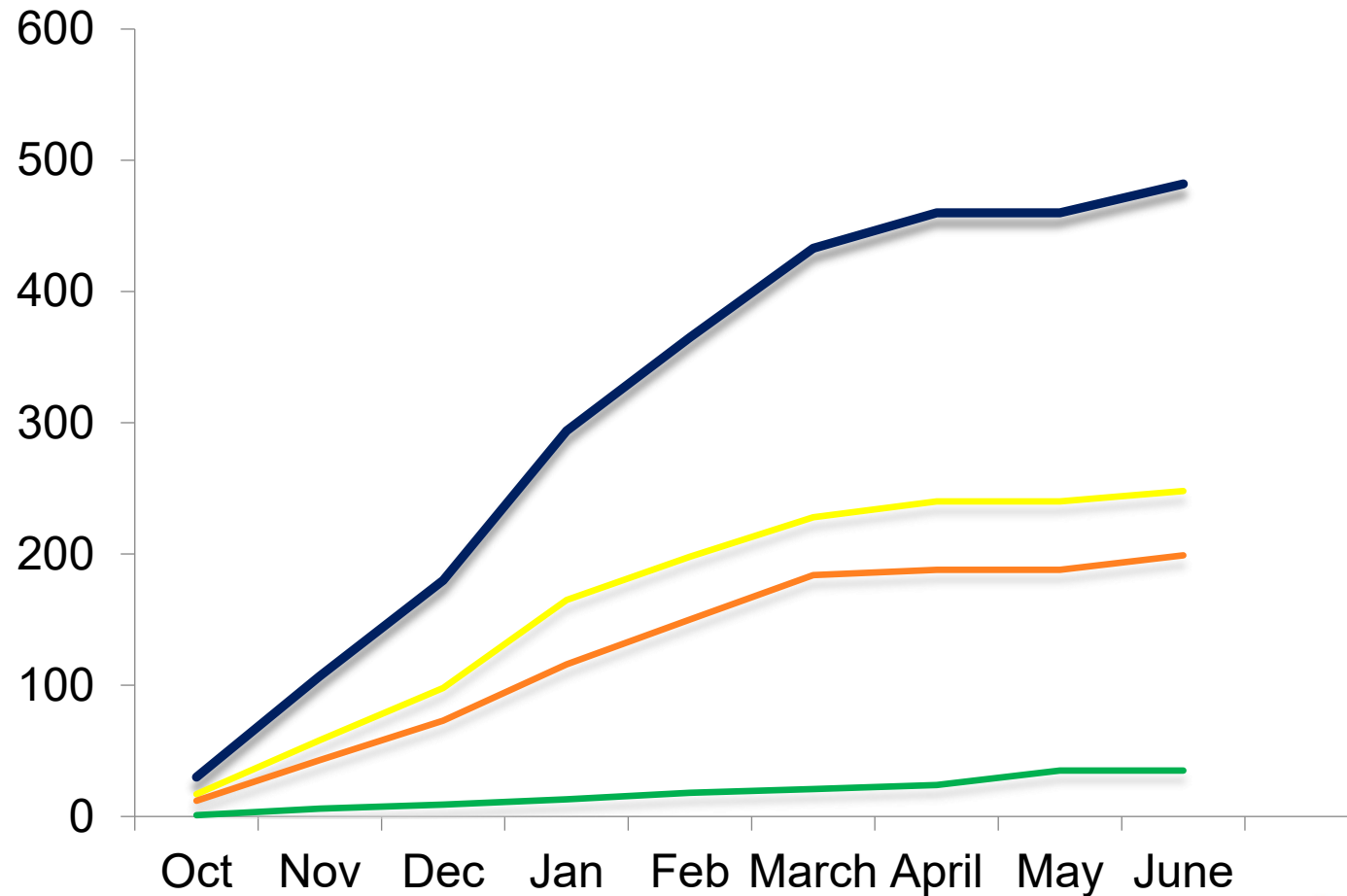


Studiestatus
Inkluderte i NOR-DRUM A: 400
Inkluderte i NOR-DRUM B: 450
Totalt inkluderte enkeltpasienter i NOR-DRUM: 635
NOR-DRUM B forventes ferdig gjennomført januar 2021. Vi planlegger nå analyser fra A-delen og submittering av abstract til EULAR. Hovedutprøver fra hvert senter vil få informasjon om dette i 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

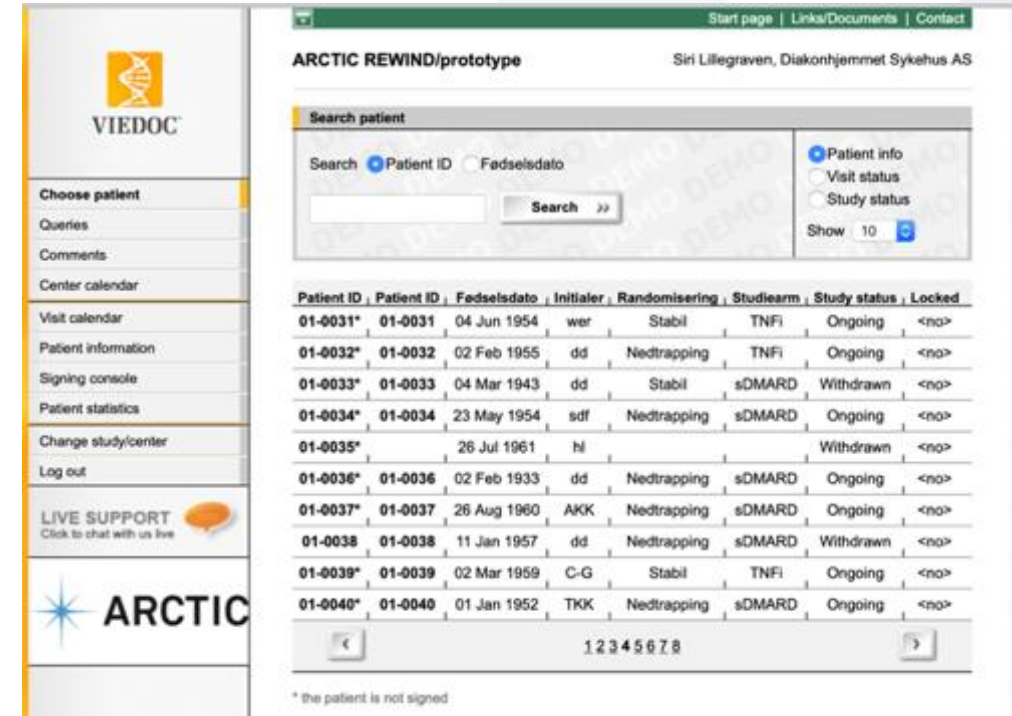
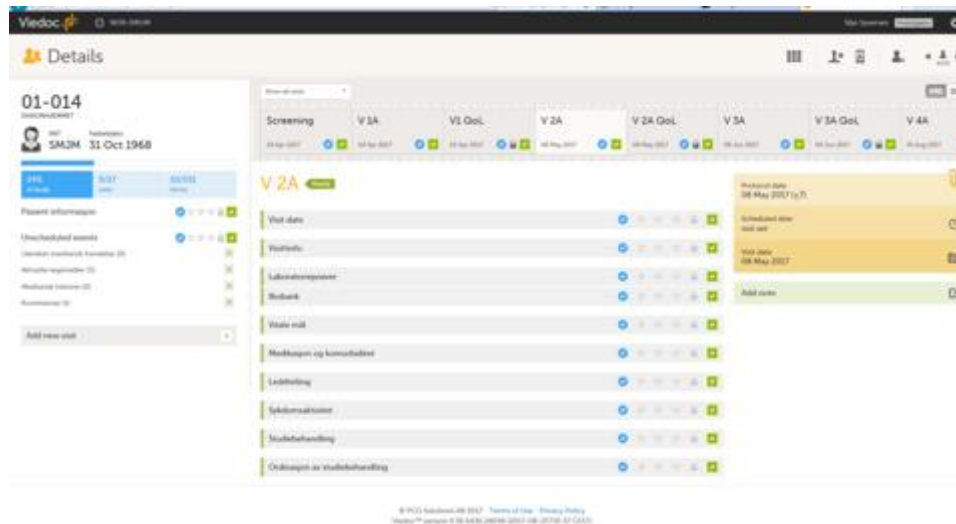
248 Gastro

199 Rheuma

35 Derma

Elektronisk datainnsamling

- Avgjørende for vellykket studie
- God erfaring med Viedoc



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

Analyser

- Flink biostatistikere
- 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



Final Version 1.0

CONFIDENTIAL

1

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



Section 1: Introduction The purpose of this document is to provide a comprehensive overview of the project's goals, objectives, and scope. It serves as a reference point for all stakeholders involved in the project. Project Goals: - Develop a robust and scalable software solution. - Improve user experience and interface. - Ensure data security and privacy. Project Objectives: - Complete the initial development phase by the end of Q3. - Conduct thorough testing and deployment by the end of Q4. - Achieve a 95% user satisfaction rate. Project Scope: The project will cover the development, testing, and deployment of the software solution. It includes the design, coding, and documentation of the system.	Section 2: Project Management Project Manager: John Doe Project Sponsor: Jane Smith Project Team: - John Doe (Project Manager) - Jane Smith (Project Sponsor) - Mike Johnson (Developer) - Sarah Lee (QA) - David Kim (UI/UX) Project Schedule: The project is scheduled to start on January 1st, 2024, and will conclude by December 31st, 2024. The timeline is divided into four quarters, with specific milestones for each. Project Budget: The total budget for the project is \$100,000. The budget is allocated across various categories, including development, testing, and deployment.	Section 3: Technical Details System Architecture: The system is built using a microservices architecture. It consists of several interconnected services that work together to provide the functionality of the application. Database: The system uses a relational database to store user data and transaction records. The database is optimized for high performance and scalability. Security: The system implements robust security measures to protect user data and prevent unauthorized access. This includes encryption, authentication, and authorization. Performance: The system is designed to handle a large number of concurrent users and transactions. It includes caching and load balancing to ensure optimal performance.	Section 4: Risk Management Risk Identification: The project team has identified several potential risks that could impact the project's success. These risks are categorized into high, medium, and low risk. Risk Assessment: The risks are assessed based on their likelihood of occurrence and the potential impact on the project. High-risk items are prioritized for mitigation. Risk Mitigation: The project team has developed a plan to mitigate the identified risks. This includes regular communication, documentation, and contingency planning.	Section 5: Conclusion The project is well-planned and has a clear path forward. The team is committed to delivering a high-quality software solution that meets the needs of the users. Next Steps: - Finalize the project plan and schedule. - Begin development and testing. - Monitor progress and adjust as needed.
Section 6: Appendix A Project Charter: The project charter is a document that defines the project's purpose, goals, and scope. It is the foundation for the project and is used to gain approval from the sponsor. Project Plan: The project plan is a document that outlines the project's schedule, resources, and budget. It is used to manage the project and ensure that it is completed on time and within budget. Project Report: The project report is a document that provides a summary of the project's progress and results. It is used to communicate the project's status to the sponsor and other stakeholders.	Section 7: Appendix B Project Schedule: The project schedule is a document that shows the project's timeline and milestones. It is used to track the project's progress and ensure that it is completed on time. Project Budget: The project budget is a document that shows the project's financial resources and costs. It is used to manage the project's budget and ensure that it is completed within budget. Project Risk Register: The project risk register is a document that tracks the project's risks and their mitigation. It is used to manage the project's risks and ensure that they are minimized.	Section 8: Appendix C Project Communication Plan: The project communication plan is a document that defines the project's communication strategy. It is used to ensure that all stakeholders are kept informed of the project's progress and results. Project Stakeholder Register: The project stakeholder register is a document that identifies the project's stakeholders and their interests. It is used to manage the project's stakeholders and ensure that their needs are met. Project Change Log: The project change log is a document that tracks the project's changes and their impact. It is used to manage the project's changes and ensure that they are implemented correctly.	Section 9: Appendix D Project Glossary: The project glossary is a document that defines the project's terminology and acronyms. It is used to ensure that all stakeholders have a common understanding of the project's terms. Project References: The project references are a list of documents and resources that were used during the project. They are used to provide context and support for the project's findings and conclusions.	Section 10: Appendix E Project Sign-off: The project sign-off is a document that is signed by the project sponsor and the project manager. It indicates that the project has been completed and is ready for deployment. Project Closure: The project closure is a document that provides a summary of the project's results and lessons learned. It is used to evaluate the project's success and identify areas for improvement.
Section 11: Appendix F Project Index: The project index is a document that provides a quick reference to the project's documents and resources. It is used to find the information needed for the project. Project Table of Contents: The project table of contents is a document that provides a detailed overview of the project's structure and content. It is used to navigate the project's documents and resources.	Section 12: Appendix G Project History: The project history is a document that provides a detailed account of the project's development and evolution. It is used to track the project's progress and identify key milestones. Project Future: The project future is a document that provides a vision for the project's future and the next steps. It is used to plan for the project's long-term success.	Section 13: Appendix H Project Acknowledgments: The project acknowledgments are a list of people and organizations that have supported the project. They are used to express gratitude and recognize the contributions of others. Project Credits: The project credits are a list of the project's authors and contributors. They are used to give credit to the individuals who have worked on the project.	Section 14: Appendix I Project Index (continued): The project index continues to provide a quick reference to the project's documents and resources. It is used to find the information needed for the project. Project Table of Contents (continued): The project table of contents continues to provide a detailed overview of the project's structure and content. It is used to navigate the project's documents and resources.	Section 15: Appendix J Project Sign-off (continued): The project sign-off continues to provide a summary of the project's results and lessons learned. It is used to evaluate the project's success and identify areas for improvement. Project Closure (continued): The project closure continues to provide a vision for the project's future and the next steps. It is used to plan for the project's long-term success.
Section 16: Appendix K Project Index (continued): The project index continues to provide a quick reference to the project's documents and resources. It is used to find the information needed for the project. Project Table of Contents (continued): The project table of contents continues to provide a detailed overview of the project's structure and content. It is used to navigate the project's documents and resources.	Section 17: Appendix L Project History (continued): The project history continues to provide a detailed account of the project's development and evolution. It is used to track the project's progress and identify key milestones. Project Future (continued): The project future continues to provide a vision for the project's future and the next steps. It is used to plan for the project's long-term success.	Section 18: Appendix M Project Acknowledgments (continued): The project acknowledgments continue to list the people and organizations that have supported the project. They are used to express gratitude and recognize the contributions of others. Project Credits (continued): The project credits continue to list the project's authors and contributors. They are used to give credit to the individuals who have worked on the project.	Section 19: Appendix N Project Index (continued): The project index continues to provide a quick reference to the project's documents and resources. It is used to find the information needed for the project. Project Table of Contents (continued): The project table of contents continues to provide a detailed overview of the project's structure and content. It is used to navigate the project's documents and resources.	Section 20: Appendix O Project Sign-off (continued): The project sign-off continues to provide a summary of the project's results and lessons learned. It is used to evaluate the project's success and identify areas for improvement. Project Closure (continued): The project closure continues to provide a vision for the project's future and the next steps. It is used to plan for the project's long-term success.

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,¹ Hilde Berner Hammer,¹ Inge Christoffer Olsen,¹ Till Uhlig,¹ Tore K Kvien,¹ Désirée van der Heijde,^{1,2} Hallvard Fremstad,³ Tor Magne Madland,⁴ Åse Stavland Lexberg,⁵ Hilde Haukeland,⁶ Erik Rodevand,⁷ Christian Hølli,⁸ Hilde Stray,⁹ Anne Noraas Bendvold,¹⁰ Dag Magnar Soldal,¹¹ Gunnstein Bakland,^{12,13} Elisabeth Lie,¹ Espen A Haavardsholm¹

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,¹ Hilde Berner Hammer,¹ Inge Christoffer Olsen,¹ Till Uhlig,¹ Tore K Kvien,¹ Désirée van der Heijde,¹ Hallvard Fremstad,³ Tor Magne Madland,⁴ Åse Stavland Lexberg,⁵ Hilde Haukeland,⁶ Erik Rodevand,⁷ Christian Hølli,⁸ Hilde Stray,⁹ Anne Lindner Noraas,¹⁰ Inger Johanne Widding Hansen,¹¹ Gunnstein Bakland,^{12,13} Siri Lillegraven,¹ Elisabeth Lie,¹ and Espen A Haavardsholm¹

BMJ

Aga A-B, et al. *RMD Open* 2016;2:e000325. doi:10.1136/rmdopen-2016-000325

eular

RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/key022

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

Nina Paulshus Sundlisæter,^{1,2} Inge C. Olsen,³ Anna-Birgitte Aga,¹ Hilde B. Hammer,¹ Till Uhlig,¹ Désirée van der Heijde,^{1,4} Tore K. Kvien,¹ Siri Lillegraven,^{1,4} and Espen A. Haavardsholm^{1,2,4}; the ARCTIC study group¹

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,^{1,2} Siri Lillegraven,¹ Anna-Birgitte Aga,¹ Joseph Sexton,¹ Inge Christoffer Olsen,^{1,3} Elisabeth Lie,¹ Hilde Berner Hammer,¹ Till Uhlig,¹ Désirée van der Heijde,^{1,4} Tore K Kvien,¹ Espen A Haavardsholm^{1,2}

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,^{1,2} Anna-Birgitte Aga,¹ Inge Christoffer Olsen,³ Hilde Berner Hammer,¹ Till Uhlig,¹ Désirée van der Heijde,^{1,4} Tore K Kvien,¹ Siri Lillegraven,¹ Espen A Haavardsholm,^{1,2} the ARCTIC study group

Arthritis & Rheumatology

AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

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,¹ Siri Lillegraven,¹ Anna-Birgitte Aga,¹ Joe Sexton,¹ Elisabeth Lie,¹ Hilde B. Hammer,¹ Inge C. Olsen,³ Till Uhlig,¹ Désirée van der Heijde,¹ Tore K. Kvien,¹ 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,¹ Siri Lillegraven,¹ Elisabeth Lie,¹ Anna-Birgitte Aga,¹ Inge Christoffer Olsen,¹ Hilde Berner Hammer,¹ Till Uhlig,¹ Maria Karolina Jonsson,^{1,2} Désirée van der Heijde,^{1,3} Tore K Kvien,¹ Espen Andre Haavardsholm,¹ 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 Høllen,^{1,2} Joseph Sexton,¹ Tore K Kvien,^{1,2} Anna-Birgitte Aga,¹ Espen A Haavardsholm^{1,2}

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,¹ Anna-Birgitte Aga,¹ Øivind Skare,¹ Lena B Nordberg,¹ Till Uhlig,¹ Hilde B Hammer,¹ Désirée van der Heijde,¹ Tore K Kvien,¹ Siri Lillegraven,¹ 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)

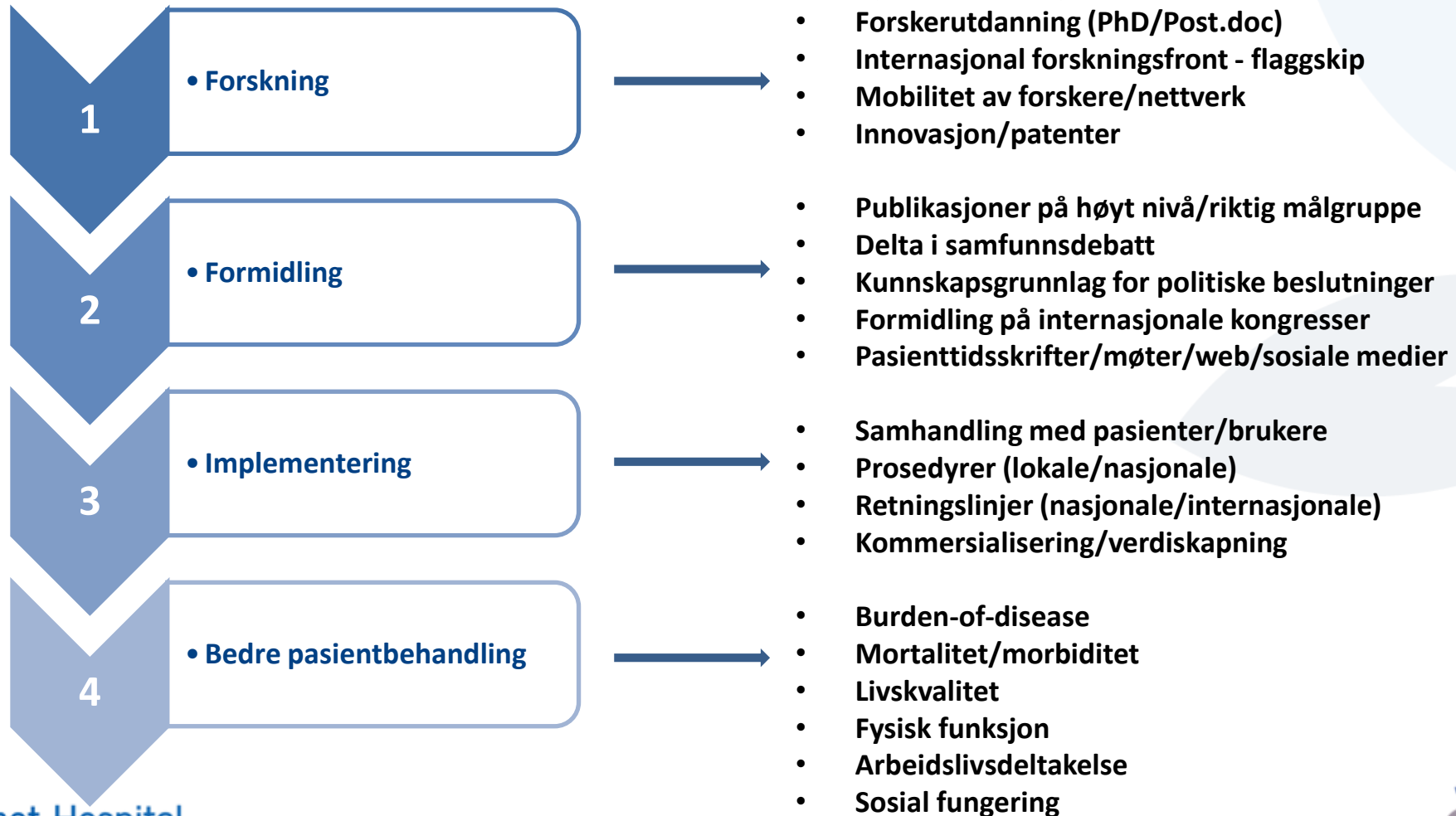
Ulf Sundin, Mikkel Østergaard, Daniel Glinatsi, Anna-Birgitte Aga, Kim Hørslev-Petersen, Merete L. Hetland, Kristian Stengard-Pedersen, Peter Junker, Bo J. Ejlertsen, Paul Bird, Philip G. Conaghan, Siri Lillegraven and Espen A. Haavardsholm

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
- Nyten av internasjonale medforfattere
 - Både i tidlig og sen fase av studien
 - Fortolkning resultater
 - Implementering

Vellykket klinisk studie



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!