MERINO:2

Methotrexate in erosive inflammatory osteoarthritis

Protocol Title:	Long-term effects of Methotrexate in adults with erosive hand osteoarthritis: A 30-month follow-up of former MERINO participants (MERINO:2).
Protocol Number:	1.1
Date:	29.07.2024
Amendment Number:	1
Country:	NOR
Compound:	Methotrexate vs. treatment as usual
Brief Title:	A 30-month follow-up of MERINO participants to evaluate long-term effects of Methotrexate in erosive hand OA.
Study Phase:	Phase 4
Acronym:	MERINO:2
Sponsor Name:	Diakonhjemmet Hospital AS
Legal Registered Address:	Box 23 Vinderen, 0319 Oslo

Regulatory Agency Identifier Number(s):

Regional committee for medical and health research ethics (REK): 715758

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Sponsor Signatory:

12.02.2024

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Protocol Amendment Summary of Changes Table

Document	Date	Version
Original protocol	12.01.2024	Version 1.0
Amendment 1	25.07.2024	Version 1.1

AMENDMENT 1, 25.07.2024

Overall rationale for the amendment: Complying with conditional approval from REK

Section #	Description of Change	Brief Rationale
Protocol title	"Long-term effects of Methotrexate in adults with erosive hand osteoarthritis: A 30-month follow-up of former MERINO participants (MERINO:2)".	A more precise phrase to harmonize with the following two changes below.
4.1 Overall design	Changed observational time from 12 months to 18 months after the completion of the MERINO trial. The follow-up in MERINO:2 will thus be scheduled 30 months after entering the MERINO trial, or 18 months after completing the MERINO trial.	To ensure higher recruitment rates, we have extended the follow-up period. The new follow-up will be scheduled 30 months after entering the MERINO trial, or 18 months after its completion. Additionally, we have clarified that follow-ups can deviate by up to 10 weeks from this time point, addressing a specification that was missing in the original protocol.
4.1 Overall design	Changed potential participants from those *completing* the MERINO trial to *all recruited* MERINO participants.	As this is a new study with a separate consent form, we propose offering the current study to all participants originally recruited for the MERINO trial. We recognize the importance of including those who did not complete the MERINO trial, including those who withdrew shortly after enrolling. These participants will have experienced an extended period of 'treatment as usual,' which will enhance the robustness of our results.
4.1 Overall design	Changed the description of participants who finished the MERINO trial and who did not request further MTX treatment from "no treatment" to "treatment as usual".	This is a more precise description of the period after completing the original MERINO trial.
Consent form	Minor word improvement of the consent form.	Comply with the conditional approval from REK as well as harmonization with the changes described above.

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List of Abbreviations

OA	Osteoarthritis
MTX	Methotrexate
RCT	Randomized controlled trial
DMARDs	Disease-Modifying Antirheumatic Drugs
NSAIDs	Nonsteroidal anti-inflammatory drugs
VAS	Visual analogue scale

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Long-term effects of Methotrexate in adults with erosive hand osteoarthritis: A 30-month follow-up of former MERINO participants (MERINO:2).

Brief Title:

A 30-month follow-up of MERINO participants to evaluate long-term effects of Methotrexate in erosive hand OA.

Regulatory Agency Identifier Number(s):

REK 715758

Rationale:

In response to the high prevalence of synovitis in hand osteoarthritis (OA) and its association with pain, there's a compelling rationale for investigating the efficacy of MTX in managing inflammatory erosive hand OA. Recent guidelines highlight the need for large, well-designed trials to assess the effectiveness of MTX. A recent trial (METHODS study) showed promising pain reduction with MTX, but due to pandemic-related protocol changes, the duration of the study was limited to six months. The ongoing MERINO trial randomizes participants to MTX or placebo for one year. After completing the MERINO trial, several participants asked for MTX open label. In the subsequent MERINO:2 study, participants from the MERINO trial will be invited to a structured follow-up 30 months after MERINO recruitment, including electronic questionnaires and hand radiographs, providing valuable long-term data on the effects of MTX in hand OA. Together, these trials aim to fill gaps in understanding the long-term impact of MTX in hand OA, particularly on structural progression.

Objectives and Endpoints:

In the MERINO:2 study, our main objectives are to explore the long-term effects of MTX in hand OA on structural progression, pain, and function. We will obtain hand radiographs and acquire patient-reported outcome measures through questionnaires:

Objectives	Endpoints
Primary	
• Effect of MTX on radiographic progression of erosive hand OA.	• Progression in Verbruggen-Veys anatomical atlas score at 18 months
Secondary	
• Effect of MTX on pain, function and life quality	• Finger joint pain previous 48 hours (VAS) at 18 months • Thumb base joint pain previous 48 hours (VAS) at 18 months • Pain most painful finger joint previous 48 hours (VAS) at 18 months • AUSCAN pain and function subscales at 18 months

	• OMERACT-OARSI responder criteria at 18 months • Patient-reported disease activity previous 48 hours (VAS) at 18 months • EQ-5D at 18 months
• Effect of MTX on radiographic progression of hand OA.	• KL grades • OARSI atlas (osteophytes, joint space narrowing, erosions)

Overall Design:

The MERINO:2 is an extension of the MERINO trial (EudraCT number 2019-004641-33, Clincaltrials.gov number NCT04579848, REK ID 2020/187524, CTIS number 2023-510523-30-00), with an expanded observational period of 18 months after ending the MERINO trial (i.e. 30 months after staring MERINO). MERINO:2 is an investigator-initiated and open-label observational study. Participants are male and female adults with erosive hand osteoarthritis. Following the completion of the MERINO trial, participants either ended their treatment or were prescribed MTX open-label (oral or s.c. 5-25mg per week as well as folic acid 1mg daily).

Brief Summary:

The primary aim is to demonstrate the superiority of Methotrexate (MTX) over treatment as usual in slowing radiographic progression over 30 months in individuals with erosive hand osteoarthritis (OA).

OA is a leading cause of disability and affecting millions worldwide, with a significant impact on knee, hip, and hand joints. Despite its high prevalence and symptomatic burden, effective disease-modifying treatments remain elusive, with current options limited to pain management and joint replacement.

MTX, recognized for its disease-modifying effects in systemic inflammatory joint diseases, offers promising potential in OA treatment, with previous trials indicating its anti-inflammatory properties and potential for joint damage reduction. In the ongoing MERINO trial, 153 participants are randomly assigned to either MTX or a placebo. Following completion of the trial, several participants have expressed interest in MTX treatment, which is sometimes used off-label for erosive hand OA patients experiencing unmanageable pain and inflammation. As a result, some MERINO trial participants will receive MTX treatment.

In the MERINO:2 study, we will conduct a structured follow-up 18 months post-MERINO trial completion, incorporating hand radiographs and pain questionnaires. This endeavor will furnish invaluable insights into the long-term effects of MTX treatment in erosive hand OA, a gap in current knowledge, particularly regarding structural progression. This will provide valuable data on long-term effects of MTX treatment in erosive hand OA, which is not currently described in the literature, especially on structural progression.

Number of Participants:

We estimate 153 recruited participants from the MERINO trial as potential candidates for the MERINO:2 trial.

Study Arms and Duration:

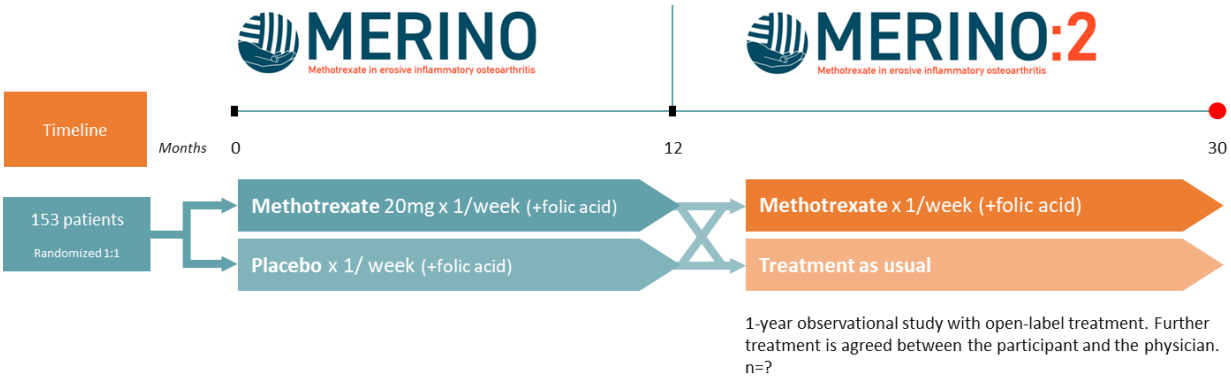
All participants recruited to the MERINO trial will be asked to provide conventional radiographs and electronic questionnaires 30 months after starting the MERINO trial. This results in four potential arms of the MERINO:2 trial, depending on the two former arms of the MERINO trial, each with a duration of 12+18=30 months:

- MTX → MTX
- MTX → Treatment as usual
- Placebo → MTX
- Placebo → Treatment as usual

Data Monitoring/Other Committee: No

1.2. Schema

Figure 1. Overview of study design



1.3. Schedule of Activities (SoA)

Overview of the data collection	MERINO								MERINO:2	
	Screen	M00	M01	M02	M03	M06	M09	M12	M12-M30	M30
Weeks	(-4)–0	1	5 +/- 1	9 +/- 1	13 +/- 2	26 +/- 2	39 +/- 2	52 +/- 2	52-130 [9]	130 +/- 10
Study information, eligibility[1], and informed consent	X								**X**	
Regular visit		X	X		X	X	X	X		
Safety monitoring			X	X	X	X	X	X	**X**	
First dose		X								
Medical drug extradition to patient		X				X			**X**	
Medical drug counting						X		X		**X**
Person characteristics										
Demographic and medical history [1]		X								
Concomitant medication	X	X	X		X	X	X	X		**X**
Safety and laboratory assessments										
Laboratory sample for screening [2]	X									
Laboratory safety monitoring			X	X	X	X	X	X	**X** [10]	
Biobank samples		X [3]				X [4]		X [4]		
Adverse events			X		X	X	X	X	**X**	
Serum hCG in fertile women	X	X	X	X	X	X	X	X	**X**	
Patient-reported outcome measures										
Hand pain on most days (yes/no)	X									
Hand pain previous 48 hours (VAS)	X	X	X		X	X	X	X		**X**
Pain in most painful joint previous 48 hours (VAS)		X	X		X	X	X	X		**X**
Hand diagram		X				X				
OMERACT-OARSI responder criteria		X	X		X	X	X	X		**X**
Australian/Canadian hand index (AUSCAN)		X	X		X	X	X	X		**X**
Heath-related quality of life (EQ-5D)		X	X		X	X	X	X		**X**
Michigan Hand Outcomes questionnaire (MHOQ)		X				X				
Hospital Anxiety and Depression scale (HADS)		X				X				
Pain Catastrophizing Scale (PCS)		X				X				
Pain Sensitivity Questionnaire (PSQ)		X				X				
Knee injury and Osteoarthritis Outcome Score (KOOS)-12		X				X				
Hip disability and Osteoarthritis Outcome Score (HOOS)-12		X				X				
Physical examination										

ACR criteria for hand, hip and knee OA	X									
Tender and swollen joint count		X	X		X	X	X	X		
Anthropometric and cardiovascular assessment [5)]		X	X		X	X	X	X		
Grip strength		X				X		X		
Pain sensitization [6)]		X				X				
Imaging outcome measures										
Chest radiograph	X									
Conventional hand radiographs	X					X		X		**X**
Ultrasound of fingers	X [7)]	X	X		X	X	X	X		
Ultrasound of hips and knees	X					X				
MRI		X				X				
Knee OA sub-study [8)]										
Synovial needle biopsy of one knee		X				X				
Knee pain previous 48 hours (VAS)		X				X				

VAS = visual analogue scale; OMERACT-OARSI = Outcome Measures in Rheumatology Osteoarthritis Research Society International; EQ-5D = EuroQol 5 dimensions; MRI = Magnetic Resonance Imaging.

1. Birth date, sex, ethnic origin, marital and work status, exercise, smoking, alcohol, hormonal factors (women), previous joint-related therapies, and comorbidities.
2. Hemoglobin, white blood cells with differentials, platelet counts, ASAT, ALAT, albumin, creatinine, GFR, CRP, ESR, IGRA, HIV, Hepatitis B and C.
3. Plasma, serum and full blood.
4. Plasma and serum.
5. Including pulse rate, systolic and diastolic blood pressure and body weight will be assessed at all visits. Height will be measured at baseline only.
6. Includes Pressure Pain Thresholds (PPT), CPM = Conditioned Pain Modulation and temporal summation.
7. Confirm two interphalangeal joints with a positive power Doppler signal of at least grade 1 or B mode grey scale synovitis of at least grade 2 on ultrasound.
8. Sixteen volunteers with concomitant knee OA.
9. Follow-up in the outpatient clinic as agreed between participant and treating physician.
10. Safety monitoring according to National recommendations in Norway for DMARD treatment.

2. Introduction

The MERINO:2 study is an extension of the ongoing MERINO trial. This trial involves participants with erosive hand OA receiving either MTX or placebo. The MERINO:2 plans for an extended observational period of the MERINO trial, 30 months after starting the original study. Some of these participants have expressed a desire to receive MTX open-label after the MERINO trial and are followed as ordinary in an outpatient clinic. The study aims to provide unique data on the long-term effects of sustained MTX treatment, particularly on structural joint damage.

2.1. Study Rationale

Based on the high frequency of synovitis in hand OA, especially in erosive disease (1), and the relationships to pain (2, 3), there is a significant rationale for testing MTX in the management of the phenotype inflammatory erosive hand OA. The updated international guidelines for management of hand OA recently concluded that future well-designed larger RCTs are needed to explore the efficacy of MTX (4), and more knowledge is needed regarding how to optimize personalized treatment in OA. A recent double-blind, randomized, placebo-controlled trial (the METHODS study) involving participants with hand OA and synovitis treated with 20 mg MTX weekly for 6 months resulted in a significant reduction in pain compared to placebo (mean between-group difference of -9.9 mm on a 100 mm visual analogue scale, 95% CI -19.3 to -0.6, p=0.037) (5). However, although the study was designed to find out whether MTX reduced pain and radiographic progression in 2 years, the COVID-19 pandemic and subsequent lockdowns in Australia altered the trial protocol, focusing on pain reduction at 6 months as the primary endpoint, and no imaging results have been published.

Participants in the ongoing MERINO trial are randomized to placebo or MTX for one year. The study encompasses extensive data collection including radiographs, ultrasound, MRI, clinical examination, laboratory tests, and a large range of patient-reported outcomes. **Several participants in the MERINO trial ask if they can receive MTX after MERINO. Although not evidence-based, MTX is occasionally used off-label in erosive hand OA patients with unmanageable pain and inflammation and is considered on an individual level in conjunction with the physician and participant.**

In this proposed open-label observational study, the MERINO:2 study, we will do a structured follow-up of all participants after the MERINO trial, some of whom will be prescribed MTX after the MERINO trial. In addition to ordinary follow-up consultations in the outpatient clinic, **we will organize electronic questionnaires and hand radiographs 30 months after entering the MERINO trial.** We see this as an opportunity to re-use existing electronic data collection schemes and ongoing collaborations with our service departments to provide a structured and long-term follow-up of participants who seek to receive MTX treatment after the MERINO RCT trial.

The MERINO and MERINO:2 trials will provide additional data to the current literature on long-term effects of MTX treatment in hand OA patients, especially on structural progression which has not yet been studied by any other group.

2.2. Background

OA is the most common joint disease and the fastest-growing cause of disability. Current estimates suggest that 250 million people worldwide are affected by knee OA (6), and similar numbers are affected by hip or hand OA. The lifetime risk of symptomatic hand OA is 40% and of symptomatic knee OA 45% (7). Main symptoms are pain, swelling, stiffness, and malformation of joints. However, **no effective disease-modifying treatment exists for OA**, and current treatment options are limited to pain reduction and joint replacement. Hence, OA is a prevalent disease with high unmet needs.

MTX is classified as a disease-modifying drug for systemic inflammatory joint diseases with acceptable tolerability and good effects on symptoms, inflammation, and disease progression. Previous OA trials have shown anti-inflammatory treatment's possible effect on reducing joint damage and facilitating bone remodelling (8, 9), but with conflicting effects on symptoms (9, 10). Therefore, we now run the MERINO trial to explore whether MTX for one year has a symptomatic, anti-inflammatory, and disease-modifying effect in erosive hand OA with an acceptable safety profile.

2.3. Benefit/Risk Assessment

Benefits:

- Understanding Long-term Effects: The study aims to provide valuable insights into the long-term effects of MTX on erosive hand OA, which could significantly contribute to the management of this condition.
- Improved Treatment Strategies: Data from this study could help in refining treatment strategies for erosive hand OA, potentially leading to better patient outcomes.
- Patient Well-being: Continuous observation and treatment could benefit the participants' health and quality of life.

Risks:

- Side Effects of the treatment: MTX is known to have side effects, which could include liver damage, lung disease, and others. Monitoring these side effects is crucial. See section 7.2.
- Ethical Considerations: The ethical implications of long-term drug administration need careful consideration, especially regarding consent and the management of any adverse effects.
- Data Management Risks: As with any clinical study, there are risks related to data privacy and the management of sensitive patient information.

2.3.1. Adverse and toxic effects of MTX

The long-term clinical efficacy and relative safety of MTX in inflammatory joint disease remain impressive. Yet, adverse effects of MTX can occur at therapeutic levels and include headache, malaise, mouth ulcers and hair-fall. In overdose, vomiting, diarrhea and gastrointestinal bleeding may occur, as well as severe bone marrow suppression and disturbance of liver function. Long-

term liver injury, normally accompanied by elevations of liver transaminases, can result in hepatic fibrosis. Liver toxicity is more likely in patients with pre-existing risk factors for liver disease, and in patients taking MTX for the treatment of psoriasis than those taking it for the treatment of RA.

MTX can induce acute pneumonitis, which can be fatal. Patients may present with acute shortness of breath and a dry, persistent cough, possibly with fever. A chest x-ray prior to initiating MTX is obtained to facilitate the diagnosis of potential lung disease at a later date.

Co-administration of folic acid 1 mg daily has been shown to reduce the risk of adverse effects such as abdominal pain and nausea, abnormal serum transaminase levels, and increases adherence with a MTX regimen.

Managing the risks of MTX in the MERINO:2 study

Given the number of documented fatalities which have arisen from simple errors in medicine dosing frequency, the most important lesson is to emphasize that MTX ***should be taken as a weekly dose only*** and to put in place procedures, safeguards and reminders to ensure this dosage is followed by the participants.

According to current clinical practice at Diakonhjemmet Hospital, every participant has consulted a nurse before receiving any study medication. Patients is advised on key symptoms of MTX toxicity such as a sore throat, mouth ulcers, fever, dry persistent cough, vomiting or diarrhea, and to report if any of these occur. We will also emphasize to the patient the differences between MTX and folic acid – cases have occurred where the two dosing regimens were inadvertently swapped by the patient.

To avoid reactivation or worsening of infectious diseases, we have screened for hepatitis B/C and tuberculosis in the original MERINO trial. Due to risk of MTX-induced lung disease, chest radiographs is obtained at screening and repeated if lung symptoms. Alcohol increases the risk for liver damage while taking MTX, and should be used with care. MTX must be discontinued three months before planned fertilization for women (due to risk of serious birth defects) and men (due to oligo- or teratozoo-spermia). Persons with planned pregnancy during the study period are thus excluded. Furthermore, MTX is excreted in breast milk in low concentrations and can accumulate in neonatal tissues; thus, it is contraindicated during breastfeeding.

A full blood count, liver and renal function tests will be carried out before starting MTX, and repeated every four weeks initially, then every three months if results have been normal and the dose is stable, according to national guidelines.

Conclusion

In systemic inflammatory joint diseases, MTX is administered at low doses (usually 10-25 mg x 1/week) and is relatively well-tolerated, provided that there is careful participant selection and regular monitoring for adverse effects and drug interactions during MTX therapy is carried out. Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with MTX are justified by the anticipated benefits that may be afforded to participants with inflammatory erosive hand OA.

2.3.2. Risk of study-related procedures

Conventional radiography

We are exposed to natural sources of radiation all the time. The average person in the U.S. receives an effective dose of about 3 mSv per year from natural radiation, which includes cosmic radiation from outer space. The amount of radiation from one adult extremity (hand, knee, etc.) x-ray equals 0.001 mSv or 3 hours of natural background radiation.

2.3.3. Benefit Assessment

Personalized medicine in OA is emerging, as it is unlikely that one single treatment will have an effect in all patients due to the heterogeneity of the disease. Previous trials have shown possible effects of biological anti-inflammatory drugs on reducing joint damage in hand OA (8), but disappointing effect on symptoms (10). To avoid failures of future OA trials, the heterogeneity of the disease must be acknowledged. The involvement of various tissues will differ across patients and at different disease stages. Further, pain is strongly influenced by genetic predisposition, psychological and social factors and differences in the pain processing system, which may affect the treatment responses. There are reasons to believe that some phenotypes may benefit from anti-inflammatory treatments, whereas others may benefit from therapies directed at bone or cartilage, central sensitization or cognitive aspects.

In clinical practice, MTX is occasionally used off-label in OA patients with unmanageable pain and inflammation, but the practice is currently not evidence-based. Previous studies (mainly open-label) have indicated a symptomatic effect in patients with knee and hand OA (11-13), but high-quality RCTs are needed to provide clear evidence in support of or against current practice. A small (n=30) open-label trial found ≥30% reduction in VAS pain in 43% of the knee OA participants given MTX, suggesting an analgesic efficacy (11). A recent small RCT of persons with erosive hand OA (n=64) showed a positive trend with larger pain relief in patients treated with MTX vs. placebo after 3 months (decrease of mean (standard deviation; SD) visual analogue scale (VAS) pain: 17.5 (28.4) vs. 8.4 (25.3); p=0.18) (14). However, the lack of inflammation in the majority of patients and the low dose of MTX (10 mg/week) make us unable to draw firm conclusions about its efficacy. Interestingly, fewer patients developed new erosions in the MTX vs. placebo arm (8% vs. 29%; p=0.09), suggesting a disease-modifying effect.

2.3.4. Overall Benefit Risk Conclusion

In summary, the potential benefits of the MERINO:2 study include a deeper understanding of MTX's long-term effects and improved patient care. Given the nature of this observational study, we are providing a structured follow-up regardless of which treatment the participants ends up receiving. Decisions on treatment are discussed between participants and the treating physician.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of MTX may be found in the summary of product characteristics (SmPC).

3. Objectives and Endpoints

In the MERINO:2 study, our main objectives are to explore the long-term effects of MTX in hand OA on structural progression, pain, and function. We will obtain hand radiographs and acquire patient-reported outcome measures through questionnaires (Table 1).

Table 1. Objectives and endpoints

Objectives	Endpoints
Primary	
• Effect of MTX on radiographic progression of erosive hand OA.	• Progression in Verbruggen-Veys anatomical atlas score at 18 months
Secondary	
• Effect of MTX on pain, function and life quality	• Finger joint pain previous 48 hours (VAS) at 18 months • Thumb base joint pain previous 48 hours (VAS) at 18 months • Pain most painful finger joint previous 48 hours (VAS) at 18 months • AUSCAN pain and function subscales at 18 months • OMERACT-OARSI responder criteria at 18 months • Patient-reported disease activity previous 48 hours (VAS) at 18 months • EQ-5D at 18 months
• Effect of MTX on radiographic progression of hand OA.	• KL grades • OARSI atlas (osteophytes, joint space narrowing, erosions)

AUSCAN = Australian/Canadian hand index; EQ-5D = EuroQol 5 dimensions; KL = Kellgren and Lawrence; MHOQ = Michigan Hand Outcomes questionnaire pain and function subscales; OARSI = Osteoarthritis Research Society International; OMERACT-OARSI = Outcome Measures in Rheumatology Osteoarthritis Research Society International; VAS = visual analogue scale.

4. Study Design

4.1. Overall Design

The MERINO:2 is an investigator-initiated and open label observational study with one-year parallel group treatment with MTX in male and female adults with erosive hand osteoarthritis.

Eligible participants are those recruited to the MERINO-trial (EudraCT number 2019-004641-33, Clincaltrials.gov number NCT04579848, REK ID 2020/187524, CTIS number 2023-510523-30-00).

After the MERINO trial, participants may either continue treatment as usual or be prescribed MTX open-label (oral or s.c. 5-25mg per week as well as folic acid 1mg daily).

Especially of interest is to compare those who first receive placebo and then treatment as usual throughout the MERINO and MERINO:2 trials with those receiving MTX throughout the whole period, as this comparison will reflect the effect of long-term treatment with MTX over 2,5 consecutive years. Further, the Placebo→MTX crossover group will complement the data from the MERINO trial on shorter MTX treatment.

4.2. Scientific Rationale for Study Design

This study stands to fill a significant gap in OA research and could potentially guide future treatment protocols. OA is a slowly progressive disease but there are no studies examining the long-term (2 year) effect on structural progression of MTX treatment in erosive hand OA. The requests to explore MTX treatment after the MERINO trial prompted us to organize the follow-up within our outpatient clinic. This arrangement enables us to efficiently collect supplementary data. This approach also capitalizes on existing collaborations with our service departments, maximizing resource utilization and ensuring comprehensive patient care.

4.2.1. Patient Input into Design

The communication with users has over the years evolved into a strong partnership at Diakonhjemmet Hospital, where patient representatives, clinicians and researchers work together to improve the quality of care for people with rheumatic diseases. The collaboration continues in this project, where two patient representatives have been involved in the protocol development, and will also be consulted during the ongoing trial and before dissemination and publication of the results. Additionally, the project leader is also co-leader of the representative organization “REMEDY pasientråd”.

4.3. Justification for Dose

Being an open-label observational study, the doses and treatment length of MTX will vary depending on the physicians and participants preferences. At the one-year control, we will use self-reported doses and The Norwegian Prescription Database (Reseptregisteret) to calculate the doses during the follow-up year.

4.4. End-of-Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the schedule of activities for the last participant in the study.

A participant is considered to have completed the study if the participant has completed one-time follow-up procedure shown in the SoA 30 months after entering the original MERINO trial.

5. Study Population

All participants entering the MERINO trial (see section 4.1) will be asked if they can voluntarily can provide a 30-month conventional radiographs and an electronic questionnaire. This results in four potential arms of the MERINO:2 trial, depending on the two former arms of the MERINO trial (Table 2).

The participants must be capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

We otherwise refer to the MERINO-protocol for study population description.

Table 2. Study Arms

MERINO	MERINO:2
12 months	*18 months*
MTX 10-20mg weekly	→ Treatment as usual
MTX 10-20mg weekly	→ MTX 7,5-20mg weekly
Placebo	→ Treatment as usual
Placebo	→ MTX 7,5-20mg weekly

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, investigational, and non-investigational medicinal products intended to be administered to the study participants during the study conduct.

6.1. Study Intervention Administered

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol (Table 3).

Table 3. Study interventions

ARM Name	Intervention	Co-medication
Intervention Name	MTX	Folic acid
Producer	Pfizer	Orifarm Generics (Orifarm Healthcare AS)
ATC	L04A X03	B03B B01
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Box size	206 (x2)	100
Unit Dose Strength(s)	Methotrexate 2.5mg	1mg
Frequency	Weekly	Daily
Dosage Level(s)	Decided by the treating physician, usually 10-20mg weekly, with a down-scaled dose the first 2-3 weeks.	1mg x 1
Route of Administration	Oral	Oral
Use	Intervention	Minimize expected adverse reactions to methotrexate
IMP and NIMP	IMP	NIMP
Sourcing	Provided by local pharmacy	Provided by local pharmacy
Packaging and Labeling	Provided by local pharmacy according to national routines.	Provided by local pharmacy according to national routines.

6.1.1. Investigational medicinal product (IMP)

MTX 2.5 mg oral tablet; standard treatment is 15 mg x 1 per week the first two weeks, and then 20 mg x 1 per week to end of study. Physician may deviate from standard treatment dose, example in the case of adverse events, preferences by the participants or similar. Subcutaneous MTX can be provided and will be treated equally to oral tablets.

6.2. Preparation, Handling, Storage, and Accountability

Only participants enrolled in the study may receive study intervention, and only authorized pharmacy staff may supply, prepare, or administer study intervention.

6.3. Assignment to Study Intervention

The treating physician will decide, based on best clinical practice, if the patient should try MTX after the MERINO-trial. Central to this approach is the collaborative effort between the physician and participant, fostering an environment where patient perspectives are integral to treatment decisions. It will be emphasized by the physician prescribing MTX open-label that this is not evidence-based treatment until results of the MERINO-trial are published. We do, however, justify the continuation of MTX based on recent results from the METHODS trial (5). In the cases where the physician finds an indication for trying MTX after the MERINO trial, usual practice would be to try MTX for three months and then evaluate whether the patient should continue the treatment or not, based on synovitis scores and self-reported effects.

As described in section 5, this result in four groups in the MERINO:2 study, but since MTX treatment length and MTX doses could vary substantial in the observational time of the MERINO:2 study, we will adjust for this in the analyses.

6.4. Blinding

This is an open-label study; potential bias will be reduced by blinding the researcher who will interpret and score the radiographs.

6.5. Study Intervention Compliance

Treatment length and doses will be assessed by questionnaires at 18 months as well as data from the The Norwegian Prescription Database (Reseptregisteret).

6.6. Dose Modification

The treating physician may decide on other doses of MTX than 20mg per week according to standard clinical practice.

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

There are currently no planned extension studies, but the participants have the possibility for continued access to the study intervention beyond completion of the study at the patient level.

6.8. Treatment of Overdose

There have been documented cases of death attributable to MTX. These have often involved patients taking MTX as a daily, rather than weekly dose due to patient, clinician and/or pharmacy error. In the United Kingdom, the National Patient Safety Authority released a report in 2004 on MTX prescribing after 25 deaths and 26 incidents of serious harm in the preceding

decade. In some of these cases, even once the error was identified, patients died due to ongoing deterioration after MTX withdrawal.

For this study, any dose of MTX greater than 30mg/week will be considered an overdose, but there is no clear dose cut-of as for when overdose symptoms can occur, especially since this is regarded a low dose treatment of MTX. No specific treatment for an overdose is recommended.

In the event of an overdose, the investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the electronic patient journal.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

- Prior therapy is recorded in the MERINO trial eCRF.
- All concomitant medication at 18 months in the MERINO:2 study should be recorded in the eCRF.
- Intra-articular corticosteroids during the MERINO:2 study will be registrered from the outpatient clinic notes.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of the study as a whole is detailed in Appendix 1.

7.1. Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue study intervention. See Section 8.3 for safety assessments.

7.2. Participant Discontinuation/Withdrawal from the Study

If study intervention is permanently discontinued, the participant will still be invited to the 12-month visit.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

Not applicable. Examination at 18 months is voluntary. Missing data due to lost to follow-up will not be subject for data imputation.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- To minimize questionnaires and procedures for the participants and the study team, we will use 12-month data from the MERINO trial as baseline data in the MERINO:2 study, including person characteristics, patient-reported outcome measures, clinical examination and imaging.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for research purposes.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

8.1. Patient-reported outcome measures

The following patient-reported questionnaires are to be answered at 18 months using ViedocMe. See Appendix 2 for language and wording of the questionnaires.

8.1.1. VAS pain

The time interval in which pain should be assessed varies across studies. A long interval may lead to recall bias, whereas a too short interval may possibly not adequately cover the whole pain spectrum. In the current study, we ask the participants about their symptoms the last 48 hours:

- Overall finger joint pain, VAS 0-100
- Overall thumb base joint pain, VAS 0-100
- Pain in most painful finger joint ("index joint") VAS 0-100; in case of two or more equally painful joints, a joint is selected randomly
- Overall disease activity in hands, VAS 0-100
- Overall pain in all body joints, VAS 0-100

8.1.2. OMERACT-OARSI responder criteria

The OMERACT-OARSI responder criteria are validated criteria to assess response to treatment in OA clinical trials (15, 16). The OMERACT–OARSI criteria for response are (1) a relative improvement in AUSCAN pain or physical function ≥50% and an absolute change ≥20 mm; or (2) a relative improvement of ≥20% with an absolute change ≥10 mm in at least two of the following three categories: AUSCAN pain, AUSCAN physical function, and patient's global assessment.

In the OMERACT-OARSI criteria, the AUSCAN pain and function subscale scores are used on a 0-100 scale. Since we used the Likert version of the AUSCAN questionnaire in this trial, the AUSCAN pain and function subscale scores were rescaled from 0-20 and 0-36, respectively, to 0-100. Absolute change was calculated as baseline minus follow-up score, and relative change as absolute change divided by baseline score.

8.1.3. Australian/Canadian Hand Index (AUSCAN)

The AUSCAN pain subscale

The hand OA-specific questionnaire AUSCAN includes five items about pain at rest and during activities (gripping, lifting, turning and squeezing objects) during the last 48 hours (17). In the MERINO trial we are using the Likert version, but AUSCAN also exists as numeric rating scales (NRS) and VAS. The response categories for all items are ranging from 0 ("None") to 4 ("Extreme"). A sum score (0-20 scale) can be calculated. There are no instructions on how to handle missing values, and the "half-rule" are applied in the MERINO trial, which means that missing items should be replaced with the mean of the answered items if 50% or more of the items in the respective subscale have been answered. The scale has been translated to Norwegian and validated (18).

The AUSCAN physical function subscale

The hand OA-specific questionnaire AUSCAN includes nine questions concerning tasks requiring grip strength and precision tasks (17). The response categories for all items are ranging from 0 ("None") to 4 ("Extreme"). A sum score (0-36 scale) can be calculated. There are no instructions on how to handle missing values, and the "half-rule" are applied in the MERINO trial. The scale has been translated to Norwegian and validated (18).

The AUSCAN stiffness subscale

The hand OA-specific questionnaire AUSCAN includes one question concerning stiffness in the hands in the morning with response options ranging from 0=none to 4=extreme (17). The scale has been translated to Norwegian and validated (18).

8.1.4. The EuroQol 5 dimensions 5 levels (EQ-5D-5L)

The generic instrument EQ-5D-5L captures five health dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) (19). The EQ-5D-5L encompasses 243 different health states and is one of the most widely used utility instruments in the field of medicine (20). The questionnaire has been translated to Norwegian, and has been used in several Norwegian studies (21). We used the five-level version (EQ-5D-5L). On the EQ-VAS the participant was instructed to self-rate their health on a 0-100 VAS, where 0=worst health and 100=best health. The EQ-5D-5L can be converted to a single summary index by using a formula with different weights to each level in the dimension. European value sets have been defined (22). Based on participant responses, an index score will be calculated to reflect the participant's HRQoL, using the preference scores published from a UK population (23).

8.2. Conventional hand radiographs

The participants are invited for bilateral hand radiographs at 18 months.

The participant is sitting with the hand on the detector (posteroanterior view), and front images are obtained (source to image-receptor distance (SID): 115 cm; exposure: 46 kVp and 2 mAs).

OA in the DIP, PIP, MCP, first carpometacarpal (CMC-1) and scapho-trapezio-trapzoidal (STT) joint will be assessed according to validated scoring systems:

- *The Kellgren-Lawrence (KL) scale* from 1957 is a global index that grades OA on a semi-quantitative five-point scale based on the presence/severity of osteophytes/ossicles, narrowing of the joint space, sclerosis of the subchondral bone, pseudocystic areas, and altered shape of bone ends (24, 25). We will use a modified version, as previously used in the Framingham study (26). The original publication includes DIP, PIP, thumb IP, MCP and CMC-1, and the STT joint will be added in the MERINO trial.
- *The Verbruggen-Veys scoring system* has been proposed for the evaluation of the anatomical phases in patients with erosive disease (N=normal, S=stationary, J=joint space narrowing, E=erosive, R=remodelled) (27). In the original publication, DIP, PIP, thumb IP and MCP (2-5) joints were included. In the MERINO trial, only the 2^{nd}-5^{th} DIP and PIP joints will be assessed. Joints with remodelling in more than 70% of the joint will be scored as E/R, whereas completely remodelled joints will be scored as R.
- Using the *OARSI atlas* from 1995 (revision from 2007) (28, 29) as a reference, the presence/severity of individual features such as osteophytes (grade 0-3) and joint space narrowing (grade 0-3), will be assessed on semi-quantitative scales. In the OARSI atlas only DIP, PIP, thumb IP and CMC-1 are included. In the MERINO trial, also the MCP and STT joints will be scored.

8.3. Safety Assessments

All participants will be monitored according to the National procedure for diagnosis, treatment and follow-up of rheumatoid arthritis in Norway (30), chapter 10.1. Blood tests recommended for monitoring: Hemoglobin, red blood cells, white blood cells with diff. Counts, platelets, ALT, creatinine, (SR and CRP). Patients with comorbidity, abnormal blood tests, and / or polypharmacy treated with DMARD may require more frequent laboratory tests than the general recommendations in the table.

Table: Monitoring interval for blood testing in patients using DMARDs

Drug	Monitoring interval based on duration of treatment		
	<3 months	3-6 months	>6 months
Metotreksat	2–4 weeks	8–12 weeks	12 weeks

8.3.1. Side effects and abnormal laboratory results

Discontinuation of study intervention is required by the investigator when a participant meets one of the conditions outlined in the algorithm below or if the investigator believes that it is in best interest of the participant.

The algorithm below provides recommended actions in case of side effects and abnormal laboratory results according to the shared care protocol by Oxford University Hospital, NHS (https://www.ouh.nhs.uk/oxparc/professionals/documents/methotrexate-scp-july-2015.pdf). In the event of a medically significant unexplained abnormal laboratory test value the test should be followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Side effects	Action
WBC < 4 x 109/l WBC < 3.5 x 109/l	Adults: Perform a differential and increase frequency of monitoring. Withhold and discuss with specialist. Bone marrow suppression can occur abruptly.
Neutrophils < 2 x 109/l	Withhold and discuss with specialist. Bone marrow suppression can occur abruptly.
Platelets < 150 x 109/l	Withhold and discuss with specialist. Bone marrow suppression can occur abruptly.
MCV >110 fl MCV >105 - 110 fl	Stop methotrexate and seek advice. Check folate, B12 and thyroid function tests and treat if appropriate. If WBC normal repeat in 4 weeks.
Liver function 2 - 3 fold rise in ALT >3 fold rise in ALT	Reduce the dose and repeat in 1 - 2 weeks. Withhold until discussed with specialist.
Renal impairment	Patients who develop dehydration, pre-renal or acute renal failure while on methotrexate should have methotrexate withheld and FBC monitored closely. Review any changes in medication particularly ACEI and ARB.
Unexplained fall in albumin	Withhold and speak to specialist.
Nausea and/or vomiting	Usually improves over time. If troublesome for adults consider: • Increasing the dose of folic acid to 5 mg daily up to 6 days a week - omitting on the day methotrexate is taken. • Splitting methotrexate dose over one evening and next morning. • A short-term anti-emetic. If unable to tolerate refer back to specialist for review.
Hair loss	Usually mild, rarely significant. Reversible on stopping drug.
Rash	Withhold treatment and discuss with specialist.

Mouth ulcers, mucositis	Mouth ulcers may respond to increasing folic acid as above. If severe despite extra folic acid stop methotrexate and refer to a specialist for advice.
Menstrual dysfunction/amenorrhoea	May occur during treatment and for a short while after cessation.
Otherwise unexplained dyspnoea or cough (especially if accompanied by fever/sweats)	Methotrexate pneumonitis may occur. Withhold treatment, arrange chest X-ray and discuss urgently with consultant.
Abnormal bruising	Withhold until FBC result available.
Sore throat or other unusual infection	Urgent FBC and withhold until FBC result available. Susceptible to opportunistic infections such as viral wart, tuberculosis and pneumocystitis.
Cervical dysplasia	Contact gynecologist.
Diarrhea	Consider reducing dose.
Fever, chills	Withhold until FBC result available

FBC=full blood count, MCV=mean corpuscular volume, WBC=white blood cells, ALT= alanine aminotransferase

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

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3.

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

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

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

All SAEs will be collected from the signing of the informed consent form until the scheduled 30-month visit (after entering the MERINO trial). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

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

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

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.6) will be followed until resolution, stabilization, or the event is otherwise explained. Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

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

8.4.5. Pregnancy

- A female/male participant must be instructed to immediately inform the investigator if she/his partner becomes pregnant during the study. For details on collection of pregnancy information, see Appendix 4.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- A pregnant participant should be withdrawn from the study.

8.4.6. Adverse Events of Special Interest

A prolonged cough of more than 4 weeks duration is of special interest and should be followed up promptly with a CT of the lungs.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Antibodies are not evaluated in this study.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The analysis and reporting will be done on all data from all participants at the time the study ends. The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.1. Statistical Hypotheses

The primary objective is to demonstrate that MTX is superior to treatment as usual in achieving slower radiographic progression at 30 months. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows:

- Null hypothesis: MTX treatment for 30 months is not different from placebo (12 months) and subsequent treatment as usual (18 months) with respect to the progression of Verbruggen-Veys scoring system in participants with erosive hand OA.

vs.

- Alternative hypothesis: MTX treatment for 30 months is different from placebo (12 months) and subsequent treatment as usual (18 months) with respect to the progression of Verbruggen-Veys scoring system in participants with erosive hand OA.

Secondary outcomes (1):

- Null hypothesis: MTX treatment for 30 months is not different from placebo (12 months) and subsequent treatment as usual (18 months) with respect to the progression of KL scale or OARSI atlas in participants with erosive hand OA.
- Alternative hypothesis: MTX treatment for 30 months is different from placebo (12 months) and subsequent treatment as usual (18 months) with respect to the progression of KL scale or OARSI atlas in participants with erosive hand OA.

Secondary objective (2)

- Null hypothesis: MTX is not different from placebo/treatment as usual with respect to change from baseline to 12/30 months in OMERACT-OARSI responder criteria, AUSCAN or EQ-5D-5L.
- Alternative hypothesis: MTX is different from placebo/treatment as usual with respect to change from baseline to 12/30 months in OMERACT-OARSI responder criteria, AUSCAN or EQ-5D-5L.

Multiplicity control is not relevant for the study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full analysis set (FAS)	All randomized participants.
Safety analysis set (SAS)	All participants who are exposed to investigational intervention.

The full analysis set will be used to analyze endpoints related to the efficacy objectives and the safety analysis set will be used to analyze the endpoints and assessments related to safety.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

9.3. Statistical Analyses

Continuous variables will be subject to linear mixed models. Binary response variables will be analyzed using logistic regression models (possibly adjusting for within-subject dependencies by mixed model approaches). Analyses at the joint level will apply generalized estimating equations (GEE) to account for dependency between joints within one person. The SAP will detail these procedures.

The hypotheses will be evaluated by the p-value associated with the between group difference at study end. A conclusion of superiority will be made if the null hypothesis is rejected on an overall significance level of 5%. The SAP will detail these procedures, as well as alternative and further supportive evaluations, such as analyses including unbalanced baseline predictors or modifications of the linear regression model in case validity assumptions are not met.

9.4. Interim Analysis

Interim analysis is not performed in this study.

9.5. Sample Size Determination

The sample size is not based on statistical considerations. All participants entering the MERINO trial will be asked to complete a 30-month follow-up visit in the MERINO:2 study. The MERINO trial aims to include 153 participants.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The MERINO:2 study is supported by a grant from the Diakohjemmet Hospital research fund of NOK 125.000,-.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They are required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Recruitment strategy

Former participants of the MERINO trial will be contacted by SMS: "We invite you to participate in a one-year follow-up examination in the MERINO trial, including hand radiographs and questionnaires. Please click the link to read more." The link will guide them to a one-page information pamphlet, from which they can click to a digital ICS with BankID identification through the University of Oslo portal "Nettskjema" and "TSD".

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by IEC members, and by inspectors from regulatory authorities.

- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

In addition to approval by the REC, the study will be reviewed and approved by the local hospital Data Protection Officer and the local hospital Research Council.

10.1.7. Dissemination of Clinical Study Data

- After completion of the study, a Clinical Study Report (including results on all study objectives) according to ICH Topic E3 will be written by the Sponsor or the designated CRO.
- The Investigators will inform the Sponsor in advance of any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.
- The Sponsor will not suppress or veto publications but maintains the right to delay publication to protect intellectual property rights.
- The study will be posted on clinicaltrials.gov

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). A web-based eCRF software solution will be used to collect study data (Viedoc™, Uppsala, Sweden). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

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

10.1.10. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is when the site first actively contacts a potential participant and will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

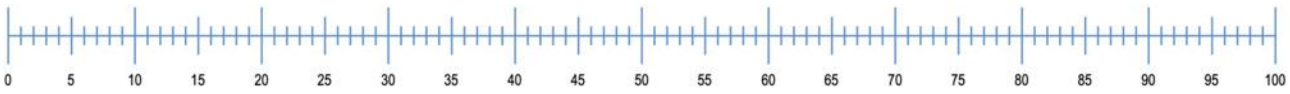
10.2. Appendix 2: Patient reported outcome measures

10.2.1. VAS pain

SYMPTOMER I LEDD (VAS)

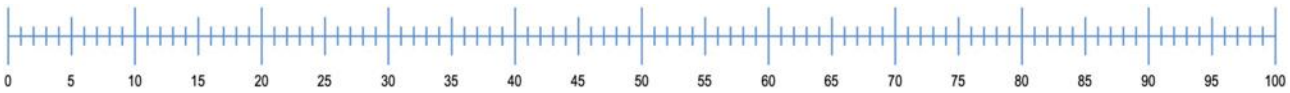
1. Hvordan vil du beskrive de leddsmertene du har hatt i fingrene (minus tommel-basis) i løpet av de siste 48 timene?

Sett en X på skalaen under, der 0 = "ingen smerter" og 100 = "verst tenkelig smerte".



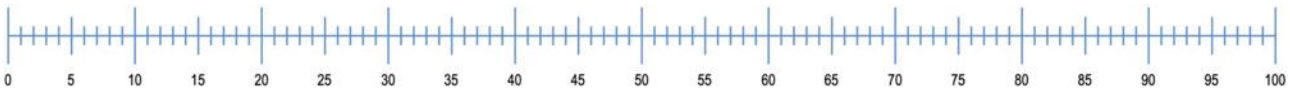
2. Hvordan vil du beskrive de leddsmertene du har hatt i tomlenes grunnledd i løpet av de siste 48 timene?

Sett en X på skalaen under, der 0 = "ingen smerter" og 100 = "verst tenkelig smerte".



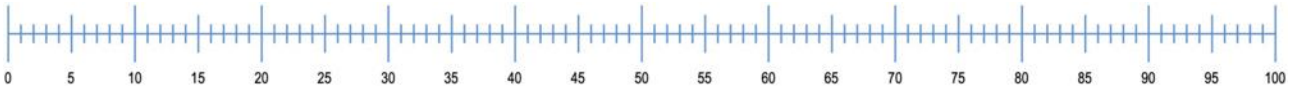
3. Hvis du vurderer det mest smertefulle fingerleddet, hvor vondt har dette leddet vært i løpet av de siste 48 timene?

Sett en X på skalaen under, der 0 = "ingen smerter" og 100 = "verst tenkelig smerte".



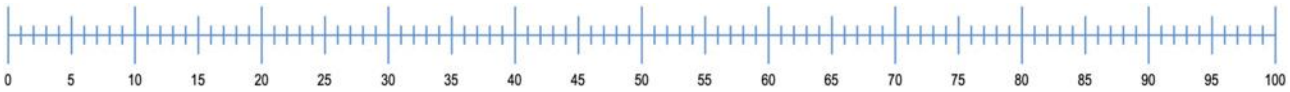
4. Vi ber deg vennligst vurdere aktiviteten i håndartrosesykdommen i løpet av de siste 48 timene. Når du tar alle symptomer med i betraktning, hvordan syns du tilstanden er?

Sett en X på skalaen under, der 0 = "ingen smerter" og 100 = "verst tenkelig smerte".



5. Hvordan vil du beskrive de leddsmertene du har hatt de siste 48 timene? Ta alle ledd i kroppen med i betraktningen.

Sett en X på skalaen under, der 0 = "ingen smerter" og 100 = "verst tenkelig smerte".



6. Har du tatt smertestillende siste 48 timer? (Paracet/Pinex, Paralgin Forte, Nobligan/Tramadol, opiater/morfin etc)

0☐ Nei

1☐ Ja

7. Har du tatt medisin siste 48 timer? (Voltaren, Ibux, Naproxen, Arcoxia, Vimovo etc)

0☐ Nei

1☐ Ja

10.2.2. Australian/Canadian Hand Index (AUSCAN)

AUSTRALIAN/CANADIAN HAND INDEX (AUSCAN)

Del A. Smerte

De følgende spørsmål gjelder hvor mye smerte du har opplevd som skyldes artrose i hendene. Angi i hvert tilfelle graden av smerte i løpet av de siste 48 timer.

Hvor sterke smerter har du i hendene dine?

1. I ro (altså når du ikke bruker hendene)

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Sterke 4☐ Ekstreme

2. Når du griper gjenstander med hendene

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Sterke 4☐ Ekstreme

3. Når du løfter gjenstander med hendene

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Sterke 4☐ Ekstreme

4. Når du snur gjenstander med hendene

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Sterke 4☐ Ekstreme

5. Når du klemmer på gjenstander med hendene

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Sterke 4☐ Ekstreme

Del B. Stivhet

Det følgende spørsmål gjelder hvor mye leddstivhet (ikke smerte) du har opplevd i hendene de siste 48 timer. Stivhet er en følelse av hindring eller hvor vanskelig du har for å bevege hendene.

1. Hvor kraftig er stivheten i hendene når du våkner om morgenen?

0☐ Ingen 1☐ Litt 2☐ Moderat 3☐ Kraftig 4☐ Ekstrem

Del C. Vanskeligheter ved utførelse av daglige aktiviteter

Følgende spørsmål omfatter din fysiske funksjon. Med dette mener vi din bevegelsesevne og evnen til å klare deg selv. For hver av de følgende aktiviteter ber vi

deg beskrive vanskelighetene du har opplevd i løpet av de siste 48 timer på grunn av artrose i hendene.

Hvor store vanskeligheter har du med følgende:

1. Skru opp kraner og lignende

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

2. Vri et rundt dør- eller skaphåndtak

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

3. Kneppe igjen knapper

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

4. Feste smykker (klokker, øreringer, mansjettknapper, halskjeder, nåler og armbånd)

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

5. Åpne et nytt glass med skrulokk

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

6. Bære en full kaffe/vannkjele med en hånd

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

7. Skrelle grønnsaker/frukt

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

8. Løfte opp store tunge gjenstander

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

9. Vri opp vaskekluter

0☐ Ingen 1☐ Litt 2☐ Moderate 3☐ Store 4☐ Ekstreme

10.2.3. The EuroQol 5 dimensions 5 levels (EQ-5D-5L)

EUROQOL 5 DIMENSIONS

Vis hvilke utsagn som passer best på din helsetilstand i dag ved å sette et kryss i en av rutene utenfor hver av gruppene nedenfor.

Gange

1☐ Jeg har ingen problemer med å gå omkring.

2☐ Jeg har litt problemer med å gå omkring.

3☐ Jeg har middels store problemer med å gå omkring.

4☐ Jeg har store problemer med å gå omkring.

5☐ Jeg er ute av stand til å gå omkring.

Personlig stell

1☐ Jeg har ingen problemer med personlig stell.

2☐ Jeg har litt problemer med å vaske meg eller kle meg.

3☐ Jeg har middels store problemer med å vaske meg eller kle meg.

4☐ Jeg har store problemer med å vaske meg eller kle meg.

5☐ Jeg er ute av stand til å vaske meg eller kle meg.

Vanlige gjøremål (for eksempel arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

1☐ Jeg har ingen problemer med å utføre mine vanlige gjøremål.

2☐ Jeg har litt problemer med å utføre mine vanlige gjøremål.

3☐ Jeg har middels store problemer med å utføre mine vanlige gjøremål.

4☐ Jeg har store problemer med å utføre mine vanlige gjøremål.

5☐ Jeg er ute av stand til å utføre mine vanlige gjøremål.

Smerte/ubehag

1☐ Jeg har verken smerte eller ubehag.

2☐ Jeg har litt smerter eller ubehag.

3☐ Jeg har middels sterke smerter eller ubehag.

4☐ Jeg har sterke smerter eller ubehag.

5☐ Jeg har svært sterke smerter eller ubehag.

Angst/depresjon

1☐ Jeg er verken engstelig eller deprimert.

2☐ Jeg er litt engstelig eller deprimert.

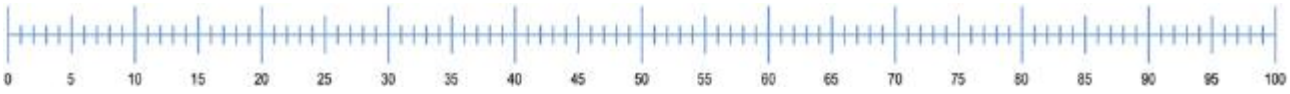
3☐ Jeg er middels engstelig eller deprimert.

4☐ Jeg er svært engstelig eller deprimert.

5☐ Jeg er ekstremt engstelig eller deprimert.

Vi vil gjerne vite hvor god eller dårlig helsen din er i dag.

Sett en X på skalaen under, der 0 = den dårligste helsen du kan tenke deg og 100 = den beste helsen du kan tenke deg.



10.2.4. Medisiner

Hvilke medisiner brukes fast (salgsnavn, dosering og administrasjonsform)?
Eksempel:

Albyl-E	*E 75 mg x 1*	*tablett*

Salgsnavn	Dosering	Adm. form
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

11.		
12.		

Hvilke medisiner brukes **ved behov** (navn, dosering)?

Salgsnavn	Dosering	Adm. form
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		

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

10.3.1. Definition of AE

AE Definition

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

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

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

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Sponsor’s Safety Risk Management department will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the Trial Master File (TMF).

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Adequate contraception includes oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or system, vasectomized partner or sexual abstinence.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This

applies only to male participants who receive methotrexate, and is a reason to blind break. The participant will be withdrawn from the study due to blind break.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Medical Monitor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Medical Monitor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Medical Monitor within 24 hours of learning of a participant's pregnancy. This applies only to female participants who receive MTX. The participant will be withdrawn from the study due to blind break and the teratogenic effect of methotrexate.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Medical Monitor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the Medical Monitor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

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