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Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study

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Keywords:	RHEUMATOLOGY, Ultrasound < RADIOLOGY & IMAGING, Observational Study

SCHOLARONE[™] Manuscripts

Administrative information

Title

Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study

Authors

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Trial registration

Data category	Information
Primary Registry and Trial Identifying	ClinicalTrials.gov
Number	NCT06133244
Date of Registration in Primary Registry	15-11-2023
Secondary Identifying Numbers	NL85445.041.23
Source(s) of Monetary or Material	UMC Utrecht, ReumaNederland
Support	
Primary Sponsor	UMC Utrecht
Secondary Sponsor(s)	N/A
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Public Title	Getting a grip on hand function
	impairment in systemic sclerosis
Scientific Title	Hand Function Impairment in Systemic
	Sclerosis: Outcomes, Mechanisms, and
	Experience (HANDSOME) Study
Countries of Recruitment	The Netherlands
	United Kingdom

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Diagnostic Tests: Imaging, blood
samples, functional tests, and physical
examination
Study Population
Patients (18 years and older) with:
1. SSc with hand contractures
2. SSc patients without contractures
and disease duration of < 4 years
3. VEDOSS patients
Ages eligible for study: ≥18 years
Sexes eligible for study: both
Accepts healthy volunteers: no
Inclusion Criteria: Age > 18 years
2.
Exclusion Criteria: Patients with diabetic
cheiroarthropathy and Dupuytren's
disease, based on expert opinion
Observational
19-04-2024
300
Recruiting
Determination of risk factors for hand
function impairment in systemic
sclerosis (SSc) patients with early
disease, very early disease, and
established hand impairment
(contractures) at 2 years follow-up

	Validation of the Dutch PASTUL
	questionnaire
Ethics Review	Approved on 19-03-2024
Completion date (estimated)	04-2028
Summary Results	N/A
IPD sharing statement	Undecided

Protocol version

V1.3 6-06-2024

Abstract

Introduction The majority of all systemic sclerosis (SSc) patients experience hand function impairment. The exact cause for this impairment is yet unknown. As impaired hand function hugely impacts daily functioning and quality of life, there is a high unmet need for effective treatments. With the availability of new imaging modalities, biomarkers, and lab techniques, opportunities arise to increase insights into the factors contributing to hand function impairment. The objective of this study is to identify risk factors and underlying mechanisms leading to hand function impairment in SSc.

Methods and analysis This is a longitudinal observational multicentre study in patients with Very Early Diagnosis of Systemic Sclerosis (VEDOSS) and SSc under care of the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG), Leiden UMC (LUMC), Radboudumc, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Medical history, clinical status, nailfold capillaroscopy, skin assessments, serum biomarker analysis, ultrasound, elastography and MRI will be performed and results related to hand function measurements.

Ethics and dissemination This study was approved by the Medical Research Ethics Committee NedMec (MREC NedMec) in the Netherlands and by HRA and Health and Care Research Wales (HCRW) in the UK. Results will be published in scientific journals and presented at scientific congresses and patient meetings.

Trial registration number NCT06133244

Keywords

Systemic sclerosis, hand function, imaging, biomarkers, observational

Word count:

Strengths and limitations of this study

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- This is the first study that extensively assesses the hand function in systemic sclerosis patients
- This is a large prospective international multidisciplinary study with a follow-up of 2 years in 300 patients
- This is the first study that explores elastography of tendons in the hand

- The results of this study can guide future clinical trials and development of treatment for hand function impairment in systemic sclerosis
- Conclusions can be limited due to the lack of prior research for comparison and the heterogeneity of the disease

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Introduction

Background and rationale

Systemic sclerosis (SSc) is a rare disease characterized by inflammation, fibrosis, and vasculopathy [1]. Clinical presentation is heterogeneous and includes skin thickening and internal organ involvement. Thus far, studies in SSc mainly focused on organ damage and mortality. However, other disease manifestations have a tremendous impact on quality of life and daily functioning.

Around 90% of SSc patients experience hand function limitation, which leads to impaired daily functioning and work participation [2,3]. An important cause of impaired hand function is contractures of the hand, which are reported in half of the patients [4]. Contractures are reported more frequently in patients with diffuse cutaneous systemic sclerosis (dcSSc) and associated with anti-topoisomerase I (ATA) positivity [5]. Only a few studies explored imaging techniques in SSc hands. Thickening of the A1 pulley and flexor tendons was associated with hand disability in a small group of patients (n=29). Soft tissue calcifications were seen in affected tendons, but this has not been studied in more detail [6,7]. In other small studies, ultrasound and MRI showed subclinical synovitis or tendinitis and bone erosions, which could also contribute to impaired hand function [7,8]. Shear wave elastography (SWE), a new imaging modality to assess the elastic properties and stiffness of soft tissue, has been studied in SSc skin and muscles but no studies have assessed hand tendons. Moreover, no studies explored tenosynovial changes and underlying biological mechanisms, especially in correlation with imaging or functional tests. This leaves clinicians 'in the dark' regarding diagnostic workup and effective management. Current management for hand symptoms includes exercises, splints, and sometimes immunosuppressive therapies. However, it is unknown which treatment is suitable for which patient and the efficacy of immunosuppressive drugs has not been confirmed in trials. As impaired hand function in SSc hugely daily functioning and with that quality of life, there is a high unmet need for effective treatments [9]. With the availability of new imaging modalities, biomarkers, and lab techniques, opportunities arise to study this problem in more detail to guide optimal treatment development.

This study aims to enhance the understanding of the mechanisms underlying hand function impairment in patients with systemic sclerosis (SSc), including development from the early phase in very early disease of systemic sclerosis (VEDOSS). The study is based on three key hypotheses: 1) Hand function in SSc is affected through various pathways involving joints, tendons, skin, and/or microcirculation. 2) Prior to the development of contractures, tissue changes—such as inflammation, fibrosis, or decreased elasticity—can be detected using imaging techniques. 3) Patients with hand impairment can be categorized into distinct subgroups based on clinical and imaging features, as well as protein markers, which may reflect different activated biological pathways.

Objectives

Primary objective

To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients.

Secondary objectives

To determine risk factors and categorize patients with hand function impairment into subgroups based on clinical, immunological, and/or imaging characteristics, thereby guiding future research toward personalized treatment strategies

To assess the impact of hand function impairment on quality of life, daily functioning, work, and participation, and explore how these impacts relate to the identified mechanisms and patient subgroups

Patient and public involvement statement

Members of the Dutch (NVLE) and UK (SRUK) systemic sclerosis patient organizations are involved in every step of this project. They have been involved in the study design and during the development of the protocol, a qualitative study was performed to explore patients' functional complaints and (unmet) needs. The study protocol has been co-produced to ensure representation and input from those with personal experiences. All questionnaires have been checked on content and feasibility. During all meetings with the entire research team, patients will be involved to share their opinions on decisions being made and provide advice on recruitment and dissemination of results.

Study setting

This is a longitudinal observational international study in patients with VEDOSS and SSc who are under care at the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG) Leiden UMC (LUMC), Radboud UMC, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years.

Study population

Patients (n=300; 18 years and older) with:

- 1) SSc with hand contractures (n=50)
- 2) SSc patients without hand contractures (n=200) and disease duration of < 4 years
- 3) VEDOSS patients (n=50)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- 1) Age >18 years
- 2) For patient populations 1) and 2):

a. Diagnosis of SSc according to the 2013 EULAR-ACR classification criteria for SSc [10] For patient population 3):

b. Diagnosis of VEDOSS, defined as the presence of RP, puffy fingers, SSc-specific autoantibodies, and abnormal nailfold capillaroscopy, while not fulfilling the 2013 EULAR-ACR classification criteria for SSc [11].

3) Only for patient population 1):

a. Hand contractures are defined as a range of motion < 75% of the normal range of at least one small hand joint of [12].

4) Willing and be able to understand the study information and sign the informed consent form.

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation:

- 1) Age < 18 years
- 2) Patients with diabetic cheiroarthropathy and Dupuytren's disease, based on expert opinion

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Study procedures

Three patient groups are included and then followed for 24 months. Table 1 shows the study procedures and data collection in these three groups.

Table	1: Ove	rview d	of study	procedures
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	Baseline	6 months	12 months	24 months
Informed consent	Х			
Medical history	х			
Nailfold capillaroscopy	х			x
Clinical status	х	х	x	x
Skin assessment	х	х	x	x
PROMs	х	x	x	x
Serum and plasma collection	x	x	x	x
Hand function assessment	x	х	x	x
Ultrasound	x	х	x	x
Elastography *	x	x	x	x
MRI *	x			
Vascular imaging **	х	x	х	x

*Sub-analysis comparing MRI with ultrasound features. UMC Utrecht only

** Sub-analysis assessing hand circulation extensively with ultrasound using a 70mHz probe. UMC Groningen only

Medical history

Clinical data collected in routine care will be retrieved at baseline. Age, sex, height, educational level, ethnicity, and auto-antibody status (ANA negative/positive, line blot and scleroderma blot auto-antibodies) are collected.

In addition, data will be collected on previous tobacco use, vasoactive and immunosuppressive medication use and dosage, digital ulcers, pitting scars, gangrene, clinical arthritis, myositis, interstitial lung disease, pulmonary hypertension, and scleroderma renal crisis.

Nailfold capillaroscopy

A capillaroscope with a magnification of 200x is used to assess all fingers, including the thumbs. At least two adjacent fields of a linear millimetre in the middle of each finger are captured and stored. Images will be scored according to EULAR criteria centrally on normal or abnormal/scleroderma patterns [13].

Clinical status

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- weight, blood pressure, (change) in tobacco use, (change in) occupation, (changes in) immunosuppressive and/or vasoactive medication use and dosage,

- new onset interstitial lung disease (y/n), pulmonary hypertension (y/n), scleroderma renal crisis (y/n)

- Hb (mmol/L), ESR (mm/h), CRP (mg/L), CK (IU/L).

Skin assessment

The modified Rodnan skin score (mRSS) (assessed by trained investigators), presence of digital ulcers (if yes: count, location), pitting scars (if yes: count, location), gangrene (if yes: location), calcinosis cutis in the hands (if yes: location), clinical arthritis ((if yes: site and joint count), and myositis will be assessed/recorded [14].

PROMs

Patient Related Outcome Measurements will be collected in the week of the study visit and the following questionnaires will be collected:

- Cochin Hand Function Scale (CHFS), containing 18 questions, structured in 5 distinct categories, designed to evaluate hand function in kitchen activities, dressing, personal hygiene, office, and other generic activities [15].

- brief Satisfaction with Appearance Scale (SWAP), containing six questions about subjective body image dissatisfaction and the perceived social impact [16].

- IMTA Productivity Cost Questionnaire (IPCQ), a standardized instrument for measuring and valuing health-related productivity losses [17].

- Utrecht Scale for Evaluation of Rehabilitation (- Participation) (USER-P), which measures both subjective and objective participation in the community [18].

- Health-related quality of life (EQ5D5L), that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression [19].

- Self-assessment of skin thickening (PASTUL), a self-reported measure of skin thickness in the upper limb [20].

- Scleroderma Health Assessment Questionnaire (SHAQ), which measures disease status changes [21].

Serum and plasma collection

Two blood samples will be collected (both a maximum of 10 ml) to obtain both serum and plasma samples during each visit. The venepuncture is performed at routine outpatient or daycare unit visits. Aliquots of both serum and plasma samples will be stored at -80 C degrees. Serum and plasma analysis will include measurement of levels of immunological markers (including cytokines) and fibrotic markers.

Hand function assessment

At all study visits, hand function will be assessed by trained investigators. Hand mobility is assessed with the range of motion of the wrist joint, range of motion of the finger joints, delta Finger-to-Palm distance [22], and the mHAMIS [23]. Grip strength is measured with the

JAMAR® dynamometer and JAMAR pinch dynamometer® for the two-point pinch, three-point pinch, and lateral pinch.

<u>Ultrasound</u>

Ultrasound will be performed by an operator/physician trained in musculoskeletal ultrasound. An ultrasound machine with a high-frequency probe (linear or hockey stick with 8-24MHz) will be used. Images of all study sites will be stored and rated centrally by the coordinating researcher in conjunction with ultrasound experts afterwards. The presence of arthritis of the wrist, distal radio-ulnar joint (DRUJ), metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints will be assessed using validated semiguantitative methods in Bmode and power Doppler setting if there was grey-scale evidence of inflammation. Furthermore, the presence of osteophytes is assessed. The first to fifth flexor and extensor tendons of both hands will be assessed longitudinally. Tenosynovitis and sclerotic thickening of tendon(-sheaths) and calcifications within tendons will be evaluated. The pulley and tendons are measured at the at the MCP joint. The fingers of the dominant hand will be assessed with ultrasound for vascular involvement. Dig 2 will be assessed standardly. In addition, fingers with ulceration if present on other fingers will be assessed. Additionally, intima media thickness (IMT) will be measured in dig 2. All arteries per finger will be assessed at the proximal phalangeal part. Qualitative scoring is performed. See Appendix 1, imaging protocol, for the full ultrasound protocol.

Elastography

In addition to the ultrasound assessment, fibrosis of the first to fifth flexor and extensor tendons of both hands will be measured quantitatively using shear wave elastography (SWE) in a subgroup of patients at the UMC Utrecht (n=100). SWE is measured with the ultrasound machine GE healthcare LOGIQ E10s using the linear ML4-20 transducer.

Vascular imaging

Another addition to the ultrasound assessment is the extensive vascular evaluation performed in patients in the UMC Groningen (n=35). The vascular protocol entails ultrasound measurements of IMT performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) which uses an ultra-high frequency ultrasound transducer (max 70 MHz). Finger pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands).

<u>MRI</u>

In a subgroup of patients included at the UMC Utrecht (n=50), a contrast-enhanced 3 Tesla MRI of the dominant hand will be done at baseline, recording the presence of synovitis, joint capsule thickening of the wrist, MCP and PIPs, and thickness or inflammation of tendons and tendon sheaths of the hands. The researcher will determine whether there are no contra-indications according to the MRI screening form used in the UMC Utrecht. The entire MRI protocol is shown in Appendix 1, imaging protocol.

Outcomes

Main study parameter/endpoints

The correlation between the Cochin Hand Function Scale (CHFS) scores and circulating biomarkers, as well as changes observed through imaging, over a two-year follow-up period will be assessed.

Secondary study parameters/endpoints

- The change in hand function at 2 years, reflected by the Cochin Hand Function Scale (CHFS) and hand function measures.
- Predictive value of imaging features and circulating biomarkers at baseline for change of hand impairment at follow-up.
- Distinct subgroups of patients based on clinical, immunological, and imaging characteristics.
- Health-related quality of life (EQ5D-5L), daily functioning (S-HAQ), work (IPCQ), and participation (USER-P) in relation to CHFS.

Sample size

For multivariable regression analysis with a continuous outcome, we need at least 10 patients per variable studied according to rule of thumb. As we anticipate including 300 patients we will be able to validly study 30 variables for their association with the (progressive) hand impairment (including patient subgroup as a covariate in the analysis) with sufficient power. We will also perform more explorative subgroup analyses per patient population as well as use data reduction techniques (e.g. principal component analysis) and/or analysis techniques more suitable for analysing outcomes with many independent variables compared to the number of patients (like partial-least squares regression or Lasso regression). Furthermore, we will explore clusters of patients developing hand function impairment using imaging and protein biomarkers to inform our multivariable analyses. Missing data will be accounted for using multiple imputation. With the above calculation and strategy, we think our cohort of 300 patients will be sufficient to obtain meaningful results.

Recruitment and consent

Subjects will be informed about the study by their treating physician and receive an information letter. Thereafter, they will have the possibility to ask questions, either during a face-to-face appointment or over the phone with the investigator or research nurses. They will be allowed sufficient time, but at least 24 hours, to consider their participation. If the subject wants to participate, a meeting will be set for signing the consent form and explaining the study procedure. This will take place at a day/time suitable for the patients, ideally combined with routine care appointments.

Data management

Data handling is described in detail in the data management plan. This has been approved by the data manager of the UMC Utrecht.

Data from patients will be handled with care, taking into consideration the required confidentiality as stated by the Dutch 'AVG ('Law for the Protection of Personal Information'), the 'Wet Gemeenschappelijke Behandelings Overeenkomst' ('Law Common Treatment Agreement'), and the privacy policy of the UMC Utrecht. The electronic patient files will be used as the source for the clinical data. Data will be pseudonymized and the key will be stored in a separate secured folder at each clinical site.

Patient material will be encoded and stored at the UMC Utrecht, department of Rheumatology & Clinical Immunology. Patient material is only used to answer the questions in this study, material is not stored for biobank purposes. Only the local investigators are permitted access to the code key. Research documents, from which patient identity can be deduced will only be accessible for third parties (for example monitors, auditors, and inspection by competent authorities) after specific consent by the participant in the informed consent document. Research documents will be kept up to 15 years after ending the research.

In all local centers, images and patient material will be stored according to local protocol and collected and analysed centrally.

Monitoring and Quality Assurance

A central independent monitor will perform yearly monitoring according to the Monitoring Plan.

Statistical methods

To predict decline in hand function (defined as an increase CHFS) at 6, 12, and 24 months we will use linear/logistic regression analysis, with as independent variables/predictors baseline patient characteristics, as well as short term (over 6 months) changes in clinical scores, imaging markers and biomarkers. When needed we will use (regression) techniques suitable for a high variable to patient/outcome ratio (see section Statistics/Power calculation)

Characteristics at baseline and changes over time seen on ultrasound will be reported for the number of patients with tenosynovitis, arthritis and/or calcifications in tendons, the mean thickness and elastography of tendons, and the A1 pulley. Linear mixed models will be used to analyse changes over time (both with time defined as follow-up time or as time since early disease/VEDOSS) regarding hand function scores and to relate these changes to changes in ultrasound and serum/plasma biomarkers.

Also joint modelling of the multivariate longitudinal data (i.e. the clinical scores, imaging- and biomarkers measured over time) and time-to-event (i.e. development of limitations of hand function) will be performed. In this analysis so called 'latent trajectories' in the longitudinal markers (i.e. not directly observed subgroups of patients with a distinct course in longitudinally measured 'markers') will be related to the development of the outcome (in this case limitations in hand function). Results can be used to obtain more insight into the development of limitations in hand function, and the possible existence of subgroups regarding the development of hand function limitations. Models may also be used to 'dynamically' predict the outcome over time. The patient subgroups (VEDOSS/SSc with/without hand impairment) will be taken appropriately into account in all analyses and/or subgroup analyses will be performed.

To further explore subgroups in patients with/without hand function limitations. Baseline clinical, imaging-, and biomarkers as well as changes over time in markers will be used in a

cluster analysis. As most likely different types of variables (i.e. linear, binary, and categorical) will be included we will use an algorithm suitable for this like k-medoid cluster analysis using partitioning around medoids. The validity of different solutions regarding the number of clusters will be evaluated using statistical criteria (e.g. silhouette width, calculated based on Gower distances) as well as clinical relevance by expert opinion (also considering the results of the above analyses) to derive a final solution. Possible confounders will be assessed and corrected for.

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Ethics and dissemination

The Medical Research Ethics Committee NedMec (MREC NedMec) reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements, the MREC NedMec issued an approval for the Netherlands. HRA and Health and Care Research Wales (HCRW) has approved the study in the UK. The study will be conducted according to the principles of the Declaration of Helsinki (2013). Results will be published in scientific journals and presented at scientific congresses and patient meetings.

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Competing interests

None

Author statement

Primary research team (University Medical Centre Utrecht, The Netherlands), responsible for study design, data collection, data management, data analysis, data interpretation, report writing, and decision to submit.

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- Dr. S.C. Mastbergen, co-PI
- Drs. M.J. Greveling, coordinating researcher

Participating research team sponsor (University Medical Centre Utrecht, The Netherlands), advising on study design, collaborating on data collection, data management, data analysis, and data interpretation.

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- E. Blamont, UK systemic sclerosis patient organisation (SRUK)
- N. Jeffries-Owen, UK systemic sclerosis patient organisation (SRUK)
- K. Fligelstone, Royal Free Hospital patient partner

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Appendix 1 Imaging protocol

Ultrasound

Materials

A high-end ultrasound machine (i.e. GE Logiq E10s, GE Healthcare, United States) will be used, equipped with one multifrequency linear probe and a high frequency (hockey stick) probe. Settings will be optimized for each machine and settings stay stable during the entire study period. The sonographer is allowed to modify depth and focus.

Variables

Outcomes	Area		
Joint effusion (1) Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP		
Synovial hypertrophy (1) Abnormal hypoechoic intraarticular tissue that is non- displaceable and poorly compressible and which may exhibit Doppler signal.	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP		
Doppler signals (1) Flow signal in the synovium must be in synovial hypertrophy to be considered as a sign of synovitis	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP		
Osteophytes Bone spurs at the end of bones	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP		
<i>Tenosynovitis</i> (2) Abnormal anechoic and/or hypoechoic tendon sheath widening related to the presence of tenosynovial abnormal fluid and/or hypertrophy	 Dorsal Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar Finger flexor digitorum (SUP/PROF) 2-5 at MCP level Flexor pollicis longus and brevis at MCP level 		
Tenosynovial effusion (2) Presence of displaceable abnormal anechoic or hypoechoic material within the synovial sheath, either localized or surrounding the tendon	 Dorsal Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar Finger flexor digitorum (SUP/PROF) 2-5 at MCP level Flexor pollicis longus and brevis at MCP level 		
Thickening of finger flexor and extensor tendons (3)	 Central slip of extensor tendons 2-5 at MCP level Extensor pollicis longus and brevis at MCP level Finger flexors 2-5 (sup+prof) at MCP level 		

	 Flexor pollicis longus and brevis at MCP level
Calcifications Hyperechoic foci with or without shadowing at volar site the digits.	Volar Digits 1-5
Thickening of A1 pulley (4,5) This annular structure situated at the level of the MCP joint consists of a strap surrounding the flexor tendon sheath. It appears as a hypoechoic band superficial to the flexor tendon sheath. Normal thickness in neutral position 0.38mm (SD 0.15) and hooked/contracted position 0.37mm (SD 0.15).(6)	 Volar A1 pulley 1-5 at the MCP level
Occlusion digital arteries	Volar
Absence of colour Doppler	 radial artery of the index finger at MCP – DIP traject
signals in a visible artery filled with hypoechoic material. even	 proper palmar digital arteries of digit 2-5 Princeps pollicis artery
with low pulse repetition	
requency and high colour	
Intima-media thickness	Volar
Thickness of tunica intima and tunica media.	 radial artery of the index finger digit at the MCP – DIP traject
Shear wave elastography (8) Stiffness of the tissue (LIMCL)	Finger flexor tendons 2-5 at MCP level
only)	 Finger extensor tendons 2-5 at MCP level
	Extensor pollicis longus and brevis at MCP level
Scoring	
Outcomes	Scoring
Joint effusion (1)	B-mode (GS 0-3)
Abnormal hypoechoic or anechoic intraarticular material	
that is displaceable and	2 = moderate
compressible, but does not	3 = severe
exhibit Doppler signal	Effusion
	Grade D
	Grade 1
	Grade 2
	Grade 3
Svnovial hypertrophy (1)	B-mode (GS 0-3)

Imaging protocol HANDSOME cohort v1.0 d.d.11-12-23 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

intraarticular tissue that is non-	U=none 1=up to the level of the horizontal line connecting bone surfaces
displaceable and poorly	the joint
compressible and which may	2=extending beyond joint line but with upper surface concave or
exhibit Doppler signal.	3=extension beyond joint line but with upper surface convex
	Hypertrophy Grade 0 Grade 1
Doppler signals (1) Flow signal in the synovium must be in synovial hypertrophy to be considered as a sign of synovitis	Grade 3 Power doppler (0-3) 0=no flow in the synovium 1=single vessel signals 2=vessel signals < half of the synovium
	Power Doppler
	Grade 1 Grade 2 Grade 3
Osteophytes Bone spurs at the end of bones	Presence y/n
<i>Tenosynovitis</i> (2) Abnormal anechoic and/or hypoechoic tendon sheath widening related to the presence of tenosynovial	Tenosynovitis (0-3) 0=no (a) 1=minimal (b) 2=moderate (c)

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Z		
3	appears as a hypoechoic band	
4	superficial to the flexor tendon	
5	sheath. Normal thickness in	
6	neutral position 0.38mm (SD	
7	0.15) and hooked/contracted	
8	position 0.37mm (SD 0.15).(6)	
9		
10	Occlusion digital arteries	Occlusion
11	Absence of colour Doppler	0 = normal
12	signals in a visible artery filled	1 = abnormal
13	with hypoechoic material, even	2 = (near) occlusion
14	with low pulse repetition	 Number of occluded arteries for each digit (0-2)
15	frequency and high colour	
16	qain.(7)	
17	Intima-media thickness	Intima-media thickness (mean max)
18	Thickness of tunica intima and	
19	tunica media.	
20	Shear wave elastography (8)	Velocity (meters per second)
21	Stiffness of the tissue (UMCU	Stiffness (kiloPascals)
22	only)	
23		6

Procedure

Ultrasound examination will be performed at baseline, 6 months, 12 months, and 24 months in all patients.

Patients will be positioned with their hands resting on a table with extended fingers facing the examiner. If full extension is not possible due to hand contractures or when in doubt during the scoring of synovial thickening and effusion in the joints, the joint can be assessed in (slightly) flexed position.

For the joints and extensor tendons, patients will rest the palms of the hands on the table. For flexor tendons, calcinosis, vascular assessment and flexor tendons, patients will rest the dorsum of the hand on the table for evaluation of the volar aspect longitudinally and transversely.

Any abnormalities of the flexor tendons will be confirmed in a cross-sectional view. Whereas, any joint abnormalities will be confirmed using a dorsal longitudinal scan.

The sonographers at the study sites will be trained on this ultrasound protocol. Examinations are reported in an eCRF, one image/video for each measure will be stored. When deemed necessary, more images/videos can be stored. Measurements are done afterwards on the stored images by the coordinating researcher.

Ultrasound imaging starts with the right hand and the linear probe according to the steps below. After all measurements of the right hand are completed, the left hand is imaged according to the same steps. Vascular imaging is only conducted in the dominant hand. In the UMCU only, elastography is performed

Additionally, at the UMCG a more extensive protocol will be performed as substudy. The vascular protocol entails ultrasound measurements performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) and an ultra-high frequency ultrasound transducer (70 MHz). Nailfold capillaroscopy (NCM) will be performed with a handheld DinoLite CapillaryScope 200 Pro (DinoLite Europe BV). Finger and toe pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands).

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- Joint effusion
 - 0 = none
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
 - Synovial hypertrophy
 - 0 = none
 - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
 - 2 = extending beyond joint line but with upper surface concave or flat
 - 3 = extension beyond joint line but with upper surface convex
- Doppler signal
 - 0 = no flow in the synovium
 - 1 = single vessel signals
 - 2 = vessel signals < half of the synovium</p>
 - 3 = vessel signal > half of the synovium
- Osteophytes
 - Presence y/n
- Intercarpal
 - Joint effusion
 - 0 = none
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
 - Synovial hypertrophy
 - 0 = none
 - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
 - 2 = extending beyond joint line but with upper surface concave or flat
 - 3 = extension beyond joint line but with upper surface convex
 - o Doppler signal
 - 0 = no flow in the synovium
 - 1 = single vessel signals
 - 2 = vessel signals < half of the synovium
 - 3 = vessel signal > half of the synovium
 - Osteophytes
 - Presence y/n



2		
3	Distal radio-ulpar joint (DRUI)	
4	- Joint effusion	
5		
6		
7		
, 8	 2 = moderate 	
0	• 3 = severe	M 1-1 12
9 10	 Synovial hypertrophy 	
10	 0 = none 	1009/3
11	 1 = up to the level of the horizontal line connecting 	O MINT
12	bone surfaces of the joint	
13	 2 = extending beyond joint line but with upper 	\times' $'$
14	surface concave or flat	
15	 3 = extension beyond joint line but with upper 	
16	surface convex	
17	 Doppler signal 	
18	• 0 = no flow in the synovium	
19	 1 = single vessel signals 	
20	2 = vessel signals < half of the synovium	
21	3 = vessel signal > half of the synovium	
22	- 0 - vessei signal > nai oi the synovium	
23		
24	 Presence y/n 	
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26		
27	Compartments of extensor tendons	
28	- Wrist extensor compartment 1	
20		
30		0
21	= 0 - 10	AMA
21		$\left(\left(\right) \right) - \left(\right)$
32	 2 = moderate 	
33	• 3 = severe	
34	 Power doppler within synovial sheath 	
35	 0 = no signal 	
36	 1 = focal signal 	
37	 2 = multifocal signal 	\rightarrow (
38	 3 = diffuse signal 	
39	 Tenosynovial effusion 	
40	 Presence y/n 	
41		
42		
43		
44	- Wrist extensor compartment 2	
45	 Tenosynovitis 	
46	• 0 = no	o A o
47	 1 = minimal 	M - M
48	 2 = moderate 	a = / 9
49	 3 = severe 	$\langle U q / q$
50	 Power doppler within synovial sheath 	0 11117
51	 0 = no signal 	
52	 1 = focal signal 	$\backslash $ $' $
53	 2 = multifocal signal 	\setminus /
54	= 2 = diffuse signal	
55	- J - UIIUSE Signal	
55		1 1
50	 Présence y/n 	
5/		
58		
59	- Wrist extensor compartment 3	
60	·	

Tenosynovitis

- 0 = no
- 1 = minimal
- 2 = moderate
- 3 = severe
- Power doppler within synovial sheath
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal .
 - 3 = diffuse signal
- ses affusion ence y/n Tenosynovial effusion



1		
2		
3		
4	- Wrist extensor compartment 4	
5		
6		0
7	- 0 - 10	AMA
, 8		
0	2 = moderate	
9	 3 = severe 	1007/1
10	 Power doppler within synovial sheath 	P) WII
11	 0 = no signal 	
12	1 = focal signal	\times 1
13	2 = multifocal signal	\mathbf{X}
14	 3 = diffuse signal 	
15		
16		
17	 Presence y/n 	
18		
19	Wrist extensor compartment 5	
20	- Whist extension compartment 5	
20	o l'enosynovitis	0
21	• 0 = no	0 M O
22	1 = minimal	M - 1-
23	 2 = moderate 	c = c 9
24	 3 = severe 	1009/7
25	 Power doppler within synovial sheath 	0 1 111 7
26	0 = no signal	
27	1 = focal signal	$\backslash $ $' /$
28	2 = multifocal signal	
29	-2 = diffuse signal	
30	• 3 = diffuse signal	
31		1 1
37	 Presence y/n 	
22		
22	Maint automa an annuartur ant C	
34	- wrist extensor compartment 6	2
35		$\alpha \beta \alpha$
36	• 0 = no	$[M_{1}] = [M_{2}]$
37	1 = minimal	$ c = c \beta$
38	 2 = moderate 	1009/7
39	 3 = severe 	O) 111 7
40	 Power doppler within synovial sheath 	
41	0 = no signal	\sim $^{\prime}$
42	 1 = focal signal 	\sim (
43	 2 – multifocal signal 	
44	-2 = diffuse signal	
45	• 3 = diffuse signal	1 1
45		
40	Presence y/n	
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Tendon width (max)

At MCP 1 level	
- MCP 1	
0	Joint effusion
	• 0 = none
	 1 = minimal
	 2 = moderate
	 3 = severe
0	Synovial hypertrophy
	 0 = none
	 1 = up to the level of the horizontal line connecting
	bone surfaces of the joint
	 2 = extending beyond joint line but with upper
	 surface concave or flat
	 3 = extension beyond joint line but with upper
	surface convex
0	Doppier signal
	 U = no flow in the synovium
	1 = single vessel signals
	2 = vessel signals < half of the synovium
	3 = vessel signal > haif of the synovium
0	Usteophytes
Extene	 Presence y/n ar pollious longue and bravia at MCP loval
- Extens	Thickening of extensor tendens
0	Tendon width (max)
At MCP 2 lovel	
- MCP 2	laint offusion
0	
	• 0 = none
	 I = IIIIIIIIII 2 = moderate
-	- J-Severe
0	0 = none
	 U = HUHE 1 = Up to the loval of the horizontal line connecting
	- i - up to the level of the joint
	 2 = extending beyond joint line but with upper
	surface concave or flat
	 3 = extension beyond joint line but with upper
	surface convex
0	Doppler signal
-	 0 = no flow in the synovium
	 1 = single vessel signals
	 2 = vessel signals < half of the synovium
	 3 = vessel signal > half of the synovium
	Osteophytes
0	

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1		
2		
3 1	At MCP 3 level	
4		
5	o Joint effusion	
7	• 0 = none	
, 8	 1 = minimal 	
9	 2 = moderate 	0
10	3 = severe	AM
11	 Svnovial hypertrophy 	
12	= 0 = none	
13	 1 = up to the level of the horizontal line connecting 	
14	hone surfaces of the joint	
15	2 = extending beyond joint line but with upper	$\sum I$
16	surface concave or flat	\backslash
17	3 = extension beyond joint line but with upper	
18	surface convex	
19	 Doppler signal 	
20	 0 = no flow in the synovium 	
21	 1 = single vessel signals 	
22	 2 = vessel signals < half of the synovium 	
23	 3 = vessel signal > half of the synovium 	
24	• Osteophytes	
25	 Presence v/n 	
26	- Central slip of extensor tendon 3 at MCP level	
27	• Thickening of extensor tendons	
28	 Tendon width (max) 	
29		
30		
31		
32		
33	- MCP 4	
34	 Joint effusion 	
35	• 0 = none	
36	 1 = minimal 	
37	 2 = moderate 	0 0 0
38	 3 = severe 	M - M
39	 Synovial hypertrophy 	c =
40	• 0 = none	$\langle 0 q \rangle$
41	 1 = up to the level of the horizontal line connecting 	(n)
42	bone surfaces of the joint	$\chi \gamma \wedge \eta$
43	 2 = extending beyond joint line but with upper 	\backslash
44 45	surface concave or flat	\backslash
45	 3 = extension beyond joint line but with upper 	
40	surface convex	Ι
47	 Doppler signal 	
40	 0 = no flow in the synovium 	
49 50	1 = single vessel signals	
51	 2 = vessel signals < half of the synovium 	
52	 3 = vessel signal > half of the synovium 	
52	 Osteophytes 	
53		
53 54	 Presence y/n 	
53 54 55	 Presence y/n Central slip of extensor tendons 4 at MCP level 	
53 54 55 56	 Presence y/n Central slip of extensor tendons 4 at MCP level Thickening of extensor tendons 	
53 54 55 56 57	 Presence y/n Central slip of extensor tendons 4 at MCP level Thickening of extensor tendons Tendon width (max) 	
53 54 55 56 57 58	 Presence y/n Central slip of extensor tendons 4 at MCP level Thickening of extensor tendons Tendon width (max) 	

At MCP 5 level

1 2

3	At MCP 5 level		
4			
5	- MCP 5	loint offusion	
6	0		
/			
8		 I = IIIIIIIIII 2 = moderate 	0
9			AMA
10		• 3 = Severe	
11	0	Synovial hypertrophy	
12		 U = none 4 = up to the lovel of the beginerated line connecting 	
13		 I = up to the level of the ioint 	
14		bone sunaces of the joint	
15		 2 – extending beyond joint line but with upper surface concerve or flat 	\setminus /
17		Surface concave of flat 3 = extension beyond joint line but with upper	
18		surface convex	
10	0	Doppler signal	1 1
20	0	$0 = \mathbf{n} 0$	
20		 1 = single vessel signals 	
22		 2 = vessel signals < half of the synovium 	
23		 3 = vessel signal > half of the synovium 	
24	0	Osteonhytes	
25	0	Presence v/n	
26	- Centra	I slin of extensor tendons 5 at MCP level	
27	- Ocnita	Thickening of extensor tendons	
28	0	Tendon width (max)	
29			
30			
31	At (D)ID lovel		
31 32	At (P)IP level		
31 32 33	At (P)IP level - IP		
31 32 33 34	At (P)IP level - IP °	Joint effusion	
31 32 33 34 35	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal	
31 32 33 34 35 36	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate	0
31 32 33 34 35 36 37	At (P)IP level - IP ○	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe	0
31 32 33 34 35 36 37 38	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy	
31 32 33 34 35 36 37 38 39	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none	
31 32 33 34 35 36 37 38 39 40	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting	
31 32 33 34 35 36 37 38 39 40 41	At (P)IP level - IP O	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint	
31 32 33 34 35 36 37 38 39 40 41 42	At (P)IP level - IP ©	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper	
31 32 33 34 35 36 37 38 39 40 41 42 43	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat	
31 32 33 34 35 36 37 38 39 40 41 42 43 44	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	At (P)IP level - IP o	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex 	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	At (P)IP level - IP ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the synovium 	
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 	At (P)IP level - IP ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the synovium 1 = single vessel signals 	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	At (P)IP level - IP ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals < half of the synovium 	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51	At (P)IP level - IP ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signal > half of the synovium 	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52	At (P)IP level	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	At (P)IP level	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	At (P)IP level . ο	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	At (P)IP level	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
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31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57	At (P)IP level	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	



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4	0	Joint effusion	
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6		1 = minimal	
7		2 = moderate	0
8		 3 = severe 	AFIA
9	0	Synovial hypertrophy	
10	0	0 = none	
11		 0 = none 1 = up to the level of the horizontal line connecting 	
12		- 1 - up to the level of the honzontal line connecting	
13		 2 – extending beyond joint line but with upper 	1
14		- 2 - extending beyond joint line but with upper	\setminus /
15		 Surface concave or flat 3 - extension beyond joint line but with upper 	
16		- 5 – extension beyond joint line but with upper	
17	0	Doppler signal	1 1
18	0	Doppier signal	
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20		I = single vessel signals	
21		2 = vessel signals < half of the synovium	
22		3 = vessel signal > half of the synovium	
23	0	Osteophytes	
23		 Presence y/n 	
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21		 3 = severe 	A = 0
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38		 3 = extension beyond joint line but with upper 	
39		surface convex	
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41 42	0	Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals	
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41 42 43 44 45 46	0	Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes	
41 42 43 44 45 46 47	0	Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
41 42 43 44 45 46 47 48	0	Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
41 42 43 44 45 46 47 48 49	0	Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
41 42 43 44 45 46 47 48 49 50	0	Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
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41 42 43 44 45 46 47 48 49 50 51 52	0	 Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium Osteophytes Presence y/n 	
41 42 43 44 45 46 47 48 49 50 51 51 52 53	0	 Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium Osteophytes Presence y/n 	
41 42 43 44 45 46 47 48 49 50 51 52 53 53 54	0	 Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium Osteophytes Presence y/n 	
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41 42 43 44 45 46 47 48 49 50 51 52 53 53 54 55 56	0	 Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium Osteophytes Presence y/n 	
41 42 43 44 45 46 47 48 49 50 51 52 53 53 54 55 56 57	0	 Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium Osteophytes Presence y/n 	



- PIP 4	loint effusion
0	$\bullet 0 = \text{none}$
	 1 = minimal
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0	Synovial hypertrophy
	 U = none 1 = up to the lovel of the herizontal line connecting
	 I – up to the level of the honzontal line connecting bone surfaces of the joint
	 2 = extending beyond joint line but with upper
	surface concave or flat
	 3 = extension beyond joint line but with upper
	Surface convex
0	0 = no flow in the synovium
	 1 = single vessel signals
	 2 = vessel signals < half of the synovium
	 3 = vessel signal > half of the synovium
0	Osteophytes
	 Presence y/n
- PIP 5	
0	Joint effusion
	• $U = none$ • $1 = minimal$
	 2 = moderate
	• 3 = severe
0	Synovial hypertrophy
	• 0 = none
	 1 = up to the level of the horizontal line connecting
	 2 = extending beyond joint line but with upper
	surface concave or flat
	 3 = extension beyond joint line but with upper
	surface convex
0	Doppier signal
	 0 - no now in the synoviam 1 = single vessel signals
	 2 = vessel signals < half of the synovium
	 3 = vessel signal > half of the synovium
0	Osteophytes
	 Presence y/n



2	
3	Ask subject to turn their hand with the palmar side up!
4	<i>,</i>
5	Palmar side of digit 1
6	 Flexor pollicus longus and brevis at MCP level
7	 Tenosynovitis
8	• 0 = no
9	1 = minimal
10	2 = moderate
11	 3 = severe
12	 Power doppler within synovial sheath
13	0 = no signal
14	 0 - no signal 1 - focal signal
15	- 1 - Iocal Signal
16	 2 - multilocal signal 3 - diffuse signal
17	 3 = diffuse signal
18	 Tenosynovial eπusion
19	Presence y/n
20	 I hickening of flexor tendons
20	 Tendon width (max)
27	- A1 pulley at MCP level
22	 Thickening of A1 pulley
23	 Max width (transverse)
24	- Digit 1
25	 Calcifications
20	Presence y/n
27	 Location
20	 Number per finger
29	
30	
31	
32	Palmar side of digit 2
33	- Finger flexors (sun + prof) 2 at MCP level
34	
35	
36	- 0 - 110 - 1 - minimal
37	- 1 - minimal
38	
39	• 5 = Severe
40	• Power doppier within synovial sheath
41	• 0 = no signal
42	 i = tocal signal
43	 2 = multifocal signal
44	 3 = diffuse signal
45	 Tenosynovial effusion
46	 Presence y/n
47	 Thickening of flexor tendons
48	 Tendon width (max)
49	- A1 pulley 2 at MCP level
50	 Thickening of A1 pulley
51	 Max width (transverse)
52	- Digit 2
53	\sim Calcifications
54	 Presence v/n
55	■ I ocation
56	 Location Number per finger
57	
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Palmar side of digit 3

0

Finger flexors (sup + prof) 3 at MCP level 0

- Tenosynovitis
 - 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
- Power doppler within synovial sheath
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal
- Tenosynovial effusion 0

Presence y/n

- Thickening of flexor tendons 0
 - Tendon width (max)

A1 pulley 3 at MCP level

.

- Thickening of A1 pulley 0
 - Max width (transverse)
- Digit 3
 - Calcifications 0
 - Presence y/n
 - Location
 - Number per finger

Palmar side of digit 4

- Finger flexors (sup + prof) 4 at MCP level
 - 0 Tenosynovitis
 - 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
 - Power doppler within synovial sheath 0
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal .
 - Tenosynovial effusion
 - Presence y/n
 - Thickening of flexor tendons 0
 - Tendon width (max)

A1 pulley 4 at MCP level

- Thickening of A1 pulley
 - Max width (transverse)
- Digit 4

0

- Calcifications 0
 - Presence y/n
 - Location -
 - Number per finger






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4	Palmar side of digit 5
5	
6	- Finger flexors (sup + prof) 5 at MCP level
7	
8	• 0 = no
9	1 = minimal
10	2 = moderate
11	 3 = severe
12	 Power doppler within synovial sheath
13	 0 = no signal
14	1 = focal signal
15	 2 = multifocal signal
16	 3 = diffuse signal
17	 Tenosynovial effusion
18	 Presence y/n
19	 Thickening of flexor tendons
20	 Tendon width (max)
21	- A1 pulley 5 at MCP level
22	 Thickening of A1 pulley
23	 Max width (transverse)
24	- Digit 5
25	
26	 Presence v/n
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28	 Number per finger
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3 4	Elastography only in UMCU and only in dominant hand, use linear probe!	
5	- Finger flexor tendons 2-5 at MCP level	
6	 Shear wave elastography 	JHH/
7	 Oneal wave clastography Velocity (meters per second) 	R
8	 Stiffness (kiloPascals) 	
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14	- Flexor pollicus longus and brevis at MCP level	
15	 Shear wave elastography 	HU-U-U-I
16	 Velocity (meters per second) 	ect of the sector
17	 Stiffness (kiloPascals) 	ed in the second
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24	Ask subject to turn their hand with dorsal side up	
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26	 Finger extensor tendons 1-5 at MCP level 	
27	 Shear wave elastography 	
28	 Velocity (meters per second) 	
29	 Stiffness (kiloPascals) 	s reij
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33		() (-) (<u>)</u> te se
24 25	 Extensor pollicus longus and brevis at MCP level 	
35	 Shear wave elastography 	
30	 Velocity (meters per second) 	
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MRI assessment

Materials

A 3 Tesla scanner (Philips Medical Systems, Best, The Netherlands) with dedicated surface coils.

Variables

Outcomes	Area	Scoring
Synovitis or tenosynovitis (9) Hyperintense signal on both STIR and fat-saturated post-gadolinium images in a thickened articular and tendon sheath synovium	 Radiocarpal Intercarpal MCPs 2-5 PIPs 2-5 	 Synovitis None/Focal/Diffuse / of Mild/moderate /severe Tenosynovitis None/Focal/Diffuse
<i>Erosions</i> (10) Sharply marginated bone lesion, with correct juxta-articular localisation and typical signal characteristics, with a cortical break visible in two adjacent planes.	 Radiocarpal Intercarpal MCPs 2-5 PIPs 2-5 	 Presence Number Location (specify joint)
Bone edema	AREA	None/mild/moderate/severe

Procedure

The MRI examination will be performed on the dominant hand. Non-enhanced transverse and coronal T1-weighted, fast spin-echo T2-weighted and short-tau inversion recovery (STIR) and/or fat-saturated proton-density sequences will be performed with contrast enhancement.

A radiologists will assess the MRI images and reported the scores in an eCRF. The MRI will be performed at baseline in the first 50 patients participating at the UMC Utrecht. MRI examinations will be performed on the day of the baseline ultrasound and read without knowledge of hand function scores.

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BMJ Open

Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study protocol

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-095283.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Feb-2025
Complete List of Authors:	Greveling, Mark; UMC Utrecht, Department of Rheumatology & Clinical Immunology Ong, Voon H.; University College London, Div of Medicine, Dep of Inflammation, Centre for Rheumatology and Connective Tissue Diseases Denton, Christopher; University College London, Div of Medicine, Dep of Inflammation, Centre for Rheumatology and Connective Tissue Diseases Foppen, W.; UMC Utrecht, Department of Radiology and Nuclear Medicine Herman, Amin; St Antonius Hospital, Department of Rheumatology Jeffries-Owen, Nick; SRUK Kortekaas, Marion; Leids Universitair Medisch Centrum, Department of Rheumatology; Flevoziekenhuis, Rheumatology Masselink, Ilse; UMC Utrecht, Department of Internal Medicine, Division of Vascular Medicine Schriemer, Rita; NVLE, Dutch Patient Organization for Systemic Autoimmune Diseases Vonk, Madelon; Radboudumc, Department of Rheumatology de Vries-Bouwstra, Jeska; Leids Universitair Medisch Centrum, Department of Rheumatology Welsing, Paco; UMC Utrecht, Department of Rheumatology & Clinical Immunology Mastbergen, Simon; UMC Utrecht, Department of Rheumatology & Clinical Immunology Spierings, Julia; UMC Utrecht, Department of Rheumatology & Clinical Immunology
Primary Subject Heading :	Rheumatology
Secondary Subject Heading:	Radiology and imaging, Research methods, Immunology (including allergy)
Keywords:	RHEUMATOLOGY, Ultrasound < RADIOLOGY & IMAGING, Observational Study

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Administrative information

Title

Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study protocol

Authors

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Trial registration

Data category	Information
Primary Registry and Trial Identifying	ClinicalTrials.gov
Number	NCT06133244
Date of Registration in Primary Registry	15-11-2023
Secondary Identifying Numbers	NL85445.041.23
Source(s) of Monetary or Material	UMC Utrecht, ReumaNederland
Support	
Primary Sponsor	UMC Utrecht
Secondary Sponsor(s)	N/A
Contact for Public Queries	handsome@umcutrecht.nl
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Contact for Scientific Queries	handsome@umcutrecht.nl
	+3188 7555 5555
Public Title	Getting a grip on hand function
	impairment in systemic sclerosis
Scientific Title	Hand Function Impairment in Systemic
	Sclerosis: Outcomes, Mechanisms, and
	Experience (HANDSOME) Study
Countries of Recruitment	The Netherlands
	United Kingdom

Health Condition(s) or Problem(s)	Systemic sclerosis
Studied	
Intervention(s)	Diagnostic Tests: Imaging, blood
	samples, functional tests, and physica
	examination
Key Inclusion and Exclusion Criteria	Study Population
	Patients (18 years and older) with:
	1. SSc with hand contractures
	2. SSc patients without contracture
	and disease duration of < 4 yea
	3. VEDOSS patients
	Ages eligible for study: ≥18 years
	Sexes eligible for study: both
	Accepts healthy volunteers: no
	Inclusion Criteria: Age > 18 years
	2.
	Exclusion Criteria: Patients with diabet
	cheiroarthropathy and Dupuytren's
	disease, based on expert opinion
Study Type	Observational
	Observational
Date of First Enrollment	19-04-2024
Date of First Enrollment Sample Size	19-04-2024 300
Date of First Enrollment Sample Size Recruitment Status	19-04-2024 300 Recruiting
Date of First Enrollment Sample Size Recruitment Status Primary Outcome(s)	Observational 19-04-2024 300 Recruiting To identify underlying mechanisms
Date of First Enrollment Sample Size Recruitment Status Primary Outcome(s)	Observational 19-04-2024 300 Recruiting To identify underlying mechanisms responsible for hand function
Date of First Enrollment Sample Size Recruitment Status Primary Outcome(s)	19-04-2024 300 Recruiting To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc)
Date of First Enrollment Sample Size Recruitment Status Primary Outcome(s)	19-04-2024 300 Recruiting To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients.
Date of First Enrollment Sample Size Recruitment Status Primary Outcome(s) Key Secondary Outcomes	19-04-2024 300 Recruiting To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients. To determine risk factors and categoria
Date of First Enrollment Sample Size Recruitment Status Primary Outcome(s) Key Secondary Outcomes	19-04-2024 300 Recruiting To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients. To determine risk factors and categoriz patients with hand function impairment
Date of First Enrollment Sample Size Recruitment Status Primary Outcome(s) Key Secondary Outcomes	19-04-2024 300 Recruiting To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients. To determine risk factors and categoriz patients with hand function impairment into subgroups based on clinical,

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	characteristics, thereby guiding future
	research toward personalized treatment
	strategies
	To assess the impact of hand function
	impairment on quality of life, daily
	functioning, work, and participation, and
	explore how these impacts relate to the
	identified mechanisms and patient
	subgroups
Ethics Review	Approved on 19-03-2024
Completion date (estimated)	04-2028
Summary Results	N/A
IPD sharing statement	Undecided

Protocol version

V1.3 6-06-2024

Abstract

Introduction The majority of all systemic sclerosis (SSc) patients experience hand function impairment. The exact cause for this impairment is yet unknown. As impaired hand function hugely impacts daily functioning and quality of life, there is a high unmet need for effective treatments. With the availability of new imaging modalities, biomarkers, and lab techniques, opportunities arise to increase insights into the factors contributing to hand function impairment. The objective of this study is to identify risk factors and underlying mechanisms leading to hand function impairment in SSc.

Methods and analysis This is a longitudinal observational multicentre study in patients with Very Early Diagnosis of Systemic Sclerosis (VEDOSS) and SSc under care of the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG), Leiden UMC (LUMC), Radboudumc, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Medical history, clinical status, nailfold capillaroscopy, skin assessments, serum biomarker analysis, ultrasound, elastography and MRI will be performed and results related to hand function measurements.

Ethics and dissemination This study was approved by the Medical Research Ethics Committee NedMec (MREC NedMec) in the Netherlands and by HRA and Health and Care Research Wales (HCRW) in the UK. Results will be published in scientific journals and presented at scientific congresses and patient meetings.

Trial registration number NCT06133244

Keywords

Systemic sclerosis, hand function, imaging, biomarkers, observational

Word count:

Strengths and limitations of this study

- This is the first study that extensively assesses the hand function in systemic sclerosis patients
- This is a large prospective international multidisciplinary study with a follow-up of 2 years in 300 patients
- This is the first study that explores elastography of tendons in the hand
- The study is conducted in collaboration with patient associations
- Conclusions can be limited due to the lack of prior research for comparison and the heterogeneity of the disease

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Introduction

Background and rationale

Systemic sclerosis (SSc) is a rare disease characterized by inflammation, fibrosis, and vasculopathy [1]. Clinical presentation is heterogeneous and includes Raynaud phenomenon, cutaneous manifestations, musculoskeletal manifestations, gastrointestinal manifestations, pulmonary manifestations, cardiac manifestations, and renal manifestations. Thus far, studies in SSc mainly focused on organ damage and mortality. However, other disease manifestations have a tremendous impact on quality of life and daily functioning.

Around 90% of SSc patients experience hand function limitation, which leads to impaired daily functioning and work participation [2,3]. An important cause of impaired hand function is contractures of the hand, which are reported in half of the patients [4]. Contractures are reported more frequently in patients with diffuse cutaneous systemic sclerosis (dcSSc) and associated with anti-topoisomerase I (ATA) positivity [5]. Only a few studies explored imaging techniques in SSc hands. Thickening of the A1 pulley and flexor tendons was associated with hand disability in a small group of patients (n=29). Soft tissue calcifications were seen in affected tendons, but this has not been studied in more detail [6,7]. In other small studies, ultrasound and MRI showed subclinical synovitis or tendinitis and bone erosions, which could also contribute to impaired hand function [7,8]. Shear wave elastography (SWE), a new imaging modality to assess the elastic properties and stiffness of soft tissue, has been studied in SSc skin and muscles but no studies have assessed hand tendons. Moreover, no studies explored tenosynovial changes and underlying biological mechanisms, especially in correlation with imaging or functional tests. This leaves clinicians 'in the dark' regarding diagnostic workup and effective management. Current management for hand symptoms includes exercises, splints, and sometimes immunosuppressive therapies. However, it is unknown which treatment is suitable for which patient and the efficacy of immunosuppressive drugs has not been confirmed in trials. As impaired hand function in SSc hugely daily functioning and with that quality of life, there is a high unmet need for effective treatments [9]. With the availability of improved imaging modalities such as ultrasound, MRI and elastography, biomarkers in serum and plasma, and lab techniques such as proteomics, opportunities arise to study this problem in more detail to guide optimal treatment development.

This study aims to enhance the understanding of the mechanisms underlying hand function impairment in patients with systemic sclerosis (SSc), including development from the early phase in very early disease of systemic sclerosis (VEDOSS). The study is based on three key hypotheses: 1) Hand function in SSc is affected through various pathways involving joints, tendons, skin, and/or microcirculation. 2) Prior to the development of contractures, tissue changes—such as inflammation, fibrosis, or decreased elasticity—can be detected using imaging techniques. 3) Patients with hand impairment can be categorized into distinct subgroups based on clinical and imaging features, as well as protein markers, which may reflect different activated biological pathways.

Primary objective

To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients.

Secondary objectives

To determine risk factors and categorize patients with hand function impairment into subgroups based on clinical, immunological, and/or imaging characteristics, thereby guiding future research toward personalized treatment strategies

To assess the impact of hand function impairment on quality of life, daily functioning, work, and participation, and explore how these impacts relate to the identified mechanisms and patient subgroups

Methods

Patient and public involvement statement

Members of the Dutch (NVLE) and UK (SRUK) systemic sclerosis patient organizations are involved in every step of this project. They have been involved in the study design and during the development of the protocol, a qualitative study was performed to explore patients' functional complaints and (unmet) needs. The study protocol has been co-produced to ensure representation and input from those with personal experiences. All questionnaires have been checked on content and feasibility. During all meetings with the entire research team, patients will be involved to share their opinions on decisions being made and provide advice on recruitment and dissemination of results.

Study setting

This is a longitudinal observational international study in patients with VEDOSS and SSc who are under care at the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG) Leiden UMC (LUMC), Radboud UMC, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Inclusion started in April 2024 and is open until April 2026, the expected end date is April 2028.

Study population

Patients (n=300; 18 years and older) with:

- 1) SSc with hand contractures regardless of disease duration (n=50)
- 2) SSc patients without hand contractures (n=200) and disease duration of < 4 years
- 3) VEDOSS patients (n=50)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1) Age >18 years

2) For patient populations 1) and 2):

a. Diagnosis of SSc according to the 2013 EULAR-ACR classification criteria for SSc [10] For patient population 3):

b. Diagnosis of VEDOSS, defined as the presence of RP, puffy fingers, SSc-specific autoantibodies, and abnormal nailfold capillaroscopy, while not fulfilling the 2013 EULAR-ACR classification criteria for SSc [11].

3) Only for patient population 1):

a. Hand contractures are defined as a range of motion < 75% of the normal range of at least one small hand joint of [12].

4) Willing and be able to understand the study information and sign the informed consent form.

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation:

1) Age < 18 years

 2) Patients with diabetic cheiroarthropathy and Dupuytren's disease, based on expert opinion. (other diseases or overlap syndromes are not excluded)

Study procedures

Three patient groups are included and then followed for 24 months. Table 1 shows the study procedures and data collection in these three groups.

Table 1: Overview of study procedur

	Baseline	6 months	12 months	24 months
Informed consent	х			
Medical history	х			
Nailfold capillaroscopy	х			x
Clinical status	х	х	х	x
Skin assessment	х	х	х	x
PROMs	х	х	х	x
Serum and plasma collection	x	х	х	x
Hand function assessment	x	х	x	x
Ultrasound	x	x	x	x
Elastography *	×	x	x	x
MRI *	x			
Vascular imaging **	x	x	x	x

*Sub-analysis comparing MRI with ultrasound features. UMC Utrecht only

** Sub-analysis assessing hand circulation extensively with ultrasound using a 70mHz probe. UMC Groningen only

Medical history

Clinical data collected in routine care will be retrieved at baseline. Age, sex, height, educational level, ethnicity, and auto-antibody status (ANA negative/positive, line blot and scleroderma blot auto-antibodies) are collected.

In addition, data will be collected on previous tobacco use, vasoactive and immunosuppressive medication use and dosage, digital ulcers, pitting scars, gangrene, clinical arthritis, myositis, interstitial lung disease, pulmonary hypertension, and scleroderma renal crisis.

Nailfold capillaroscopy

A capillaroscope with a magnification of 200x is used to assess all fingers, including the thumbs. At least two adjacent fields of a linear millimetre in the middle of each finger are captured and stored. Images will be scored according to EULAR criteria centrally on normal or abnormal/scleroderma patterns [13].

Clinical status

- weight, blood pressure, (change) in tobacco use, (change in) occupation, (changes in) immunosuppressive and/or vasoactive medication use and dosage,

- new onset interstitial lung disease (y/n), pulmonary hypertension (y/n), scleroderma renal crisis (y/n)

- Hb (mmol/L), ESR (mm/h), CRP (mg/L), CK (IU/L).

Skin assessment

The modified Rodnan skin score (mRSS) (assessed by trained investigators), presence of digital ulcers (if yes: count, location), pitting scars (if yes: count, location), gangrene (if yes: location), calcinosis cutis in the hands (if yes: location), clinical arthritis ((if yes: site and joint count), and myositis will be assessed/recorded [14].

<u>PROMs</u>

Patient Related Outcome Measurements will be collected in the week of the study visit and the following questionnaires will be collected:

- Cochin Hand Function Scale (CHFS), containing 18 questions, structured in 5 distinct categories, designed to evaluate hand function in kitchen activities, dressing, personal hygiene, office, and other generic activities [15].

- brief Satisfaction with Appearance Scale (SWAP), containing six questions about subjective body image dissatisfaction and the perceived social impact [16].

- IMTA Productivity Cost Questionnaire (IPCQ), a standardized instrument for measuring and valuing health-related productivity losses [17].

- Utrecht Scale for Evaluation of Rehabilitation (- Participation) (USER-P), which measures both subjective and objective participation in the community [18].

- Health-related quality of life (EQ5D5L), that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression [19].

- Self-assessment of skin thickening (PASTUL), a self-reported measure of skin thickness in the upper limb [20].

- Scleroderma Health Assessment Questionnaire (SHAQ), which measures disease status changes [21].

Serum and plasma collection

Two blood samples will be collected (both a maximum of 10 ml) to obtain both serum and plasma samples during each visit. The venepuncture is performed at routine outpatient or daycare unit visits according to standard protocol protocol in a non-fastened state and not taking diurnal changes into account due to practical feasibility [22]. Aliquots of both serum and plasma samples will be stored at -80 C degrees. Serum and plasma analysis will include measurement of levels of immunological markers (including cytokines) and fibrotic markers.

Hand function assessment

At all study visits, hand function will be assessed by trained investigators. Hand mobility is assessed with the range of motion of the wrist joint, range of motion of the finger joints, delta

Finger-to-Palm distance [23], and the mHAMIS [24]. Grip strength is measured with the JAMAR® dynamometer and JAMAR pinch dynamometer® for the two-point pinch, three-point pinch, and lateral pinch.

<u>Ultrasound</u>

Ultrasound will be performed by an operator/physician trained in musculoskeletal ultrasound. An ultrasound machine with a high-frequency probe (linear or hockey stick with 8-24MHz) will be used. Images of all study sites will be stored and rated centrally by the coordinating researcher in conjunction with ultrasound experts afterwards. The presence of arthritis of the distal radio-ulnar joint (DRUJ), metacarpophalangeal (MCP), and proximal wrist. interphalangeal (PIP) joints will be assessed using validated semiguantitative methods in Bmode and power Doppler setting if there was grey-scale evidence of inflammation. Furthermore, the presence of osteophytes is assessed. The first to fifth flexor and extensor tendons of both hands will be assessed longitudinally. Tenosynovitis and sclerotic thickening of tendon(-sheaths) and calcifications within tendons will be evaluated. The pulley and tendons are measured at the at the MCP joint. The fingers of the dominant hand will be assessed with ultrasound for vascular involvement. Dig 2 will be assessed standardly. In addition, fingers with ulceration if present on other fingers will be assessed. Additionally, intima media thickness (IMT) will be measured in dig 2. All arteries per finger will be assessed at the proximal phalangeal part. Qualitative scoring is performed. See Appendix 1, imaging protocol, for the full ultrasound protocol.

Elastography

In addition to the ultrasound assessment, fibrosis of the first to fifth flexor and extensor tendons of both hands will be measured quantitatively using shear wave elastography (SWE) in a subgroup of patients at the UMC Utrecht (n=100) [25]. SWE is measured with the ultrasound machine GE healthcare LOGIQ E10s using the linear ML4-20 transducer.

Vascular imaging

Another addition to the ultrasound assessment is the extensive vascular evaluation performed in patients in the UMC Groningen (n=35). The vascular protocol entails ultrasound measurements of IMT performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) which uses an ultra-high frequency ultrasound transducer (max 70 MHz). Finger pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously [26]. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands) [27].

<u>MRI</u>

In a subgroup of patients included at the UMC Utrecht (n=50), a contrast-enhanced 3 Tesla MRI of the dominant hand will be done at baseline, recording the presence of synovitis, joint capsule thickening of the wrist, MCP and PIPs, and thickness or inflammation of tendons and tendon sheaths of the hands. The researcher will determine whether there are no contra-

indications according to the MRI screening form used in the UMC Utrecht. The entire MRI protocol is shown in Appendix 1, imaging protocol.

Outcomes

Main study parameter/endpoints

The correlation between the Cochin Hand Function Scale (CHFS) scores and circulating biomarkers, as well as changes observed through imaging, over a two-year follow-up period will be assessed.

Secondary study parameters/endpoints

- The change in hand function at 2 years, reflected by the Cochin Hand Function Scale (CHFS) and hand function measures.
- Predictive value of imaging features and circulating biomarkers at baseline for change of hand impairment at follow-up.
- Distinct subgroups of patients based on clinical, immunological, and imaging characteristics.
- Health-related quality of life (EQ5D-5L), daily functioning (S-HAQ), work (IPCQ), and participation (USER-P) in relation to CHFS.

Sample size

For multivariable regression analysis with a continuous outcome, we need at least 10 patients per variable studied according to rule of thumb. As we anticipate including 300 patients we will be able to validly study 30 variables for their association with the (progressive) hand impairment (including patient subgroup as a covariate in the analysis) with sufficient power. We will also perform more explorative subgroup analyses per patient population and calculate variance inflation factors (VIFs) as well as use data reduction techniques (e.g. principal component analysis) and/or analysis techniques more suitable for analysing outcomes with many independent variables compared to the number of patients (like partial-least squares regression or Lasso regression). Furthermore, we will explore clusters of patients developing hand function impairment using imaging and protein biomarkers to inform our multivariable analyses. Missing data will be accounted for using multiple imputation. With the above calculation and strategy, we think our cohort of 300 patients will be sufficient to obtain meaningful results.

Recruitment and consent

Subjects will be informed about the study by their treating physician and receive an information letter. Thereafter, they will have the possibility to ask questions, either during a face-to-face appointment or over the phone with the investigator or research nurses. They will be allowed sufficient time, but at least 24 hours, to consider their participation. If the subject wants to participate, a meeting will be set for signing the consent form and explaining the study procedure. This will take place at a day/time suitable for the patients, ideally combined with routine care appointments.

Data management

Data handling is described in detail in the data management plan. This has been approved by the data manager of the UMC Utrecht.

Data from patients will be handled with care, taking into consideration the required confidentiality as stated by the Dutch 'AVG ('Law for the Protection of Personal Information'), the 'Wet Gemeenschappelijke Behandelings Overeenkomst' ('Law Common Treatment Agreement'), and the privacy policy of the UMC Utrecht. The electronic patient files will be used as the source for the clinical data. Data will be pseudonymized and the key will be stored in a separate secured folder at each clinical site.

Patient material will be encoded and stored at the UMC Utrecht, department of Rheumatology & Clinical Immunology. Patient material is only used to answer the questions in this study, material is not stored for biobank purposes. Only the local investigators are permitted access to the code key. Research documents, from which patient identity can be deduced will only be accessible for third parties (for example monitors, auditors, and inspection by competent authorities) after specific consent by the participant in the informed consent document. Research documents will be kept up to 15 years after ending the research.

In all local centers, images and patient material will be stored according to local protocol and collected and analysed centrally.

Monitoring and Quality Assurance

A central independent monitor will perform yearly monitoring according to the Monitoring Plan.

Statistical methods

To predict decline in hand function (defined as an increase CHFS) at 6, 12, and 24 months we will use linear/logistic regression analysis, with as independent variables/predictors baseline patient characteristics, as well as short term (over 6 months) changes in clinical scores, imaging markers and biomarkers. When needed we will use (regression) techniques suitable for a high variable to patient/outcome ratio (see section Statistics/Power calculation)

Characteristics at baseline and changes over time seen on ultrasound will be reported for the number of patients with tenosynovitis, arthritis and/or calcifications in tendons, the mean thickness and elastography of tendons, and the A1 pulley. Linear mixed models will be used to analyse changes over time (both with time defined as follow-up time or as time since early disease/VEDOSS) regarding hand function scores and to relate these changes to changes in ultrasound and serum/plasma biomarkers.

Also joint modelling of the multivariate longitudinal data (i.e. the clinical scores, imaging- and biomarkers measured over time) and time-to-event (i.e. development of limitations of hand function) will be performed. In this analysis so called 'latent trajectories' in the longitudinal markers (i.e. not directly observed subgroups of patients with a distinct course in longitudinally measured 'markers') will be related to the development of the outcome (in this case limitations in hand function). Results can be used to obtain more insight into the development of limitations in hand function, and the possible existence of subgroups regarding the development of hand function limitations. Models may also be used to 'dynamically' predict the outcome over time. The patient subgroups (VEDOSS/SSc with/without hand impairment) will be taken appropriately into account in all analyses and/or subgroup analyses will be performed.

To further explore subgroups in patients with/without hand function limitations. Baseline clinical, imaging-, and biomarkers as well as changes over time in markers will be used in a cluster analysis. As most likely different types of variables (i.e. linear, binary, and categorical) will be included we will use an algorithm suitable for this like k-medoid cluster analysis using partitioning around medoids. The validity of different solutions regarding the number of clusters will be evaluated using statistical criteria (e.g. silhouette width, calculated based on Gower distances) as well as clinical relevance by expert opinion (also considering the results of the above analyses) to derive a final solution. Possible confounders will be assessed and corrected for.

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Ethics and dissemination

The Medical Research Ethics Committee NedMec (MREC NedMec) reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements, the MREC NedMec issued an approval for the Netherlands. HRA and Health and Care Research Wales (HCRW) has approved the study in the UK. The study will be conducted according to the principles of the Declaration of Helsinki (2013). Results will be published in scientific journals and presented at scientific congresses and patient meetings.

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Competing interests

None

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Author statement

 Julia Spierings is the project's guarantor and initiator, and she has been involved in every step of the process. Mark Greveling contributed to writing the protocol and was involved in the methodology for the study procedures.

Voon Ong, Christopher Denton, Amin Herman, Douwe Mulder, Madelon Vonk, Jeska de Vries-Bouwstra, and Simon Mastbergen participated in setting up the study and writing the protocol.

Wouter Foppen and Marion Kortekaas were responsible for the imaging procedures.

Nick Jeffries-Owen and Rita Schriemer served as patient representatives during the study setup.

Ilse Masselink was involved in the hand function measures.

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Appendix 1 Imaging protocol

Ultrasound

Materials

A high-end ultrasound machine (i.e. GE Logiq E10s, GE Healthcare, United States) will be used, equipped with one multifrequency linear probe and a high frequency (hockey stick) probe. Settings will be optimized for each machine and settings stay stable during the entire study period. The sonographer is allowed to modify depth and focus.

Variables

Outcomes	Area
Joint effusion (1) Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Synovial hypertrophy (1) Abnormal hypoechoic intraarticular tissue that is non- displaceable and poorly compressible and which may exhibit Doppler signal.	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Doppler signals (1) Flow signal in the synovium must be in synovial hypertrophy to be considered as a sign of synovitis	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Osteophytes Bone spurs at the end of bones	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
<i>Tenosynovitis</i> (2) Abnormal anechoic and/or hypoechoic tendon sheath widening related to the presence of tenosynovial abnormal fluid and/or hypertrophy	 Dorsal Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar Finger flexor digitorum (SUP/PROF) 2-5 at MCP level Flexor pollicis longus and brevis at MCP level
Tenosynovial effusion (2) Presence of displaceable abnormal anechoic or hypoechoic material within the synovial sheath, either localized or surrounding the tendon	 Dorsal Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar Finger flexor digitorum (SUP/PROF) 2-5 at MCP level Flexor pollicis longus and brevis at MCP level
I hickening of finger flexor and extensor tendons (3)	 Central slip of extensor tendons 2-5 at MCP level Extensor pollicis longus and brevis at MCP level Finger flexors 2-5 (sup+prof) at MCP level

	Flexor pollicis longus and brevis at MCP level
Calcifications Hyperechoic foci with or without shadowing at volar site the digits.	Volar • Digits 1-5
Thickening of A1 pulley (4,5) This annular structure situated at the level of the MCP joint consists of a strap surrounding the flexor tendon sheath. It appears as a hypoechoic band superficial to the flexor tendon sheath. Normal thickness in neutral position 0.38mm (SD 0.15) and hooked/contracted position 0.37mm (SD 0.15).(6)	 Volar A1 pulley 1-5 at the MCP level
Occlusion digital arteries Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain.(7)	 Volar radial artery of the index finger at MCP – DIP traject proper palmar digital arteries of digit 2-5 Princeps pollicis artery
<i>Intima-media thickness</i> Thickness of tunica intima and tunica media.	 Volar radial artery of the index finger digit at the MCP – DIP traject
Shear wave elastography (8) Stiffness of the tissue (UMCU only)	 Finger flexor tendons 2-5 at MCP level Flexor pollicis longus and brevis at MCP level Finger extensor tendons 2-5 at MCP level Extensor pollicis longus and brevis at MCP level
Scoring	
Outcomes	Scoring
Joint effusion (1) Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal	B-mode (GS 0-3) 0 = none 1 = minimal 2 = moderate 3 = severe Effusion Grade 0 Grade 1 Grade 1
Supovial hypertrophy (1)	Grade 2 Grade 3 B-mode (GS 0-3)

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	3=severe (d)
	 Power doppler within synovial sheath (0-3) 0=no signal (a) 1=focal signal (b) 2=multifocal signal (c)
	a (a) (a) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c
<i>Tenosynovial effusion</i> (2) Presence of displaceable abnormal anechoic or hypoechoic material within the synovial sheath, either localized or surrounding the tendon	Presence y/n
Thickening of finger flexor and extensor tendons (3)	Tendon width (max)
<i>Calcifications</i> Hyperechoic foci with or without shadowing at volar site the digits.	 Presence y/n Location: tendon, tendon sheat, periarticular, soft tissue Number per finger
Thickening of A1 pulley (4,5) This annular structure situated at the level of the MCP joint consists of a strap surrounding the flexor tendon sheath. It	Max width (transverse) of every finger

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appears as a hypoechoic band superficial to the flexor tendon sheath. Normal thickness in neutral position 0.38mm (SD 0.15) and hooked/contracted position 0.37mm (SD 0.15).(6)	
Occlusion digital arteries Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain.(7)	 Occlusion 0 = normal 1 = abnormal 2 = (near) occlusion Number of occluded arteries for each digit (0-2)
Intima-media thickness Thickness of tunica intima and tunica media.	Intima-media thickness (mean max)
Shear wave elastography (8) Stiffness of the tissue (UMCU only)	Velocity (meters per second)Stiffness (kiloPascals)

Procedure

Ultrasound examination will be performed at baseline, 6 months, 12 months, and 24 months in all patients.

Patients will be positioned with their hands resting on a table with extended fingers facing the examiner. If full extension is not possible due to hand contractures or when in doubt during the scoring of synovial thickening and effusion in the joints, the joint can be assessed in (slightly) flexed position.

For the joints and extensor tendons, patients will rest the palms of the hands on the table. For flexor tendons, calcinosis, vascular assessment and flexor tendons, patients will rest the dorsum of the hand on the table for evaluation of the volar aspect longitudinally and transversely.

Any abnormalities of the flexor tendons will be confirmed in a cross-sectional view. Whereas, any joint abnormalities will be confirmed using a dorsal longitudinal scan.

The sonographers at the study sites will be trained on this ultrasound protocol. Examinations are reported in an eCRF, one image/video for each measure will be stored. When deemed necessary, more images/videos can be stored. Measurements are done afterwards on the stored images by the coordinating researcher.

Ultrasound imaging starts with the right hand and the linear probe according to the steps below. After all measurements of the right hand are completed, the left hand is imaged according to the same steps. Vascular imaging is only conducted in the dominant hand. In the UMCU only, elastography is performed

Additionally, at the UMCG a more extensive protocol will be performed as substudy. The vascular protocol entails ultrasound measurements performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) and an ultra-high frequency ultrasound transducer (70 MHz). Nailfold capillaroscopy (NCM) will be performed with a handheld DinoLite CapillaryScope 200 Pro (DinoLite Europe BV). Finger and toe pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands).

Wrist bones

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Radiocarpal

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0	Joint effusion	
	 0 = none 	
	1 = minimal	
	 2 = moderate 	
	 3 = severe 	
0	Synovial hypertrophy	
	• 0 = none	0
	1 = up to the level of the horizontal line connecting	7
	bone surfaces of the joint	
	 2 = extending beyond joint line but with upper 	
	surface concave or flat	
	 3 = extension beyond joint line but with upper 	
	surface convex	
0	Doppler signal	
	 0 = no flow in the synovium 	
	 1 = single vessel signals 	
	 2 = vessel signals < half of the synovium 	
	 3 = vessel signal > half of the synovium 	
0	Osteophytes	
	 Presence y/n 	
- Interca	arpal	
0	Joint effusion	
	• 0 = none	
	 1 = minimal 	
	 2 = moderate 	
	• 3 = severe	
0	Synovial hypertrophy	
	• 0 = none	100
	1 = up to the level of the horizontal line connecting	6
	bone surfaces of the joint	
	2 = extending beyond joint line but with upper	
	surface concave or flat	
	 3 = extension beyond joint line but with upper 	
	Sufface convex	
0	Doppier signal	
	• 0 = no now in the synovium	
	 I = single vessel signals 2 = vessel signals < half of the synavium 	
	- 2 - vessel signals > half of the synovium	
	- 5 - vesser signal < nali 01 the Synovium	
0		
	• Presence y/n	





3 Distal radio-ulnar joint (DRUJ) 4 Joint effusion 0 5 0 = none6 1 = minimal . 7 2 = moderate 8 3 = severe 9 Synovial hypertrophy 0 10 0 = none11 . 1 = up to the level of the horizontal line connecting 12 bone surfaces of the joint 13 2 = extending beyond joint line but with upper 14 surface concave or flat 15 3 = extension beyond joint line but with upper 16 surface convex 17 Doppler signal 0 18 0 = no flow in the synovium 19 1 = single vessel signals 20 2 = vessel signals < half of the synovium 21 3 = vessel signal > half of the synovium 22 Osteophytes 0 23 Presence y/n 24 25 26 27 Compartments of extensor tendons 28 Wrist extensor compartment 1 29 Tenosynovitis 0 30 0 = no 31 1 = minimal32 2 = moderate 33 3 = severe34 Power doppler within synovial sheath 0 35 0 = no signal36 1 = focal signal 37 2 = multifocal signal 38 3 = diffuse signal 39 Tenosynovial effusion 0 40 Presence y/n 41 42 43 Wrist extensor compartment 2 44 Tenosynovitis 0 45 0 = no46 47 1 = minimal2 = moderate 48 3 = severe 49 50 Power doppler within synovial sheath 0 51 0 = no signal52 1 = focal signal 53 2 = multifocal signal 54 3 = diffuse signal 55 Tenosynovial effusion 0 56 Presence y/n 57 58 59 Wrist extensor compartment 3 60

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Imaging protocol HANDSOME cohort v1.0 d.d.11-12-23 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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5	 0 = 10 1 = minimal 	AMA
6	 2 = moderate 	c = /
/	• 3 = severe	
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10	 1 = focal signal 	$\sum ($
11	 2 = multifocal signal 	$\sum ($
12	 3 = diffuse signal 	
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Tenosynovitis

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- 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
- Power doppler within synovial sheath
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal
- o Tenosynovial effusion
 - Presence y/n
- Wrist extensor compartment 5
 - Tenosynovitis
 - 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
 - Power doppler within synovial sheath
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal
 - Tenosynovial effusion
 - Presence y/n

Wrist extensor compartment 6

Tenosynovitis

- 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
- Power doppler within synovial sheath
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal
- Tenosynovial effusion
 - Presence y/n





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6	At MCP 1 level		
7	- MCP 1		
8	0	Joint effusion	
9		 0 = none 	
10		 1 = minimal 	
11		 2 = moderate 	000
12		 3 = severe 	M 1-1 (M
13	0	Synovial hypertrophy	
14		• 0 = none	1007
15		 1 = up to the level of the horizontal line connecting 	
10		bone surfaces of the joint	A
17		 2 = extending beyond joint line but with upper surface concerve or flat 	
19		 Surface concave of fiat 3 = extension beyond joint line but with upper 	
20		surface convex	
21	0	Doppler signal	1 1
22	Ũ	 0 = no flow in the synovium 	
23		 1 = single vessel signals 	
24		 2 = vessel signals < half of the synovium 	
25		 3 = vessel signal > half of the synovium 	
26	0	Osteophytes	
27		 Presence y/n 	
28	- Extens	or pollicus longus and brevis at MCP level	
29	0	Thickening of extensor tendons	
30		 Tendon width (max) 	
32	At MCP 2 level		
33			
34	- MCP 2		
35	0	Joint effusion	
36		• 0 = none	
37		 1 = minimai 2 = moderate 	0
38			AMA
39	0	Synovial hypertrophy	H
40	0	• 0 = none	
41		 1 = up to the level of the horizontal line connecting 	
43		bone surfaces of the joint	
44		 2 = extending beyond joint line but with upper 	χ'
45		surface concave or flat	\setminus (
46		 3 = extension beyond joint line but with upper 	λ (
47		surface convex	
48	0	Doppler signal	
49		 0 = no flow in the synovium 4 = single waged signals 	
50		 1 = single vessel signals 2 = vessel signals < helf of the supervision 	
51		 2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium 	
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55	- Centra	I slin of extensor tendon 2 at MCP level	
56	⊖ Ocitica	Thickening of extensor tendons	
57	0	 Tendon width (max) 	
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At MCP 3 level

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5	- MCP 3		
б	0	Joint effusion	
7		 0 = none 	
8		 1 = minimal 	
9		 2 = moderate 	a A a
10		 3 = severe 	M - M
11	0	Synovial hypertrophy	
12		• 0 = none	V J9/7
13		1 = up to the level of the horizontal line connecting	N I J V7
14		bone surfaces of the joint	
15		 2 = extending beyond joint line but with upper 	$\backslash $ $' $
16		surface concave or flat	\setminus /
17		 3 = extension beyond joint line but with upper 	
18		surface convex	
19	0	Doppler signal	1 I
20	-	 0 = no flow in the synovium 	
21		 1 = single vessel signals 	
22		 2 = vessel signals < half of the synovium 	
22		= 3 = vessel signal > half of the synovium	
23	0	Osteonbytes	
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20	- Central	This leaving of extension tendens	
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31	At MCP 4 level		
31 32 22	At MCP 4 level		
31 32 33	At MCP 4 level	2.	
31 32 33 34	At MCP 4 level - MCP 4 °	Joint effusion	
31 32 33 34 35 26	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none	
31 32 33 34 35 36	At MCP 4 level - MCP 4 0	Joint effusion • 0 = none • 1 = minimal	
31 32 33 34 35 36 37	At MCP 4 level - MCP 4 0	Joint effusion • 0 = none • 1 = minimal • 2 = moderate	0,00
31 32 33 34 35 36 37 38 20	At MCP 4 level - MCP 4 o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe	9 9 9
31 32 33 34 35 36 37 38 39	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy	
31 32 33 34 35 36 37 38 39 40	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none	
31 32 33 34 35 36 37 38 39 40 41	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting	
 31 32 33 34 35 36 37 38 39 40 41 42 42 	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint	
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper	
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat	
31 32 33 34 35 36 37 38 39 40 41 42 43 44	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex	
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal	
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium	
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 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	At MCP 4 level - MCP 4 °	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence v/n	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	At MCP 4 level - MCP 4 ° ° • • • • • • • •	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	At MCP 4 level - MCP 4 ° ° ° • • • • • • •	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n I slip of extensor tendons 4 at MCP level Thickening of extensor tendons	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	At MCP 4 level - MCP 4 ° ° ° · · · · · · · · · · ·	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n I slip of extensor tendons • Tendon width (max)	
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57	At MCP 4 level - MCP 4 ° ° ° • •	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface concex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n I slip of extensor tendons • Tendon width (max)	
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2			
3	At MCP 5 leve	I	
4			
5	- MCP 5		
6	0	Joint effusion	
7		• 0 = none	
8		 1 = minimal 	
9		 2 = moderate 	Δ
10		• 3 = severe	M
11	0	Synovial hypertrophy	
12		• 0 = none	
13		 1 = up to the level of the horizontal line connecting 	(\mathcal{O})
14		bone surfaces of the joint	$\backslash \gamma$
15		2 = extending beyond joint line but with upper automatication of the second	
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1/		 3 = extension beyond joint line but with upper 	1
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19	0	Doppier signal	
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21		 I = single vessel signals 2 = vessel signals < helf of the supervision 	
22		 2 = vessel signals < half of the synovium 2 = vessel signal > helf of the synovium 	
25		• 3 = vessel signal > hall of the synovium	
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25	Contro	Presence y/n	
20	- Centra	Thiskering of extension tendons 5 at MCP level	
27	0	I nickening of extensor tendons	
20		I endon width (max)	
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30 31 32	At (P)IP level		
30 31 32 33	At (P)IP level - IP	Q	
30 31 32 33 34	At (P)IP level - IP o	Joint effusion	
30 31 32 33 34 35	At (P)IP level - IP o	Joint effusion • 0 = none	
30 31 32 33 34 35 36	At (P)IP level - IP ○	Joint effusion • 0 = none • 1 = minimal	
30 31 32 33 34 35 36 37	At (P)IP level - IP ○	Joint effusion • 0 = none • 1 = minimal • 2 = moderate	o f
30 31 32 33 34 35 36 37 38	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe	9 (
30 31 32 33 34 35 36 37 38 39	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy	
30 31 32 33 34 35 36 37 38 39 40	At (P)IP level - IP ○	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none	
30 31 32 33 34 35 36 37 38 39 40 41	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting	
30 31 32 33 34 35 36 37 38 39 40 41 42	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint	
30 31 32 33 34 35 36 37 38 39 40 41 42 43	At (P)IP level - IP ©	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	At (P)IP level - IP o	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	At (P)IP level - IP o	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex 	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	At (P)IP level - IP ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the surpryime 	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	At (P)IP level - IP ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the synovium 1 = single vessel signals 	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49	At (P)IP level - IP ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals 	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	At (P)IP level - IP ο	Joint effusion	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51	At (P)IP level - IP ο	Joint effusion	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52	At (P)IP level - IP ο	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Demonsor u/p	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	At (P)IP level - IP ο	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	At (P)IP level	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium Osteophytes • Presence y/n	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	At (P)IP level - IP ο ο	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	At (P)IP level - IP ο	Joint effusion • 0 = none • 1 = minimal • 2 = moderate • 3 = severe Synovial hypertrophy • 0 = none • 1 = up to the level of the horizontal line connecting bone surfaces of the joint • 2 = extending beyond joint line but with upper surface concave or flat • 3 = extension beyond joint line but with upper surface convex Doppler signal • 0 = no flow in the synovium • 1 = single vessel signals • 2 = vessel signals < half of the synovium • 3 = vessel signal > half of the synovium Osteophytes • Presence y/n	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 57	At (P)IP level ο	 Joint effusion 0 = none 1 = minimal 2 = moderate 3 = severe Synovial hypertrophy 0 = none 1 = up to the level of the horizontal line connecting bone surfaces of the joint 2 = extending beyond joint line but with upper surface concave or flat 3 = extension beyond joint line but with upper surface convex Doppler signal 0 = no flow in the synovium 1 = single vessel signals 2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium Osteophytes Presence y/n 	



1 = up to the level of the horizontal line connecting

2 = extending beyond joint line but with upper

3 = extension beyond joint line but with upper

2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium

1 = up to the level of the horizontal line connecting

2 = extending beyond joint line but with upper

3 = extension beyond joint line but with upper

2 = vessel signals < half of the synovium 3 = vessel signal > half of the synovium

bone surfaces of the joint

0 = no flow in the synovium 1 = single vessel signals

surface concave or flat

surface convex

bone surfaces of the joint

0 = no flow in the synovium 1 = single vessel signals

surface concave or flat

surface convex

3	- PIP 2	
4	0	Joint effusion
5		0 = none
6		1 = minimal
7		 2 = moderate
8		3 = severe
9	0	Synovial hypertrophy
10	-	 0 = none
11		1 = up to the
12		bone surface
13		 2 = extending
14		surface conc
15		 3 = extension
16		surface conve
17	0	Doppler signal
18		• 0 = no flow in
19		1 = single ves
20		2 = vessel sid
21		 3 = vessel sig
22	0	Osteophytes
23	Ŭ	 Presence v/n
24		r reseries ym
25		
26	- PIP 3	
27	- 111 5	laint offusion
28	0	
29		 0 = none 1 = minimal
30		 1 - minimar 2 - moderate
31		
32	_	= J = Severe
33	0	
34		$\bullet 0 = \text{finding}$
35		 I = up to the
36		Done surface
37		
38		
39		
40	0	Doppler signal
41	0	
42		 0 = 10 100 III 1 = single ver
43		
44		
45		 S = Vessel sig
46	0	
47		 Presence y/n
48		
49		
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51		
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1			
2			
3	- PIP 4		
4	0	Joint effusion	
5		0 = none	
6		1 = minimal	
7		 2 = moderate 	0
8			AM
9	0	Synovial hypertrophy	
10	0		
11		 0 - Holle 1 - up to the level of the herizental line connecting 	
12		 I – up to the level of the holizontal line connecting 	
13		Done surfaces of the joint	X7 *** /]
14		- 2 - extending beyond joint line but with upper	
15		Surface concave of filat	
16			
17		Doppler signal	1 1
18	0	= 0 = no flow in the even vium	
19			
20		 I = single vessel signals 2 = vessel signals 	
21		2 = vessel signals < nalf of the synovium	
22		3 = vessel signal > nait of the synovium	
23	0	Osteophytes	
24		 Presence y/n 	
25			
26			
27			
28			
29	- PIP 5		
30	0	Joint effusion	
31		• 0 = none	
32		1 = minimal	
33		 2 = moderate 	0 0 0
34		 3 = severe 	M [-] (9
35	0	Synovial hypertrophy	
36		• 0 = none	$\langle 0 0 q \rangle$
37		 1 = up to the level of the horizontal line connecting 	O MUL
38		bone surfaces of the joint	
39		 2 = extending beyond joint line but with upper 	\times γ
40		surface concave or flat	\mathbf{X}
41		3 = extension beyond joint line but with upper	
42		surface convex	
43	0	Doppler signal	
44		 0 = no flow in the synovium 	
45		1 = single vessel signals	
46		 2 = vessel signals < half of the synovium 	
40		3 = vessel signal > half of the synovium	
48	0	Osteophytes	
49	-	 Presence y/n 	
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55 56			
50 57			
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Ask subject to turn their hand with the palmar side up!

Palmar side of digit 1

Flexor pollicus longus and brevis at MCP level 0

- Tenosynovitis
 - 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
- Power doppler within synovial sheath 0
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal
 - Tenosynovial effusion
 - Presence y/n
- Thickening of flexor tendons 0
 - Tendon width (max)

A1 pulley at MCP level

.

- Thickening of A1 pulley 0
 - Max width (transverse)
- Digit 1

0

0

- Calcifications
 - Presence y/n
 - . Location
 - Number per finger

Palmar side of digit 2

- Finger flexors (sup + prof) 2 at MCP level
 - Tenosynovitis 0
 - 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
 - Power doppler within synovial sheath 0
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal
 - Tenosynovial effusion
 - Presence y/n
 - Thickening of flexor tendons 0
 - Tendon width (max)

A1 pulley 2 at MCP level

- Thickening of A1 pulley 0
 - Max width (transverse)
- Digit 2 0

0

- Calcifications
 - Presence y/n
 - Location
 - Number per finger





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1	
2	
3	Palmar side of digit 3
4	Finner flowers (over 1 and) 2 of MOD lovel
5	- Finger flexors (sup + prof) 3 at MCP level
6	
/	• 0 = 110 • 1 = minimal
8	1 = 11111111a1
9	
10	- J - Severe - Dewor depoter within synovial sheath
17	0 = 0 = no signal
12	 0 - 10 Signal 1 - focal signal
14	 1 - local signal 2 = multifocal signal
15	-2 = intuitiocal signal $= 3 = diffuse signal$
16	
17	
18	 Thickening of flexor tendons
19	 Tendon width (max)
20	- A1 pulley 3 at MCP level
21	• Thickening of A1 pulley
22	 Max width (transverse)
23	- Digit 3
24	• Calcifications
25	 Presence v/n
26	 Location
27	 Number per finger
28	
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29 30 31	Palmar side of digit 4
29 30 31 32	Palmar side of digit 4
29 30 31 32 33	Palmar side of digit 4 - Finger flexors (sup + prof) 4 at MCP level
29 30 31 32 33 34	Palmar side of digit 4 - Finger flexors (sup + prof) 4 at MCP level Tenosynovitis
29 30 31 32 33 34 35	Palmar side of digit 4 - Finger flexors (sup + prof) 4 at MCP level o Tenosynovitis • 0 = no
29 30 31 32 33 34 35 36	Palmar side of digit 4 - Finger flexors (sup + prof) 4 at MCP level O Tenosynovitis 0 = no 1 = minimal
29 30 31 32 33 34 35 36 37	Palmar side of digit 4 - Finger flexors (sup + prof) 4 at MCP level O Tenosynovitis 0 = n0 1 = minimal 2 = moderate
29 30 31 32 33 34 35 36 37 38	Palmar side of digit 4 - Finger flexors (sup + prof) 4 at MCP level O Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe
29 30 31 32 33 34 35 36 37 38 39	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath
29 30 31 32 33 34 35 36 37 38 39 40	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal
29 30 31 32 33 34 35 36 37 38 39 40 41	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 0 = no signal
29 30 31 32 33 34 35 36 37 38 39 40 41 42	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 2 = diffuse signal
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Dependence u/n
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Presence y/n
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max)
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Thickening of A1 pulley
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Max width (transverse)
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Max width (transverse)
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 51	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Max width (transverse)
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Max width (transverse) Digit 4 Presence y/n
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Max width (transverse) Digit 4 Presence y/n Location Presence y/n
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	 Palmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Max width (transverse) Digit 4 Calcifications Presence y/n Location Winther per finger
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	 Falmar side of digit 4 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Thickening of A1 pulley Max width (transverse) Digit 4 Calcifications Presence y/n Location Number per finger
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57	 Finger flexors (sup + prof) 4 at MCP level Tenosynovitis 0 = n0 1 = minimal 2 = moderate 3 = severe Power doppler within synovial sheath 0 = no signal 1 = focal signal 2 = multifocal signal 3 = diffuse signal Tenosynovial effusion Presence y/n Thickening of flexor tendons Tendon width (max) A1 pulley 4 at MCP level Max width (transverse) Digit 4 Calcifications Presence y/n Location Number per finger



E.

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Palmar side of digit 5

- Finger flexors (sup + prof) 5 at MCP level

- o Tenosynovitis
 - 0 = no
 - 1 = minimal
 - 2 = moderate
 - 3 = severe
- $\circ \quad \text{Power doppler within synovial sheath} \\$
 - 0 = no signal
 - 1 = focal signal
 - 2 = multifocal signal
 - 3 = diffuse signal
 - Tenosynovial effusion
 - Presence y/n
- Thickening of flexor tendons
 - Tendon width (max)

A1 pulley 5 at MCP level

- Thickening of A1 pulley
 - Max width (transverse)

- Digit 5

- Calcifications
 - Presence y/n
 - Location
 - Number per finger

reliezonz

2		
3		\circ \cap $-$
4		
5	Only look at the arteries in the dominant hand!	$\bigcap = [=]$
6	 Radial artery index finger at MCP-DIP section 	
7	 Occlusion 	Nº 10
8	0 = normal	
9	1 = abnormal	
10	 2 = (near) occlusion 	
11	 Intima media thickness 	
12	 Max thickness on section 	
13		·
14		
15		
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10		
17		
18		
19		
20		\sim
21		$() \vdash \cap$
22		$\left(\left 1 \right \right) = \left(\left 1 \right \right)$
23	- Princeps pollicus artery at MCP-IP section	1211
24	\circ Occlusion	LU-3-34
25	• 0 = normal	
26	■ 1 = abnormal	
27	$= 2 = (near) \operatorname{occlusion}$	
28		
29) = =)
30		\circ \cap '
31		
32	 Proper palmar digital arteries of digit 2-5 at MCP level 	0 HHE
33	• Occlusion	
34	• 0 = normal	
35	 1 = abnormal 	
36	 2 = (near) occlusion 	
27	 Number of occluded arteries for each digit (0-2) 	
20		
20		
39	Proper palmar	
40	digital arteries	
41		
42	Radial artery of index finger	
43		
44	Common	
45		
46		
47		
48	palmar arch	
49		
50	pollicis artery	
51	palmararch	
52		
53	antery	
54		
55		
56		
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 Flexor pollicus longus and brevis at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) Ask subject to turn their hand with dorsal side up Finger extensor tendons 1-5 at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) Extensor pollicus longus and brevis at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) 	 Finger flexor tendons 2-5 at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) 	
 Ask subject to turn their hand with dorsal side up Finger extensor tendons 1-5 at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) Extensor pollicus longus and brevis at MCP level Shear wave elastography Velocity (meters per second) Shear wave elastography Velocity (meters per second) Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) 	 Flexor pollicus longus and brevis at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) 	
 Extensor pollicus longus and brevis at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) 	Ask subject to turn their hand with dorsal side up Finger extensor tendons 1-5 at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) 	
	 Extensor pollicus longus and brevis at MCP level Shear wave elastography Velocity (meters per second) Stiffness (kiloPascals) 	

MRI assessment

Materials

A 3 Tesla scanner (Philips Medical Systems, Best, The Netherlands) with dedicated surface coils.

Variables

Outcomes	Area	Scoring
Synovitis or tenosynovitis (9) Hyperintense signal on both STIR and fat-saturated post-gadolinium images in a thickened articular and tendon sheath synovium	 Radiocarpal Intercarpal MCPs 2-5 PIPs 2-5 	 Synovitis None/Focal/Diffuse / of Mild/moderate /severe Tenosynovitis None/Focal/Diffuse
<i>Erosions</i> (10) Sharply marginated bone lesion, with correct juxta-articular localisation and typical signal characteristics, with a cortical break visible in two adjacent planes.	 Radiocarpal Intercarpal MCPs 2-5 PIPs 2-5 	 Presence Number Location (specify joint)
Bone edema	AREA	None/mild/moderate/severe

Procedure

The MRI examination will be performed on the dominant hand. Non-enhanced transverse and coronal T1-weighted, fast spin-echo T2-weighted and short-tau inversion recovery (STIR) and/or fat-saturated proton-density sequences will be performed with contrast enhancement.

A radiologists will assess the MRI images and reported the scores in an eCRF. The MRI will be performed at baseline in the first 50 patients participating at the UMC Utrecht. MRI examinations will be performed on the day of the baseline ultrasound and read without knowledge of hand function scores.

L'EZ ONI

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